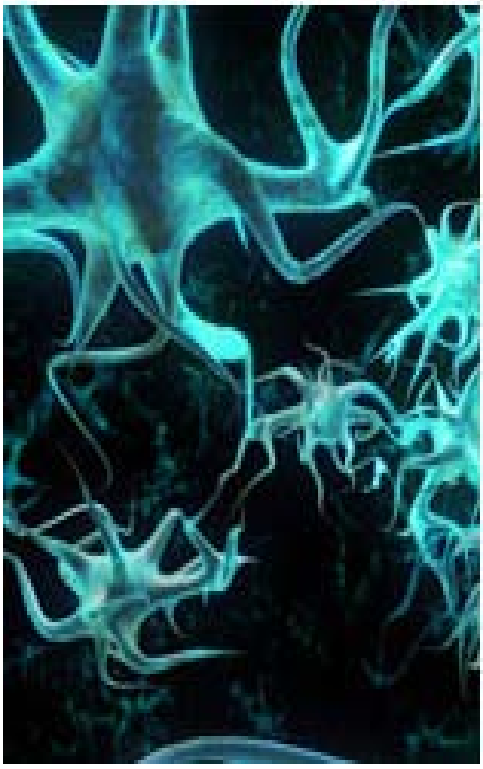

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Abstracts

Oral Presentations

Oral Presentations I

What is disconnected and where?

ASSESSING THE DISCONNECTION SYNDROME IN SCHIZOPHRENIA: MODEL BASED PATH ANALYSIS OF fMRI DATASETS

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Background: Cognitive deficits in schizophrenia have been associated with "cognitive dysmetria" related to a disruption of large-scale information processing networks. The present sequence of fMRI studies examined the hypothesis of altered effective connectivity within a defined cortical–subcortical–cerebellar network subserving working memory functions.

Methods: Twelve schizophrenic patients treated with either typical or atypical antipsychotics and six drug-free schizophrenic patients were studied with fMRI and compared to normal controls. All subjects performed a 2-back working memory task. Cortical–subcortical–cerebellar effective connectivity was examined with structural equation modeling (SEM) using AMOS 4.0.

Results: Drug-free patients and patients under typical antipsychotics demonstrated reduced interhemispheric cortico-cortical connectivity. This finding is consistent with studies indicating altered integrity of interhemispheric fiber tracts and Crow's hypothesis of schizophrenia as a "transcallosal misconnection syndrome". In drug-free patients, enhanced thalamo-cortical and prefrontal intrahemispheric connectivity was detected.

Conclusion: The result could be integrated into a model of deficient thalamo-cortical filter functions. The higher neuronal connection strength in patients might be related to underlying cortical inefficiency. Enhanced thalamo-cortical effective connectivity could be observed in treated patients as well thereby indicating trait characteristics of this finding. The results are demonstrating the general feasibility to use SEM analysis for the study of effective connectivity and are supporting the notion of functional disconnection in schizophrenia.

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A DIFFUSION TENSOR IMAGING STUDY OF SCHIZOPHRENIA

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Background: Patients with schizophrenia show subtle changes in pre-frontal, temporal and cerebellar volumes and evidence of dysconnectivity in functional imaging studies. These findings may reflect a disruption of white matter tract connections. Previous DTI studies of white matter in schizophrenia have produced conflicting results: four have reported differences in Fractional Anisotropy (FA), and four have not. However, sample sizes in studies to date have been small, and the methods for processing DTI data are still evolving. In the present study, we used a voxel-based approach to examine the FA in frontal white matter tracts in larger groups than have previously been investigated.

Methods: Thirty-three patients meeting DSM-IV criteria for schizophrenia, and 39 IQ- and age-matched controls, were scanned with an optimised, multi-direction DTI sequence, on a 1.5 T GE MRI scanner. After correction for eddy-current induced distortions, the tensor was calculated and FA maps produced. Non-diffusion

doi:10.1016/j.schres.2003.10.001

weighted scans were registered to the MNI template, using FSL, giving a new template to which all scans were re-registered, and the final realignment parameters then applied to the FA maps. After inspection for image quality and gross abnormality, group analysis was performed on the FA maps using XBAMM (a nonparametric package), with cluster and voxel thresholds of $p < 0.01$ and $p < 0.002$.

Results: Preliminary analysis found the schizophrenic subjects to have decreased FA in the areas of the left uncinate, right superior longitudinal fasciculus and bilateral corpus callosum.

Conclusion: Schizophrenia is associated with changes in white matter pathways connecting frontal, temporal and posterior cortical areas.

WHITE MATTER INTEGRITY IN SCHIZOPHRENIA—DTI AND MTR VOXEL-WISE ANALYSIS

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Background/objective: Diffusion Tensor Imaging (DTI) is a technique that is sensitive to the water movement in the brain and may help to characterize white matter abnormalities in schizophrenia. To date, diffusion studies in schizophrenia show lower anisotropic diffusion within white matter, likely due to loss of coherence of white matter fiber tracts. Candidate processes involve changes in the number and/or density of interconnecting fiber tracts as well as changes in myelination. The aim of this study is to compare white matter findings using two imaging techniques, DTI and magnetization transfer imaging (MTR), the latter a saturation technique sensitive to myelin alterations.

Methods: Ten right-handed chronic male schizophrenia patients and 10 male controls were scanned using Line-Scan-Diffusion-Imaging and T1-weighted techniques with/without saturation pulse (MTR). Four-millimeter-thick coronal images were acquired for DTI/MTR on a 1.5-T GE Echo-speed-system and analyzed using SPM99 software. Both DTI relative anisotropy and MTR maps of the white matter were normalized to the MNI space, and smoothed with a 12-mm Gaussian kernel. Group differences for both DTI/MTR were calculated using a General Linear Model.

Results: Lower diffusion anisotropy was observed, bilaterally, in the schizophrenia group compared to controls, for white matter in the frontal region (including the cingulate bundles), and in the left posterior region (including the arcuate fasciculus, internal capsules and corpus callosum). MTR maps showed lower myelin density in the internal capsules and in frontal regions, but not in the corpus callosum or in arcuate fasciculus.

Conclusion: Findings demonstrate that some of the diffusion changes in schizophrenia may be attributed to myelin alterations. This disruption may be secondary to neuronal disorganization.

A DTI STUDY OF THE CORPUS CALLOSUM IN FIRST-EPISODE SCHIZOPHRENIA

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Background/objective: The corpus callosum (CC) is the largest white matter tract in the brain. Diffusion Tensor Imaging (DTI) enables examination of cellular cytoarchitecture in vivo. A previous study in our group, using region of interest (ROI) methodology with DTI, has shown evidence of neuropathological changes in the CC, in patients with chronic schizophrenia. Other studies have also shown evidence of change in the CC. However, little is known about the biological correlates and functional significance of these findings, or if these changes are the result of illness chronicity. The aim of this study was to examine the CC for neuropathological changes, with DTI, in patients with first-episode schizophrenia (FE-SCZ)—removing the confounder of illness chronicity.

Methods: DTI was performed in 20 FE-SCZ (mean age = 25 years) and 29 healthy controls (mean age = 28 years). Mean diffusivity and fractional anisotropy were used to measure fibre organisation and directionality. The same ROI (splenium and genu of the CC) matching our previous study of patients with chronic schizophrenia were chosen.

Results: No significant differences were seen in both the splenium and genu when the FE-SCZ and control groups were compared. Age also had no effect in predicting DTI changes.

Conclusion: The absence of DTI changes in the splenium and genu of the CC in FE-SCZ patients contrasts with changes found previously using DTI in chronic patients. A possible conclusion is that focal disruptions, as measured by DTI in these regions, are not present at an early stage of the illness.

CONFIRMATION OF SEVERE LOSS OF SUBICULAR DENDRITIC SPINES IN SCHIZOPHRENIA

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Background: We reported [Arch. Gen. Psychiatry 57 (2000) 349] that the density of spines on the apical dendrites of left subicular pyramidal cells, impregnated by the Rapid Golgi method, was 79% lower in a group of chronically institutionalized schizophrenia subjects (mean age 66) than in a comparison group without history of psychiatric disease.

Methods: We now present confirmatory data from a younger sample of subjects autopsied at the Institute for Forensic Medicine in Skopje, Macedonia. In this preliminary analysis, we compare four schizophrenia subjects (mean age 45) with four subjects free of psychiatric disease (mean age 34). Mean post mortem interval for each group was 12 h. Psychiatric diagnoses (or their absence) were determined by interviews with survivors and by review of psychiatric records with the modified Diagnostic Evaluation After Death. Tissue was fixed in phosphate-buffered formalin for 2–3 years prior to Golgi–Kopsch impregnation of the left hippocampus. At least five well-impregnated pyramidal neurons were analyzed from each subiculum by raters masked to clinical information. Spines along the main shaft of the apical dendrite were counted manually in successive 60-μm segments.

Results: Spine density was decreased 82% in the segment 60–120 μm from the cell body ($t = 16.3$, $df = 6$, $p < 0.0005$), and similarly in other segments.

Conclusion: This provides preliminary confirmation of our earlier result with a superior staining technique, applied to a younger sample. The similar findings for older and younger subjects suggest that the deficit in spines is stable through much of the illness.

Acknowledgments: Supported by MH64168, MH60877. NARSAD, and the Lieber Center for Schizophrenia Research.

GABAERGIC NEURONS IN SCHIZOPHRENIA: COMPARATIVE MORPHOMETRY OF CORTICAL AND SUBCORTICAL STRUCTURES

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Background: A broad spectrum of schizophrenic symptoms may by explained by disturbed mechanisms of neuronal inhibition. Moreover, several post mortem studies reported a decrease in terminals and/or mRNA of glutamic acid decarboxylase (GAD), the enzyme that synthesises GABA, in the prefrontal cortex. The present study was performed to determine the number of GAD containing (i.e. GABAergic) neurons in several cortical and subcortical structures in schizophrenics and normal controls.

Methods: GAD containing neurons were stained by immunohistochemistry in whole brain serial sections (20 μm, formalin fixed, paraplast embedded) in 10 schizophrenics and 10 controls matched for age, sex, post mortem delay and fixation time. In both hemispheres, numerical densities were determined in the thalamus (nn. reticularis, lateralis, dorsomedialis), temporal cortex (Heschl gryrus, superior temporal gyrus, parahippocampal gyrus) and hippocampus.

Results: There was a bilateral highly significant two-fold increase of GAD immunoreactive cells in all areas of the temporal cortex. In contrast, there was a reduction of GAD-neurons by about 30% in the lateral and reticular nucleus of the thalamus. No change was observed in the hippocampus.

Conclusion: Reduced numbers of GAD immunoreactive neurons in the thalamus may reflect a primary neuropathological defect in schizophrenia, while increased densities of stained GABAergic cells in temporal cortex may be caused by chronic neuroleptic treatment, known to enhance GAD expression in some brain regions. Divergent results in different brain regions underline the need for comparative analysis of many brain areas in schizophrenia.

ALTERED DENSITY OF INTERSTITIAL WHITE MATTER AND LAYER I NEURONS IS ACCOMPANIED BY DECREASED REELIN EXPRESSION IN THE DORSOLATERAL PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background/objective: Interstitial white matter neurons (IWMNs) are studied in schizophrenia as markers of aberrant subplate and cortical development. Together with the decreased expression of the key neurodevelopmental gene reelin in schizophrenia, changes in the density and/or distribution of IWMNs provide support for an early developmental component to the disorder. Recently, we have confirmed that IWMN density is

increased in schizophrenia, while their expression of reelin is decreased. The current study extends our investigation of IWMNs and reelin to the dorsolateral prefrontal cortex in 11 subjects with schizophrenia and 13 matched controls, and includes another reelin expressing cell population, layer I neurons.

Methods: Neuronal density in the white matter and layer I was assessed using the neuron specific marker NeuN. IWMN density was increased in superficial white matter in schizophrenia ($P = 0.008$) but was unaffected in deep white matter, whilst for layer I, neuronal density was decreased in schizophrenia ($P = 0.017$). Using in situ hybridization with 35S-labelled oligonucleotides, reelin mRNA was quantified over individual neurons in the white matter and layer I. Both neuronal populations exhibited decreased reelin expression in schizophrenia (IWMNs, $P = 0.009$; layer I, $P = 0.012$). Further analyses revealed significant effects of gender on reelin mRNA, and a significant diagnosis-by-gender interaction in layer I.

Results: These findings support neurodevelopmental theories of schizophrenia and suggest a possible link between reelin and IWMNs in the pathogenesis of the disorder. With its role in several critical processes including synaptogenesis and neuronal migration, decreased reelin expression may contribute to aberrant synaptic connectivity seen in schizophrenia.

Acknowledgments: SLE was supported by the Margaret Temple Fellowship of the British Medical Association. Additional support came from the Stanley Medical Research Institute.

Oral Presentations IIA

Should we be treating the prodrome?

OLANZAPINE VS. PLACEBO FOR PRODROMAL SCHIZOPHRENIA

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Background: This is the first multi-site randomized, double-blind, placebo controlled clinical trial of Olanzapine in the prodromal phase of schizophrenia.

Methods: Sixty consenting patients meeting prodromal criteria (mean age 17.7 years, 65% male) received Olanzapine 5–15 mg or placebo for year one and no pills for year 2. *Results:* (1) Conversion. Twenty patients developed psychosis by 2 years (33% overall conversion rate). Fifteen converted in year 1, 10 on placebo and 5 on Olanzapine ($p = 139$).

Results: Compared to placebo, Olanzapine conversions received less prescribed study drug (7.7 vs. 10.5 mg, ns) and were less compliant in number of days taking drug (73% vs. 93%, ns). (2) Symptoms. Year 1 LOCF mean change analysis found attenuated positive prodromal symptoms (Scale of Prodromal Symptoms) significantly reduced in severity from baseline for drug but not for placebo; severity returned in year 2 for the Olanzapine group when drug was removed. Psychotic symptoms (PANSS), depression (MADRS), and mania (YMS) were minimal at baseline and changed little over both years. (3) Safety. Analysis found no drug/placebo differences for EPS in year 1; but weight gain and pulse were higher for drug (by 8.8 kg and 9 beats/min, respectively). Significance. Olanzapine reduces conversion to psychosis by 50%, a difference suggestive but not significant. Olanzapine appears effective in treating prodromal symptoms, which rebound when drug is stopped. Olanzapine is associated with weight gain and increased pulse, but not EPS.

Conclusion: Treatment recommendations require more research, and future studies need larger samples with higher ratios of true positive prodromal patients.

A RANDOMISED, CONTROLLED TRIAL OF NEW ATYPICAL DRUGS VERSUS CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: A single-blind, multicentre RCT compared the class of new (non-clozapine) atypical drugs with clozapine in patients in the NHS whose medication was being changed because of poor clinical response to two or more antipsychotic drugs.

Methods: The primary outcome was the Quality of Life Scale. Secondary clinical outcomes included symptoms (PANSS), side effects and participant satisfaction. Economic outcomes were costs of health and social care and a utility measure. A total of 136 (98% of the planned sample) participants were randomised. Follow up at 52 weeks, blind to treatment allocation, was complete in 87%.

Results: The intent to treat comparison of new atypicals compared with clozapine in people with more narrowly defined treatment resistance showed an advantage for commencing cloza-

pine in quality of life (QLS) at trend level ($p = 0.08$) and in symptoms (PANSS), that was statistically significant ($p = 0.01$), at 1 year. Clozapine showed approximately a 4-point advantage (not statistically significant) on QLS score at 52 weeks, against the predicted 10 points, and approximately a 5-point advantage on PANSS total score. Clozapine showed a trend towards having less total extrapyramidal side effects ($p = 0.1$). Participants reported at 12 weeks that their mental health was significantly better with clozapine than with new atypicals ($p < 0.05$). Net costs of care varied widely, with a mean of £33,588 in the clozapine group and £28,122 in the new atypical group, not a statistically significant difference. Of these costs, 4.0% and 3.3%, respectively, were due to antipsychotic drug costs.

Acknowledgment: This study was funded by NHS R&D Health Technology Assessment.

A RANDOMISED CONTROLLED TRIAL OF COGNITIVE THERAPY FOR THE PREVENTION OF PSYCHOSIS IN PEOPLE AT ULTRA-HIGH RISK

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Background: There have been recent advances in the ability to identify people at high risk of developing psychosis. This has led to interest in the possibility of preventing the development of psychosis.

Methods: A randomised controlled trial compared cognitive therapy (CT) with treatment as usual in 58 patients at ultra-high risk of developing a first episode of psychosis. CT was provided within the first 6 months, and all patients were monitored on a monthly basis for 12 months.

Results: Logistic regression demonstrated that CT significantly reduced the likelihood of progression to psychosis as defined on the PANSS over 12 months. In addition, it significantly reduced the likelihood of being prescribed antipsychotic medication and of meeting criteria for a DSM-IV diagnosis of a psychotic disorder. Analysis of covariance showed that CT also significantly improved positive symptoms of psychosis in this population over the 12-month period.

Conclusion: CT appears to be an acceptable and efficacious intervention for people at high risk of developing psychosis.

Oral Presentations IIB

Are there alternative treatments?

NAVIGATED BRAIN STIMULATION (NBS)—NOVEL TOOL FOR THE STUDY OF SCHIZOPHRENIA

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Background: The human brain can be stimulated non-invasively by targeted magnetic field pulses that induce small electric currents, thereby triggering neurons into action. The popularity of this technique, transcranial magnetic stimulation (TMS), has grown dramatically during the last few years. Until now, most TMS experiments have been limited to the stimulation of the motor cortex because the only immediately observable effects of magnetic stimulation have been muscle responses. Recently, however, it has been demonstrated that the cortical effects of TMS can also be observed directly, for example by means of electroencephalography (EEG) and positron emission tomography (PET).

Methods: To realize the full power of brain stimulation, we have developed a stimulation system that combines image-guided targeting, determination of the dose of the stimulation, and the recording and display of TMS-evoked electric brain activity (EEG).

Conclusion: We have added the tools required for accurate characterization of local cortical excitability as well as the functional connections within the brain. This promises to be a very powerful method in the study of schizophrenia with the known alterations of brain's connectivity and the cortical excitation–inhibition balance.

ETHYL-EICOSAPENTAENOIC ACID (E-EPA) SUPPLEMENTATION IN EARLY PSYCHOSIS

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Background/objective: Randomized controlled trials (RCTs) of 2 g E-EPA in the treatment of schizophrenia have returned equivocal findings, with three positive results (Peet et al., 2001; Emsley et al., 2003), and one negative (Fenton et al., 2002). This is the first RCT of E-EPA in FEP. The objective of this study was to investigate the effects of 2 g E-EPA in first-episode psychosis (FEP).

Methods: Eighty FEP patients participated in a 12-week, placebo-controlled, double-blind, randomized trial of 2 g E-EPA.

Results: The E-EPA and Placebo groups did not differ on demographic or clinical characteristics at baseline. The sample was acutely unwell (mean total exBPRSvs4 = 62). Sixty patients (75%) completed the trial. Simple comparisons using ANCOVA covarying for baseline score showed no significant effect of Group on BPRS, SANS, and CGI total scores, at week 12. At week 3, however, there was a significant main effect of Group for BPRS total score [$F(1,31) = 9.75$, $p = 0.004$] in treatment responding patients, with those on EPA scoring 9 points lower. Treatment response was defined as a 10-point reduction in total BPRS score between baseline and week 3.

Conclusion: E-EPA appears to be an effective and well-tolerated add-on treatment that can accelerate symptom recovery in treatment-responsive patients with FEP.

Oral Presentations IIC

What are the costs?

DROPOUT RATES IN PLACEBO-CONTROLLED AND ACTIVE-CONTROL CLINICAL TRIALS OF ANTIPSYCHOTICS—A META-ANALYSIS

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Background/objective: Dropout rates in randomized clinical trials of antipsychotics have consistently been reported to be high and the use of a placebo-controlled design is hypothesized to be one of the reasons for this. The main objective of this paper is to investigate this hypothesis in a meta-analysis of available data.

Methods: The meta-analysis was based on all published pivotal pre-registration trials of the second-generation antipsychotics risperidone, olanzapine, quetiapine, amisulpride and ziprasidone, amounting to a total of 17 trials comprising 6733 subjects. Data were analyzed by a random effect meta-regression approach.

Results: Dropout rates in the active treatment arms were significantly higher in placebo-controlled trials (PCT) than in clinical trials with an active comparator (ACT); weighted mean dropout rates were 48.7% (PCT) vs. 28.1% (ACT) for second generation antipsychotics (odds ratio 2.42, 95% confidence interval: 1.71–3.44) and 60.1% (PCT) vs. 37.6% (ACT) for classical antipsychotics (odds ratio 2.49, 95% confidence interval: 1.46–4.27). Within PCTs attrition rates were significantly higher in the placebo arms than during treatment with second-generation antipsychotics (60.7% vs. 49.7%, odds ratio 1.56, 95% confidence interval: 1.28–1.90). Moreover, within the subset of trials in which both second generation and classical antipsychotics were used, dropout rates were significantly higher with classical antipsychotics.

Conclusion: Use of a placebo-controlled design had a major impact on the high dropout rates observed in clinical trials of antipsychotics. As high dropout rates compromise the generalisability of such studies, it is suggested that potential alternatives for the PCT should receive more attention in the future.

NEUROLEPTIC DYSPHORIA, NEW ANTIPSYCHOTICS AND THE EMERGING SCIENCE OF SUBJECTIVE TOLERABILITY

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Background: Neuroleptics conspicuously lack abuse potential and many patients love to hate them. The same clinical population on the other hand is known to have increased susceptibility to substance abuse. Our recent neuroimaging studies, using a SPECT dopamine depletion strategy in medication-free schizophrenia with and without a history of neuroleptic dysphoria, have demonstrated the link between basal dopamine activities in the nucleus accumbens and the development of dysphoria. It is evident that the study of neuroleptic dysphoria is inextricably linked to broader issues such as pleasure, responsivity, hedonic regulation and reward mechanisms, which involve the same neural substrate in the brain. Neuroleptics, by virtue of their dopaminergic blocking effect, induce dysphoric responses, while drugs with abuse liability, on the other hand, produce euphoric responses, through enhancing dopaminergic transmission in the same mesolimbic circles. The shared characteristics: subjectivity, role of reinforcement mechanisms and identification of common neurobiological substrates make it logical to classify the spectrum of these drug-induced dysphoric and euphoric states as "disorders of subjective tolerability" as suggested previously by Awad et al. (1995).

Reference

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Pundit Session (Oral III)

Violence: its implications for treatment

ANTISOCIAL BEHAVIOUR MAY PLAY A ROLE IN THE AETIOLOGY OF SCHIZOPHRENIA

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Background/objective: Epidemiological investigations have consistently found that persons who develop schizophrenia are at increased risk for violent criminality and for a pattern of antisocial behaviour that emerges early in life and remains stable. Yet, aetiological research on schizophrenia has consistently ignored these findings. The aim of this project is to review findings that support the proposition that knowledge about the aetiology of schizophrenia may be imprecise, in part, because antisocial behaviour and associated personality traits have been ignored. Studies comparing the development of children at supposed genetic risk for schizophrenia to children at low risk have contributed substantially to the current understanding of the determinants of schizophrenia. Yet, despite the fact that one of the first high-risk studies showed that almost one-third of the mothers with schizophrenia and less than 5% of those with no mental disorder had a history of criminality, the other high-risk studies have failed to take account of the criminality of either the mothers or fathers. Criminality may index a stable pattern of antisocial behaviour, including substance abuse, and stable antisocial behaviour is known to be associated with particular genes, behaviours during pregnancy that impact negatively on the fetus, poor parenting practices, and aggressive behaviour. Investigations of the genetic, obstetric and early childhood factors that play a role in the development of schizophrenia have not taken account of antisocial behaviours on the part of the parents. Similarly, studies do not take account of antisocial behaviours in childhood that may contribute to the development of schizophrenia in genetically vulnerable individuals.

PSYCHOSIS, CRIME AND FIRST ONSET OF SCHIZOPHRENIA: A POPULATION-BASED STUDY

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Objective/methods: In order to estimate the prevalence of offending and to describe the profile of offending in persons with schizophrenia, compared to those with other psychiatric disorders and those with no psychiatric history, we undertook record linkage between 219,052 individuals on the Western Australian psychiatric register and 388,370 individuals on the criminal offenders database. The total number of cross-linked individuals was 52,091, including 23.8% of psychiatric contacts and 13.4% of offender contacts.

Results: Analysis of the total study population indicated differential contact with the justice system by diagnostic group. Overall 48.5% of individuals with drug and/or alcohol-related diagnoses and 39.1% of individuals with personality disorders had contact with the justice system, compared to 32.5% with schizophrenia. The majority of offenders with a psychiatric history had been arrested prior to any contact with psychiatric services. Survival analysis demonstrated that first contact with psychiatric services was most likely to occur within the first year of arrest. This was true both for offenders with schizophrenia and those with another psychiatric diagnosis. Analysis by birth cohort (1955–1959, 1960–1964, 1965–1969) indicated that the proportion of persons with schizophrenia arrested prior to contact with psychiatric services was increasing over time.

Conclusion: Early offending and/or a history of substance abuse may be prodromes or early manifestations of schizophrenic illness confounding the determination of first onset of psychosis.

CONTROLLED STUDY OF A COGNITIVE SKILLS INTERVENTION TO REDUCE OFFENDING BEHAVIOUR IN FORENSIC PATIENTS WITH PSYCHOTIC ILLNESS

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Background/objective: The origin of much offending behaviour is similar for mentally disordered offenders (MDOs) and non-mentally disordered offenders. However, forensic mental health services rarely utilize the types of cognitive-behavioural interventions, such as Reasoning and Rehabilitation (R&R), which have been demonstrated to reduce offending behaviour in non-mentally disordered prisoners and probationers. R&R is a 72-session multi-faceted, highly structured, manualised program which is designed to teach offenders social-cognitive pro-social skills. We aimed to evaluate the feasibility of conducting R&R with MDOs and to provide initial estimates of effectiveness with this population.

Methods: This study used a non-randomized controlled design. Two groups of inpatient MDOs were recruited from medium secure forensic psychiatric units and were prospectively evaluated. All study participants were male, had a psychotic illness, and IQ above 70. The treatment group ($n = 18$) attended a full program of R&R. The control group ($n = 17$) received treatment as usual. Measures of social problem solving skills, coping behaviours, self-esteem and anti-social/criminal attitudes were administered before and following the intervention.

Results: The two treatment groups were closely matched. There were only three dropouts in the R&R group. The R&R group had a significantly better outcome on measures of social problem solving (SPSI-R:S), coping responses (CRI) and on some measures of criminal/antisocial attitudes (Crime Pics II). Data on antisocial behaviour have yet to be analysed.

Conclusion: This exploratory study demonstrated that it is feasible to deliver R&R to MDOs. The intervention demonstrates promise as a method of reducing recidivism in patients with psychotic illness who are at high risk of violent and nonviolent offending.

VIOLENT BEHAVIOR AND LACK OF INSIGHT IN SCHIZOPHRENIA

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Objective: Lack of insight has a profound impact on the management of schizophrenia. Given the public health significance of this issue, understanding the relationship between illness and propensity for violence is of considerable importance.

Methods: One hundred and twenty-two violent patients with schizophrenia were interviewed in a jail or court psychiatric clinic and were evaluated on measures of symptoms, illness severity, insight into illness, and legal consequences of their illness ('forensic insight'). A community sample of nonviolent patients served as a control group.

Results: Violent patients were significantly more likely (18.9% vs. 0%); ($\chi^2 = 23.2$, $p < 0.001$), than nonviolent patients to meet DSM-IV criteria for a comorbid diagnosis of antisocial personality disorder or substance abuse/dependence (58% vs. 9%); ($\chi^2 = 62.0$, < 0.001); 48% of violent patients were actively abusing substances at time of the offense. The majority of violent patients (77%) also showed evidence of active psychotic symptoms at the time of the violent incident and, overall, patients who had committed violent acts were significantly (all $p < 0.001$) more symptomatic on PANSS total score, positive and general psychopathology (but not negative symptom) subscales and had significantly poorer psychosocial functioning. Violent patients had marked deficits in insight, with 71% scoring 4 (moderate deficit) or more and 12.7% having exhibited an extreme lack on insight (score of 7) on the PANSS insight item. Violent patients had significantly greater deficits in insight than nonviolent patients, evident on both PANSS insight and SUMD items. Insight deficits on SUMD were strongly correlated with PANSS insight scores for both groups. Additionally, PANSS total score and SUMD lack of awareness was positively correlated in both violent ($r = 0.39$, $p < 0.001$; $n = 118$) and nonviolent ($r = 0.38$, $p < 0.001$; $n = 109$) patient groups. Violent patients also exhibited poor 'forensic insight', with narrow distribution of scores on Eisner scale. Lack of insight into illness among violent patients was also strongly correlated with lack of 'forensic insight'. Poor scores on the PANSS insight item were associated with failure to accept responsibility for crime (Spearman's $r = 0.51$, $p < 0.001$) and inability to appreciate the relationship of illness to crime ($r = 0.58$, $p < 0.001$). There was an association between lack of forensic insight and symptom severity. Inability to appreciate the relationship of illness to crime was moderately correlated ($r = 0.31$, $p = 0.001$) with PANSS total score.

Conclusion: Patients with schizophrenia who commit violent acts have severe insight deficits, including lack of awareness of the legal implications of their behavior.

HOMICIDE OFFENDERS AND PSYCHIATRIC MORBIDITY: A SWEDISH POPULATION STUDY

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Objective: We examined psychiatric diagnoses of all individuals convicted of homicide and attempted homicide in Sweden from 1988 to 2001 ($n = 2005$).

Methods: High quality national crime and hospital registers were linked to investigate standardized psychiatric diagnoses of homicide offenders.

Results: Psychiatric diagnoses were obtained in 1625 (81%) homicide offenders. One in five had a psychotic illness, and about half had a substance use or personality disorder; 10% had no diagnosis.

Conclusion: This investigation used a more comprehensive method for identifying psychiatric illness in homicide offenders and found higher rates of psychiatric morbidity than previous studies. This underlines the importance of psychiatric assessment in homicide offenders and suggests that treatment might have a preventive role.

REDUCING VIOLENT VICTIMIZATION IN SEVERE MENTAL ILLNESS

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Background: Violent victimization a common experience for those with severe mental illness. Little attention has focused on how to identify those at risk or on ways to reduce this risk. The aims of this study were to (1) to establish risk factors for violent victimization in community dwelling patients with psychosis and (2) to assess the impact of intensive case management (ICM) on violent victimization compared to standard care (SCM).

Methods: Six hundred and ninety-one patients with established psychosis were interviewed using a battery of instruments and randomized to ICM (caseload 10–15) or SCM (caseload 30 plus) for 2 years. The 2-year prevalence of violent victimization was estimated and compared between treatment arms. To identify significant predictors of violent victimization, those reporting this outcome were compared to others on a range of sociodemographic and clinical characteristics.

Results: Twenty-three percent of patients reported being assaulted in the follow-up period, with those in the ICM arm being significantly less likely to be violently victimized. Victims of violence were significantly more likely to have a personality disorder, use illegal substances, have a younger age onset of illness and to have less contact with their families.

Conclusion: Increased contact with community psychiatric workers reduced violent victimization in severely mentally people living in inner cities. Violent victimization could not be explained by the individual's own perpetration of violence. Identified risk factors in the study contribute to the growing body of evidence that should allow us target those most at risk with effective interventions.

NEUROLOGICAL IMPAIRMENT AND PATTERNS OF VIOLENT BEHAVIOR IN SCHIZOPHRENIA OUTPATIENTS

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Objective: Violence in schizophrenia has been related to neurological impairment, including reports that relate persistent violent behavior with more severe neurological impairment.

Methods: A group of 48 previously violent patients were assessed for neurological signs and invited to participate in an ongoing longitudinal study, in which patients' key relative are interviewed every month during 1 year for any possible violent episode. So far, 40 patients have completed the neurological evaluation, by means of the Neurological Evaluation Scale (NES), and the 1-year follow-up screening for violence. Additionally, a sample of 37 previously nonviolent schizophrenia patients underwent the same neurological evaluation.

Results: Previously violent patients showed significantly more neurological impairment for the total NES score and "sensory integration" and "sequencing of complex motor acts" subscales than the nonviolent sample. Along the 1-year follow-up period, 45% of the previously violent patients did not show any violent episode, 30% persistently showed episodes of mild violence severity, and 25% showed few but severe violence episodes. The persistently violent subgroup showed significantly higher rates of neurological impairment for the "sequencing of complex motor acts" subscale than the other two groups, with no differences between the first and third subgroups.

Conclusion: Neurological impairment is related to violent behavior in schizophrenia patients. The fact that frontal–prefrontal neurological signs are associated with persistency of violent behavior supports the presence of two different patterns of violent behavior in schizophrenia: one secondary to psychotic symptoms, and a more persistent form related to neurological disinhibition.

Oral Presentations IVA

Where are the semantic deficits in schizophrenia?

ARE SEMANTIC PROCESSING DEFICITS IN SCHIZOPHRENIA AN ACCESS OR STORAGE PROBLEM?

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Background: Semantic processing deficits are central to cognitive abnormalities in schizophrenia and have been inconsistently related to either poor access or poor storage of semantic information.

Methods: Thirty-two patients with schizophrenia and 32 IQ- and age-matched normal controls performed a new word definition task and a semantic priming task. Both tasks compared high- and low-frequency stimuli and performance across three sessions; with access problems predicted if there were frequency effects and an inconsistent pattern across sessions and storage problems predicted if there was consistent performance across sessions.

Results: On the word definition task, patients made multiple errors and had lower scores. Nevertheless, they showed consistent performance across the three sessions (number correct on the forced choice component: session 1 = 87.3 out of 120 items, session 2 = 88.9 and session 3 = 86.1) and no significant effects of frequency, therefore, supporting a storage problem. On the semantic priming task, patients also demonstrated consistent performance across sessions, although conversely there was an effect of frequency. Patients showed greater priming of high-frequency stimuli compared with low frequency, whilst controls demonstrated the opposite pattern (patients: high = 87.4 ms, low = 25.2 ms and controls: high = 20.9 ms, low = 34.6 ms) ($F(1,63) = 7.6$ p=.008), thus, the priming task supporting both storage and access difficulties.

Conclusion: We speculate the data indicates that a disorganised storage of semantic information is the primary problem in schizophrenia, with both tasks showing a consistent performance pattern across sessions. The semantic priming task, additionally, revealed an access difficulty when there was a reliance on automatic rather than controlled processing.

SENTENCE-LEVEL LANGUAGE COMPREHENSION IN SCHIZOPHRENIA INVESTIGATED WITH fMRI

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Background/objective: Deficits in language processing are a major feature in schizophrenia. In particular, it has been shown that patients are less sensitive to semantic context violations in sentence processing. We investigated brain activation with functional magnetic resonance imaging while subjects read sentences with a semantically congruent or incongruent word.

Methods: Thirteen patients with DSM IV schizophrenia and 13 healthy control subjects read sentences silently and judged by pressing one of two buttons whether the sentence was semantically correct in meaning. Thirty short German sentence pairs, constructed de novo, served as stimuli. The sentences had either a congruent (e.g. "Das Klavier ist ein Musikinstrument" [the piano is a musical instrument]) or incongruent ("Das Klavier ist eine Tomate [the piano is a tomato]) ending. Sentences in the two groups of stimuli were matched for length, tense and word frequency. Each sentence was presented visually for 5-s with a 3-s interstimulus interval. Data was collected from the whole brain (22 slices, slice thickness 5 mm, TR = 2 s, TE = 40 ms) using a 1.5-T fMRI system.

Results: Preliminary results show that healthy subjects show a maximum of activation for the differential contrast congruent vs. incongruent meaning in the left angular gyrus, no differential activation was found in the patient group in this region.

Conclusion: Left posterior temporal lobe dysfunction and decreased hemispheric lateralisation may underlie semantic error detection on a sentence level in schizophrenia.

SITUATIONAL ROLES (SIGMA-ROLES) IMPAIRMENT IN SCHIZOPHRENIA AND SPD

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Background: By Σ-roles, we mean to indicate those items giving wide contextual coordinates. Our hypothesis is that a deictic disintegration affects schizophrenic patients, i.e. that there is a disconnection between a given situation and the patients' way of analyzing reality, hence Σ-roles elaboration is impaired.

Methods: We have implemented three tests in order to assess with accuracy Σ-role impairments in schizophrenia and Schizotypal Personality Disorder: Comprehension test of morphosyntactic elaboration of Σ-roles (TEM-Σ), production test of morphosyntactic elaboration of Σ-roles (TEP-Σ), test of elaboration of events in sequence (TES). To date, we have used them with the purpose of assessing Σ-role impairments in a population of schizophrenic and SPD outpatients (Schizophrenics = 8; SPD = 2). We employed as controls ten healthy people without history of psychiatric illnesses matched to our patients' group for sex, age and education.

Results: TEM-Σ, TEP-Σ and TES detected severe damages in temporal, modal and aspectual morphosyntactic elaboration in comprehension and production: TEM-Σ = $p < 0{,}0001$, TEP-Σ = $p = 0{,}0003$, TES = $p = 0{,}0368$. The results are consistent with heavy impairments concerning Σ-role elaboration in the schizophrenic and SPD group. The tests showed also a positive correlation between Formal Thought Disorders (FTD) severity and Σ-role impairments (Pearson correlation r statistic = 0,89; $p = 0{,}0005$). The outcomes show that the so-called deictic disintegration affects schizophrenic and SPD patients.

Conclusion: The results can be seen in the light of specific impairments affecting modular language parsing in schizophrenia and SPD and relatively to the cognitive overload and reality fragmentation reported in literature.

Oral Presentations IVB

Is word retrieval lateralized in schizophrenia?

REDUCED HEMISPHERIC SPECIALIZATION FOR LANGUAGE IN RIGHT-HANDED SCHIZOPHRENIC PATIENTS

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Background/objective: Literature supports the hypothesis that schizophrenia could be related to lateralized brain dysfunction but few functional cerebral imaging studies have explored language processing in schizophrenia and none has researched specifically changes in specialization of functional language cortical areas. The hypothesis was that schizophrenia is characterized by a functional change in specialization of language-related cortical regions.

Methods: Twenty-one schizophrenic patients (DSM-IV) and 21 controls, all right-handed, matched on sex, age and level of education were instructed to listen to stories in French and Tamil alternatively during functional magnetic resonance imaging. Functional asymmetry indices (FAI) were computed in 18 right and left cortical areas (AROIs) involved in language processing. Analyses of the FAI differences between each patient and his control were proceeded. Individual analyses were performed in order to described and characterize functional patterns in each patient compared to the control subject.

Results: FAI means were smaller in patients than in controls ($p < 0.01$) in the 18 AROIs taken as a whole and in the middle frontal (F2) and temporal (T2) gyri, the precuneus and the pars triangularis of the inferior frontal gyrus. Reduced leftward specialization was found in 20 of 21 patients (95.2%) compared to their controls in at least one cortical language area.

Conclusion: This study supports the hypothesis that schizophrenia is characterized by a reduced hemispheric specialization in particular in cortical language areas.

REGIONAL DIFFERENCES IN fMRI ACTIVATION PATTERNS DURING LINGUISTIC TASKS IN SCHIZOPHRENIC PATIENTS AND HEALTHY SUBJECTS

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Objective: fMRI was used to investigate differences in brain regions involved in linguistic processing between schizophrenic patients and healthy subjects.

Methods: Twenty right-handed schizophrenic patients (currently hallucinating or with a history of auditory hallucinations) and 20 healthy volunteers matched on task performance, handedness and demographic variables underwent functional MRI in a 3T scanner while performing two aurally and visually presented paced covert

language tasks: a verb generation to a cue noun and a semantic decision task contrasted with tone listening and tone discrimination, respectively. Post-processing was performed with SPM99, and included realignment, spatial normalization, smoothing and single subject, group, and inter-group statistics. Between group differences were assessed using two-sided *t*-test.

Results: When verb generation was compared with tone listening schizophrenic patients showed less activity in the left posterior superior temporal sulcus (BA21) than controls. Increased activity was found in the superior occipital and lingual gyri (BA 19 and 17). On a semantic decision task contrasted with tone discrimination, no significant differences in activations were found under comparable task performance.

Conclusion: Attenuated engagement of the posterior left temporal cortex, a region known to be involved in external speech processing, and enhanced engagement of visual areas, implicated in motion processing and smooth eye pursuit, were identified in the patient group. The current findings are consistent with results from previous studies, lacking comparable task performance. Our results provide further evidence of disturbed neuronal processing of language tasks in schizophrenic patients.

GRAY AND WHITE MATTER DENSITY ABNORMALITIES IN MONOZYGOTIC AND SAME-SEX DIZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA USING VOXEL-BASED MORPHOMETRY

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Background: Gray and white matter brain tissue volume decreases in schizophrenia have been related to genetic risk factors and disease related (possibly non-genetic) factors (Hulshoff Pol et al., Biological Psychiatry, 2003, in press). However, whether genetic and environmental risk factors in the brains of patients with schizophrenia are differentially reflected in *focal* gray or white matter *density* changes is not known.

Methods: 1.5 T MRI brain-scans of 11 monozygotic and 11 same-sex dizygotic twin-pairs discordant for schizophrenia were acquired and compared to 11 monozygotic and 11 same-sex dizygotic healthy control twin-pairs using voxel-based morphometry (Hulshoff Pol et al., Arch Gen Psychiatry, 2001). Linear regression analysis was done in each voxel for the average and difference in gray and white matter density separately in each twin-pair, with group (discordant, healthy) and zygosity (monozygotic, dizygotic) as between subjects variables, and age, sex, and handedness as covariates. The two-tailed critical threshold *t*-value ($p < 0.05$) was corrected for multiple comparisons using random field theory resulting in $t > 6.0$.

Results: The *t*-maps revealed a focal decrease in gray matter density and focal increase in white matter density in the left medial orbitofrontal gyrus in the twin-pairs discordant for schizophrenia as compared to the healthy twin pairs ($t(38) = 6.34$).

Conclusion: Changes in left medial orbitofrontal density may reflect the increased genetic risk to develop schizophrenia.

ASSESSING A SINGLE THOUGHT IN SCHIZOPHRENIA

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Objective: We investigated whether the minimal cognitive operation of thinking of a just-seen stimulus (*refreshing*) is impaired in schizophrenia.

Method: Twenty-four patients with schizophrenia and 24 normal comparison subjects were instructed to read aloud words as they appeared on a screen. Critical words were presented once (*read* condition), immediately repeated (*repeat* condition), or followed by a dot signaling the participants to think of the just previous word and to say it again (*refresh* condition). Verbal response times were compared across conditions. On a surprise test, participants were asked to recognize all the words they had seen previously and to give *remember*, *know*, or *guess* responses according to whether they recognized words on the basis of conscious recollection, familiarity, or guessing.

Results: Although mean response times did not significantly differ between groups in the *read* and *repeat* conditions, patients with schizophrenia were slower to say words than comparison subjects on the *refresh* trials. Despite lower levels of overall performance, long-term memory of patients benefited from refreshing (relative to reading) to the same extent as in comparison subjects. In addition, the pattern of remember, know and guess responses were not different between groups for items that had been refreshed.

Conclusion: Schizophrenia impairs an elementary process, useful for maintaining just-activated information. Interestingly, the effect of the refresh operation on long-term memory was preserved. This suggests that controlling the processes involved at encoding might be a way to remediate in part the memory deficits in schizophrenia.

Pundit Session (Oral V)

Are there risk factors other than genes?

CANNABIS AND SCHIZOPHRENIA: THE EFFECTS OF THE USE OF CANNABIS ON NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIA

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Background: Substance abuse among people that suffer from schizophrenia is high compared to the general population and is estimated to be 30–50%. Cannabis seems to be the substance of choice. Results of previous studies about causes and its effects on schizophrenia are inconsistent.

Methods: In order to test the hypothesis that the use of cannabis has a negative impact on the course of the disease, we perform a cohort study. Various neuropsychological measures, particularly global information processing and memory tasks were assessed by various tasks (e.g. CVLT; DOT; SOT) in 150 patients. Symptomatology (PANSS; MADRS), medication, substance abuse and the reasons for use were also assessed.

Results: Forty-two percent of the patients used cannabis in the last month before inclusion. Most of the patients were male and significant younger than the non-users. The mean duration of cannabis use was 11 years. No differences were found in a cross sectional comparison between cannabis users and non-users, with respect to neurocognitive functioning. Patients seem to abuse cannabis as self-medication.

Conclusion: Our study suggests that the use of cannabis might be associated with an earlier onset of schizophrenic symptoms and is accompanied with the use of other substances and alcohol. In contrast with what was expected no differences could be found between the two groups. Many cannabis using patients claim a positive effect on their ability to sustain attention, which is one of the reasons for abuse. Follow up is necessary to assess the impact on the course of schizophrenia.

RAISED INCIDENCE OF PSYCHOSIS IN ALL MIGRANT GROUPS IN SOUTH LONDON, NOTTINGHAM AND BRISTOL: THE AESOP STUDY

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Background/objective: It is not yet clear whether the raised incidence of psychosis in people of African-Caribbean heritage in the UK applies to other migrant groups. The aims of this project are (a) to calculate the overall incidence of psychosis in each of three geographically defined study centres and (b) to elucidate the rates of psychosis in all migrant groups.

Method: The AESOP study identified all first presentation psychotic individuals over a 2-year period. Sociodemographic information, including ethnicity, and both ICD10 and DSMIV diagnoses were obtained. Rates (cases per 100,000 population per year) were calculated using denominator data from the 1991 census corrected for underenumeration, and were standardised for age using the population of England and Wales. Rate ratios (RR) were calculated using Poisson regression.

Results: Across the three centres, 570 cases were identified. The overall rate of psychosis in London (54.5: 95% CI 48.1–60.8) was over twice that of Nottingham (24.9; 21.5–28.4) and Bristol (24.2; 17.8–30.5). Rates for schizophrenia, manic psychosis and depressive psychosis all followed a similar pattern. Rate ratios for migrant groups were all elevated significantly, both in men and women, compared to whites: Black Caribbeans 6.8 (95% CI 5.6–8.3), Black Africans 6.0 (4.5–7.9), Indians 3.8 (2.0–7.1), Pakistanis 5.0 (2.6–9.7) and Other Asians 6.5 (3.2–13.2). Strikingly, the RRs both for Black Caribbean women and for women from all the Asian groups were higher than their male counterparts.

Conclusion: These results broaden the aetiological focus away from a narrow ethnicity perspective and towards the complex effects of migration and urbanisation, and their likely interaction.

VITAMIN D SUPPLEMENTATION DURING THE FIRST YEAR OF LIFE AND RISK OF SCHIZOPHRENIA: A FINNISH BIRTH-COHORT STUDY

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Background/objective: Based on clues from epidemiology and animal experiments, low vitamin D during early life has been proposed as a risk factor for schizophrenia. The aim of this study was to explore the association between the use of vitamin D supplements during the first year of life and risk of developing schizophrenia.

Methods: Subjects were drawn from the Northern Finland 1966 Birth Cohort ($n = 9114$). During the first year of life, data were collected about the frequency and dose of vitamin D supplementation. Our primary outcome measures were schizophrenia, psychotic disorders other than schizophrenia, and non-psychotic disorders as diagnosed by age 31 years. Males and females were examined separately.

Results: In males, the use of either irregular or regular vitamin D supplements was associated with a reduced risk of schizophrenia (Risk ratio (RR) = 0.08, 95% CI 0.01 – 0.95; RR = 0.12, 95% CI 0.02 – 0.90, respectively) compared with no supplementation. In males, the use of at least 2000 IU of vitamin D was associated with a reduced risk of schizophrenia (RR = 0.23, 95% CI 0.06 – 0.95) compared to those on lower doses. There were no significant associations between either the frequency or dose of vitamin D supplements and (a) schizophrenia in females, nor with (b) nonpsychotic disorder or psychotic disorders other than schizophrenia in either males or females.

Conclusion: Vitamin D supplementation during the first year of life is associated with a reduced risk of schizophrenia in males. Preventing hypovitaminosis D during early life may reduce the incidence of schizophrenia.

'INCREASE IN INSANITY' NOT LINKED TO SCHIZOPHRENIA

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Objective: This study assesses claims made by Hare (1988) that the documented rise in psychiatric morbidity during the 19th and 20th centuries was associated with an increased incidence in schizophrenia.

Methods: We make cross-sectional comparisons of psychiatric morbidity in one urban, industrialized community over more than 100 years. The administrative incidence of schizophrenia in Nottingham from 1978 to 1980 (Cooper et al.) and 1992 to 1994 (Brewin et. al.) is compared with new data from the same geographical population for 1881 – 1902.

Results: For the period 1881 – 1902, 41 cases of schizophrenia were obtained through retrospective diagnosis, using Research Diagnostic Criteria, of a random 14.5% sample of first admissions to Nottingham Asylum ($n = 330$).

N.N. rated all records. Blind and independent rating of 7% by G.D. provided a kappa statistic of 0.79. Using population statistics standardised administrative incidences of schizophrenia for the three periods were calculated and compared.

Whilst a greater than 100-fold increase has been reported in both local and national rates of total psychiatric morbidity over the period of study, there is no evidence of a significant increase in the incidence of schizophrenia. This stability in the epidemiology of schizophrenia at a geographical level is found despite important demographic changes in Nottingham including an 11-fold increase in Non-White ethnic groups.

Conclusion: These data suggest the officially declared increase in psychiatric morbidity was neither caused nor paralleled by increases in the incidence of schizophrenia.

ADOLESCENTS WITH A PRE-EXISTING VULNERABILITY FOR PSYCHOSIS ARE MORE LIKELY TO DEVELOP SYMPTOMS IF THEY GROW UP IN AN URBAN ENVIRONMENT

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Background: There may be no other issue in schizophrenia research with more far-reaching public health implications than the finding that young people growing up in an urban environment accumulate an increased risk for schizophrenia. Previous work has suggested that the urban environment impacts on this risk function by facilitating the expression of a pre-existing vulnerability for psychosis, but direct confirmation has been lacking (Van Os et al., 2003a,b).

Method: A cohort of 1211 adolescents from the EDSP study aged 13–17 years (mean: 15.1 years), growing up in contrasting urban and non-urban environments, completed a self-report measure of psychosis proneness (SCL-90 psychosis scale) at baseline and at the first follow-up around 1-year post-baseline (T1), and were interviewed by trained psychologists for the presence of psychotic symptoms at the second follow-up around 3-year post-baseline (T2).

Results: Psychosis proneness at baseline and T1 strongly predicted psychotic symptoms at T2. However, this risk, on the additive scale, was much stronger in adolescents growing up in an urban environment (risk difference: 25%, $P < 0.0001$), than for those dwelling in a non-urban environment (risk difference: 9%, $P = 0.12$). Differences were independent of age, sex, drug use, social class and family history of psychosis, and the SCL-90 psychosis scale at T2.

Conclusion: These findings add credence to the suggestion that a powerful environmental moderator of genetic risk for psychosis is more prevalent in urban environments.

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IS URBANICITY A SUFFICIENT CAUSE FOR EXPRESSION OF PSYCHOSIS?

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Background: Growing up in an urban area has been shown to be associated with an increased risk of psychotic disorder in later life. While it is commonly held that only a tiny fraction of exposed individuals will develop schizophrenia, recent evidence suggests that expression of psychosis in exposed individuals may be much more common, albeit at attenuated levels.

Methods: Findings are based on a population sample of 2548 adolescents and young adults aged originally 14–24, and followed up over almost 5 years up to ages 17–28 years. Trained psychologists assessed all these subjects with the core psychosis sections on delusions and hallucinations of the Munich-Composite International Diagnostic Interview.

Results: Growing up in an urban area was associated with an increased risk of expression of psychosis in the adolescents and young adults (adjusted OR 1.30, 95% CI 1.02–1.65) after controlling for, gender, SES, any drug use, family history of psychosis and any psychiatric diagnosis in the adolescent or their parent.

Conclusion: The proxy environmental risk factor that urbanicity represents may be sufficient to shift a relatively large section of the adolescent population along a continuum of expression of psychosis. Other causal influences may be required to make the transition to schizophrenia in adult life.

ADVANCED PATERNAL AGE ASSOCIATED WITH AN ELEVATED RISK FOR SCHIZOPHRENIA IN MALE OFFSPRING

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Background: Recent studies reported that advanced paternal age at birth is a risk factor for schizophrenia in the adult offspring. However, whether the effect of paternal age on the risk differs according to gender of the offspring remains unknown.

Methods: We explored the association between advanced paternal age and the risk of schizophrenia in relation to gender of the subjects. We obtained contemporaneously recorded and special notes of "the Mother and Child Health Handbook (MCHH)" for each of the 107 individuals with DSM-IV schizophrenia, and of the 239 unrelated healthy controls. Odd ratios (ORs) were calculated for the risk for schizophrenia associated with factors of interest using logistic regression analysis. Paternal age was defined as the age of the father when the subject was born, and then the subjects were grouped into three using tertiles of its distribution.

Results: When compared with the offspring with paternal age <28 years (reference), those with paternal age of 28–32 years were at greater risk with the OR of 2.4 (95% CI 1.1–5.2), and those in the oldest father group (paternal age of 33 years and over) had an over three-fold increased risk (OR = 3.3, 95% CI 1.3–8.8). For male offspring in the oldest father group, the corresponding risk was

further increased (OR = 5.7, 95% CI 1.8–17.9), whereas, in females, the corresponding OR was 3.3 (95% CI 1.2–8.6).

Conclusion: Our findings suggest that advanced paternal age at birth may confer risk for developing schizophrenia in the offspring, and this risk increasing effect is more conspicuous in male than female offspring.

Acknowledgment: Dr. Takei would like to thank the Stanley Medical Research Institute for financial support.

Oral Presentations VI

Is it possible to predict who develops schizophrenia?

EARLY AND 3-YEAR SUSTAINED INTERVENTION IN FIRST EPISODE SCHIZOPHRENIA: RELAPSE, STABILIZATION AND ITS PREDICTORS

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Background: Early intervention in the earliest stage of florid psychosis in schizophrenia should alter the heterogeneous, but predominantly unfavourable outcome and clinical deterioration into a more benign type.

Methods: In a 5-year intervention study, all referred young patients with schizophrenia and related disorders were randomized after admission to our outpatient intervention programme or to standard outpatient facilities elsewhere. Predictors of outcome were assessed at admission and during the first 6 months of follow-up. Outcome was assessed at 12, 18, 24, 30 and 36 months after first presentation with the Life Chart Schedule (WHO, 1992). Twenty of the 200 patients who were referred and found eligible dropped out before admission. Of the 180 patients randomized to the integrated in- and outpatient treatment programme, 169 patients (9.4%; male 83%, female 17%) were in treatment 18 and 36 months after the first presentation.

Results: During 18-month intervention, 97 (57%) of the patients remitted after their first psychotic episode. Seventy-two (43%) experienced at least one psychotic relapse or developed continuous psychotic symptoms. Survival analysis revealed that lack of insight (OR 3.08, CI 1.46–6.5), non-compliance (OR 2.23, CI 1.36–3.66) and cannabis abuse (OR 2.28,CI 1.4–3.7) during the first 6 month period of the treatment program predicted unfavourable disease outcome after 18-month intervention. Between these predictors, significant relations were found. After 3 years, the 18-month outcome patterns were found to stabilize with a group of 60% young non-relapsing patients and with a 40% relapsing group.

Conclusion: Early and sustained intervention appears to be beneficial for 60% of young patients with a first psychotic episode of schizophrenia. Forty percent of the young patients, a treatment-reluctant group, failed to benefit from the intervention program. Lack of insight, non-compliance and cannabis abuse during the first 6 months outpatient treatment turned out to be predictors of a relapsing or chronic outcome. These patterns stabilized after 3-year intervention.

NEUROPSYCHOLOGICAL PERFORMANCE OVER TIME IN PEOPLE AT HIGH RISK OF SCHIZOPHRENIA AND CONTROLS

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Background: Previous neuropsychological assessments of relatives of schizophrenics have shown subtle impairments compared to controls in verbal memory and executive function tasks. Stable differences between those at high risk of schizophrenia and controls in these areas, may be indicative of a genetic vulnerability to schizophrenia, while those who go on to develop schizophrenia may show decrements in performance over time, marking psychosis onset.

Methods: Baseline predictors of schizophrenia and performance changes between the first and last neuropsychological assessments were examined in 118 high risk participants (of which 13 are now schizophrenic, 56 have had psychotic symptoms and 49 have not) and 30 controls, using repeated measures ANCOVAs, controlling for IQ, time and practice.

Results: Controls performed significantly better than all high-risk participants on immediate ($F_{(3,133)} = 5.11$, $p = 0.002$) and delayed ($F_{(3,133)} = 5.02$, $p = 0.003$) prose recall and high-risk participants who are now ill on the CVLT delayed recall ($F_{(3,133)} = 3.3$, $p = 0.024$) and HSCT scaled score ($F_{(3,137)} = 4.25$, $p = 0.007$), at both assessments, before and after controlling for IQ.

Conclusion: There were no significant groups by time interactions, suggesting that those who became ill did not show a differential decrement in performance over time. Stable differences between groups over time suggest a trait deficit, which is relatively unaffected by presence of psychotic symptoms. The

poorer verbal memory performance at both assessments of those who became ill suggests that this trait is more pronounced in those who go on to develop schizophrenia.

POOR EXECUTIVE FUNCTION AT AGE 13 PREDICTS LATER SCHIZOPHRENIFORM DISORDER: A LONGITUDINAL BIRTH COHORT STUDY

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Background: There is compelling evidence that individuals with schizophrenia exhibit impairment on a wide range of neuropsychological tasks notably those involving attention, language and memory. However, it is not known whether such deficits predate the diagnosis.

Methods: The Dunedin Multidisciplinary Health and Development Study is an unselected prospective birth cohort of 1037 individuals born in Dunedin, New Zealand between April 1, 1972 and March 31, 1973. Study members have participated in ten assessments between ages 3 and 26 including a neuropsychological test battery at age 13. Of the 850 cohort members who participated in the study at age 13, complete neuropsychological assessment data is available on 710 subjects.

Results: Psychiatric diagnostic interviews conducted at age 26 revealed that 21 of these individuals fulfilled diagnostic criteria for schizophreniform disorder, 10 for mania and 198 for depressive disorder or anxiety disorder. Study members with a subsequent diagnosis of schizophreniform disorder performed significantly worse than the other groups at age 13 on the Trails B test (time to completion), the Grooved Pegboard test (both left and right hands), and the Rey Auditory Verbal Learning Test (delayed recall and recognition). No significant differences were noted between the groups on the Rey Osterreith Copy score, the Wisconsin Card Sort Test or on Verbal Fluency.

Conclusion: These results indicate that deficits in executive functioning, verbal memory, learning and psychomotor speed are evident before the onset of schizophrenia in a representative birth cohort.

A DECISION ANALYSIS MODEL TO ASSESS THE FEASIBILITY OF EARLY DETECTION OF PSYCHOSIS IN THE GENERAL POPULATION

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Objective: To evaluate the feasibility of Early Detection (ED) of psychosis in the general population.

Method: Decision Analysis (DA) was used to compare the efficiency of ED to that of Detection as Usual (DU) to prevent the occurrence of adverse outcomes (death; hospitalization, or unemployment) over five years on an hypothetical cohort of subjects aged from 15 to 34 years old. DA was based upon optimistic models with several assumptions favoring ED. Sensitivity analysis was used to explore how the findings were affected by varying the different probabilities.

Results: ED would be effective in preventing the occurrence of adverse outcomes only if detection tests with high specificity (>88%) were available and if a high number of subjects were screened. The numbers needed to screen would be 20,000 subjects to prevent one death, 641 to prevent one hospitalization, and 847 to prevent one unemployment.

Conclusion: Implementing ED in the general population is of questionable feasibility to prevent the occurrence of major adverse outcomes due to incident psychosis. As focusing ED in high-risk groups cannot be considered as an alternative effective strategy from a public health point of view, a temporary conclusion drawn from the present DA is that evidence supporting feasibility of ED of psychosis is currently lacking.

DETECTING SCHIZOPHRENIA IN THE EARLY PRODROME

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Background: In English-speaking countries, the Melbourne 'ultra-high-risk' approach employing attenuated and transient

psychotic symptoms and a state-trait combination is mainly used for an early detection of psychosis and special instruments for its assessment have been developed. A broader time-related approach is adopted in Germany, distinguishing between early and late prodromal stages with the early prodromal state being defined by cognitive and perceptive basic symptoms and the state-trait combination.

Methods: For the quantitative assessment of basic symptoms, a 40-item scale with six subscales, the Schizophrenia Prediction Instrument, Adult version (SPI-A), was developed. In its prospective evaluation study, any 1 of 10 cognitive–perceptive basic symptoms with good prospective accuracy according to the Cologne Early Recognition Study (Klosterkötter et al., 2001) served as inclusion criteria. By August 2003, 25 of 147 individuals (17%) had already transited to psychosis within 12 months on average (S.D. = 7.6; range: 2–33).

Results: Comparisons between the transited and non-transited group revealed significantly higher subscale totals at baseline in the transited group for the SPI-A subscales 'Cognitive Disturbances' ($p = 0.0004$), 'Overstrain' ($p = 0.030$) and 'Body Perception Disturbances' ($p = 0.036$) as well as the 'Negative Symptoms' ($p = 0.004$) of the Scale of Prodromal Symptoms (SOPS) but not of attenuated or transient 'Positive Symptoms' of the SOPS ($p = 0.093$) after adjustment for multiple testing.

Conclusion: The transition rate after 1 year on average already indicates predictive validity that is expected to further increase in time.

Reference

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GENETICALLY PREDISPOSED OFFSPRING WITH SCHIZOTYPAL FEATURES: AN ULTRA-HIGH RISK GROUP FOR SCHIZOPHRENIA?

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Background: Schizotypy has emerged in recent years as a promising *clinical* endophenotype of the schizophrenia diathesis. Deficits on tasks that depend on intact prefrontal function and structural integrity have also emerged as highly plausible *biobehavioral* endophenotypes of the illness. However, the relationship between clinical and biobehavioral endophenotypes has not been systematically assessed in adolescent offspring of schizophrenia patients (OS).

Methods: We assessed whether measures of schizotypy in OS subjects were predictive of deficits in working memory and executive function, as well as prefrontal morphology. Schizotypy was measured by combining the Perceptual Aberration and Magical Thinking subscales of the Chapman and Chapman scales. Cognitive deficits were assessed using the Wisconsin Card Sort and Oculomotor-delayed response tasks. Prefrontal abnormalities were assessed using morphometric analyses of high-resolution MRIs.

Results: OS subjects had significantly elevated levels of schizotypy compared to controls. OS subjects with axis I psychopathology had higher schizotypy scores than those without and controls ($p < 0.0001$). OS subjects with high schizotypy made more perseverative errors on the WCST ($p < 0.002$) and showed age-mediated deficits on the ODR task ($p < 0.02$) compared to their non-schizotypal counterparts or healthy controls. These neurocognitive deficits were also associated with reductions in heteromodal and particularly prefrontal gray matter concentration ($p < 0.001$).

Conclusion: The results indicate important correlations between clinical and neurocognitive endophenotypic markers of the illness. Schizotypal adolescent offspring may therefore form a hyper vulnerable sub-group among individuals genetically predisposed to schizophrenia.

SCHIZOPHRENIA AND DEPRESSION—A DOUBLY CONTROLLED STUDY OF ONSET AND COURSE IN FIRST ADMISSIONS FOR SCHIZOPHRENIA, DEPRESSION AND IN HEALTHY CONTROLS

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Background: Focusing on psychopathology, behaviour, functional impairment and illness course we studied descriptive and causal associations of schizophrenia, depressive symptoms and depressive episodes.

Methods: Depressive symptoms were assessed in 232 first episodes of schizophrenia (ABC Study sample), retrospectively using the IRAOS and in a representative subsample of 130 of these patients prospectively until 5 years after first admission. This subsample was compared with 130 age- and sex-matched healthy controls and with equally matched first admissions for depressive episodes.

Results: The lifetime prevalence of depressive mood (>2 weeks) at first admission for schizophrenia was 83%. The onset of schizophrenia was most frequently marked by depressive symptoms, which on average appeared more than 4 years before

first admission. They were followed by negative symptoms and cognitive and social impairment. Symptoms and functional impairment at the early stages of both disorders overlapped considerably. It was not until the emergence of some specific symptoms, mainly psychotic, that made schizophrenia and depression distinguishable. In the first psychotic episode, 71% presented clinically relevant depressive symptoms, 23% fulfilled the ICD-10 criteria for a depressive episode. With the remission of psychosis also the proportion of patients with depressive symptoms decreased and remained stable on average over the 5-year course.

Conclusion: The high frequency of depressive symptoms at the prepsychotic stage and their increase and decrease with the psychotic episode support the hypothesis that depression might be expression of an early-milder-stage of one and the same neurobiological process that later leads to psychosis.

FINE MOTOR FUNCTION DEFICITS IN INDIVIDUALS AT RISK FOR SCHIZOPHRENIA-CONFOUNDING FACTORS (FEPSY STUDY)

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Background: Fine motor function deficits could be risk factors for developing psychosis as suggested by studies in individuals at risk for psychosis. But as to our knowledge, there have not been prospective investigations with standardised methods so far. Within the Basle FEPSY study on the early recognition of psychosis, fine motor function was examined with a computerised test battery (Wiener Testsystem, Schuhfried, 1997) in individuals at risk for psychosis and healthy controls.

Methods: The patients were consecutively recruited from our specialised early recognition clinic at the Basle University Psychiatric Outpatient Department. After screening, the first individuals identified as being at risk for psychosis and healthy, age-matched controls were examined with the computerised test battery "Motorische Leistungsserie". The paradigms of these tests are: (1) aiming, (2) steadiness, (3) line tracking, (4) resorting long/short pins, and (5) tapping. The influence of sedative medication was controlled for. Cannabis use, medication, age, sex, and educational level were analysed as statistical confounding factors (analyses of covariance).

Results: There were significant differences between at risk individuals and controls in steadiness, dexterity, precision of arm/hand as well as wrist/finger velocity. The differences were most pronounced in dexterity ($p < 0.001$) and arm/hand velocity ($p < 0.001$). The analyses of confounding factors showed that only two paradigms (line tracking and resorting pins) significantly separated the two groups independently of sex, educational level, cannabis use, age, and medication.

Conclusion: Fine motor function deficits investigated with the help of a standardised and computerised test battery are useful in identifying individuals at risk for psychosis, especially if confounding factors are statistically controlled for.

Oral Presentations VII

Mismatch negativity: a measure of NMDA receptors or lateralized sensory processing?

KETAMINE-INDUCED DEFICITS IN ENCODING IN HEALTHY VOLUNTEERS: COMPARISON TO CORRESPONDING DEFICITS IN SCHIZOPHRENIA

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Background/objective: Administration of the NMDA receptor antagonist ketamine is associated with schizophrenia-like behavioral and cognitive effects suggesting an important role of this receptor in key aspects of schizophrenia. Available evidence from human and animal studies indicates that NMDA receptor dysfunction is associated with deficient encoding of information. The hypothesis was tested (1) that NMDA blockade leads to deficits in encoding of auditory information and (2) that these deficits are comparable to those described in schizophrenia. Event-related potential measures that are assumed to represent strength of encoding of auditory information (mismatch negativity as function of deviant probability).

Methods: N1 maximum as a function of increasing interstimulus intervals were investigated during ketamine administration in healthy volunteers ($n = 21$) and separately in patients with chronic schizophrenia ($N = 22$).

Results: Preliminary analyses demonstrate that ketamine administration was associated with decrease MMN rise as a function of decreasing deviant probability and smaller maximal N1 amplitudes, but unchanged recovery function. These findings are consistent with impaired encoding. Patients with schizophrenia showed deficits in ERP measures which were highly similar to those induced by ketamine in healthy volunteers.

Conclusion: These results provide further support for the hypothesis that dysfunction of NMDA receptor dependent neurotransmission may underlie some aspects of abnormal information processing in schizophrenia. Our results are consistent with results of other studies that demonstrated a particular involvement of NMDA receptors in encoding of information. Their dysfunction may contribute to abnormalities in encoding of information at preattentive stages in the processing chain in schizophrenia.

FRONTAL AND TEMPORAL LOBE SOURCES FOR MISMATCH NEGATIVITY (MMN) IN SCHIZOPHRENIA: AN ERP AND MR-ANATOMICAL IMAGING STUDY

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Background: MMN is an electrophysiological measure of automatic auditory change detection. A smaller MMN in patients with schizophrenia[1,2] may reflect altered frontal activity[3].

Methods: Following our report on the coordinates for frontal and temporal lobe dipole-loci contributing to normal MMN[4], we replicated this result using brain electrical source analysis (BESA) and MR-images of the brain in 14 healthy subjects (34.8 years) and compared it with 17 patients (32 years) 15 years after the onset of schizophrenia.

Results: For MMN associated with a frequency deviant tone, asymmetric loci in the superior-temporal and left anterior-cingulate gyri were replicated, while that in the right inferior-frontal gyrus moved to the mid-frontal border (residual variance [RV] < 1%). Patients showed a modest MMN reduction, a weaker left temporal lobe source but essentially similar loci (RV ~ 1%). Discrete changes in the locus of left temporal and cingulate sources were illustrated by plotting volumes around the group solution for individual's data to 2% RV, with the radius illustrating the standard deviation of the distance to the better solutions for other subjects' loci (also using a 2% RV criterion). The left temporal lobe source was marginally more medial in patients (5 mm, $p < 0.01$), while the left cingulate was more rostral (10 mm, $p < 0.0001$).

Conclusion: The data show a degree of compensation of function despite altered source locations in the left hemisphere.

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ALTERED MISMATCH RESPONSES IN THE PLANUM TEMPORALE IN SCHIZOPHRENIA: AN fMRI AND MEG STUDY

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Background/objective: Mismatch negativity (MMN) or field (MMNm) is an event-related brain response that is sensitive to deviations within a sequence of repetitive auditory stimuli. It is thought to reflect short-term sensory memory and is independent of higher level cognitive processes. MMN is reduced in patients with schizophrenia. Little is known about the mechanisms of this decreased response, the contribution of the different hemispheres and its locus of generation.

Methods: Groups of patients with schizophrenia ($n = 12$) and matched controls ($n = 12$) were studied. A novel MMN auditory oddball design was generated using the noise created by a functional Magnetic Resonance Imaging (fMRI) scanner, thus avoiding any interfering background sound. Stimuli were composed of amplitude (-9 dB) and duration (76 ms shorter) deviants in a randomized sequence. The scanner noise was recorded and applied to the same subjects in a whole-head Magnetoencephalography (MEG) device. Neuromagnetic and haemodynamic responses to the identical stimuli were compared between the patients and controls.

Results: As expected, neuromagnetic mismatch fields were smaller in the patient group ($p < 0.05$). More specifically, a lateralization of duration mismatch to the right was only found in controls (between groups $p < 0.05$). For the relative amplitude of the BOLD signal (measured with fMRI), differences emerged only in the secondary (planum temporale), but not primary (Heschl's gyrus) auditory cortex. Duration deviants achieved a right hemispheric advantage only in the control group ($p < 0.001$, between groups n.s.). A significantly stronger lateralization to the left (both groups $p < 0.001$) was found in the patients for the amplitude mismatch (between groups $p < 0.01$).

Conclusion: The data support the view of altered hemispheric interactions in the formation of the short-term memory traces necessary for the integration of auditory stimuli. This process is predominantly mediated by the planum temporale (secondary auditory cortex). Altered hemispheric interaction of regions within the superior temporal plane could be in part responsible for language-mediated cognitive (e.g. verbal memory) and psychopath-

ological (hallucinations, formal thought disorder) symptomatology in schizophrenia.

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EVENT-RELATED POTENTIAL MISMATCH NEGATIVITY IS RELATED TO THOUGHT DISORDER IN SCHIZOPHRENIC PATIENTS

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Background/objective: Mismatch negativity (MMN) is an auditory ERP elicited when infrequent sound is presented in the sequence of repetitive sounds. The main generators of MMN are located in the superior temporal lobe, and its generation is critically dependent on NMDA receptor functioning. Previously, we demonstrated that MMN reduction is related to cognitive deficits in schizophrenia (Krljes, 2003). In order to further understand this deficit, the present study was set to investigate the clinical correlates of MMN dysfunction in schizophrenia.

Methods: Forty-seven patients with schizophrenia and 47 age-matched healthy controls participated in the study. MMN was obtained for frequency and duration deviants. PANSS ratings, as well as duration of illness, number of admissions, and chlorpromazine equivalents were obtained within 7 days of MMN testing.

Results: Exploratory correlation analysis showed that only the positive symptom sub-scale of PANSS was significantly associated with MMN amplitudes. Following, stepwise regression analysis was performed in order to evaluate the relative weight of different positive symptoms on MMN. Results showed that only Conceptual Disorganisation scores were predictive of MMN amplitude ($b = 0.73$, $p < 0.01$).

Conclusion: These findings are in the line with previous studies showing that Superior Temporal pathology and NMDA changes are associated with thought disorder in schizophrenia (Shenton, 1992; Rajarethinam, 2000; Adler, 1999). Our findings suggest that NMDA receptor functioning in STL may be crucial to pathogenesis of thought disorder in schizophrenia.

MISMATCH NEGATIVITY IN 22q11 DELETION SYNDROME—EVIDENCE FOR PSYCHOSIS-LIKE DEVELOPMENTAL DISRUPTION

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Background: 22q11 Deletion Syndrome (22q11DS) is associated with heart and palate malformations, other variable somatic anomalies, learning disability, and psychiatric disturbance; a high rate of schizophrenia (10–40%) has been reported in affected adults, for reasons that are unclear. This study aimed to acquire evidence for genetic disruption of specific developmental processes that may explain the later emergence of psychotic illness in this condition.

Methods: Adolescents and young adults with 22q11DS were compared to age- and IQ-matched controls on a range of cognitive measures previously found to index vulnerability to psychosis. Auditory event-related potentials provided strong evidence for schizophrenia-like disruption in 22q11DS; mismatch negativity, an ERP elicited by any discriminable change in a repetitive auditory sequence, was reduced in amplitude at frontal electrodes but not at temporal sites. Anomalous context-dependent ERPs to speech stimuli were also observed. No such deficits were found in children with Specific Language Impairment, although other abnormalities in auditory processing were apparent.

Results/conclusion: Abnormal auditory ERPs were associated with a psychiatric profile akin to schizotypal personality disorder in some 22q11DS individuals. The association between these impairments supports the view that MMN indexes neurophysiological processes relevant to psychotic illness. The severity of neurocognitive abnormalities in 22q11DS was found to be modulated by the *catechol-o-methyl transferase*^{met}*158*^{val} polymorphism on the single non-deleted chromosome 22. Functional variants of the *COMT* gene have been associated with risk for schizophrenia and schizophrenia-like cognitive abnormalities in the general population. Thus developmental dysregulation of catecholamine systems may at least partially explain the association between 22q11DS and psychosis.

REPEATED APPLICATIONS OF KETAMINE TO RATS AS A POSSIBLE MODEL OF SCHIZOPHRENIA: REMARKABLE CELLULAR CHANGES

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Background: Recently, we established the repeated application of subchronic doses of the non-competitive NMDA-receptor agonist ketamine to rats as a new, promising animal paradigm of schizophrenia (Becker et al., 2003).

Methods/results: Here we show by means of immunohistochemistry that this treatment induces typical changes in the cellular expression of certain cellular markers. The calcium sensor protein VILIP-1 is reduced in its expression in hippocampal pyramids but increased in hippocampal interneurons of treated rats. Increases in the density of hippocampal interneurons expressing neuronal NOS and c-Fos were found in ketamine rats, whereas the number of parvalbumin-immunoreactive hippocampal interneurons was strongly reduced in these animals.

Conclusion: Amazingly, some of these cellular changes parallel those observed in human schizophrenia (Bernstein et al., 2003). Supported by NBL-3 of BMBF of Germany.

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MMN IMPAIRMENT IS RELATED TO COGNITIVE DEFICITS IN SCHIZOPHRENIA: THE SPECIFICITY AND IMPLICATIONS

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Background/objective: A number of studies proposed that NMDA system dysfunction is responsible for cognitive symptoms in schizophrenia. However, the main limitation is that due to the lack of suitable ligands it is difficult to measure NMDA activity in vivo. Thus, we investigated the relationship between mismatch negativity (MMN), an auditory ERP that is thought to be critically dependant on NMDA receptor functioning and cognitive function g in a cohort of schizophrenic patients. Based on the earlier studies that suggested a significant relationship between NMDA receptor dysfunction and cognitive performance in schizophrenia, we predicated that a similar relationship would be present between MMN and cognitive functioning in our schizophrenic sample.

Methods/results: The results supported our predictions. Schizophrenic patients had significantly lower MMN amplitudes. Additionally, the magnitude of MMN in schizophrenia correlated with cognitive performance. Furthermore, we investigated if these finding are specific to schizophrenia or are a feature of psychotic illness, or cognitive deficits per se. Thus, we measured MMN in a group of patients with bipolar affective disorder and those with Alzheimer's disease. Results showed that although the intensity of psychotic symptoms did not differ between BP and schizophrenia, there was a significant difference between MMN amplitudes. Additionally, MMN response was found to be normal in the patients with AD, although they were vastly impaired on all of neuropsychological measures.

Conclusion: The results suggest that the relationship between MMN and cognitive decline is specific to schizophrenia, and is not a feature of psychosis, or cognitive dysfunction per se.

Oral Presentations VIII

Where and when does brain structural change progress?

PROGRESSION OF DISEASE-SPECIFIC GRAY MATTER DEFICITS IN TWINS DISCORDANT FOR SCHIZOPHRENIA

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Background: The goal of this study was to analyze whether disease-specific brain alterations in twins show a progressive component.

Methods: Magnetic resonance images of five twin-pairs discordant for schizophrenia and five control twin-pairs were acquired at two time points (mean difference 10.8 months [S.D. 3.3] for discordant twin pairs and 26.4 months [S.D. 9.9] for control twins). We applied an automated voxel-based morphometric method to first compute gray matter segmentations, then calculate intra-pair differences (i.e. between related twins), and finally compare group differences, and changes over time.

Results: Cross-sectional analysis at the first time-point revealed significant differences between twin-pairs discordant for schizo-

phrenia and control twin-pairs in several cortical areas (including dorsolateral and medial prefrontal, inferior and superior temporal and parietal cortex, and cerebellum). Longitudinal analysis revealed that affected twins lost significantly more gray matter over time than their healthy co-twins in comparison to healthy twin-pairs in similar or adjacent regions as in the cross-sectional analysis.

Conclusion: These results show cortical and cerebellar alterations in affected twins of monozygotic pairs discordant for schizophrenia to have a progressive component, which are likely to be disease-specific rather than genetic in origin.

LONGITUDINAL STUDY OF MRI GRAY MATTER VOLUME IN TREATMENT-NAÏVE SCHIZOPHRENIA: EVIDENCE FOR COGNITIVE DYSMETRIA

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Background: Cross-sectional Magnetic Resonance Imaging (MRI) studies have consistently described gray matter volume abnormalities in schizophrenia. However, the longitudinal status of these abnormalities is yet to be established. Previous MRI studies assessing longitudinal brain morphology in schizophrenia have examined patients on long-term antipsychotic treatment using manual region-of-interest based image analysis techniques. Recently, automated techniques have enabled the morphological assessment of whole brain with good sensitivity and without intra- and inter-observer bias.

Methods: In this prospective study, after obtaining informed consent, MRI gray matter volume was examined in treatment-naive schizophrenia patients ($n = 10$) and age-, sex-, handedness- and education-matched healthy comparison subjects ($n = 10$) at baseline and after 1-year follow-up. We hypothesized schizophrenia patients to have significantly greater longitudinal gray matter volume reduction than controls. We used a fully automated image analysis technique that utilized the principles of both deformation-based morphometry as well as optimized voxel-based morphometry implemented within Matlab 6.1 through SPM 2.

Results: Schizophrenia patients had significantly greater ($p < 0.0001$) longitudinal gray matter volume loss than comparison subjects in right middle and medial frontal gyri, left precentral gyrus, left inferior parietal lobule, left superior temporal gyrus, right fusiform gyrus, left and right thalami, right claustrum and left and right cerebellum.

Conclusion: The study findings provide one of the first descriptions of progressive cortical, thalamic, and cerebellar gray matter volume loss in treatment-naïve schizophrenia using a fully automated, unbiased image analysis technique. These findings of longitudinal gray matter volume reduction may support involvement of neural circuit implicated for cognitive dysmetria in schizophrenia.

PROGRESSIVE BRAIN VOLUME CHANGES IN THE FIRST YEAR OF ILLNESS PREDICT FIVE-YEAR OUTCOME OF SCHIZOPHRENIA

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Background: In first-episode schizophrenia, progressive brain volume changes have been found after the first year of the illness. This study examined associations between early progressive brain volume changes and 5-year outcome in schizophrenia.

Method: Thirty-one first-episode patients with schizophrenia were included in this longitudinal study. MRI brain scans were obtained at inclusion (T0) and after 1-year (T1). Intracranial, total brain, cerebral gray and white matter, cerebellar, lateral and third ventricle volumes were measured. After a follow-up period of 5.3 (S.D. = 0.8) years global outcome was measured with the Camberwell Assessment of Need (CAN) and clinical outcome was measured with the Positive and Negative Syndrome Scale (PANSS). To examine associations between early progressive brain volume changes (T1 minus T0) and 5-year outcome Pearson product-moment correlations were performed with intracranial volume and age as covariates.

Results: Total brain volume decreases over the first year correlated significantly with negative symptoms ($r = -0.38$, $df = 27$, $p = 0.04$) at 5-year follow-up. Gray matter volume decreases correlated significantly with positive symptoms ($r = -0.40$, $df = 27$, $p = 0.03$) and negative symptoms ($r = -0.54$, $df = 27$, $p = 0.002$). Lateral ventricle volume increases correlated significantly with the total score of the CAN ($r = 0.54$, $df = 27$, $p = 0.003$).

Conclusion: These findings suggest that medium-term symptomatic and global outcome is predicted respectively by early gray matter loss and lateral ventricular enlargement. It furthermore underscores the importance examining dynamic rather than static changes in brain structures in relation to predicting outcome of schizophrenia.

ABNORMAL CORTICAL FOLDING IN THE RIGHT FRONTAL LOBE MAY PREDICT PSYCHOSIS IN THOSE AT GENETIC HIGH RISK OF SCHIZOPHRENIA

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Background: Patterns of gyral folding may contribute to an understanding of the neuropathological characteristics of schizophrenia and the development of the disease. Previous gyral comparisons of schizophrenic and control groups have found differences in the temporal and frontal lobes but a lack of consensus remains, possibly due to sample variance and the largely unknown neurodevelopmental etiology of the disease.

Methods: As part of the Edinburgh high-risk project, this study involves analysis of the gyri of young adults categorized as first episode schizophrenics, healthy controls and individuals at high risk of developing schizophrenia. Utilizing the Gyrification Index (G.I.: the ratio of complete gyral contours to their outer, exposed contours), we previously found increased right temporal lobe G.I. values in first episode schizophrenics compared to controls. To help identify possible cortical predictors of schizophrenia, we used the same method to assess the baseline structural MRI scans of high-risk individuals who subsequently developed schizophrenia and a matched group of those who remained well. We hypothesized that between-group differences in G.I. associated with schizophrenia would be restricted to the frontal and temporal regions whilst the parietal and occipital were considered as control regions where the G.I. measures were expected to be similar in the two groups.

Results: We found that the right frontal lobe of the subsequently psychotic individuals showed significantly increased G.I. ($p < 0.01$).

Conclusion: This finding has important implications for understanding the developmental etiology, the differentiation of trait and state characteristics and the prediction of psychosis in schizophrenia.

PATTERNS OF GREY MATTER LOSS DISCRIMINATE BETWEEN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Objective: This study addressed the hypothesis that schizophrenia and bipolar disorder are separate disorders by examining the brains of schizophrenic, bipolar and unaffected individuals from families in which the disorder appears to breed true, and from families where there is a history of both schizophrenia and bipolar disorder. The results were compared to a group of healthy subjects.

Methods: DSM-IV diagnoses of probands were confirmed using the OPCRIT symptom checklist. The status of unaffected relatives and controls was confirmed using the SADS-L. Participants then underwent an MRI scan of the brain. Images were analysed using SPM99.

Results: Patients with schizophrenia and their relatives were recruited from families with a history of schizophrenia only. In addition, patients with bipolar disorder and their relatives were recruited from families where there was (a) a history of bipolar disorder only or, (b) a history of schizophrenia and bipolar disorder. A group of controls were also scanned. Reductions were found in middle prefrontal gyrus, insula and amygdala in schizophrenic subjects which were not present in either bipolar group. Thalamic density was reduced in all groups compared to controls.

Conclusion: Specific patterns of grey matter reduction were found in schizophrenic subjects. In contrast, decreased thalamic grey matter appeared common to all groups. These results suggest that fronto-temporal grey matter loss may be a consequence or risk factor for schizophrenia specifically, but that thalamic grey matter reduction is a vulnerability factor for psychotic illness in general.

GREY MATTER CHANGES AS PEOPLE AT HIGH RISK DEVELOP SCHIZOPHRENIA

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Background: Magnetic resonance imaging (MRI) has demonstrated abnormalities of brain structure, particularly of the temporal lobes, in schizophrenia. These are thought to be neurodevelopmental in origin, but when they become evident is unknown. A study of what happens to the brain structure of individuals at high risk of schizophrenia, before they fall ill, is crucial to understanding the illness and therefore to the potential development of preventative measures and treatments. The Edinburgh High Risk Study addresses this issue.

Methods: Voxel-Based Morphometry was used to map changes over time in Grey Matter Probability Density (GMPD), in 65 individuals at high risk of schizophrenia and 19 healthy individuals.

Results: Neither group showed any increase in GMPD over time. In the high-risk group, significant declines in GMPD were found in the temporal lobes, the right frontal lobe, and right parietal lobe, over a period of approximately 2 years. In the control group, a single change was found in the right gyrus rectus, over the same period. The high-risk group had greater reductions in GMPD than healthy individuals, and those at high risk who had psychotic symptoms showed greater reduction in GMPD than those at high risk who did not have psychotic symptoms. In addition to this, those individuals at high risk who developed schizophrenia also showed reductions in GMPD, in the left temporal lobe, up to 5 years before they fell ill.

PROGRESSIVE VENTRICULAR ENLARGEMENT: A 10-YEAR FOLLOW-UP STUDY

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Background: For the past decade, the controversy over whether brain structural changes detected in patients with schizophrenia are progressive has been in the forefront. We and others have conducted longitudinal follow-up studies of both patients beginning at their first episode and also when they have already become chronic. Although the studies to date generally show some greater change in patients with schizophrenia compared with controls even over relatively short time spans, the specific results are inconsistent, the same regions showing change are not replicated, with the possible exception of ventricular enlargement, and the time span between scans and the timing in the course of illness are not similar across studies. In addition, no clear clinical relevance of these findings stand out except some trend when chronic patients only are studied over time indicating that progressive ventricular enlargement may be associated with poor outcome.

Methods: We studied a cohort of first-admissions for a schizophreniform psychosis beginning in 1988 and following them with serial MRI scans over a period of approximately 10 years. A community control group was also ascertained and studied over time. A total of 50 patients and 20 controls received multiple MRI scans through 5 years of follow-up, while 26 patients and 10 controls had scans completed at the 10-year follow-up. The identical scanning sequence was used on the same 1.5 T Signa scanner for all years of the study.

Results: At the end of the first 5 years, subsequent to the first episode, significant ventricular enlargement (Left>R) and bilateral hemispheric volume reduction were detected in the patients compared with controls. When examined after 10 years of follow-up, approximately 1/3 of the patients continued to show some progressive ventricular enlargement, but not hemispheric volume change. Whole temporal lobe volume did not show any reduction over time. Surprisingly, no clinical differences were detected between those patients who had ventricular volume expansion and those who did not.

Conclusion: These results suggest that while progressive brain structural change after the onset of schizophrenia may be sufficient to explain the ventricular enlargement reported in chronic patients with schizophrenia by numerous investigators, its clinical significance is questionable. There are many reasons why changes may be detected in MRI scans over time. Aside from technical artifacts, physiological changes unrelated to illness, but that differ between patients and controls could have an effect, as could any chronic treatment regime. More studies are needed using the latest MRI technology and larger sample sizes with more frequent and consistent time points during the illness course to define the nature of these brain structural changes and their significance.

Oral Presentations IX

Which genes and what is the evidence?

IDENTIFICATION AND VARIATION SCREENING OF A HIGH-RISK HAPLOTYPE IN THE DYSTROBREVIN BINDING PROTEIN 1 (DTNBP1) GENE FROM THE IRISH STUDY OF HIGH-DENSITY SCHIZOPHRENIA FAMILIES

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Background: We reported linkage of schizophrenia to chromosome 6p24–p22 in a sample of 270 multiply-affected families from Ireland. Initial replications and metanalyses supported these linkage findings. Linkage disequilibrium analysis of a dense microsatellite map of the region showed association in the interval D6S260–D6S1676. Single nucleotide polymorphisms (SNPs) in the dystro-

brevin binding protein 1 (DTNBP1) gene, the human ortholog of murine dysbindin, showed strong association with schizophrenia by a variety of tests.

Methods/results: As a follow-up to the report by Straub et al. (2002), we have identified a haplotype block defined by eight of the SNPs used in these analyses and a specific schizophrenia high-risk haplotype within this block. The haplotype block corresponds to the 5′-most exons of DTNBP1 and is approximately 30 kb in size. In our schizophrenia families, we observe excess transmission of the haplotype ($p=0.02$, by PDT), which is found in 55 affected offspring in 38 (14%) of our 270 families. Cladistic analysis identifies the relationships between the seven common haplotypes within this block that account for 94% of founders in the sample. Analysis of the geographical origin of these families shows no evidence for a specific founder effect within Ireland. Sequencing of the 30-kb core haplotype region plus all additional exons and 2 kb of promoter sequence is 93% complete and has identified four novel variants specific to the high-risk haplotype so far.

Conclusion: None of these have any obvious functional significance, but further bioinformatics and family analyses are underway currently.

RGS4 GENE POLYMORPHISM, COGNITION AND IN VIVO NEUROBIOLOGY IN FIRST EPISODE SCHIZOPHRENIA

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Background: Our group recently reported significant association and linkage between schizophrenia and regulator of G-protein signaling (*RGS4*) gene polymorphisms. The association has now been replicated. Prior postmortem brain analysis showed decreased *RGS4* mRNA expression in the prefrontal cortex of schizophrenia patients compared to matched control subjects. RGS family of proteins regulates the G-proteins that function as second messengers for neurotransmitters such as dopamine, serotonin and glutamate. However, the relationship between RGS4 gene polymorphism and the cognitive and neurobiological abnormalities in schizophrenia is poorly understood. We studied the neurocognitive, neuroimaging and spectroscopic characteristics of RGS4 gene polymorphism in first episode schizophrenia patients and healthy subjects.

Results: In this study, we report results of exploratory analyses that assess the relationship between one of the upstream variations (SNP1), which is ~ 6 kb from the RGS4 transcription site and neurocognitive and neuroimaging measures. Concept formation as measured by the Wisconsin Card Sorting Test ($p=0.026$) and trail making test ($p=0.019$), and working memory as measured by digit span test ($p=0.014$) were significantly impaired in those homozygous for G alleles. Convergent with this observation, we observed that the right dorsolateral prefrontal cortex ($p=0.018$) was smaller in G allele homozygotes. Multi-voxel ^{31}P magnetic resonance spectroscopy revealed elevation in the broader underlying component of the phosphodiester (PME2PDE2) resonance in the right prefrontal cortex in G homozygotes.

Conclusion: Our observations suggest that RGS4 genetic polymorphism may be associated with distinct neuropsychological and neuroimaging abnormalities observed in schizophrenia though the cause–effect relationship is unclear. Analyses for association of other SNPs are in progress.

GENOTYPE–PHENOTYPE RELATIONSHIP FOR RECENTLY IDENTIFIED SUSCEPTIBILITY GENES FOR SCHIZOPHRENIA

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Background: The examination of variants of positional candidate genes in candidate regions identified by linkage analysis have been successfully tested for association with schizophrenia: DTBN1 on chromosome 6p, G72 on chromosome 13q, neuregulin1 on chromosome 8p. These associations turned out to be replicable but not consistently so. The strength of the associations with the disorder is modest and might be due to differential effects of different neurobiological components underlying schizophrenia (endophenotypes). Although the functional variants impacting on the risk of schizophrenia still have to be identified, the disease-associated risk haplotypes can be explored for associations with endophenotypes.

Methods: We defined endophenotypes by morphometric and neuropsychological dimensions in 90 family members of probands with schizophrenia.

Results: The analysis of the genotype–phenotype relationship proposed an effect of the risk haplotype of DTNB1 on the volume of gray matter of prefrontal cortex; preliminary evidence proposes a parental effect which might indicate epigenetic influences.

AN ASSOCIATION STUDY OF DOPAMINERGIC GENES IN A SAMPLE OF 283 DUTCH SCHIZOPHRENIC PATIENTS

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Background: Genes involved in dopamine neurotransmission have been suggested to contribute to the development of schizophrenia. However, reported associations of the disorder with genetic markers close to dopaminergic genes have shown inconsistent results. Possible explanations are differences in phenotyping, genetic heterogeneity, low-marker informativity, or sample sizes with insufficient power.

Methods: Here, we present an association study of seven genes involved in dopamine synthesis, transport and degradation and four dopamine receptor genes. The sample consisted of 208 schizophrenic patients and 288 unmatched control individuals. All patients had at least three Caucasian grandparents of Dutch ancestry. DSM-IV diagnosis of schizophrenia was made using the Comprehensive Assessment of Symptoms and History (Andreasen, 1987) and additional information from medical records and clinicians. Initially, for the efficient screening of multiple microsatellite markers, a DNA pooling technique was used that derives allele frequencies from pool patterns, after correction for PCR-induced stutter. For each gene preferably more than one microsatellite marker was selected, either intragenic or close to the gene.

Results: Significantly different allele frequencies were found for three markers close to or within the DRD5 receptor gene ($p = 0.04$, $p = 0.003$ and $p = 0.001$). In an extended sample of 283 schizophrenic patients and 585 unmatched controls, we are currently genotyping these, and additional markers individually. This approach allows the study of association with schizophrenia subtypes.

Conclusion: Both the results of the pooled association study and of individual genotyping in a large Dutch sample will contribute to the understanding of the involvement of dopaminergic genes in schizophrenia.

A NEW NEUREGULIN HAPLOTYPE IS ASSOCIATED WITH SCHIZOPHRENIA IN THE DUTCH POPULATION

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Background: Genetic variations in the neuregulin gene were first reported to be associated with schizophrenia in Iceland, and this finding has been replicated in Scottish, English/Irish, and Chinese patient samples. However, replication in other populations is necessary to evaluate the role of neuregulin as a general schizophrenia susceptibility gene.

Methods: We recruited 283 unrelated Dutch schizophrenic patients, all diagnosed according to DSM-IV criteria, and 585 unmatched controls. Two markers from the previously reported at-risk haplotype were tested, as well as a new microsatellite that was defined from human sequence data.

Results: For single nucleotide polymorphism (SNP) NRG221533, the most frequent T allele was associated with schizophrenia ($p = 0.02$). Remarkably, in previous studies the C allele was associated with schizophrenia. A haplotype of SNP NRG221533 and the new microsatellite at 18 kilobases from the SNP was also associated ($p = 0.02$). Hardly any association was detected with the previously reported microsatellite located at 115 kb from the SNP.

Conclusion: Thus, in the Dutch population a new haplotype with a different SNP allele was associated with schizophrenia. This suggests an independent mutation event, and indicates that SNP NRG221533 is not the causal variant. This finding further strengthens the support for neuregulin as a schizophrenia susceptibility gene in different populations, and restricts the candidate region for identifying a causative mutation. The at-risk haplotype is now being correlated to clinical characteristics.

WHAT HAPPENED TO PROTOCADHERIN/X AND PROTOCADHERIN/Y IN HOMINID EVOLUTION

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Background: In 1877, Broca suggested that language was associated with lateralization within the brain. Evidence that a gene for asymmetry is in the X–Y homologous class focuses interest on the X to Y reduplicative transposition 2 to 3 million years ago in the hominid lineage, that created a region of homology on the Y short arm to a block on the X chromosome long arm, that was followed by a paracentric inversion (at present undated). Within the Xq21.3/Yp homologous region, the genes *ProtocadherinX and Y* have been identified that code for cell surface adhesion molecules in a class of axonal guidance factors.

Methods/results: We identified the chimpanzee, bonobo, gorilla, and orangutan and mouse sequence equivalents of the *ProtocadherinX/Y* gametologues (*PCDHX/Y*). Sequence comparisons with *PcdhX* in apes and mouse provide evidence of purifying selection during mammalian and hominoid evolution, but in the hominid lineage purifying selection has been lost in a domain-specific manner with evidence of positive selection on the ectodomain of *PCDHX* and on the cytoplasmic domain of *PCDHY*. In terms of the amino acid sequence, the changes in the hominid lineage have been more radical than those in the chimpanzee/bonobo lineage.

Conclusion: We argue that these changes are relevant to the evolution of the sexual dimorphism of cerebral asymmetry, a putative correlate of language, and therefore to psychosis.

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DIFFERENTIAL GENE EXPRESSION IN SCHIZOPHRENIA: RESULTS OBTAINED FROM SUPPRESSION SUBTRACTIVE HYBRIDISATION

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Objective/methods: In order to obtain insight into functional abnormalities occurring in schizophrenia, we have focussed on the analysis of gene expression at the mRNA level using rapid autopsy brain tissue obtained as part of a long-term prospective study, We are currently using a range of expression profiling techniques to identify differentially expressed genes in defined brain regions including differential display, gene chip microarrays and suppression subtractive hybridisation (SSH).

Results: We report here results obtained using SSH to isolate differentially expressed genes in superior temporal cortex (BA22) of schizophrenics compared to controls. One major sequence found to be under expressed in people with schizophrenia was selected for further analysis. This was a 190-bp transcript showing identity to a sequence important in neurodevelopment. Differential expression was initially confirmed by slot blot analysis of a panel of 6 controls and 6 schizophrenics from the Imperial College Schizophrenia Brain Bank at Charing Cross (ICSBB). These results were further authenticated in a larger panel (12 control and 12 patients with schizophrenia) from the Stanley Foundation by real-time PCR with primer sets specific to this gene where we found a 40% significant decrease in mRNA levels ($p < 0.02$) in patients compared to normal controls.

Conclusion: This gene has been shown to be a potent inhibitor of the neurodevelopmental wnt signalling pathway and may therefore be a relevant candidate in the pathology of schizophrenia.

Posters

Early Detection

1. DURATION OF UNTREATED ILLNESS (DUI) IN FIRST-ONSET PSYCHOSIS IN THE UNITED KINGDOM

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Background/objective: The Duration of Untreated Illness (DUI) may have an effect on treatment outcome of psychoses. Shortening it is a principal aim of early intervention (EI). DUI is defined as the time between the earliest changes in behaviour related to the illness and contact with psychiatric services. The aim of this study is to estimate the DUI among affected individuals in population-based samples and to provide a benchmark for EI services.

Methods: We studied a population-based cohort of 167 subjects meeting DSM-III-R psychotic disorder criteria and aged between16 and 64 in the city of Nottingham, UK, incident between 1992 and 1994. We will include three other samples in our larger study (AESOP). We estimated DUI using question 1.4 of the Personal and Psychiatric History Schedule. DUI was also estimated retrospectively from follow-up at 3 years.

Results: In the first Nottingham sample, the median DUI was 3 months with a range between 0 and 100 months and a 75 percentile of 6 months. DUI was longer for men than for women.

Conclusion: Initial results are generally in line with estimates from elsewhere, though relatively short. Inclusion of three further

samples will increase precision. Definition of DUI is a crucial issue for comparison.

2. EARLY RECOGNITION OF PSYCHOSIS—THE BASEL FEPSY STUDY, SAMPLE DESCRIPTION AND TRANSITION RATE TO PSYCHOSIS OF AT-RISK INDIVIDUALS

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Objective: The aim of the Basel FEPSY study is to develop a "risk index" for schizophrenic psychosis using a prospective, multilevel approach. Here, we report on recruitment, sample description and transition rate of 58 at-risk individuals.

Methods: We established a specialised early recognition clinic at our psychiatric outpatient department, and screened individuals referred with suspected schizophrenic psychosis. Our screening instrument assesses prodromal signs according to DSM III-R as well as other known risk factors. Psychopathology was assessed with the BPRS and the SANS (BPRS cut-off scores for transition to psychosis according to Yung et al., 1998).

Results: From 1.3.2000 to 28.2.2003, we screened 206 individuals. 76 were already psychotic, 98 were identified as at-risk, of these $n = 58$ consented to participate. We found a similar pattern of prodromal signs, early indicators and risk factors in the at-risk sample as in the first episode patients. BPRS mean global score was 40.5, SANS summary score was 7.5. The annual transition rate to psychosis was 18%.

Conclusion: Our transition rate is lower compared to the one reported by Yung et al., 2003 (40.8% within 12 months). This may be age-related, also, some of the individuals in our sample are not high, but low risk. Klosterkötter et al. (2001) report a transition rate of 49.4% over 9.6 years in patients with prodromal symptoms. Our transition rate lies in between these other two prospective studies.

3. MULTI-MODAL NEUROIMAGING OF FRONTO-STRIATAL CIRCUITS IN THE PRODROME AND SUBSEQUENT STAGES OF SCHIZOPHRENIA

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Objective: Using multimodal neuroimaging, including functional MRI and electrophysiology, we examined prefrontal activation and event-related potentials associated with visual and auditory executive processes in three cross-sectional groups representing disease progression of schizophrenia spectrum psychotic disorders.

Methods: Fifty-three individuals from four groups (control, high-risk, first episode and chronic schizophrenia) were studied with functional MRI and event-related potentials while performing an auditory–visual oddball task.

Results: Electrophysiological indices of target detection revealed a decline with disease progression, reflected in group differences emerging as early as the prodromal stage in high-risk individuals, and further declining with disease progression. fMRI findings revealed that individuals at high-risk for schizophrenia experiencing prodromal symptoms showed significantly smaller activation to task-relevant target events in frontal regions (anterior cingulate gyrus, inferior frontal gyrus, middle frontal gyrus) compared to controls. Activation associated with target stimuli demonstrated a linear stepwise decline in activation over the cross-sectional groups representing disease progression. The chronic and first episode groups showed significantly lower activation than the control group while the high-risk prodromal subjects showed activation trending towards that of the first episode group.

Conclusion: These results suggest that prefrontal function declines prior to illness onset in individuals experiencing prodromal symptoms and hence may represent a vulnerability marker in assessing the risk of developing psychotic disorders among high-risk individuals. These findings also represent the first multimodal imaging of high-risk individuals, as compared to first episode and chronic patients, and indicate that fronto-striate function declines progressively during the course of illness.

4. MEMORY IMPAIRMENTS IDENTIFIED IN PEOPLE AT ULTRA HIGH-RISK FOR PSYCHOSIS WHO LATER DEVELOP FIRST EPISODE PSYCHOSIS

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Objective: While cognitive deficits are frequently reported in psychotic disorders, it is unclear whether these impairments predate illness onset and to what extent they are predictive of later transition to psychosis.

Method: Ninety-eight symptomatic and help-seeking patients meeting inclusion criteria for entry to an ultra-high-risk for psychosis treatment program were compared to 37 equivalent controls. Thirty-four percent of the ultra high-risk group developed psychosis over the course of the investigation. Measures of premorbid and current IQ, attention, memory and executive function were obtained, including subtests from the Wechsler Memory Scale-Revised (WMS-R). Analyses compared the two outcome groups derived from the ultra high-risk sample (UHR) to the control group. The UHR groups included those who became psychotic UHR-P), and those who did not become psychotic (UHR-NP).

Results: Overall, the UHR subjects were significantly impaired in Performance IQ ability compared to controls. Further, impairments were also found in the Visual Reproduction subtest and the Verbal Memory Index (predominantly due to lower Logical Memory scores) of the WMS-R that were specific to the subsequently psychotic group. No other memory, attentional or executive tasks discriminated between any of the groups.

Conclusion: These findings suggest that visuo-spatial processing and some memory deficits were apparent from before the full expression of psychotic illness. Cognitive performance on more complex tasks requiring rapid registration and efficient recall may be compromised prior to development of first episode psychosis. Further experimental tasks that challenge these cognitive domains are required to clarify the predictive value of these results.

5. WHAT WE NEED TO KNOW ABOUT PRIMARY CARE-BASED INTERVENTION IN EARLY PHASES OF PSYCHOSIS

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Background: General Practitioners (GPs) play a pivotal role on the pathways to care of individuals suffering from early psychotic phases (Lincoln et al., 1998; Addington et al., 2002). This is true not only for initial diagnosis, but also for further intervention, in particular in rural regions, where psychiatric service provision is in general only sparsely developed.

Methods: In a northwestern semi-urban region in Switzerland, a low threshold referral service has been established which offers assessments of at-risk patients at GPs' practices and at patients' homes. Referred at-risk patients are included in a prospective study and comprehensively followed-up at monthly to 3-monthly basis, narrowly focussing on prodromal symptoms. Subjects are assessed with the SCID (DSM-IV), SPI-A, SIPS/SOPS, PANSS, PAS, an obstetric questionnaire and a comprehensive neuropsychological battery. In a naturalistic setting, patients are offered to receive follow-up treatment by GPs or by our specialised outpatient clinic. We investigated whether characteristics from patients choosing follow-up treatment in our specialised outpatient clinic differed from those patients receiving follow-up treatment from GPs.

Results: Preliminary results suggest that patients treated in our clinic are more symptomatic, have higher impairments in neurocognitive functioning and a more insidious onset of their illness as will is shown in the 1-year results of the pilot phase.

6. THE MAUDSLEY EARLY ONSET SCHIZOPHRENIA STUDY: RELATIONSHIPS BETWEEN BRAIN STRUCTURE AND PRODROMAL DETERIORATION IN PATIENTS' FUNCTION

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Background/objective: In the Maudsley Early Onset Schizophrenia (EOS) study, we have already shown abnormalities in brain structure and premorbid function in patients with onset before the age of 17. Furthermore, patients' function deteriorates significantly during the prodromal phase of their illness. The aim of this analysis was to determine which brain structures are associated with patients' functional changes just prior to the onset of psychosis.

Methods: Structural magnetic resonance imaging (MRI) data of the brain were obtained from 40 EOS patients. Premorbid function was measured with the Premorbid Adjustment Scale (PAS). The change in PAS score between childhood and adolescence was used in a correlational analysis of the MRI data using SPM.

Results: Deterioration in patients' level of functioning was associated with volume reductions in the cerebellar vermis, right cerebellar hemisphere and inferior frontal lobe as well as in the anterior cingulate, insula and superior temporal gyrus bilaterally.

Conclusion: Our results indicate that the earliest deficits seen in schizophrenia are within brain regions that show progressive changes after the onset of psychosis in EOS. This suggests that the brain mechanisms underlying the relatively nonspecific changes seen in the prodromal phase may be the same as those involved in the production of psychotic symptoms.

7. CLINICAL AND PERSONALITY CHARACTERISTICS OF PSYCHOSIS-PRONE INDIVIDUALS

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Background: A frequently used strategy in cross-sectional studies involves the identification of at-risk individuals on the basis of their psychometric characteristics. However, few investigators have assessed the predictive validity of these measures of psychosis-proneness. We hypothesized that in addition to differing in terms of personality traits, individuals identified as at-risk on the basis of their Chapman scale scores at Time 1 would be diagnosed with schizophrenia-spectrum disorders at follow-up (Time 2).

Methods: In the present study, we recontacted and interviewed 135 young adults approximately 5 years following their initial assessment with the Chapman scales. The at-risk groups consisted of high scorers on the Perceptual Aberration and/or Magical Ideation scales ($n = 59$) and high scorers on the revised Social Anhedonia scale ($n = 32$). The controls ($n = 44$) scored below 0.5 SD of the same-sex group means on each of the Chapman scales.

Results: At the follow-up, the groups differed in terms of their likelihood of having a schizophrenia-spectrum diagnosis, chi-square $(2) = 10.89$, $p < 0.01$. The at-risk groups reported significantly greater negative affect, as well as more frequent and severe psychotic-like experiences relative to the controls.

Conclusion: These findings support the predictive validity of the Chapman psychosis-prone scales and may enhance the power of early detection efforts.

8. RISK OF PSYCHOSIS IN INDIVIDUALS EXPERIENCING PRODROMAL SYMPTOMS

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Background/objective: Schizophrenia and related psychotic disorders are disabling and distressing conditions. Early identification offers the possibility of early intervention. Recently, there has been growing interest in identifying individuals at high risk of a schizophrenia spectrum disorders prior to onset of the full syndrome, with the hope of secondary prevention and decreasing risk of functional decline. The goal of this pilot study is to determine risk of psychosis in individuals experiencing prodromal symptoms, and to identify clinical characteristics that predict risk of schizophrenia spectrum disorders.

Methods: We have recruited 30 individuals meeting specific diagnostic criteria for prodrome (Criteria of Prodromal States, "COPS"). Baseline study evaluations included the SOPS, modified versions of the SOS, SCID, a standard neurocognitive battery, and the UPSIT. Clinical status was evaluated monthly, and neurocognitive and olfactory status evaluated at 6- and 12-month follow-up. The study subjects include 15 men and 16 women, with a mean age of 20.32.

Results: At the time of entry into the study, subjects reported a 47.92 duration of prodromal symptoms. By 1-month follow-up 13%, by 6-month follow-up 33% and by 12-month follow-up 48% had developed a psychotic disorder.

Conclusion: High-risk individuals can be identified, however, strategies that increase the diagnostic specificity will improve their prognosis through preventative interventions.

9. OPINIONS OF MOTHERS ON THE FIRST PSYCHOTIC EPISODE AND THE START OF TREATMENT OF THEIR CHILD

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Background: Parents, especially mothers, have a critical role in initiating psychiatric treatment for their child with first-episode schizophrenia. Knowledge of attitudes of mothers towards the illness of their child prior to psychiatric treatment and towards the start of treatment is essential for the development of interventions for reducing duration of untreated psychosis (DUP).

Methods: In the present study, mothers ($n = 61$) of consecutively admitted patients with recent-onset schizophrenic disorders were interviewed about: their views on the nature of the symptoms at first occurrence of psychotic symptoms in their child and views on the main reason for psychiatric treatment; their perception of problems in initiating psychiatric treatment; and suggestions they might have for getting treatment started at an earlier point in time.

Results: About 57% of the mothers did not think that their child had a psychosis at first occurrence of psychotic symptoms. Most of the mothers who immediately thought that their child suffered from a psychotic disorder supposed that this disorder was caused by use of street drugs. About one-third (32.8%) of the mothers thought that

the reluctance of patients to acknowledge that they needed help was the major obstacle in initiating psychiatric treatment.

Conclusion: More than half of the mothers perceived factors related to the delivery of professional care as problems in initiating psychiatric treatment. Given the reluctance of patients to accept treatment, these problems further complicate the initiating of treatment. Mothers emphasize that a more active approach by professional caregivers could reduce treatment delay.

10. PROD-SCREEN: SCREENING FOR PRODROMAL SYMPTOMS OF PSYCHOSIS AMONG PSYCHIATRIC OUTPATIENTS

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Background: PROD-screen is an instrument for screening for prodromal symptoms of psychosis. According to the data from DEEP-study, PROD-screen functions well with mixed samples and with first-degree relatives of schizophrenic patients, being able to distinguish prodromal cases from noncases. But PROD-screen did not work when used in clinically highly relevant population of new psychiatric outpatients, presumably due to high levels of symptoms reported in this sample in general.

Methods: We developed this screening procedure in a more qualitative direction by including also reports of verbal responses to symptom queries presented in the screen, and using these verbal responses as the basis for deciding screen positivity. On all symptom questions responded with "Yes", the subject was asked to give a detailed description of what kind of symptom prompted him/her to respond positively. The evaluation of these symptom descriptions was made independently by two experienced psychiatrists, who jointly decided which subjects were asked for a research interview. In connection with the EPOS-study, the Turku group has screened new attenders to psychiatric open care systematically and 600 screens have been evaluated. Kappa for agreement in independent evaluation of screens was 0.59 ($p < 0.000$) and 24% of screens were eligible for a research interview.

Results: Fifty-four subjects have been investigated to date and from this group 8 were excluded and 33 fulfilled prodrome criteria (Basic symptoms or SIPS positive symptoms). Positive predictive value of screening for prodromal state is 72%.

Conclusion: Adding evaluation of qualitative data to PROD-screen makes it a powerful tool for detecting prodromal syndromes.

11. THE EARLY RECOGNITION INVENTORY: STRUCTURE, RELIABILITY AND INITIAL RESULTS

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Background/methods: Our Mannheim centre contributes to the German Schizophrenia Research Network a set of assessment instruments: the Early Recognition Inventory (ERIraos), a two-step procedure for the assessment of psychosis risk: (a) a 17-item checklist and (b) a comprehensive 105 items symptom list, which includes a time grid for the documentation of symptom severity and development in monthly steps. We train and supervise the interviewers at the early intervention centres. We started a reliability study and compare interviewer ratings with standard ratings. Kappas for "symptom present in the year before interview" range between 0.41 and 0.87, for the rating of "subjective stress associated with the symptom" between 0.33 and 0.81. The reliabilities increased from the first to the second assessment.

Results: Prodromal symptoms assessed by the checklist have been present at least in 16.3% (ideas of reference) risk persons and in a maximum of 79.5% (tension, nervousness, restlessness). Checklist symptoms are more frequent in the late prodrome compared to the early prodrome ($p < 0.05$ for eight symptoms). The most frequent prodromal symptoms are nonspecific (negative symptoms: loss of energy, loss of concentration, social withdrawal; depressive symptoms: depressive mood, loss of self-confidence, increased fatigability). Symptom onset dates back between 4.7 and 9.1 years. The earliest symptom is "preoccupation with mysterious things", but this item probably indicates a schizotypal personality trait. Seventy-three percent of the patients fulfilled checklist criteria already 1 year before inclusion in the intervention study.

12. OUTCOME AND COST-EFFECTIVENESS OF INTERVENTION FOR PEOPLE AT ULTRA-HIGH RISK OF FIRST EPISODE PSYCHOSIS

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Background: Clinical intervention for young people at ultra-high or incipient risk for schizophrenia and related disorders is an active

focus for research. Several centres have demonstrated that it is feasible to detect and engage a subset of those with a very high rate of early transition to first episode psychosis. This study reports a follow up at 3 years of a cohort of 92 UHR cases treated at the Melbourne PACE Clinic between 1996 and 1998 (McGorry et al., 2002). Data on diagnostic and functional outcome are reported.

Methods/results: A total of 30 patients from the original 92 had progressed to FEP, although not all could be interviewed. The subgroup who progressed to first episode psychosis are compared with a matched comparison group from the EPPIC program. The cost-effectiveness of the PACE model is explored using this methodology.

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13. EVALUATING PRODROMAL SYMPTOMS AND SYNDROMES: PREDICTIVE VALIDITY, INTER-RATER RELIABILITY, AND TRAINING TO RELIABILITY

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Background: International investigations of patients at imminent risk for developing psychosis require measures that can reliably and validly diagnose prodromal syndromes, rate symptom severity, and track changes in symptoms over time. Further, the ability to train raters across sites to reliability is essential in order to successfully conduct multi-site studies.

Methods: We have developed the Structured Interview for Prodromal Symptoms (SIPS) and the Scale of Prodromal Symptoms (SOPS). This poster will detail our initial and ongoing psychometric studies concerning reliability, predictive validity, and rater training.

Results: The SOPS intraclass correlation for prodromal symptoms was 0.95 for the total score and above 0.75 for all four subscales (Positive, Negative, Disorganized, and General symptoms). Data from 35 trainees at six sites demonstrated that agreement among raters before training was poor (kappa = 0.31). Post training agreement among all 35 was in the excellent range (kappa = 0.87). The SIPS demonstrated predictive validity for the conversion to psychosis, predicting the onset of psychosis in 43% of identified prodromal cases within 6 months, 50% of cases within 12 months, 62% of cases within 18 months, and 62% of cases within 2 years.

Conclusion: Our studies show that a valid, high-risk, prodromally symptomatic state can be identified with satisfactory psychometric precision using the SIPS and SOPS.

14. BRIEF SELF-REPORT SCREEN TO DETECT THE SCHIZOPHRENIA PRODROME

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Background: Screening for prodromal symptoms in clinical populations could increase both clinicians' and researchers' abilities to identify patients at imminent risk for developing psychosis. We are developing the PRIME Screen, a brief self-report measure intended to be used in primary care and other clinical settings. The ultimate intent of the screen is for screen positive individuals to be referred for a more complete diagnostic evaluation.

Methods: Thus, far 22 patients referred for prodromal evaluation (10 prodromal or newly psychotic and 12 neither prodromal nor psychotic) have been administered a preliminary screen and have then been evaluated by raters, blind to the screen results, with a Structured Interview for Prodromal Syndromes to determine diagnostic status.

Results: In the developmental phase, the measure contained 34 items, each scaled 1–7. Preliminary data analysis reveals that it is possible, using a method that counts the number of items meeting a threshold rating, to create a brief 12-item scale with a sensitivity of 0.90 and perfect specificity in our sample.

Conclusion: The PRIME Screen with its brevity and promising psychometric properties may offer a novel and effective approach to early identification. Further testing is warranted, particularly in nonclinical populations.

15. THE DANISH OPUS-TRIAL: A RANDOMISED CONTROLLED TRIAL OF INTEGRATED TREATMENT AMONG 547 FIRST-EPISODE PSYCHOTIC PATIENTS. ONE AND TWO YEARS FOLLOW-UP

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Background: OPUS is the first large randomised controlled trial of integrated treatment versus standard treatment of first-episode psychosis.

Methods: A total of 547 first-episode psychosis patients were randomly assigned to either integrated treatment by a multidisciplinary psychosis team or treatment as usual. The integrated treatment consisted of assertive community treatment, psychoeducational multi-family groups, social skills training and antipsychotic medication. Each patient was assessed comprehensively (SCAN, SAPS, SANS) at baseline and after 1 and 2 years by independent researchers.

Results: At 1-year follow-up, data from hospital records was available for 93% of the patients. A total of 419 (77%) participated in 1-year follow-up interviews. Patients in integrated treatment had better outcome concerning positive and negative symptoms, which was not explained by more patients receiving antipsychotic medication. Patients in integrated treatment were more satisfied with treatment. More patients in integrated treatment started or continued education and more lived independently. Fewer patients in integrated treatment had co-morbid alcohol or drug abuse at 1-year follow-up, and fewer had been admitted. Patients in integrated treatment used 61 (mean) bed days during the first year of follow-up, while patients in standard treatment used 81 (mean) bed days. Results of 2-year follow-up will be presented.

Conclusion: The study adds to the evidence of the effectiveness of Assertive Community Treatment, and the results indicate that this treatment model, slightly modified with more focus on elements of special relevance for the population of first-episode psychotic patients, also can be implemented in this patient group with positive effects.

16. A RANDOMISED CONTROLLED TRIAL OF AN EARLY DETECTION TEAM IN FIRST EPISODE PSYCHOSIS: THE LEO CAT TRIAL

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Background: This trial is to evaluate the impact of a new Early Intervention team on pathways to care and engagement in treatment of young people with first episode psychosis. This team (LEO CAT) is part of a larger Early Intervention service, the Lambeth Early Onset (LEO) service, for young people (aged 16–35) living in an inner city London borough. The LEO service comprises a community follow-up team, an acute 18 bed Inpatient Unit, an early detection team (LEO CAT) and a research team for those at high risk of psychosis (OASIS). LEO CAT is closely linked to primary care services, provides GP training in early detection, responds rapidly to referrals and provides initial home-based acute treatment.

Methods: The LEO CAT trial involves a cluster randomisation of the 59 GP practices in Lambeth (only intervention practices receive the services of LEO CAT). A survey of GP knowledge and practice in early psychosis has been undertaken already and will be repeated at the end of the trial. All first episode psychosis patients referred to mental health services in Lambeth (LEO CAT or standard services) are followed up by the LEO service for two years. Measures of Duration of Untreated Psychosis, Pathways to Care, psychopathology, co-morbidity, social functioning, insight, engagement and treatment adherence are conducted at entry and at 18 months follow-up.

17. NEUROCOGNITIVE ABNORMALITIES IN EARLY AND LATE PRODROMAL PHASES-EVIDENCE FOR A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Background: Two major goals of prospective high-risk research are to study the unfolding of the illness and to identify biobehavioral risk factors.

Methods: To contribute to these goals under the restricted conditions of a cross-sectional design, neurocognitive profiles were investigated in five samples: $N = 179$ healthy controls, $N = 38$ patients in the early prodromal phase, $N = 90$ patients in the late prodromal phase, $N = 86$ first-episode (FE) patients, and $N = 88$ patients with >1 episode. Prodromal patients in the early phase were defined by self-perceived neurocognitive abnormalities (basic symptoms) or decline in psychosocial functioning and one more risk factor (first-degree relative with schizophrenia spectrum disorder or obstetric complications). The late prodromal phase was defined by attenuated positive symptoms and/or Brief Limited Intermittent Psychotic Symptoms (BLIPS) following international consensus criteria. The neurocognitive test battery comprised scores for pattern recognition, attention, spatial working memory,

verbal and visual memory, and verbal and conceptual executive functions.

Results: Results showed that clinically defined prodromal patients were already selectively disturbed in verbal executive and memory functions. When compared with the early phase patients in the late prodromal phase demonstrated additional attentional deficits (primarily with verbal stimuli). FE-patients presented a generalized neuropsychological deficit profile with further decline in more chronic patients. Group differences were influenced by demographic, psychopathological, and psychopharmacological effects, but could not be explained by these factors.

Conclusion: Results support a neurodevelopmental model of schizophrenia and a progressive course of the illness. The observed neurocognitive abnormalities are consistent with a primary affection of left frontotemporal networks in the prodromal phase.

18. PREMORBID FUNCTIONING AND OUTCOME IN FIRST EPISODE SCHIZOPHRENIA

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Background/objective: Kraepelin and Blueler suggested that early subtle manifestations of schizophrenia can be present for many years before formal diagnosis and that the severity of these is associated with outcomes in schizophrenia. Empirical support comes primarily from small samples using retrospectively collected data. This study aimed to test the hypothesis using data from two distinct sources: (a) population-based cohort and (b) from the largest treatment cohort of first episode psychosis.

Methods: The population-based cohort is from the Israeli Draft Board Registry, which contains measures of intellectual and behavioral functioning for 17 year olds, which was merged with the National Psychiatric Hospitalization Case Registry. The association between functioning prior to first hospitalization and pattern of hospitalizations was examined for persons who had been tested at least 1 year prior to their first hospitalization for schizophrenia ($N = 996$). The treatment cohort is from a multi-center international drug trial of 534 patients suffering early episode psychosis. Patients were to be treated for at least 1-year (median = 205 days). Measures included the Cannon-Spoor Premorbid Adjustment Scale (PAS), PANSS, CGI severity of illness, a cognitive battery and the Extrapyramidal Symptoms Rating Scale (ESRS).

Results: In both cohorts, functioning prior to first episode was associated with outcomes. In the population-based cohort, fewer inpatient days per year and single versus multiple admissions were associated with better pre-first hospitalization functioning. In the treatment cohort, better premorbid functioning was associated with improvement on the PANSS total, CGI severity, cognitive functioning and ESRS.

Conclusion: Premorbid functioning may be useful for prognostic subtyping and may represent a specific biological process with phenomenological correlates.

19. COMPARISON OF INCLUSION CRITERIA FOR AN EARLY DETECTION OF PSYCHOSIS STUDY CROSS DIFFERENT COUNTRIES—FIRST RESULTS FROM THE EUROPEAN PREDICTION OF PSYCHOSIS STUDY, EPOS

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Background: First results from early detection and intervention in psychosis studies utilising the Melbourne 'ultra-high risk' approach indicated that the majority of subjects were included on the basis of attenuated psychotic symptoms (APS). Yet, psychopathology was not assessed consistently across the centres.

Methods: EPOS, funded by the European Commission within the Fifth Framework Programme 'Quality of Life and Management of Living Resources', is the first trans-European multicentre study in that field and aims at establishing a foundation for an integrative early detection network in Europe. In line with the 'ultra-high risk' approach, subjects are included on basis of attenuated and transient psychotic symptoms assessed with the SOPS and the combination of familial risk and/or schizotypal personality disorder plus 30%-reduced functioning. In addition and extending the 'ultra-high risk' approach, a risk-enriched criterion of having 2 of 9 cognitive basic symptoms was included. The distribution was examined of these inclusion criteria across approximately 200 persons included in this prospective naturalistic field study by the centres of the four participating countries (Germany, Finland, The Netherlands and UK) in the light of the different health care systems and awareness campaigns.

Results: Of the 35 subjects included in the German centres by September 2003, only 51.4% presented themselves with APS probably reflecting the effects of a large, established awareness campaign. At the same time, of the 33 subjects included in the Finnish centre from patients attending psychiatric care, 84% presented themselves with APS.

20. INCIDENCE OF PATIENTS VULNERABLE TO PSYCHOSIS: RESULTS OF THE EPOS PROJECT

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Background: Because of low incidence and high number of false-positive cases, interventions for preventing the onset of psychoses in the general population seem not to be feasible. A more promising approach is to detect subjects vulnerable-to-psychosis (VPT) from the patients attending psychiatric care. Within the European Prediction of Psychosis Study (EPOS), Turku EPOS Group has developed a model for detecting VPT subjects from the psychiatric outpatient population.

Methods: Consecutive 16- to 35-year-old psychiatric outpatients of the Turku Centre fulfilled a screening instrument (PROD screen) and gave written a description about the symptoms they were suffering from. On the basis of descriptions, the senior researchers made a decision for further examinations in which the VTP was defined by severity and frequency of currently occurring Basic Symptoms and/or SIPS/SOPS positive symptoms.

Results: About 24% of the 600 screened patients, starting their new outpatient treatment period, were assessed to be possible VTP subjects. In further examination, 63% of them were assessed to be at current risk of psychosis (ACROP).

Conclusion: This means that 15% of psychiatric patients starting their outpatient treatment period are ACROP subjects and, in addition to their usual psychiatric treatment, may also require a special interventions for preventing the onset of psychotic episode.

21. REDUCTION OF NAA/CHOLINE AND NAA/CREATINE RATIOS IN THE TEMPORAL CORTEX IN PATIENTS WITH A PRODROMAL PHASE OF SCHIZOPHRENIA

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Background: In recent years, different research groups have focussed on the prodromal phase of schizophrenia. However at present, no test exists that could predict if one subject with prodromal symptoms will develop the full-blown disease. Neurobiological parameters, which can be measured in vivo like magnetic resonance spectroscopy (MRS), might be useful for predicting future schizophrenia. Some studies show alterations of neuronal function in several cortical and subcortical regions in schizophrenia by MRS.

Methods: In this study, 9 subjects showing prodromal symptoms of schizophrenia, 7 subjects with DSM-IV schizophrenia and 26 healthy subjects were enrolled. We performed MRS and examined ratios of *N*-acetyl-aspartate (NAA)/choline (Cho), NAA/Creatine (Cr) in the left temporal cortex.

Results: A significant influence of diagnosis was found for the NAA/Cho-ratio ($F=4.68$, $p=0.02$) and NAA/Cr-ratio ($F=5.75$, $p=0.009$). In subsequent subgroup analyses for the NAA/Cho-ratio, a significant difference between prodromal patients and controls ($P=0.036$) was revealed. There were no significant differences between schizophrenics vs. prodromes or schizophrenics vs. controls. The subgroup analyses for the ratio NAA/Cr revealed significant differences between prodromal patients and healthy controls ($p=0.018$) and between schizophrenics and prodromes ($p=0.032$) as well. There was no significant difference between schizophrenics and controls.

Conclusion: In summary, we could show that ratios of NAA/Cho and NAA/Cr were reduced in prodromal schizophrenia. These data suggest that MRS could be used to detect the prodromal phase of schizophrenia.

22. CONSTRUCT VALIDITY OF THE SCHIZOPHRENIA PREDICTION INSTRUMENT, ADULT VERSION (SPI-A)

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Background: In Germany, a time-related approach to early detection of psychosis has been adopted distinguishing between early and late prodromal stages. Therein, the early prodromal stage is defined by cognitive–perceptive basic symptoms and a state-trait combination, the late one by attenuated and transient psychotic symptoms.

Methods: For the quantitative assessment of basic symptoms, a new 40-item scale with 6 subscales, SPI-A, was developed on prospective and retrospective binary data using cluster and facette analyses. As part of the evaluation study, cross-sectional comparisons between potentially prodromal subjects ($n = 147$), and first episode patients with schizophrenia ($n = 122$) and non-psychotic affective disorder ($n = 49$) were carried out.

Results: Though partly failing significance, the schizophrenic sample showed higher subscale totals than the prodromal and, except for 'Dynamic Deficits', the affective group and, apart from 'Overstrain' and 'Dynamic Deficits', the prodromal higher ones than the affective sample. Furthermore, the scale structure was largely confirmed in the prodromal and schizophrenic sample despite the shift from binary to ordinal data. As expected, it was not confirmed in the group with non-psychotic affective disorder.

Conclusion: Thus, the internal construct validity of the SPI-A for (potential) schizophrenia was replicated, so that subscale totals can be calculated. Besides, further evidence of a good construct validity of the scale is given by the group comparison of the subscale totals, placing prodromal patients closer to patients with schizophrenia than those with mood-disorder. Results of facette analyses also indicate that the SPI-A can be further shortened to optimize the time–utility ratio.

23. THE BRUDERHOLZ STUDY: A PROSPECTIVE PILOT STUDY OF AT-RISK PATIENTS IN NORTHWESTERN SWITZERLAND

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Background: Individuals suffering from early psychosis often receive adequate assessment and treatment only after considerable delays. Besides illness-related factors, inconsistencies in the current mental health system cause such delays. General Practitioners (GPs) are often contacted first by these individuals (Lincoln et al. 1998; Addington et al. 2002). Thus, education and sensitisation of GPs about signs and symptoms of developing psychosis may shorten delays in assessment and treatment.

Methods: In a northwestern semi-urban region in Switzerland, a low threshold referral service has been established which offers assessments at GPs' practices and at patients' homes. Each GP ($n = 232$) of the catchment area, either individually or in small groups, was sensitised about warning signs of emerging psychosis. A newsletter is sent to GPs every 3 months. Simultaneously, public awareness is regularly increased by public posters and publications. Referred at-risk patients are included in a prospective study and comprehensively followed-up at monthly to 3-monthly basis, narrowly focussing on prodromal symptoms. Subjects are assessed with the SCID (DSM-IV), SPI-A, SIPS/SOPS, PANSS, PAS, an obstetric questionnaire and a comprehensive neuropsychological battery. Patients with other diagnosis serve as a control group.

24. PRODROMAL SYMPTOMS OF FIRST-EPISODE SCHIZOPHRENIA IN CHINESE PATIENTS: A NATURALISTIC STUDY IN SINGAPORE

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Background/objective: The prodrome of schizophrenia is an elusive period characterized by nonspecific symptomatology. Yet, it is a critical time of neurodevelopment offering opportunities for early diagnosis and intervention if reliably identified. Significant progress has been made in Europe, America and Australia, but few such studies exist in Asia. We thus aimed to retrospectively study prodromal symptoms of first-episode schizophrenia compared with non-psychotic patients to determine its cross-cultural validity.

Methods: Eighty first-episode Chinese schizophrenia patients from several treatment settings were studied in detail, and 70 non-psychotic patients served as comparisons. We also obtained corroborative information from family, with whom most (90%) of our patients reside. We compared results on standardized national examinations if it overlapped with the prodromal period (for 35 patients and 58 controls).

Results: Neurotic symptoms were common but mostly not specific to the prodrome. Compared to controls, the schizophrenia prodrome comprised more symptoms associated with attenuated positive (mean 1.28 (S.D.1.06) vs. 0.34 (S.D.0.63), $p < 0.001$) and negative symptoms (2.96 (S.D.1.67) vs. 0.91 (S.D.1.31), $p < 0.001$), cognitive symptoms (1.95 (S.D.1.05) vs. 0.81 (S.D.0.84), $p < 0.001$), disorganized behaviours (1.57 (S.D.1.23) vs. 0.84 (S.D.1.09), $p < 0.001$), and deterioration in role functioning (1.14 (S.D.0.69) vs. 0.37 (S.D.0.64), $p < 0.001$). Examination scores in mathematics also deteriorated more between ages 12 and 16 years in those destined to develop schizophrenia (16.02 (S.D.15.20) vs. 8.55 (S.D.15.61), $p = 0.026$).

Conclusion: Our findings are consistent with conceptualizations regarding pre-psychotic cognitive, social and functional deterioration, and support the need to develop more specific prospective strategies for identification and treatment of the prodrome in our community.

Predictors of Illness Development

25. THE P300 WAVE IN SUBJECTS AT HIGH RISK FOR PSYCHOSIS

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Background/objective: Event-related potentials provide a non-invasive method to evaluate neural activation related to cognitive and perceptual processes. Compared to controls the P300 wave in people with schizophrenia has reduced amplitude and delayed latency. Similar P300 wave deviances have been observed in the unaffected relatives of people with schizophrenia; the P300 wave may thus be an endophenotype for schizophrenia. We studied the P300 in subjects who have 'prodromal' symptoms that are associated with a high risk of transition to psychosis.

Methods: Thirteen subjects meeting PACE criteria for the At-Risk Mental State (ARMS) and 29 controls performed a P300 'oddball task'. The latency and amplitude of the P300 wave were compared between groups adjusting for age and sex using linear regression models.

Results: There was a trend ($p = 0.07$) for the P300 amplitude to be smaller in ARMS subjects [7.9 (4.1) ìV] than controls [11.1 (6.7) ìV]. There was no significant difference in P300 latency.

Conclusion: These preliminary results suggest that the P300 amplitude may be a useful premorbid marker of a vulnerability to develop psychosis. Should this be confirmed in a larger sample, the P300 might be useful in identifying people at high risk for psychosis.

26. HEALTH AND DEVELOPMENT IN THE FIRST FOUR YEARS OF LIFE IN OFFSPRING OF WOMEN WITH SCHIZOPHRENIA AND AFFECTIVE PSYCHOSES: WELL-BABY CLINIC INFORMATION

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Background: Deviations in developmental milestones and personality characteristics have been found in individuals who later develop schizophrenia (Sc) and in offspring of patients with Sc. Question remains as to the exact nature of these deviations and their specificity for Sc. The Swedish high-risk study provides a unique opportunity to study diathesis characteristics associated with these psychoses.

Methods: Offspring of women with a history of schizophrenia and affective (Aff) psychoses ($n = 84$), as well as normal-risk control offspring ($n = 100$), were studied from age 0 to 4 years, using prospectively recorded information from Well-Baby Clinic records. Blind assessment of an average of 25 contacts per subject yielded data concerning early life developmental, physical and psychosocial factors.

Results: As compared with controls, offspring of women with schizophrenia showed significantly increased rates of delayed walking, visual dysfunction, language skill disorders, enuresis, disturbed behavior (especially poor social competence), exposure to psychosocial stressors, absence of breastfeeding, multiple accumulated risk characteristics, and a trend toward more disturbed biological functions, especially in nutrition/digestion. Schizophrenia risk characteristics did not include impaired hearing, minor malformations or physical illness leading to treatment. Offspring of mothers with affective disorder showed only significantly increased rates of delayed walking and exposure to psychosocial stressors, with less total aggregation of risk characteristics. Extending schizophrenia and affective disorder 'core' risk groups to include 'spectrum' cases did not influence the results.

Conclusion: The results suggest differences in the diathesis associated with risk for schizophrenia vs. affective psychosis. The importance of these early risk characteristics for the later development of psychopathology is being investigated in this sample.

27. PREDICTING SCHIZOPHRENIA USING STRUCTURAL MAGNETIC RESONANCE IMAGING

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Methods: Data from the 213 subjects of the Edinburgh High Risk study of Schizophrenia (EHRS) were used to assess the role of

the Amygdala-hippocampal complex (AHC), the remaining temporal lobe and the thalamic nuclei in schizophrenic illness, assessing the right and left sides separately. These volumes were measured on entry to the study and expressed as proportions of the whole brain volume. This procedure was repeated in a subgroup of 86 subjects after an interval of approximately 18 months. Onset of a first episode of schizophrenic illness within subjects at high risk was assessed over a 5-year period.

Results: The left temporal lobe reduced in size over time within all study groups. However, relatively rapid decay of the left temporal lobe was observed just prior to onset in those who fell ill and these subjects then exhibited the lowest AHC proportions on the left side. High-risk subjects tended to have lower left thalamic volumes than healthy controls but these volumes were stable over time in all groups. An interaction effect was found in that high-risk subjects with relatively high left thalamic volumes did not seem to suffer illness onset on experiencing rapid temporal lobe reduction. These findings were similar but less marked on the right side of the brain.

28. REDUCTION OF SUPERIOR TEMPORAL GYRUS VOLUME IN YOUNG OFFSPRING OF PATIENTS WITH SCHIZOPHRENIA

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Background: Disturbances in thought and language are core features of schizophrenia and a faulty development of the language system has been proposed as a cause of schizophrenia. The Superior Temporal Gyrus (STG), a heteromodal auditory and language association cortex, has been consistently found to be smaller in schizophrenia. However, the genetic and/or neurodevelopmental underpinnings of STG alterations in schizophrenia are unknown. Non-psychotic children with increased genetic risk for schizophrenia exhibit language deficits but STG has not been studied in this population.

Methods: In this study, we measured right and left STG using MRI in 29 young non-psychotic offspring of patients with schizophrenia and 28 age- and sex-matched comparison subjects without family psychiatric history.

Results: Analyses of variance using GLM controlling for age and intracranial volume, showed significant differences between the groups in right STG ($F = 8.479$; $df = 1.56$; $p = 0.005$) and left STG ($F = 6.494$; $df = 1.56$; $p = 0.014$). Left STG volume showed a significant inverse correlation with age in HC (partial $r - 0.4041$; $df = 24$; $p = 0.041$) but not in HR subjects (partial $r = -0.2125$; $df = 26$; $p = 0.278$).

Conclusion: These findings provide new evidence that STG abnormalities may result from genetically mediated developmental deviance reflecting increased susceptibility. Further studies and follow up will help understand the role of STG in the premorbid vulnerability and its role in the pathophysiology in schizophrenia.

29. A PROSPECTIVE STUDY OF OFFSPRING OF WOMEN WITH PSYCHOSIS: VISUAL DYSFUNCTION IN EARLY CHILDHOOD PREDICTS SCHIZOPHRENIA-SPECTRUM DISORDERS IN ADULTHOOD

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Background/objective: Children with visual dysfunction have been characterized by increases in premature birth, low birth weight, neurological and brain abnormalities, and impaired visual perception and cognitive function, which are similar to deviations found in patients with schizophrenia and their relatives. We prospectively investigated (a) whether visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood in high-risk and normal-risk individuals, and (b) whether visual dysfunction in childhood is related to neurological abnormality at different ages.

Method: Offspring of mothers with psychosis and mothers with no history of psychosis were prospectively studied from before birth to adulthood. The subjects were assessed with a standard test of vision at 4 years of age. Neurological examinations were blindly performed in infancy and at 6 and 22 years of age. DSM-III-R Axis I and II disorders were blindly assessed at the (93%-effective, $n = 166$) follow-up at 22 years of age.

Results: In the total sample and among offspring of mothers with psychosis, both visual dysfunction at 4 years of age, and its severity, were significantly associated with schizophrenia-spectrum disorders in adulthood but no other psychiatric disorders. Visual dysfunction at 4 years of age was significantly related to neurological abnormality at 6 years of age, but not in infancy or at 22 years of age.

Conclusion: Visual dysfunction at 4 years of age selectively predicts schizophrenia-spectrum disorders in adulthood among offspring with heightened risk for psychosis; this probably reflects disturbed neurological development that is genetically mediated.

Risk Factors

30. SIGNS OF NEURODEVELOPMENTAL DYSFUNCTION IN EARLY ONSET PSYCHOSIS

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Objective: The purpose of the study is to identify premorbid developmental and adjustment variables associated with early onset psychosis as part of a prospective cohort study aimed at determining markers for the development of different psychoses.

Methods: Psychomotor, language, and learning developmental factors were collected in first episode psychosis patients consecutively admitted to an adolescent unit and matched normal controls. The Obstetric Complication Scale (OCS) and the premorbid adjustment (PAS) were also administered. Twenty-one adolescents with first-episode psychosis (diagnosed with the K-SADS) and 29 matched controls were compared at baseline.

Results: Preliminary results did not show differences between groups for psychomotor development, reading and writing or language development. More adolescents with first-episode psychosis than controls were academically underachievers (61% compared to 27%). No group differences were observed in prenatal, or at-birth obstetric complications. Premorbid disability was higher in patients than in normal controls ($p < 0.001$). Positive and Negative Symptom Scale (PANSS), and the Cannon-Spoor Premorbid Adjustment Scale (PAS) were administered to the group of patients. Preliminary data indicated significant positive correlations for total number of negative symptoms and global adjustment score during infancy ($p = 0.007$), and early adolescence ($p = 0.006$).

Conclusion: We have not been able to probe a worse developmental pattern or more obstetric complication in a group of early onset first episode psychosis compared with a group of matched normal controls. Premorbid disability was higher in patients than controls. Poor premorbid adjustment during infancy and early adolescence correlated positively with negative symptoms.

31. BEHAVIOURAL CAUTIOUSNESS IN YOUNG ADULTS BORN VERY PRETERM

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Background: Children born prematurely are at an increased risk of experiencing a variety of neurological, cognitive, and behavioural problems as they develop. A distinctive pattern of behaviour problems, characterised by high levels of activity and inattention, has been described in this population. Research concerning the adult outcome of premature birth suggests a higher than expected rate of schizophrenia.

Methods: The present study explored behavioural outcome in young adults born very preterm. We studied 41 very preterm cases and 28 term-born controls aged 17–19 years. Behavioural outcome was assessed using a semi-structured interview, which probed four aspects of psychosocial functioning: school history, antisocial behaviour, substance use and social functioning.

Results: Young adults born very preterm reported lower levels of anti-social and risk-taking behaviour than their full-term peers. The level of anti-social behaviour was particularly low in young women born preterm. Both groups gave similar responses to questions about social functioning, but there was a tendency for members of the preterm group to have experienced more bullying at school than controls.

Conclusion: The more cautious behaviour of the very preterm group was unexpected. The literature on childhood outcome of prematurity would lead one to expect high levels of problem behaviour in this population. Increased parental monitoring in survivors of preterm birth could be responsible for their low levels of aberrant behaviour. The increased frequency of anxiety and of chronic health problems reported in this population may also mediate their ability or desire to engage in anti-social or risk taking behaviours.

32. PREMORBID IQ AND THE RISK OF SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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Background: Evidence from longitudinal studies provides strong support for the notion that impaired intellectual performance assessed premorbidly, increases the risk of developing schizophrenia. Similar evidence with respect to affective disorders is less clear.

Methods: We have previously reported data from a Swedish cohort of approximately 50,000 18-year-old male conscripts followed-up until their mid-30s. Approximately 200 subjects devel-

oped schizophrenia and lower IQ emerged as a significant risk factor. We have had the opportunity to revisit the cohort so that the follow-up period total is now 27 years. Three-hundred sixty-two subjects have been given a primary diagnosis of schizophrenia, 223 other non-affective psychoses, 113 psychotic depression ($N = 113$) and 108 bipolar disorder with or without psychosis.

Results: Lower pre-morbid IQ was associated with an increased risk of developing schizophrenia (adjusted OR across a 9-point IQ scale = 1.26, 95% CI 1.19, 1.33), other non-affective psychoses (adjusted OR = 1.24, 95% CI 1.15, 1.33) and psychotic depression (adjusted OR = 1.19, 95% CI 1.09, 1.31). There was no association between IQ and risk of bipolar disorder (adjusted OR = 0.99, 95% CI 0.89, 1.09).

Conclusion: These results confirm the finding that pre-morbid IQ increases the risk of developing schizophrenia, other non-affective psychotic disorders, and psychotic depression, but suggest that the risk of bipolar disorder is not similarly increased.

33. PSYCHOPATHOLOGICAL DIMENSIONS IN THE AESOP FIRST ONSET PSYCHOSIS STUDY

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Background: There is growing evidence that psychotic symptoms segregate in psychopathological dimensions. However, previous studies on symptom dimensions have often used relatively small samples of patients with chronic psychosis. We investigated underlying psychopathological dimensions in a large epidemiological sample of patients with first onset psychosis.

Methods: We recruited 335 patients (57% female, mean age 30.1 ± 9.9, 49% DSM IV schizophrenia/schizophreniform disorder, 51% other psychotic disorder). We analysed a wide range of symptoms and signs with ratings obtained from the SCAN (WHO). A principal components factor analysis was performed on symptom scores, using Varimax rotation. An eigenvalue of greater than one was set as the criterion for the retention of factors.

Results: The factor analysis revealed six factors accounting for 51% of the variance, giving rise to the following dimensions: Factor 1, Manic dimension (14% variance) consisted of six items consistent with mania; Factor 2, Negative dimension (9% variance) consisted of four items corresponding to negative symptoms; Factor 3, Depressive dimension (9% variance) consisted of 4 depressive items; Factor 4, Reality distortion (7% variance) consisted of 6 items, delusions and hallucinations; Factor 5, Disorganisation dimension (5% variance) consisted of 3 items suggestive of disorganisation; Factor 6, Nonspecific psychotic dimension (5% variance) consisted of 4 items.

Conclusion: The pattern of item segregation shows that clustering of symptoms reported in chronic studies, emerges even in first onset psychosis.

34. UNWANTEDNESS OF PREGNANCY AND RISK OF SCHIZOPHRENIA IN CHILD. THE EFFECT OF GENDER, FAMILY HISTORY OF PSYCHOSIS, AND AGE AT ONSET

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Background/objective: Unplanned pregnancy may have harmful consequences. Earlier we reported that unwanted children had an increased risk for schizophrenia but the causal chain remained open. The aim of this study was to explore the effect of gender, family history of psychosis, and age at onset.

Method: Data were collected prospectively from the Northern Finland 1966 Birth Cohort. In second trimester of pregnancy, mothers were asked whether the pregnancy was unwanted, wanted, or mistimed but wanted. Schizophrenia diagnoses were obtained from the national register. Data on family history (FH) of psychoses in first-degree relatives were collected from hospital and outpatient notes in interviews using Family Interview for Genetic Studies (FIGS).

Results: One-hundred eleven cases of DSM-III-R schizophrenia were identified between 16 and 31 years; cumulative incidence of 0.9%, compared with 1.8% from unwanted pregnancies (OR 1.8; 95% CI 1.0–3.3). When stratified by gender, the effect persisted among females (OR 3.5, 1.8–6.8) but not among males (1.3, 0.7–2.5). Forty-four percent of the schizophrenia patients with positive FH were unwanted and had early age at onset (mean 20.6 years). Respective figure was 15% for schizophrenia subjects without FH (age at onset mean 23.1 years) and 12% for non-schizophrenia cases.

Conclusion: Unwantedness seems to be a proxy-risk factor for genetic risk. We recommend the use of FH as proxy genetic variable when examining developmental pathways to schizophrenia. Improving fertility regulation may decrease the incidence of schizophrenia.

Acknowledgments: This work was supported by the grants from the Finnish Academy, Sigrid Juselius Foundation, and the Stanley Medical Research Institute.

35. PSYCHOSES, SOCIOENVIRONMENTAL RISK FACTORS AND ETHNICITY: A CASE-CONTROL STUDY IN THE UK

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Background: Despite evidence of a genetic component in the pathogenesis of psychoses, exact multi-factorial aetiologies remain unknown. Evidence indicates an increased rate of psychoses in the African-Caribbean population in the UK, and ecological studies suggest that this may be attributable to acute exposure to socio-environmental risk factors, such as deprivation and social isolation, at the individual-level.

Methods: An unmatched case-control study (ÆSOP: Nottingham; $n=410$) to identify socio-environmental risk factors for psychoses used unconditional logistic regression to identify risk factors for psychoses. An interaction term was fitted to determine whether significant risk factors pertain especially to the African-Caribbean population.

Results: Significant risk factors for psychoses included; having no confidante [OR: 5.74; 95%C.I.: 2.37–13.91]; no contact with friends [OR: 5.27; 95%C.I.: 1.57–17.70]; being single or divorced, and; separation from parents during childhood. Evidence of interaction between childhood separation and ethnicity [$p=0.11$] suggests the African-Caribbean population may be at increased risk compared with other ethnic groups. Ethnicity could not be identified as an independent risk factor for psychoses; power was low.

Conclusion: An increased risk of psychoses is associated with restricted social networks. Although it is impossible to categorically refute reverse causality as an alternative explanation, this study presents evidence to support the literature suggesting an aetiological association between risk of psychoses and premorbid social functioning, originating in (but not limited to) childhood. There is some evidence that this risk may be particularly acute for the African-Caribbean in the UK, something to be confirmed in a larger sample.

36. ELEVATED RISK OF PREGNANCY AND DELIVERY COMPLICATIONS IN BIRTHS TO MOTHERS WITH AFFECTIVE PSYCHOSIS

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Background: The role of pregnancy and birth complications (PBCs) in the aetiology of affective psychosis is unclear. The question of whether births to mothers with affective psychosis are at increased risk of PBCs has not been investigated.

Aim: To use Swedish national registers to investigate the prevalence of five PBCs (stillbirth, neonatal death, pre-term delivery (PTD), low birth weight (LBW) and smallness for gestational age (SGA)) in births to mothers with affective psychosis.

Method: The sample comprised birth records on 5618 births to mothers with affective psychosis, and 1,552,453 births to mothers without this diagnosis, representing over 99% of births in Sweden between 1983 and 1997.

Results: There were significant elevations in risk for LBW (OR 1.36, 95% CI 1.21–1.55), PTD (OR 1.29, 95% CI 1.15–1.45), smallness for gestational age (OR 1.31, 95% CI 1.13–1.51) and stillbirth (OR 1.62, 95% CI 1.14–2.31). All associations were attenuated after adjusting for maternal age, parity, smoking, cohabitation, education level, immigrant status and pregnancy-induced hypertensive disease, with risks for LBW and PTD remaining significant. Smoking was the most important confounder for all associations. Risks for all complications except SGA were greater for mothers diagnosed during pregnancy.

Conclusion: Mothers with affective psychosis have an excess of PBCs in their pregnancies. Possible explanations for this include genetic effects, psychotropic medication, alcohol or drug misuse, or poor compliance with antenatal care. Awareness of these risks is important for general adult psychiatrists and obstetricians.

37. SEQUELAE OF UNCOMPLICATED PERIVENTRICULAR HAEMORRHAGE OR LATERAL VENTRICLE DILATATION FOLLOWING PREMATURE BIRTH IN ADOLESCENCE: IS THERE A RELATIONSHIP WITH SCHIZOPHRENIA?

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Objective: To investigate if, in children born preterm, the presence of uncomplicated periventricular haemorrhage (PVH) and PVH with ventricular dilatation (PVH+DIL) on birth ultrasound, is associated with damage in specific grey and white matter areas in

adolescence, that could account for a specific vulnerability to develop schizophrenia.

Methods: Eighty-two preterm individuals (born at < 33 weeks gestation) participated. All had an ultrasound at birth. They were divided in three groups according to ultrasound findings: 20 had PVH, 12 had PVH+DIL, 50 had a normal ultrasound (NORMAL). Magnetic Resonance Imaging (MRI) scans were collected at 14–15 years. We compared differences in distribution of grey and white matter in the three groups, using SMP99.

Results: The PVH group, compared to NORMAL, had grey matter reductions in Middle Temporal (bilaterally) and Right Superior Frontal Gyri; white matter reductions in Left Middle Occipital, Right Parahippocampal Gyri and Precuneus. PVH+DIL compared to NORMAL had grey matter reductions in Posterior Cingulate (bilaterally), Left Superior Temporal and Postcentral Gyri, Limbic Lobe. Compared to the PVH group, the PVH+DIL had grey matter reductions in the Right Posterior Cingulate, Superior Temporal (bilaterally), Left Lingual and Postcentral Gyri, and white matter reductions in the Cingulate and Middle Occipital Gyri.

Conclusion: Brain injury sustained in the perinatal stage, as detected by ultrasound, is associated with selective areas of grey and white matter changes in adolescence. The identification of direct damage on the developing brain together with the indirect or post-injury impact on other structures adjacent to the injury might help understanding the relationship between schizophrenia and obstetric complications.

38. SOCIAL DEPRIVATION, ETHNICITY AND INCIDENCE OF SCHIZOPHRENIA IN NOTTINGHAM 1997–1999

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Background/objective: African-Caribbean people in the United Kingdom have more schizophrenia and other psychoses than the white population. Social deprivation has been associated with both an increased incidence and prevalence of psychotic disorders. Our aim was to investigate the role of neighbourhood social deprivation on incidence rates of schizophrenia and other psychoses in different ethnic groups. Our hypothesis was that neighborhood social deprivation would partly explain higher rates of psychoses in the African-Caribbean population.

Methods: The Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study collected all incident cases of psychosis in Nottingham between 1997 and 1999. The population data of electoral wards by ethnicity was collected from the 1991 census. The Multiple Deprivation Index 2000 was used to summarise neighbourhood deprivation in each ward.

Results: Annual incidence rates in the white population for broadly defined schizophrenia were highest in the most deprived wards compared with the least deprived wards (19 vs. 10 cases per 100 000). Incidence of other psychoses was also higher (17 vs. 8 cases) in the most deprived areas. On the contrary, incidence rates of psychoses in the African-Caribbean population were not increased in the most deprived areas.

Conclusion: We conclude that incidences of schizophrenia and other psychoses are substantially (two times) elevated in areas with high deprivation, but there seems to be no association between deprivation and incidence in the African-Caribbean population. One possible reason is social support, which is may be higher in the African-Caribbean population in the socially deprived areas, where this ethnic group predominantly lives.

39. HELSINKI HIGH-RISK STUDY: DEVELOPMENTAL PROBLEMS PREDICT FUTURE PSYCHIATRIC MORBIDITY IN OFFSPRING OF MOTHERS WITH PSYCHOTIC DISORDER

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Objective: To investigate whether childhood developmental factors are associated with morbidity to psychotic disorders among offspring of mothers with psychotic disorders.

Methods: High-risk (HR) mothers were all females born between 1916 and 1948 who had been treated because of schizophrenia, schizoaffective disorder, or schizophreniform disorder in Helsinki before 1975 and who had given birth between 1960 and 1964. Their offspring born between 1960 and 1964 formed the HR cohort ($n = 179$). Controls comprised the previous same-sex deliveries in the same maternity hospital. Using all available information from childhood and school developmental records, we assessed the childhood and adolescence development of HR offspring and controls.

Results: We found childhood and school health cards for 159 HR and 99 control offspring. Compared to controls, HR children more often had not learned to walk by 12 months, had more psychiatric symptoms during childhood and adolescence, had more often neurological signs, and were more often socially inhibited during the school-age. HR children of mothers with schizophrenia had more often psychiatric symptoms during childhood or adolescence, and were more often socially

inhibited during the school-age compared to controls. Among HR children, we found that neurological impairment predicted later development of schizophrenia spectrum disorders. Neurological impairment, and psychiatric symptoms during childhood or adolescence predicted later development of any psychotic disorder.

Conclusion: HR children have more often developmental problems compared to control children. Childhood developmental factors predict the development of schizophrenia spectrum and all psychotic disorders among HR offspring.

40. LIFE EVENTS AMONG FIRST-CONTACT PSYCHOSIS IN SÃO PAULO, BRAZIL: A PRELIMINARY ANALYSIS

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Background: Most studies about stress and functional psychosis have focused on the association between life events and psychotic episodes, despite the position of the index episode in the disease course. The aim of the present study is to estimate the relative risk of the association between life events and first contact psychosis, considering two main diagnoses groups: schizophrenia spectrum disorders and affective disorders.

Method: This is a population based case-control study individually matched by sex and age group. All adults (18–64 years) resident in a defined catchment area who had had a first contact with any mental health service due to a psychotic episode were eligible. Psychiatric diagnosis was obtained with the SCID-I and life events were assessed with the Paykel Interview for Recent Life Events.

Results: Thirty-nine pairs of cases and controls have been included so far, of whom 22 (56.4%) men. Twenty-five (64.1%) had a diagnosis of schizophrenia spectrum disorders and 14 (35.9%) had a diagnosis of affective disorders. The OR for matched case-control pairs were 0.5 (95% CI: 0.08 to 2.34) for schizophrenia spectrum disorders and 8.0 (95% CI: 1.07 to 355.00) for affective disorders.

Conclusion: The association between life events and first contact psychosis in São Paulo seems to suggest that the stress role in the genesis of schizophrenia spectrum disorders and affective disorders might be different. A larger sample may give more precise estimates of such association.

Acknowledgments: Funded by the Wellcome Trust, UK and FAPESP, Brazil.

41. SIBSHIP COMPOSITION DURING UPBRINGING AND SCHIZOPHRENIA RISK

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Objective: The potential association between sibship characteristics and the risk of schizophrenia have been investigated by several authors [1–6]. However, methods have differed and results have been conflicting. We explore the association between schizophrenia, sibship size, the age composition of siblings, and history of half siblings, while accounting for potential confounders.

Method: We established a population-based cohort of 763 thousand people using data from the Danish Civil Registration System. Schizophrenia was identified by linkage with the Danish Psychiatric Central Register. Using the person-identifiable information on all siblings, we calculated the sibship size, ages of older siblings at birth, ages when mother gave birth to younger siblings, and the age when getting half-siblings for the first time ever.

Results: Overall, 2536 people developed schizophrenia during the 7.5 million person-years of follow-up. Only children and children with more than four siblings had significantly increased risks. This association was confounded by change of residence and urbanicity during upbringing. Children having siblings 0 to <7 and 11 to <15 years younger had a significant increased risk while children having siblings 2 to <11 and $\geqslant 12$ years older had a significant decreased risk of schizophrenia. Children with a history of half-siblings had a significant increased risk.

Conclusion: The increased risk associated with younger siblings and the decreased risk associated with older siblings in some ages had no biological plausible explanation. The increased risk in children with half-siblings may be explained by undiagnosed mental illness in these children's parents, although other explanations apply.

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42. EPILEPSY AS A RISK FACTOR FOR SCHIZOPHRENIA AND SCHIZOPHRENIA-LIKE PSYCHOSIS

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Background: Evidence has suggested an increased risk for schizophrenia-like psychosis associated with epilepsy, but little is known about differences of this risk related to age onset and type of epilepsy, and no study has been large enough to evaluate how and to what extent this risk is influenced by family histories of psychosis and of epilepsy.

Methods: Using data from Danish longitudinal registers, we established a population-based cohort of 2.1 million persons and obtained information on epilepsy, psychosis and other personal data at birth. We analyzed data with log-linear Poisson regression and adjusted for potential confounders.

Results: We found an increased risk of schizophrenia (RR: 2.90, 2.56–3.29) and schizophrenia-like psychosis (RR: 3.34, 3.05–3.67) for people with a history of epilepsy even after adjusting for potential confounders. The relative risk was similar for both men and women but it was stronger for people at higher age. Moreover, both a family history of psychosis and a family history of epilepsy were significant risk factors for schizophrenia or schizophrenia-like psychosis; and the effects of epilepsy in both the cases and family members negatively interacted with that of family history of psychosis, they were significantly stronger among persons without a family history of psychosis. In addition, the elevated risk associated with epilepsy was more pronounced for people who had their first onset of epilepsy at a higher age.

Conclusion: There is a strong association between epilepsy and schizophrenia or schizophrenia-like psychosis, and the two conditions may share common genetic or environmental causes.

43. OBSTETRIC COMPLICATIONS AS AN AETIOLOGICAL FACTOR IN MZ TWINS WITH SCHIZOPHRENIA

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Objective: The aim of this study was to explore the incidence of a history of obstetric complications (OC) in groups of monozygotic (MZ) twins varying in their concordance for schizophrenia. We hypothesized that (i) the rate of OC would be greater in pairs with at least one schizophrenic member and that (ii) OC would have a greater impact in discordant twin pairs.

Methods: Thirty-two pairs of MZ twins concordant for DSM IV schizophrenia, 21 MZ discordant pairs and 48 MZ healthy control pairs were assessed using a modified version of the Lewis Murray scale for obstetric complications. Summary scores for total complications, pregnancy, delivery and neonatal periods were calculated.

Results: Pairs in which at least one member had schizophrenia were associated with a significantly higher rate of total and neonatal complications ($p=0.002$ and $p=0.015$, respectively). The discordant twin pairs had the highest rates for total, pregnancy and delivery complication scores. A significant ordered effect (Disc>Concord>Control) was found but only for the total complications score ($p=0.008$), though a similar but nonsignificant trend was found for neonatal complications ($p=0.052$). There were no significant findings between members of the same twin pair, in particular between MZ discordant ill and their well co-twins.

Conclusion: These data suggest that OC are associated with the later development of schizophrenia in MZ twin pairs and that the impact of these complications may vary according to the twins' concordance for the illness. However, these events are likely to be nonspecific and heterogeneous in terms of the particular pathological process that they represent.

44. PRENATAL VITAMIN D DEFICIENCY CAUSES BEHAVIOURAL CHANGES IN ADULT OFFSPRING: EVIDENCE OF DOPAMINERGIC DYSREGULATION

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Background: Vitamin D and corticosterone appear to be active neurosteroids. Maternal vitamin D deficiency in rats alters brain development and causes persistent morphological, cellular and molecular changes in the brains of their offspring. Prenatal exposure to excess glucocorticoids has also been shown to disrupt brain development.

Methods: In this study, we examined the behavioural consequences in adult rats who were subject to these two early life exposures. We used 10-week-old male offspring of Sprague–Dawley rats which had been made deficient in vitamin D throughout pregnancy or given a 200-mg corticosterone pellet during the last week of pregnancy (in a 2×2 factorial design). Two specific behaviours were examined: locomotion in the open field and sensorimotor gating using prepulse inhibition (PPI) of the acoustic startle response.

Results: We found that vitamin D depletion but not prenatal corticosterone treatment caused spontaneous hyperlocomotion in the open field. There were no effects of vitamin D depletion or corticosterone on acoustic startle or PPI. However when given a low dose of apomorphine (0.5 mg/kg), the offspring of vitamin D deplete dams only displayed impaired PPI.

Conclusion: These findings suggest that vitamin D deficiency in utero may permanently alter dopaminergic functioning, producing both sensitivity to the dopamine agonist, apomorphine and spontaneous hyperlocomotion. We conclude that maternal vitamin D deficiency alters specific behaviours that appear to be unaffected by prenatal corticosterone administration.

45. INTRAUTERINE GROWTH RETARDATION (IUGR) IN SCHIZOPHRENIA

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Background/objective: Several lines of evidence suggest that adverse events during gestation are associated with an increased risk of schizophrenia. Whether or not these early events are reflected in low birthweight remains controversial. Inconsistent findings may reflect problems with maternal report, insufficient statistical power, or differences in the definition of low birthweight. The purpose of this study was to investigate the impact of maternal report and the definition of low birthweight on research findings.

Methods: Detailed maternally reported obstetric information was obtained from a large group of patients with schizophrenia ($N = 450$). For a subset of patients, obstetric information was obtained from both maternal report and hospital records.

Results: Very high correlations were found between maternal report and birth records for birthweight ($r = 0.98$) and gestational age ($r = 0.92$) and mean values were similar for birthweight (3452 versus 3448 g) and gestational age (40.0 versus 39.1). For patients, neither the proportion below 2501-g birthweight (7.1%) nor mean birthweight (3347 g) significantly differed from that of the general population (6.16%, 3400 g). Mean gestational age for patients was similar to that of the general population (39.7 versus 39.4) but patients were more likely than expected to have a gestational age of less than 37 weeks (8.9% versus 5.3%; $p = 0.03$). The percentile birthweight-for-gestational-age was also significantly lower in patients than in the general population ($p < 0.001$).

Conclusion: Birthweight in schizophrenia is lower than in the general population but this effect may be missed if gestational age is not taken into account. The present results are consistent with IUGR in schizophrenia.

46. SEASONAL FLUCTUATION OF OBSTETRIC COMPLICATIONS AT BIRTH IN PRESCHIZOPHRENIC OFFSPRING

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Background: It has been recently suggested that seasonal fluctuation in birthweight (i.e., low birthweight), one of obstetric

complications (OCs), is associated with an increased risk of schizophrenia and, on the other hand, winter birth has been established as a risk factor for the disorder. Therefore, we hypothesized that preschizophrenic offspring would also have seasonal fluctuation in the rate of OCs per se.

Methods: We obtained contemporaneously recorded, special notes of "the Mother and Child Health Handbook (MCHH)" for the 99 individuals with DSM-IV schizophrenia. We also obtained MCHHs from 234 unrelated healthy controls. As the risk period of birth, we defined winter as months, January to March, and non-winter as the remaining months. For the assessment of OCs, we extracted the detailed obstetric data from the MCHHs. The subjects who had had at least one definite OC according to the scale of Lewis and Murray (1989) were designed as the presence of a history of OC.

Results: Winter-born schizophrenia patients were found to have an approximately three-fold increased rate of OCs compared to those patients born in non-winter (OR = 2.7, 95% CI 0.8–9.0). In controls, there was no difference in the rate of OCs between the winter-born and the non-winter-born (OR = 1.2, 95% CI 0.4–3.0).

Conclusion: These findings suggest that winter birth may mediate the occurrence of OCs which in turn elevates the risk for a subsequent development of schizophrenia.

Acknowledgment: Dr. Takei would like to thank the Stanley Medical Research Institute for financial support.

47. DEAFNESS OR HEARING IMPAIRMENT: A RISK FACTOR FOR PSYCHOSIS

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Background: Deafness or hearing impairment is known to be associated with psychosis. In addition, several authors have suggested that the psychosis phenotype exists as a continuum in nature, ranging from normal to pathological experiences. Therefore, subjects from the general population can be investigated to further clarify the alleged association between deafness or hearing impairment and the development of psychosis-like experiences.

Method: A prospective cohort study was conducted, in which 7076 individuals from the general population were interviewed with the Composite International Diagnostic Interview at baseline and 1 and 3 years later (the NEMESIS study). Hearing impairment or deafness over the past 12 months was assessed at baseline using self-report measures. Incident positive psychosis-like symptoms were assessed 3 years later.

Results: Logistic regression analyses revealed that deafness or hearing impairment was strongly associated with the development of positive psychosis-like symptoms at 3-year follow-up (Hallucinations: OR 7.03 95% CI 1.57–31.43; Delusions: OR 5.46 95% CI 1.25–23.93). This association remained after adjustment for level of discrimination, childhood abuse, urbanicity, neuroticism, cannabis use, unemployment and marital status (Hallucinations: OR 6.68 95% CI 1.29–34.54; Delusions: OR 5.37 95% CI 1.12–25.83).

Conclusion: These results confirm that deafness or serious hearing impairment increases the risk for developing psychosis-like symptoms in a general population sample. These results add to the idea that perceptual abnormalities may be causally related to the formation of positive symptoms.

48. MOTHER–INFANT BONDING IN SCHIZOPHRENIC PATIENTS AND THEIR UNAFFECTED SIBLINGS

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Background/objective: Poor maternal interaction and obstetric complications are both thought to be risk factors for schizophrenia. However, it remains unclear whether such early risk factors act independently or whether there is an interaction with genetic vulnerability. The aim of this study was to examine the relationship between mother–infant bonding and prenatal and perinatal risk factors, using data collected on patients with schizophrenia and their unaffected siblings from the Maudsley Family Study.

Methods: Data on maternal bonding, prenatal stress and obstetric complications (OCs) were obtained by maternal interview and postal questionnaires for: 19 familial probands, 22 of their unaffected siblings, 30 non-familial probands and 56 of their unaffected siblings. OCs were assessed using the Lewis–Murray scale. Data on prenatal stress were obtained using a modified version of the List of Threatening Experiences Questionnaire and maternal bonding was assessed using the Mother–Infant Bonding Questionnaire. Analysis was performed using logistic multiple regression, controlling for gender and clustering observations of individuals within families to account for non-independence of measures.

Results: Mothers reported bonding difficulties for patients from the familial proband group (OR = 5.7, 95% CI: 1.46–22.38, $p = 0.01$) but not for unaffected siblings. No bonding difficulties were reported for the non-familial probands or siblings. Bonding difficulty was not explained by the presence of prenatal stress or OCs.

Conclusion: These results appear to indicate that difficulties in the early mother–child relationship may confer an increased risk for schizophrenia among children from multiply-affected families. Both maternal and child-related factors are likely to be involved.

49. HIPPOCAMPAL AND ANTERIOR CINGULATE MORPHOLOGY IN SUBJECTS AT ULTRA HIGH-RISK FOR PSYCHOSIS: THE ROLE OF FAMILY HISTORY OF PSYCHOSIS

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Background: While neuroimaging studies have consistently revealed structural brain anomalies in established schizophrenia, the mechanism (i.e. inherited vs. acquired) by which these anomalies arise is still unclear. Previously, we have reported hippocampal volume and anterior cingulate cortex (ACC) surface morphological anomalies in people at putatively ultra high-risk (UHR) for psychosis. However, these earlier studies did not examine the contribution of family history (FH).

Methods: In this paper, we examine the contribution of family history on these MRI-derived measures (hippocampal volume and ACC surface morphology) in 79 right-handed male UHR subjects (35 FH+ and 44 FH–), compared with 49 healthy male normal volunteers.

Results: Preliminary analyses showed that the UHR group as a whole have smaller whole brain volumes. In addition, those without a FH of psychosis had significantly smaller left hippocampal volumes, when compared to those with a FH. Interestingly, measures of left ACC morphology (i.e. cingulate sulcal continuity and paracingulate sulcal morphology) were also anomalous in the UHR group without a FH of psychosis, although these were only at the trend level ($p = < 0.1$).

Conclusion: These findings suggest that familial predisposition alone is not sufficient to produce anomalies in hippocampal or ACC morphology in subjects at ultra high-risk for psychosis. Indeed, it appears from our data that such a predisposition makes it less likely that anomalies will be present. This means that there may be a number of routes to 'risk for psychosis', with only some of them genetic.

Genetics

50. NIACIN TEST, PLA2 ACTIVITY AND PGE2 LEVELS IN SCHIZOPHRENIA AND IN MOOD DISORDERS

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Background: Alterations in phospholipid metabolism have been studied in schizophrenia. Increased PLA2 activity in serum and in platelets was demonstrated in several studies. In contact with skin, niacin provokes erithema due to the liberation of prostaglandins from macrophages. Some authors found absent response to niacin more often in schizophrenia (83%) than in controls (23%). In the present study, cutaneous response to niacin.

Methods: PLA2 activity in serum and in platelets and seric PGE2 levels were evaluated in 61 schizophrenic patients, 60 mood disorders patients (40 bipolar and 20 unipolar) and 62 healthy individuals. Forty-five patients from the schizophrenia group were re-evaluated after 8 weeks of treatment with new generation antipsychotics.

Results: Niacin test poorly differentiated the schizophrenic group (26.2% with absent response) from the others (9.7% in controls and 13.3% in mood disorders; $p = 0.034$). PLA2 activity in serum was increased in schizophrenia (312 ± 117) compared to bipolar disorder (277 ± 77), depression (276 ± 105) and control groups (239 ± 75) ($p = 0.002$). PLA2 activity in platelets was also increased in schizophrenia. There were no significant differences in PGE2 among the groups. Niacin test was not able to separate a subgroup of schizophrenic patients with disturbed phospholipid metabolism, once there was not any association between absent response to niacin and PLA2 or PGE2. Absent niacin response was associated to negative symptoms in schizophrenia ($p = 0.039$). After treatment, there was a reduction in PLA2 activity (301 ± 105 before and 233 ± 49 after; $p < 0.01$), but there was not significant variation in niacin response.

51. COMT GENOTYPE AND COGNITIVE FUNCTION IN VCFS ADULTS WITH AND WITHOUT PSYCHOSIS

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Background: Velo-cardio-facial syndrome (VCFS) is a genetic disorder which is associated with chromosome 22q11 deletion, a variable clinical phenotype, and an increased risk of developing psychosis. Specific cognitive deficits include impairments in visuo-perceptual ability, problem solving and planning, and abstract and social thinking. The typically deleted region contains the gene for catechol-*O*-methyltransferase (COMT), an enzyme that degrades dopamine. Therefore, most people with VCFS have haploinsufficiency of COMT. Recent studies have suggested that a functional polymorphism of COMT ($Met^{158}Val$) influences performance on tasks of executive function and attention in patients with schizophrenia. We studied the effect of COMT genotype on global neurocognitive ability in adults with VCFS with and without psychosis.

Methods: DNA from 19 adults with VCFS (9 psychotic and 10 non-psychotic) and 22q11 deletion were genotyped for the $Met^{158}Val$ genetic polymorphism in the COMT gene that results in variations in enzymatic activity. Subjects completed a comprehensive neuropsychological test battery containing measures of intellectual ability, executive function, attention, visuospatial function and memory.

Results: Eleven subjects (58%) had the Met allele whereas 8 (42%) possessed the Val allele. There was no significant difference in allelic distribution in VCFS individuals with and without psychosis. Within the total study population, those with the Met allele performed significantly better on (1) the Silhouettes subtest of the Visual Object Space Perception battery and (2) at problem level 5 of the Tower of London test of Planning ability.

Conclusion: COMT $Met^{158}Val$ polymorphism may underlie cognitive deficits observed in adults with VCFS who have haploinsufficiency of COMT.

52. GENERALISED COGNITIVE IMPAIRMENTS IN NONPSYCHOTIC RELATIVES OF SCHIZOPHRENIC PATIENTS

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Introduction: Neurocognitive impairments have been described in relatives of schizophrenic patients, indicating that they may be an indicator of genetic liability for the disorder. This also strengthens the notion of cognitive dysfunction as a core feature of schizophrenia, as it is associated with the genetic liability for the disorder regardless of its clinical expression. However, the precise nature of these deficits is not fully clear yet. We set out to explore this issue by comparing schizophrenic probands, relatives and controls on an extensive number of functions.

Methods: Seventy-five stabilized schizophrenic patients, 43 of their nonpsychotic first-degree relatives, and 26 healthy controls were tested on a neuropsychological battery.

Results: ANCOVAs showed, after covarying out the effects of number of years of education and age, that patients performed worse than relatives and these than controls on IQ ($F = 6.59$, $p = 0.002$), verbal working memory ($F = 6.88$, $p = 0.001$), immediate ($F = 12.85$, $p < 0.0001$) and delayed ($F = 17.01$, $p < 0.0001$) logical memory and semantic fluency ($F = 3.88$, $p = 0.02$). Relatives were not significantly different from patients on visual span and WCST perseverative errors, and both did significantly poorly than controls.

Conclusion: We found that nonpsychotic relatives of schizophrenic patients differed from control subjects on a wide variety of cognitive functions. This generalised profile of impairments across multiple cognitive domains is similar to that found for schizophrenics, the difference being one of magnitude. Interestingly, our relatives performed closer to patients than controls on visual memory and WCST. Our results give support to the conceptualisation of cognitive dysfunction as a promising endophenotype of schizophrenia.

Acknowledgments: This work has been funded by *Fundació La Marató de TV3* de Catalunya.

53. HOMER 1A INDUCTION: A NOVEL SIGNAL TRANSDUCTION SYSTEM DIFFERENTIALLY AFFECTED BY TYPICAL AND ATYPICAL ANTIPSYCHOTICS? IMPLICATION FOR D2 RECEPTOR BLOCKADE

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Background: Dopamine D2R blockade is considered a crucial mechanism for the onset of antipsychotic effects and experimental evidence suggest that this may be true at least partially for the new generation of antipsychotics. Homer is a family of proteins at glutamatergic postsynaptic density, a highly specialized structure

for signal transduction and receptor trafficking. Constitutive forms (Homer 1b/c, Homer 2) and an inducible form (Homer 1a) have been described for this gene. A differential effect on Homer 1a by typical and atypical antipsychotics has been reported (de Bartolomeis et. al, 2002).

Methods: Sprague–Dawley rats were injected i.p. with haloperidol (0.8 mg/kg), clozapine (20 mg/kg), ziprasidone (4 or10 mg/kg) or vehicle and sacrificed after 90 min.

Results: Quantitative molecular imaging of Homer 1a, by means of in situ hybridization, detected a statistically significant increase of Homer mRNA in the dorsolateral caudate–putamen of haloperidol and ziprasidone 10 mg/kg groups (ANOVA: $p < 0.001$). Homer 1a expression in clozapine 20 mg/kg and ziprasidone 4 mg/kg treated animals was significantly lower than in the haloperidol group.

Conclusion: These results: (1) demonstrate that ziprasidone 4 mg/kg and clozapine 20 mg/kg (considered in the range of doses with demonstrated antipsychotic feature in preclinical models) significantly separate from haloperidol 0.8 mg/kg with respect to Homer induction; (2) expand the possibility that Homer signal transduction system may be differentially affected by typical and atypical APS and (3) suggest a potential involvement of dopamine D2 R blockade in Homer 1a induction. The study was partially supported by an unrestricted grant from Pfizer Italia.

54. AN ASSOCIATION STUDY OF THE CYP1A2 C-164A AND T-3591G POLYMORPHISMS AND RESPONSE TO CLOZAPINE

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Background: The cytochrome P450 enzyme CYP1A2 is involved in the metabolism of several psychotropic agents, including clozapine (Aitchison et al., 2000a). There is wide interindividual variation in CYP1A2 activity (Aitchison et al., 2000a), and several polymorphisms in *CYP1A2* have been identified, including SNPs in the 5′ flanking region (Aitchison et al., 2000b).

Methods: We have investigated the association with the intron 1 *CYP1A2* polymorphism ($C_{-164}A$, Sachse et al., 1999), and the $T_{-3591}G$ SNP with response to clozapine, determining the frequency of the SNPs by PCR-RFLP analysis in 282 Caucasian patients treated with clozapine.

Results: Analysis by genotype and by allele gave no significant association between response and the $C_{-164}A$ or $T_{-3591}G$ alleles. In addition, haplotype analysis showed no significant association between a particular haplotype of the two *CYP1A2* polymorphisms and response. The genotypic distribution for the $C_{-164}A$ results was in Hardy–Weinberg equilibrium, and the allele frequencies for the $C_{-164}A$ SNP were A = 0.69, C = 0.31, and for the $T_{-3591}G$ SNP were T = 0.84, G = 0.16.

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55. PROTEOME ANALYSIS OF ANTERIOR CINGULATE CORTEX IN MAJOR PSYCHIATRIC DISORDERS IN THE 6–9 IMMOBILISED PH GRADIENT

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Background: The basis of cytoarchitectual changes observed previously in the anterior cingulate cortex (ACC) in schizophrenia, major depressive disorder (MDD) and bipolar disorder (BPD) are not known but may be revealed using proteomic methods. Improved protein separation may be achieved using newly developed narrow range pH gradients such as those covering the 4–7 and 6–9 pH ranges.

Methods: This study used two-dimensional gel electrophoresis (2DGE) and mass spectrometry to compare and identify disease-specific protein changes in schizophrenia, MDD, and BPD in the ACC. Immobilised pH gradients (IPG) of 6–9 were used on the Stanley Foundation Brain Consortium brain series (comprising 15 subjects per group from each of MDD, BPD and schizophrenia). Groups are well matched for important confounding variables. Gel image analysis was undertaken using the software Progenesis 2003.1 (NonLinear Dynamics). Data was analysed using ANCOVA.

Results: In the IPG 6–9 gels, 18 spots, present in 40 or more cases, were found to be differentially expressed within the disease groups. Of these, three have been identified so far using peptide mass profiling by MALD-TOF-MS. These are carbonic anhydrase I, flavin reductase and neuronal protein NP25. Altered expressions of two forms of fructose biphosphate aldolase (identified as a candidate protein in a previous proteomic investigation) were observed at trend level.

Conclusion: Our findings replicate and extend the findings of previous proteomic analyses. The potential role of these proteins in the pathophysiology of these brain disorders will be explored further.

Acknowledgments: This research is funded by the Stanley Medical Research Institute and the Wellcome Trust.

56. GENETIC MARKERS ASSOCIATED WITH SCHIZOPHRENIA ON CHROMOSOME 8 CAN PREDICT SPECIFIC BRAIN ABNORMALITIES WITH MAGNETIC RESONANCE IMAGING

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Background/objective: Genetic linkage studies of schizophrenia on chromosome 8p21–22 have provided replicated evidence for the presence of a schizophrenia susceptibility locus. Neurobiological correlates of this genetic variant of schizophrenia have not been reported previously. The present study aimed to identify marker alleles specific to chromosome 8 variant schizophrenia and determine if the presence of these alleles predicts differences in brain morphology.

Methods: We used allelic association studies to fine-map a schizophrenia susceptibility locus on chromosome 8p22 and applied voxel based morphometric analysis of structural magnetic resonance scans to test if expression of chromosome 8p22 marker alleles influenced regional distribution of cerebral grey and white matter in patients with schizophrenia. Significant allelic association was tested in four populations using marker-to-marker linkage disequilibrium and extended transmission disequilibrium tests. Significant differences in global and regional cerebral tissue compartments were examined using unbiased voxel-wide multiple regression analysis of control and schizophrenic patient groups.

Results: Specific alleles at three marker loci were found that allowed selection of a group of chromosome 8p22 associated schizophrenics from a comparison group of non-chromosome 8p22 schizophrenic subjects. Analysis of magnetic resonance imaging scans from the two patient groups and controls showed that chromosome 8p22 associated schizophrenia predicted reduced orbitofrontal cortex grey matter volume compared to non-chromosome 8 schizophrenia or controls. Conversely, non-chromosome 8 schizophrenia predicted reduced in grey matter volume temporal lobe cortices, including the temporal pole, hippocampus and inferior temporal cortex.

Conclusion: The findings indicate that genetic variation in susceptibility to schizophrenia is also expressed in morphometric variation in cortical grey matter.

57. THE DEFICIT SYNDROME OF SCHIZOPHRENIA AND NEUREGULIN1

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Background: Recent genetic studies have suggested a dysfunction of the neuregulin1 gene as a possible risk factor for schizophrenia (Stefansson et al., 2002). The association of neuregulin1 with NMDA glutamate receptors in the brain suggests glutamate dysfunction in schizophrenia. Blockade of NMDA receptors induces schizophrenia like symptoms including negative symptoms and cognitive impairment. Patients with the at-risk neuregulin1 haplotype might therefore be expected to show more negative symptoms than patients without an association to the at-risk haplotype and a more severe form of the illness.

Methods: Case records of 200 patients who took part in a molecular genetic study equally divided in relation to the at risk haplotype were examined and a diagnosis of Deficit or Non-Deficit schizophrenia was made as a marker for persistent negative symptoms. In addition, other clinical markers for the severity of illness and demographic information were collected.

Results: Preliminary results indicate that patients with an association with the neuregulin1 haplotype are more likely to receive a diagnosis of the deficit syndrome, have an earlier age of onset, are more likely to be on depot medication, are more likely to live in assisted accommodation and receive disability benefits at an earlier age.

Conclusion: A possible dysfunction of the neuregulin1 gene may be associated with a more severe form of schizophrenia.

Reference

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58. ANALYSIS OF DOPAMINE DRD2 GENE AND NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIC PATIENTS

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Background/objective: The dopaminergic system has long been implicated in the pathophysiology of schizophrenia and, more recently, in the modulation of the prefrontal activity involved in several cognitive tasks (Weinberger et al., 2000). A functional polymorphism of DRD2 gene (− 141C *Ins/Del*) has been associated with schizophrenia, suggesting that a decreased frequency of the *Del* allele may contribute to the elevation of D2 receptor density (Arinami et al., 1997). The aim of this study was (i) to test the previously described association and (ii) to analyse the influence of this polymorphism on some executive functions explored in patients with the Wisconsin Card Sorting Test (WCST) and the Trail Making Test b (TMTb).

Methods: The sample consisted of 135 schizophrenic patients who met DSM-IV criteria and 175 healthy individuals.

Results: The comparison of schizophrenic and control subjects showed that patients had a significant excess of − 141C *Ins* allele ($p = 0.003$). Likewise, and according to previous studies, patients showed an increased frequency of the − 141C *Ins/Ins* genotype ($p = 0.002$). The odds ratio for schizophrenia associated with this genotype was 2.77 (95% CI 1.38–5.62). Finally, DRD2 genotype was not associated with the performance on the WCST and TMTb in patients.

Conclusion: Our results seem to indicate a moderate implication of the DRD2 gene in the vulnerability to schizophrenia. However, more extensive studies should be conducted in order to clarify the involvement of this gene in prefrontal functioning both in patients and healthy individuals.

Acknowledgements: This work was supported by the *Fundació Seny* and the *Fundació La Marató de TV3* (Spain).

59. A DHPLC INVESTIGATION OF GENOMIC SEQUENCE OF PROTOCADHERIN X/Y, A CANDIDATE GENE-PAIR FOR SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: Protocadherin X and Protocadherin Y (PCDHX and PCDHY) are cell-surface adhesion molecules expressed predominantly in the brain. The *PCDHX/Y* gene-pair was generated by an X–Y translocation approximately 3 million years ago that gave rise to the *Homo sapiens*-specific region of Xq21.3 and Yp11.2 homology. Genes within this region are expected to code for sexually dimorphic human characteristics, including for example cerebral asymmetry—a dimension of variation, which has been suggested is relevant to psychosis.

Methods: We examined differences in 214 patients with schizophrenic or schizoaffective psychosis in the genomic sequence of 4192 bp coding and 3544 bp flanking non-coding sequence of *PCDHX* and 4035 bp coding and 3050 bp flanking non-coding sequence of *PCDHY* using Denaturing High Performance Liquid Chromatography (DHPLC).

Results: Three coding variants were detected in *PCDHX* and two in *PCDHY.* However, none of the detected polymorphisms nor the intronic variants could be related to psychosis within families. Low-sequence variation suggests selective pressure against sequence change in modern humans in contrast to the structural chromosomal and sequence changes including fixed X–Y differences that occurred in this region earlier in hominid evolution.

Conclusion: Our findings exclude sequence variation in *PCDHX/Y* as relevant to the aetiology of psychosis. However, we note the unusual status of this region with respect to X-inactivation. Methylation studies of the 5′ end of the gene-pair are underway, using genomic DNA from affected families and monozygotic twins.

60. BRAIN MORPHOMETRY, GENE MAPPING AND DNA POLYMORPHISMS: A MULTIDISCIPLINARY APPROACH TO THE STUDY OF SCHIZOPHRENIA

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Background/objective: Many genomic loci have been described to be associated with schizophrenia. Furthermore, there is a huge number of human genes related to neurogenesis. We compiled the following data to pursue the hypothesis that schizophrenia is a neurodevelopmental disorder.

Methods: We selected 11 candidate genes and genotyped 47 controls and 69 schizophrenic patients of a Brazilian cohort for polymorphisms in these genes. The polymorphisms selected include seven coding SNPs (Single Nucleotide Polymorphisms),

observed in genes: JAG2, WIF1, REELIN, PCDH12, PCDHB11, SMPD1, BDNF; two non-coding SNPs (WNT7a, WNT3a); one insertion in a 3′ UTR region (NOGO); and one polymorphic CAG repeat (RAI1).

Results: The allelic and genotype analysis between controls and schizophrenic patients detected association close to statistical significance between heterozygous (G/A) and homozygous (G/G) individuals for a polymorphism in the JAG2 gene ($p = 0.06$) and for a higher presence for the A allele in schizophrenic patients for the PCDHB11 gene ($p = 0.057$). When MRI data were included in our analysis many significant statistical associations were obtained, such as: Frontal Gyrification Index (GI) alterations in individuals who were heterozygous (G/A) for the JAG2 gene ($p = 0.03$); alterations in ventricular volumes in heterozygous (C/G) and homozygous (G/G) individuals for the REELIN gene ($P = 0.01$) and GI asymmetry for heterozygous (G/A) individuals for the PCDH12 gene ($P = 0.008$). In a next step of this study, the cumulative effect of the simultaneous presence of these polymorphisms associated with schizophrenia will be evaluated. An increase in our sample size will permit the validation of the consistency of these preliminary findings.

Financial support: CNPq, FAPESP, ABADHS, Applied Biosystems.

61. COMT GENE POLYMORPHISM AND BRAIN METABOLISM (18FDG PET) IN SCHIZOPHRENIA

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Background/objective: Dopamine is postsynaptically broken down by catechol-*O*-methyl transferase (COMT). The genetic polymorphism at codon 158 of the COMT gene (22q11.2) influences COMT catalytic activity. COMT Val/Val genotype is able to inactivate released dopamine more rapidly comparing with the Met/Met genotype. The influence of COMT polymorphism is more important in prefrontal cortex than in striatum. Decreased prefrontal glucose metabolism is connected with negative symptoms and cognitive dysfunction of schizophrenia. The goal of our study was to determine the role of COMT polymorphism and dopamine action in the prefrontal metabolism and information processing.

Methods: We tested the hypotheses whether COMT polymorphism regulates the prefrontal metabolism and if it is involved in psychopathology and cognitive outcome in a group of schizophrenic subjects ($n = 45$). The resting metabolism was evaluated by the ^{18}fluoro-deoxyglucose positron emission tomography (PET) and DNA analysis was based on polymerase chain reaction determining the Val–Met polymorphism in the COMT gene.

Results: In the subgroup of Met/Met homozygotes, we found a higher glucose metabolism in dorsolateral prefrontal metabolism bilaterally (Inferior Frontal Gyrus, Brodmann area 9 and 47, $p = 0.001$) comparing with the Val/Val subgroup. In addition, the cognitive outcome was influenced by the COMT polymorphism.

Conclusion: Our data confirm the hypothesis that a higher dopamine level (given by the Met/Met COMT allele) is connected with a higher metabolism in prefrontal cortex and with a better cognitive outcome in schizophrenia. These results have diagnostic and treatment implications.

Acknowledgments: This project was supported by the grant CNS LN00B122 MSMT CR and IGA NF/6033-3/2000 MZ CR.

62. A GENETIC ASSOCIATION BETWEEN THE KPNB3 LOCUS AND SCHIZOPHRENIA IN A CHINESE POPULATION

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Background/objective: In a recent study, rs626716, a single nucleotide polymorphism (SNP) of a T to C base change at the KPNB3 locus on 13q32, was found to be associated with schizophrenia in a British population. To validate further this initial finding, the present work was designed to detect three KPNB3 SNPs, including rs2761072, rs626716 and rs624066, as described in the previous study, among a Chinese population.

Methods: We totally recruited 202 Chinese family trios consisting of fathers, mothers and affected offspring with schizophrenia.

Results: The transmission disequilibrium test (TDT) showed that of three SNPs detected, rs627216 was significantly associated with schizophrenia ($\chi^2 = 8.99$, $P = 0.003$), but the other two did not show allelic association with the illness. Of 404 parents, 178 were heterozygous at rs626716. These heterozygous parents had transmitted 69 T-alleles and 109 C-alleles to their affected offspring.

Conclusion: The present results give strong evidence supporting the hypothesis of a KPNB3 association with schizophrenia.

63. EXPRESSION PATTERNS OF OCT6 AND ITS ASSOCIATION WITH GFAP AND APOE IN THE TEMPORAL LOBE AND ANTERIOR CINGULATED CORTEX IN SCHIZOPHRENIA AND DEPRESSION

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Background: OCT-6, a POUIII domain transcription factor—is associated with neural development. In rodent brain, it is expressed in migrating cortical neurons but is gradually turned off postnatally such that expression is absent in older adults. We have recently shown ectopic neuronal expression of OCT-6 in brains of schizophrenic patients but not in matched controls. This study attempts to replicate this observation using specimens from the Stanley foundation consortium, to discover regulatory targets of OCT-6, and to investigate other genes known to be abnormally regulated in neurological brain conditions, such as GFAP and APOE.

Methods: OCT-6 expression was examined in paraffin and fresh frozen cryostat sections from temporal lobe (TL) and anterior cingulated cortex (ACC) in 15 schizophrenic, bipolar disorder (BD), manic depression (MD) subjects and 15 matched controls using IHC and ISH. GFAP and ApoE expression was also studied in the TL and ACC in schizophrenic and matched control specimens by ISH and immunofluorescence experiments respectively. Candidate gene expression was studied using reporter constructs transfected into heterologous cells in vitro.

Results: Extensive OCT-6 immunoreactivity and mRNA was present in TL and ACC in the majority of schizophrenic (14 out of 15), BD (10 out of 15) and MD (13 out of 15) cases, whilst there were 4 out of 15 matched controls that expressed OCT6 immunoreactivity and/or mRNA. GFAP and *ApoE* expression was wide in the TL and ACC of both schizophrenic and control specimens. Interestingly, there was a distinct cellular co-localization between OCT6 and *ApoE* with OCT6+ve/*ApoE*+ve neurons to be found predominantly in the schizophrenic specimens but not in the few controls that expressed OCT-6. This subpopulation of OCT-6+ve/*ApoE*+ve cells was GFAP-ve suggesting that ApoE is also expressed in neurons. Reported constructs revealed two novel genes, *Epsti1* and *LRRC14*, that are regulated by OCT-6.

Conclusion: Presence of Oct-6 expression in schizophrenia, BD and MD but only in a few controls confirmed our initial finding of OCT-6 up regulation in psychotic brain. The cellular localization pattern between OCT-6 and *ApoE* suggests an association between the expression of these two genes. The identification of two novel downstream neuronal targets of OCT-6 may provide clues to the developmental aetiology of schizophrenia.

Acknowledgment: This study was supported by The Stanley Medical Institute.

64. PATTERNS OF FAMILIAL TRANSMISSION OF PSYCHOTIC DIMENSIONS IN A GENERAL POPULATION TWIN STUDY

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Background: Previous work has suggested that the positive and negative symptoms of psychosis can be measured in both clinical and non-clinical samples in which they show similar patterns of genetic transmission. However, as these dimensions of psychosis are strongly correlated with each other, any study investigating their pattern of familial transmission should take into account their considerable co-variation and demonstrate specificity and independence of transmission.

Methods: Two-hundred and thirty female twin pairs (140 monozygotic and 90 dizygotic) were randomly selected from the East Flanders Prospective Twin Survey. Sub-clinical psychotic experiences were assessed with the CAPE, a 42-item self-report questionnaire, constructed to measure (sub)-clinical psychotic experiences in the general population. Regression analyses were used to validate familiality of transmission and to test transmission specificity and independence.

Results: Familiality of transmission of positive and negative psychotic symptoms was confirmed. The familial transmission of each dimension was also found to be specific and independent of the other.

Conclusion: The present study affirmed the pattern of familial transmission and demonstrated the specificity and independence of the familial transmission for both positive and negative psychotic experiences, suggesting familial, presumed genetic, homotypia and etiological distinctness of positive and negative psychotic experiences in the general population, that may be continuous with clinical psychotic disorder.

65. ASSOCIATION STUDIES BETWEEN DRD2, DAT AND COMT GENETIC POLYMORPHISMS AND SCHIZOPHRENIA

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Background/objective: Dopaminergic genes are targets in the studies of susceptibility to schizophrenia. We have previously investigated the ser-9-gly polymorphism in the dopamine D3 receptor gene between 141 schizophrenics and 189 matched controls. No allelic or genotypic association was found. The aim of the present study is the investigation of the potential contributions of the Taq1 A Dopamine D2 Receptor (DRD2), Dopamine Transporter (DAT1) and G1947A (Val108/158Met) Catechol-*O*-Methyltransferase (COMT) polymorphisms to the susceptibility for schizophrenia.

Methods: We analysed the Taq1 A DRD2, DAT1 and COMT Val108/158Met variants distribution in a sample of 210 DSM-IIIR schizophrenic patients and 226 sex-, age- and ethnic-matched controls.

Results: No differences were found in either allelic (DRD2: $\chi^2 = 0.24$, $p = 0.62$; DAT: $\chi^2 = 8.82$, 7*df*; $p = 0{,}26$; COMT: $\chi^2 = 0.19$, $p = 0.66$) or genotypic (DRD2: $\chi^2 = 0.91$, $p = 0.63$; DAT: $\chi^2 = 12.12$; 4*df*; $p = 0.51$; COMT: $\chi^2 = 2.9$, $p = 0.23$) distributions.

Conclusion: These data do not support relevant contributions of the genetic variants analysed to schizophrenia susceptibility in our sample.

66. EFFECTS OF HALOPERIDOL ON SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN SCHIZOPHRENIC PATIENTS

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Background: Previous studies had reported that serum brain-derived neurotrophic factor (BDNF) levels were decreased in chronic schizophrenic patients [Toyooka et al., 2002]. Recent evidence suggests that BDNF might be involved in antipsychotic action in the central nervous system, and some researchers have reported that prolonged treatment with haloperidol significantly down-regulates hippocampal BDNF protein level. However, it is unknown whether this antipsychotic drug has the similar effect on the peripheral system. In this study, we attempted to investigate the potential effect of haloperidol on patient's serum BDNF level.

Methods: A case control study was performed on 22 chronic schizophrenic patients, under haloperidol treatment, and 22 normal controls, age and sex matched. BDNF level was measured by two-site enzyme immunoassay (ELISA) method. No differences were found in the BDNF level between patients (41.46 ± 10.72 ng/ml) and controls (38.41 ± 7.55 ng/ml).

Conclusion: Further research is under way to more fully understand the effect of drug treatment on serum BDNF levels and whether drug treatment normalizes serum BDNF levels.

Reference

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67. GENDER DIFFERENCES IN AGE AT ONSET IN SCHIZOPHRENIA: A META-ANALYSIS AND META-REGRESSION EXAMINING THE EFFECTS OF FAMILY HISTORY AND STUDY DESIGN

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Background/objective: Previous studies have shown that male gender and positive family history tend to confer an earlier age at onset (AAO) in schizophrenia. We aimed to derive pooled estimates of the gender difference and family history difference in AAO.

Methods: A search of the Medline and Web of Science databases, from 1987 to 2001, was performed and the resulting papers were examined. Studies were only included if diagnoses used ICD-9, DSM-III-R or later versions. Forty-six studies reported separate AAO for each gender and 13 reported AAO

for subjects with and without a family history of schizophrenia. A random-effects meta-analysis was performed to obtain pooled estimates of age differences by gender and family history. A meta-regression analysis examined the impact of heterogeneity between studies on gender difference (diagnostic system, inclusion of schizoaffective disorder, prospective, retrospective and first-onset study designs, and economic development (developing/developed country)).

Results: Males became ill 2.5 years (95% CI 1.8–3.1) earlier than females, and this gender difference was greater for studies reporting earlier AAO. Subjects with a positive family history of schizophrenia had a slightly earlier age of onset in males (1.5 years, 0.1–2.9) but this effect was much greater in females (4.7 years, 3.0–6.4). Differences in study design did not affect estimates of gender difference.

Conclusion: The analysis confirmed that males have an earlier onset than females. This effect seems independent of study design. The interaction between gender and genetic effects could be explained by a late-onset, non-genetic subtype of schizophrenia, which is more common in females.

68. GENETIC LOADING IN SCHIZOPHRENIA IN RELATION TO THE AT-RISK HAPLOTYPE OF THE NRG1 GENE

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Background: Recent genetic studies have found an association between schizophrenia and the NRG1 gene (e.g. Stefansson et al., 2002). To assess whether or not an association with the at-risk haplotype for NRG1 is associated with a more familial form of the illness, we calculated genetic loading for probands diagnosed with schizophrenia in relation to genotype. Detailed genealogical records in Iceland make it possible to assess family history not only in first- and second-degree relatives but also in more distant family members.

Methods: Case records of 200 schizophrenic patients who took part in a molecular genetic study were examined and data collected on family history of schizophrenia. Genetic loading was calculated using a previously established method (Lawrie et al., 2001) using information about first-, second- and third-degree relatives for those patients who had a family history of psychosis. By dividing the sample into those with high and low genetic loading, we examined the relationship in relation to the at-risk NRG1 haplotype.

Results: Preliminary uncorrected analysis shows a higher genetic loading for patients with an association to the NRG1 at-risk haplotype indicating that a possible dysfunction of the NRG1 gene is associated with a high frequency of schizophrenia in relatives of affected probands.

References

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69. AN ASSOCIATION STUDY OF A SOD2 GENE POLYMORPHISM TO METHAMPHETAMINE PSYCHOSIS

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Background: Intramitochondrial superoxide dismutases 2 (SOD2) play a critical role in protecting cells against damage from free radicals for catalyzing the conversion of the superoxide radicals. On the other hand, as one of possible pathophysiological mechanisms for methamphetamine (MAP) psychosis, cell damage caused by free radicals that are derived from MAP use has been postulated.

Methods: Therefore, we explored whether a polymorphism of SOD2 would be associated with the development of MAP psychosis. We recruited 116 patients with MAP psychosis (95 males and 21 females) and 189 healthy controls (144 males and 45 females) for the study. For the MAP group, we divided them into 2 clinical subtypes: 68 patients with a transient type of psychosis (i.e., good prognosis) and 48 patients with a prolonged type of psychosis (poor prognosis), according to the course of the manifestation of psychosis.

Results: We found a significant difference in the high activity type of SOD2 gene polymorphism between individuals with transient MAP psychosis and the comparison subjects ($p = 0.033$, odds ratio (OR) = 1.82). No such polymorphism was detected in those with prolonged MAP psychosis. The association between SOD2 polymorphism and a transient type of MAP psychosis was evident in males alone ($p = 0.0057$, OR = 2.48). Male patients with transient-type psychosis had a 2.5-fold higher rate of the high activity allele compared to the male controls.

Conclusion: Our results suggest that in males but not female, a polymorphism of the SOD2 gene may be associated with the course of psychosis.

70. NEUROPSYCHOLOGICAL FUNCTIONS AMONG THE SCHIZOPHRENIA PATIENTS' RELATIVES

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Background: Neuropsychological impairment has been suggested as a manifestation of the familial predisposition to schizophrenia.

Methods: In order to study neuropsychological characteristics of brain functions among the non-psychotic relatives of schizophrenic patients and estimate the validity for the discrimination of high-risk groups for schizophrenia, 187 subjects were investigated: 109 parents, 25 sibs and 53 controls. Neuropsychological methods of Louria school were used. They included the analysis of functional peculiarities of cortical–subcortical, subcortical–frontal, subcortical–parietal–occcipital and subcortical–temporal brain regions of both hemispheres separately by parameters of audio-verbal and visual memory praxis, gnosis, speech, and attention.

Results: The results showed wide spectrum of neuropsychological abnormalities for all the studied brain regions of both hemispheres in parents and sibs as compared with controls. However, multivariate integral characteristics of function of left and right subcortical, left subcortical–frontal and left subcortical–temporal regions were the most important for the differentiation of the studied groups. Errors for the discrimination of the siblings group (high genetic risk group) and the group of controls (low genetic risk group) on the whole and taking into account the sex varied from 7% to 18%.

Conclusion: The studied neuropsychological predictors can be used for the future development of complex criteria of genetic risk for schizophrenia.

71. IL1RN GENETIC VARIABILITY IS ASSOCIATED WITH VENTRICLE ENLARGEMENT IN SCHIZOPHRENIC PATIENTS

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Background: Magnetic Resonance Imaging (MRI) studies have reported morphological and volumetric peculiarities in brains of schizophrenic patients. Two issues have been discussed in the literature: (i) whether these changes arise from an altered neurodevelopment or from neurodegenerative processes occurring in adulthood and (ii) what is the contribution of genetic factors to these abnormalities.

Methods: We analysed dorsolateral prefrontal cortex grey matter and both hippocampal and ventricular volumes in 26 DSM-IV diagnosed schizophrenic patients of Spanish origin. T1-weighted MRI scans were acquired using a 1.5 T Philips Gyroscan system. Scans were transformed into Talairach space and segmented into grey matter, white matter and CSF using Statistical Parametric Mapping (SPM). MRI data were adjusted for age and brain volume using regression parameters from a healthy control group ($n=45$). Structural measurements were expressed as residuals representing excess (if positive) or defect (if negative) illness-related volumes in the corresponding regions. IL1B and IL1RN genes, involved in neurodevelopment and neurodegenerative processes, and TP53 gene, involved in apoptotic processes, were analysed in the patient sample.

Results: We found an association between a polymorphism (intron 2-VNTR) of IL1RN gene and ventricle enlargement. Patients carrying VNTR-allele*2 showed a significant enlargement of both left ($P=0.002$) and right ($P=0.01$) ventricles. Sex and illness duration were controlled for in the analyses.

Conclusion: Our results suggest that this gene could play a role in the ventricular volumetric changes observed in schizophrenic patients.

Acknowledgment: This study was supported by Fundació "La Caixa".

72. A COMPARATIVE EVALUATION OF CANDIDATE BIOLOGICAL ENDOPHENOTYPES FOR SCHIZOPHRENIA, FROM A SINGLE COHORT

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Background/objective: Previous studies have found several neurophysiological endophenotypes that each co-vary individually with

schizophrenia. These endophenotypes have been proposed as substitutes for, or as adjuncts to, the diagnostic phenotype, in genetic analysis of the illness. Results from these studies are based on different cohorts or, when multiple results are reported, on differing paradigms, so as to make comparisons difficult. We extend these investigations to compare four neurophysiological endophenotypes (MMN, P50, P300 and antisaccade error rate), to determine whether results from a single cohort that has been tested with all paradigms are consistent with previous individual findings. We then contrast the individual features, and a weighted combination of features, to determine the best endophenotype for diagnostic group prediction.

Results: Results from all four candidate endophenotypes replicated previous findings of deficits in the patient group. The MMN, P50, and P300 features similarly replicated deficits in the family member group, although the antisaccade feature did not. There was a significant correlation between MMN and antisaccade features, and between P50 and antisaccade features, using the complete cohort. A logistic regression model, based on all four features, significantly represented the diagnostic grouping (Chi-squared = 32.9), with 80% accuracy in predicting group membership. The antisaccade feature, however, did not significantly contribute to this model.

Conclusion: A composite endophenotype, derived from this model, is proposed as a means of refining the proband and family member groups, prior to undertaking genetic analysis.

73. STUDY OF THE ASSOCIATION BETWEEN THE BDNF VAL66MET POLYMORPHISM WITH PSYCHOSIS AND NEUROCOGNITIVE PREFRONTAL FUNCTIONS

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Background: Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic factor family and promotes the development, regeneration, survival and function of neurons. BDNF mRNA levels have been found to be altered in the hippocampus and dorsolateral prefrontal cortex of schizophrenic patients compared to normal controls (Egan et al., 2003; Weickert et al., 2003). The BDNF *val66met* polymorphism was associated with poorer episodic memory and abnormal hippocampal function in schizophrenic patients, their siblings and control subjects (Egan et al., 2003). However, no genetic association between this polymorphism and schizophrenia was found.

Methods: The aim of this study was to examine in a sample of 94 discordant sibs for psychosis the effects of this polymorphism on putative prefrontal tests such as the WCST and the TMTb, plus a sustained attention task, the CPT-IP Additionally, we explored the association between psychosis and the BDNF val66met polymorphism in a family-based association study ($n = 94$ quadruplets).

Results: The BDNF genotype had no significant effect on the cognitive scores for either the affected and unaffected sibs: (i) WCST (patients: $F = 0.1$, $P = 0.9$; healthy sibs: $F = 0.4$, $P = 0.7$), (ii) TMTb (patients: $F = 0.2$, $P = 0{,}8$; healthy sibs: $F = 1.8$, $P = 0.2$) and (iii) CPT (patients: $F = 0.4$, $P = 0.6$; healthy sibs: $F = 0.2$, $P = 0.8$). The TDT analysis showed a preferential transmission of allele Val from heterozygous parents to the affected offspring ($P = 0.002$) suggesting the involvement of this gene in the vulnerability to schizophrenia.

Acknowledgment: This study was supported by the Vada and Stanley Foundation.

74. AN ASSOCIATION STUDY OF 5-HTT, CCK-A AND DRD4 GENES WITH DIMENSIONS OF AUDITORY HALLUCINATIONS

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Background/objective: Genetic studies in schizophrenia have used different strategies including the analysis of elementary phenotypes. There are several advantages to choose auditory hallucinations as a clinical phenotype. First, hallucinations are one of the most frequent symptoms (50–80%) in schizophrenic patients. Second, hallucinations are a qualitative symptom comparatively easy to measure. Third, the presence of auditory hallucinations is probably the only symptom with the possibility to have a neurobiological marker in neuroimaging studies. Beside all these arguments, some studies have found hallucinations associated to 5-HT2 polymorphism in other neurological disorder such a Alzheimer disease and epilepsy with auditory features. The aim of this study is to assess the association between auditory hallucinations in psychosis and some polymorphisms of the DRD2, DRD3, DRD4, 5HT2A, 5-HTT and CCK-A genes.

Methods: The sample consisted of 110 psychotic patients with auditory hallucinations and 98 healthy controls. Auditory hallucinations were assessed using PSYRATS scale. This scale has 11 items to evaluate different dimensions of auditory hallucinations.

Genomic DNA was obtained from peripheral blood leukocytes of each sample using standard phenol–chlorophorm method.

Results: Significant associations were found among intensity of distress related with auditory hallucinations and D4, and 5-HTT polymorphisms. Persistent hallucinations were also associated with CCK-A polymorphism.

Conclusion: Our data support the results obtained in previous studies by other groups. To our knowledge, this is the first study to establish a relationship among genetic polymorphism and specific dimensions of auditory hallucinations.

75. QUALITATIVE MRI BRAIN ABNORMALITIES IN SCHIZOPHRENIC PATIENTS AND THEIR UNAFFECTED FIRST-DEGREE RELATIVES

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Background/objective: Brain structural abnormalities are consistently reported in groups of patients with schizophrenia and may be related to the genetic predisposition for the illness. We sought to investigate whether qualitative ratings of abnormalities on MRI scans are found in excess in a large sample of schizophrenic patients and their unaffected first-degree relatives.

Methods: Hard copies of MRI scans were reviewed by experienced neuroradiologists blind to subject status for patients with schizophrenia ($n = 105$), their unaffected first-degree relatives ($n = 152$) and healthy controls ($n = 119$). Fifty-eight of the patients and 71 of the relatives came from multiply affected families. MRI scans were rated for the presence of ventricular enlargement (VE), sulcal enlargement (SE), ventricular asymmetry (VA) and congenital abnormalities (CA; including cavum septum pellucidum, congenital cysts, mega-cisterna magna).

Results: Logistic regression with robust standard errors controlling for age and gender demonstrated a trend for higher rates of VE (OR = 2.7; one-sided $p < 0.06$) and SE (OR = 1.7; $p < 0.07$) in patients with schizophrenia compared to controls. There was no difference in rates of VA or CA between the groups, and the rate of MRI abnormalities in relatives did not differ from that in controls. Patients from multiply affected families but not those from singly affected families had a significantly higher rate of VE compared to controls (OR = 3.8; $p < 0.02$).

Conclusion: These results, utilising qualitative data, support previous findings from our group suggesting that ventricular enlargement may reflect the impact of susceptibility genes for schizophrenia on brain structure, since it was found most prominently in those subjects most likely to carry such genes.

76. THE KPNB3 LOCUS IS ASSOCIATED WITH SCHIZOPHRENIA IN A BRITISH POPULATION

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Objective: We report here on the detection of 7 single nucleotide polymorphisms (SNPs) present on 13q32 among 121 British family trios consisting of fathers, mothers and affected offspring with schizophrenia.

Methods: These 7 SNPs were genotyped by using the PCR-based restriction fragment length polymorphism analysis. The transmission disequilibrium test (TDT) demonstrated that of these 7 SNPs, rs626716, a T to C base change at the KPNB3 locus, was associated with schizophrenia ($\chi^2 = 7.2$, $P = 0.07$).

Results: Of 242 parents, 20 were heterozygous. These heterozygous parents had transmitted 4 T-alleles and 16 C-alleles to their affected offspring. To further validate the rs626716 association, we analysed a haplotype system composed of 3 SNPs at the KPNB3 locus with the program TRASNMIT v2.5. The global χ^2 test showed strong association between the KPNB3 haplotype system and schizophrenia ($\chi^2 = 11.11$, $df = 2$, $P = 0.0039$), and the $1 - df$ χ^2 test for individual haplotypes showed that the rs2761072(T)–rs626716(C)–rs624066(T) haplotype was excessively transmitted by parents to affected offspring ($\chi^2 = 8.89$, $P = 0.0029$).

Conclusion: Because the KPNB3 finding has been replicated in a Chinese population, it could be hypothesized that the KPNB3 locus may contain a variant underlying schizophrenia.

77. THE UFD1L LOCUS IS ASSOCIATED WITH SCHIZOPHRENIA IN A CHINESE POPULATION

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Background: Individuals with velo-cardio-facial syndrome (VCFS) caused by chromosomal microdeletions in the 22q11 (del22q11) have a high incidence of psychiatric disorders. The del22q11 region may bear a schizophrenia susceptibility gene.

Methods: The present study was conducted with the detection of four single nucleotide polymorphisms (SNPs) located in the middle of the del22q11 region among 181 schizophrenic family trios of Chinese Han descent.

Results: The transmission disequilibrium test (TDT) showed that of these four SNPs, rs1547931 present at the UFD1L locus was associated with schizophrenia ($P = 0.021$), but the other three did not show such an association. Estimated linkage disequilibrium (LD) between paired SNPs indicated that these four SNPs were in strong LD, suggesting that the multilocus test was not independent. Moreover, the analyses for haplotype systems, consisting of two, three or four SNPs, also showed a genetic association with schizophrenia, in which the rs1473109–rs2238769–rs1547931 haplotype system was the strongest ($\chi^2 = 22.49$, $df = 3$, $P = 0.00005$).

Conclusion: The present results give further evidence supporting the hypothesis that the UFD1L locus may be associated with schizophrenia.

78. ASSOCIATION STUDIES OF THE NOTCH4 LOCUS AND THE TNXB LOCUS WITH SCHIZOPHRENIA IN CHINESE AND JAPANESE POPULATIONS

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Background: Both the NOTCH4 gene and the TNXB gene are located in the major histocompatibility complex (MHC) region of the human genome. They are about 100 kb apart. In recent studies, these two genes were found to be strongly associated with schizophrenia in a British population.

Methods: To replicate the initial findings, we conducted a family-based study in 141 Chinese family trios of Han descent, and a case-control study with Japanese samples collected from 241 unrelated schizophrenic patients and 420 unrelated healthy individuals.

Results: In the Chinese population, the TNXB locus did not show a genetic association with schizophrenia, but rs520692, a coding single nucleotide polymorphism (SNP) present at the NOTCH4 locus, was associated with the illness ($P = 0.017$). In the Japanese sample, although the NOTCH4 gene was not associated with schizophrenia, two SNPs present at the TNXB locus showed an allelic association, including rs1009382 ($P = 0.012$) and rs204887 ($P = 0.030$).

Conclusion: These findings suggest that on the one hand genetic heterogeneity of schizophrenia may be one of the commonest reasons for poor replication in the genetic analysis of human complex disease, and on the other hand, the association study is very likely to show different pictures among ethnic groups due to different frequencies of the disease-underlying variants between different populations.

Epidemiology

79. SEASONAL VARIATION IN BIRTH WEIGHT IN A LARGE UK POPULATION-BASED COHORT OF TERM BIRTHS TO PRIMIPAROUS MOTHERS

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Background: Season of birth effects in schizophrenia risk are variously explained by artefact, changes in photo period or factors affecting maternal infection rates. Whatever the cause, it appears to be a robust finding in different datasets. One possible explanation is the association of seasonality with an alternative independent risk factor for schizophrenia, for example low birth weight. Seasonality in birth weight in the developing world may be due to marked seasonal fluctuations in temperature, rainfall and maternal malarial infection. For example, Gambia records greater than 300-g differences in birth weight between seasons. In developed countries, seasonal effects are inconsistent because the effect maybe small and samples have been underpowered. Confirming seasonality of birth weight effects in a UK population might provide insights into the seasonality effects in schizophrenia risk.

Methods: We explored the effect of season of birth and sex on birth weight in a population-based cohort of term births delivered to primiparous mothers in Scotland (UK) during 1985–1998 ($n = 355{,}663$). On average babies born in Summer or Autumn were 9.3 g (95% CI 6.2–12.4 g, $p < 0.001$) heavier than those born in Winter or Spring. The mean birth weight in female babies was 3310.6 g compared to 3431.9 g in males. There was no evidence of an effect of season of birth on the sex ratio of births ($p = 0.322$), or that offspring sex modified the association between seasonality and birth weight ($p = 0.606$).

Conclusion: These findings are consistent with the notion that part of the seasonality effect in schizophrenia risk may be explained by birth weight variation.

80. PARENTAL AND SIBLING DEATH AND RISK OF SCHIZOPHRENIA: A DANISH REGISTER BASED STUDY

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Background/objective: In this study, we explored the relationship between death of a parent or sibling and risk of subsequent schizophrenia while considering whether the death was due to suicide or for other reasons, and adjusting for a range of factors that might confound or modify the relationship including age at time of the parent's death, time between the death and the first hospital admission, parental age, family psychiatric history, parental wealth and urbanisation of place of birth.

Methods: We conducted a time-matched nested case-control design using Danish national longitudinal registers comprising prospectively collected information. The sample included 7704 first admissions with ICD-8 or ICD-10 schizophrenia admitted to a psychiatric facility in Denmark between 1981 and 1998 and 192 590 individually time-, age- and gender-matched population controls identified through national registers, and their parents and siblings.

Results: In models adjusting for confounders, death of a parent or sibling by suicide was associated with increased risk for schizophrenia, with only modest effects found for deaths due to other causes. The increased risk associated with parental death was age dependent and higher for those who were young at the time of death.

Conclusion: As the increased risk of schizophrenia from death of a parent or sibling was greatest for deaths by suicide, particularly if it occurred at a young age, it is likely that the increased risk is mediated by genetic factors or by interaction between genetic risk for schizophrenia and the impact of the death on the child.

81. SCHIZOPHRENIA AND MIGRATION: A META-ANALYSIS

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Objective: To provide a quantitative index of the effect size associated with migration.

Methods: Meta-analysis. Medline was searched for English-language publications appearing between 1977 and 2003. Population-based incidence studies concerning migrants were included if numerators and denominators were provided and age correction was performed or subsequently could be performed. Relative risks for migrant groups were extracted or calculated for each study. Data extraction and categorization of migrant group characteristics were performed by the two authors independently. Significant heterogeneity across studies indicated the use of a mixed effects meta-analytic model.

Results: When only first-generation migrants (40 effect sizes) were included in the analysis, the mean weighted relative risk (RR) for developing schizophrenia was 2.7 (95% CI: 2.3–3.2). Separate analysis performed for second-generation migrants (7 effect sizes) yielded a RR of 4.5 (95% CI: 1.5–13.1). An analysis performed for studies concerning first- and second-generation migrants and studies not distinguishing between generations (50 effect sizes) yielded a RR of 2.9 (95% CI: 2.5–3.4). Subgroup comparisons yielded greater effect sizes for migrants from developing countries (RR = 3.3; 95% CI: 2.8–3.9) vs. developed countries (RR = 2.3; 1.7–3.1). Moreover, risks were higher for migrants belonging to ethnic groups with black (RR = 4.8; 3.7–6.2) vs. white (RR = 2.3; 1.7–3.1) and non-white, non-black (RR = 2.2; 1.7–2.9) skin colour.

Conclusion: Negative selection cannot be the sole explanation for the strong association found between migration and schizophrenia. The profile of risk emerging across these subgroups suggests rather that psychosocial adversity may play an important role in the aetiology of schizophrenia.

82. MORTALITY IN A COHORT OF PATIENTS WITH SCHIZOPHRENIA

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Objective: Facing the lack of national data, a specific research concerning mortality of schizophrenic patients cared in the French community health system was undertook in 1993 by a research unit.

Methods: 3470 schizophrenic patients (ICD10), included at random, as in or out patient, aged 18–64 were registered.

Observations concerning physical health, suicidal behavior, drug consumption and psychotropic medication have been registered at inclusion and renewed every 3 years. This cohort has been going on for 9 years now but national specific causes are available only till 1999. A comparison of mortality between patients and general population has been made by the standardized mortality ratio (SMR). The Cox Model was used for the multivariate analyses.

Results: Deaths (307) were observed during the 6-year follow-up vs. 83.2 expected. The SMR was 3.5 for men and 4.4 for women. Suicide represented one death out of three. The percentage of suicides in the total number of deaths was more than half during the first year of observation (54%). In the fifth year, it only represented one case out of four. All natural causes of death were over-represented, including cancer.

Conclusion: Mortality among schizophrenic patients remains high and must still be documented.

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83. THE NORTHERN IRELAND FIRST EPISODE STUDY

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Background/objective: The Northern Ireland First Episode Study is the first such study to examine all cases of psychosis arising in this region of the UK. The study area has a population of 770,000, amounting to half the entire population of the region, and has relatively low rates of drug misuse. It is hypothesized that the incidence of psychoses, including schizophrenia, in the region will not be significantly different from incidence rates seen in other parts of the British Isles. Similarly, it is hypothesized that the incidence rate in rural areas under study will not be significantly different to that in urban areas. Other hypotheses relating to neuropsychological parameters are outlined in a separate submission.

Methods: The study is designed to identify all cases of psychosis in persons under 65 presenting to psychiatric services for the first time over a 2-year period, with follow-up of each case after 1 year and 3 years.

Results: We report results from the first phase of recruitment (January 2003–present). Ninety-five cases were referred to the study in this period. Thirty-nine percent of these have a current diagnosis of schizophrenia giving an incidence rate of schizophrenia of 6.4 cases/100,000 per year. This rate is lower than the rate of 12–15/100,000 per year reported in comparable studies.

Conclusion: These results indicate that the incidence of schizophrenia in Northern Ireland may be lower than expected.

84. CHILDHOOD MOTOR MILESTONES AND TEACHER RATINGS OF PERFORMANCE IN PHYSICAL EDUCATION (PE): PROSPECTIVE ASSOCIATIONS AMONG TWO DISTAL MARKERS OF MOTOR DEVELOPMENT IN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Background/objective: Prospectively collected data on pre-morbid motor development have been associated with risk for schizophrenia and other psychoses. Little is known about associations among different markers of motor development in early childhood and later adolescence. We examined associations among two motor risk factors using prospective data from the 1966 North Finland birth cohort in which adult psychiatric diagnoses have been established.

Methods: We tested the hypotheses that secondary school teachers' ratings of performance in Physical Education (PE) would be *related* to the *same* continuum of motor development measured at age 1 year by parental reports (of the age at which two motor milestones were attained: sitting and walking). Second, we examined whether scores on this latent motor "factor" *differed* among cases (DSM diagnoses of schizophrenia and other psychoses) and over eight thousand general population controls. We applied an Item Response Theory model to define our continuum of motor development as a normally distributed (latent) variable. This approach enabled reported milestones and teacher ratings to be appropriately model as discrete, ordered categorical outcomes, rather than as continuous measures. Gender differences in measurement parameters and impact of missing data were addressed during modelling using a multiple group approach in Mplus and maximum likelihood estimation in STATA gllamm.

Results: Effect sizes for mean differences between groups (Schizophrenia, Other psychoses vs. Controls) on the standardised latent trait ranged from 0.2 to 0.5 (Cohen's *d*) indicating substantial motor deficits in those who later developed schizophrenia and other psychoses, but low correlations between these diverse motor markers over time (Pearson's $r < 0.15$ for Boys and Girls).

85. INCIDENCE OF ADOLESCENT-ONSET PSYCHOSIS IN THE TRENT REGION OF THE UK

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Background: The incidence and demographic correlates of psychosis occurring in early and mid adolescence is essentially unknown. Almost all incidence studies of schizophrenia have excluded patients < 16 years of age.

Methods: Epidemiology of Psychosis in Childhood (EPIC) is a population-based, first contact, incidence study of adolescent-onset psychoses. All new cases of psychosis in young people age 16 or under were ascertained from the UK. Trent region (population 5 million) during a 4-year period (1997 and 2000 inclusive). All cases referred to the study were assessed using SCAN and OPCRIT and consensus DSM-IV/ICD-10 diagnoses were made.

Results: 107 young people (age 10–16) were referred to EPIC. 67 cases were given an ICD-10 diagnosis of schizophrenia ($N = 38$; 57%), affective psychosis ($N = 25$; 37%) or unspecified non-organic psychosis ($N = 4$; 6%). The incidence for all psychoses (population at risk age 6 to 16 years) was 2.4 per 100,000 person years (95% CI 1.9–3.1). The incidence of psychosis was similar in girls and boys. The age specific incidence rate increased from 1.5 per 100,000 person years in early adolescence (age 10–13), to 6.7 per 100,000 person years in mid adolescence (age 14–16). The highest age specific incidence was 8.5 per 100,000 person years at age 16. There was a slight increased risk of psychosis in young people from all ethnic minorities combined (IRR 2.1; 95% CI 0.9–5.0). However, young people specifically from an African Caribbean background were at a significantly increased risk of psychosis compared with white youth (IRR 10.1; 95% CI 3.1–31.0). Low social class was also linked to an increased risk of psychosis (IRR 2.8; 95% CI 1.3–5.9).

Conclusion: Adult-type psychotic disorders (schizophrenia and affective psychoses) can be reliably identified from age 10 onwards and occur with increasing incidence during early and mid-adolescence. The increased incidence of psychosis in African Caribbean adolescents mirrors findings from adult populations in the UK and Europe. The risk of psychosis associated with ethnicity extends across the age range suggesting aetiological continuity between adolescent and adult-onset psychoses.

86. SCHIZOAFFECTIVE DISORDERS AND FAMILY HISTORY OF ADMISSIONS

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Background: Schizoaffective disorder is related to both schizophrenia and to affective disorders. No population-based study has investigated the association between the risk of schizoaffective disorders and familial aggregation of schizophrenia and affective disorders. The aim of this study was to determine whether a psychiatric history of schizoaffective, bipolar and schizophrenia admissions among parents and siblings affect the risk of being admitted with a schizoaffective diagnosis and to compare this result with the parallel analyses where we looked at bipolar and schizophrenia admissions, respectively, as the outcome. We wanted to see if there was another distribution of family history of psychiatric admissions among these persons.

Method: We established a register based cohort study of 2.4 million persons born in Denmark after 1952. Totally, 1925 persons were admitted with a schizoaffective disorder during approximately 38 million person years. Relative risks were estimated by Poisson regression.

Results: There was an equal familial aggregation of bipolar and schizophrenia admissions in relatives of schizoaffective patients, but an unequal distribution in relatives of bipolar or schizophrenic patients. The relative risk of getting admitted with a schizoaffective disorder was 2.82 (95% CI 2.54–3.12) if at least one family member had been admitted to a psychiatric hospital. There was an additionally risk of 2.60 (2.13–3.16) and 3.10 (2.49–3.85) if the admission had been with schizophrenia or a bipolar disorder, respectively.

Conclusion: The study suggests that the schizoaffective disorder is not simply a subgroup of either bipolar disorder or schizophrenia but may be genetically linked to both.

87. A SYSTEMATIC REVIEW OF THE INCIDENCE OF SCHIZOPHRENIA: THE DISTRIBUTION OF RATE ITEMS AND THE INFLUENCE OF METHODOLOGY, URBANICITY, SEX AND MIGRANT STATUS

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Objective: The aim of this review was to systematically review studies related to the incidence of schizophrenia, to categorize taxonomic features of the studies and to explore the distribution of rate items derived from these studies.

Methods: Studies published between 1965 and 2001 were identified via electronic databases, reviewing citations and writing to authors. Studies were divided into core studies, migrant studies, cohort studies and 'other special groups'. Between- and within-study filters were applied in order to identify discrete rate items. The review identified 97 core studies, 24 migrant studies, 23 cohort studies and 14 studies of other special groups. These studies (drawn from 33 countries) generated 1456 rate items.

Results: Based on discrete core data for persons, the distribution was asymmetric (positively skewed) while the median value (10–90% quantiles) was 14.9 (7.0–43.0) per 100,000. Apart from the finding that older studies reported higher rate items, the overall quality and methodological features of the studies did not significantly differentiate the rate distributions. The distribution of rate items was significantly higher in males compared to females (male/female rate ratio median = 1.40, 10–90% quantiles = 0.86–2.37). Those studies conducted in urban versus mixed urban–rural catchment areas generated significantly higher rate item distributions. The distribution of rate items in migrants was significantly higher compared to native-born (migrant/native-born rate ratio median = 2.71, 10–90% quantiles = 0.67–7.64).

Conclusion: Rate items reporting the incidence of schizophrenia display prominent overall variation, and have significant differences when sorted by sex, migrant status and urbanicity.

88. INCIDENCE OF FIRST CONTACT PSYCHOSIS IN SÃO PAULO, BRAZIL: PRELIMINARY RESULTS

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Objective: Data on the incidence of psychoses in large urban centres of developing countries are scarce, and may help to understand the aetiology of such diseases. The aim of the present study is to estimate the incidence of first-contact psychosis in São Paulo, Brazil.

Methods: Individuals aged 18–64 years, resident in a defined geographic area of São Paulo, who had a first contact with any mental health service (public or private) due to a psychotic episode in the period from 1st July 2002 to 30th June 2003 were traced and then assessed with standardised instruments. Psychiatric diagnoses according to DSM-IV criteria were established with the SCID-I. Population at-risk data were drawn from the 2000 Brazilian population census.

Results: Sixty-nine first-contact psychosis cases were identified and assessed. Total population at risk was 926,081, yielding an unadjusted rate of 7.5/100,000 person-years (95% CI: 5.8 to 9.4). The rate for schizophrenia spectrum disorders was 4.8/100,000 (95% CI: 3.5 to 6.4). First-contact psychosis rates decreased linearly with age, from 12.3/100,000 in the 18–24 age group to 1.7/100,000 in the 55–64 age group.

Conclusion: First-contact psychosis incidence rates in São Paulo were at the lower extreme of estimates found in previous studies in several countries. Data collection is planned to continue for further 18 months to get more precise estimates.

Acknowledgment: Funded by the Wellcome Trust, UK.

89. SEASONALITY OF BIRTH IN PATIENTS WITH SCHIZOPHRENIA IN JAPAN

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Objective: Although most studies from western society found excess of birth during winter or early spring among patients with schizophrenia, this has not been found in Japanese sample. We investigated the finding using a large Japanese sample.

Methods: Distributions of monthly birth numbers of patients with schizophrenia were compared to those of the general population. Patients were from the governmental data, numbering 8788.

Results: A significant birth excess during winter to early spring was found in males and females with schizophrenia compared to the general population.

Conclusion: There is a significant birth excess during winter to early spring for schizophrenia in Japan. The authors considered that the discrepancy between the current study and the previous Japanese studies was caused by small sample size and selection bias in the previous Japanese studies.

90. REPRODUCTIVE PATHOLOGY BEFORE AND AFTER THE ONSET OF SCHIZOPHRENIA

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Background: There are conflicting reports as to whether the risk of obstetric complications (OCs) is increased in women who give birth after the onset of schizophrenia compared to those who give birth prior to illness onset.

Methods: We examined this using population-based data from a record linkage between 79,599 women on the Western Australian psychiatric case register and 308,022 births on the midwives database (identifying 382 mothers with a diagnosis of schizophrenia who gave birth 1980–1992). Comparison mothers were randomly selected from mothers on the midwives database who had no recorded history of psychiatric illness.

Results: Using multivariate modelling to adjust for confounding, we found that mothers giving birth after the onset of schizophrenia (but not those giving birth before illness onset) were significantly more likely to experience OCs relative to comparison mothers (OR = 1.13; 95% CI 1.01–1.27). Many individual OCs were more frequent in births after illness onset. The risk of greater socioeconomic disadvantage and single marital status was also increased for births after, compared to births before, illness onset. However, the frequency of two OCs, fetal distress and birthweight adjusted for gestational age, was not affected by the timing of birth relative to illness onset, while the risk of these OCs was increased significantly in mothers with schizophrenia compared to comparison mothers.

Conclusion: Disease onset and attendant behavioural and psychosocial factors may be associated with the risk of many OCs in mothers with schizophrenia. Others appear unaffected by disease onset, implicating genetic liability and/or premorbid risk factors (e.g. smoking) in their occurrence.

91. HIGH RATES OF COMPULSORY ADMISSION AMONG AFRICAN-CARIBBEAN AND AFRICAN PATIENTS IN THE LONDON-ARM OF THE AESOP FIRST ONSET STUDY

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Background: Many studies have found high rates of compulsory admission to psychiatric hospital in the UK among Black patients. However, the Black group used in comparisons is often heterogeneous, comprising both African-Caribbean and African patients. In distinguishing between these two ethnic groups, we sought to test the hypothesis that both African-Caribbean and African ethnicity would be independently associated with compulsory admission in a cohort of patients with a first episode of psychosis.

Method: Data was collected as part of the London-arm of the AESOP project. All White British ($n = 84$), African-Caribbean ($n = 126$) and African ($n = 64$) patients with a first episode of psychosis who made contact with psychiatric services over a 2-year period were included. Data relating to pathways to care, sociodemographic characteristics, and clinical presentation were collected from patients, relatives and case notes.

Results: Compared with the White British group, both African-Caribbean and African patients were significantly more likely to be compulsorily admitted (African-Caribbeans: OR 3.25; 1.76–6.01; $p < 0.01$; Africans: OR 4.03; 1.98–8.22; $p < 0.01$). When potential confounders were controlled for, African ethnicity remained significant (Adj. OR 2.86, 1.18–6.92, $p = 0.02$), but African-Caribbean ethnicity did not (Adj. OR 1.88, 0.88–4.04, $p = 0.10$). The confounders independently associated with compulsory admission were: Risk to others (Adj. OR 3.14, 1.62–6.08, $p < 0.01$), No GP referral (Adj. OR 2.24, 1.08–4.67, $p = 0.03$) and Criminal justice referral (Adj. OR 8.02, 3.27–19.69, $p < 0.01$).

Conclusion: These findings suggest that rates of compulsory admission are high in both African-Caribbean and African patients. The analysis further suggests that the factors determining compulsory admission occur differentially in each ethnic group. This confirms the importance of distinguishing between Black ethnic groups as a basis for understanding, and developing initiatives to reduce, high rates of compulsory admission among these patients.

92. INTERACTION IN THE ETIOLOGY OF SCHIZOPHRENIA: PROBLEMS AND PROSPECTS FOR RISK FACTOR STUDIES

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Background: Gene–environment interactions are often invoked as important in the etiology of schizophrenia, and recent studies have suggested that interacting genetic and environmental factors may cause a substantial proportion of all cases of schizophrenia. It is well documented that there is a genetically determined heterogeneity of susceptibility to schizophrenia, but molecular genetic studies have not been able to identify single major genes responsible for a large proportion of this heterogeneity, and it would seem reasonable to postulate that a set of gene variants are necessary but not sufficient causes in most cases of schizophrenia. Epidemiological studies have identified a number of non-genetic factors associated with schizophrenia risk but generally relative risks are small, and it could be postulated that non-genetic factors can only produce schizophrenia in a relatively small susceptible proportion of the population. However, if one accepts that, joint exposure to both a subset of genes and non-genetic factors is important in the etiology of a substantial proportion of schizophrenia cases, this would have important implications for the interpretation of studies of genetic as well as non-genetic risk factors. It would imply that most studies are based on misspecified models, many would systematically underestimate the effect of the factors studied, and there is no consensus as to how gene–environment interaction should be assessed.

93. INCIDENCE OF SCHIZOPHRENIA IN SURINAM

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Background: To date, no schizophrenia incidence study has been carried out in South America. Surinam is a former Dutch colony in South America. Migration from Surinam to The Netherlands has been on a very large scale and several Dutch studies have shown an increased incidence among the immigrants from Surinam. We tested the hypothesis that this phenomenon is explained by a high incidence in Surinam.

Method: One-year first-contact incidence study in Surinam (450,000 citizens). Collaboration with all GPs and psychiatrist in the country. All patients who made a first-in-lifetime contact with a physician were examined using a diagnostic interview (CASH). During a diagnostic meeting, three psychiatrists (one from Surinam, two from the Netherlands) discussed the patient's history and made a consensus DSM-IV diagnosis. To compare the risk for Surinamese immigrants to the Netherlands to that for the population of surinam, we used data from the incidence study in The Hague, The Netherlands, in which the same inclusion criteria and the same instruments had been employed (Selten et al., 2001, Br J Psychiatry, 178, 367–372).

Results: The incidence rate of schizophrenic disorders (DSM-IV:295.x) among people aged 15–54 was 1.86 per 10,000 (normal). The risk for Surinamese immigrants to the Netherlands (first generation) was significantly higher: age- and sex-adjusted Relative risk = 2.1 (95% CI: 1.2–3.8).

Conclusion: This is the first population-based incidence study in South America. The increased incidence among Surinamese immigrants to the Netherlands is not explained by a high incidence in Surinam.

94. PATTERNS OF PSYCHIATRIC HOSPITAL ADMISSION FOR SCHIZOPHRENIA AND RELATED PSYCHOSIS IN ENGLAND: A RETROSPECTIVE CROSS-SECTIONAL SURVEY

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Background: A number of studies have quantified local patterns of psychiatric inpatient admissions for schizophrenia but no previous analysis has sought to investigate recent national patterns for England. *Aim*: To investigate patterns of psychiatric hospital admissions for schizophrenia for 16–64 year olds in England using Hospital Episode Statistics (HES).

Methods: We obtained data for hospital admissions for April 1999 to March 2001 using the HES, which records all admissions to public hospitals in England. We calculated the mean annual admission rates (using appropriate census population denominators) by ICD10 diagnosis groups, region, sex and age. We also investigated length of stay in hospital (median, and proportions staying for greater than 90 and 365 days).

Results: There were 55561 admissions for schizophrenia and related psychosis (ICD F20–F29) in this period at a rate of 0.85 per 1000 population. They accounted for 26.9% of all admissions nationally which is less than that of the largest group, depression and anxiety (29.4%). These proportions were similar for all regions except London where psychosis accounted for the highest percentage of admissions (37.8%). More males than females were admitted for schizophrenia and related psychosis but this male excess was reversed in the age group 55–64. Length of stay in hospital

exceeded 90 days in 19.2% and exceeded 1 year in 2.7% of patients.

Conclusion: There are some distinct national and sex and age differences in hospital admission for schizophrenia and related psychoses. Such figures are important locally and nationally in developing and planning mental health services.

95. INCREASED INCIDENCE OF SCHIZOPHRENIA AMONG IMMIGRANTS TO THE NETHERLANDS

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Background/objective: The incidence of schizophrenia among several immigrant groups to The Netherlands has been found to be increased in a previous study (Br J Psych 2001; 178:367–72). Since the numbers of cases in this study were small, we conducted another incidence study and combined the data of the two cohorts.

Methods: Two-year incidence study in The Netherlands, using similar methods to the previous incidence study. All subjects who made a first contact with a physician in the city of The Hague for a psychotic disorder were diagnosed by two psychiatrists, using information from semi-structured interviews with the patients (CASH) and their key-informants (IRAOS).

Results: Among men, the combined data showed increased risks of schizophrenia, schizophreniform disorder or schizo-affective disorder (DSM-IV) for Surinamese (age-adjusted relative risk first generation 1.9; 95% CI 1.1–3.4; second generation 2.6; 1.3–5.3), Moroccans (first generation 4.9; 3.0–7.9; second generation 7.6; 3.6–16.0) and other, non-Western immigrants (first generation 2.0; 1.2–3.5; second generation 3.5; 1.6–7.8). The risks for Turkish males were not significantly increased (first generation 1.2; 0.6–2.6; second generation 2.1; 0.8–6.0). Among women, risks were increased for Surinamese (first generation 3.3; 1.7–6.4; second generation 4.3; 1.5–11.7), and for other, non-Western immigrants (only second generation: 7.4; 2.7–20.0). Compared to the previous study, the data of the present study showed trends towards decreased risks among Surinamese of both generations, and towards increased risks for Turks of the second generation.

Conclusion: The incidence of schizophrenia is increased among first- and second-generation immigrants. The findings might be explained by socio-cultural factors.

Incidence

96. SOCIAL ADVERSITY CONTRIBUTES TO HIGH MORBIDITY IN PSYCHOSES IN IMMIGRANTS—A NATIONAL COHORT STUDY IN TWO GENERATIONS OF SWEDISH RESIDENTS

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Background/objective: Recent reports have indicated that immigrants have an elevated risk of schizophrenia as well as an increasing tendency for social exclusion. The aim of this study was to compare rates of schizophrenia and other psychoses in immigrants and their children of different ethnic groups with the majority population in Sweden in relation to social adversity.

Method: The study population consists of a national cohort of 1.47 million adults (born 1929–1965) and 1.16 million children and youth (born 1968–1979) in family households from the national census of 1985. Multivariate Cox regression analyses of proportional hazards were used to estimate the relative risk of socio-economic household indicators from 1985 and 1990 (single adult household, adults having received social welfare, parental unemployment, urban residency, housing and SES) on hospital admissions during 1991–2000.

Results: First as well as second-generation immigrants had higher age- and sex-adjusted risk ratios for schizophrenia as well as for other psychoses (RRs 1.4–3.1 and 1.0–2.0, respectively) compared with the Swedish majority population. These risk ratios decreased considerably after adjusting for socio-economic indicators, for all groups, but particularly for the non-European immigrants. However, an elevated risk still remained in the Finnish and Eastern and Southern European study groups.

Conclusion: A higher risk of schizophrenia and psychoses was found in two generations of immigrants of diverse ethnicity. The results indicate that social adversity contribute to the higher risk.

97. THE FALL OF CATATONIA?

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Background/objective: Catatonia was originally described as a separate disease entity by Kahlbaum in 1874. Several authors described a decline of catatonic schizophrenia in the first half of the past century. In the 1970s, it was concluded that catatonic schizophrenia was a rare disorder. Several explanations for this decline have been advanced such as the introduction of antipsychotics, an increase of active rehabilitation and changes in the psychiatric taxonomies. Recently, the interest in the catatonic dimension was revitalised by the introduction of dimensional diagnostic approaches. The present study was designed to elucidate the frequency of catatonic schizophrenia in two samples of patients with schizophrenia.

Methods: The first sample included 19309 patients admitted to a general psychiatric hospital between 1980 and 2001. The second comprised 701 patients that were included from 1994 to 2002 in the schizophrenia research project of the University Medical Center Utrecht. Classification was performed according to the DSM. The subtype of catatonic schizophrenia was established in 7.8% of the patients in the period 1980–1989. In the sample covering the years 1990–2001, a significantly lower percentage of 1.3 was found ($p < 0.001$). In the Utrecht sample, the prevalence of catatonic schizophrenia was 0.9%.

Conclusion: It is concluded that the recognition of catatonic symptoms is strongly influenced by the diagnostic process itself which leads to a virtual decline of the prevalence.

Clinical Symptoms and Syndromes

98. PERSONALITY DIMENSIONS IN YOUNG ADULTS BORN PRETERM AND THEIR RELATION TO SCHIZOPHRENIA

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Background: Very preterm birth (VPT–less than 33 weeks gestation) is associated with later neuromotor and cognitive impairment, reduced school performance and increased rates of psychiatric illness, and has been consistently implicated in the aetiology of schizophrenia. Several follow-up studies have demonstrated increased anxiety and social rejection and reduced self-esteem in preterm individuals in childhood and adolescence but few studies have examined the effects of preterm birth on adult personality.

Methods: We assessed 107 very preterm individuals and 66 term-born controls at age 18–19 years with the Eysenck Personality Questionnaire-Revised (EPQ-R).

Results: The following scores were derived: Extraversion; Neuroticism; and Psychoticism (a measure of thoughtlessness and recklessness rather than of psychosis). VPT individuals had significantly lower Extraversion scores [$t = 2.38$; $df = 171$; $p = 0.018$] and higher Neuroticism scores [$t = -2.46$; $df = 171$; $p = 0.015$] than term-born controls. They had lower Psychoticism scores than term-born controls, but this did not reach statistical significance [$t = 1.66$; $df = 171$; $p = 0.099$].

Conclusion: These results agree with the literature suggesting that VPT individuals tend to be more risk averse and less extravert than their term-born peers and indulge in less antisocial behaviour. The higher neuroticism scores in VPT individuals may be related to their increased incidence of chronic physical health problems, and may also confer a predisposition to psychiatric illness. A tendency to be relatively more introverted and socially isolated may be associated with the possible increased incidence of schizophrenia in this group.

99. INSIGHT AND AFFECT IMPAIRMENT IN SCHIZOPHRENIA

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Background/objective: Evaluation of affect in patients is overall present in research of schizophrenia and it poses significant clinical problem in diagnostics and treatment. Relation between affect and insight of illness in schizophrenic patients remains unclear at present. Treatment of schizophrenia should attempt to enhance insight, and consequently improve outcome of illness for individual patient. The aim of this pilot study was to explore possible correlation between affect impairment and insight of illness, in the patients with schizophrenia.

Methods: Sample comprised 21 (12 male, 9 female) patients, diagnosed according to DSM-IV. Mean age was 29 years, range from 18 to 35 years. Mean age of onset of psychosis was 21.2 years, range from 17 to 26 years. For all patients, two previous episodes of illness were confirmed. Patients were in the remission, on maintenance antipsychotic therapy. Patients were rated with PANSS, CGI,

EPRS, GAF scale and SANS. Patients fulfilled insight scale that included statements on illness, symptoms, sense of well being and knowledge of illness and treatment.

Results: Initial findings indicate that affect impairment in our sample correlates positively with insight of illness, especially in the domain of negative symptom awareness and the need for the treatment. Positive symptoms, presence of side effects and global clinical state showed no correlation with insight.

Conclusion: Affect impairment could be significant in the evaluation of the treatment plan for individual patients, as it seems to have an influence on reduced insight about the illness.

100. ARE AUDITORY–VERBAL HALLUCINATIONS ASSOCIATED WITH AUDITORY EMOTIONAL PROCESSING DEFICITS?

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Background: It has long been established that people with schizophrenia exhibit difficulties when processing emotion. However, only a minority of this research has investigated auditory processing of emotion. Furthermore, no studies to date have examined the relationship between this deficit and the symptom of Auditory–Verbal Hallucinations (AVH).

Methods: In the present study, participants completed four tasks: emotional dichotic listening task, non-linguistic emotional sounds, diagnostic assessment of non-verbal accuracy (DANVA) and sentence prosody. To date, 23 DSM-IV schizophrenics and 26 age-matched normal controls have been recruited. Patients were divided into two groups, 9 with no history of AVH and 14 with a definite history of AVH.

Results: The patients had lower scores on all four tasks compared to controls. However, importantly, two of the tasks revealed a significant group difference between no-AVH and AVH patients. The AVH patients had a reduced scores when processing non-linguistic sounds ($F = 5.8$ $p = 0.006$ no-AVH = 3.8 and AVH = 2.9 out of 5), especially sad non-linguistic sounds (no-AVH = 4.6 and AVH = 3.5) and overall on the sentence prosody task ($F = 8.06$ $p = 0.001$, no-AVH = 13.0 and AVH = 10.3 out of 22), but especially happy sentences (no-AVH = 19.2 and AVH = 9.9).

Conclusion: The data suggest that patients with prominent AVHs show reduced sensitivity on some auditory emotional tasks over and above patients who do not have a history of AVH, or normal controls. This does not appear to be specific to any emotion across the tasks, but indicates this deficit may lie in the mislabelling or over-processing of the emotional content of voices, perhaps due to the frequently emotionally charged nature of their hallucinations.

101. BERKSON'S BIAS: PSYCHOTIC SYMPTOM CLUSTERS DIFFER WITH SEVERITY?

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Background: Clinical selection bias (Berkson's bias) might result in subjects with overlapping conditions being more likely to be studied (Tien, Costa, and Eaton, 1992). Not treatment setting, but illness severity is probably responsible for this difference, since admission is often determined by non-psychiatric factors (Boardman, Hodgson, Lewis, and Allen, 1997).

Methods: A convenient sample of 610 mentally ill patients (75.5% with a diagnosis of schizophrenia) was assessed with the Brief Psychiatric Rating Scale (Ventura et al., 1993). Subjects were characterized on clinical status (admitted = 57%; ambulatory = 43%) and illness severity (average BPRS item score 1.0 = 17%; 1.1–2.0 = 21%; 2.1–3.0 = 29%; 3.1–4.0 = 19% 4.1–5.0 = 10%; 5.1–6.0 = 3% and 6.1–7.0 = 1%).

Results: The association of positive and negative symptoms was equal for patients from clinical or ambulatory treatment centers ($r = 0.55$ vs. $r = 0.48$; n.s.). In contrast, paranoia and hallucinations ($r = 0.30$ vs. $r = 0.52$; $z = -2.58$, $p < 0.01$) and anxiety and depression ($r = 0.42$ vs. $r = 0.65$; $z = -3.20$, $p < 0.001$) were rated more similar in ambulatory settings than in clinical. The association between positive and negative symptoms ($F(1,5) = 1.41$; ns.) and paranoia and hallucinations ($F(1,5) = 0.76$; ns.) was nonsignificant over different grades of severity, but a significant association existed for anxiety and depression ($F(1,5) = 57.72$, $p < 0.001$).

Conclusion: We could not replicate that primary psychotic symptoms are more related in clinical samples compared to ambulatory patients, nor for patients with raising levels of severity. All these patients suffered from severe mental illness. Another picture may exist in a general population sample of psychotic traits.

102. DIMENSIONS OF DELUSION AND HALLUCINATION RATING SCALES IN EARLY SCHIZOPHRENIA

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Background: An existing cross sectional factor analysis of the Psychotic SYmptom RATing Scale (PSYRATS) in chronic schizophrenia shows the Delusions Scale to have two dimensions and Auditory Hallucinations Scale three. We followed up a different population to examine the possible reproducibility and stability of these factors.

Methods: Three-hundred and nine patients were recruited from consecutive admissions with first or second episodes of DSM IV schizophreniform disorder, schizophrenia, schizoaffective disorder, delusional disorder or psychosis NOS, to day- or in-patient units, from defined catchment areas over 26 months. Eighty-five percent were first episode. The PSYRATS was completed within 2 weeks of admission, after 6 weeks and 3, 9 and 18 months. The Delusions Scale on all patients, and the Auditory Hallucinations Scale on those hallucinating, was subjected to factor analysis (principal axis factoring: PAF) and multidimensional scaling (MDS) at each stage.

Results: The distress and severity items of the Delusions Scale formed two groups at each stage on MDS and formed two factors after PAF. The Auditory Hallucinations Scale distress items formed one group/factor, and the beliefs about voices, location and control items another group/factor, consistently. The remaining amount/disruption items formed a consistent group on MDS but loaded inconsistently onto factors on PAF, at each stage. Intensity of distress linked the distress and amount groups.

Conclusion: There is evidence from two different analytic methods for broadly consistent dimensions describing the experiences of delusions and auditory hallucinations, similar to those in chronic sufferers.

103. A PET STUDY OF ACTION ATTRIBUTION IN NORMALS AND PATIENTS WITH SCHIZOPHRENIA

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Background: One of the most striking features of schizophrenia is that patients do not experience some of their actions and personal states as their own. The so-called first-rank symptoms (FRS) may be associated to an impaired recognition of one's own actions or thoughts, leading the patients to misattribute their own states to another agent.

Methods: In the present study, we examined regional cerebral blood (rCBF) flow in relation with a task of action attribution. We used a device that allowed us to modify the subject's degree of control of the movements of a virtual hand presented on a screen (3).

Results: Results showed that in normal subjects (1), two main brain areas present a modulation of their activity as a function of the degree of discrepancy between the movement executed and the movement seen on the screen: the right inferior parietal lobule (angular gyrus) and the insular cortex. In schizophrenics, we did not find any co-variation between the degree of distortion and rCBF in neither right inferior parietal cortex nor in. However contrasting the two extreme conditions revealed hyperactivation in the right angular gyrus insula (2).

Conclusion: This abnormal pattern of activation may underlie FRS production.

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104. A CONFIRMATORY FACTOR ANALYSIS OF THE POSITIVE AND NEGATIVE SYMPTOM SCALE

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Background/objective: Since 1991, there have been published 18 studies with different 5-factor solutions for the PANSS. All are slightly different. Several attempts to confirmatory factor analysis

have failed. The five-factor solution by White et al. (1997) is at the basis of the contemporary scoring system, but the fit was far from satisfactory. The aim of this study was to do a confirmatory factor analysis on all five-factor solutions which have been published with a large database to decide over the best five-factor solution.

Methods: 6012 subjects were collected from different studies in the Netherlands (1875) and other European countries (4137; with courtesy to Janssen-Cilag that made their European database accessible for this study).

Results: No satisfactory fit was found for any of the five-factor solutions. In addition, the original three- and four-factor solution could not be fitted. The White solution had the highest indices (NFI 0.731; NNFI 0.710; CFI 0.734; rCFI 0.731), but was far from the needed 0.90 for each index.

Conclusion: The three-factor solution must now be abolished since it does not fit well with the data. Of all five-factor solutions, the contemporary White solution fits best, but actually is not satisfactory. The items of the PANSS are too generally formulated and tend to measure a g-factor for mental illness.

105. PLEASURABLE AUDITORY HALLUCINATIONS IN PSYCHOTIC PATIENTS

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Background: Auditory hallucinations are one of the most frequent and characteristic symptoms in patients with schizophrenia and in recent years, the interest in these phenomena has increased. It is now common to separate the perceptive from the emotional component in auditory hallucinations. Given the fact that emotional response rather than the psychotic experience itself differentiates between patients and non-patients, the differentiation between the hallucinatory phenomenon itself and the emotional experience that it provokes becomes an important object for study. However, there are practically no studies on whether voices can be perceived as pleasurable.

Methods: One-hundred and six patients with auditory hallucinations (89 schizophrenia and 17 other psychosis) were assessed with the PSYRATS scale for auditory hallucinations, including an added item on whether the experience was pleasurable. Twenty-eight patients (26%) reported the voices as a pleasurable experience and 10 of them did so frequently.

Results: Pleasurable perception of voices showed negative associations with amount and intensity of distress, degree of negative content and loudness. Positive associations were apparent with chronicity and perceived control over the voices.

Conclusion: Therefore, pleasurable hallucinations can be detected in a substantial proportion of patients, and cross validated with existing instruments. The dynamics of psychosis may entail more than toxic effects of intrusive symptoms. The existence of pleasurable psychotic experiences in patients with chronic and multimodal hallucinations suggests that some individuals make positive symptomatic adjustments over the course of their illness, which may modify treatment needs and outcome. It would seem that this finding has therapeutic implications.

106. THE PREVALENCE AND CORRELATES OF SELF-REPORTED PSYCHOTIC SYMPTOMS IN THE BRITISH POPULATION

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Background/objective: The psychosis phenotype is generally thought of as a categorical entity and a diagnosis is made by applying criteria derived from clinical observations. However, there is increasing evidence that psychosis exists in the population as a continuum of severity rather than as an all-or-none phenomenon. This study investigated the factors associated with self-reported psychotic symptoms using data from the UK 2000 National Survey of Psychiatric Morbidity.

Method: A cross-sectional sample of 8580 respondents aged 16–74 from the British population were interviewed. Questions covered mental health, physical health, substance use, life events, and socio-demographic variables. The Psychosis Screening Questionnaire (PSQ) was used to screen for psychotic symptoms.

Results: 5.5% of the sample endorsed one or more question on the PSQ. Factors independently associated with psychotic symptoms were cannabis dependence, alcohol dependence, victimisation, recent stressful life events, non-white ethnicity, lower educational qualifications and neurotic symptoms. Male gender was a risk factor for paranoid thoughts, whereas female gender was associated with hallucinatory experiences.

Conclusion: Self-reported psychotic symptoms are less common in the British population than in other populations. The demographic and clinical correlates of these self-reported psychotic symptoms are generally similar to the risk factors for clinical psychosis.

107. AGREEMENT BETWEEN SELF-RATED AND CLINICALLY ASSESSED SYMPTOMS IN SUBJECTS WITH PSYCHOSIS

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Objective: The aim was to explore the capacity of acutely ill patients with psychosis ($n = 40$) to self-report their symptoms by comparing self-assessment and objective measures.

Methods: Positive, negative and depressive symptoms were rated using the Scale for the Assessment of Positive Symptoms, the Scale for the Assessment of Negative Symptoms and the Calgary Depression Scale. Insight level was measured using the Scale to assess Unawareness of Mental Disorder. Patients were asked to self-report positive, negative and depressive symptoms using the Community Assessment of Psychic Experience (CAPE).

Results: Patients presenting with acute psychotic disorders had a fair assessment of positive, negative and depressive symptoms. Significant associations were found between self-reported and objective measures of positive, negative and depressive symptoms, independently of insight level. Individual positive and negative symptoms were correctly self-assessed, except for persecutory delusion and alogia, respectively.

Conclusion: These results suggest that self-report questionnaires can be used in educative programs to favour the patient therapeutic alliance.

108. IS OUR CONCEPT OF SCHIZOPHRENIA INFLUENCED BY BERKSON'S BIAS?

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Background: High rates of comorbidity in clinical practice, such as the comorbidity between the positive and negative features of schizophrenia, may be in part an artefact if both positive and negative features independently influence help-seeking behaviour and need for mental health care(MHC).In clinical samples, therefore, the phenomenon will result in a higher estimate of the comorbidity between these two dimensions than would be in case if non-clinical samples were investigated—a selection bias known as a treatment seeking bias or Berkson's bias (Berkson, 1950).

Methods: We explored to what degree the concept of schizophrenia might be the result of Berkson's bias by investigating whether positive and negative psychosis dimensions independently contribute to patient status in a Dutch general population sample. In a prospective cohort study, 7076 individuals were interviewed with the Composite International Diagnostic Interview Schedule at baseline and 1/3 years later. Lifetime positive and negative psychotic experiences (PPE, NPE) were assessed at baseline. MHC-use was assessed at baseline, and prospectively 1/3 years later.

Results: The rating of MHC was strongly associated with NPE and PPE, both retrospectively and prospectively, and the effects remained strong and significant in the analyses with both variables included.

Conclusion: The results suggest that the concept of schizophrenia, as a unitary entity with high comorbidity between positive and negative dimensions, is in part the result of Berkson's bias. In clinical samples, the association between dimensions may be spuriously high because both positive and negative dimensions contribute to patient status.

109. IS POOR INSIGHT IN SCHIZOPHRENIA PART OF A MORE GENERALIZED DEFICIT IN SELF-REFLECTIVE AWARENESS: A PILOT METACOGNITIVE STUDY

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Background/objective: The present study was designed to assess the hypothesis that poor insight in schizophrenia is part of a broader and more generalized deficit in self-reflective, metacognitive abilities. Support for this hypothesis comes from preliminary data in two different lines of research; the first, suggesting that poor insight in schizophrenia may be more strongly related to measures of free-choice, metacognitive functioning than to measures of neurocognitive functioning per se; and the second, introducing the concept of

self-reflexivity as a crucial element in the construction of accurate and coherent self-representation.

Methods: To assess our hypothesis we evaluated 40 schizophrenia patients with the Scale to asses Unawareness of Mental Disorder (SUMD), the Self Representation Inventory developed by Blatt et al. and the metacognitive version of the Wisconsin Card Sorting Test (WCST) developed by Koren et al.

Results: Our results showed that metacognition and reflective self-awareness had a significant contribution to the prediction of poor insight over and above that of executive functioning alone.

Conclusion: These findings suggest that poor insight in schizophrenia may indeed be mediated by deficits in the ability to monitor internal functions. That is, the ability to construct an accurate concept of self as having a mental disorder is dependent on the ability to self-reflect.

110. VALIDATION OF PETERS ET AL. DELUSIONS INVENTORY (SHORT-FORM) IN CHINESE POPULATION

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Background: Psychotic symptoms have been suggested as a continuum that normal population may also experience hallucination and delusional ideas.

Methods: Peters et al. Delusions Inventory (PDI-21) is a well-validated scale designed to measure delusional ideations in general population. It is a multidimensional scale with 21 individual items and three rating dimensions: distress, preoccupation and conviction on each item, respectively. It was translated into Chinese and validated in 108 Hong Kong university students. Backward translation was adopted to minimize any deviation on sentences meaning from original scale. Internal consistency was found to be satisfactory that the Cronbach alpha of reliability was 0.66.

Results: The mean of distress, preoccupation and conviction was 6.63, 6.34 and 8.92 in the scoring range of 0 to 105, respectively. The correlations of these three rating scales were significant ($p < 0.01$). Among the 21 items, some were rated more frequently than others. For examples, 74.1% of the students felt that people are not what they seem to be, 46.8% felt that people seem to drop hints about them and 37.6% believed in the power of witchcraft.

Conclusion: The results show that Chinese university students do experience some psychotic-like symptoms but with mild distressing, preoccupation and conviction levels. Further studies are required to improve the sample base with a more diverged normal population as well as to compare the scores with psychotic patients.

111. A CASE OF VISUAL BROADCAST IN SCHIZOPHRENIA

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Background: Thought broadcast has been variously defined, but essentially involves the passive diffusion of thoughts, which can, therefore, become available to others. The mechanism of diffusion has been linked to domains of speech and language, and hence to the auditory system. In contrast, we report a case of 'visual broadcast'.

Method and results: Our patient is a gentleman (38 years) with a long-standing diagnosis of paranoid schizophrenia. His most recent deterioration was characterised by prominent auditory hallucinations, thought broadcast and delusions of reference. Following admission to psychiatric hospital, he began to describe phenomena which had previously not been recorded. He had a long-standing reluctance to bathe, preferring to 'strip wash'. He described an experience by which he felt images of his naked body were transmitted to and *seen* by others. His own visual perceptions were firstly represented in internal space and then passively disseminated, enabling millions of people, worldwide, to view them, causing him great distress, embarrassment and ultimately inhibiting his actions. Examination by an ophthalmologist revealed only mild shortsightedness. No other pathology was found on clinical examination. Standard blood tests were also normal.

Conclusion: It is well established that, in schizophrenia, there are ego boundary disturbances involving thoughts—perhaps these extend and also involve perceptions. Further examples of such phenomena may help to elucidate the underlying broadcast mechanism, irrespective of precise broadcast 'content'.

112. THE FACTOR STRUCTURE FOR POSITIVE AND NEGATIVE SYMPTOMS IN SIBPAIRS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a prevalent (1%) and chronic disorder with considerable heterogeneity. Attempts have been made to elucidate the heterogeneity of the schizophrenia phenotype by exploring the relationships (factor analysis based) between the various symptom dimensions (e.g. positive and negative) and possible subtypes.

Method: Xhosa schizophrenia sibpairs ($n = 99$) concordant for schizophrenia were evaluated for the presence of positive and negative symptom dimensions with the SAPS and SANS rating scales. An unlimited number of factors model was run.

Results: Five components were identified: a positive symptom component (delusions and hallucinations), a negative symptom component (affective flattening, alogia, avolition and anhedonia), a thought disorder component, impaired attention and bizarre behaviour components. These five components accounted for 82.5% of the total variance.

Conclusion: These concordant siblings allowed us to investigate shared familial factors in schizophrenia. Our sibpair group showed a replication of previous finding with regards to the universality of symptom patterns. Comparing these symptom components with those of a non-sibpair sample may help us to identify those components with a more familial underpinning.

113. THE ASSOCIATION BETWEEN CLINICAL VARIABLES IN REFRACTORY PSYCHOSIS AND NEUROPSYCHOLOGICAL PERFORMANCE

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Background/objective: The majority of studies investigating the association between cognitive deficits and different symptoms of schizophrenia used broad syndrome dimensions and failed to identify consistent patterns. The aim of this research was to study the relationships between selective cognitive domains and specific syndrome characteristics.

Methods: Seventy-one in-patients (46 males and 25 females) with refractory psychosis completed a comprehensive neuropsychological battery including assessment of premorbid IQ (National Adult Reading Test), current performance IQ (Raven's Progressive Matrices), logical memory, attention and visual–spatial perception. Patients were also rated for current symptoms using the Operational Criteria Checklist for Psychotic Illness (OPCRIT).

Results: Stepwise regression analyses obtained a negative association between premorbid IQ and scores on ''delusions and hallucinations lasting for 1 week'' ($R = 0.26$, $df = 64$, $p = 0.036$) and between current IQ and scores on ''all hallucinations'', i.e., visual and auditory ($R = 0.28$, $df = 62$, $p = 0.024$), after adjusting for patients' gender and illness duration. No OPCRIT items were associated with patients' perceptual organisation skills and logical memory, as well as deterioration of cognitive functioning defined as difference in IQ points between scores of premorbid and performance IQ.

Conclusion: The presence of positive symptoms in refractory psychosis is associated with decreased premorbid and current IQ, regardless of patients' gender and illness duration. These results corroborate previous findings that lower premorbid cognitive functioning may be a precursor of the onset of illness. They also indicate that positive symptoms such as hallucinations may be associated with self-monitoring deficits, resulting in poorer performance on cognitive tasks.

114. AN EXAMINATION OF THE RELATIONSHIP BETWEEN TRAUMA AND HEARING VOICES IN PSYCHIATRIC AND NON-PSYCHIATRIC POPULATIONS

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Background/objective: Cognitive-behavioural models have implicated trauma as a potential contributory factor in the development and maintenance of auditory hallucinations. The present study examined the relationship between trauma and auditory hallucinations in two groups of voice hearers: psychiatric voice hearers (PVH; $n = 22$) and non-psychiatric voice hearers (NPVH; $n = 21$).

Methods: Self-report measures were used to assess the nature of traumatic life events experienced and any associated psychological sequelae; and the characteristics of and beliefs about voices. Measures of anxiety and depression were also employed.

Results: The results indicated that significantly more PVH reported hearing voices more frequently and for longer periods of time than NPVH. PVH also typically reported negative voice content, increased distress, a lesser degree of control over the voices, and a greater degree of disruption caused by the voices.

The groups had significantly different beliefs about the voices they heard, with PVH describing their voices as significantly more malevolent and omnipotent. PVH reported significantly higher degrees of associated anxiety and depression than NPVH.

With regard to trauma, PVH reported experiencing significantly more traumatic life events over the lifespan than NPVH. They also reported significantly more severe psychological symptoms associated with trauma (re-experiencing, avoidance and arousal).

Conclusion: Results from multiple regression analyses suggest that unresolved trauma may account for a significant proportion of the variance in individuals' beliefs about voices. Beliefs about voices were shown to account for a significant proportion of the variance in depression scores, however, trauma symptoms were a superior predictor of anxiety scores.

115A. THE TEMPORAL EVOLUTION OF AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA

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Background/objective: Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia. Neuroimaging studies have identified a set of areas associated with AVH but the role of different regions in the pathophysiology of hallucinations remains unclear. We used functional magnetic resonance imaging (fMRI) to examine how the brain activity associated with AVH in schizophrenia changed over the course of individual hallucinatory events.

Methods: We studied two male dextral patients with DSM-IV schizophrenia, experiencing frequent and intermittent AVH despite treatment with atypical antipsychotics. Subjects pressed a button to signal the onset and ending of an AVH. This was repeated for every AVH they experienced during the 5-min session while 100 T2∗BOLD contrast echoplanar MR images were acquired using a 1.5-T GE System. The data were analysed by wavelet-based permutation of the data and voxels activated at $p < 0.0005$ level of significance were identified. The early and late phases of AVH were examined by repeating the analysis after shifting the hallucination (button press) log with respect to the fMRI time series in steps of one scan (3 s).

Results: The results demonstrated activation of the left inferior frontal gyrus and the right middle temporal gyrus prior to the perception of AVH, with activation in the left inferior frontal/insula and the middle and superior temporal gyri bilaterally occurring when subjects subsequently perceived auditory verbal hallucinations.

Conclusion: These data are consistent with the notion that AVH result from the misidentification of self-generated verbal material.

115B. ANXIETY, NOT DEPRESSION, IS ASSOCIATED WITH SHORT-TERM OUTCOME IN ACUTE SCHIZOPHRENIA

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Background/objective: There is some controversy about the value of affective symptoms in prediction of the treatment outcome in patients suffering from acute exacerbation of schizophrenia. Some authors report that presence of depressive symptoms in acute phase of illness is associated with more favorable outcome but this relationship was not confirmed by others. The correlation between anxiety and depression is usually substantial and in line with Kay's factor analysis of PANSS, depressive and anxiety symptoms are analyzed jointly as they cluster together forming a distinct "affective" factor. We were interested in looking at anxiety and depressive symptoms separately, to determine whether they may have different prognostic value.

Methods: The sample of 105 patients, diagnosed with DSM-IV schizophrenia was assessed with PANSS and Calgary Depression Scale (CDSS) at admission and at discharge. Mean age was 36.4 ± 12.3 years, duration of illness 11.5 ± 9.8 years, number of previous hospitalizations 6.7 ± 9.9. Data were analyzed using Spearman Rank Correlations.

Results: Baseline anxiety (G2 item from the PANSS) was significantly correlated with a treatment outcome assessed by the % change from baseline in total PANSS score at discharge ($r = 0.63$; significant after Bonferroni correction $p < 0.003$). Depressive symptoms (C1–C9 items from CDSS and G1, G3 and G6 items from the PANSS were not correlated with treatment outcome (all $r < 0.27$).

Conclusion: Despite its limitations (correlational method, anxiety measured using single item from a scale), the current analysis suggests that anxiety and depression should be considered as separate dimensions of psychopathology in schizophrenic patients.

116. GESTALT PERCEPTION CHANGES IN PSYCHOSIS: RESULTS FROM A CONTROLLED PSYCHOPHYSICAL STUDY

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Background: The general hypothesis of this empirical study was that schizophrenia spectrum patients show an impairment of their capabilities to generate and/or retain perceptual/cognitive patterns ('gestalts') compared to nonpatient controls. The secondary hypothesis was that such impairments correlate with psychotic symptoms. A further assumption concerned the patients' ability of 'intersensory binding', i.e. how different sensory modalities (e.g. auditory and visual stimuli) are integrated into a coherent perceived scene; a mixing of sequential information from different sources was expected that may characterize psychotic information processing.

Methods: Computer-based psychophysical tasks were implemented that provoked various gestalt illusions such as apparent motion and motion-induced blindness. The stability of gestalt perception was then measured by the duration of these phenomena and by the hysteresis effect. Intersensory binding was operationalized by assessing the effect acoustic stimuli have on Michotte-like motion perception. We tested $N = 32$ schizophrenia patients (81% males; mean age 27.2 years) and 32 control subjects matched with respect to age, sex, and educational background.

Results: Patients tended to perceive longer durations of gestalt phenomena (higher perseveration) in circular apparent motion, whereas gestalt perception (hysteresis) was generally unimpaired. An association between PANSS scores and gestalt phenomena was found. Patients showed markedly decreased binding capabilities.

Conclusion: These specific findings add to the growing evidence for altered perceptual organization in schizophrenia.

117. DIMENSIONS OF PSYCHOPATHOLOGY AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Objective: Different manifestations of schizophrenia may be related to impairments in different regions of the brain. We hypothesize that negative and disorganized symptoms are more related to cognitive deficits like excitatory, affective and positive dimensions.

Methods: Cross-sectional study with 63 outpatients that fulfill DSM-IV criteria for schizophrenia. Patients were administered the Positive and Negative Symptom Scale (PANSS) and a neuropsychological battery that included the Mini-Mental Status Examination (MMSE), Stroop test, Trail Making Test A (TMTA) and B (TMTB), WAIS vocabulary, digits and SIMBOL DIGITS sub-scales, Wisconsin Card Sorting Test, FAS (verbal fluency), TAVEC (Spanish version of the California Verbal Learning Test), Continuous Performance Test. Correlation coefficients between each of the cognitive tests and the five dimensions of the PANSS were calculated. Significance level was established at a type I error of 0.01.

Results: Sixty-four percent of patients were male and mean age was 44 years (S.D. 10). Patients were mostly chronic (mean duration of illness of 7.4 years, S.D. 8.4) and moderately severe (mean PANSS score 58.4, S.D. 10.1). Impairment in executive functioning (WCST) was related to the disorganized dimension. Impaired attention was associated to a higher severity in negative (CPT) and disorganized symptoms (CPT and digit span), and also positive and depressive symptoms (CPT). Memory was mostly impaired in patients with disorganized symptoms (TAVEC).

Conclusion: Our results confirm that patients with schizophrenia with symptoms of disorganization have a higher level of cognitive impairment. Positive and depressive symptoms are mostly related to attention deficits.

118. SIMILARITIES IN THE REORGANIZATION OF THE BRAIN BETWEEN DRUG DEPENDENCE AND DELUSIONAL DISORDER

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Background: Listening to patients responsively reveals a striking similarity between a drug of abuse and a delusion. A drug, similarly to the theme of a delusion, becomes an idol or object of worship which controls a patients' life. Intelligent patients will express how much they value their idols, will defend them and behave accordingly despite the awareness that their symptoms are harmful. Examples are the doctor who fails to stop smoking even after surgery for lung cancer or the physicist who admits that the explanation of his verbal acoustic hallucinations is scientifically absurd but still believes in their reality. The neurobiology of the development from abuse to dependence is comparable to the process of transition from prepsychotic state to paranoid psychosis. The vulnerability of the developmental neurocircuitry in adolescence is common ground from which both drug dependence and/or schizophrenia evolves. Metabolic hyperactivity in dopaminergic brain areas (esp. nucleus accumbens) has been detected in both, drug dependence and schizophrenia. Drugs acting on dopaminergic activity remain the best modality in the treatment of schizophrenia. Sporadic clinical reports have found a favourable response in drug dependence. An exception might be nicotine: antipsychotics of the I generation increase the number of cigarettes smoked by the patients. Generally, antipsychotics of the II generation (esp. in depot injectable form) could facilitate treatment of drug dependence.

119. THE RELATIONSHIP BETWEEN ATTITUDES TOWARDS THE ILLNESS AND INSIGHT IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: Studies have shown that patients with psychiatric illness not only feel being discriminated by others, but also discriminate themselves. It is expected that such findings would hinder their acceptance and insight of the illness. The present study aims to explore the relationship between attitudes towards the psychiatric label and insight of the illness.

Methods: A 30-item symptom checklist including psychotic symptoms and general stress responses was constructed. Patients with schizophrenia were asked to decide which items were psychotic symptoms. Thirty-two patients with schizophrenia were randomly assigned into the experimental and control groups. Patients in the experimental group were explained that the checklist contained psychotic symptoms he/she had prior to completing the checklist, while such an explanation was not given in the control group.

Results: The preliminary results showed that patients in the experimental group ($N = 17$) committed more errors (mean error rate = 0.56) in differentiating psychotic symptoms from general stress responses than the control group ($N = 15$) (mean error rate = 0.42). Patients in the experimental group also tend to include psychotic symptoms into general stress responses (mean commission errors = 10) than the control group (mean commission errors = 8).

Conclusion: However, due to the limitations of the small sample size and between-group design, conducting a within-subject study would be useful to confirm the relationship between patients' internalization of psychiatric label and awareness of psychotic symptoms.

120. A GENERALIZED COGNITIVE DEFICIT IN INTEGRATING DISCONFIRMATORY EVIDENCE UNDERLIES DELUSION MAINTENANCE IN SCHIZOPHRENIA

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Background: Disregarding disconfirmatory evidence is an important aspect of delusion maintenance in schizophrenia. However, it is not clear whether this is a natural product of holding a strong belief, or a generalized cognitive bias.

Methods: In the present study, we compared delusional and non-delusional schizophrenic patients on their ability to integrate disconfirmatory evidence. Participants were 52 adults with schizophrenia; 36 were currently experiencing delusions. Initially, participants were presented with a pictured scene, and were asked to rate the plausibility of each of four written interpretations. These four interpretations were of three types: one that is eventually (given more information) obviously true; two that appear plausible initially, but eventually prove to be inaccurate (lures); and one that is absurd. Next, another picture—which displayed additional background information about the first scene—was presented, and subjects were asked to re-rate the plausibility of the four interpretations. Finally, a third picture—again adding background information—was presented and interpretations were rated a final time. Twelve series of pictures were presented to each participant.

Results: The results confirmed that, compared to non-delusional schizophrenics, delusional schizophrenics were biased against reducing their plausibility ratings for lure interpretations over the course of a trial. That is, despite having information that made their initial interpretation implausible, they failed to revise appropriately their plausibility ratings.

Conclusion: These results suggest that, relative to non-delusional patients, individuals experiencing delusions demonstrate a generalized cognitive bias towards disregarding disconfirmatory evidence.

121. VOICE SELECTIVE AREAS IN AUDITORY CORTEX ARE SENSITIVE TO FAMILIARITY IN HALLUCINATION-LIKE VOICES

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Background: In schizophrenia, auditory verbal hallucinations (AVHs) may be experienced as familiar (identity known) or unfamiliar. In a functional imaging model of familiar AVHs, we

predicted that, compared with unfamiliar voices, familiar hallucination-like voices would be associated with greater activation in 'voice selective' areas of the auditory cortex.

Methods: Eleven right-handed, healthy male volunteers (mean age 34.9 years, S.D. = 8.47) took part in this study. Inside the scanner, 40 familiar and 40 unfamiliar voices were presented in a pseudo-randomised order. The familiar voices were those of people personally known to the subjects. Subjects were asked to identify the familiar and unfamiliar voices, using a response box. Functional magnetic resonance imaging data were acquired using a 1.5-T Eclipse system (Marconi Medical Systems, Ohio) at the University of Sheffield, and were analyzed using statistical parametric mapping (SPM99). A fixed-effects analysis ($p < 0.001$, uncorrected for multiple comparisons, extent threshold more than 5 voxels) was employed.

Results: Comparison of the familiar with the unfamiliar condition was associated with increased activation in the left middle temporal gyrus (BA 22; $x = -50$, $y = -16$, $z = -8$; 108 voxels), right superior temporal sulcus (BA 21; 60, −46, 8; 51 voxels) and posterior cingulate gyrus (BA 31; −4, −43, 43; 54 voxels).

Conclusion: Our findings suggest that regions in the middle temporal gyrus and superior temporal sulcus, previously described as 'voice selective', are sensitive to the quality of familiarity in hallucination-like voices. Involvement of these areas during actual AVHs might explain the variable attribution of familiarity to hallucinated voices.

Symptoms in the General Population

122. DO DIFFERENT PSYCHOTIC SYMPTOMS DIFFERENTIALLY PREDICT NEED FOR CARE IN THE GENERAL POPULATION?

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Background: The association between a psychotic symptom and the development of need for care is mediated by several factors, in particular degree of associated distress and previous exposure to experience of psychosis. The present study investigated to what degree different symptoms of psychosis arising in the general population are differentially associated with need for care.

Methods: Eighty-three subjects, who in the 3 years before had had two prior assessing the presence of psychosis, were interviewed about the presence of psychosis and the degree of associated distress. Need for care was assessed by four clinicians. Of the 83 subjects, 24 (29%) had need for care. The possible mediating role of distress and previous exposure to experience of psychosis was investigated in statistical models of the cross-sectional association between need for care and psychotic experiences.

Results: Hearing Voices, Other Hallucinations and Experience of Control were all associated with need for care. These associations were largely explained by distress and previous exposure to psychotic symptoms, with the exception of Hearing Voices, where the mediating effect was small due to the fact that around two-thirds of the Hearing Voices group did not experience any distress.

Conclusion: Associations between psychotic symptoms and need for care were mediated by distress and previous exposure to psychotic symptoms, with the exception of Hearing Voices.

123. THE SIGNAL DETECTION PROFILE OF HALLUCINATION PRONE INDIVIDUALS IN A NON-CLINICAL SAMPLE

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Background: Recent studies have suggested that isolated psychosis-like symptoms are found in non-clinical populations. Signal detection (SD) tasks offer a useful paradigm for exploring proneness to hallucination-like phenomena and the nature of the phenomena themselves.

Methods: A sample of 1206 healthy volunteers (mean age 22.5; 35% male) completed the Unusual Experiences subscale from the O-LIFE schizotypy questionnaire (Mason et al., 1995) and the Launay-Slade hallucinations questionnaire. Three groups (n = high: 30; medium: 15; low: 18) were selected according to their scores: high proneness (>1 S.D. above group mean on both scales); medium proneness (around the mean) and low proneness (<1 S.D. below group mean). The SD experiment consisted of exposure to 5-s epochs of white noise during 60% of which a voice was presented, followed by 3-s of silence, when participants indicated whether or not a voice had been present. This experiment was repeated three times.

Results: High proneness (HP) participants reported significantly more false positives (reporting the presence of a voice when it was absent) than medium proneness, who reported more than the low proneness group ($F = 3.93$, $df = 2,60$, sig. = 0.025). There was no difference in the rates of false positives across the three trials, but the response time of the HP group only significantly decreased over

the three trials ($p = 0.023$), suggesting a progressive readiness to report abnormal phenomena.

Acknowledgment: This work was supported by the Stanley Medical Research Institute.

124. DEVELOPMENTAL COURSE OF SCHIZOTYPY IN COMMUNITY ADOLESCENTS: NEGATIVE AND MIXED SCHIZOTYPY AT AGE 13 PREDICT SCHIZOTYPIC TRAITS AND NEUROCOGNITIVE DYSFUNCTION AT AGE 17

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Background/objective: Longitudinal assessment of neurocognitive performance in schizotypy should reduce the heterogeneity of the condition and enhance our understanding of its etiology and development. Barrantes-Vidal et al. (2003) conducted a cluster analysis of schizotypic traits in a community sample of adolescents (mean age 13 years) that yielded negative, mixed, positive, and low schizotypy clusters. Cross-sectional analyses indicated that the negative and mixed clusters had poorer neurocognitive functioning than the positive and low schizotypy clusters. The present study is a 4-year longitudinal reassessment of the adolescents originally assessed. The study examines the schizotypic and neurocognitive profile of participants in the four clusters.

Methods: Participants include 135 adolescents (mean age 17 years) who completed a neurocognitive battery including the CPT-IP, CVLT, and WCST, and the OLIFE schizotypy questionnaire.

Results: As expected, ANOVAs showed that the negative and mixed clusters scored higher on negative schizotypy relative to the positive and low clusters at the follow-up assessment. The mixed cluster, and to a lesser extent the negative cluster, were significantly impaired on verbal memory, sustained attention, and executive functioning. The positive cluster scored higher on positive schizotypy at the follow-up, but did not exhibit impaired neurocognitive performance.

Conclusion: Patterns of schizotypic traits identified at age 13 appear to be stable across adolescence. Mixed and negative schizotypy at age 13 was associated with negative schizotypy and impaired neurocognitive functioning at age 17. This suggests that negative schizotypy involves subtle but stable biobehavioural dysfunction throughout adolescence.

125. VALIDITY AND RELIABILITY OF SELF-REPORTED PSYCHOSIS USING CAPE

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Background: General population longitudinal cohort studies have demonstrated the prognostic validity of self-reported psychosis, but data on reliability and cross-validation with interview-based measures of psychosis-like symptoms are sparse.

Methods: At baseline, a three-dimension self-report (CAPE42: positive, negative and depression) measure of psychosis proneness was collected in a general population sample ($n = 496$ individuals). At follow-up (mean interval: 7 months), a three-dimension interview-based measure (SIS-R: positive, negative and disorganisation), the three psychosis dimensions of the BPRS (positive, negative and disorganisation) as well as a repeat self-report with the CAPE42 was collected.

Results: Baseline self-reported positive and negative dimensions of psychosis were specifically and independently associated with their equivalent interview-based dimension at follow-up, with standardised effect sizes of 0.4–0.6. Similarly, self-reported dimensions at baseline were strongly and specifically associated with their equivalent self-reported measure at follow-up (standardised effect sizes of 0.7–0.8).

Conclusion: Self-reported dimensions of psychosis-like symptoms appear to be reliable and valid. These findings may explain their high degree of prognostic validity observed in cohort studies.

126. NEUROLOGICAL SOFT-SIGNS IN NON-CLINICAL SCHIZOTYPY

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Background: Neurological soft-signs (NSS) are more prevalent in patients with schizophrenia and their first degree relatives than in normal subjects. Few studies have examined the correlates of NSS within normal groups.

Methods: This study examined NSS in students obtained from a population ($n = 1206$) which had completed the O-LIFE and the Launay-Slade Hallucination Scale (LSHS). A High Schizotypy (High-S) group ($n = 28$) scoring 1 S.D. above the mean on both the Unusual Experiences subscale (O-LIFE) and the LSHS, and a Low-S group ($n = 30$) of age- and sex-matched controls scoring below these cut-offs were further examined with the Neurological Examination Scale (NES).

Results: No subject had an Axis-I psychotic disorder and cannabis use was equally prevalent in both groups. ANOVA of the main subgroups of the NES [Sensory Integration, Motor Coordination, Complex Motor Skills, Other Soft-Signs (OSS)] showed a significant result for OSS only ($F = 5.41$, $p = 0.024$) with the High-S group demonstrating greater severity. Further ANOVA was then carried out on items of the OSS subscale. Right-sided Mirror Movements ($F = 7.37$, $p = 0.009$) and right sided Gaze Impersistance ($F = 4.78$, $p = 0.033$) were both significantly increased in the High-S group, whilst trend increases were apparent for left sided Mirror Movements ($F = 3.72$, $p = 0.059$) and right-sided Grasp Reflex ($F = 3.48$, $p = 0.068$).

Conclusion: NSS may represent a number of underlying pathophysiologies. Disinhibition soft-signs have been shown to be most similar in severity in patients with schizophrenia and their siblings. Of these Mirror movements may be the best marker of both familial and phenomenological psychosis-proneness.

Acknowledgment: This study was supported by the Stanley Medical Research Institute.

127. WEB-BASED SCREENING OF PSYCHOTIC SYMPTOMS: POSSIBILITIES AND PROBLEMS

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Background: Surveys of unselected general population samples have shown that at large number of individuals report any experience resembling the clinical psychosis concept. The Internet can be an effective medium for collection of such epidemiological large-scale psychology- and psychiatry-related data.

Method: 50 000 women (40–60 years) received an invitation letter containing instructions, a personal login and the web address to the Women Health and Lifestyle Study. The questionnaire contained questions concerning physical activity, smoking, alcohol, diet, childbearing, hormone therapy, self-reported medical conditions, depression and psychotic symptoms. The instrument Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002; see http://cape42.homestead.com) was translated to Swedish and adapted as an online screening for positive psychotic symptoms.

Results: We have so far obtained a 45% response rate (including one reminder) and we have no indications that the response rate is lower among questions concerning psychiatric symptoms compared to other part of the health survey. The Swedish personal national registration number and population-based registers guarantee basic information on responders and non-responders. The data permit analysis of co-morbidity and risk factors associated with self-reported positive psychotic symptoms.

Conclusion: The Internet provides an inexpensive, easily maintainable way to collect data on psychiatric symptoms on a large-scale basis in the population, even if a poor response rate may hamper the potential for prevalence estimation. Studies examining this new tool more closely are needed to guide future web-based strategies.

128. POPULATION-SURVEY COMPARING HALLUCINATING AND NON-HALLUCINATING ADULTS AS TO HEALTH, WAY OF LIVING AND HEALTH CARE CONSUMPTION

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Objective: Population-survey comparing hallucinating and non-hallucinating adults as to health, way of living and healthcare consumption.

Methods: Descriptive study with self-report questionnaire of a randomized (2%) sample of the population (>20 year). Statistical analyses: SPSS for windows 11. Differences were tested by means of parametric (independent samples two-tailed *t*-tests) and nonparametric tests (chi-square); alpha set at 0.05.

Results: Response-rate = 57.5% ($N = 3552$). Mean age for group was 49.5 year, for hallucinators 45.7 ($p < 0.01$). Percentages reporting only 1 hallucination were respectively 1.6 (voices), 1.0 (visions), and 1.3 (smell). Year-prevalence was, respectively, 3.0, 2.2, 2,3 and 5.5 for any hallucination. Except for visions, females reported more hallucinations. Substantially more younger patients (< 50 years) reported hallucinations. Hallucinating people reported poorer general health, physical, psychic and social functioning

($p < 0.001$). They had significantly more comorbidity on most somatic disorders ($p < 0.001$), except for hypertension, diabetes, arthritis, malignity and diseases of kidney, liver or gallbladder. During the preceding 3 months, hallucinating people consulted significantly more their family doctors, medical specialist, social workers, home nursing. They were prescribed significantly more and more different types of medication in the preceding 2 weeks, except for sleeping pills and antibiotics. Their cannabis ($p < 0.001$) and amphetamine ($p < 0.05$), but not the alcohol consumption was significantly higher. Almost half reported modest to severe loneliness, twice as much as the general population, and significantly more social disability ($p < 0.001$).

129. LONGITUDINAL ASSESSMENT OF SCHIZOTYPIC YOUNG ADULTS

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Background: The reliable identification of schizotypic individuals should facilitate our understanding of the development of schizophrenia and ultimately hasten the development of prophylactic treatment interventions.

Methods: The present study reports complete findings from the initial assessment and preliminary findings from a 3-year reassessment of schizotypic young adults. Participants (age: M = 19.1; S.D. = 1.1) identified by the Revised Social Anhedonia Scale ($n = 78$) and control subjects ($n = 68$) completed a neurocognitive battery, questionnaires assessing social functioning and personality, and a structured diagnostic interview.

Results/conclusion: Cross-sectional results indicated that the Social Anhedonia group had elevated ratings of positive, negative, schizotypal, schizoid, and paranoid symptoms, poorer performance on neurocognitive measures, and impaired social and overall functioning relative to the control subjects. Confirmatory factor analyses supported a three-factor solution with positive symptom, negative symptom, and cognitive disorganization dimensions. We have presently reinterviewed half of the sample at the follow-up assessment. Thus, far two of the Social Anhedonia participants and none of the control group have transitioned into psychotic disorders (delusional and schizophreniform disorders). Preliminary findings replicate the cross-sectional group differences and support the stability of schizotypic symptoms. The inclusion of scores on the Magical Ideation Scale and performance on the CPT was found to augment the prediction of symptoms at the follow-up assessment. The Revised Social Anhedonia is a promising measure of schizotypy and the present study provides the opportunity to examine the predictive validity of the scale in conjunction with other established psychometric and neurocognitive measures of vulnerability for schizophrenia.

130. ALEXITHYMIA AND SCHIZOTYPY

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Objective: We examined the association between alexithymia and psychometric schizotypy in non-clinical subjects.

Methods: One-hundred and seven non-clinical subjects completed the brief version of the Schizotypal Personality Questionnaire (SPQ-B), the Launay-Slade Hallucinations Scale (LSHS), the 21-item version of the Peters et al. Delusions Inventory (PDI-21), and the Bermond-Vorst Alexithymia Questionnaire (BVAQ).

Results: Correlational analyses (for the whole population) revealed that the cognitive-perceptual and disorganisation sub-scores of the SPQ-B were inversely correlated with the total BVAQ score. In contrast, the interpersonal sub-score of the SPQ-B was positively correlated with the total BVAQ score. In addition, when we compared a group of subjects with high hallucination-proneness ($n = 48$) and a group with low hallucination-proneness ($n = 52$), we observed a significant difference between the two groups on the fantasising and emotionalising dimensions of the BVAQ. A group of subjects with high delusion-proneness ($n = 49$) and a group with low delusion-proneness ($n = 52$) were also compared, revealing a significant difference between the two groups on the identifying and emotionalising dimensions of the BVAQ. Finally, correlational analyses (for the whole population) revealed that the fantasising and emotionalising dimensions of the BVAQ were correlated with all types of hallucinatory experiences (i.e. sleep-related hallucinations, vivid daydreaming, intrusive thoughts, and auditory hallucinations), with the exception of visual hallucinations.

Conclusion: These findings suggest that alexithymia is differentially associated with positive and negative psychometric schizotypy. In particular, hallucination-proneness seems to be related to increased sensitivity to emotional arousal and increased fantasising, whereas delusion-proneness seems to be related to increased sensitivity to emotional arousal and difficulties in identifying emotions.

Cerebral Asymmetry

131. LOSS OF PLANUM TEMPORALE ASYMMETRY IN ADOLESCENT ONSET PSYCHOSIS

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Background: In accord with Crow's hypothesis of altered cerebral asymmetry and language lateralisation in psychosis, meta-analysis of adult schizophrenia studies reported loss of asymmetry in the planum temporale (PT)[1], a structure that coincides with Wernicke's speech region. In contrast, PT asymmetry was reported to be unchanged in childhood onset schizophrenia[2]. Investigation of PT asymmetry in adolescent onset psychosis may offer insight into the discrepancy between adult and childhood findings.

Methods: We quantified PT asymmetry from 3D MR images of 35 adolescents (20 male, mean age = 16.60) with schizophrenia or schizoaffective disorder and 31 adolescent controls (19 male, mean age = 15.81). Images were smoothed and segmented in normalized space, and grey matter images were flipped about the $x = 0$ axis. These mirror images were subtracted voxel-by-voxel from the unflipped images to give difference images showing areas of unequal grey matter between cerebral hemispheres. A PT mask was created from a mean difference image and was used to extract mean PT asymmetry for each individual.

Results: Patients had significantly less leftward PT asymmetry than controls ($p = 0.040$); however, exclusion of a statistical outlier in the control group reduced this effect to a trend ($p = 0.063$).

Conclusion: Together with previous findings, this result in adolescents with psychosis suggests that later onset may yield greater alteration of asymmetry in language related cortical areas.

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132. EVIDENCE FOR ALTERED CEREBRAL LATERALITY IN EARLY ONSET SCHIZOPHRENIA

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Background: Few studies have examined cerebral laterality in early onset schizophrenia.

Methods: We investigated 33 first episode patients compared to 30 normal controls using neuropsychological, divided visual field (DVF) and neuroimaging measures in order to determine if anomalies in cerebral laterality that are observed in adults with schizophrenia are also present in late childhood and adolescent onset patients (mean age = ~ 16 years).

Results: Relative to controls, early onset patients demonstrated reduced right-hand skill ($p < 0.05$), absence of leftward visual perceptual bias ($p < 0.01$), reduced left hemisphere language processing asymmetries on the DVF ($p < 0.05$) but not on the dichotic listening task (n.s.). Alterations in cerebral asymmetry were also present and interacted with sex ($p < 0.01$). Compared to sex-matched controls, males showed a significant reduction in left hemisphere volume ($p < 0.05$) whereas females showed a reduction in rightward asymmetry ($p < 0.05$). Correlations between cerebral asymmetry of the anterior cingulate and verbal fluency in controls ($r = 0.35$, $p < 0.05$) were absent in schizophrenic cases.

Conclusion: Together, the results indicate reduction or loss of cerebral dominance and asymmetry in early onset cases consistent with the view that the relationship between the hemispheres is anomalous in schizophrenia.

133. CONSISTENCY IN THE RELATIONSHIP BETWEEN DEGREE OF FUNCTIONAL LATERALIZATION AND LEVEL OF COGNITIVE FUNCTION, BETWEEN DATASETS AND MEASURES

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Background: It has been previously demonstrated, in data from the 1958 UK NCDS birth cohort, that functional lateralization as measured by a box-marking task is positively related to higher cognitive function. That is, loss of functional asymmetry is associated with impaired cognitive performance (1). An approach that avoided several potential confounds came to the same conclusion (2), although this was perhaps not surprising since it employed the same dataset as the original finding. While this finding supports theories suggesting increased cerebral lateralization provides a selective advantage, attempts to replicate it have met with mixed success.

Methods: A similar analysis was conducted in a different sample ($n = 533$), measured using the well-known Annett pegboard test.

Results and conclusion: The results are consistent with the original analysis: Loss of functional asymmetry is associated with impaired cognitive performance.

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134. POSITIVE SYMPTOMS, DURATION OF ILLNESS AND MEDICATION PREDICT DICHOTIC LISTENING PERFORMANCE IN 129 SCHIZOPHRENIC PATIENTS

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Background/objective: Dichotic listening (DL) performance in schizophrenia has been shown to vary with subgroup characteristics. DL with consonant–vowel syllables is a measure of hemispheric asymmetry and the functional integrity of the left temporal lobe language areas. Abnormalities of these brain areas may be related to positive symptoms, duration of illness and medication. We wanted to test whether these variables predict DL performance. Previous studies have involved inadequate sample sizes to test intra-group variability, and have not taken the high inter-correlations between the clinical variables into account.

Methods: We pooled patients from four previous DL studies to create a large and heterogeneous group of 129 schizophrenic patients. The DL procedure also included attentional instructions, making it a dual-task test. Structural Equation Modelling (SEM) was used to confirm expected relationships, allowing for complex inter-correlations between the clinical variables.

Results: A model where positive symptoms, duration of illness and medication predicted DL performance showed the best fit to the data. Positive symptoms predicted a laterality component in DL. More positive symptoms were related to dysfunctions of the left temporal lobe language areas. Duration of illness and medication predicted an attention component in DL.

Conclusion: Possibly the effect of illness length and medication, indicating chronicity, disrupt the interaction between frontal attentional networks and temporal lobe language areas.

135. BRAIN TORQUE RELATES TO LATERALITY OF MOTOR FUNCTION BUT NOT HAND PREFERENCE

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Background: According to Crow's hypothesis, laterality of function should relate to underlying structural asymmetry. We have previously shown that brain torque (leftward occipital and rightward frontal asymmetry) does not differ in strongly (above 70%) left- and right-handed individuals [1].

Methods: Here, we present data from 29 healthy right-handed subjects (12 male) who completed behavioural [Annett Handedness Inventory (AHI) and Annett pegboard test] and functional MRI (block design finger tapping with alternating left hand, right hand and rest) assessments of hand dominance as well as having a structural MR scan. Subjects AHI scores were between 6 and 24, which equates to 25–100% right handed. Scanning was performed on a 1.5-T Siemens Sonata, fMRI analysis was performed using (fMRI Expert Analysis Tool, www.fmrib.ox.ac.uk/fsl) and brain torque was measured using LowD [2].

Results: Average activation in these right-handed subjects was significantly more lateralised when using right than left hand for finger tapping ($F = 5.2$, $p < 0.001$). No significant correlation was found between Annett pegboard laterality and fMRI laterality; however, a significant correlation between fMRI laterality for right finger tapping and brain torque ($r = 0.6$, $p = 0.01$) was observed.

Conclusion: Taking the results of this and the previous study [1] together, it appears that while the side of hand preference does not relate to structural asymmetry, the degree to which the function is lateralized does.

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136. THE ASSOCIATION BETWEEN POSITIVE SCHIZOTYPAL TRAITS AND HANDEDNESS IN A NON-CLINICAL SAMPLE

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Background: Crow and others suggest loss of cerebral dominance contributes to the aetiology of schizophrenia. This is referred to as the ''right shift'', and may have a genetic basis. Others such as Van Os describe schizotypy and schizophrenia as a continuum between healthy variation and severe mental illness. These two approaches suggest loss of hemispheric dominance could also be present in non-clinical subjects scoring highly on positive schizotypal traits (e.g., delusional ideation).

Methods: To test this prediction, we assessed schizotypy (as measured by the Oxford-Liverpool Inventory of Feelings and Experiences; OLIFE) as a function of handedness (as measured by the Edinburgh Oldfield Handedness Inventory) in a Canadian sample of healthy twins. The sample was split (above the 75th percentile, below the 25th percentile, and between the 25th and 75th percentile) using their scores on a Positive Schizotypy factor derived from the O-LIFE and their Oldfield Inventory handedness score (left, right and mixed).

Results: Cross-tabulation indicated that relative to the left- and right-handed subjects, the distribution of the mixed handed individuals was significantly (chi-square, $p < 0.05$) skewed towards high-positive features of schizotypy and away from low-positive features of schizotypy. This association appeared to be specific to the Positive Schizotypy factor, as the same analyses carried out on other schizotypy-related factors derived from the O-LIFE (e.g. 'Introvertive Anhedonia' and 'Anxiety') were not significant.

Conclusion: This study confirms that the ''loss of hemispheric dominance'' account of schizophrenia may extend to the positive features of schizotypy.

137. HANDEDNESS IN SCHIZOPHRENIC PATIENTS

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Background: It has been hypothesized that a decreased cerebral lateralisation could underlie the schizophrenic symptomatology. Handedness is a frequently used index for cerebral asymmetry. The disturbed lateralisation would lead to an increase in mixed handedness in schizophrenic patients. Objective and subjective measures for handedness were developed often leading to inconsistent results.

Methods: In our study, the handedness of 104 schizophrenic patients was evaluated subjectively by means of Annett's questionnaire in which people are asked to indicate which hand they preferably use for a number of every day actions. Patients were additionally asked to actually perform the actions questioned to objectively assess their handedness.

Results: Our results show a discrepancy between the objective and subjective registration of Annett's questionnaire: 37.5% patients are categorised as mixed handed on the basis of their own responses whereas 58.6% of patients are observed to be mixed handed when they actually have to perform the actions. No significant differences were found between male and female patients on the subjective measure of handedness. The objective measure of handedness however revealed mixed handedness to be significantly more frequent in male patients (66.7%) than in female patients (46.3%).

Conclusion: The significant difference between the results of objective and subjective measures of handedness motivates the use of objective measures of handedness in schizophrenic patients especially since these patients often suffer from severe cognitive deficits.

138. IS THE INTENSITY OF SCHNEIDERIAN SYMPTOMS RELATED TO HANDEDNESS AND SPEECH DISORDER IN SUBJECTS WITH PSYCHOSIS?

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Objective: To explore the links between Schneiderian First-Rank Symptoms (FRS), handedness and speech disorder in subjects with psychosis.

Methods: A Schneiderian score was calculated by summing 7 items of the Scale for the Assessment of Positive Symptoms exploring first-rank symptoms in 33 hospitalized patients presenting

with psychotic symptoms. Speech disorder was rated using the Scale for the Assessment of Thought, Language and Communication Disorders (TLC). Handedness was assessed using the Edinburgh Handedness Inventory.

Results: Higher Schneiderian score was independently predicted by reduced right-hand preference and by lower TLC score. The associations between Schneiderian score and lateralisation or speech disorder were independent from level of psychotic and depressive symptoms, and from categorical diagnosis.

Conclusion: The present study adds further support to the hypothesis that loss of normal cerebral asymmetry may be implicated in the emergence of FRS.

139. NEUROPATHOLOGY OF SCHIZOPHRENIA: SUBCORTICAL AND LIMBIC SYSTEM STRUCTURES ASYMMETRY DEMONSTRATED WITH STRUCTURAL MRI

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Background/methods: According to the increase in evidence for the role of brain structural lateralized abnormalities in the pathophysiology of schizophrenia, 19 schizophrenia patients and 10 matched healthy controls were examined. Three-millimeter Coronal T1-weighted 3D magnetic resonance images were acquired on a 0.5-T magnet Tomikon S50, Bruker (Germany). The hippocampal, caudate, amygdala and putamen volumes were calculated. The age of onset and duration of the illness, and severity of positive and negative symptoms also were estimated. The correlation analysis between tomographic and clinical parameters was performed.

Results: The findings showed significant inverse correlations of the left hippocampus, left caudate volumes with illness duration and the left amygdala volume with severity of negative symptoms ($p < 0.05$). The putamen volume inversely correlates with severity of negative symptoms either in the left or right side ($p < 0.05$). The correlations between left caudate and left putamen volumes and severity of positive symptoms were direct.

Conclusion: These results indicate a role for asymmetric abnormalities of subcortical and limbic structures in the pathogenesis of schizophrenia.

Language

140. DISPROPORTIONATE IMPAIRMENT IN SEMANTIC, RELATIVE TO PHONEMIC, VERBAL FLUENCY IN SCHIZOPHRENIA: DIFFERENTIAL DEFICIT IN CLUSTERING

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Objective: The purpose of the current study was to investigate whether patients with schizophrenia present disproportionate impairment in semantic, relative to phonemic, fluency. Specifically, we explored whether this impairment could be explained by differential deficits in clustering or switching strategies.

Methods: The Greek Verbal Fluency Test was administered to 119 patients with schizophrenia and 225 age- and education-matched healthy controls. We calculated the total number of words generated, the number of words related by clusters, and the number of switches on the semantic and phonological fluency tasks separately.

Results: Patients with schizophrenia generated fewer total words, words related by clusters and switches than healthy controls in each of the fluency tasks. When the total number of words produced was used as a covariate, differences between the two groups in number of words related by clusters and switches disappeared. We found a significant group × fluency type interaction for total word production, suggesting disproportionate impairment in semantic, compared with phonemic, fluency in schizophrenia. Moreover, a significant group × fluency type interaction emerged for the number of words related by clusters, but there was no group × fluency type interaction for switches, suggesting that the disproportionate semantic deficits could be attributed to a disproportionate impairment in the number of words related by clusters and not in the number of switches.

Conclusion: Patients with schizophrenia used the same strategies as healthy controls to perform on a word fluency test, but they used them less effectively. Disproportionate impairment in semantic fluency in schizophrenia resulted from a differential deficit only in clustering. Therefore, disproportionate impaired category fluency in schizophrenia may be primarily due to disorganization and not to inefficient access and retrieval from semantic store.

141. SEMANTIC INFORMATION PROCESSING IN SCHIZOPHRENIA: AN EXAMINATION OF THE DISTANCE AND CONGRUENCY EFFECT

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Background: Patients with schizophrenia frequently display problems processing semantic knowledge and have difficulties with some aspects of cognitive control.

Methods: An experimental paradigm was created to examine semantic knowledge representation, retrieval and processing, as well as cognitive control in patients with schizophrenia as compared to control participants. This was operationalized by examining (1) the ''distance effect'', namely that judgments about stimuli further apart in size are faster and more accurate than judgments for stimuli whose sizes are more similar, and (2) the ''congruency effect'', namely that processing congruent information is quicker and more accurate than processing incongruent information. Participants rapidly determined whether one of two stimuli presented on a computer monitor was larger or smaller in the real world than the other. Stimuli pairs were either words or their corresponding images (e.g., ''bee'' and ''sailboat''). We manipulated real-world ''distance'' within the stimuli pairs in terms of size (e.g., ''bee'' and ''sailboat'', or ''bee'' and ''lightbulb''). We also manipulated ''congruency'' between real-world size and physical size on the monitor of the image pairs (e.g., small ''bee'' and large ''sailboat'', or large ''bee'' and small ''sailboat''), a task requiring a degree of cognitive control.

Results: Crucially, we found that both the distance and congruency effects were qualitatively equivalent across groups.

Conclusion: This suggests that some aspects of semantic knowledge are represented equivalently in patients and controls, and that patients can use this information to override incongruent information in a manner similar to controls.

142. A NOVEL APPROACH TO MEASURING COHERENCE AND INCOHERENCE IN SPEECH

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Background/objective: Communicating ideas and thoughts through the medium of language is a fundamental aspect of human behavior. Incoherent discourse, with a disjointed flow of ideas, is a cardinal symptom in psychosis. Measuring the coherence of thoughts is complex. We sought to develop and validate an objective, reliable and automatic computational tool with which to measure coherence and incoherence in speech in schizophrenia.

Methods: As a framework, we adopted a theoretical approach to modeling semantics of discourse, focusing on such factors as the choice of words, expression of meaning, relatedness of discourse and coherence. A variety of language tasks were employed in which discourse was generated (e.g., word generation from word association and verbal fluency tasks, and discourse from conversations and structured interviews). This discourse was rated for coherence by humans as well as by Latent Semantic Analysis (LSA), a computational linguistic technique for extracting and inferring relations of expected contextual usage of words in passages of discourse (Landauer and Dumais, 1997).

Results: Importantly, there was a strong relationship between our novel experimental measures and human ratings of thought disorder, and our automated approach was able to predict group membership in a manner similar to blind human raters.

Conclusion: Analysis of discourse using LSA suggests that disordered thinking in schizophrenia occurs at both association and higher level planning stages. The resulting methodological framework has broad relevance to understanding specialized aspects of semantic processing, drug studies that monitor treatment responsiveness, cognitive neurophysiological mapping studies that index neural dysfunction and genetic studies that explore phenotypes.

143. RELATIONSHIP BETWEEN LANGUAGE FUNCTION AND BRAIN DAMAGE IN PRETERM ADOLESCENTS

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Introduction/objective: Structural MRI studies have reported smaller cortical volumes and larger lateral ventricles in preterm-born adolescents compared to controls. Decreased volume has been observed in superior temporal and cingulate gyri, parietal and frontal lobes. In terms of neuropsychological outcome, preterm individuals perform poorly on verbal fluency tasks. Similar neuropsychological impairments are often found in schizophrenia. The present study is an investigation of structural brain abnormalities and whether they are associated with poor language production in preterm adolescents.

Methods: A sample of 14–15-year-old individuals born at less than 33 weeks of gestation completed the Controlled Oral Word

Association Test, a measure of verbal fluency. Two groups were compared according to task performance: 11 individuals who scored half standard deviation (S.D.) below the mean score; and 12 individuals who scored half S.D. above the mean score. Grey and white matter deficits were compared between the two groups, using SPM99.

Results: Poor performance in the verbal fluency task was associated with grey matter reductions bilaterally in cingulate and left middle frontal gyri, and right precuneus. White matter deficits were found in left middle frontal and right inferior frontal gyri, right basal ganglia, left parahippocampal gyrus and parietal lobe.

Conclusion: As in schizophrenia, poor verbal fluency performance in preterm individuals seems to be associated with structural and possibly functional deficits in the frontal lobes. In fact, the regions implicated in poor verbal fluency performance in preterm adolescents are similar to the regions that show abnormal neuronal activation in schizophrenia during performance of tasks involving higher cognitive functions.

144. IMPROVED AUDITORY HALLUCINATIONS AND REDUCED PRIMARY AUDITORY AREA'S ACTIVATION FOLLOWING TMS

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Background: Recent studies reported beneficial effects of low-frequency transcranial magnetic stimulation (TMS) of speech associated cortical areas on auditory hallucinations in patients with medication-resistant hallucinations. Therefore, incorporating functional imaging may help to elucidate the physiological changes induced by TMS. We investigated the question whether decreased hallucinations after TMS therapy corresponded to changes in activation of auditory cortices.

Methods: Using functional magnetic resonance imaging (fMRI), activation of the auditory cortices was assessed prior to and after a 4-week TMS series of the left superior temporal gyrus in a patient with medication-resistant auditory hallucinations.

Results: Hallucinations improved slightly after the third and profoundly after the fourth week of TMS. Activation in the primary auditory area decreased, whereas activation in the operculum and insula remained stable.

Conclusion: Combination of TMS and repetitive fMRI may enhance our understanding of the biological basis of hallucinations in schizophrenia, and elucidate the physiological changes induced by TMS.

145. THE ROLE OF PRAGMATICS IN THEORY OF MIND DEFICITS IN SCHIZOPHRENIA. DIFFERENCES BETWEEN SCHIZOPHRENIA AND DEPRESSION

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Background: According to developmental psychological studies theory of mind development is connected with the development of pragmatic language skills. On the other hand, developmental psychopathological studies suggest that preschizophrenic children exhibit language deviances early in the childhood, and it may play significant role in inappropriate development of theory of mind skills. According to our hypothesis, patients with schizophrenia would be impaired in tasks requiring pragmatic language skills and it would relate to weak performance in tasks requiring theory of mind skills.

Methods: Twenty-eight patients with schizophrenia and 20 control patients with non-psychotic depression took part in the study. Participants were presented two first-order, two-second order theory of mind tasks and two metaphor and two irony tasks for the assessment of theory of mind skills. Four short "question and answer" vignettes examined the decoding of the violation of the maxim of relevance as pragmatic language skills.

Results: Patients with schizophrenia performed significantly worse in the irony and maxim tasks, but there was no correlation between the performances in the irony and in the maxim tasks, whereas in the depression group a weak correlation remained. However, there was a significant relationship between the performances in the irony and maxim tasks considering the whole studied population.

Conclusion: Our results suggest that the theoretical correlation prevails in non-schizophreniform states only. The theory of mind deficits of people with schizophrenia cannot be explained with pragmatic language deficits alone, and the manifest impairment is the consequence of disturbances of multiple cognitive processes.

146. IMPAIRED SYNTAX PRODUCTION IN SCHIZOPHRENIA IS MEDIATED BY THE TEMPORAL LOBE

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Background: The production of grammatically complex sentences is impaired in schizophrenia. We examined the neural correlates of syntax production in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI).

Methods: Blood oxygenation level dependent (BOLD) contrast was measured with fMRI while six patients with schizophrenia and six healthy control subjects spoke about seven Rorschach inkblots for 3 min each. Subjects produced varying amounts of simple and complex sentences during each run. In a within-subject design, the number of simple and complex sentences was correlated separately with the BOLD contrast in the two runs from each participant that showed the highest variance in sentence complexity.

Results: In control subjects, the number of complex sentences produced was correlated with activation in the posterior portion of the middle temporal gyrus bilaterally (BA 21, 39). In patients, this correlation was evident in the left posterior middle temporal gyrus but not the right.

Conclusion: An association between the production of syntactically complex sentences and engagement of the posterior temporal cortex is consistent with data from functional imaging studies in healthy volunteers. The absence of activation in the right posterior temporal cortex in patients with schizophrenia might contribute to the articulation of grammatically more simple speech in people with this disorder.

147. MEASUREMENT OF LATERALITY USING FUNCTIONAL MRI

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Background: Testing Crow's hypothesis that functional laterality is altered in patients with psychosis requires that methods for accurate assessment of laterality in vivo are established. Previous laterality fMRI studies (e.g. Ref. [1]) have generally compared the number of 'active' voxels in a volume of interest (VOI) in one hemisphere relative to the other.

Methods: Here, we measure laterality for two block design paradigms in 33 control subjects (16 male) and 12 patients with psychosis (7 male). Language laterality was assessed using a word generation task and motor laterality was assessed using finger tapping (alternating hands). We examined the effects of different statistical thresholds ($z = 2.3$, 4.8, 7.3) on voxel count laterality and also computed the mean percentage signal change. We also examined the effect of VOI selection by extracting (1) whole hemisphere, (2) anatomically derived (middle and inferior frontal gyri for language; pre- and post-central gyri for motor) and (3) functionally derived (based on the group activation maps) VOIs.

Results: Mean voxel count laterality increased in each VOI as the threshold was increased. The anatomically derived VOI gave significantly higher mean laterality indices than the whole hemisphere VOI for each method of calculating laterality ($p < 0.05$). Patients had significantly reduced language laterality relative to controls as assessed by voxel counting in the anatomically defined VOI at a threshold of $z = 2.3$ ($p = 0.04$).

Conclusion: Sensitivity of laterality measures differs according to the method used, but preliminary results are supportive of the hypothesis that lateralisation is reduced in patients with psychosis.

Reference

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148. SENTENCE COMPREHENSION IN SCHIZOPHRENIC SUBJECTS WITH AUDITORY HALLUCINATIONS: AN EVENT-RELATED fMRI STUDY

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Background: Auditory hallucinations are a common feature in schizophrenia that may resist to pharmacological treatment. Neuroimaging studies suggest that auditory hallucinations arise, at least in part, from activation of brain areas underlying speech perception and comprehension.

Methods: We used event-related fMRI to explore the cerebral response to speech comprehension in 15 schizophrenic patients with auditory hallucinations and 15 healthy volunteers. Subjects listened to sentences standardised and randomised in French, unknown foreign languages, or silence. To ensure that the subjects paid attention to sentences, they were required to perform a phoneme detection task. Images were analysed using SPM99. The contrast between languages isolated the brain area underlying speech comprehension (1).

Results: In controls, the contrast French versus foreign languages classically engaged the temporal and frontal cortex, especially in left hemisphere. Between-group comparison revealed reduced responsivity of Wernicke's area and gyri angularis to speech comprehension in patients.

Conclusion: The attenuated engagement of Wernicke's area, usually engaged in speech comprehension, is consistent with this area's contribution in physiopathology of auditory hallucinations. Present result further suggests a competition for a common neural substrate by auditory hallucinations and speech comprehension.

Reference

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149. DISTURBANCES OF PROSODY IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: It has been proposed that patients with schizophrenia have difficulties with emotional prosody but the fundamental mechanism of this abnormality has not yet fully explored. In this study, we studied patients with schizophrenia to elucidate whether the disturbance of prosody was restricted to domain of emotional prosody or related to a more fundamental ability to discriminate pitch and timing parameter of linguistic and musical prosody.

Methods: We examined 12 patients with schizophrenia and compared them with normal controls performing linguistic and musical prosody discrimination tasks with pitch and timing parameters as well as an emotional-prosody detection task. In the linguistic/musical prosody discrimination tasks, subjects were asked to discriminate whether pairs of sentences or musical sequences were similar or different. In the emotional-prosody task, they were required to judge whether sentences sounded emotional or neutral.

Results: Preliminary results show that patients' performance was comparable to controls in pitch discrimination during the linguistic-prosody task. In the musical-prosody tasks, patients performed significantly worse than controls in a task requiring pitch discrimination. In the emotional-prosody judgment task, patients performed significantly worse than controls. Correlation analysis revealed that disturbance of emotional prosody was not correlated with performance on pitch and timing discrimination tasks.

Conclusion: We conclude that patients with schizophrenia have some deficit in processing of linguistic and musical prosody, which might be independent of disturbance of emotional prosody. We plan to examine the association of these prosodic deficits with changes in patients symptom severity.

150. THOUGHT DISORDER IN PATIENTS AFFECTED BY SCHIZOPHRENIA AND BIPOLAR ILLNESS: A CONTROLLED STUDY

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Background: Thought disorders occur frequently in psychoses. Experimental studies have shown that both schizophrenic and bipolar patients display higher amounts and relevant specific qualities of thought disorder when compared with healthy subjects. Moreover genetic epidemiologic studies suggest a genetic component in the transmission of such symptoms in twins. The findings of higher levels of thought disorder and qualitative specificity of formal thought disorder in schizophrenia and bipolar disorder is derived from American studies using Thought Disorder Index (TDI) (Johnston and Holzman, 1979; Solovay et al., 1986), but the generalizability of these findings to other cultural and linguistic contexts has not yet been elucidated.

Methods: A sample of 10 schizophrenic patients, 10 bipolars and 10 non-psychiatric controls were assessed for thought disorder with the Italian version of the TDI. The mean age of the groups was 35.9, 50.2 and 36.6 years, and the TDI score was 66.8, 31.6 and 3.7. Diagnoses were made according DSM-IV and ICD-10 Research Criteria.

Results: Schizophrenic and bipolar patients show statistically significant higher Thought Disorder Score when compared to healthy controls (ANOVA: F 4.9, df 2.27; $p = 0.015$). Age did not account for these differences, since the result was unchanged when age was covaried in an ANCOVA (ANCOVA F 3.28, df 2.26; $p = 0.038$).

Conclusion: The present study confirms what previous studies have shown, but now in a different cultural and linguistic background, that schizophrenic and bipolars show formal thought disorders when compared with non-psychiatric subjects.

151. EVIDENCE OF SEMANTIC DISORGANISATION USING SEMANTIC PRIMING IN INDIVIDUALS WITH HIGH SCHIZOTYPY

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Background: Semantic processing deficits are central to cognitive abnormalities in schizophrenia and are particularly evident using semantic priming tasks. However, semantic priming research in schizophrenia has often been criticised for methodological artefacts and confounds, including long hospitalisations and medication of patient samples. Utilising high schizotypes (psychosis prone individuals) can overcome the confounds involved in studying actively symptomatic schizophrenics.

Methods: In the current study, 24 high and 30 low scorers on the *O-LIFE* schizotypy scale (from a sample of 251 students) were selected for testing. All subjects were administered a lexical-decision semantic priming task where half the stimuli had a short 200-s stimulus onset asynchrony (SOA, length of time from onset of prime to onset of target) and half the stimuli had a long 750-ms SOA.

Results: Low schizotypes showed greater priming at the 200-ms SOA than at the 750-ms SOA (37 and 19 ms), whilst individuals with high schizotypy showed the opposite pattern (12 and 43 ms) ($F(1,54) = 5.7$, $p < 0.02$). The pattern shown by the low schizotypes replicates earlier work by the authors using other normal control samples; establishing in normals there is greater priming under conditions of automatic spreading of activation. Furthermore, the data shows there is not an increase in automatic spreading of activation in high schizotypy (less priming at the 200-ms SOA). There has been controversy in previous schizophrenia research over whether there is increased priming under automatic conditions.

Conclusion: The data presented here suggest that when confounds are controlled for there is not an increase in automatic semantic priming in schizophrenia or related individuals.

152. LANGUAGE COMPREHENSION AND THOUGHT DISORDER IN SCHIZOPHRENIA

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Background/objective: Previous research has demonstrated abnormal language function in schizophrenia, including decreased functional lateralization. Disturbed language function may be a primary determinant of thought disorder (TD), a cardinal symptom of schizophrenia. Our lab and others have found TD to be associated with an increased extent of activation in bilateral temporal and parietal regions during performance of language tasks. The current study investigates the association between TD and abnormal language function during passive auditory comprehension using fMRI. We predicted that patients would show a greater extent of activation than control subjects in response to language stimuli, and that the severity of TD would be positively correlated with activation within these areas. We also predicted that schizophrenic subjects would show decreased lateralization of language function relative to controls, and that this pattern would correlate with TD.

Methods: Subjects heard 30-s blocks of English and reversed English speech. TD was assessed with the Thought and Language Index. Activation in regions defined with an exclusionary mask of areas activated during English comprehension in schizophrenic subjects but not controls supported our hypothesis of a greater extent of activation in patients.

Results: The schizophrenic subjects showed a greater extent of activation than controls in areas associated with language processing, including bilateral temporal and parietal regions. There were no significant correlations between TD and either the extent of activation or functional lateralization.

153. IN MALE ADOLESCENTS WITH NORMAL COGNITIVE FUNCTIONING, IMPAIRED READING COMPREHENSION IS ASSOCIATED WITH INCREASED RISK FOR LATER SCHIZOPHRENIA

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Background/objective: Disorders in language abilities are common in patients with schizophrenia, and some investigators claim that impaired language abilities are linked to the etiology of schizophrenia. We asked if impaired reading comprehension in adolescence increases risk for later schizophrenia.

Methods: We identified 240,781 Israeli-born male adolescents screened by the Israeli Draft Board, whose general cognitive abilities were within normal limits. Of these, 3229 (1.3%) had the third % lowest scores on a reading comprehension test. We followed these adolescents for later hospitalization for schizophrenia using the Israeli Psychiatric Hospitalization Case Registry.

Results: Of these male adolescents with impaired reading comprehension, 13/3229 (0.4%), compared with 361/237,552 (0.2%) were later hospitalised for NAPD. After controlling for cognitive and social functioning, the presence of non-psychotic psychiatric disorder in the draft board assessment and SES, the association with later schizophrenia was significant, RR = 1.8, 95% CI: 1.033 – 3.178.This

finding was specific for poor reading comprehension: in a group of 5671 males with impaired arithmetic abilities, defined as scoring 2 S.D.s lower on a mathematics test relative to their scores on a test of general cognitive functioning, the risk for later schizophrenia was not increased, RR = 0.431, 95% CI: 0.138–1.345.

Conclusion: In adolescent males, very poor reading comprehension in the presence of normal general cognitive functioning is associated with increased risk for later schizophrenia. This specific dysfunction of language processes might be a pre-psychotic manifestation of the language dysfunction common in schizophrenia, or a risk factor for schizophrenia.

154. FUNCTIONAL DISCONNECTIVITY IN SUBJECTS AT GENETICALLY ENHANCED RISK OF SCHIZOPHRENIA

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Background: It is generally accepted that schizophrenia is associated with neuronal abnormalities, but it has not been possible to explain the associated symptoms and cognitive deficits on the basis of specific, localised structural or functional disturbances. This has led to the suggestion that deficits could arise from abnormal interactions between brain regions, particularly involving connections with the prefrontal cortex. However, it remains unclear whether abnormal interactions in the established state relate to symptoms, medication, or genetic vulnerability.

Methods: We are engaged in an ongoing study of young adults at high genetic risk of schizophrenia. Functional connectivity analysis was carried out on fMRI scans from 21 controls and 69 high risk subjects performing a covert verbal initiation task. We also sought to confirm the connectivity results in two other tasks performed during the same scanning session; an encoding and a retrieval task.

Results: We found decreased prefrontal–medial temporal, and increased prefronto-parietal connectivity in high risk subjects as a group compared to controls across two different tasks. Across all three tasks reduced lateral–medial prefrontal connectivity in high-risk subjects was found in comparison with the controls. This deficit was also associated with the degree of genetic risk within the high risk group.

Conclusion: These results, all in a situation uncontaminated by effects of anti-psychotic medication, suggest there are abnormalities in connectivity in high-risk subjects which reflect genetic vulnerability to the disorder.

155. AN EVENT RELATED FUNCTIONAL MRI STUDY OF VERBAL ENCODING AND RETRIEVAL IN PEOPLE AT HIGH RISK OF SCHIZOPHRENIA AND CONTROLS

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Background: Neuropsychological evidence suggests that healthy relatives of schizophrenics are impaired to a lesser degree in the same functional domains as their schizophrenic relatives, above all in verbal memory. Recent results from neuroimaging studies of memory indicate brain activation differences between schizophrenics and controls in the frontal, temporal and parietal lobes. Abnormal brain responses in high risk groups relative to controls, in areas essential for effective memory processing, may reflect a biological vulnerability to schizophrenia.

Methods: We used event-related fMRI to assess brain activation during a verbal encoding and retrieval task in 68 high-risk participants and 21 controls.

Results: There were no significant task performance differences between groups. High risk participants showed a significantly greater fMRI response in the right parietal and bilateral occipital lobes during encoding and in the right middle frontal gyrus (BA 10) during correct retrieval relative to controls. Controls showed a significantly greater response in the left posterior cingulate gyrus and right precuneus during encoding, but no larger responses relative to the high-risk group during retrieval.

Conclusion: This clearly represents a qualitative difference between subjects at high risk of schizophrenia and controls in fMRI responses during verbal encoding and successful retrieval processing. Exaggerated brain responses in the high-risk group relative to controls could be attributed to a compensatory increased activation in genetically disrupted neuronal networks to achieve equivalent performance success.

Structural Imaging

156. NEUROPSYCHOLOGICAL CORRELATES OF STRUCTURAL BRAIN ALTERATIONS IN SCHIZOPHRENIA: A VOXEL-BASED MORPHOMETRY STUDY

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Objective: The study investigated structural brain alterations and their neuropsychological correlates in schizophrenia using voxel-based morphometry (VBM) method.

Methods: Forty-five patients (male 27, female 18) with chronic schizophrenia ($n=41$) and first-episode schizophrenia-like psychosis ($n=4$) and 43 closely matched healthy controls (male 25, female 18) underwent a magnetic resonance imaging scanning and a neuropsychological assessment of immediate verbal and visuospatial memory, set-shifting, cognitive flexibility, working memory, speed of information processing, attention, inhibition, and visuo-motor speed. Structural brain images were pre-processed according to the optimised VBM protocol in SPM99, as described by Good et al. (2001, Neuroimage). Statistical parametric maps of modulated grey matter images, adjusted for age and sex, were thresholded at $p<0.001$ (uncorrected).

Results: Patients exhibited disproportional (to the whole brain volume) grey matter volume reduction of the left hemispheric regions, including the inferior frontal gyrus (BA 47), lingual gyrus (BA 17), and temporal pole (BA 38), as well as a trend increase of the left putamen and an area adjacent to the left retrosplenial cortex. A smaller temporal pole was associated with slower verbal information processing and worse inhibition of pre-potent response; a smaller lingual gyrus with deficient visuo-motor speed; a larger putamen with the deficits of sustained attention and working memory; and a larger area of the posterior lobe with better immediate verbal memory and learning.

Conclusion: The study confirms the presence of left-hemispheric regional grey matter volume alterations in schizophrenia and reveals, for the first time to our knowledge, the specific neuropsychological correlates of these alterations identified using VBM.

157. A POPULATION-BASED MRI STUDY OF FIRST-EPISODE PSYCHOSIS IN BRAZIL

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Objective: There have been few population-based neuroimaging studies of psychosis, and none have been carried out in developing countries. We used MRI to examine a sample of patients with first-episode psychosis from São Paulo, Brazil.

Methods: Patients ($n=38$) with first-episode psychosis (ICD10 F20–29,F30–39) were recruited from a defined geographical area of São Paulo. Mean age was 27.3 (S.D. = 8.3) years, 19 subjects were male, mean illness duration was 18.5 (S.D. = 10) weeks, and 52.6% had been on antipsychotic medication for at least 2 weeks. Twenty-one patients met criteria for schizophreniform psychosis, 16 for affective psychosis, and 1 had a brief psychotic episode. Healthy subjects from the same area served as controls ($n=36$, age = 30.2 (S.D. = 8) years, 18 males). T1-weighted SPGR images were acquired using a GE Signa-LX 1.5-T system (124 slices, 1.5 mm thickness, TE = 5.2 ms, TR = 21.7 ms, flip-angle = 20°, matrix = 256 × 192). Segmented gray matter images were compared between groups with SPM2, using optimized VBM (Good et al., 2001).

Results: The first-episode psychotic group showed clusters of decreased gray matter relative to controls ($p<0.001$, uncorrected; >50 voxels) in the right pulvinar ($Z=4.09$; 153 voxels) and left fusiform gyrus ($Z=3.61$; 88 voxels). Patients with schizophreniform psychosis had less gray matter than patients with affective psychosis in the orbitofrontal cortex ($Z=3.45$; 55 voxels), but more in the superior frontal gyrus ($Z=4.13$; 182 voxels).

Conclusion: First-episode psychosis in patients from a developing country was associated with subtle volumetric abnormalities involving the thalamus and left temporal lobe. Differences in prefrontal volume were evident between patients with schizophreniform and affective psychoses.

Acknowledgment: Funded by the Wellcome Trust-UK.

Reference

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159. LIMBIC AND STRIATAL GREY MATTER EXCESS IN FIRST-ONSET SCHIZOPHRENIA

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Objective: We performed voxel-based morphometric analysis of structural MRI scans of first-episode schizophrenic subjects to identify abnormality in the volume of brain regions.

Methods: Eighteen patients consecutively admitted to the Accident and Emergency Department with a first-episode diag-

nosis of Schizophrenia were recruited. Twenty-eight normal healthy volunteers matched for age, sex, parental socioeconomic status, ethnicity, and handedness were recruited from the local community. Five patients were neuroleptic-naïve, and the rest had received neuroleptic medication for an average of a week prior to scanning. The whole brain near axial dual-echo data set was analysed using BAMM software (Brain Analysis Morphological Mapping version 2.5, Cambridge University). This allowed fully automated brain segmentation into grey and white matter and significant volume differences between patient group and controls were mapped across the brain.

Results: Results indicated that the two groups did not differ in the whole brain volume, grey matter nor cerebrospinal fluid volume. However, significant unilateral grey matter excess in the patient group was noted in the cingulate gyrus, parahippocampal gyrus, caudate, putamen and globus pallidus.

Conclusion: These results suggest that there is abnormality of the striato-limbic circuitry in early psychosis.

160. THE EFFECTS OF ATYPICAL AND TYPICAL ANTIPSYCHOTICS ON BRAIN STRUCTURE IN THE ÆSOP FIRST-ONSET PSYCHOSIS STUDY

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Background: Neuroimaging studies have shown that typical neuroleptics may increase volume, metabolism and relative blood flow in the basal ganglia, and that these actions can be reverted or not apparent with atypical antipsychotics. The mechanisms underlying the different actions of neuroleptics remain poorly understood. Patients at their first psychotic episode are currently more likely to receive atypical antipsychotics or low dose typical antipsychotics. Therefore, they represent an ideal sample to investigate differential effects of neuroleptics on brain structure.

Aims: This study investigated the effect of neuroleptics on brain structure in 90 patients at their first psychotic episode ($n = 35$ female; mean age 27 ± 8 years; $n = 50$ DSM IV Schizophrenia/Schizophreniform, and $n = 40$ DSM IV Other Psychosis). Of these, 50 patients were taking typical neuroleptics, 16 were taking atypicals, and 24 were drug-free.

Methods: Dual-echo MRI data were acquired at 1.5 T. Differences in grey matter between groups were estimated at each intracerebral voxel after registration of images in standard space.

Results: (1) In comparison to drug-free subjects, subjects on typical neuroleptics showed ($p < 0.002$): Larger grey matter volume of basal ganglia; smaller grey matter volume of the right insula and bilateral precuneus. (2) Subjects taking only atypical neuroleptics, compared to drug-free subjects, showed larger grey matter volume of the thalamus (bilaterally) ($p < 0.001$).

Conclusion: Even the short-term use of typical neuroleptics is associated with basal ganglia and cortical volume changes. Typical and atypical neuroleptics seem to affect the brain differently and this may partly explain their differences in efficacy and side-effect profile.

161. GREY MATTER CHANGES ON MRI ARE ASSOCIATED WITH MPAS IN THE AESOP FIRST-ONSET PSYCHOSIS STUDY

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Background: Minor physical anomalies (MPAs) are found with elevated frequency amongst those diagnosed with schizophrenia, providing evidence to support the neurodevelopmental hypothesis. Further evidence comes from the consistent finding that those who develop schizophrenia are more likely to demonstrate structural brain abnormalities. We wished to examine the relationship between the presence of minor physical anomalies and brain morphology (MRI) in a first episode psychosis sample.

Methods: This study investigated the brain structure of 60 patients at their first psychotic episode ($n = 24$ female; mean age 27 years S.D. 7.2; $n = 22$ schizophrenia; $n = 14$ mania; $n = 24$ other psychosis). MPAs were assessed using an abridged version of the Lane (1997) scale. A total score was generated and the sample divided into two groups (high and low MPA groups each with 30 subjects). Dual-echo MRI data were acquired at 1.5 T. Differences in grey matter between groups were estimated at each intracerebral voxel after registration of images in standard space.

Results: In comparison with the low MPA group, subjects with high MPAs showed the following differences ($p<0.002$): Larger grey matter volume of basal ganglia (bilateral), thalamus (bilateral), inferior temporal gyrus (right), lingual gyrus (bilaterally), and cuneus (right); smaller grey matter volume at the level of the lobulus paracentralis (bilaterally), with extension anteriorly into the dorsal frontal gyrus, posteriorly into the precuneus, and inferiorly into the cingulate gyrus (left).

Conclusion: The occurrence of high MPA frequency was found to be associated with grey matter volume changes on MRI in this study of first episode psychosis.

162. SUBCORTICAL CHANGES ASSOCIATED WITH ANTIPSYCHOTIC RESPONSE

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Background: Abnormalities within the cortico-striato-thalamo-cortical circuit have been suggested in schizophrenia. Diminished volumes of thalamus, striatum, and cortical gray have been described in neuroleptic-naive schizophrenics. Myelinated fibers connecting these information processing centers have been reported to be swollen, and to have impaired integrity on diffusion (tensor) imaging. The effects of antipsychotic drugs and of antipsychotic response upon such pathology has not been clarified.

Methods: Sixteen neuroleptic-free schizophrenics and controls were serially assessed for psychosis (SAPS) and for volumetric change of both cerebral white matter and of gray matter associated with thalamus, striatum, and cerebral cortex before and following 4 weeks of treatment with conventional or atypical antipsychotics.

Results: While no volumetric changes were found in controls, patients who had responded (SAPS reduction >25) had significant increases in thalamic and striatal volumes ($p < 0.05$), together with decreases in white matter volume ($p < 0.05$) as compared to poor responders. Companion diffusion tensor imaging (DTI) documented increased "integrity" (partial normalization) of the impaired myelinated connections among the information processing centers ($p < 0.05$). Cortical gray increases were found only in atypical antipsychotic-treated patients ($p < 0.03$).

Conclusion: Though antipsychotics themselves do not appear to alter brain structure in all schizophrenics, patients who experience antipsychotic response (SAPS reduction >25) during treatment appear to have partial restoration of integrity of myelinated connections among critical subcortical information processing centers, together with enhancement of thalamic and striatal volumes. Similar changes in cortical gray appear only in patients treated with atypical, but not conventional antipsychotics.

163. BRAIN VOLUME CHANGES IN 109 PATIENTS WITH SCHIZOPHRENIA COMPARED TO 130 CONTROL SUBJECTS: A 5-YEAR LONGITUDINAL MRI STUDY ACROSS THE AGE RANGE

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Background: Schizophrenia is generally characterized by a progressive decline in functioning. Although structural brain abnormalities are considered important to the pathology, it is not resolved whether the brain abnormalities become more prominent over time. Brain volume decreases over time, particularly in the first years of the illness (Cahn et al., 2002), have been reported in several studies, suggesting a progressive deterioration. A relationship with clinical deterioration or outcome has been suggested. However, whether these progressive brain abnormalities are restricted to the early stages of the disease or are also involved in the more advanced stages is not known.

Methods: For this purpose, we rescanned 109 patients and 130 control subjects from a large sample of first episode and chronic patients with schizophrenia ($n = 159$) and control subjects ($n = 158$) (Hulshoff Pol et al., 2001, 2002) on the same 1.5-T scanner using the identical scan protocol with an average time interval of respectively 5.0 (S.D. = 0.47, range 4.0–6.3) and 4.9 (S.D. = 0.32, range 4.2–5.7) years ($F = 1.41$; $p = 0.24$). Age ranged from 16 through 68 years at first measurement. Volumes of intracranium, whole brain, cerebral grey and white matter, third and lateral ventricles, and cerebellum were measured. Diagnostic interviews were carried out and information on symptoms and outcome was acquired.

Conclusion: This study will contribute to our understanding of brain volume changes in first onset and chronic schizophrenia over the adult age range.

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164. COVARIANCE OF 3D CRANIOFACIAL AND PALATE SHAPE: IMPLICATIONS FOR DYSMORPHOGENESIS IN SCHIZOPHRENIA

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Background/objective: In schizophrenia, minor physical anomalies of the face and palate have been reported as indices of dysmorphogenesis, but little is known of how these external and

internal elements of the cerebral–craniofacial complex might be related. This was investigated among the general population.

Methods: Facial surfaces of 73 volunteers [28 male, 45 female] were recorded in 3D using a handheld laser scanner. Twenty-four 3D landmarks were located on each facial surface. Width, depth and height of the palate were measured using a palatometer. Analyses were performed on raw palate measures, which record palate form [form is shape plus size], and on size-adjusted palate measures, which record palate shape. Relationships between palate measures and facial shape were investigated by regressing palate measures onto principal components of shape variation for males and females separately. Regression models were visualised using 3D graphics.

Results: Palate form correlated with facial shape: for males, palate width [$R^2 = 0.62$, $P < 0.001$] and height [$R^2 = 0.46$, $P < 0.001$]; for females, palate height [$R^2 = 0.15$, $P < 0.05$]. Palate shape correlated with facial shape: for males, palate width [$R^2 = 0.36$, $P < 0.01$], height [$R^2 = 0.30$, $P < 0.01$] and depth [$R^2 = 0.48$, $P < 0.01$]; for females, palate width [$R^2 = 0.27$, $P < 0.01$], height [$R^2 = 0.07$, $P < 0.05$] and depth [$R^2 = 0.32$, $P < 0.001$].

Conclusion: These analyses and visualisations indicate that facial and palatal morphology are related, in a manner that reflects the intimacy of their origins over early fetal life.

Acknowledgment: These studies were supported by the Stanley Medical Research Institute.

165. GRAY AND WHITE MATTER CHANGES IN SCHIZOPHRENIA, RESULTS FROM ROI-BASED AND VBM-BASED METHODS

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Background: Several separate studies on a MRI-sample of controls, schizophrenic patients and their relatives were conducted to finally derive a characteristic pattern of changes and to identify an endophenotype, thus depending not only on the identification of significant differences but also on the interpretation of measurements with no such results. Aim of this study was the mutual confirmation of results and conclusions by comparing two different methods for the detection of changes in the distribution of gray and white matter.

Methods: A region-of-interest-based study calculated volumes for prefrontal, frontal, parietal, occipital and temporal lobe, cerebellum and gyrus cinguli, separately for both hemispheres. This was accomplished by manually delineating a representative subsample, constructing probabilistic templates in normal space and finally segmenting the complete sample by coregistration. The effected segmented volumes were combined with an automatic segmentation into gray matter, white matter and CSF. A second study comprised a voxel-based morphometric analysis aimed at differences of local gray and white matter concentration. It was carried out using standard procedures commonly performed together with SPM. Both studies separately underwent enquiries regarding reliability. The results from both studies were systematically compared regarding identification of changes, spatial overlapping, significance, effect size and effort.

Results: Both methods found gray matter loss primarily in prefrontal lobe but also in other regions. Generally the findings were comparable. The voxel-based method enabled a finer spatial description of affected regions. The ROI-based method however exhibited higher sensitivity in some regions and allowed better quantification.

Conclusion: The combination of results yielded higher elucidating power.

166. LENGTH OF UNTREATED PSYCHOTIC SYMPTOMS AND EFFECTS ON BRAIN STRUCTURE IN THE ÆSOP FIRST-ONSET PSYCHOSIS STUDY

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Background: Mounting evidence supports the hypothesis that the duration of untreated psychosis prior to first psychiatric contact adversely affects acute treatment response and short-term outcome. However, there is little evidence on the effects of illness length on factors likely to relate to pathogenesis, such as brain structure. This study investigates the association between length of untreated psychotic symptoms and structural brain changes in individuals experiencing their first psychotic episode. As these subjects were only exposed to antipsychotics for a short time, brain changes are unlikely to be the consequence of long term antipsychotic treatment.

Methods: Dual echo MRI data were acquired at 1.5 T for 90 subjects at time of first psychotic episode ($n = 35$ female; mean age 27 ± 8 years; $n = 50$ DSM IV Schizophrenia/Schizophreniform, and $n = 40$ DSM IV Other Psychosis). Differences in grey matter in relation to length of untreated psychotic symptoms were estimated at each intracerebral voxel after registration of images in standard space.

Results: Median length of untreated psychotic symptoms was 43 days. Longer duration of untreated psychotic symptoms was associated ($p < 0.002$) with a cluster of reduced grey matter

volume located in the precuneus (bilaterally), extending anteriorly to the lobulus paracentralis; posteriorly to the superior parietal lobule. No correlation was identified between length of untreated symptoms and total grey matter, white matter, or lateral ventricular volume.

Conclusion: The duration of untreated psychotic symptoms is significantly correlated to structural brain changes in subjects experiencing first episode psychosis.

167. THE COGNITIVE RELEVANCE OF A STRUCTURAL ENDOPHENOTYPE IN PSYCHOSIS

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Background: There is accumulating evidence for structural endophenotypes in psychosis. The functional significance of such endophenotypes, however, remains unclear. In a recent study using computational morphometry, we found grey matter deficits in fronto-thalamic-cerebellar brain regions in patients with psychosis, as well as cerebellar volume deficits in non-psychotic first-degree relatives of psychotic patients (Marcelis et al., 2003). The present study investigated in the patients whether the alterations in brain structure were associated with lower cognitive performance.

Methods: Magnetic resonance imaging scans and six neuropsychological measures were obtained in 31 psychotic patients. Computational morphometric techniques (BAMM software; Brain Activation and Morphological Mapping) identified brain areas whose grey matter density varied significantly with cognitive performance.

Results: Reduced grey matter density in the left cerebellar hemisphere was associated with reduced speed of complex information processing as measured by the Modified Trailmaking Test. In addition, there was a positive correlation between grey matter density in areas of the thalamus, caudate nucleus and putamen on the one hand, and performance on the semantic fluency task on the other hand. In another region of the thalamus and caudate nucleus, however, grey matter density correlated negatively with semantic fluency, which might be explained by confounding effects of medication or by compensatory mechanisms.

Conclusion: The findings suggest that brain abnormalities that have been identified as structural endophenotypes in psychosis are associated with cognitive performance. Computational morphometry is a useful method to detect the functional significance of a structural endophenotype.

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168. VOXEL-BASED MORPHOMETRY OF CO-MORBID SCHIZOPHRENIA AND LEARNING DISABILITY: ANALYSES USING PARAMETRIC AND NONPARAMETRIC STATISTICAL METHODS

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Background/objective: We employed voxel-based morphometry (VBM) to compare the distributions of grey matter in structural MRI brain scans of patients with co-morbid learning disability with schizophrenia, schizophrenia alone, learning disability alone and normal controls. Our primary aim was to replicate a previous ROI finding that co-morbids and schizophrenics belong to the same population.

Results: Nonparametric analysis in normalised space showed no significant differences in grey matter distribution between the co-morbid and schizophrenia groups. Furthermore, this analysis showed significant grey matter reductions in the co-morbid and schizophrenia groups when compared to the learning disabled or the normal controls. Parametric analysis localised the significant grey matter reductions between the normal controls and the co-morbid and schizophrenia groups to the prefrontal and temporal lobes. The normalised space parametric analysis also identified an area of increased grey matter, on the inferior aspect of the postcentral gyrus, in the learning disabled alone compared to the other groups. Parametric and nonparametric analysis of native space tissue distributions, derived through modulation, confirmed the similarity in grey matter volumes of the co-morbid and schizophrenia groups. Native space analyses also confirmed the ROI finding that the learning disabled group possess the least and normal controls the most grey matter for the cohort.

Conclusion: Overall these VBM results replicate previous ROI findings and are compatible with the view that co-morbid learning disability with schizophrenia is a severe form of schizophrenia, rather than a consequence of learning disability. VBM has the facility to compare grey matter distributions in this structurally diverse cohort.

169. DURATION OF ILLNESS AND STRUCTURAL BRAIN ABNORMALITIES IN THE AESOP FIRST ONSET PSYCHOSIS STUDY

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Background: It is unclear whether structural brain abnormalities exist premorbidly in schizophrenia or develop (or become more severe) during the early stages of psychosis.

Methods: We investigated the association between duration of illness (DOI) and structural brain abnormalities in 90 first-episode psychosis patients (55 male, mean age 27 years, ICD10 schizophrenia $n=44$, other psychosis $n=46$). Dual-echo MRI data was acquired at 1.5 T. Differences in grey and white matter volume between the patients and 90 healthy controls were estimated at each intracerebral voxel after registration of the images in standard space.

Results: The patients had: (1) bilateral grey matter excesses in the lenticular nuclei and lingual gyrus ($p<0.002$): (2) internal capsule white matter deficits (bilateral) and parietal lobe white matter excesses (bilateral) ($p<0.003$). In the schizophrenia patients, there was no association between DOI and brain tissue volume in these regions. In the 'other psychosis' patients, longer DOI correlated with reduced grey matter in the right lentiform nucleus ($r=-0.44$, $p=0.002$) and lingual gyrus ($r=-0.31$, $p=0.04$) and with increased white matter in the right internal capsule ($r=0.38$, $p=0.01$), left internal capsule ($r=44$, $p=0.002$) and right inferior parietal lobe ($r=0.36$, $p=0.01$). (Duration of antipsychotic use and symptomology were not associated with the structural changes in either group.)

Conclusion: Structural brain abnormalities present in first-episode psychosis are linked to DOI in non-schizophrenic disorders but are relatively stable in schizophrenia. Structural brain abnormalities in first-episode schizophrenia may be more longstanding and more likely to have a neurodevelopmental origin than those observed in other psychotic disorders.

170. CHANGE IN CAUDATE NUCLEUS VOLUME AFTER THREE-MONTH TREATMENT IN DRUG-NAIVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Differences in degree of caudate volume expansion in schizophrenia patients treated with antipsychotic compounds, has been related to variable D_2-receptor affinity between compounds. However, volumetric imaging studies in the initial treatment phase directly comparing the effect of typical and atypical compounds are lacking. Hypothesis: Brief exposure to typical, but not atypical, antipsychotic compounds leads to increased caudate volume in drug-naive first-episode schizophrenia patients.

Methods: Twenty drug-naive patients (mean age = 26 years) with first-episode schizophrenia were randomly allocated to treatment with Zyclopenthixol ($n=8$) and Risperidone ($n=12$). The caudate nucleus was manually traced on MRI-scans (3D T1-weighted MPRAGE sequence on 1.5-T Siemens Vision Scanner) by a single rater blind to subject identification (Intraclass Correlation Coefficient = 0.96) before, and after 12 weeks of antipsychotic exposure.

Results: Patients in the two medication groups did not differ significantly with respect to gender, handedness, socio-economic status, education, height, weight or duration of untreated psychosis. There were no significant group differences in total caudate volumes at baseline or follow-up between patients treated with Zuclopenthixol (mean daily dose = 10 mg) and Risperidone (mean daily dose = 3 mg), but a significant Time × Group interaction ($p<0.04$) was evident, with caudate volume being larger at follow-up compared to baseline only in the zuclopenthixol group ($p<0.01$).

Conclusion: In drug-naive patients with first-episode schizophrenia, caudate volume increase is observed after a brief exposure to a typical, but not atypical antipsychotic compound. This may be explained by differences in striatal D_2-receptor affinity.

171. INCREASED PITUITARY VOLUME IN PATIENTS OF THE ÆSOP FIRST-ONSET PSYCHOSIS STUDY

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Background: Patients with psychosis have neuroimaging and neuropathological abnormalities that could be explained, at least

in part, by a stress-related activation of the hypothalamic–pituitary–adrenal (HPA) axis during the acute phase of the psychosis.

Methods: We examined pituitary volumes in patients at the first episode of a schizophrenic, affective, or other psychosis, to investigate the relationship between the development of psychosis and changes in the hormones involved in the stress response, especially the HPA axis hormones. Pituitary volume was measured using 1.5-mm, coronal, 1.5-T MRI images, in 98 patients ($n = 36$ female; mean age 27 ± 8 years, $n = 51$ DSM IV Schizophrenia/Schizophreniform, $n = 31$ DSM IV Affective Psychosis, $n = 16$ DSM IV Other psychosis) and 96 controls ($n = 40$ female; mean age 30 ± 9 years).

Results: Patients with first-episode psychosis had larger pituitary volumes than controls (+18%, $P = 0.001$). There was no difference in pituitary volume between patients who were receiving neuroleptics and those who were drug-free at the time of the MRI scan ($n = 23$).

Conclusion: The first episode of a psychosis is associated with a larger pituitary volume, and we suggest that this is due to activation of the HPA axis.

172. OLFACTORY FUNCTION AND LIMBIC REGION VOLUMES IN SCHIZOPHRENIA

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Background: Olfactory deficits in schizophrenia have been widely reported. Brain regions implicated in the pathophysiology of schizophrenia overlap with those involved in olfaction. Olfactory measures have been used to assess the functional integrity of the brain in patients with schizophrenia. Few studies have examined whether they are lateralized, and the neural substrates for these deficits in schizophrenia are still unknown.

Methods: In this study, we examined the relationship between olfactory functions and volumes of temporo-limbic (hippocampus/amygdala) and prefrontal (orbitofrontal) brain regions in young male patients with schizophrenia and healthy comparison subjects, matched for sex and age. Measures of main olfactory functions included threshold, discrimination and identification performance (Sniffin' Sticks). Odor-judgement measures included intensity, familiarity, edibility and pleasantness ratings. Olfactory measures were assessed unirhinally. Volumes of the brain regions of interest were measured using magnetic resonance imaging (MRI).

Results: Patients performed more poorly than healthy subjects in their ability to detect an odor in low concentrations (threshold), to discriminate between qualitatively different odors (discrimination), and to identify odors, as well as on several odor judgements measures. There were no group by nostrils interactions, indicating a lack of lateralization of the effects. Compared with healthy subjects patients showed bilateral smaller hippocampus and amygdala volumes. In patients, smaller volumes of the hippocampus were significantly correlated with poorer discrimination performance.

Conclusion: The results corroborate and extend previous findings of olfactory deficits as well as temporo-limbic structure volume reduction in schizophrenia, and suggest that olfactory deficits, namely impairments in discrimination, are associated with morphometric abnormalities in the hippocampus.

173. RELIABILITY OF BRAIN VOLUME MEASUREMENTS FROM MRI: A MULTICENTER CALIBRATION STUDY

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Background: Schizophrenia imaging studies including many subjects often require MRI scans from more than one site. Quantitative brain measures from MRI are susceptible to scanner properties and acquisition parameters. Variability of scanners and acquisition protocols between sites must be taken into consideration.

Methods: Six healthy volunteers were scanned at five research sites. For volumetric analysis three-dimensional T1-weighted scans of the whole head were acquired on 1.5-T MRI scanners. The scans were put into Talairach orientation (no scaling) and corrected for scanner RF-field nonuniformity.[1] Total brain, cerebellum, gray and white matter of the cerebrum, lateral and third ventricular segmentations were done semi-automatically, using mathematical morphology operations, based upon thresholds obtained from the intensity histograms.[2] Comparability between volumes of different sites was measured by calculating the intra-class correlation coefficient (ICC).

Results: The ICCs for most volumes of interest were higher than 0.92. The ICCs for the third ventricle volume were between 0.70 and 0.93. For one site, the ICCs for the gray and white matter

volumes were 0.71 and 0.86, respectively. In order to obtain gray and white matter volumes that were in good agreement between the sites, part of the segmentation procedure had to be recalibrated for each site.

Conclusion: Images from different scanners in a multicenter set-up yield reproducible volumes of interest. Small structures (third ventricle) and separation of gray and white matter need special attention, and may require a calibration of the segmentation procedure.

References

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174. HIPPOCAMPUS AND AMYGDALA VOLUMES IN PSYCHOSES IN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Objective: The aim of the study was to define volume and shape differences of hippocampi and amygdalae in psychoses. Effects of perinatal or genetic risks, duration of illness, scholastic performance and early development on hippocampal or amygdala volumes were studied.

Methods: The Northern Finland 1966 Birth Cohort is an unselected, general population birth cohort ascertained during mid-pregnancy. All subjects with psychosis were invited for a survey in 1999–2001 including MRI scan of the brain. Controls were randomly selected from the cohort not known to have psychosis. Volumes of hippocampi and amygdalae were measured in 82 psychotic patients (43 males) including 56 subjects with schizophrenia and 26 subjects with other psychotic disorder and in 104 controls (62 males).

Results: A small reduction in hippocampal volume in the psychotic group disappeared when adjusted for total brain volume. Similarly, mean amygdala volume in psychotic subjects did not differ from controls. The right hippocampus and amygdala were significantly larger than the left in all groups. Within the psychosis group, hippocampal and amygdala volumes were the same for subjects with perinatal risks and those without. Length of illness, scholastic performance or developmental delay had no effect. Surprisingly, the subjects with genetic risk had larger hippocampal volume than subjects without the risk. Any evidence of hippocampal volume reduction in psychotic patients was explained by whole brain volume reduction in this sample. Perinatal events that have been suggested as of etiological importance in structural pathology had no effect, but there was some evidence of genetic mediation of hippocampal volume.

175. THALAMUS VOLUME AND SHAPE IN THE UNAFFECTED SIBLINGS OF SCHIZOPHRENIA SUBJECTS

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Background: Anatomical abnormalities of various brain structures have been reported in schizophrenia subjects and their relatives and may be related to genetic vulnerability. In literature, it is reported that the thalamus of schizophrenic patients is decreased. Thalamus volume and shape was measured in patients and healthy siblings to study the changes as a marker of genetic vulnerability for schizophrenia.

Methods: Magnetic resonance (MR) scans were collected in 13 pairs of schizophrenics and their unaffected siblings from families with multiple affected members, in 12 schizophrenics from families without another affected member, and in 10 healthy controls. Thalamus volume and shape were compared using large-deformation high-dimensional brain mapping (HDBM-LD).

Results: We observed a decrease in thalamic volume, covaried for total cerebral volume, in the schizophrenia subjects without affected members in their families (6% loss, $F = 2.93$; $p = 0.008$). In Schizophrenics from families which were multiple affected by the illness, we also found a decrease of the volume (2%), but the change was not significant. Healthy family members show no volume reduction of the thalamus.

Conclusion: This finding is in contrast to the finding in the hippocampus that we reported recently on the same sample. In contradiction to the thalamus, the hippocampal volume and shape is changed in healthy and ill members from multiple affected families in a similar way as in schizophrenic patients from families without a history of the illness.

Acknowledgments: This research was supported by the Deutsche Forschungsgemeinschaft (Fa 241/2-3) and PHS grants MH56584 and MH62130.

176. WHITE MATTER ABNORMALITIES IN FIRST EPISODE PSYCHOSIS AND HIGH RISK SUBJECTS

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Background: There is increasing evidence that changes in connections linking brain regions may be critically important in schizophrenia. The extent to which white matter abnormalities are related to being at risk of psychosis as opposed to having a psychotic disorder is unclear.

Objectives: To compare white matter tracts in people who are at high risk of psychosis, patients with recently developed psychosis, and healthy volunteers.

Methods: Thirty controls, 15 drug naive patients in their first psychotic episode and 15 'at risk mental state' subjects (defined according to PACE criteria) aged 18–26 years underwent diffusion tensor imaging.

Results: Images were analysed using software which examined fractional anisotropy in each voxel in standard MNI space. The first episode group showed reduced fractional anisotropy in the right superior longitudinal and fronto-occipital fasciculi relative to the at risk and control groups.

Conclusion: Abnormalities in the tracts connecting the frontal and temporal cortex were evident in patients with first episode schizophrenia, but not in people with prodromal symptoms at high risk of psychosis.

White Matter Abnormalities

177. MAGNETIZATION TRANSFER IMAGING IN CHRONIC SCHIZOPHRENIA

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Objective: The aim of the study was to investigate if magnetization transfer imaging (MTI), analyzed on a voxel-by-voxel basis, would identify areas of abnormal magnetization transfer ratio (MTR) in patients with schizophrenia.

Methods: Fifteen schizophrenic patients and 18 healthy controls matched on handedness and demographic variables underwent MTI and T1-weighted structural MRI in a 3-T scanner. Postprocessing was performed with SPM99 and included coregistration of the MT-weighted and non MT-weighted images, calculation of the MTR maps, normalization of all MTR maps and smoothing. Between group differences in the MTR maps were assessed using two-sample *t*-test. Significant increases or decreases in MTR were detected at an individual voxel threshold of $p < 0.001$. A structural voxel-based morphometry (VBM) analysis on each patient's and control's T1-weighted images was also performed.

Results: Group comparisons revealed no significant MTR changes, although there was a trend for MTR reduction in the left superior temporal gyrus in patients compared with controls prior to correction for multiple comparisons ($p < 0.001$ uncorrected). No MTR increases were observed in patients compared with controls. VBM did not reveal significant differences in gray matter density or volume between the groups.

Conclusion: MTI and voxel-by-voxel statistical analysis used in the study failed to identify regions of significant MTR reductions in schizophrenic patients and did not reflect the enhanced sensitivity of MTI to the subtle structural brain changes in schizophrenia compared to conventional T1-weighted imaging. Our results are contrary to the previous findings of widespread MTR abnormalities reported in recent literature.

178. STRUCTURAL BRAIN ABNORMALITIES MAY BE PROGRESSIVE IN SCHIZOPHRENIA

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Background: Magnetisation Transfer Ratio (MTR) may be more sensitive than conventional volumetric imaging to structural brain abnormalities in both chronic and first-episode schizophrenia populations (Foong et al., 2001; Bagary et al., 2003). We predicted that MTR abnormalities would be more widespread in chronic schizophrenia.

Methods: We acquired magnetisation transfer images from 29 first-episode schizophrenia patients; 30 matched control subjects; 25 chronic schizophrenia patients and 25 matched control subjects using a 1.5-T scanner. Images were processed using voxel-based morphometry (VBM) which allows automated whole brain structural analysis, therefore limiting observer bias and providing significant advantages over conventional labour intensive region of interest studies. SPM99 (Wellcome Department of Cognitive Neurology, London) was used for image processing and statistical analysis. Group comparisons of regional differences in MTR were made.

Results: Group comparisons revealed more widespread MTR abnormalities in chronic schizophrenia, particularly in the left prefrontal cortex and parieto-occipital cortex bilaterally.

Conclusion: Based on this cross-sectional study of first-episode and chronic schizophrenia populations MTR abnormalities in schizophrenia may be progressive, at least in some patients. Longitudinal studies are required to confirm these findings.

179. GLIAL CHANGES MEASURED BY [11C](R)-PK11195 PET IN PATIENTS WITH PSYCHOSIS AND COGNITIVE DECLINE ARE ASSOCIATED WITH IMPAIRED EVENT RELATED POTENTIAL MISMATCH NEGATIVITY

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Background: The activation of microglia is an early response to neuronal damage even in the absence of neuronal cell death. The transition of microglia from the normal resting to the activated state is associated with an increased expression of 'peripheral benzodiazepine binding sites' (PBBS). Thus, the up-regulation of PBBS is a measure of disease activity. (R)-PK11195 is a specific ligand for the PBBS, that labeled with carbon-11 can be used for positron emission tomography (PET).

Methods: In this study, mismatch negativity (MMN) to frequency and duration deviants was recorded from 32 electrodes in 16 patients with schizophrenic psychosis. Glial activation was measured in vivo by [11C](R)-PK11195 PET.

Results: Patients with schizophrenic psychosis showed significantly increased [11C](R)-PK11195 binding throughout the cortex with some regional accentuation in the frontal lobes. A significant correlation was found between the reduction in the amplitude of mismatch negativity and increased [11C](R)-PK11195 binding across all regions The in vivo detection of increased [11C](R)-PK11195 binding in schizophrenic psychosis indicates (a) the occurrence of microglial activation which—being an early event in neurodegenerative disease—in turn suggests the presence of an active tissue pathology(b) that this process is not narrowly localized to one region of the brain and (c) that higher [11C](R)-PK11195 binding is associated with more severely impaired MMN.

Conclusion: The latter may suggest that impaired MMN provides a measure reflecting the disease state, i.e. actively progressing, and the degree of subtle overall tissue pathology (rather than is anatomical location).

180. CORRELATIONS BETWEEN COGNITIVE DEFICITS AND BRAIN ABNORMALITIES IN BIPOLAR PATIENTS USING MAGNETISATION TRANSFER IMAGING

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Background: Recent evidence has challenged the traditional view of bipolar disorder as a 'benign' illness, as clinical, neuropathological, neuroimaging and neuropsychological studies have demonstrated functional decline, brain abnormalities, and cognitive deficits in bipolar patients. Magnetization Transfer Imaging (MTI) is an MRI technique with neuropathological sensitivity superior to conventional MRI, which exploits the transfer of magnetization between bound and free water molecules producing a loss of signal quantified as Magnetization Transfer Ratio (MTR). Using MTI, our group has demonstrated that Bipolar II patients (and not Bipolar I) have significant brain abnormalities mainly affecting temporal lobes and parietal associative areas (Bruno et al., submitted for publication). The same patients underwent extensive neuropsychological assessment and correlations between cognitive abnormalities and structural brain changes were explored.

Methods: Thirty-six DSM-IV bipolar patients (25 type I, 11 type II) who had been scanned on a 1.5-T GE scanner, were assessed by a trained neuropsychologist. Tests in which at least a quarter of the patients showed a moderate to severe deficit relative to standard normative data were analysed for correlation with MTR changes using SPM99.

Results: Significant correlations between MTR reduction and cognitive deficits were found only in Bipolar II patients in the left and right anterior cingulate ($p < 0.00$) for IQ and in the superior and middle temporal gyri for IQ ($p = 0.02$) and verbal memory ($p = 0.03$).

Conclusion: Bipolar II patients show more cognitive decline and brain abnormalities than Bipolar I patients. The neuropsychological deficits correlate to MTR reduction in areas relevant for cognitive functions.

181. DIFFERENTIAL STRUCTURAL ALTERATIONS OF WHITE MATTER TRACTS IN SCHIZOPHRENIC HALLUCINATIONS

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Background: For the origin of auditory hallucinations, it has been hypothesized that alterations in connectivity between frontal and temporal speech related areas might play an essential role. These circuits are assumed to become dysfunctional during the generation and monitoring of inner speech. Magnetic resonance diffusion tensor imaging is a relatively new in vivo method to investigate the directionality of cortical white matter tracts. Using diffusion imaging, we investigated whether previously described abnormal activation patterns observed during auditory hallucinations relate to changes in structural interconnections between frontal and temporal speech related areas.

Methods: A 1.5-T MR scanner was used to assess fractional anisotropy and 3-D anatomy in 13 patients prone to AH, in 13 patients without auditory hallucinations and in 13 healthy controls. Voxel based *t*-tests for anisotropy maps restricted to white matter areas were computed between the groups.

Results: We found in patients with hallucinations highest directionality in the temporo-parietal arcuate fasciculus and anterior corpus callosum compared to controls. Compared to patients without hallucinations we found differences most pronounced in the left arcuate fasciculus and cingulate bundle.

Conclusion: Here, we postulate that the alterations of WM fiber tracts in patients with frequent hallucinations may lead to abnormal activation in regions related to the acoustical processing of external stimuli. This abnormal activation may account for the patients' conviction that the AH are not self-generated but attributed to the outer world.

182. IS MYELINATION OF HEMISPHERIC WHITE MATTER REDUCED IN SCHIZOPHRENIA?

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Background: It has been suggested that the essential basis for enduring abnormal traits in schizophrenia is the relative absence of rapidly conducting cortico-cortical axons. From this, explanations have been derived for impairments in perception, cognition, motor control, language and thought (Miller, Schiz Res 37, 177, 178), the vulnerability to psychotic destabilization (Miller, Schiz Res 49,140) and electrophysiolopical abnormalities (Miller, Schiz Res, 53,222). The present poster extends the scope of this theory to include evidence on brain morphology and tissue characteristics.

Methods/results: In morphological terms, one implication of the theory is that there be a reduction in the proportion of myelinated axons in schizophrenia. A consequence of this would be a volume reduction of hemispheric white matter (WM). A few studies show this, but mainly group differences do not reach statistical significance. A meta-analysis of published studies was performed showing a volume reduction of $\sim 3\%$. Tissue characteristics revealed by signal intensity in CT and MRI (including magnetization transfer imaging) show group differences compatible with loss of myelination. Diffusion tensor imaging shows reduction of anisotropy of WM in schizophrenia. It is suggested that this arises because fine calibre/unmyelinated axons form smaller axon bundles than myelinated ones, so that bundles with different orientations tend to occur within a single voxel. Post-mortem studies in several cortical regions show decrease in size of pyramidal cells in schizophrenia, which would also be expected if WM contained a smaller proportion of myelinated axons.

183. THE ASTROGLIAL PROTEIN S100B IS INCREASED IN SCHIZOPHRENIC PATIENTS WITH PREDOMINANT NEGATIVE SYMPTOMS

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Objective: S100B, a calcium binding cytokine produced by astroglial cells, evolves paracrine and autocrine effects on neurons and glial cells. It regulates the balance between proliferation and differentiation in neurons and glial cells affecting protective and apoptotic mechanisms. Post mortem studies demonstrated a deficit in synapses and dendrites in brains of patients with schizophrenia.

Recent studies showed increased S100B levels in medicated acutely psychotic patients with schizophrenia as well as unmedicated or drug naive patients with schizophrenia. One study reported a positive correlation between negative symptoms (cognitive impairment, social and emotional withdrawal, affective flattening) and S100B.

Methods: S100B serum levels (quantitative immunoassay) and psychopathology (PANSS) were examined at intake, after 12 and 24 weeks of standardized treatment in 98 chronic schizophrenic patients with predominant negative symptoms.

Results: Compared to age- and sex-matched healthy controls the schizophrenic patients showed significantly increased S100B concentrations on admission, after 12 and after 24 weeks of treatment. High PANSS negative scores were correlated with high S100B levels. Regression analysis including psychopathology subscales and S100B identified negative symptomatology as the predicting factor for S100B.

Conclusion: S100B is not only elevated in an acute stage of disease but remains increased for at least half a year after acute exacerbation. Considering psychopathology negative symptomatology appears to be the predicting factor for the S100B concentration. This might indicate that S100B in schizophrenic patients either promotes apoptotic mechanisms itself or is released from astrocytes attempting to repair a degenerative or destructive process.

Neuropathology

184. MBP AND SP12 DISTRIBUTION IN RELATION TO MIGRATIONAL DISTURBANCES IN SCHIZOPHRENIA

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Background: Limbic pathologies including the entorhinal cortex are well replicated findings in schizophrenia. Within the entorhinal cortex, cytoarchitectonic abnormalities and a disturbance in the normal synaptic structure are well known phenomena of this disease. Recently, we were able to replicate the dislocation of pre-alpha-cell-clusters, a finding which further supports the neurodevelopmental hypothesis of schizophrenia.

Methods: In order to elucidate synaptic and myelin associated changes relating to these migrational disturbances, we stained sections of formalin fixed tissue for sp12 (antibody against SNAP-25) of seven schizophrenic and eight control subjects and for MBP (myelin basic protein) of 18 schizophrenic and 10 control subjects. We performed an automated image analysis to measure the staining intensity and the fraction of stained area. Afterwards, we calculated a staining-index which consisted of the fraction of stained area × staining-intensity.

Results: Statistical analysis showed a significant increase of stained area in schizophrenia patients compared to healthy controls in the sp12-cases (+46.8%, $p = 0.03$) and no significant difference concerning MBP (-7.4%, $p = 0.29$). However, we revealed a trend for less MBP stained fibres in schizophrenia ($p = 0.081$). Overall, no correlation between sp12 and MBP parameters with pre-alpha-cell abnormalities was found.

Conclusion: Preliminary evidence suggests a link between migrational disturbances and myeloarchitecture in the entorhinal cortex in schizophrenia.

Acknowledgment: This project is supported by the Stanley Medical Research Institute.

185. A STEREOLOGICAL STUDY OF THE MEDIODORSAL (MD) NUCLEUS OF THE THALAMUS IN SCHIZOPHRENIA, BIPOLAR DISORDER AND MAJOR DEPRESSIVE DISORDER

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Background/objective: The Medial Dorsal Nucleus (MD) of the thalamus has a critical role in cortical functioning due to its reciprocal connections with key brain regions such as the prefrontal cortex and limbic cortices. Some, but not all, previous stereological studies of the MD nucleus in schizophrenia have provided evidence for reduced MD volume with accompanying reductions in total neuron number. The aim of our present investigation was to assess MD volume, neuronal and glial total number as well as neuronal somal size in the MD nucleus in schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD) and compare to controls ($n = 15$ for each group, Stanley Foundation Brain Consortium series).

Methods: We have employed stereologically based methods to assess neuronal and glial density. MD volume was estimated via the Cavalieri method. Results were analysed using ANCOVA.

Results: No evidence for alterations in the total number of neurons or glia within the MD were observed between groups. Nor were any differences in neuronal somal size observed between groups. ANCOVA revealed group differences in MD volume ($p = 0.029$)(PMI, fixation and gender as covariates). Post hoc analyses showed that MD volume was unchanged in schizophrenia and BPD but increased in MDD ($p = 0.025$). No group differences in processed tissue section thicknesses were seen.

Conclusion: Our negative findings for schizophrenia are in agreement with other recent stereological studies of the MD nucleus which have failed to reveal hypothesised reductions in total neuronal number.

Acknowledgements: Supported by the Stanley Medical Research Institute and The Wellcome Trust.

186. REDUCED DENSITY OF CALBINDIN IMMUNOREACTIVE INTERNEURONS IN THE PLANUM TEMPORALE IN SCHIZOPHRENIA

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Background: Reduced density of calbindin containing interneurons in the prefrontal cortex in schizophrenia has been reported (Beasley et al., 2002; Biol Psych 52:708–715). Calbindin is a calcium binding protein (CBP) present in a subpopulation of GABAergic neurons restricted mainly to layer II of the cortex. Reduced CBP expression will reduce the excitability of interneurons causing disinhibition of pyramidal cells. A reduction of CBP containing cells will have a similar effect. We have previously reported a downward shift in the size of pyramidal cells in layer III of the planum temporale (PT) (Walker et al., 2002; Schiz Res, 53 special issue:105).

Methods: A single paraffin-embedded, 10-mm-thick section from the PT of each hemisphere was prepared from a group of 12 patients with schizophrenia and 12 controls. Calbindin containing cells were stained using an antibody (C-28 K), and a Cresyl violet counterstain visualised the background. Superimposed counting boxes were used to sample within layer II of the PT.

Results: A bilateral reduction in calbindin cell density was found in patients (ANOVA, $p = 0.02$, covarying for fixation time).

Conclusion: The majority of Calbindin-containing cells in the mature brain are double-bouquet cells which have characteristic vertically oriented dendrites and axon bundles. By exercising inhibitory control over pyramidal cells in a columnar arrangement, they contribute to the column acting as a cohesive unit. Loss of columnar inhibition may have a similar effect to that of increased columnar density reported in schizophrenia (Buxhoeveden and Casanova; Biol Psych 47:681–683) both resulting in reduced columnar segregation.

187. A STEREOLOGICAL INVESTIGATION OF ORBITOFRONTAL FRONTAL CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER; EVIDENCE FOR A DISEASE-SPECIFIC PATHOLOGY

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Background: The orbitofrontal cortex (OFC) has been implicated in schizophrenia and in affective disorders from functional and structural neuroimaging investigations. Neuronal size reductions and a glial cell deficit in the caudal OFC have been observed previously in Major Depressive Disorder (MDD), but no morphometric investigation of this region has been undertaken in either schizophrenia or Bipolar Disorder (BPD).

Methods: This study investigated cell density and size within the caudal OFC in subjects with schizophrenia, MDD, BPD and normal controls (15 subjects per group). We used the optical dissector and the nucleator to estimate neuronal and glial density and size within each cortical layer.

Results: We found that age at death predicted neuronal size ($p = 0.028$), and glial cell density ($p = 0.09$). Therefore, in or analysis we adjusted for these variables, and also for tissue fixation period and post-mortem interval. Neither glial cell density nor neuronal density differed between groups. Neuronal size was reduced in BPD (layer 1, 21%, $p = 0.007$; layer 5, 20%, $p = 0.05$). There was a significant interaction effect of brain hemisphere and group on neuronal size in layer 3 ($p = 0.001$), with evidence for reduced layer 3 neuronal sizes in MDD ($p < 0.001$), and BPD ($P = 0.06$) in the right hemispheres.

Conclusion: These data support the view that caudal OFC is implicated BPD and MDD disorders. The evidence of this study indicates that caudal OFC region is spared in schizophrenia.

Acknowledgements: Supported by the Wellcome Trust and the Stanley Medical Research Institute.

188. CYTOARCHITECTURAL ABNORMALITIES IN THE DENTATE GYRUS OF SCHIZOPHRENIC PATIENTS: A POSTMORTEM MORPHOMETRIC STUDY

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Background: The pathophysiology of schizophrenia is thought to involve structural and functional abnormalities of the hippocampal formation.

Methods: This postmortem morphometric study was conducted to detect disturbed cytoarchitecture in the dentate gyrus of schizophrenic patients. Microscopic images of the hippocampal formation at the level of the lateral geniculate body in silver-stained coronal sections were obtained from 15 schizophrenic and 15 control AC–PC oriented brains. Images were acquired as digitized gray level images with a CCD camera. Outlines were drawn manually to define regions of interest (ROIs) containing the granule cell layer of the dentate gyrus. Following spatial filtering, the granule cell layer was segmented from the surrounding white matter employing an adaptive threshold. The size of area covered by granule cell perikarya was measured in each ROI and entered into statistical analysis.

Results: Results revealed a significant left-sided decrease of the area covered by perikarya in schizophrenic patients compared to controls ($F = 5.611$; $p < 0.05$). There were no significant group differences with respect to brain weight, postmortem delay, or age of death. Our results provide further evidence for cytoarchitectural abnormalities in the left hippocampal formation, supporting the concept of disturbed lateralization as relevant constituent of the pathophysiology of schizophrenia.

Conclusion: The applied automated morphometric method can be used as an observer-independent tool to further localize schizophrenia-associated structural abnormalities in hippocampal subregions and adjacent cortices.

Acknowledgements: This study was supported by the Theodore and Wada Stanley Foundation.

Functional Imaging

189. VOICE RECOGNITION AND MISATTRIBUTION BIAS: AN fMRI STUDY

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Background/objective: How a sensory experience is appraised may depend on the subject's beliefs and expectancies. These 'top-down' processes may be particularly influential when the nature of the sensory stimulus is ambiguous. The aim of this study was to identify the brain areas involved in deciding the source of external speech.

Methods: Eleven healthy male volunteers were scanned whilst listening to recordings of single words spoken in either their own or another person's voice. Half the words were acoustically distorted and half were not. Subjects indicated whether the word was self/non-self in origin via a button press. They could also register an unsure response. The BOLD response was measured using a 1.5-T camera, in an event-related design.

Results: Participants were particularly likely to make misattribution errors when they listened to their own distorted speech: they misidentified their voice as being that of another. Processing their own distorted speech was associated with activation in prefrontal, anterior cingulate and lateral temporal cortex. However, the correct identification of their distorted speech as self was associated with greater prefrontal and anterior cingulate activation than its misidentification as being non-self in origin. The latter was associated with greater engagement of the superior temporal gyri.

Conclusion: The engagement of prefrontal and anterior cingulate cortex in association with the correct identification of one's own speech may reflect the involvement of these region in the top down modulation of auditory processing. Deficits in this, process in schizophrenia could contribute to the misattribution of self-generated verbal material and the experience of auditory verbal hallucinations.

190. INFLUENCE OF PARACINGULATE SULCUS MORPHOLOGY ON ACTIVATIONS IN SCHIZOPHRENIA: A fMRI STUDY

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Objective: Deficits in cognitive priming, and in detection of interferences between stimuli, have been reported in schizophrenia. We previously observed impaired anterior cingulate activations (1,2). We hypothesized that presence or absence of a paracingulate sulcus (PCS) (3) could influence brain activity patterns, as suggested by a preliminary report (4).

Methods: Thirteen schizophrenic patients were compared to twelve controls. Two sub-groups of patients were further defined according to the presence or absence of a PCS. fMRI data were acquired using an event-related paradigm (1) with a task that engages both priming and conscious conflict monitoring processes.

Results: fMRI results showed a hypoactivation in a bilateral cingulo-frontal and parietal network in schizophrenia patients. Furthermore, hypoactivations were mainly related to the absence of a PCS in some patients.

Conclusion: Results further suggest that regional hypoactivations might be modulated by the underlying paralimbic structure.

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191. VISUAL WORKING MEMORY CAPACITY LIMITATIONS IN EARLY-ONSET SCHIZOPHRENIA INVESTIGATED WITH fMRI

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Background/objective: Reduced working memory capacity has been demonstrated in schizophrenic patients. Previous neuroimaging studies have failed to explain this reduction. The aim of this study was to identify the substrates of reduced working memory capacity in the cortical working memory network of schizophrenic patients.

Methods: We used fMRI in 10 early-onset schizophrenic patients (mean age 17.1) performing a delayed discrimination task. Controls were matched for handedness, age, gender, and parental education. Working memory load was varied by presenting one to three abstract visual objects. The probe was shown after a 12-s delay.

Results: Schizophrenic patients activated the same brain areas as controls during task performance. In the patients, activation in the dorsolateral prefrontal cortex increased monotonically towards the highest memory load condition. However in the frontal eye fields and the parietal lobule, it peaked at memory load two and declined towards memory load three. This was accompanied by a significant drop of accuracy. While this dissociation of memory load effects has been previously identified as a substrate of working memory capacity constraints, it occurred at a lower level of memory load than it did in controls (Linden et al., Neuroimage, in press).

Conclusion: The dissociation of memory load effects between the dorsolateral prefrontal cortex and the visual attention network suggests that similar mechanisms for memory capacity operate in both groups. However, patients reach the limit of cortical activation earlier than controls. Attention-related brain areas outside the dorsolateral prefrontal cortex may contribute to the reduced working memory capacity in schizophrenia.

192. TREATMENT ASSOCIATED BRAIN CHANGES DURING EMPATHY TASKS IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: Difficulty with social interactions is a key clinical feature of schizophrenia. We explored, using fMRI, empathy tasks in patients with schizophrenia. We wished to test the hypothesis that there is "normalisation" of the brain response to empathy tasks in patients after treatment.

Methods: Thirteen DSM-IV schizophrenic inpatients (12 males, 1 female; mean age 32 ± 8 years) were scanned twice: initially following admission and subsequently following treatment and significant improvement (average 89 days later). Nine healthy controls (8 males, 1 female; mean age 29 ± 10 years) were scanned twice (average 83 days between scans). Functional data were acquired, at the University of Sheffield, using a 1.5-T Marconi Scanner and images analysed using SPM99. A random-effects analysis ($p < 0.001$, uncorrected) was employed.

Results: At the initial scan, patients show decreased activation in the middle temporal gyrus (BA 21), superior frontal gyrus (BA 8) and the precuneus (BA 31) of the left hemisphere, compared with controls. At the second scan, patients showed decreased activation in the right middle frontal gyrus (BA 10) and thalamus, compared with controls. Within schizophrenic subjects, the second scans showed small areas of increased activation in right middle frontal gyrus (BA 10) and fusiform face area of the right inferior temporal cortex (BA 37) compared with initial scans.

Conclusion: These findings support neuroimaging studies implicating temporo-prefrontal underactivation in patients with schizophrenia during Theory of Mind tasks. This preliminary data is consistent with the hypothesis that brain activation in temporo-frontal regions in patients with schizophrenia partially "normalises" after treatment.

193. TREATMENT INDUCED BRAIN CHANGES DURING FORGIVENESS TASKS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Forgiveness is partly dependent upon interpretation of others' emotions. We developed a 'theory of mind' based task in which subjects made forgivability judgements about others' criminal behaviour. We explored, using fMRI, forgivability tasks in patients with schizophrenia. We wished to test the hypothesis that there is "normalisation" of the brain response to forgivability tasks in patients after treatment.

Methods: Thirteen DSM-IV in-patient schizophrenic patients (12 males; group mean age 32 ± 8 years) and nine healthy controls (8 males; group mean age 29 ± 10 years) were scanned and then underwent a second fMRI scan (average 89 and 83 days after the first scan, respectively). Patients were re-scanned after hospital discharge and significant clinical improvement. Functional data were acquired at the University of Sheffield using a 1.5-T Marconi scanner, and images were analysed using SPM99. We report results using a random-effects analysis ($p < 0.001$, uncorrected).

Results: Compared with controls, patients showed decreased activation in the left middle temporal gyrus (BA 21) and fusiform face area of right temporal cortex (BA 19) on the initial scan. Patients showed decreased activation in the bilateral middle frontal gyrus (BA 6/9), right anterior cingulate gyrus (BA 24) and thalamus on the second scan. Within schizophrenia subjects, there was a suggestion of increased activation in right middle frontal gyrus (BA 10) and left superior temporal gyrus (BA 21) after treatment.

Conclusion: Our preliminary findings suggest temporo-frontal underactivation during forgiveness tasks in schizophrenia with a suggestion of some reversibility after treatment.

194. INVESTIGATING THE FUNCTIONAL INTEGRITY OF BRAIN SYSTEMS INVOLVED IN EXECUTIVE FUNCTIONS IN SCHIZOPHRENIC PATIENTS

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Background/objective: Recent functional neuroimaging studies indicate that different brain systems underlie working memory in humans. A presumably phylogenetically older, multimodal working memory system, which is also present in non-human primates, is implemented by several domain-specific prefronto-parietal and prefronto-temporal networks. Another system, which probably developed later in the context of the evolution of language, is supported by mainly left-hemispheric speech areas mediating explicit verbal rehearsal (Gruber, 2001, 2002; Gruber and von Cramon, 2001, 2003). Further evidence suggests that these networks may also be involved in other executive functions like selective attention and action control (Gruber et al., 2003). The aim of the present study was to identify specific dysfunctions of these networks in schizophrenic patients.

Methods: So far, 14 patients suffering from paranoid schizophrenia according to the criteria of ICD-10 and DSM-IV have been experimentally tested with regard to specific components of phonological and visuospatial working memory using a modified Sternberg paradigm (Gruber and von Cramon, 2003).

Results: Preliminary data analyses revealed at least two groups of patients. While half the patients did not show any clear deficit, different patterns of selective deficits were found in the other patients. These selective deficits could be attributed to impaired functioning of distinct brain systems which have been identified using functional magnetic resonance imaging.

Conclusion: The preliminary findings of this ongoing study suggest a high degree of heterogeneity even in the paranoid

subsyndrome of schizophrenia with respect to the presence or absence of dysfunctions of specific neuronal networks involved in executive functions.

195. DIFFERENT BOLD RESPONSE BETWEEN PATIENTS WITH SCHIZOPHRENIA AND CONTROLS DURING THE CONTINUOUS PERFORMANCE TEST: GENERAL VERSUS DIFFERENTIAL DEFICIT?

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Background: This study compares two methods of analysing differences in BOLD-signals during the continuous performance test in patients with schizophrenia and healthy controls.

Methods: Thirteen outpatients and 15 controls were recruited. Single digits from 0 to 9 were presented one at a time centrally on a visual display. Participants were instructed to press with their index finger of the dominant hand a response button for non-targets and with their middle finger an adjacent button when the target, digit "8", appears. Stimuli were presented for 200 ms with a 2000-ms interstimulus interval. Targets were presented pseudorandomly ($p = 1/6$). Scanning was performed with a Siemens Magnetom Vision 1.5 T with echoplanar imaging capability. Scan acquisition was time locked to each stimulus onset. In order to reveal commonalities in the difference of BOLD-signal during correct and incorrect responses, a conjunction analysis was performed contrasting patients and controls during both conditions. To evaluate any added effect of error commission a 2×2 ANOVA was performed for group and response and the interaction term between both factors was studied.

Results: Activations at target detection irrespective of response accuracy shows a fronto-thalamic-cerebellar network dysfunction in schizophrenia. Analysis with group and response accuracy as factors shows a bilateral difference in inferior frontal regions, less activated in patients at trials with an erroneous response.

Conclusion: General differences between controls and patients are found in a widespread network during task performance. Recruitment of frontal areas with less activation at incorrect responses reveals a failure of the network at higher processing demands.

196. SCHIZOPHRENIA PATIENTS SHOW ABERRANT PREFRONTAL ACTIVATION DURING WORKING MEMORY PERFORMANCE UNDER NEGATIVE MOOD INDUCTION

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Background/objective: Negative affect plays a relevant role in the psychopathology of schizophrenia. Moreover, impaired cognitive performance is a core symptom of the disorder. However, little is known about the effect of negative affect on cognitive performance in schizophrenia patients. Hence, in order to find out more about the interactive relation between affect and cognition as well as its underlying cerebral correlates, subjects were scanned by means of fMRI while carrying out a combined 0-back/2-back continuous performance task. Simultaneously, negative emotion was induced by olfactory stimulation with fermented yeast. To date, 8 patients with schizophrenia and 10 healthy persons have taken part.

Results: Results point to differential effects of negative affect on cognitive performance in patients and healthy persons despite similar subjective ratings regarding the effect of the negative olfactory stimulation on subjective affectivity. On the cerebral level, we found increased activation in several areas, especially in the prefrontal cortex, during the negative emotional condition in patients performing the working memory task, which was not visible in the group of the healthy persons.

Conclusion: Further data is needed to substantiate this finding which hints at anomalies in prefrontal activation patterns brought about by a negative affective state during cognitive performance.

197. AN fMRI STUDY OF STATE-DEPENDENT ABNORMALITIES OF FRONTAL LOBE FUNCTION DURING WORKING MEMORY IN SCHIZOPHRENIA

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Background: Patients with schizophrenia sometimes exhibit under-activity of frontal cortex, yet under other circumstances, they exhibit over-activity. Possibly these findings reflect differences related to phase or severity of illness. When the function of a brain region is mildly compromised, compensatory processes might lead to excessive activation during task performance, whereas under-activity might be observed when compensation is no longer adequate. Alternatively, it might be that treatment alleviates an intrinsic tendency towards pathological over-activity, revealing residual under-activity.

Methods: To address this question, we employed fMRI to measure brain activity during the 2-back working memory task in 10 siblings at risk for schizophrenia, 10 first episode patients at the commencement of treatment and again after 6 weeks treatment, in 12 stable treated patients, and in 13 healthy controls. All groups exhibited activation of lateral frontal cortex and suppression of activity in medial frontal regions and in the ventral striatum, during performance of 2-back relative to 0-back. However, the medial suppression of activity was greater in the siblings than in the healthy controls or the treated stable patients, while in the first episode patients, the medial suppression was greater at onset than after 6-week treatment.

Conclusion: These observations suggest that excessive suppression of activity in medial frontal regions during 2-back relative to 0-back might reflect a pathological process that predisposes to schizophrenia, and is alleviated by treatment.

198. EPISODIC MEMORY IN SCHIZOPHRENIA: AN fMRI STUDY

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Background/objective: Semantic and episodic memory dysfunction have been reported in people with schizophrenia. A novel episodic memory questionnaire was developed from the false memory task of Roediger and McDermott (1995). This task was piloted in normal controls ($N=25$) and people with schizophrenia ($N=20$). The latter group made significantly more responses to 'false' lure words ($p<0.025$) and recognised fewer 'true' targets than controls ($p<0.012$). It is hypothesised that increased responses to false items results from hippocampal damage (Holdstock et al., 2002). This "damage hypothesis" was then used as a model for the episodic memory deficits seen in schizophrenia, 3T fMRI was used to investigate this further.

Methods: Fifteen right-handed males with a DSM-III-R diagnosis of schizophrenia and 15 male, age, handedness and premorbid IQ-matched control participants completed the modified memory task, in the fMRI scanner, over a 20-min period. Images were analysed with SPM and group independent subspace analysis.

Conclusion: The two analyses produced convergent results with greater activation in anterior left parahippocampal gyrus in the patient group, particularly associated with the false condition. Controls showed greater medial temporal lobe activity in the true condition. The results are consistent with the complementary learning systems model of O'Reilly, whereby failure of hippocampal function leads to an increased reliance on familiarity based mechanisms within the parahippocampal cortex.

199. AN fMRI STUDY OF EXECUTIVE FUNCTION IN 1ST EPISODE SCHIZOPHRENIA

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Background/objective: Patients in the first episode of psychosis show deficits on tests of executive function. We used fMRI to examine the neural correlates of a task that engages executive function in first episode patients and controls.

Methods: Ten patients meeting DSM-IV criteria for a first episode of schizophrenia/schizophreniform psychosis were compared with 12 controls, matched for sex, age, ethnicity and IQ. Three patients were drug-naïve but the mean duration of antipsychotic treatment where started was 15 days. The BOLD response was examined using a 1.5-T MRI scanner. Subjects were scanned while making random self-selected movements of a joystick. This was contrasted with a rest condition in a blocked design.

Results: Performance on the task (response time and randomness of movements) did not differ between controls and patients. Patients showed less activation than controls in supplementary motor, prefrontal, striatal and cerebellar cortex. Within the patient group, activation in the thalamus, cerebellum, prefrontal and primary motor cortex varied with both current medication dose and cumulative dose.

Conclusion: Differences in brain activation during an executive task were evident in patients with first episode psychosis and controls. However some of these appeared to be related to effects of antipsychotic medication, despite the use of low doses of atypicals and limited cumulative exposure.

200. PRELIMINARY EVIDENCE FOR ANTERIOR CINGULATE DYSFUNCTION DURING DYNAMIC FACIAL EXPRESSION PROCESSING IN SCHIZOPHRENIA

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Background: We used event-related fMRI and dynamic facial stimuli to define the neural basis of difficulties in interpreting facial expressions described in schizophrenia. Medial prefrontal cortex processes facial expression and is structurally abnormal in schizophrenia. We hypothesised impaired activation in the medial prefrontal cortex in people with schizophrenia.

Methods: Whilst scanning, we presented 80 2-s silent video clips comprising faces that expressed emotions (happy or sad) or neutral activity (eating or yawning). Nine right-handed males (five with schizophrenia, four controls) pressed one of two buttons to indicate whether or not they thought each face expressed an emotion. We used the University of Sheffield 1.5-T Eclipse scanner to acquire images, analysed using SPM99; reported at $p < 0.001$, uncorrected.

Results: Patients were significantly less accurate than controls in attributing emotional state ($p < 0.05$). Compared with controls, patients had reduced activity in the anterior cingulate gyrus (BA24; 4, 35, 2; 75 voxels), the right superior temporal gyrus (BA22; 65, −38, 18; 30 voxels) and the left occipitofrontal fasciculus (−24, −32, 22; 21 voxels). Conversely, patients showed greater activation in bilateral superior parietal lobes (BA7; right: 20, −65, 60, 31 voxels; left: −6, −67, 58, 22 voxels).

Conclusion: To our knowledge this is the first fMRI study to use dynamic, hence more life-like, stimuli to investigate this aspect of schizophrenia. Preliminary results suggest that people with schizophrenia under-recruit areas that process emotional expression, particularly the anterior cingulate, which may result in impaired performance.

Acknowledgment: We gratefully acknowledge funding by the Margaret Temple Fellowship (British Medical Association).

201. PROTEOME ANALYSIS OF ANTERIOR CINGULATE CORTEX IN MAJOR PSYCHIATRIC DISORDERS IN THE 4–7 IMMOBILISED PH GRADIENT

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Background: Marked alterations in neuronal and glial size and density have been observed in the anterior cingulate cortex (ACC) in schizophrenia, major depressive disorder (MDD) and bipolar disorder (BPD). The basis for these morphological changes may be revealed through proteomic methods such as two-dimensional gel electrophoresis (2DGE). In this method, protein separation is improved by using narrow range pH gradients such as pH 4–7 and 6–9.

Methods: 2DGE and mass spectrometry were used in this study to compare and identify disease-specific protein changes in schizophrenia, MDD, and BPD in the ACC. We applied immobilised pH gradients (IPG) 4–7 to the Stanley Foundation Brain Consortium brain series (comprising 15 subjects per group from each of MDD, BPD and schizophrenia). Gel image analysis was undertaken using Progenesis 2003.1 (NonLinear Dynamics). Data was analysed by ANCOVA.

Results: In the IPG 4–7 gels, 33 spots, present in 40 cases or more, were found to be differentially expressed in the disease groups. Of these, 17 have been identified using peptide mass profiling by MALDI-TOF-MS. These include altered expression of DRP 1, DRP 2, DRP 3, two forms of creatine kinase, succinyl-coenzyme A, tubulin alpha 4, tubulin beta 1, tubulin beta 5, GR75 mitochondrial protein, IEFS and nuclear ribonuclearprotein K, VAB-2.

Conclusion: These findings replicate and extend previous observations of altered protein expression in psychiatric disorders. Some of our findings are novel, and the potential role of these proteins in the pathophysiology of these brain disorders needs to be explored further.

Acknowledgment: Research supported by the Stanley Medical Research Institute and the Wellcome Trust.

202. EXPLORING THE NEURAL SUBSTRATE OF VISUO-SPATIAL WORKING MEMORY USING A DELAYED MATCH TO SAMPLE PARADIGM AND fMRI

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Background/objective: Working memory deficits are widely reported in schizophrenia. These deficits are present from the earliest stages of illness including the prodrome.

Methods: We explored the neural correlates of visuo-spatial working memory using a modified version of the Delayed Match to Sample (DMTS) paradigm from the Cambridge Neuropsychological Test Automated Battery (CANTAB) in 11 healthy controls using functional Magnetic Resonance Imaging. The paradigm engages three principle components of visuo-spatial working memory, encoding, maintenance and retrieval. We utilised two maintenance delays of 4 and 12 s in addition to a 'Simultaneous' recall condition. All data were acquired at 1.5 T and analysed using established nonparametric techniques.

Results: Independent of the length of the preceding maintenance delay, recall was associated with activation of an extensive fronto-parietal circuit involving bilateral inferior frontal gyrus, left middle frontal gyrus and cingulate gyrus, bilateral superior parietal lobule, the fusiform gyrus and the thalamus. As the length of the maintenance delay increased, activation at recall decreased in the inferior frontal gyrus particularly on the right and bilateral superior parietal regions. When activation at successful recall was compared to unsuccessful trials, success was associated with greater activity in bilateral dorsal occipital regions, the superior parietal lobule as well as the inferior frontal gyrus particularly on the right.

Conclusion: These data suggest that the magnitude of activity detected in cortical regions, supporting visuo-spatial working memory processes vary with length of maintenance delay, proportionally to the success with which the task is completed and represent the functional substrate of visuo-spatial working memory.

203. fMRI OF AMYGDALA ACTIVATION DURING FACIAL EMOTION PROCESSING IN SCHIZOPHRENIA

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Background/objective: Facial expressions of emotion are frequently used in neuroscience as probes for emotion processing in functional magnetic resonance imaging (fMRI). Recent fMRI studies have indicated limbic activation in response to emotional stimuli, albeit with imaging methods which have recently been called into question. The present study employs a high resolution EPI protocol optimised for the amygdala and 3 T to investigate possible differences in emotion processing between patients with schizophrenia and healthy controls.

Methods: Fifteen patients with schizophrenia (DSM-IV) and 15 age- and sex-matched healthy controls viewed images of faces displaying happiness, sadness, anger, fear as well as a neutral aspect. fMRI was used to measure BOLD signal changes as subjects alternated between tasks requiring discrimination of the emotional valence of faces (positive or negative) and age (over 30 or under 30). Measurements were carried out using a 3-T Medspec S300 whole-body system. An optimised EPI protocol was employed; oblique axial slices of 2-mm thickness, a 128×128 matrix, TEeff = 46 ms, with 12 axial slices in TR = 2 s.

Results: Activation in the amygdalae and in the fusiform gyrus was detected in patients and controls when both tasks (emotional and age discrimination) were considered in combination.

Conclusion: These results provide evidence for the involvement of limbic structures during facial emotion processing in the patient and control groups. A high resolution EPI protocol combined with high field strength (3T) has proved capable of detecting robust activation in the amygdala and the fusiform gyrus.

204. IS THE THEORY-OF-MIND DEFICIT IN SCHIZOPHRENIA DUE TO AN IMPAIRMENT OF ALLOCENTRIC SIMULATION? AN fMRI STUDY

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Background: Patients with schizophrenia have what is called a Theory-of-Mind deficit, i.e. their ability to understand the mental states of other individuals is impaired. As previous results of ToM-tasks have shown, patients exhibit less frontal activation than healthy volunteers in functional imaging studies. Patients further have difficulties in assessing the appearance of three-dimensional objects from a different perspective (allocentric simulation), whereas they perform similar to the control group in mental rotation tasks. Langdon and Coltheart's behavioural studies 2001 linked the ToM-impairment with a deficit in allocentric simulation.

Methods: Using functional magnetic resonance imaging (fMRI), we investigate the neuronal correlates of mental rotation and allocentric simulation in patients with schizophrenia and healthy controls. Subjects are presented with an array of four cubes of different colours. The first task involved the subjects to mentally rotate the array. In the second task, the participants are asked to anticipate the appearance of the same array from a different perspective.

Results: Allocentric simulation elicited left frontal activation in healthy volunteers. In contrast, this activation pattern was not observed in patients with schizophrenia. Allocentric simulation, being an abstract form of ToM, is linked to the left frontal lobe in control subjects.

Conclusion: The insufficient performance of schizophrenic patients might be due to their inability to activate the frontal cortex.

205. PARIETO-PREFRONTAL DYSFUNCTION AND EFFECTS OF LONG-TERM TYPICAL AND ATYPICAL ANTIPSYCHOTIC TREATMENT IN ELDERLY, CHRONIC SCHIZOPHRENIC PATIENTS: AN fMRI STUDY

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Background: Functional magnetic-resonance-imaging is a promising method for non-invasive assessment of cortical activation. In our previous study in first-episode schizophrenic patients, we demonstrated prefrontal hypofunction during a visual and auditory paradigm. However, functional alterations of activation patterns in elderly schizophrenic patients after a long disease and aging process and medication history are unknown. We hypothesized that prefrontal dysfunction is detectable in elderly, chronic schizophrenic patients and that effects of long-term treatment with typical neuroleptics differ from clozapine treatment.

Methods: fMRI scans were acquired on a commercial Siemens Vision 1.5-T scanner using a multislice 2D-epi-sequence. A Paradigm using simultaneous visual (6-Hz checkerboard) and auditory (drum music) stimulation in block design was applied to 25 chronic schizophrenic patients (mean age 64 years) and 20 age- and gender-matched healthy controls. Nine patients received long-term treatment with typical neuroleptics, nine received clozapine and seven combined treatment. Statistical analysis was performed using SPM99b.

Results: In all schizophrenic patients, BOLD-response was decreased in the parietal and prefrontal cortex compared to controls. Patients treated with clozapine showed more activation posterior parietal, prefrontal and in the anterior cingulate gyrus compared to patients treated with typical neuroleptics. The group with combined treatment showed the same results as patients solely treated with clozapine. The brain regions shown to be affected are involved in emotion and cognition as well as in visio-acoustic information processing.

Conclusion: Our results suggest, that prefrontal and parietal dysfunction is a landmark in chronic schizophrenic patients and that clozapine shows restoring effects.

206. MALE AND FEMALE VOICES ACTIVATE DISTINCT AREAS OF THE MALE BRAIN

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Background: In schizophrenia, hallucinated voices are more likely to be perceived as male. Gender identification from speech involves processing many acoustic parameters, including pitch, formant frequency and frequency shifts. We used fMRI to test the hypothesis that male and female voices activate distinct brain areas, not attributable to simple pitch effects or conscious gender attribution.

Methods: Hallucination-like stimuli uttered by 24 speakers were recorded then progressively pitch-shifted into the gender-ambiguous pitch range, giving "male-natural" (unaltered), "male-unnatural" (pitch-shifted), "female-natural" and "female-unnatural" stimuli. An outside-scanner psychophysical experiment ($n = 65$, male = 33) helped identify robust "gender-ambiguous" stimuli, which were used on 12 male subjects (mean age = 27.3 years) in an event-related fMRI experiment (1.5-T system). The task required indicating the perceived gender of each stimulus. Images were analysed using a fixed-effects model in SPM99 at $p < 0.001$, uncorrected.

Results: Behavioural data showed gender-assignment of natural stimuli was accurate; male- and female-unnatural stimuli were perceived as of opposite gender (47% and 59%, respectively). Female-natural voices effected greater activation in the right anterior superior temporal (ST) gyrus (BA 38; $Z = 3.91$), near the ST sulcus, when compared to male-natural. Conjunction analysis of all-female against all-male voices showed similar activation in the ST gyrus (BA 40; $Z = 4.65$).

Conclusion: We found evidence for auditory cortex areas selectively activated by female voices in male subjects. Gender-ambiguous stimuli demonstrated that this could not be explained by simple pitch perception or willed gender-assignment. This study supports the idea that regions within auditory cortex help in processing nuances of speech that collectively define the speaker's gender.

207. INCREASED CORTICAL RESPONSE TO FEARFUL FACES IN PARANOID SCHIZOPHRENIA: fMRI STUDY

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Background: Facial emotional expressions serve as useful cues facilitating everyday social interactions. An abnormal processing of facial expressions may underlie communication difficulties in schizophrenic patients.

Methods: Using event-related 1.5-T fMRI, we have examined processing of fearful emotional expressions in 12 schizophrenia patients and 9 healthy volunteers. Among the patients, 6 had predominantly paranoid symptoms and the 6 others were in remission (non-paranoid group). During the scanning, subjects were required to judge the gender of neutral and fearful facial expressions of various intensities.

Results: Generic brain activation within healthy volunteers comprised increased BOLD response in visual cortex, insula, bilateral frontal, parietal and anterior cingulate cortices to intensely fearful compared with neutral expressions, whilst all schizophrenic patients activated the insula, orbitofrontal, occipital, superior and inferior temporal and bilateral parietal cortices to this contrast. Comparison (ANOVA) of the paranoid schizophrenics and healthy volunteers revealed greater activation in the former within the temporal pole, left inferior frontal, and left parietal cortices, whilst non-paranoid schizophrenics showed greater activation than healthy volunteers in left inferior frontal and left parietal areas. The paranoid schizophrenics showed greater activation compared with non-paranoid schizophrenics in right orbitofrontal, left temporal, left middle temporal and left parietal cortices.

Conclusion: These findings indicate that paranoid schizophrenics demonstrated greater activation in areas implicated in emotion processing (orbitofrontal cortex, temporal pole) compared with both normal controls and non-paranoid patients, and we suggest that increased activity within these regions may be associated with psychopathology of paranoid schizophrenia.

208. DECREASED INHIBITION RESULTS FROM A FAILURE TO ACTIVATE THE STRIATUM IN SCHIZOPHRENIA

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Background: Some of the cognitive deficits observed in schizophrenia are attributed to impaired inhibitory control over automatic processes. A task used to measure inhibitory control is the stop-signal task, in which responses have to be withheld to stop-trials appearing randomly within a series of targets (i.e. go-trials). In this study, we focussed on the activation underlying the go-trials preceding stop-trials.

Methods: Sixteen patients and 18 matched controls performed a stop-signal task with two motor conditions, during fMRI. In the automatic condition, subjects had to respond to every go-trial, whereas in the controlled condition 20% of the trials was a stop-trial, requiring subjects to withhold their response. The difference in performance between the automatic condition and the go-trials from the controlled condition reflects an increased preparatory cautiousness in responding to the go-trials.

Results: Patients and healthy controls performed similar on the automatic motor condition and showed similar brain activation. Contrasting the automatic with the controlled condition revealed an increased activation bilateral in the striatum for controls. Furthermore, in controls striatal activation increased as the likelihood of a stop-trial within the controlled condition increased. Behavioural results showed a significantly lower accuracy level on stop-trials for patients.

Conclusion: Whereas patients were able to perform the automatic task, their failure to use context-information regarding likelihood of stop-signal appearance in the controlled condition resulted in (a) failure to recruit the striatum and (b) significantly lower stop accuracy level. Since the striatum is regulated by prefrontal structures, impaired performance is associated with deficient frontal top-down regulation of striatal inhibitory processes.

209. NEURAL CORRELATES OF FIRST- AND THIRD-PERSON-PERSPECTIVE IN SPATIAL COGNITION

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Background: Disturbances in perspective taking is assumed to play a relevant role in the pathophysiology of schizophrenia.

Methods: To study the neural correlates of first-person-perspective (1PP) centered upon one's own body as opposed to the third-

person-perspective (3PP), a virtual scene with an avatar and red balls in a room was presented from different camera viewpoints to normal volunteers ($n = 11$) in a functional magnetic resonance imaging (fMRI) experiment. The task was to count the objects as seen either from the avatar's perspective (3PP) or one's own perspective (1PP). Reaction times were increased and percent correctness scores were decreased in 3PP as opposed to 1PP. fMRI data were analyzed with SPM99 in each subject and nonparametric statistics on the group level (SnPM).

Results: Differential increases of neural activity were found in mesial superior parietal and right premotor cortex during 3PP (relative to 1PP) whereas differential increases during 1PP (relative to 3PP) were found in mesial prefrontal cortex, posterior cingulate cortex and superior temporal cortex bilaterally.

Conclusion: The data suggest that mesial cortical areas are involved in decisional processes when the spatial task is solved from one's own viewpoint, whereas egocentric operations from another person's perspective differentially draw upon cortical areas known to be involved in spatial cognition.

Neurochemistry

210. FIRST HUMAN STUDY OF THE SIGMA-1 RECEPTOR RADIOTRACER [123I]TPCNE

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Background: Sigma-1 receptors are possible targets for antipsychotic drug development. We report the first human study with 1(*trans*-[123I]iodopropen-2-yl)-4-[(4-cyanophenoxy)-methyl]piperidine (TPCNE), a potential SPET probe for this receptor.

Methods: High specific activity [123I] TPCNE (>58 000 MBq/μmol) was administered as a single bolus injection (160 MBq) to a healthy male volunteer (male, 31 years) and dynamic SPET scans were performed over a period of 5.5 h. Venous blood samples ($n = 6$) were taken between 20 and 210 min.

Results: Brain uptake was rapid with a widespread distribution, reaching a maximum after 30 min, with no significant clearance during the time of the scan. Blood clearance was slow ($T1/2 = 70$ min with a constant background of 64%). After 20 min, the ratio of the activity in whole blood to plasma was 0.14 and this figure dropped to 0.07 by 210 min p.i. Due to the low activity content in plasma, we were unable to perform metabolite analysis using conventional HPLC analysis with an online radioactivity detector.

Conclusion: This novel SPET tracer for the sigma-1 receptor shows high brain uptake with clear delineation of gray and white matter. The scan was well tolerated with no adverse effects. Brain uptake appeared irreversible with no signal washout over time (activity reached a plateau in all areas over the 5-h period). Further studies will assess the effect of haloperidol on tracer uptake and kinetics.

211. EPHRIN-A5, A WIRING MOLECULE FOR LIMBIC AND NEOCORTICAL CIRCUITS

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Background/objective: The neurodevelopmental hypothesis of schizophrenia posits that subtle modifications in brain wiring during pre- and perinatal periods, in combination with environmental perturbations during adolescence, are necessary for the expression of the disease. However, there is only limited information about genes involved in the assembly of neuronal circuits and how changes in the expression of these genes lead to alterations in neuronal connectivity. We used an animal model to examine the effects of the deletion of a single gene, ephrin-A5, on thalamocortical and cortical circuit formation. Ephrin-A5, one of the ligands for Eph receptor tyrosine kinases, exhibits a highly dynamic expression pattern in distinct regions of the cortex and thalamus during early developmental stages. Using different in vitro assays, we found that ephrin-A5 is a multifunctional wiring molecule for different populations of cortical and thalamic axons. The expression of ephrin-A5 is consistent with this molecule regulating, in alternative ways, specific components of thalamic and cortical circuits.

Methods: To test this directly, we examined brains from ehprin-A5 knockout mice.

Results: These anatomical studies revealed a subtle miswiring of limbic thalamic projections and stereotyped changes in neocortical circuits.

Conclusion: Thus, the functional characterization of brain wiring molecules, in combination with transgenic techniques, can generate mouse models that allow to study how abnormal gene expression during fetal development can lead to permanent defects in brain circuits involved in higher functions.

212. NMDA BINDING IS ALTERED IN SCHIZOPHRENIA AND MODULATED BY ANTIPSYCHOTIC DRUGS: AN [^{123}I]CNS 1261 STUDY

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Background: Several lines of evidence point towards glutamatergic *N*-methyl-D-aspartate (NMDA) receptor hypofunction in the pathophysiology of schizophrenia. [^{123}I]CNS 1261 is a novel SPET ligand, binding with high affinity (K_i = 4.2nM) and high specificity to the MK 801/PCP/ketamine site within the NMDA receptor channel, reflecting the distribution of functionally active receptors.

Methods: We have used [^{123}I]CNS 1261 to investigate NMDA receptor binding in healthy normal volunteers (NV, n = 13), drug free (DFS, n = 5), typical antipsychotic treated (TAS, n = 8), and Clozapine-treated (CZS, n = 10) schizophrenic patients. SPET studies were performed with either a bolus protocol and kinetic analysis or a bolus/infusion protocol and equilibrium analysis. Receptor binding was quantified by the total volume of distribution (V_T), and, to eliminate the effects of nonspecific binding, by the outcome measures $BP_1 = V_T - V_R$ and $BP_2 = (V_T - V_R)/V_R$, where the reference V_T value, V_R, was obtained from whole cortex. Both ROI-based and voxel-based analyses were performed.

Results: The uncorrected V_T values showed a global reduction in the whole brain (including white matter) for drug-treated patients relative to healthy volunteers and drug-free patients. This could be attributed to a nonspecific change in plasma protein binding. BP_1 and BP_2 values showed altered binding in DF compared to NV in different cortical and subcortical regions (with increases and decreases noted). Antipsychotic drugs significantly modulated these alterations.

Conclusion: Our data supports an NMDA receptor dysfunction hypothesis of schizophrenia, and suggests the glutamatergic system may be an important mediator of antipsychotic drug action.

213. ALTERATIONS IN PHOSPHOLIPID METABOLISM AND TREATMENT RESPONSE IN FIRST-EPISODE PSYCHOSIS

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Background: Neuroimaging and laboratory studies provide evidence for abnormal membrane phospholipid, specifically the phospholipid essential polyunsaturated fatty acids (EPUFAs) metabolism early in the course of schizophrenia.

Methods: First-episode psychosis patients (N = 16) at baseline and after 6 months of antipsychotic treatment were compared with normal subjects on indices of oxidative stress [(1) antioxidant enzymes: superoxide dismutase (SOD), glutathione peroxidase (GSHPX), and catalase (CAT); and levels of plasma lipid peroxides, and (2) the EPUFA's linolenic acid (LA), arachidonic acid (AA), nervonic acid (NA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA)].

Results: At baseline, patients exhibited significant reductions in antioxidant enzymes, increased plasma lipid peroxides, and reduced membrane EPUFAs. These biochemical measures normalized after 6 months of antipsychotic treatment. Furthermore, changes in biochemical measures were correlated with clinical symptomatology.

Conclusion: These results suggest a pathophysiological role for membrane phospholipid dysfunction early on in schizophrenia. These data also complement emergent information on the efficacy of dietary supplementation as an augmentation for refractory patients.

214. BEHAVIOURAL OUTCOMES OF PRENATAL VITAMIN D DEFICIENCY IN RATS

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Background/objective: There is accumulating evidence for an important role for vitamin D in brain function, including our recent observations that animals deprived of vitamin D in utero had brains that were altered in shape at birth, with increased cell proliferation and reduced levels of NGF and GDNF. In the

current study we examined the hypothesis that vitamin D deficiency during two separate developmental periods alters adult behaviour.

Methods: Rats were conceived and born to mothers receiving a vitamin D-deficient diet and housed without UV light. At birth, the litters were reduced to three males and three females and half the mothers were placed under normal vitamin D conditions whilst half remained under vitamin D deplete conditions. At weaning, all animals were fed the normal diet. Mothers, and all animals at weaning, were rendered normocalcaemic with calcium supplemented water (2 mM). Control animals were born to mothers fed a normal diet but subject to similar litter size and calcium supplementation. At 10 weeks, all animals were subject to the holeboard test, elevated plus maze test, social interaction, prepulse inhibition of the acoustic startle response and a forced swim test.

Results: Early vitamin D deficiency selectively enhanced locomotion in the holeboard test and increased activity in the elevated plus maze. Thus, early vitamin D deficiency appeared to induce quite specific behavioural deficits in adulthood, without inducing severe learning or motor abnormalities.

Conclusion: These observations are consistent with an increase in dopaminergic tone, a finding previously reported in vitamin D-depleted animals.

215. SPATIAL BIAS DEFICIT IN RATS WITH LOW GLUTATHIONE DURING DEVELOPMENT: AN ANIMAL BEHAVIOUR MODEL WITH RELEVANCE TO SCHIZOPHRENIA

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Background: Glutathione (GSH) has been shown to be decreased in prefrontal cortex and cerebrospinal fluid of patients with schizophrenia (Do et al., 2000). Because GSH is an important endogenous anti-oxidant that protects cell from damage, its diminution could lead to synaptic loss resulting in abnormal neuronal connectivity.

Methods: In our animal model, rats were treated from P5 to P16 with L-buthionine-(*S*,-*R*)-sulfoximine (BSO), an inhibitor of GSH synthesis. This treatment induces a transitory (P5–P18) decrease in brain GSH levels by 40–50% (Rougemont et al., 2002). Cognitive function was evaluated in adult rats using the homing board task (Schenk, 1989). The animal's capacity to perform place learning using visual, olfactory and tactile sensory modalities was assessed.

Results: We found in BSO-treated rats, impaired spatial bias when all controlled visual and olfactory cues were removed. Place learning was precise when only one olfactory cue was present (trained arena). However, place learning became inaccurate in rats with GSH deficit when five new different olfactory cues (one for each arena) were used.

Conclusion: Our data suggest that these deficits are not attributable to sensory impairments but rather problems arising at the level of integration. The olfactory deficit observed in the proposed animal model is consistent with the reported olfactory identification and discrimination impairment in schizophrenia.

216. GLUTATHIONE DEFICIT IN SCHIZOPHRENIA: A NEW VULNERABILITY FACTOR FOR MISCONNECTIVITY?

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Background: Glutathione (GSH) is decreased in cerebro-spinal fluid and prefrontal cortex of schizophrenics (Do et al., 1995, 2000). GSH protects against free radicals, produced by dopamine (DA) metabolism. GSH deficit could lead to degenerative processes in surroundings of dopaminergic terminals, producing microlesions of synaptic terminals and dendritic spines. This structural misconnectivity would be responsible for positive, perceptive and cognitive symptoms. GSH deficit could lead to functional misconnectivity by depressing NMDA neurotransmission, in analogy to effects of phencyclidine. Our experimental data are consistent with this mechanism: pharmacologically decreasing [GSH], with or without blocking DA uptake (GBR12909), in neuronal cultures, brain slices or developing animals, induces morphological and behavioral changes similar to those observed in patients (Rougemont et al., 2002; Castagné et al., 2002, 2003; Grima et al., 2003;Steullet et al., 2003;Cabungcal et al., 2003). Lipid peroxidation: In neuronal cultures (a) DA decreased [GSH]; (b) when [GSH] is depleted, DA further diminishes [GSH]. (c) In developing rats, [GSH] depletion increases brain lipid peroxidation. Dendritic spines: (a) In neuronal cultures, low [GSH] and DA induce decreased density of neural processes. (b) Developing rats with low [GSH] and GBR12909 showed decrease in normal spines in prefrontal pyramids and decrease in GABA-parvalbu-

mine immunoreactivity. *NMDA-dependant synaptic plasticity*: GSH depletion in hippocampal slices impairs long-term potentiation. *Cognition*: Developing rats with low [GSH] and GBR showed deficit in object recognition and olfactory integration at adulthood.

Conclusion: Thus, GSH deficit during development could constitute a vulnerability factor for schizophrenia.

217. PROTON MAGNETIC RESONANCE SPECTROPY OF THE THALAMUS AND FRONTAL WHITE MATTER IN FIRST-EPISODE PSYCHOSIS

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Background: A proton magnetic resonance spectroscopy (1H MRS) study was conducted to investigate neurometabolite concentrations in first episode psychosis patients. Previous studies have indicated a possible decrease in *N*-acetylaspartate (NAA) in specific brain regions in schizophrenia. The effect of antipsychotic medications is still unclear, and many studies focussed strictly on cortical tissue.

Methods: In this study, 1H MRS was used to measure concentrations of NAA, Choline (Cho) and Creatine (Cre) in two 3.24-ml voxels centered in the left minor forceps (WM) and left thalamus. Spectra were acquired on a GE 1.5-T scanner using a PRESS sequence, and corrected for T1 and T2 relaxations, and CSF content. The subject group consisted of first episode psychosis patients ($n = 37$ WM, $n = 33$ thalamic) and healthy controls ($n = 16$ WM, $n = 23$ thalamic). The patient group included those never treated with antipsychotic medications ($n = 4$ WM, $n = 6$ thalamic), minimally medicated (less than 6 weeks of treatment, $n = 8$ WM, $n = 9$ thalamic) and those treated with medications for greater than 6 weeks ($n = 25$ WM, $n = 18$ thalamic).

Results: Mean values of concentration were similar to those reported in the literature for healthy subjects. However, no differences were found in concentrations of any of the metabolites between control and patient groups for either the white matter (pNAA = 0.5037, pCre = 0.2894, pCho = 0.9872) or the thalamic region (pNAA = 0.3260, pCre = 0.6561, pCho = 0.9809). Furthermore, no differences were found between any of the treatment subgroups.

Conclusion: Continued expansion of the sample size will allow analysis of specific diagnostic groups and change over time with follow up scans.

218. THE DISTRIBUTION OF THE VITAMIN D RECEPTOR AND THE ENZYME RESPONSIBLE FOR IT'S SYNTHESIS IN HUMAN BRAIN

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Background/objective: Based on data from epidemiological studies, we have proposed that low prenatal vitamin D is a risk factor for schizophrenia. It has been shown that the vitamin D receptor (VDR) is present in the developing and adult rat brain, and that the enzyme (CYP1α hydroxylase) required for the synthesis of the active moiety (1,25 dihydroxy vitamin D3) has been identified in rat and human brains. This suggests that vitamin D may have autocrine/paracrine roles in the brain and should therefore be considered a 'neurosteroid'. However, little is known about the role/distribution of VDR or this enzyme in human brain. The aims of this study were (a) to examine the presence/distribution of the VDR, and (b) to examine the distribution of CYP1α hydroxylase, in the adult human brain.

Methods/results: Based on post-mortem tissue from five individuals (who were free of neuropsychiatric illness prior to death), we found that the VDR and the enzyme were widely distributed throughout the brain. Concerning the VDR, immunochemical staining was strictly nuclear, and dense staining was recorded within hippocampal subfields, outer cortical laminae, in certain sub-cortical regions and in the granule layer of the cerebellum. CYP1α hydroxylase, which was widely distributed in both cells and processes, was particularly evident in macrocellular regions within the basal forebrain, the substantia nigra, the granular layers within the hippocampus and in Purkinji cells.

Conclusion: These results increase the biological plausibility for considering vitamin D a compound of interest in neuropsychiatric disorders.

219. TRANSIENT PRENATAL AND EARLY LIFE HYPOVITAMINOSIS D INDUCE PERMANENT ALTERATIONS IN BRAIN MORPHOLOGY, CELL DENSITY AND GENE EXPRESSION CONSISTENT WITH ALTERATIONS OBSERVED IN SCHIZOPHRENIA

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Background: Based on data from ecological and analytic epidemiological studies, we have proposed that low prenatal vitamin D is a candidate risk-modifying factor for schizophrenia. Previously, we demonstrated that low prenatal vitamin D adversely affected brain development in neonatal rats (Eyles et al., 2003, Neuroscience, 118(3): 641–53).

Methods: Here, we examine the impact of both prenatal and early life hypovitaminosis D on various outcomes in the adult rat brain. We compared the brains of adult offspring from control vs. vitamin D deplete dams who were either repleted with vitamin D (a) at birth or (b) at weaning.

Results: In the offspring of depleted dams, we found a significant persistent dose-related increase in lateral ventricle volume and alterations in anterior cingulate and prefrontal cortical cell densities (consistent with the known prodifferentiation properties of this steroid). We also observed a reduced expression of NGF as well as a down-regulation of transcripts coding for GABAA alpha 4 receptor, MAP2 and Neurofilament L in the deplete group. An increase in prefrontal cortical cell density and a reduction in MAP2 and neurofilament (and therefore presumably neuronal architecture) are all in accordance with the proposal that schizophrenia is a disease of reduced connectivity/neuropil.

Conclusion: These findings provide further evidence that vitamin D is involved in brain development. Moreover, the persistent ventriculomegaly and apparent reduction in the expression of structural neuronal transcripts confirms the biological plausibility of early life hypovitaminosis D as a risk factor for schizophrenia.

220. IS THE NIACIN SKIN FLUSHING TEST A TOOL IN THE DIAGNOSIS OF SCHIZOPHRENIA?

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Background/Objective: There are no biological markers to diagnose schizophrenia or for its vulnerability. The niacin skin flush test may develop into a diagnostical tool (Ward, 1998; Messamore, 2003). In our clinic, the discriminative abilities between patient groups and also the interrater reliability, sensitivity and specificity of the test were examined. We hypothesized that the niacin test would discriminate between schizophrenia (less flushing) and depression (normal flushing) or healthy controls (normal flushing). The test should not discriminate between controls and patients with depression.

Methods: Subjects of the three groups were tested with 0.1 M niacin and water (control), both applied on the arm. Digital pictures of the flushing were evaluated by 10 independent raters. Statistics: Mann–Whitney *U*, one tailed. Seventeen controls, 18 patients with schizophrenia and 17 patients with a depression were included. The interrater reliability was good (kappa 0,73).

Results: The niacin skin test did not discriminate between depression and healthy controls (Mann–Whitney $U=132$, $p=0.885$). In contrast, the skin test did discriminate between patients with schizophrenia and controls (Mann–Whitney $U=65$, $p=0.0085$) and also between patients with schizophrenia and depression (Mann–Whitney $U=82$, $p=0.027$). The sensitivity and specificity were both 0.75.

Conclusion: The test has a good interrater reliability and discriminates well between healthy controls and depressed patients on one hand and patients with schizophrenia on the other hand. Future studies are needed before this test can be used in clinical practice.

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221. HIGHER SERUM TRIGLYCERIDES IN EARLY ONSET SCHIZOPHRENIA

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Background: Patients with schizophrenia often have disturbances in lipid regulation. We report the correlation between serum triglyceride levels and onset age of schizophrenia.

Methods: Our Northern Finland 1966 Birth Cohort study sample consisted of 31 cohort members (18 men and 13 women) with a diagnosis number 295 (ICD-8 or ICD-9), or F20 (ICD-10). All diagnoses were scrutinized and validated for the DSM-III-R criteria. Serum triglycerides were determined after overnight fast by enzymatic methods.

Results: We found higher triglyceride levels in patients who were <20 years old at the beginning of schizophrenia (mean ± S.D. 1.7+0,7; $N=17$) as compared with patients with later onset (1.4 ± 0.9; $N=14$) or nonhospitalized controls (1.2 ± 0.7; $N=5453$). The Mann–Whitney *U*-test showed a significant difference between the first and third group ($p<0.01$), and the Pearson correlation coefficient showed a negative correlation between the age at onset and the level of serum triglycerides ($r=-0.35$, $p=0.05$).

Conclusion: One explanation may be that there is a genetic linkage between hypertriglyceridemia and severe forms of schizophrenia. On the other hand, cognitive disorders in these patients may cause poor dieting, and a more prolonged exposure to antipsychotics may further raise the triglyceride levels.

222. PHENCYCLIDINE INCREASES DIALYSATE AMINO ACID LEVELS IN THE RAT MEDIODORSAL THALAMUS WHICH CAN BE NORMALISED BY ANTIPSYCHOTICS

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Background: The mediodorsal thalamic nucleus (MDT) is the primary thalamic projection area to the medial prefrontal cortex (mPFC). Altered MDT activity may underlie clinical psychosis as increased thalamic activity is observed during psychotic episodes.

Methods: In this study, microdialysis is employed to examine the effect of the psychomimetic phencyclidine (PCP) alone and in combination with haloperidol or clozapine on dialysate glutamate (Glu), aspartate (Asp) and GABA levels in the MDT of intact conscious rat brain. Data is shown as mean ± S.E.M. percentage change from basal values and statistically compared (two-way repeated measures ANOVA followed by post hoc Student's *t*-test) versus the control (vehicle alone) group.

Results: PCP (10 mg/kg i.p.) is associated with sustained increases in Glu ($+454 \pm 162\%$, 80 min, $p<0.05$), Asp ($+240 \pm 76\%$, 80 min, $p<0.05$) and GABA ($+111 \pm 16\%$, 80 min, $p<0.01$) levels in the MDT. Administration of haloperidol (0.3 mg/kg i.p.) is associated with sustained decreases in Glu ($-35 \pm 4\%$, 140 min, $p<0.05$) and Asp ($-48 \pm 9\%$, 100 min, $p<0.01$) but had no effect on GABA levels in the MDT. In contrast, clozapine (30 mg/kg i.p.) is associated with sustained decreases in Glu ($-34 \pm 6\%$, 140 min, $p<0.05$), Asp ($-55 \pm 7\%$, 100 min, $p<0.01$) and GABA ($-22 \pm 3\%$, 140 min, $p<0.05$) levels in the MDT. Co-administration of PCP together with haloperidol or clozapine reverses the sustained increase in Glu, Asp and GABA levels in the MDT associated with PCP alone.

Conclusion: These findings suggest that psychosis may be associated with increased extracellular Glu, Asp and GABA levels in the MDT which can be normalised by antipsychotics. The MDT may therefore represent a novel target for antipsychotic drug action.

223. ABNORMALITIES IN THE DOPAMINE SYSTEM IN SCHIZOPHRENIA MAY LIE IN ALTERED LEVELS OF DOPAMINE RECEPTOR-INTERACTING PROTEINS

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Background: A dopamine hypothesis remains a dominant lead in the studies of pathophysiology of schizophrenia, because it is based on the fact that dopamine receptors are targets of all antipsychotic medications. However, attempts to detect abnormalities in the dopamine system of schizophrenics did not produce consistent results. Recently, a group of dopamine receptor-interacting proteins has been identified, which modify and expand the receptor functionality.

Methods: To access whether these molecules are compromised in schizophrenia, the levels of proteins (Western blot) and messages (real-time RT-PCR) for two such proteins, calcyon (which allows D1 receptors to induce intracellular calcium release) and NCS-1 (which allows calcium to regulate D2 receptor activation) were evaluated in the schizophrenic cases from the Stanley Foundation (prefrontal cortex) and Mount Sinai (prefrontal and occipital cortex) brain collections.

Results: The prefrontal cortex of schizophrenics in both collections showed up-regulation of protein and message levels of calcyon and NCS-1. The levels of these proteins were closely correlated with those of their messages, suggesting that changes are transcription-driven. In the occipital cortex, only the messages were up-regulated. There was a strong correlation between the levels of calcyon and NCS-1 in the tissue from schizophrenic patients.

Conclusion: The up-regulation of calcyon and NCS-1 in schizophrenic cases from two different collections indicates that abnormalities in the dopamine system in this disease may lie in altered levels of dopamine receptor-interacting proteins. In addition, the correlation between changes in calcyon and NCS-1 suggests that

they may reflect a deficit in the same intracellular signaling (possibly calcium-related) cascade constituting a primary molecular basis of schizophrenia.

224. EFFECT OF ANTIPSYCHOTIC MEDICATION ON THE ERYTHROCYTE MEMBRANE PHOSPHOLIPID TRANSLOCATION

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Background: Numerous data are suggesting abnormalities on the expression of lipids at the erythrocyte membrane level in schizophrenic patients. Here, we investigated different antipsychotics in order to evaluate their effect on the normal phospholipid migration during the aging process.

Method: We labelled erythrocytes from control subjects with several compounds able to determine the specific location of some critical phospholipids for schizophrenia on the bilayer membrane leaflet. After incubation with several antipsychotic medications, we measured the time to expression of phosphatidylethanolamine (PE) on the outer membrane leaflet. PE was chosen because it is a major constituent of the membrane inner leaflet and a critical phospholipid in the schizophrenia lipid hypothesis. As antipsychotic medication are known to modify the membrane lipid order and organization, we expected a modification in the time to migration of PE depending on the chosen antipsychotic and its relative concentration. The time to migration was compared to a control situation (without antipsychotic).

Results: The kinetics of expression of PE from the inner to the outer membrane leaflet is generally slower in the antipsychotic situation at clinically relevant dosages, but depends on the chosen antipsychotic.

Conclusion: These data suggest that there is a different type of interaction between the membrane and the various antipsychotic compounds. This may in turn suggest that the therapeutic effect of antipsychotics may partly be due to their membrane lipid interaction for instance at the synapse level.

225. EFFECTS OF 5-HT1A RECEPTOR AGONIST 8-OH-DPAT AND D2 RECEPTOR ANTAGONIST HALOPERIDOL ON LOCOMOTION – ANIMAL MODEL OF SCHIZOPHRENIA

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Background: Mechanisms of action of atypical antipsychotics regarding their unique clinical effectivity still remain unclear. The role of various receptor systems through which these drugs act is one of the possible keys.

Methods: In our lab we have targeted the effects of agonism on 5-HT_{1a} receptor in animal model of psychosis. We have modeled the psychosis using the NMDA receptor antagonist dizocilpin (MK-801) and we have monitored the locomotor activity of rats in the open field as an output marker of psychotic-like reaction. We have evaluated the effect of the 5-HT_{1a} receptor agonist 8-OH-DPAT and haloperidol, a classical antipsychotic with D_2 receptor antagonistic properties, on hyperlocomotion induced by MK-801.

Results: Our experiments proved that haloperidol decreased the hyperlocomotion induced by MK-801 in a dose dependent fashion, even in higher doses it produced almost complete immobility of rats. 8-OH-DPAT was not effective in decreasing hyperlocomotion after MK-801, vice-versa hyperlocomotion was potentiated. When 8-OH-DPAT was administered concurrently with haloperidol, it reduced the effect of haloperidol, thus leading to an increase in locomotor activity compared to haloperidol treatment alone. Furthermore we have found, that 8-OH-DPAT led to a marked preference of the peripheral parts of the arena in our setting.

Conclusion: According to our results, we might conclude, that haloperidol decreased the psychotic-like reaction of rats, producing marked hypolocomotion in higher doses. 8-OH-DPAT potentiated the hyperlocomotion in our model and produced peripheral movement of rats within the arena. Finally, 8-OH-DPAT reversed the haloperidol induced hypolocomotion when administered concomitantly with haloperidol.

226. SERUM CREATINE KINASE ACTIVITY IN TREATED SCHIZOPHRENIA AND SCHIZOAFFECTIVE PATIENTS

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Background: Marked elevations of serum creatine kinase (SCK) have been associated with treatment with both typical (TN) and atypical neuroleptic agents (ANA). The purpose of this study was to estimate prospectively the SCK activity in schizophrenia and schizoaffective patients treated with TN and ANA.

Methods: After screening of 460 adult (aged 19–65 years) schizophrenia and schizoaffective outpatients, we excluded 268 subjects suffering from clinically significant physical disorders, receiving parenteral medication or ECT. The study group consisted of 192 patients diagnosed with schizophrenia or schizoaffective disorder who began their oral treatment (clozapine [$n=45$], olanzapine [$n=37$], risperidone [$n=38$], quetiapine [$n=20$], haloperidol [$n=20$] or perphenazine [$n=32$]) according to the decision of their treating psychiatrist. Blood samples for CK determinations were collected at baseline, at least monthly for the first 3 months and every 3 months up to 1 year. Treatment compliance was periodically assessed using the reports of nursing staff or family members and mental status alterations were monitored using the Brief Psychiatric Rating Scale (BPRS).

Results: During the first 18 months of study, 1200 blood samples were collected and 10 evaluated patients, treated with clozapine ($n=6$), olanzapine ($n=2$), perphenazine ($n=2$) were found having persistent (at least in three determinations) hyper-CKemia -525.5 ± 250.0 IU/l (mean $\pm$ S.D.), in range 250–950 IU/l. Another 15 patients exhibited occasional (one or twice) hyper-CKemia in the same range. No correlation between SCK levels and BPRS scoring in these patients was found.

Conclusion: The preliminary results of this comparative study indicate that incidence of the persistent hyper-CKemia in patients treated with neuroleptics in our sample (5.2%) is compatible with previous reports (2–10%). However, the magnitude of hyper-CKemia is less than reported previously (1000–10 000 IU/l). The severity of the psychiatric symptoms do not correlate with the SCK levels. It is of note, that the vast majority (8 of 10) hyper-CKemic patients were treated with ANA (clozapine and olanzapine). We suppose, that 5-HT_{2A}-receptor blockade, which is common to the ANA, might be involved in increases of SCK activity. Further investigation of neuromuscular dysfunction in schizophrenia and schizoaffective patients is warranted.

227. ANTIPSYCHOTIC MODULATION OF EVOKED DOPAMINE EFFLUX IN THE RAT NUCLEUS ACCUMBENS SHELL IN VITRO

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Background: The nucleus accumbens (NAc) can be anatomically divided into shell and core regions which receive projections from the ventral tegmental area and substantia nigra, respectively.

Methods: We have investigated modulation of evoked dopamine release in the rat NAc shell in vitro by the selective D3 receptor antagonist, SB-277011, and the antipsychotic drugs, clozapine, haloperidol and sulpiride, all of which are D2/D3 receptor antagonists, and aripiprazole, which is a reported D2/D3 receptor partial agonist. Dopamine efflux was electrically evoked from rat NAc shell and measured using fast cyclic voltammetry.

Results: In the NAc shell, clozapine (300 nM), haloperidol (30 nM) and sulpiride (300 nM) increased dopamine efflux to $114 \pm 7\%$, $141 \pm 16\%$ and $182 \pm 15\%$ of control ($n=4$), respectively. In contrast, SB-277011 (30–300 nM), had no effect on dopamine efflux ($n=4$). The D2/D3 receptor agonist, 7-OH-DPAT (10–100 nM), inhibited dopamine efflux in a concentration-dependent manner to $37 \pm 5\%$ of control ($n=4$). All four antagonists attenuated the 7-OH-DPAT-induced inhibition with pA2 values of 8.6, 7.6, 7.3 and 8.2 for haloperidol, sulpiride, clozapine and SB-277011, respectively. Aripiprazole significantly inhibited dopamine efflux to $74 \pm 6\%$ ($n=6$) and $76 \pm 7\%$ of control at 15 and 150 nM, respectively ($n=4$). SB-277011 (300 nM) had no effect on the aripirazole (15 nM)-induced inhibition ($n=6$) but sulpiride (300 nM) partially reversed its inhibition of dopamine efflux ($n=5$).

Conclusion: The inhibition of dopamine efflux by aripiprazole and its reversal with a mixed D2/D3 receptor antagonist, but not a selective D3 receptor antagonist, suggest that aripiprazole exhibits D2 receptor partial agonism in this preparation.

228A. INCREASED CALCIUM-INDEPENDENT SERUM PHOSPHOLIPASE A2-ACTIVITY IN EARLY SCHIZOPHRENIA BUT NOT IN CHRONIC STAGES OF THE DISORDER

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Background/Objective: The relevance of altered phospholipid metabolism for the pathophysiology of schizophrenia has been a matter of debate since more than a decade, when 31-phosphorous magnetoresonance spectroscopy studies revealed a decrease of phospholipid precursors and an increase of membrane breakdown products in the prefrontal cortex of schizophrenia patients. Increased membrane degradation was reported in unmedicated first episode patients, but not in chronic stages suggesting a disturbed phospholipid metabolism in the initial phase of disorder (Stanley et al., 1995). The deregulated phospholipid degradation was attributed to an increased phospholipase (PL)A2 activity. Therefore we aimed to investigate PLA2-activity in early and chronic stages of schizophrenia.

Methods: Activities of a calcium-independent serum PLA2 were measured in 41 unmedicated first onset schizophrenia patients, 23 unmedicated chronic patients and 53 healthy controls by means of thin-layer chromatography using the PLA2-specific fluorescent substrate NBDC6-HPC. In each measure, the origin of the detected enzyme activity was verified by a positive control.

Results: Analysis of all data revealed a significantly higher PLA2-activity in schizophrenia patients. Group comparison between first onset and chronic patients revealed an at a trend level increased enzyme activity in the early stage of disorder. Accordingly, PLA2-activity was significantly negative correlated with duration of illness.

Conclusion: Our results corroborate the attribution of deregulated phospholipid breakdown to disturbed PLA2-function. They are suggestive, that phospholipid pathology is crucial in the early phase of schizophrenia.

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228B. IMPAIRED NIACIN SENSITIVITY IN ACUTE BUT NOT IN CHRONIC SCHIZOPHRENIA—A NIACIN-PATCH-TEST STUDY

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Background: Impaired flush response after niacin (vitamin B3) stimulation is recently discussed as biological marker of deregulated phospholipid metabolism in schizophrenia. Recent studies of our group showed impaired niacin sensitivity in different groups of acute psychosis patient suggesting that alterations of phospholipid degradation might be crucial especially in an early phase of disorder.

Methods: To further explore this assumption, we compared niacin sensitivity of 32 unmedicated acute and 26 unmedicated chronic schizophrenia patients and each patient group with age- and gender-matched healthy controls. Niacin was applied in three dilution steps (0.1, 0.01, 0.001 M) onto the inner forearm skin. Any skin response was assessed in 3-min intervals over 15 min using optical reflection spectroscopy.

Results: Whereas acute patients showed significantly diminished niacin response at the 0.001 M niacin concentration compared to controls, no significant group effects were found between chronic patients and controls. Comparison of the healthy groups revealed a weaker skin response in the older group, an age effect being previously reported in other populations by our group. In contrast, skin reaction of acute patients was significantly diminished as compared to chronic patients.

Conclusion: These results support the hypothesis that alterations of phospholipid degradation pathways are crucial in the early acute phase of disorder but less important in chronic stages.

229. DECREASE IN BRAIN GLUTATHIONE (GSH) IN SCHIZOPHRENIA: EFFECTS OF A DEFICIENCY IN GSH ON SYNAPTIC TRANSMISSION AND PLASTICITY

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Background: Observations point to dysfunction of GSH metabolism in schizophrenia. Patients show a deficit in GSH in the cerebrospinal fluid and prefrontal cortex. In addition, a deficit in GSH and a reduction in activity of two GSH-related enzymes were observed postmortem in the caudate region of patients. Since GSH potentiates NMDA receptors via extracellular redox-sites, a deficit in brain GSH could reduce the functionality of NMDA receptors and be implicated in NMDA hypofunction in schizophrenia.

Methods: Using extracellular recordings in the CA1 region and stimulating the Schaffer collaterals, we investigated synaptic transmission, including NMDA-dependent plasticity, in the CA1 region of GSH-depleted and control slices of rat hippocampus. GSH depletion was obtained with either ethacrynic acid (EA) or L-buthionine-(*S*,*R*)-sulfoximine (BSO).

Results: Both treatments induced ~40% decrease in GSH. Neither EA nor BSO altered the basic synaptic transmission as shown by the stimulus/fEPSPs response curves. The paired-pulse facilitation was reduced after both treatments, suggesting that lowering GSH altered presynaptic mechanisms involved in neurotransmitter release. Both treatments caused also an increase in excitability of the CA1 pyramidal cells. Finally, the induction of long-term potentiation, which is mediated by NMDA receptors in the CA1 region, was blocked by the EA treatment and was significantly reduced after BSO treatment.

Conclusion: These results indicate that a decrease in GSH alters mostly synaptic plasticity, including short-term facilitation depen-

dent on presynaptic mechanisms for neurotransmitter release and NMDA-dependent long-term potentiation. Thus, a GSH deficit, as observed in schizophrenia, could be involved in the hypofunction of the NMDA receptors in schizophrenia.

230. ATYPICAL ANTIPSYCHOTICS PREFERENTIALLY OCCUPY CAUDATE NUCLEUS D2/D3 RECEPTORS WITHIN THE STRIATUM: A VOXEL-BASED ANALYSIS

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Background: We have previously reported that atypical antipsychotic medications preferentially occupy extrastriatal D_2/D_3 receptors, thereby avoiding EPSEs. The striatum is not exclusively motor in function, however. The putamen is primarily responsible for integrating motor function while the caudate nucleus has prominent associative and limbic connections. We aimed to investigate whether atypical antipsychotics show selective binding within the striatum.

Methods: Eight amisulpride-treated patients, six risperidone-treated patients and six controls were recruited. Dynamic SPET studies were performed over a 5-h period after bolus injection of [^{123}I]epidepride. ROI-based reference tissue kinetic modelling was performed for caudate and putamen, using cerebellum as a reference region. Voxel-based analysis was performed using a Logan-type graphical method. BP maps were generated for each subject and realigned to a common template. User-independent ROI analysis was performed and mean drug occupancy maps were generated.

Results: D_2/D_3 receptor occupancy by atypical antipsychotic drugs was greater in head of caudate than in putamen using both standard ROI-based and user-independent voxel-based analyses. The standard ROI analysis revealed mean occupancy values for amisulpride of 63% and 45% (caudate, putamen, $p < 0.0001$) and for risperidone of 50% and 24% (caudate, putamen, $p = 0.0001$). The voxel-based analysis revealed mean occupancy values for amisulpride of 51% and 37% (caudate, putamen, $p < 0.0001$) and for risperidone of 42% and 31% (caudate, putamen, $p = 0.0001$).

Conclusion: These novel data reveal selective regional binding by atypical antipsychotic drugs at dopamine D_2/D_3 receptor sites within the striatum and highlight an additional mechanism by which these drugs may attain their beneficial clinical profile with low EPSEs.

231. EFFECT OF HALOPERIDOL ON DETERGENT RESISTANT MEMBRANE (DRM) FROM HUMAN ERYTHROCYTES: AN X-RAY DIFFRACTION ANALYSIS

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Background: Numerous data are suggesting abnormalities on the expression of lipids at the erythrocyte membrane level in schizophrenic patients. Antipsychotic medication such as chlorpromazine not only acts by binding on the dopamine D2 receptors but are also known to modify the membrane organisation and structure. Here, we investigated the effect of haloperidol on DRM from human erythrocytes.

Method: We exposed human erythrocytes DRM to an X-ray synchrotron beam (Daresbury, UK) in order to assess their diffraction pattern.

Results: When compared to the same DRM sample, the haloperidol added DRM will give a different diffractogram profile in the temperature range between 10 and 50 °C. This result suggests a stable intercalation of haloperidol into the phospholipid bilayer DRM. This result is reinforced by the finding of an enlarged phospholipid bilayer DRM after haloperidol exposure.

Conclusion: These data could be repeated with a range of antipsychotic compounds in order to explore the interaction between antipsychotic compounds and membrane structure. This may suggest that the antipsychotic therapeutic effect may partly be due to its membrane lipid interaction for instance at the synapse level.

232. ALTERED D-SERINE METABOLISM IN SCHIZOPHRENIA? A POST-MORTEM STUDY USING STANLEY CONSORTIUM BRAINS

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Background/objective: Recent genetic studies report an association of several glutamate-related gene polymorphisms with schizophrenia. One such gene, coding for D-amino acid oxidase (DAAO),

is thought to be involved in the degradation of D-serine, which is proposed to be the endogenous modulator at the glycine site of the NMDA-R complex. We have measured levels of D-serine and DAAO mRNA in Stanley Consortium brains from controls and patients with schizophrenia, bipolar disorder and depression.

Methods: Paraffin-fixed sections of the dorsolateral prefrontal cortex (DLPFC) were incubated with polyclonal antibodies to D-serine (Chemicon, 1:800). Immunoautoradiography with [^{35}S]-labelled secondary antibody (Amersham) was used to detect D-serine-antibody complexes. Frozen DLPFC sections were incubated with [^{35}S]-labelled antisense oligonucleotide probe for DAAO using in situ hybridisation. Optical density measures were taken from film autoradiographs of D-serine antigen and DAAO mRNA in grey and white matter of BA9.

Results: Reductions in D-serine in grey matter of BA9 were found in schizophrenia (33%) and bipolar disorder (37%), but were of borderline statistical significance (Multivariate ANOVA; $p = 0.07$). DAAO mRNA was increased in schizophrenia (27%) relative to all other diagnoses, but again only reaching borderline significance ($p = 0.06$). D-Serine/DAAO ratios differed significantly between groups ($p = 0.03$), with LSD post hoc analysis revealing a decrease in schizophrenia relative to controls ($p = 0.05$) and depression ($p = 0.01$).

Conclusion: These results are compatible with the possibility that reduced levels of D-serine due to enhanced metabolism by DAAO may contribute to impaired NMDA-R function in schizophrenia and to the efficacy of adjunctive glycine/D-serine treatment.

233. COGNITIVE DYSFUNCTION IN PATIENTS WITH SCHIZOPHRENIA IS CONNECTED WITH ABERRANT TYROSINE TRANSPORT

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Background: Cognitive dysfunction is a core feature in schizophrenia. The mechanisms behind are unknown even if dopamine function seems to play a role. This may explain why tyrosine supplementation can improve cognitive functioning. Interestingly tyrosine transport is changed in schizophrenic patients suggesting that tyrosine kinetics may be connected with cognitive dysfunction in schizophrenia.

Methods: Fibroblasts from 36 patients with schizophrenia were cultured from skin biopsy specimens. With labelled (14C) and unlabelled tyrosine uptake values were determined in the cells. The kinetic parameters of tyrosine, Km (micromoles per litre) and Vmax (micromoles per minute per milligram of protein) were calculated. In the same patients, cognitive functioning was evaluated by a comprehensive neuropsychological test battery and compared with 55 healthy controls.

Results: Patients with high affinity of tyrosine to transport sites, i.e. low Km had poorer cognitive performance than patients with low affinity, i.e. high Km. The maximal transport capacity (Vmax) did not discriminate schizophrenic patients with cognitive dysfunction. The patients performed worse in most cognitive test as compared with the healthy controls.

Conclusion: These results indicate an association between high affinity (low Km) of tyrosine to transport sites and cognitive dysfunction in schizophrenia. Changes in tyrosine transport probably influence dopamine function and thereby cognitive functioning. However, our findings of a relation between low Km and cognitive dysfunction may have a more complex background. Both are trait variables and it is suggested that the connection is related to genetically determined membrane factors that disturb communication/transmission among neurons.

234. DECREASED DORSOLATERAL PREFRONTAL CORTEX *N*-ACETYLASPARTATE IN FIRST-EPISODE PSYCHOSIS IN ADOLESCENCE

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Background/objective: Low concentrations of *N*-acetyl-aspartate (NAA) are interpreted as a marker of neural integrity alteration. Proton magnetic resonance spectroscopy (1H-MRS) studies have demonstrated reduced NAA signal in the hippocampus, thalamus and dorsolateral prefrontal cortex (DLPFC) of both chronic and first-episode schizophrenia patients. Determine if concentrations of NAA are reduced in the DLPC in first-episode psychosis in adolescence.

Methods: Twenty-three adolescents with first-episode psychosis and 33 matched controls were evaluated. The single volume proton spectra were obtained from the right and left DLPFC area using a PRESS sequence (TE = 136 ms, TR = 1500 ms, NEX = 128) in a 1.5-T Philips Gyroscan ACS with and without water suppression. The sample volume was 6.75 cc, including white/grey matter and cerebral spinal fluid. Signal processing was performed by a nonlin-

ear algorithm (AMARES). Partial volume effects were corrected applying multivariate linear regression using white and grey matter volume as variables.

Results: NAA/water ratios were not significantly different between groups. Nevertheless, there was a 30% reduction in the NAA signal in the grey matter and a 20% reduction in the white matter in the left DLPFC of patients compared with controls. No differences were observed in the right DLPFC.

Conclusion: Despite the lack of significant differences, the observed specific reduction in NAA in the left DLPFC suggests that a neural damage may be present, at least in a subgroup of patients, at the time of first psychotic symptoms.

Electrophysiology

235. INEFFICIENT COORDINATION OF SLOW OSCILLATIONS IN SCHIZOPHRENIA

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Background: Four independent groups have reported decreased error-related negativity (ERN) amplitude in schizophrenia (Kopp and Rist, 1999; Mathalon et al., 2002; Alain et al., 2002; Bates et al., 2002). Error-related negativity is a response-locked event-related potential (ERP) that reflects activity in the anterior cingulate cortex that is thought to be part of an error detection system (Falkenstein et al., 2000). It has recently been suggested that evoked theta oscillations underlie the ERN (Luu and Tucker, 2001; Luu et al., 2003). This suggests that patients with schizophrenia may be unable to efficiently recruit theta activity during error detection.

Methods: We performed power spectrum and wavelet analyses on EEG/ERP data collected during performance of a visual go/no-go task designed to elicit errors in 21 patients with schizophrenia and 21 healthy people.

Results: Our findings show that evoked delta and theta oscillations are not coordinated effectively in schizophrenia during error detection. Conversely, there is evidence that in a resting state, patients with schizophrenia show increased slow-wave (delta and theta) activity (Fehr et al., 2003).

Conclusion: Perhaps pathological slow-wave activity during resting states inhibits efficient recruitment of slow oscillations for specific functions.

236. ALTERED AUDITORY RECOVERY CYCLE FUNCTION IN SCHIZOPHRENIA: AN ERP STUDY

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Background: Converging evidence from event-related potential (ERP) and behavioural studies demonstrates that patients with schizophrenia display deficits in early stages of auditory information processing. It has been suggested that such deficits may reflect altered inhibitory processing.

Methods: The present study measured the recovery cycle of the auditory N100 ERP component in 17 patients with schizophrenia and 17 age- and sex-matched healthy volunteers. Patients performed a simple visual distraction task while listening to 80 dB SPL, 1000 Hz tones presented via headphones. Tone pairs were presented with an intra-pair interval of 1, 3, 5 or 7 s, with a pseudorandom inter-pair interval ranging from 9 to 13 s. N100 mean amplitude was measured for the initial tone of each pair (S1) and for each of the S2 inter-pair intervals (1s, 3s, 5s, 7s).

Results: Patients with schizophrenia had significantly reduced N100 amplitudes for S1 stimuli compared to healthy volunteers ($p = 0.012$). For N100 amplitudes elicited by S2 stimuli, a significant quadratic effect was present for healthy volunteers ($p = 0.01$). N100 amplitudes were smaller for S2 stimuli in 1s, 3s and 5s pairs, while amplitudes for S2 in 7s pairs did not differ from S1 N100 amplitudes. In patients with schizophrenia, the quadratic effect for N100 elicited by S2 stimuli was not significant. In the patient group, N100 elicited by S2 in 5s and 7s pairs was greater than that elicited by S1 stimuli.

Conclusion: These results support the hypothesis of altered inhibitory processing of auditory stimuli in schizophrenia.

Acknowledgments: Support contributed by: Australian Rotary Health Research Fund (Ian Scott Fellowship) and NISAD.

237. FACILITATION AND REDUCTION OF PREPULSE INHIBITION: RELATIONSHIPS TO THE POSITIVE AND NEGATIVE DIMENSIONS OF PSYCHOMETRIC SCHIZOTYPY

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Background/objective: Schizophrenic patients and individuals high in schizotypy have been shown to have reduced Prepulse Inhibition (PPI), a measure of sensorimotor gating. However, the evidence is inconsistent as to whether any specific symptoms are associated with this deficit. This study assessed whether any dimensions of schizotypy, which are analogous to the symptom clusters that occur in schizophrenia, are associated with deficits in PPI.

Methods: Prepulse inhibition was tested in 51 healthy volunteers, across a range of prepulse-to-pulse intervals (30–2000 ms). All participants also completed the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), a questionnaire measuring four dimensions of schizotypy.

Results: Multiple regression analyses revealed that individuals high in *cognitive disorganisation* showed *reduced* PPI at 60 and 120 ms. In contrast, at these same intervals, individuals high in *introvertive anhedonia* had *greater* PPI. There were no effects of schizotypy upon habituation.

Conclusion: These data indicate that individuals high in *cognitive disorganisation* fail to gate excessive information occurring within approximately a 60–120-ms interval. However, those high in *introvertive anhedonia* have an increased ability to inhibit information in this same time interval. It might therefore be tentatively suggested that PPI might be altered differentially in schizophrenic patients with different symptom profiles, which would have implications for their information processing capacities.

238. SCHIZOPHRENIC PATIENTS HAVE SLOW NEURAL AND HEMODYNAMIC RESPONSES: ERP AND fMRI EVIDENCE

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Background: While there are many reports of reduced amplitude of the hemodynamic response function (HRF) in schizophrenia, there are no reports of delayed HRFs. Recently, Henson et al. (Neuroimage 2002, 15:83–97) proposed a new method for testing latency differences (<2 s) in HRFs. Traditionally, event-related brain potentials (ERPs), with superb temporal resolution (<1 ms), have revealed small (~ 25–50 ms), significant delays in neural responses in schizophrenia in the late positive ERP component (P300). Using ERP and functional magnetic resonance imaging (fMRI) methods, we asked whether hemodynamic responses would show a delay similar to that seen in P300 in schizophrenia.

Methods: In separate sessions, ERP and fMRI data were collected while 12 patients with DSM-IV schizophrenia and 12 healthy controls performed a visual oddball task. Stimuli were infrequent target Ks and frequent Xs, presented every 1–3 s pseudorandomly, with 7–24 s between Ks. The general linear model in SPM99 yielded parameter estimates for the HRF and its temporal derivative (TD). Beta images reflecting HRF amplitude to target stimuli were minimally thresholded ($p < 0.25$), and latencies were estimated for surviving voxels using TD and HRF beta values.

Results: Patients had a larger proportion of voxels with late HRFs than controls. A sub-analysis of subjects with sufficient data (both early and late HRFs in each region of interest compared to the idealized HRF) revealed that the HRFs from left temporal lobe and anterior cingulate cortex were both ~ 250 ms later in patients than controls.

Conclusion: The hemodynamic delay is greater than, but consistent with, the neural delay often observed in cognitive ERPs in schizophrenic patients. We believe this is the first report of a delay in the hemodynamic response in schizophrenia.

239. VISUAL WORKING MEMORY DEFICITS IN EARLY-ONSET SCHIZOPHRENIA: A COMBINED fMRI AND EEG STUDY

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Background: Working memory deficits in schizophrenia may be caused by deficits in the encoding as well as the maintenance of information. The underlying neural deficits need to be clarified, ideally with a combination of functional neuroimaging at high spatial and EEG at high temporal resolution.

Objective: The contribution of different working memory component processes to the deficit observed in patients.

Methods: We used EEG and fMRI in 10 early-onset schizophrenic patients (mean age 17.1) performing a delayed discrimination task. Controls were matched for handedness, age, gender, and parental education. Working memory load varied from one to three visual objects. The probe was shown after a 12-s delay.

Results: Our design allowed us to separate encoding, maintenance and retrieval related activity in the fMRI and EEG. Analyses

of the P1, N1, and P3 components of the ERP were performed at parieto-occipital and frontal sites, which also displayed the strongest level of activation in the fMRI. Schizophrenic subjects reached the capacity limit of fMRI activation at lower load levels than healthy controls and showed smaller amplitudes for both early and late ERPs. Furthermore, whereas controls exhibited an effect of load on the P3-complex, no such differentiation was evident in the patient group.

Conclusion: Smaller ERP amplitudes and reduced memory load-related fMRI activation suggest that both an abnormality of early stages as well as higher order cognitive functions contribute to working memory impairments in schizophrenia. The combination of electrophysiology and neuroimaging offers unique insights into the impaired neural dynamics of schizophrenia.

240. TEST–RETEST RELIABILITY OF ERP COMPONENTS OF P300, P50 AND DURATION MISMATCH NEGATIVITY IN MONOZYGOTIC TWINS

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Background: Event-related potentials (ERPs) have been widely studied as a possible endophenotype of schizophrenia.

Methods: We examined the test–retest reliability of three ERP components (P3, P50 and MMN) and estimated their heritabilities and measurement errors using model-fitting analyses. ERPs were recorded with a 19-channel electroencephalograph (EEG) from 10 monozygotic twin pairs on two occasions with an average interval of 22.26 days. P3 was assessed using an auditory oddball paradigm. P50 was recorded with a conditioning-testing paradigm and MMN was elicited by a duration auditory oddball task. Zygosity was determined using a questionnaire.

Results: P3 amplitude, P3 latency and MMN amplitude showed significant reliability (ICC = 0.77, 0.81, 0.69, respectively) and high twin correlations (ICC = 0.64, 0.89, 0.63, respectively). For P50, T/C ratio was not reliably measured (ICC = 0.28). Twin correlation was modest (ICC = 0.49). Model fitting analyses, assuming the absence of shared environment, indicated that the presence of genetic and measurement variance components (h^2 and m^2) for the ERP measures. The standardized variance components estimates were: $h^2 = 0.62$, $m^2 = 0.38$ for P3 amplitude, $h^2 = 0.75$ and $m^2 = 0.12$ for P3 latency, $h^2 = 0.69$ and $m^2 = 0.31$ for MMN amplitude, and $h^2 = 0.42$, $m^2 = 0.58$ for P50 T/C ratio.

Conclusion: Although ERP components are highly heritable, measurement error, particularly for P50 ratio, is substantial. We are now (1) exploring ways to reduce measurement error for P50 ratio, (2) conducting power analyses to optimize study design, and (3) proceeding to a full study to examine the genetic bases of ERPs and their relationship to schizophrenia and bipolar disorder.

241. BRAIN SOURCES FOR CHANGE-DETECTION: AN ERP-STUDY IN PATIENTS AT THE OUTBREAK OF EARLY-ONSET SCHIZOPHRENIA AND 15-YEARS LATER

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Background: Severer illness, poorer prognosis and impaired brain structure are reported for patients with an early-onset of schizophrenia[1,2]. Is this reflected in early stimulus processing?

Methods: This study compares an electrophysiological measure of automatic, auditory attention-related function and its sources in the brain for 19 patients (17.5 years) at onset, and 17 patients 15 years after an early onset with age-matched healthy subjects.

Results: Mismatch Negativity (MMN), recorded from 32 sites during a simple visual vigilance task, was associated with a rare tone shorter than the standard. Brain electrical source analysis (BESA) confirmed bilateral frontal and temporal lobe dipoles[3]. Both patient groups showed a smaller MMN than the controls. There were several signs of illness progression in the older patient group: (a) a visual vigilance decrement was only evident in the older patients, (b) the left superior temporal source was weaker, (c) the left cingulate source changed orientation, (d) the right inferior/mid-frontal source was active later. This illness-related progression of a cognitive impairment is consistent with a neurodevelopmental hypothesis[4], initial structural impairments in young patients[5] contrasting with more variable or sporadic changes in those with a later onset[6,7].

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242. FUNCTIONAL CHANGES OF AUDITORY EVOKED POTENTIALS AND SPONTANEOUS BRAIN ELECTRICAL ACTIVITY DURING AUDITORY HALLUCINATIONS

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Background: Schizophrenia is a very common and affects one in every hundred people. Hallucinations are one of its core symptoms. In the last century, a concept of a brain-based origin of hallucinations was developed, but the exact cause or the generating cerebral location remained unclear until today.

Methods: Here, we investigated schizophrenic patients who are prone to auditory hallucinations and perceived their voices during the measurement. Spontaneous brain electrical activity and auditory evoked potentials (AEP) were recorded. The patients were asked to indicate by button press when they started to hear voices and again when the voices terminated. Based on this information, periods with hallucinations were separated from those without. EEG and AEP were analyzed separately for both periods. Brain electrical sources of the spontaneous EEG were estimated with low-resolution electromagnetic tomography (LORETA). In the analysis of the AEP further, the Global Field Power (GFP) was calculated.

Results: Brain electrical activity was highest in the temporal lobe during hallucinations. For the AEP, GFP and LORETA amplitudes were lower during hallucinations than between hallucinations with a left hemispherical pronunciation.

Conclusion: We hypothesize that the reduced AEP amplitudes during hallucinations are due to an internal pre-activation of the auditory cortex, competing for processing resources with the external stimuli.

243. THE RELATIONSHIP BETWEEN AUDITORY P300 AND PSYCHOLOGICAL AND MRI CHARACTERISTICS IN PATIENTS WITH SCHIZOPHRENIA

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Background: The auditory P300 is well established as an index of cognitive deviations in schizophrenia. However, its relationships with the indices at the other levels of pathogenesis of the disease are less known.

Methods: The preliminary analysis was carried out in the group of 10 right-handed patients with schizophrenia (31.9 ± 11.7 years). The patients underwent auditory oddball paradigm (tones, 60 dB, 80% non-targets (1000 Hz) and 20% targets (2000 Hz)). In the same day, they underwent psychological tests aimed at the examination of attention and memory. MRI examination was carried out within the same week, on a 0.5-T Tomikon S50 tomograph (Bruker, Germany). The hippocampal, caudate, and amygdala volumes were calculated.

Results: Deviations in attention stability significantly negatively correlated with P300 amplitude (in T4) and positively—with P300 latency (in C4). The deficiency in memorization (assessed by reproduction) significantly negatively correlated with P300 amplitude in F4, C3, Cz, C4, P3, Pz and the deficiency in memorization (assessed by recognition) significantly positively correlated with P300 latency in P4. The volume of left caudate nucleus significantly positively correlated with P300 latency in C3, Cz, Pz, and the volume of right caudate nucleus–with P300 latency in C3.

Conclusion: Considering the preliminary character of the findings, we should note, nevertheless, the relationship between reduction of P300 and its latency prolongation with the deficiency in attention and memory functions. Correlations between neurophysiological and structural parameters were significant only for P300 latency.

244. SYNTAX OF EEG MICROSTATES IN FIRST EPISODE, ACUTE, MEDICATION-NAIVE SCHIZOPHRENICS

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Background: EEG microstate analysis parses ongoing brain electric activity (multichannel EEG recordings) into building blocks (or, elements) of mentation (e.g., abstract versus concrete) in the subsecond time range (mean durations around 100 ms).

Methods: EEG data from 27 acute, first-episode, medication-naïve, productive schizophrenics and their 27 controls was segmented into microstates (modified k-means clustering). Thereby, all microstates were assigned to four classes (A, B, C, D). To assess microstate syntax, transition frequency between the microstates of the four classes was evaluated as percentage of all transitions in each subject. Preferred direction of transition for the six possible transition pairs between the four microstate classes was compared between patients and controls.

Results: There was a significant interaction between subject groups (patients and controls) and transition pairs (2 subject groups × 6 transition pairs ANOVA). Preferred transition pairs were C-to-A and A-to-D in patients, D-to-A and A-to-C in controls, i.e. in patients reversed to controls (C-A-D versus D-A-C). –The syntax of brain electric microstates (of mentation elements) reveals brain mechanisms of mentation.

Conclusion: Based on the present, still very limited knowledge about functional significance of the elements, the observed, altered concatenation of the elements of mentation in schizophrenic thinking suggests that in controls, a step of abstract thought (microstates class A) is preceded by a step of increased and followed by lowered attention, whereas in patients, an abstract thought step (class A) is preceded by low and followed by increased attention.

245. REDUCED MISMATCH NEGATIVITY IS ASSOCIATED WITH IMPAIRED VERBAL MEMORY AND POOR FUNCTIONING IN SCHIZOPHRENIA PATIENTS

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Background: Patients with schizophrenia exhibit deficits that range from abnormalities in early auditory sensory processing to impairments in later, integrative neurocognitive operations. Mismatch Negativity (MMN) is a preattentional ERP component evoked 50–150 ms following the onset of infrequent, physically deviant stimuli. While several studies have replicated the finding of reduced MMN in schizophrenia, little is known about the everyday functional consequences of MMN deficits or the relationship of MMN deficits to core neurocognitive abilities such as verbal memory.

Methods: Schizophrenia patients ($n = 25$) and nonpsychiatric subjects ($n = 25$) were tested on the MMN duration-deviant paradigm. EEG was continuously recorded from 34 scalp electrodes while subjects passively listened to tones of either 50 ($P = 0.90$) or 100 ($P = 0.10$) ms duration. The California Verbal Learning Test (CVLT) and Global Assessment of Functioning (GAF) scale were used to examine the regional correlates of MMN deficits in schizophrenia patients.

Results: Schizophrenia patients had significantly reduced mismatch responses over frontocentral regions, confirming previous reports. MMN amplitude was significantly correlated with measures of short- and long-delayed recall as well as ratings of functioning in schizophrenia patients. Highest correlations of MMN related deficits in cognition and functioning (e.g., rho = – 0.65) were evident at frontocentral recording sites.

Conclusion: MMN impairment is associated with verbal memory deficits and lower clinician ratings of everyday functioning in schizophrenia patients. MMN is predictive of "downstream" deficits in integrative cognitive operations necessary for enhanced functioning in schizophrenia patients. MMN correlates with cognition and outcome and may be a useful target for developing drugs geared to improve cognitive and functional deficits in schizophrenia.

246. AUDITORY ERPS AND EMOTIONAL INTERFERENCE IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: There is converging evidence for emotional processing deficits in schizophrenia, but the question of whether and how these deficits interfere with cortical stimuli processing remains unresolved. Later component event-related potentials (ERPs), offer a window into the emotional interference in the cortical stimuli processing in schizophrenia on a fraction of a second time scale. The scalp-recorded P300 components of the event-related brain potential are commonly reduced in patients with schizophrenia, but to date no ERP study of emotional interference in cortical stimuli processing in schizophrenia has been published, using a complex affective oddball-paradigm (CAOP). In CAOP participants count rare tones, to ensure that their attention is engaged on the target stimuli, while passively observing emotional pictures. This study serves to explore emotional interference in cognitive processing through CAOP in schizophrenics.

Methods: Oddball-paradigm auditory ERPs were recorded while presenting a set of 72 photographic slides obtained from the International Affective Picture System (24 high arousal/pleasant, 24 low arousal/neutral, and 24 high arousal/unpleasant slides) to 10 schizophrenic patients and 11 normal controls (matched for sex and age).

Results: Between subjects-analysis showed that schizophrenic had greatly diminished P300 amplitude for all emotional conditions, comparatively with controls. Within-subjects analysis showed that schizophrenics had no P300 amplitude differences for any type of emotional stimulation. On the contrary, controls showed an attentional shifting for pleasant emotional stimulation, but not for unpleasant or neutral ones.

Conclusion: These findings suggest suboptimal cortical stimuli processing under emotional stimulation, in schizophrenics, indicating an attentional disturbance worsened by emotional stimulation.

247. EVIDENCE FOR COROLLARY DISCHARGE DYSFUNCTION IN THE SOMATOSENSORY SYSTEM IN SCHIZOPHRENIA

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Background: Self-monitoring is fundamental to normal cognitive and motor functioning. It allows on-line modifications of thoughts and actions. An efference copy of a planned action may be sent through a "feed forward" mechanism to the appropriate sensory cortex, preparing it for the arrival of the sensation, thereby dampening associated sensory responses. This explains suppression of somatosensory sensation during movements. Disruption of corollary discharge mechanisms may underlie positive symptoms of schizophrenia, particularly those where self-generated thoughts are misattributed to external sources (Feinberg, 1978; Frith, 1995).

Methods: To test this, we compared somatosensory responses during self-prepared and passive movements using event-related brain potentials (ERPs) in 14 patients with schizophrenia (DSM-IV) and 15 age-matched controls. An early positive (P100) ERP component was elicited by somato-motor stimulation to the right index finger delivered by an externally controlled plunger on two types of trials: (1) Self-prepared movements—Subjects were preparing to lift their finger in response to a visual cue when the plunger was activated, (2) Passive movements—Subjects were passively viewing a visual cue when the plunger was activated (i.e., no response preparation). ERPs from these two trial types were compared.

Results: In controls, somatosensory responses to plunger stimulation were larger during passive than self-prepared movements, consistent with suppression of somatosensory activation by response preparation and its associated corollary discharge. In patients, this difference was not significant.

Conclusion: Somatosensory activation is less inhibited during self-prepared movements in patients with schizophrenia than in controls, perhaps due to a failure of corollary discharge to inhibit sensory response.

248. DECREASED AMPLITUDE OF THE P3 COMPONENT IN SIMPLE REACTION TIME BUT NOT CHOICE REACTION TIME DURING ACUTE EPISODES OF SCHIZOPHRENIA

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Background: Increased reaction time and reduced amplitude of the P300 component in event-related potential studies has been reported as both a trait and state marker of schizophrenia.

Methods: We measured ERP to a simple reaction time and a choice reaction time task during the acute phase of illness and 6 weeks after treatment in 10 patients with schizophrenia.

Results: The amplitude of the P300 component in the simple reaction time task is attenuated at time 1 and increases at time 2. The p300 component to the choice reaction task is stable between time 1 and time 2 and is similar in amplitude to the p300 component to the simple reaction time task at time 2. This result indicates that the cognitive demands of the task interact with the course of illness. The decrease in amplitude of the p300 component is most pronounced during the acute phase of illness for simple tasks that demands speed in processing and improves with treatment. The p300 component to choice reaction time tasks does not appear to change with treatment.

Conclusion: These results are consistent with our previous report of increased reaction time to the same simple reaction time task in treated patients with persistent illness compared to treated patients with fluctuating illness and no significant difference between the two groups for reaction times to the choice reaction time tasks. Comparison of deficits in simple response p300 and choice p300 might provide an index of relative severity of acute and chronic pathological processes in schizophrenia.

249. IMPAIRED BRAIN SYSTEMS OF VISUAL ATTENTION IN THE PRODROMAL, EARLY, AND LATE STAGES OF SCHIZOPHRENIA

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Objective: To gain more insight into the pathogenesis and pathophysiology of schizophrenia, we recorded event-related brain potentials (ERPs) from individuals in the pre-onset, recent-onset, and chronic stages of schizophrenia and healthy controls while they performed a visual attention task.

Results: In contrast to controls, subjects at the initial, early, and later phases of schizophrenia generated little or no characteristic early selection positive and negative brain potentials while attending to stimulus color.

Conclusion: These results provide the first physiological evidence for the hypothesis that disruption of visual attention and brain function is an enduring and core feature of schizophrenia that is evident before and after its onset.

250. MISMATCH NEGATIVITY TO DURATION, FREQUENCY AND INTENSITY DEVIANT SOUNDS IN SCHIZOPHRENIA: A COMPARISON OF SHORT DURATION OF ILLNESS, LONG DURATION OF ILLNESS AND HEALTHY FAMILY MEMBERS

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Background/objective: Advances in the understanding of the MMN generators and their hypothesized responses to different experimental manipulations have better enabled us to explore the underlying causes of the robust reduction in MMN in schizophrenia. The aim of this study was to explore the behaviour of deficits in automatic sound processing in individuals with schizophrenia and their healthy family members as indicated by the mismatch negativity (MMN) component of the auditory event-related potential.

Methods: MMN produced to duration, frequency and intensity deviant tones was recorded in patients with short duration of illness (SDI $n=13$), long duration of illness (LDI $n=20$), first-degree relatives of patients (FDR $n=17$) and age-matched community controls. The MMN was recorded at two deviant probabilities (6% and 25%).

Results: In the sub-sample tested to date, a significant MMN reduction is only observed in the patient LDI group relative to matched controls. There is some evidence that this is dependent on deviant type and probability. For example, significant reductions in MMN amplitude were observed in the LDI group to both duration and frequency deviant sounds and in the SDI group to duration deviants only. When group differences are explored separately for each deviant probability condition, significant reductions occurred at the low (6%) deviant probability only for both LDI and SDI groups.

Conclusion: Results provide tentative support for compromised connectivity between hypothesised sub-generators of the MMN and a progression of this deficit across the course of the illness.

251. DEFICIENT ATTENTIONAL MODULATION OF EARLY INFORMATION PROCESSING IN SCHIZOPHRENIA

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Background: Abnormalities in attention are well documented in schizophrenia. We investigated in an auditory selective attention task if such deficits also affect preattentive processing of sensory information. Processing negativity (PN) is an event-related potential (ERP) that is observed when among two or more input streams of stimuli one particular stream is selectively attended to. It reflects attentional modulation of processing of information entering the attended input stream or 'channel' and manifests as a negative deflection in ERPs to the attended stimuli. PN has a latency between 100 and 300 ms, depending on the particular paradigm. Abnormal PN has been described not only in chronic schizophrenia, but also in patients with Parkinson's disease with prominent frontal deficits.

Methods: We investigated PN in a selective attention task in which subjects had to attend to either a stream of high (1500 Hz) or low (750 Hz) tones. Subjects were 21 normal controls,

15 first episode patients, 18 recent-onset patients (between 18 and 60 months after their first episode) and 23 chronic patients.

Results: The analysis demonstrated significant differences between the groups ($F_{1,73} = 2.82$, $p < 0.05$). Post hoc analyses showed significantly smaller PN in the recent-onset and chronic patient groups than the normal controls, while the difference between first-episode patients and controls only reached a trend-level of significance. Additional analyses revealed that all patients showed different topographical distribution of PN: While controls showed the main activity at central electrodes, all patient groups demonstrated a more anteriorly located peak.

Conclusion: These results demonstrate that the top-down attentional modulation of auditory information processing is deficient in schizophrenia, resulting in impaired separation of to-be-attended and to-be-ignored input channels at relatively early stages of information processing. Although first-episode patients were not as severely impaired as recent-onset and chronic patients potentially reflecting a certain sampling bias in our study, the highly similar topography among all patients indicates that the underlying pathology may represent a trait marker like other abnormal indices of frontal lobe functioning in schizophrenia.

252. P3B AND NOVELTY P3A IN FIRST-EPISODE AND CHRONIC SCHIZOPHRENIA

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Methods: Auditory P3a and P3b event-related potentials that were suggested to reflect the automatic and selective attention processes respectively, were evaluated in 29 first-episode and 27 chronic schizophrenia patients compared to 46 control subjects. All patients were evaluated during the acute phase of their illnesses. P3a and P3b components were assessed by applying a novelty and an oddball paradigm, respectively.

Results: P3b amplitude was decreased in first-episode patients compared to controls ($p < 0.05$). The topography of P3b showed a difference between the first-episode group and control subjects ($p < 0.04$), such that the P3b amplitude was decreased more in central and parietal areas than in frontal areas ($p < 0.004$). A widespread decrease in P3b ($p < 0.0001$) and P3a amplitude ($p < 0.001$) was observed in the chronic schizophrenia group compared to controls. In first-episode schizophrenia, P3a amplitude did not differ from that of controls. No group differences for P3a and P3b latency were obtained.

Conclusion: These results suggest that in the first-episode of schizophrenia, selective attention processes are impaired, although somewhat differently from that in chronic schizophrenia, but the automatic attention processes, which are deteriorated in chronic schizophrenia, are preserved.

Eye Movements

253. SMOOTH PURSUIT AND ANTISACCADE EYE MOVEMENTS IN MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA

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Background/objective: Deficits on the smooth pursuit and antisaccade eye movement tasks have been suggested to be markers of the genetic liability to schizophrenia. Here, we report results from an ongoing investigation of these measures in monozygotic twins discordant for schizophrenia.

Methods: Ten twin pairs discordant for a DSM-IV diagnosis of schizophrenia (6 male, 4 female pairs; mean age = 34.30 years, S.D. = 13.02) and 10 healthy control twin pairs (5 male, 5 female pairs; mean age = 31.80 years, S.D. = 9.75) were tested on constant-velocity smooth pursuit (12, 24, 36, and 48°/s) and antisaccade (60 trials, target eccentricities $\pm 6°$ and $\pm 12°$) performance using infrared oculography (sampling frequency 500 Hz). Zygosity was established on the basis of a twin likeness questionnaire.

Results: Results indicate that the performance of the unaffected members of the discordant pairs fell in between those of their affected co-twins and healthy control twins for most variables. "Large" effect sizes (ES) of comparisons between unaffected co-twins and control twins were observed for antisaccade latency (ES = 1.27), smooth pursuit gain at 36°/s (ES = − 1.04) and 24°/s (ES = − 1.01), and antisaccade gain (ES = 0.69). "Medium" effect sizes were observed for smooth pursuit gain at 12°/s (ES = − 0.57) and 48°/s (ES = − 0.53) and antisaccade error rate (ES = 0.40). Significant inter-twin correlations were found in the controls for antisaccade error rate ($r = 0.79$, $p = 0.007$) and SPEM gain at 36°/s ($r = 0.80$, $p = 0.006$) and 48°/s ($r = 0.77$, $p = 0.02$); no significant correlations were observed in the discordant group.

Conclusion: These results provide support for the hypothesis that smooth pursuit and antisaccade deficits index genetic liability to schizophrenia.

254. STRUCTURAL NEURAL CORRELATES OF ANTISACCADE AND PROSACCADE EYE MOVEMENTS

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Background: Saccade tasks have been used to study the pathophysiology and genetics of schizophrenia. Lesion and functional neuroimaging studies have implicated frontal, parietal, and subcortical areas in performance. However, the structural (volumetric) neural correlates are less well studied.

Methods: This study examined correlations between performance on the antisaccade and prosaccade tasks and grey matter volume (covarying for age) using voxel-based morphometry implemented in SPM99. Thirty-two healthy individuals (14 males, 18 females; mean age = 33.31, S.D. = 13.12) underwent magnetic resonance imaging at 1.5 T and antisaccade and prosaccade assessment (60 trials, target eccentricities $\pm 6^\circ$ and $\pm 12^\circ$) using infrared oculography (sampling frequency 500 Hz).

Results: Statistical parametric maps set at $p < 0.001$ threshold revealed that antisaccade error rate was negatively correlated with frontal lobe grey matter (BA8 extending to BA6; centred at $x = 27$; $y = 18$; $z = 50$) and left posterior cerebellar lobe volume ($x = -16$; $y = -86$; $z = -21$). Antisaccade latency was negatively correlated with frontal lobe grey matter volume (BA47; $x = 50$; $y = 33$; $z = -12$); spatial accuracy was correlated with left posterior cerebellar lobe volume ($x = -15$; $y = -95$; $z = -19$). On the prosaccade task, latency was negatively correlated with frontal lobe grey matter volume (BA47; $x = 42$; $y = 24$; $z = -6$); spatial accuracy was negatively correlated with right inferior cerebellar lobe ($x = 11$; $y = -64$; $z = -61$) and frontal lobe volume (BA47; $x = 47$; $y = 39$; $z = -18$).

Conclusion: Our findings confirm the involvement of a fronto-cerebellar network in the control of antisaccade and prosaccade eye movements and suggest that the volume of relevant brain regions may be a critical determinant of performance in healthy populations. Future studies are needed to examine these relationships in patients with schizophrenia.

255. SACCADIC SET-SHIFTING AND REWARD-DEPENDENT INHIBITION OF RETURN IN FIRST-EPISODE PSYCHOSIS

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Background: We used a novel saccadic eye movement task in which distinct patterns of performance have been demonstrated following damage to ventromedial and other areas of the prefrontal cortex (Hodgson et al. Neuropsychologia, 40: 1891–901, 2002).

Methods: Patients with affective and schizophreniform first-episode psychosis and matched controls performed a set-shifting task in which they made saccades to one of two spatial locations in response to the colour of a central cue, followed by positive or negative feedback. Two specific processes can be investigated. First, as in standard set-shifting tasks, there is a measure of perseveration of a learned set when stimulus-response contingencies are unexpectedly changed. Secondly, a location-specific inhibitory effect can be determined following unexpected negative feedback, again when stimulus-response contingencies are changed.

Results: Patients were slower and less accurate overall. However, they were no different to controls on a measure of perseveration, in contrast to previous findings of patients with prefrontal injury. Patients also demonstrated the same reward-dependent inhibition of return as controls. This latter effect was abolished in a patient with a focal lesion of ventromedial prefrontal cortex (Hodgson et al. 2002).

Conclusion: Thus, despite an overall performance decrement, set shifting was relatively intact in first-episode psychosis, a finding consistent with our previous research. We have also previously reported abnormal performance on a gambling task, sensitive to ventromedial prefrontal function. The current finding, that automatic processing of negative reinforcement appears normal in first-episode psychosis, calls into question the role of negative reinforcement in mediating the deficits on the gambling task.

256. REFLEXIVE ORIENTING TRIGGERED BY GAZE-DIRECTION IS ENHANCED IN SCHIZOPHRENIA

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Background/objective: Reflexive shifts of attention triggered by another person's gaze sustain shared attention, the joint focussing of attention by self and other upon some feature of the environment of mutual interest. Shared attention provides the most basic *meeting of minds* and underpins the development of normal social cognition. Reflexive social-orienting is mediated by the superior temporal sulcus, a region implicated in the neuropathology of schizophrenia, and social cognition impairments are characteristic of schizophrenia. This study investigated reflexive and controlled social-orienting in schizophrenia.

Methods/results: In Exp. 1, detection-RTs for targets appearing right or left of a central image of a head turned right, left or straight-ahead were recorded in 30 patients with schizophrenia and in 24 controls. Targets appeared in cued locations 50% of the time. Cue-target intervals were 100, 300 and 800 ms. Patients, but not controls, showed an RT advantage for non-predictive congruent cues at 100 ms SOA. The congruency advantage at longer SOAs was similar in patients and controls. In Exp. 2, targets appeared 300 or 800 ms after a central image of a head turned away from the target 80% of the time. Detection-RTs for 20 patients and 20 controls did not differ as a function of cue-type.

Conclusion: People with schizophrenia show rapid reflexive orienting of attention in the direction of another person's gaze. Further, findings suggest that gaze-direction cues have a special hold on attention since neither patients nor controls could completely override the attentional pull of a head turning, even when that head reliably turned the wrong way.

258. SCHIZOTYPY AND EYE MOVEMENT DYSFUNCTION: SEPARATE MARKERS FOR SCHIZOPHRENIA

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Background: Schizotypal Personality Disorder (SPD) shows biological links to schizophrenia. If SPD is a vulnerability indicator for schizophrenia, then patients with schizophrenia should have greater scores on measures of schizotypy than the normal population. In addition, given that eye movement deficits (smooth pursuit eye movement and antisaccade performance) may be biological markers of the latent trait of schizophrenia, poor eye movement performance should be more prevalent among high schizotypy scorers.

Methods: We examined these hypotheses in two experiments and found contradictory results.

Results: In experiment 1, scores on the Schizotypal Personality Questionnaire (SPQ: Raine, 1991) were higher in 19 medicated patients with schizophrenia than 79 normal participants, especially for subscales "no close friends" and "constricted affect". These results support the notion that SPD features are associated with schizophrenia. 10% of normal participants scored above the patient mean on the total score suggesting that this group might be at risk for schizophrenia. In experiment 2, smooth pursuit (SPEM) and antisaccade (AS) performance in 95 students were found to be unrelated to schizotypy. Adding a concurrent working memory task to the eye movement tasks also did not reveal a relationship between schizotypy and eye movement. Only elevated neuroticism was associated with poorer AS performance, suggesting that anxiety may be a factor in schizophrenia.

Conclusion: It is possible that eye tracking and schizotypy form two separate vulnerabilities for schizophrenia and that the combination of high schizotypal features and eye movement deficits may a particular risk.

Neurological Soft Signs

259. AN APPLE FOR A TABLE; A CAR FOR A COW: A SIMPLE COUNT ON CATEGORY FLUENCY IS SUFFICIENT?

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Objective: This study attempted to demonstrate the use of conventional simple "count" of category in semantic fluency test may not sufficiently reflect the actual performance of patients with schizophrenia and normal controls.

Methods: A cross-sectional design was adopted with a total of 187 patients with schizophrenia and 98 normal controls. Participants were asked to generate as many exemplars from within a semantic category as they could in 3 min. Four types of common categories encountered in daily life were selected for this study; they were

animal, means of transport, food, and furniture. The Rasch model was undertaken for data analysis. This model is a measurement model which provides probabilistic additive conjoint measurement. Data which fit the model, given certain testable assumptions, are unidimensional, have order, additivity and specific objectivity. A logit transformation is obtained, providing interval level measurement for the trait under consideration.

Results: The findings indicated that the psychological distance, in terms of logits unit, was not at an equal interval within each category across the 3-min interval in both patients and healthy controls. The logits between different categories were also found to be inconsistent in both groups.

Conclusion: These preliminary findings suggest that we should not simply equate different category scores when we study semantic categorization. Such a simple "count" of categories may not truly reflect the actual performance of patients and normal controls. Future study should further examine a more representative and accurate measurement of semantic categorization.

260. SENSITIVITY AND SPECIFICITY OF NEUROLOGICAL SIGNS USING THE CAMBRIDGE NEUROLOGICAL INVENTORY IN CHINESE PATIENTS WITH SCHIZOPHRENIA

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Objective: This study attempted to examine the sensitivity and specificity of neurological signs in Chinese patients with schizophrenia.

Methods: A total of 250 schizophrenic patients and 90 normal controls were recruited. The Cambridge Neurological Inventory (CNI) was used to assess the prevalence of neurological signs. The CNI consists of seven subscales. Three soft signs subscales (motor coordination, sensory integration, disinhibition) and four hard signs subscales (extrapyramidal signs, dyskinesia, catatonia, pyramidal signs).

Results: The findings showed that patients exhibited significantly more signs than normal controls in all subscales but pyramidal signs ($p < 0.00005$). Significant differences were also found in total soft signs, total hard signs as well as total neurological signs ($p < 0.0005$). In view of sensitivity and specificity, the three subscales of soft signs showed a relatively better sensitivity and specificity as compared with the remaining hard signs. Improvement in sensitivity and specificity was demonstrated when the subscales were collapsed into total soft signs, total hard signs and total neurological signs. A cut-off of 4 in total soft signs yields a sensitivity of 0.63 and specificity of 0.71; whereas a cut-off of 1 in total hard signs yields a sensitivity of 0.78 and specificity of 0.89. A cut-off of 5 in total neurological signs also gets a sensitivity of 0.81 and specificity of 0.73. High levels of neurological abnormality characterize schizophrenic patients.

Conclusion: An extended assessment battery of CNI provides even better discrimination of patients from normal controls, and soft signs are more differentially associated with schizophrenia than are hard signs in the Chinese sample.

261. NEUROLOGICAL DYSFUNCTION AND ITS RELATIONSHIP TO SYMPTOMATOLOGY AND PREMORBID INTELLIGENCE IN SCHIZOPHRENIA

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Background: To examine the association between neurological dysfunction and positive and negative symptoms and premorbid intelligence.

Methods: We assessed neurological functioning in 53 patients with (DSM-III-R) schizophrenia using the Neurological Evaluation Scale (NES). Their psychopathology was rated on the Positive and Negative Syndromes Scale (PANSS) and premorbid IQ on the National Adult Reading Test (NART).

Results: Regression analysis identified general psychopathology scores ($p < 0.0001$), anergia scores ($p = 0.04$) and NART scores ($p = 0.003$) as significant predictors of neurological dysfunction.

Conclusion: Soft neurological signs in patients with schizophrenia are associated with symptomatology and significantly poorer premorbid IQ. Neurodysfunction may be related to attentional impairment due to patient symptomatology at time of examination and earlier cognitive factors such as premorbid IQ.

262. NEUROLOGICAL SIGNS IN SCHIZOPHRENIA: THEIR RELATIONSHIP TO PSYCHOTIC SYMPTOMS, TREATMENT OUTCOME AND EXTRAPYRAMIDAL SYMPTOMS

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Background: While neurological signs are well recognized in patients with schizophrenia, little is known about their relationship to other aspects of the illness. We investigated the relationship of neurological signs to psychiatric symptoms, duration of untreated psychosis, treatment outcome, risk of extrapyramidal symptoms (EPS) and stability over time.

Methods: The Neurological Evaluation Scale (NES) was applied to 62 first-episode subjects with minimal antipsychotic exposure. We determined the factor structure of the NES alone, and then of the combined NES and Positive and Negative Symptom Scale (PANSS). Associations were sought between the NES factors and the duration of untreated psychosis, treatment outcome and the development of acute EPS and tardive dyskinesia (TD).

Results: Five NES factors were identified, explaining 68% of the variance. The combined analysis suggested that psychiatric symptoms and neurological signs are not closely related. In addition, NES factors were not significantly correlated with duration of untreated psychosis, or remission or relapse rates at 12 and 12 months. A significant association was found between the NES repetitive motor factor and the later onset of TD ($p = 0.01$). NES factors changed over time, possibly as a result of superimposed EPS.

Conclusion: Neurological signs are not closely related to psychiatric symptoms, and do not predict treatment outcome. Certain neurological signs may have value in identifying patients at risk for TD.

263. VULNERABILITY MARKERS OF SCHIZOPHRENIA: A FAMILIAL ANALYSIS OF NEUROLOGICAL SOFT SIGNS AND MINOR PHYSICAL ANOMALIES

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Background/objective: Neurological soft signs (NSS) and minor physical anomalies (MPAs) are two putative indices of neurodevelopmental abnormalities identified in schizophrenic patients and their biological relatives. Either genetic or environmental factors may be responsible for the familial similarities of these vulnerability markers. The aim of this study was to determine whether NSS and MPAs are aggregated within 22 nuclear families (probands with schizophrenic spectrum disorders and non-psychotic parents and one sibling).

Methods: Ratings on NSS were obtained with the Neurological Evaluation Scale Spanish version, composed by four subscales: sensory integration (SI), motor coordination (MC), sequencing of complex motor acts (SCMA), and others (O). MPAs were evaluated with a reduced version of the Waldrop Scale.

Results: For NSS (i) the comparison of patients with their parents showed no significant differences, (ii) patients had higher scores than their siblings in two subscales (SAMC: $Z = 2.81$, $p = 0.005$; O: $Z = 3.73$, $p < 0.0001$) and (iii) siblings differed significantly from their parents in all subscales scores (SI: $Z = 2.12$, $p = 0.034$; MC: $Z = 2.06$, $p = 0.039$; SCMA: $Z = 3.70$, $p < 0.0001$; O: $Z = 3.42$, $p = 0.001$). For MPAs, patients presented significantly increased scores than their parents ($Z = 2.04$, $p = 0.040$) but no differences appeared with their siblings. The intra-familial transmission model showed similarities within families for the NSS sensory integration area (ICC = 0.44; $F = 1.79$; $p = 0.042$) but not for MPAs.

Conclusion: In spite of the preliminary nature of the sample, these results support previous findings suggesting the existence of intra-familial transmission, at least in part, of NSS but not of MPAs, which could be more dependent on epigenetic influences.

Acknowledgment: This work was supported by the *Fundació La Marató de TV3* (014430/31) (Spain).

264. MULTI-DEVELOPMENTAL ABNORMALITIES IN SCHIZOPHRENIA: DEFINING NEW PHENOTYPE–GENOTYPE STRATEGIES

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Background: Compelling evidences suggest that neurodevelopmental disruption could predispose to schizophrenia, and that Neurological Soft-Signs (NSS), Minor Physical Anomalies (MPAs) and dermatoglyphic Fluctuating Asymmetries (FAs) are frequently found in patients with schizophrenia and in their biological relatives. Co-assessment of these developmental phenotypes could lead to the validation of a composite phenotype based on a combination of developmental markers, especially interesting as a quantitative phenotype for extensive genetic studies of schizophrenia.

Methods: Three samples (patients with DSM-IV schizophrenia, non-psychotic first-degree relatives and healthy controls) were assessed for NSS, MPAs and FAs. A multivariate analysis was also used to provide comprehensive results.

Results: Patients and their biological relative had higher scores of NSS, MPAs and FAs than healthy controls. Multiple Regression Analysis of NSS, MPAs and FAs showed a specific pattern of neurodevelopmental abnormalities in each group.

Conclusion: There seemed therefore to be a differential pattern of NSS, MPAs and FAs in schizophrenic patients and their relatives. A better specification of this pattern could provide new insights in the context of the neurodevelopmental hypothesis of schizophrenia. The combination of these markers could also constitute a composite phenotype useful for genetic studies.

265. MINOR PHYSICAL ANOMALIES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background/objective: There is substantial evidence of an association between schizophrenia in adult life and disturbances to neural and craniofacial development during gestation. This association may not be specific to schizophrenia. The aim of this study was to assess the rates of developmental minor physical anomalies (MPAs) in patients with bipolar disorder, patients with schizophrenia, and controls.

Methods: We conducted a detailed examination of craniofacial MPAs in 60 patients with DSM-III-R bipolar disorder, 60 patients with DSM-III-R schizophrenia and 72 control subjects.

Results: Patients with bipolar disorder and patients with schizophrenia had increased rates of MPAs compared to controls, concentrated in the ears, mouth and head dimensions. Bipolar disorder had a particularly strong association with anomalies of the ear, and schizophrenia had a particularly strong association with anomalies of the mouth, especially anomalies of palate shape. The distribution of MPA total scores was shifted upwards in both illness groups, compared to controls.

Conclusion: The rates of MPAs in patients with bipolar disorder are higher than those of controls and are similar, though not identical, to those of patients with schizophrenia. Prenatal disturbances to neural and craniofacial development may increase risk of a range of psychiatric syndromes, including bipolar disorder and schizophrenia.

266. NEUROLOGICAL SOFT SIGNS IN PSYCHOSIS; DIAGNOSTIC SPECIFICITY, DURATION OF UNTREATED PSYCHOSIS AND EVOLUTION OVER THE FIRST 4 YEARS OF ILLNESS

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Background: Although neurological soft signs (NSS) are well described among patients with schizophrenia, the neurology of other psychoses is relatively unexplored and few comparative studies have prospectively examined these signs in first-episode patients.

Methods: We assessed neurological functioning in 242 patients presenting with a first episode of psychosis (in accordance with DSM-IV diagnosis) using the Condensed Neurological Examination (CNE) and the Neurological Evaluation Scale (NES). We sought to determine whether NSS were specific to patients with schizophrenia, bipolar affective disorder and other forms of psychosis. We also examined the factors associated with neurodysfunction at first presentation and at 4-year follow-up and determined the relationship between NSS and functional outcome of these patients.

Results: NSS were not specific to any diagnostic group. Neurological functioning was closely associated with psychopathology at first presentation. NSS at presentation were also associated with mixed hand preference and fewer years spent in education. At follow-up, there was a statistically significant improvement in neurological functioning. Persistent neurodysfunction at this stage was related to duration of untreated psychosis, enduring negative symptoms and associated with poorer outcome.

Conclusion: Schizophrenia and bipolar disorder are indistinguishable in terms of neurodysfunction at presentation. Neurological functioning improves during the first 4 years after presentation. At both presentation and 4 years NSS closely parallels symptomatology indicating that NSS may be a function of symptomatology or possibly an independent factor operates equally upon both symptoms and neurological function.

Treatment: Miscellaneous

267. ENHANCED ATTENTION WITH RIVASTIGMINE IN SCHIZOPHRENIA: AN fMRI STUDY

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Background/objective: Cognitive impairment is a central feature of schizophrenia and has a greater impact on illness outcome than positive and negative symptoms. The use of acetylcholinesterase inhibitors to enhance cognitive functions in patients with schizophrenia has recently begun to be explored. The current study assessed the neural correlates of the effects of rivastigmine, a CNS-selective, acetylcholinesterase inhibitor, given as an add-on therapy to antipsychotics-treated schizophrenic patients with moderate cognitive impairments on sustained attention using functional magnetic resonance imaging (fMRI). The study used a placebo-controlled randomised double-blind longitudinal design.

Methods: Nineteen patients stable on antipsychotics, 10 assigned to receive rivastigmine, and 9 assigned to receive placebo, completed the baseline and 12 weeks assessments consisting of a clinical interview, neuropsychological testing and functional magnetic resonance imaging (fMRI). The fMRI task used a periodic block design, and involved three alternating 30-s conditions: rest (Cond 1), monitoring of a non-zero number among a series of zeros (Cond 2), and monitoring of a specific number in the 6-digit arrays [Cond 3]. On-line data (via button presses) were acquired from all patients on both occasions while they underwent fMRI. The results revealed an improvement (from baseline to 12 weeks) in reaction time for Cond 2, but not for Cond 3, in patients who received rivastigmine treatment (with no such effect seen in those who received placebo), and this was accompanied with an increased blood oxygenation level-dependent regional brain activity in the left cerebellum.

Acknowledgment: The study was funded by the Stanley Research Institute.

268. PUBLISHING PATTERNS OF THE FOUR DRUGS MOST COMMONLY REPORTED IN SCHIZOPHRENIA TRIALS

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Background/objective: We now have to manage avalanches of incoming reports of trials. Of course, results must be disseminated to convince readers of the findings. However, with the gathering quantity of papers, often from only a few studies, readers must be proficient skiers not to become CONFUSED. Finally, the over-publication avalanche could be seen as a CORRUPTION of both medical journalism and of readers with little more than advertising propaganda. We aimed to quantify the number of publications of randomised trials relevant to the most frequently used drug interventions for schizophrenia.

Methods: We searched the Cochrane Schizophrenia Group's register of trials, calculated the frequency of drug interventions and imported data sets into MS Excel.

Results: Between 1954 and 2002, there were 2879 publications of the four most commonly reported antipsychotics used as interventions in trials for people with schizophrenia (chlorpromazine [672], haloperidol [1460], risperidone [754], olanzapine [672]). The number of reports has increased dramatically since 1990 (2612 [74%]).

Conclusion: This avalanche of publication is confusing. The number of studies is also greater than before but, recently, salami publication has increased at an exponential rate. Such salami publication is unlikely to be the result of the researchers needs to "publish or perish". It is more likely to be a function of industry's need to publicise. Sheer weight of numbers of reports can result in readers being led to think that the data are of good quality, accurate and meaningful, when they may not be. All randomised studies should be registered and unique trial ID numbers published on every subsequent report.

269. IS IT WORTHWHILE CHANGING CLINICALLY STABLE SCHIZOPHRENIC OUT-PATIENTS WITH MILD TO MODERATE RESIDUAL SYMPTOMS AND/OR SIDE EFFECTS FROM CONVENTIONAL TO ATYPICAL ANTIPSYCHOTICS?

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Background: The efficacy of the atypical antipsychotics has so far been demonstrated almost exclusively in first-episode,

relapsed or treatment resistant patients. Although it is well known that most schizophrenic patients respond only partially to treatment with neuroleptics, very little is known whether and when one can expect further treatment benefits by switching clinically stable out-patients from conventional to atypical antipsychotics.

Methods: Fifty schizophrenic, clinically stable out-patients treated with conventional neuroleptics were randomised either to continue their conventional neuroleptic(s), (with a mean dose of 312 chlorpromazine equivalents) or switch it to olanzapine with a starting dose of 10 mg. The Patients where evaluated using PANSS, for efficacy and Simpson-Angus (ep-symptoms) and Barnes (akathisia) rating scales at baseline and after 2, 6 and 12 weeks.

Results: Forty-six patients completed the study. After 12 weeks, patients on olanzapine showed significant improvement in PANSS total, -general, -positive and negative scores in the range of 18–20% and Simpson–Angus (63% improvement) and Barnes scores (71% improvement) ($p < 0.001$) as compared to the patients on conventional antipsychotics.

Conclusion: It may be worthwhile considering switching clinically stable out-patients with residual symptoms or—side effects from conventional antipsychotics to olanzapine.

270. CLINICAL PRACTICE GUIDELINES IN SCHIZOPHRENIA: HOW TO SELECT THE BEST ONE?

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Background: Clinical practice guidelines (CPG) are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. The objective of this study was to analyze the quality of all published schizophrenia CPG to select the most appropriate.

Methods: A bibliographic search was conducted and the CPG retrieved were selected according to a minimal set of inclusion criteria. Then, the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was applied by two independent raters to each CPG. The AGREE instrument consists of 23 items in six domains. Each domain is intended to capture a separate dimension of guideline quality and a score can be calculated by each of them.

Results: Ten CPG were identified through the bibliographic search. There was a great variation on dimension scores among these documents. Overall, the CPG analyzed had limited quality, although there were three that had the higher scores in three of the dimensions (rigor of development, presentation, and applicability). There was one CPG which had the highest scores on each dimension meaning that the likelihood to achieve its intended outcome is great and, therefore, it is the one to be implemented.

Conclusion: The best CPG about the management of schizophrenia to be used in clinical practice can be selected by a specific instrument of CPG critical appraisal. However, if this CPG has not been developed for the health system where is going to be implemented, then it should be updated with local data.

271. ATYPICAL ANTIPSYCHOTICS IN CLUSTER A PERSONALITY DISORDERS: A PRELIMINARY REPORT

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Background/objective: Recent epidemiological and psychobiological studies indicate that psychopharmacology is promising, even for the treatment of personality disorders. Particularly, psychotropic agents may have a positive effects on personality disorders showing a close relationship to Axis I Disorders (e.g. schizotypal personality disorders). Atypical antipsychotics have been proposed as therapeutic agents in cluster A and cluster B personality disorders. The aim of this study was to evaluate the efficacy of atypical antipsychotics on a sample of patients with Cluster A Personality Disorders according to DSM-IV criteria.

Methods: Nine outpatients with a DSM-IV diagnosis of Schizoid ($N = 3$) or Schizotypal Personality ($N = 6$) Disorders were treated with flexible doses of olanzapine (2.5–5 mg die) or quetiapine (75–300 mg die) for at least 6 months according with an open design. Patients were assessed by trained psychiatrists with semi-structured interviews based on DSM-IV criteria for Axis I and Axis II diagnosis. Patients with Axis I diagnoses were excluded. Brief Psychiatric Rating Scale (BPRS) scores were recorded at baseline and after 6-month treatment. Data were analyzed using ANOVA with repeated measures.

Results: A significant improvement was found on the BPRS total scores ($F = 21.352$; $p < 0.0001$).

Conclusion: The results from this preliminary study appear to suggest that in cluster A personality disorders the treatment with an atypical compound could be beneficial. Further studies on larger samples and a statistical analysis considering the effects of drug therapy on specific psychopathological dimensions associated with cluster A personality disorders are warranted. We are currently enlarging the sample and extending the follow-up.

272. USE OF A SECLUSION ROOM IN A REHABILITATION SETTING FOR SCHIZOPHRENIC PATIENTS, A 10-YEAR PROSPECTIVE STUDY

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Background: The use of a seclusion room, with or without physical restraints, is often a traumatic experience for patients.

Methods: The use of seclusion procedures to control violence and suicidal or disturbed behaviour was prospectively monitored in a systematic way on a treatment and rehabilitation ward for psychotic patients.

Results: At the onset of the study, seclusion procedures were frequent (1 year more than 200 incidents per year, often of long duration). This finding was the start of an extensive training programme for nurses and carers on 'how to deal with aggression' and attitude changes towards disturbed behaviour in order to prevent seclusion. After the implementation of this programme, seclusion incidents dropped dramatically over the next year. The average frequency has dropped to 5 per year on average and remained the same over the last 5 years, although the number of involuntary admitted patients on the ward has increased from less than 1% at the beginning of the study to 30% today. In parallel with the change of attitude on the ward is the introduction of novel antipsychotics. Today, nearly all patients are treated with novel antipsychotics.

Conclusion: A comprehensive educational and practical training on how to deal with aggression and disturbed behaviour together with adequate pharmacological treatment is an effective way to prevent seclusion measures in psychotic patients.

273. ACCESS TO STANDARD PSYCHIATRIC CARE THROUGH ASSERTIVE COMMUNITY TREATMENT FOR DIFFICULT-TO-ENGAGE PATIENTS IN A SWISS CONTEXT

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Background: Assertive community treatment (ACT) proved to be an effective way of caring for severely mentally ill people in the community. There is however a lack of evidence on how it can be implemented in European mental health systems. Lausanne's ACT interventions target on «difficult to engage» or high users patients, and aim at linking patients with less intensive care. Aims: Retrospective evaluation of the applicability and outcome of ACT in Lausanne.

Methods: Measure of social and clinical outcome with standardized instruments (HoNOS, CTRS, MCAS), substance use, social network and motivation in 75 consecutive subjects treated between 2000 and 2002.

Results: Two third of patients suffered from psychosis. 48% had a comorbid substance use disorder (33% cannabis use). Marked improvement in most clinical and social problems, collaboration, motivation and social network support ($p < 0.001$) were observed over the treatment period, despite severe and multiple initial problems in clinical and social domains. 70% of interventions lasted less than 6 months.

Conclusion: Assertive community treatment can be a useful treatment alternative and way to access to standard care for difficult-to-engage patients. Despite initial unfavourable conditions, 95% patients will collaborate with professionals through milieu outreach interventions. Potential of improvement and motivation may then be greater than expected. Social network also becomes more available, which may contribute to maintain recovery after intensive community treatment stops. However, some patients need intervention of a longer duration.

274. CLINICAL TRIAL OF ALLOPURINOL ADJUVANT THERAPY FOR POORLY RESPONSIVE SCHIZOPHRENIA

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Objective: To evaluate the xanthine oxidase inhibitor allopurinol, which inhibits degradation of purines, as an adjuvant treatment for schizophrenic patients with poor response to antipsychotics.

Methods: double-blind, placebo-controlled, crossover clinical trial of add-on allopurinol (300 mg b.i.d.) for poorly responsive schizophrenia. Thirty-five patients were enrolled, of which 23 completed the 12 weeks of study (mean baseline PANSS 83 ± 15). Eighteen of these patients also completed a P50 evoked potential evaluation.

Results: allopurinol was well tolerated and produced significant improvement in all PANSS scores compared to placebo (in mean % change): total (-15 ± 12 versus 7 ± 20), positive symptoms (-21 ± 17 versus 11 ± 42), negative symptoms (-8 ± 13 versus 7 ± 16) and general symptoms scores (-13 ± 13 versus 7 ± 17). Nine patients improved more than 20% in PANSS total score under

allopurinol treatment whereas none responded in the placebo phase. Comparing baseline characteristics of responders and non-responders, responders tended to be younger (33 ± 11 and 42 ± 10 years, $P = 0.056$) and had a shorter duration of illness (15 ± 10 and 25 ± 9 years, $P = 0.03$). P50 auditory sensory gating failed to improve with allopurinol treatment. Uric acid levels decreased for all patients during allopurinol treatment compared to baseline and placebo levels (baseline 4.5 ± 1.7, placebo 4.9 ± 1.6, allopurinol 2.2 ± 0.9, $P < 0.001$), suggesting compliance to treatment.

Conclusion: Allopurinol was an effective and well-tolerated adjuvant treatment for poorly responsive schizophrenia, especially for refractory positive symptoms. Response was more evident in younger patients with shorter course of the disorder. These results corroborate our previous open label study, warranting further investigation.

Acknowledgment: Stanley Medical Research Institute.

275. ACUTE MANIA AND PSYCHOTIC SYMPTOMS IN BIPOLAR PATIENTS: THE EFFICACY OF TREATMENT WITH RISPERIDONE AND OLANZAPINE

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Background/objective: Some aspects of the antimaniacal therapy in bipolar psychosis are subject to improvement. A high rate of patients do not respond to stabilizing drugs and the latency for response is long; the use of traditional neuroleptics is characterized by extrapyramidal side effects and by a high frequency of depressive symptoms that remarkably reduce the compliance of patients. The objective of this study is to estimate the efficacy of two atypical antipsychotics, Risperidone and Olanzapine, compared with Haloperidol in acute manic episodes.

Methods: The sample consists of 56 patients, all of whom have been evaluated with the YMRS at the beginning and at the end of their hospitalization; the three groups are similar in average age. In order to estimate the effects of different variables. A multiple regression was carried out using the delta % of the YMRS as a dependant variable and the drug, the beginning YMRS and the age as independent variable.

Conclusion: Riperidone and Haloperidol overlap in their ability to treat the acute mania of Bipolar I Disorder; the efficacy of Olanzapine has not been proved and it would require a perspective randomized study with conventional and atypical neuroleptics.

276. PATHWAYS TO CARE OF FIRST-ADMITTED SUBJECTS WITH PSYCHOSIS IN SOUTH WESTERN FRANCE

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Background/objective: A limited number of studies have assessed the pathways to care of patients with first-episode psychosis. The aim of the study was to describe the pathways to care of subjects with psychosis between onset of psychosis and first admission, and to examine the demographic and clinical factors influencing access to care.

Methods: Number and type of helping contacts since onset of first psychotic symptoms were assessed using multiple sources of information in 86 subjects with psychosis first-admitted in two hospitals of South Western France. Characteristics independently associated with long delays between onset of symptoms and first helping contact, first treatment and first admission were explored using logistic regressions.

Results: 12% of subjects were first admitted without any previous helping contact. The patients were seen by a median of two helpers (maximum 7). For most patients (70%), the first helping contact was a health care professional, and the same proportion of patients had a first contact with a GP or a psychiatrist. The type of first contact was not predicted by demographic or clinical characteristics. Subjects with poor premorbid functioning or at-risk behaviour were more likely to have a delayed access to care.

Conclusion: The delay in access to care may not be totally attributed to inadequate management by health professionals, but may be a characteristic of the disease itself, at least in part independently of the organisation of the health system.

277. ARIPIPRAZOLE: A COCHRANE REVIEW

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Background/objective: Treatment of schizophrenia with older antipsychotic drugs can be problematic since many people may experience disabling adverse effects. Aripiprazole is said to be an 'atypical' medication with good antipsychotic properties and minimal adverse effects. To evaluate the effects of aripiprazole for people with schizophrenia.

Methods: The reviewers searched the Cochrane Schizophrenia Group's Register (May 2003). References were inspected, the authors, relevant pharmaceutical companies and the Federal Drug Administration (FDA, USA) were contacted. All clinical randomised trials comparing aripiprazole with placebo, antipsychotic drugs for schizophrenia. We extracted data independently. For homogenous dichotomous data, the random effects, relative risk (RR), and 95% confidence interval (CI) and, where appropriate, the numbers needed to treat (NNT) were calculated on an intention-to-treat basis.

Results: The search identified 42 papers which appeared to fulfill the initial selection criteria. Bristol Myers-Squibb supplied information on a further 20 previously unidentified papers after we found them on the FDA website. We have already identified studies that involve over 1200 patients randomly allocated to receive ariprazole versus comparable drugs including olanzapine, haloperidol and risperidone.

Conclusion: Aripiprazole, now licensed in several countries, seems to be supported by randomised controlled trials (RCT) of substantial size. Access to relevant, but poorly disseminated FDA data has been problematic.

278. MODAFINIL MODULATES PREFRONTAL FUNCTION IN SCHIZOPHRENIA

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Background: Modafinil is a putative cognitive enhancer. We studied the behavioural and functional anatomical consequences of its acute administration in men with negative symptoms of schizophrenia.

Method: Seventeen stable, right-handed, male, schizophrenia patients (mean age 38 years), participated in a double-blind, placebo-controlled, cross-over study, receiving either modafinil 100 mg or placebo across two study days (1 week apart, order counterbalanced). Functional imaging data were acquired 2-h post-administration using a 1.5-T MR system; subjects performing a working memory protocol (the '2-back' versus '0-back' control condition).

Results: Group functional imaging data were analysed using a random effect model in SPM99. In the modafinil vs. placebo comparison, we found increased activation solely in the anterior cingulate cortex (ACC), during the 2-back, compared to 0-back condition (Brodmann area 38; $Z = 3.14$). For each subject, we then extracted an estimate of fMRI signal change in ACC, during the 2-back. Differences in signal change and behavioural performance between modafinil and placebo conditions were significantly and positively correlated (rho = 0.42; one-tailed $p = 0.04$). This correlation reflected increased fMRI signal in the majority of subjects, with concomitant improvement in memory performance in half, and decreased signal in a minority of subjects, most of these exhibiting reduced performance following modafinil administration.

Conclusion: Modafinil modulates ACC function in schizophrenia and may improve cognition in some patients. However, its effects are not uniform in this syndrome and further research is needed to characterise those subjects who may benefit.

Acknowledgment: This study was funded by a project grant awarded by Cephalon UK.

279. SHARED DECISION-MAKING—A NEW CONCEPT IN PSYCHIATRY: RESULTS OF A RANDOMISED CONTROLLED TRIAL

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Background: Patients suffering from schizophrenia probably constitute one of the populations most excluded from medical decisions. This might be due to their assumed or existing reduced decisional capacity. However, previous research on decisional capacity in schizophrenia shows that most patients can show performance equal to that of non-ill controls when adequately informed.

Method: In this randomised trial on the use of a decision aid on antipsychotic drug choice, the feasibility of sharing treatment decisions (1) with psychotic inpatients was evaluated. Patients in the interventional group (decision aid+"shared decision" between physician and patient on medication) are compared to patients receiving "usual care" in regard to their satisfaction with care, perceived involvement and knowledge.

Results: The ability of patients to participate in therapeutic decisions depended strongly on the psychopathology and the course of the illness. However, a considerable proportion of even seriously ill patients were able to successfully participate in decision-making. On discharge from hospital, patients in the interventional group had better knowledge of their illness and reported higher perceived involvement than patients in the control group.

Conclusion: Patients with schizophrenia are in many cases able and willing to participate in important clinical decisions such as antipsychotic drug choice. Further, the use of a decision aid has a positive impact on several variables known to affect treatment adherence. These findings may be important in reducing existing prejudices about a reduced decisional capacity of schizophrenic patients.

Reference

Hamann J., Leucht S., Kissling W., 2003. Shared decision making in psychiatry. Acta Psychiatr. Scand. 107 (6), 403–409.

280. PHARMACOLOGICAL TREATMENT OF AMBULATORY SCHIZOPHRENIC PATIENTS IN BELGIUM

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Background/Objective: Current pharmacological treatment of schizophrenic patients in Belgium was evaluated in a nation-wide naturalistic study. Data were obtained on all treated patients (DSM-IV 295.xx), either out-patients or patients attending a day-hospital, in selected sites. The aim is to collect data on minimally 1000 patients.

Methods: Anonymous clinical and demographic data was collected together with all current medication, both psychiatric and somatic. For exploratory purposes information on screening for somatic side effects and the assessment of cognitive function was collected.

Results: An interim analysis on 900 patients (AVG age 40 years, AVG N admissions 5, AVG GAF 62) indicate a high penetration of the use of novel antipsychotics. 70% of patients are treated with novel antipsychotics, either in monotherapy (77%) or in combination with classical (13%) or sedative antipsychotics (10%). Detailed analysis will evaluate dosing regimes of the different antipsychotics. Polypharmacy (use of concomitant medication) with other drugs is frequent (AVG total N drugs 2.9); antidepressants (40%), benzodiazepines (37%), anticholinergics (22%), mood stabilisers (15%) and somatic medication (28%). Only one in three patients gets a routine screening for metabolic side-effects and only one out of four had an ECG in the past 6 months. Evaluation of cognitive function is rare and is only performed in 8% of patients.

Conclusion: This study confirms not only the high penetration of novel antipsychotics in the current ambulatory treatment practice of Belgian psychiatrists but also the frequent use of concomitant medication. Evaluation of the recently reported somatic side effects and a systematic evaluation of cognitive function is not yet common practice.

281. HALLUCINATION FOCUSED INTEGRATIVE TREATMENT INDUCES STATISTICALLY SIGNIFICANT SUBJECTIVE AND OBJECTIVE IMPROVEMENTS IN CHRONIC SCHIZOPHRENIA PATIENTS WITH PERSISTENT VOICES

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Background: Hallucination focussed Integrative Treatment (HIT) aims at enhancing control, quality of life and social functioning and at reducing symptoms and subjective burden. HIT integrates motivational interviewing, cognitive behavior treatment, coping training, single family treatment with CAU.

Methods: RCT design: Seventy-six chronic drug-refractory schizophrenics (mean age 36 years; S.D. = 11.2) with auditory hallucinations (mean 11 years; S.D. = 1.0) were randomised over HIT and CAU. Independent assessment (Auditory Hallucination Rating Scale, Positive And Negative Symptoms Scale, WHO-Qol and Groningen Social Disabilities Schedule, Costs) occurred pre- and post-treatment. Groups differed not significantly on relevant sociodemographics, diagnostics (psychopathology and coping-behavior), medication or medical history at baseline. Statistical analysis: intention to treat of all patients included, irrespective of actual treatment; Student's t, chi-square with significance set at $p < 0.05$, Mann–Whitney U-test, Cost-utility and multivariate cost-sensitivity analyses. Results after 9 months treatment.

Results: (1) Post-treatment group mean-scores of medication were not statistically different (haldolequivalents: $t = 0.555$, $df = 64$, $p = 0.58$). (2) Low non-adherence (14%). (3) Hit is cost-effective (lower price for better improvement). (4) Results

of HIT are significantly ($p<0.05$) better on: Symptoms: PANSS-dimensions positive ($p<0.001$); disorganization; total; (depression: $p<0.057$). NNT vary from 2 (positive dimension) to 4–5 (disorganization, depression), Burden: AHRS-dimensions distress, interference, duration and control, Quality of life, Social functioning: GSDS-roles household, parent and total with $p<0.01$ on family and partnership. NNT varying from 3 (household, family) to 7 (occupation). Fifty-one percent improved more than 20% in social functioning.

Conclusion: Chronic schizophrenic patients with persistent voices improve significantly better on HIT than on CAU. HIT is cost-effective and effects generalize to subjective burden, control, psychopathology, quality of life and social disabilities.

282. EFFECTIVENESS OF MULTI-FAMILY TRAINING AFTERCARE FOR THERAPY REFRACTORY VOICE-HEARERS: A PILOT STUDY

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Background: In a RCT, it was demonstrated that Hallucination-focussed Integrative Treatment (HIT) improves subjective burden, symptoms, quality of life and social functioning significantly better than routine care in chronic schizophrenia patients with therapy-refractory auditory hallucinations. At 4-year follow-up 60% of patients had retained improvement and 30% had further improved. Despite the significant improvement, social functioning remained deficient in most patients.

Methods: Multifamily-HIT was composed for patients who insufficiently improved on HIT or had a decrease in improvement over time. Multifamily-HIT is a 12 session–4 h training aiming at optimal coping with voices and rehabilitation skills. Twelve patients and 10 relatives followed this training and were assessed at onset and upon 6-month follow-up. Duration of illness and of hearing voices were more than 10 years. Instruments: Patients Auditory Hallucination Rating Scale, Positive and Negative Symptom Score, Groningen Social Disabilities Scale, Symptom Checlist-90; Relatives Involvement Evaluation Questionnaire, Symptom Checklist-12. Statistics: Wilcoxon signed rank test (z-scores), paired samples t-test.

Results: The following significant improvements at 6-month follow-up were found: (1) Subjective burden of voices (AHRS) on frequency × duration; anxiety and interference ($p<0.05$) and control of voices ($p<0.01$). (2) Quality of life on WHOQol ($p<0.05$). (3) Psychotic symptoms (PANSS) $p<0.01$ on positive symptoms, disorganization and total score. (4) Psychopathology (SCL'90): reduction in symptoms on all dimensions except agoraphobia. Significant reduction ($p<0.05$) in anxiety and insufficiency in thinking and activities. (5) Social functioning (GSDS) on household role and total score ($p<0.01$), on citizenship and social role ($p<0.05$). (6) Relatives improved on the IEQ on habituation to and coping with symptoms, and change in relationship ($p<0.05$).

Conclusion: HIT in a multi-family-treatment format might be considered an effective treatment for voice-hearing patients (partly) refractory to both usual treatment and HIT. The results of treatment generalize beyond the target symptom to social functioning and subjective burden.

283. NEGATIVE SYMPTOMS OF SCHIZOPHRENIA ARE IMPROVED BY THE ADDITION OF PAROXETINE TO NEUROLEPTICS: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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Background: This study was designed to confirm the positive treatment effect of Paroxetine as an add-on therapy to neuroleptics with respect to the treatment of negative symptoms in chronic schizophrenia seen in our pilot study (1).

Methods: Twenty-nine patients with chronic schizophrenia as defined by DSM-IV who scored at least 20 points on the negative subscale of the Positive and Negative Syndrome Scale (PANSS) were treated with 30 mg Paroxetine or placebo in a double-blind placebo-controlled study for 12 weeks. Ratings included the PANSS, measures of the affective state (Hamilton Rating Scale for Depression [HAM-D]), extrapyramidal side-effects and Paroxetine side-effects.

Results: Twenty-nine patients entered the study, six dropped out. The data of the remaining 23 were analysed. The mean score of the negative subscale of the PANSS decreased considerably in the Paroxetine group compared to the placebo group ($p=0.061$, two-sample–t-test for the differences). The effects were most pronounced concerning blunted affect ($p=0.029$) and abstract thinking ($p=0.019$). The mean HAM-D score remained constant.

Conclusion: The study confirms the efficacy of Paroxetine with respect to the treatment of negative symptoms in chronic schizophrenia.

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284. AUGMENTING CLOZAPINE WITH AMISULPRIDE IN TREATMENT RESISTANT SCHIZOPHRENIA

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Background: The treatment of schizophrenia sufferers who fail to respond to adequate trials of neuroleptics remains a major challenge. Whilst clozapine is still regarded as the gold standard for treatment resistance, recent data and clinical experience confirms that in spite of its proven superior efficacy, up to 50% of resistant patients treated with clozapine continue to experience disabling symptoms. Many different strategies have been attempted to improve efficacy, once such has been the to increase D2 blockade by the addition of sulpiride to clozapine treatment.

Method: Twenty chronic inpatients with schizophrenia who had been shown to be treatment resistant to conventional antipsychotic and who had remained symptomatic despite adequate treatment with clozapine where selected to receive amisulpride as adjunctive treatment. At baseline assessment, all subjects were titrated to 400 mg amisulpride per day and then reassessed after 8 weeks by a blinded rater, at both visits a PANSS was completed.

Results: Analysis showed statistically significant improvement in PANSS Total Score ($t = 3.49$; $df = 18$; $p = 0.003$); PANSS Negative Subscale Score ($t = 3.22$; $df = 18$; $p = 0.005$) and PANSS Depression Factor Score ($t = 3.89$; $df = 19$; $p = 0.001$).

Conclusion: This study suggests that addition of the second-generation antipsychotic amisulpride to a stable treatment regime with clozapine in a treatment-resistant schizophrenia population may offer additional benefits in terms of negative and depressive symptoms.

285. ATTITUDES TO ATYPICAL AND CONVENTIONAL ANTIPSYCHOTIC TREATMENT IN CLINICIANS PARTICIPATING IN THE CUTLASS STUDY

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Background: In the context of a pragmatic, randomised, controlled trial examining the clinical effectiveness of conventional and atypical antipsychotics (CUtLASS: Cost Utility of the Latest Antipsychotics in Severe Schizophrenia) in partially and markedly treatment-resistant schizophrenia, we investigated the views of participating clinicians that might be relevant to their recruitment of patients. A survey was conducted to ascertain the extent of their clinical equipoise regarding conventional and atypical antipsychotics, and their attitudes to trial management issues, RCT evidence, and factors that might influence prescribing decisions.

Methods: 262 clinicians were sent an anonymous questionnaire, and invited to respond to nine statements (from 'strongly agree', to 'strongly disagree').

Results: Of the 112 clinicians who responded, 71% supported the CUtLASS study. 39% agreed with the statement that the clinical efficacy of atypicals was superior to conventional antipsychotics, while 27% disagreed and 34% were undecided. Thus, only a third of participating clinicians revealed uncertainty on a key question being tested in the CUtLASS study. However, the vast majority (97%) considered that atypicals were associated with less severe side effects. 89% agreed RCTs were the 'gold standard' for evidence-based practice in this context. Asked to identify key influences on prescribing practice (such as review articles, RCT evidence, published guidelines and clinical experience), the highest proportion of clinicians (36%) used a combination of such sources.

Conclusion: In clinical studies, recruitment strategies relying on referrals from clinicians can have low yield. The findings of this study suggest that surveys of participating clinicians are a potential mechanism for exploring relevant attitudes.

286. EFFECT OF DIAGNOSTIC HETEROGENEITY ON RESPONSE TO ETHYL-EICOSAPENTAENOIC ACID (EPA) IN FIRST-EPISODE PSYCHOSIS

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Background/Objective: Recent research has found that first-episode psychosis (FEP) patients with a diagnosis of schizophreniform [Szform] disorder demonstrate a more impaired niacin skin reaction than those with other psychotic diagnoses. This implies a greater essential fatty acid (EFA) deficit in this subgroup, with implications for a differential response of psychotic symptoms to EFA supplementation.

Methods: A 12-week, double-blind, randomized, placebo controlled study of 2 g EPA in 80 drug-naïve or early treated FEP patients was conducted.

Results: There were no significant differences between the EPA and Placebo groups on demographic or clinical characteristics at baseline. The total mean BPRS score for the sample was 62.0. ANCOVA showed no main effect of Group (EPA vs. Placebo) for BPRS total score at week 12. An examination of the treatment response of the diagnostic groups (31.3% DSM IV schizophrenia [Sz], 35% Szform, 33.6% other psychotic disorders, i.e., major depression with psychosis, schizoaffective disorder and psychosis NOS), however, showed a trend for a beneficial effect of EPA on total BPRS score in the combined Sz/Szform group only, at week 6 ($p = 0.08$). A significant Group by Diagnosis interaction was also seen for the SANS total score ($p = 0.036$) at week 9.

Conclusion: Our observation that the transient effect of EPA on psychotic symptom scores appears restricted to schizophrenia and schizophreniform psychosis, suggests a differential response to EPA compared to placebo in these more homogeneous diagnostic subgroups.

287. SUBJECTIVE RESPONSE TO ANTIPSYCHOTICS DEPENDS ON SOME DEMOGRAPHICAL AND CLINICAL VARIABLES

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Background: Publications concerning subjective aspects of antipsychotic therapy in schizophrenia usually fail to demonstrate any demographic and clinical differences between patients with positive and negative response.

Method: One hundred newly admitted patients with a DSM-IV diagnosis of schizophrenia, schizophreniform and schizoaffective disorder were included in the study. Drug Attitude Inventory (DAI) and Neurolpetic Dysphoria Scale (NDS) were administered to assess subjective response. Patients' psychopathology was assessed with PANSS and Calgary scale.

Results: Forty-six women and 54 men were included. Women were older than men (34 years vs. 28.7, $p = 0.016$) and had more previous hospitalizations (4.9 vs. 3.0, $p = 0.03$). The concordance rate between assessment with DAI and NDS were high (Spearman = 0.58). The group with positive subjective response (68% of whole group according to NDS) differ from the group with negative subjective response (32%) as regards: gender (men 18.5%, women 47.8%, $p = 0.002$), age (18–20 years 57% negative response, over 60 years 62% negative response in comparison with patients age 20–35, 33.3% negative response, 35–50 years 5,3% negative response), level of education (more dysphoric patients in less educated group), social support (more patients with negative response received disability payment, 31% vs. 13%) and more with positive response had a job (26.5% vs. 0%) and own family (13% vs. 6%). With respect to PANSS scores, patients with positive response were less severe ill (PANSS total 85.9) than that with negative response (PANSS total 93.2, $p = 0.07$).

Conclusion: Patients with negative symptoms were more often in the youngest and oldest groups, were less educated, had more social support, didn't work and had more psychotic symptoms than patients with positive response.

288. NEUROPROTECTIVE EFFECTS OF LOW-DOSE LITHIUM IN INDIVIDUALS AT ULTRA-HIGH RISK OF DEVELOPING PSYCHOSIS: A CASE SERIES

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Background/objective: Recent evidence suggests that there is an active biological process occurring during the development of psychosis (Berger, Wood, and McGorry, 2003). Research to date has indicated that neurodevelopmental changes may occur during the transition to a full-blown psychotic illness. Previous post-mortem analysis of the temporal cortex of patients with schizophrenia and bipolar disorder, demonstrated a 25% reduction of bcl-2 protein, indicating apoptotic regulatory mechanisms may be affected. Neuroprotective agents such as lithium may counteract such postulated regressive processes and support neurotrophic development. Preclinical studies using low-doses of lithium (0.3

mmol/l) found neuroprotective effects in the frontal cortex, hippocampus and striatum (Manji, 1999). Clinical studies have also demonstrated an increase in overall *N*-acetyl-aspartate (NAA) concentrations in the frontal, temporal, parietal and occipital lobes in bipolar individuals following 4 weeks of lithium treatment. In light of these findings, the PACE Clinic (Melbourne, Australia) is currently conducting an open-label trial using low-dose lithium (450 mg) in a cohort of individuals at 'ultra-high risk' for a first-episode psychosis. The trial is investigating whether low-dose lithium may prevent the progression to a psychotic illness or reduce the severity of subthreshold symptoms and subsequent episodes. Patients in the trial are continuing to have monthly interviews to assess patterns and fluctuation of psychopathology, and to investigate the efficacy of low-dose lithium in this 'ultra-high risk' cohort.

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289. FAMILY INTERVENTION FOR SCHIZOPHRENIA

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Background/objective: The principles of family intervention are commonly used for people with schizophrenia. The Cochrane review has been updated with new important data. The aim of this study was to update the estimate of effects of family psychosocial interventions compared with standard care.

Methods: We searched the Cochrane Schizophrenia Group Register (November 2002), reliably selected randomised studies focusing on families of people with schizophrenia and comparing family psychosocial intervention with standard care, reliably extracted data and, when appropriate, synthesised results. Relative risk (RR), their 95% confidence intervals (CI) and number needed to treat (NNT) were estimated.

Results: Family intervention may decrease relapse ($n = 721$, 14 RCTs, RR relapse ~ 1 year 0.72 CI 0.6–0.9, NNT 7 CI 5–16). These data are heterogeneous and the trend over time veers towards the null and disappears with longer follow up. Family intervention may also encourage compliance with medication ($n = 369$, 7 RCTs, RR 0.74 CI 0.6–0.9, NNT 7 CI 4–19) but does not affect attrition of individuals/families ($n = 327$, 4 RCTs, RR attrition at 3 months 0.86 CI 0.3–2.1). Family intervention neither prevents nor promotes suicide ($n = 377$, 7 RCTs, RR 0.79 CI 0.4–1.8). A recent cluster randomised study was poorly reported.

Conclusion: Initial positive effects of family intervention are somewhat less evident in recent studies. This well-recognised pattern in drug trials may equally apply to non-pharmacological interventions. Some good effects of family intervention seem likely to remain, although applicability of results will always be debatable because the quality of interventions may be greater than can be provided in routine care.

290. EFFECTS OF RIVASTIGMINE ON SLEEP IN PATIENTS WITH SCHIZOPHRENIA: PRELIMINARY RESULTS

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Objective: The present study compares sleep of patients with schizophrenia before and after rivastigmine, an acetylcholinesterase inhibitor.

Methods: The sleep of 13 patients with schizophrenia stabilized with atypical neuroleptics (11 M, 2 W, 29.7 ± 6.3 years old) was recorded for two consecutive nights in a sleep laboratory and for a third night following 12 weeks of rivastigmine treatment. Posology increased from 3 to 6 mg/day during the first month to progressively increase at 9 mg/day, taken at mealtime. Medication was well tolerated. Sleep stages of night 2 (baseline) and night 3 (rivastigmine) were compared using paired *T*-tests.

Results: Compared to baseline, sleep with following rivastigmine treatment showed reduced sleep efficiency: increased number of awakenings and time spent awake following sleep onset, increased percentage of stage 1 and decreased percentages of stage 2. Percentage of slow-wave-sleep (SWS = stages 3+4) was decreased in the first part of the night, followed by an increase during the last third of the night. There was no difference whatsoever on any REM sleep parameters between both nights, and minutes of total sleep time was not changed either.

Conclusion: These results show that 12 weeks of rivastigmine combined with atypical neuroleptics increases waking and light sleep, which is a marker of increased cholinergic activity. On the

other hand, the initial inhibition of SWS was compensated for latter in the night and that REM sleep was not impaired. This suggests that the possible benefits of sleep on daytime cognitive functioning are not disturbed by rivastigmine treatment.

291A. A METHOD FOR EXAMINING EFFICACY BY DOSAGE IN FLEXIBLE DOSE CLINICAL TRIALS

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Background/objective: In flexible dose trials, drawing conclusions about the association between dosage, efficacy and safety can be misleading since prescribed dosage is often adjusted based on the severity of patients symptoms and treatment response. The aim of this study was to estimate efficacy by dose in a flexible dose trial, while avoiding the confound of individualized clinical assessment of patients treatment needs.

Methods: Data were from a large clinical trial of risperidone vs. haloperidol in first-episode psychosis ($n = 555$). To examine efficacy and safety by dose, prescribing pattern groups of risperidone ($n = 278$) were formed. Centers were grouped by the maximum last dose that they used with any of their patients. Three groups emerged (a) a group of centers ($n = 17$) whose maximum last dose never exceeded 4 mg, who treated 99 patients, (b) a group of centers ($n = 8$) with a maximum last dose of 5 mg, who treated 46 patients and (c) a group of centers ($n = 16$) with a maximum last dose greater than 5 mg, who treated 133 patients. Mean change in total PANSS and ESRS (Parkinsonism+Dystonia+Dyskinesia) until endpoint were compared between the three groups.

Results: There were no significant differences in clinical improvement between the groups of centers. However there was a significant linear increase of extra pyramidal signs and symptoms (EPSS), as measured by the ESRS, in the patients treated by the two groups of centers who used higher maximum dosing (groups b and c) than in the lower dosing centers (a).

Conclusion: Results suggest that treating first episode patients with lower dosages of risperidone appears to be preferable.

291B. COMPARISON OF QUETIAPINE, OLANZAPINE AND RISPERIDONE IN PATIENTS WITH SCHIZOPHRENIA: INTERIM RESULTS OF A RANDOMISED, RATER-BLINDED STUDY

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Objective: Compare the efficacy and tolerability of quetiapine, olanzapine and risperidone in patients with schizophrenia. Interim results are reported following 8-week treatment in a 16-week study.

Methods: Multicentre, randomised, parallel-group, rater-blinded study of inpatients with a PANSS score >4 on 2 items of the positive subscale, flexibly dosed with 400–800 mg/day quetiapine, 10–20 mg/day olanzapine or 4–8 mg/day risperidone. Efficacy measures include PANSS total, subscale and BPRS hostility cluster scores. EPS assessed using SAS and BAS. Statistical analysis was not performed; mean scores calculated on a LOCF basis.

Results: 22 patients were randomised to quetiapine, 16 to olanzapine, 12 to risperidone; baseline PANSS total scores were 106.4, 104.1 and 94.4, respectively. Reduction in PANSS total score was 31% with quetiapine (mean dose 600 mg/day), 25% with olanzapine (mean dose 15 mg/day) and 21% with risperidone (mean dose 5 mg/day). Improvements in PANSS subscale scores were observed. BPRS hostility cluster score decreased by 37%, 29% and 17% from baseline with quetiapine, olanzapine and risperidone, respectively. Changes in SAS scores were relatively small (quetiapine: 3.3 to 2.8; olanzapine: 4.3 to 2.9; risperidone: 4.8 to 5.0). BAS scores changed from 1.4 to 1.0 (quetiapine), 0.4 to 0.6 (olanzapine), 0.7 to 2.3 (risperidone). 36% olanzapine-treated patients had weight gain >5% compared with 17% for risperidone and 13% for quetiapine patients.

Conclusion: These interim data suggest all three agents have similar efficacy but quetiapine demonstrated a better tolerability profile, as treatment-emergent EPS occurred with risperidone and an increased incidence of weight gain with olanzapine.

292. USES AND ADVANTAGES OF DAY HOSPITAL IN PSYCHIATRIC PATIENTS: AN ALTERNATIVE WAY OF CARE

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Background: The psychiatric day hospital is used in extra or intra-hospital within and allows to accompany the patients towards a plan of rehabilitation guaranteeing the patients the re-entry in the society, protecting them from those factors that threaten their psychological stability, dosing the protection degree regarding the external, social and familiar and above all consolidating the improvements obtained in the long-term hospitalization. The objective of the study is to estimate like and if the day hospital can be employed in psychiatric within and to be used as a method of prevention and as pre- and post-critic filter.

Methods: The sample is constituted by 179 cases and has been described in its socio-demographic variables and clinical ones; moreover, as measures of outcome of the service have been estimated the indices of use (number and duration of the hospitalizations) and have been analysed the modality of shipment to the day-hospital.

Results: The more obvious and significant results derive from the analysis of the indices of use of the service; we evidenced a reduction of the full time hospitalizations, of the number of the days of the hospitalizations and of the cases of the sample it has not been assisted any more to the full-time hospitalizations.

Conclusion: The day-hospital has been revealed favorable for the patient, who can more easily be reinstated in a program of social rehabilitation, and for the hospital structure, that benefits from the reduction of the number of hospitalizations, of their duration and therefore altogether of expenses.

293. EFFECTS ON POSITIVE SYMPTOMS AND TOLERABILITY OF RIVASTIGMINE IN PATIENTS WITH SCHIZOPHRENIA AND COGNITIVE IMPAIRMENT

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Background: Previous studies using Acetylcholinesterase inhibitors (Achi) like rivastigmine for dementia and Parkinson's disease have illustrated improvement in cognitive impairments. Conversely, very few studies using rivastigmine in schizophrenia have shown potential effectiveness in managing these same deficits. Given that increasing Achi could theoretically alter positive symptoms, clinicians have to be cautious about a prescription with this kind of medication. In addition, side effects such as nausea, vomiting with the elderly population are often a reason to discontinue the treatment. Hence, changes in symptoms and tolerability require investigation in the younger clinical population such as schizophrenia patients.

Methods: We conducted a study with 19 schizophrenia patients treated with atypical neuroleptics with a longitudinal assessment of their cognitive impairment. The posology was administered in function of tolerability of the patients. The first-day patients received 3 mg/day reaching 6 mg/day for the first month and progressively increased to 9 mg/day. The duration of treatment was 3 months. Instruction was to take rivastigmine medication during each meal.

Results: The PANSS score did not show an aggravation of the positive symptoms (total score at baseline = 18; at endpoint = 17; ns). Change in Panss total score and subscores were all nonsignificant. 26% of patients showed a transient episode of nausea. 21% of patients showed a transient episode of vomiting. A regional gastroenteric epidemic during the trial might explain a portion of this proportion.

Conclusion: These preliminary results show that the usual main side effect of rivastigmine are less frequent than in elderly population and that the psychotic symptoms are not heightened.

294. BRIEF PSYCHIATRIC RATING SCALE AND CLINICAL GLOBAL IMPRESSIONS IN EVALUATION OF SYMPTOMS IN SCHIZOPHRENIC PATIENTS TAKING TYPICAL AND ATYPICAL ANTIPSYCHOTICS

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Objective: To measure symptomatic improvement with the Brief Psychiatry Rating Scale (BPRS) and Clinical global impressions (CGI) in schizophrenic patients taking typical and atypical antipsychotics.

Methods: BPRS and CGI were used in order to assess symptomatic improvement in 100 patients with paranoid schizophrenia, according to DSM-IV-TR criteria. Previous to inclusion in our study, all patients were treated with typical or atypical antipsychotics for a period of at least 1 month. The first assessment (baseline) was made upon the inclusion. The second assessment was made after 6 months of continuous treatment with typical or atypical antipsychotics (haloperidol, flufenazine; clozapine, quetiapine, risperidone and olanzapine).

Results: At baseline, there was no significant difference between two groups of patients. After 6 months of continuous treatment, patients treated with atypical antipsychotics scored

significantly better in BPRS items regarding emotional withdrawal, depressive mood, uncooperativeness, and blunted affect. On the other hand, there was no significant difference on CGI scale at second assessment.

Conclusion: Results indicate superiority of atypical over typical antipsychotics in reducing negative and general symptoms of schizophrenia.

295. ACT IN BELGIUM, A PILOT STUDY FROM THE BRUSSELS NIGHT HOSPITAL

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Background: Assertive Community Treatment (ACT) is one of the most studied and effective psychosocial interventions. Until recently, ACT programmes and psychiatric home-care was unavailable in Belgium.

Methods: From the setting of the Brussels Nighthospital, we performed the first ACT trial in Belgium with a grant from the National Government. Care was delivered by highly trained nurses. Prospective 3-year follow-up data were collected and compared in a mirror-design. 95% of patients suffered from chronic schizophrenia. The average case-load was 1 carer for 10 patients, who received on average one intervention per week, lasting on average 1 h.

Results: Global levels of symptomatology were stable and there was a mild but significant improvement in global functioning. Over the 3-year period, the average dose of antipsychotic medication could gradually be reduced. The interventions were well accepted by both the patient and the family. Quality of life improved significantly. There was a 30% reduction in hospitalisation rate, and a highly significant 72% reduction in lengths of stay. Per patient there was a 8400 Euro reduction per year in treatment costs.

Conclusion: An adapted ACT model of home-based rehabilitation with highly trained staff is an effective and cost-saving intervention, also in the Belgian mental health context.

296. LONG-TERM EFFECTIVENESS OF CLOZAPINE THERAPY IN TREATMENT-REFRACTORY SCHIZOPHRENIA: RESULTS OF A 5 TO 14 YEAR FOLLOW-UP STUDY

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Background: Clozapine is, arguably, the most effective antipsychotic drug; yet it is significantly under-used due the apprehension associated with its initiation and long-term monitoring. The present study was undertaken to empirically examine various aspects of long-term clozapine use.

Methods: The study is a descriptive, naturalistic follow-up study of clinically stabilized outpatients [n = 151] who have been treated with clozapine continuously for a period ranging between 5 and 14 years. Five aspects of treatment were evaluated—feasibility, tolerability and compliance, effectiveness and benefits, risks and side effects, and organizational issues. Subjects were evaluated clinically, and their prevailing symptoms, side effects, functional status, health services utilization and quality of life were quantified with standardized rating scales.

Results: The cohort's profile was as following: 77.8% were males, mean age was 41.5; mean treatment duration was 8 years and mean treatment dosage was 431 mg. Clozapine was tolerated well, with evidence of significantly reduced hospitalizations ($\div^2 = 24.8$, $p < 0.0001$), improved functioning (62% lived independently in the community) and superior quality of life during the follow-up. Self-appraised side effects were of mild to moderate severity, and satisfaction with treatment was uniformly high. The prevalence of metabolic and cardiovascular events was similar to the rates reported in comparable samples of schizophrenic patients receiving other antipsychotic drugs, but significantly higher than those seen in general population.

Conclusion: These results are helpful in reassuring patients, families and physicians, that long term clozapine therapy is feasible, acceptable and beneficial. More patients should be given the benefit of a clozapine trial, while keeping the relative benefits and risks in perspective.

297. SOMATIC MEDICATION IN HOSPITALISED SCHIZOPHRENIC PATIENTS IN BELGIUM

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Background/objective: This study aims to outline different aspects of somatic drug use: the use of anticonception in female

psychotic patients, the use of somatic medication to combat side effects of antipsychotic drug treatment, treatment of detected metabolic disorders, somatic medication as an indication for 'real' somatic co-morbidity.

Methods: PECC (Psychosis Evaluation tool for Common use by Caregivers) is a recently developed computerised assessment instrument that combines different functional and symptomatic outcome measures and allows for regular assessments of psychotic patients. At each assessment point, the symptoms and side effects of pharmacological treatment are evaluated and the current pharmacological and non-pharmacological treatments are registered.

Results: Currently, 1215 schizophrenic patients are being followed with PECC. The majority of these patients are male (61.1%). Patients have been ill for 9.2 years on average and have a mean age of 35.5 years (STD = 12). Although we are dealing with a relatively young population, one third (32.5%) of these patients are treated with one to five different somatic drugs. Our results show that only 17% of the women in our study use oral anticonception. 19.3% of somatic drugs are used to combat antipsychotic side effects like akathisia (29.2%), low blood pressure (30.1%) and constipation (40.7%). The most frequent somatic co-morbid disorders are: hypertension (13.7%), COPD (10%), epilepsy (6.5%) and thyroid disorders (3.7%). Treatment of detected metabolic disorders is present in 2.4% of patients for diabetes and 1.5% for lipid disorders. According to published prevalence data on metabolic disorders this could indicate an underdiagnosis.

298. HALOPERIDOL DOSE FOR THE ACUTE PHASE OF SCHIZOPHRENIA: A COCHRANE REVIEW

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Background/objective: Haloperidol is a benchmark, accessible antipsychotic against which the effects of newer treatments are gauged. The aim of this study was to determine the best range of doses for haloperidol for treating acutely ill people with schizophrenia.

Methods: We searched the Cochrane Schizophrenia Group's Register (December 1999), inspected all relevant references, and contacted companies. We selected studies involving people with acute schizophrenia, randomising dose ranges of non-depot haloperidol, and reporting clinically meaningful outcomes. We reliably extracted data and calculated Relative Risk on an intention-to-treat basis.

Results: We included 16 trials. No studies compared >1.5–3.0 mg/day haloperidol with higher doses. Low doses (>3–7.5 mg/day) did not result in loss of efficacy (no clinically important improvement, versus >7.5–15 mg/day $n = 48$, 1 RCT, RR 1.09 CI 0.7–1.8; versus >15–35 mg/day $n = 81$, 2 RCTs, 0.95 CI 0.8–1.2). >3–7.5 mg haloperidol/day had a lower rate of clinically significant extrapyramidal adverse effects than higher doses (versus >7.5–15 mg/day $n = 64$, 2 RCTs, RR 0.12 CI 0.01–2.1; versus >15–35 mg/day $n = 144$, 3 RCTs RR 0.59 CI 0.5–0.8, NNH 3 CI 2–6; versus >35 mg/day $n = 86$, 2 RCTs, RR 0.70 CI 0.5–1.1).

Conclusion: No results are conclusive and all are based on small, short, studies. It would be understandable, however, if clinicians were cautious in prescribing doses in excess of 7.5 mg/day of haloperidol to a person with uncomplicated acute schizophrenia, and if people with schizophrenia were equally reticent to take greater doses. Further research is needed regarding the efficacy and tolerability of the >1.5–3.0 mg/day dose range.

299. PATIENTS WITH SCHIZOPHRENIA INTOLERANT OF OR INADEQUATELY RESPONSIVE TO RISPERIDONE SUCCESSFULLY SWITCHED TO QUETIAPINE

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Objective: To examine the clinical benefit of quetiapine in a subgroup of patients from the SPECTRUM (Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication) trial who switched to risperidone due to intolerance or inadequate response.

Methods: This multicentre, open-label, noncomparative study, comprised a 1-week cross-titration period (quetiapine was increased to 400 mg/day and previous antipsychotic withdrawn) followed by 11 weeks' flexible dosing (up to 750 mg/day).

Results: Patients ($n = 55$) previously treated with risperidone (mean final dose 4.4 mg/day) received quetiapine at a mean modal dose of 483 mg/day; 67.3% patients completed the study. Significant decreases from baseline in PANSS total (-18.5) and positive (-2.9), negative (-5.8) and general psychopathology (-9.4) subscale scores were seen after 12 weeks of quetiapine treatment. 63% and 40% patients had >20% and >30% improvements, respectively, in PANSS total score. Furthermore, by Week 12 65% patients had CGI Severity of Illness score of 1, 2 or 3. 64% achieved clinical benefit from switching. Depressive symp-

toms decreased significantly from baseline (CDSS score −2.88), including 26 patients deemed clinically depressed at baseline (−5.5). Parkinsonism and akathisia improved significantly (SAS score −2.8, BAS score −0.5). Quetiapine was well tolerated; 9.1% patients withdrew due to AEs, the most common being transient somnolence (16.4%), asthenia and dry mouth (both 5.5%).

Conclusion: Patients switched to quetiapine after inadequate response or intolerance to risperidone demonstrated consistent, significant improvement in schizophrenia and associated symptoms. Quetiapine was well tolerated and demonstrated significant improvements in parkinsonism and akathisia.

300. INCIDENCE AND EARLY COURSE OF FIRST EPISODE PSYCHOSIS; BASELINE DATA FROM THE MEDICATION STRATEGIES IN FIRST ONSET SCHIZOPHRENIA STUDY

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Background: Trials on relapse-rates after first psychotic episodes support long-term anti-psychotic treatment. However relapse-prevention is not the sole contributor to quality of life.

Methods: The Mesifos study is designed to assess differential effects of short (6 months, then targeted) versus sustained (2 years) antipsychotic drug treatment on quality of life in patients recovering favorably from a first psychotic episode. From October 2001 until January 2003 first psychotic episode patients ($n=378$), in a 3.2 million inhabitants catchment area, aged 18–45 years, were asked for informed consent.$N=130$ refused or were lost before any assessment. Of the remaining 248 patients, $n=175$ were included after diagnostic assessment, applying narrow criteria for first episodes: no actual antipsychotic treatment or remission longer than 3 months nor previous remission longer than 6 months. Those patients recovering within 6 months after starting antipsychotics, and remaining stable for another 6 months ($n=128$) were included in the actual trial of targeted versus sustained treatment. Patients are followed up 2 years after first remission. Non-remitting and relapsing patients and patients who refuse trial are followed up as well. First assessment is at remission, or, in case of non-remission, 6 months after starting antipsychotics. The second assessment is after 6 months (before trial), the third and final assessments are after 15 and 24 months. We obtained baseline data on incidence of first psychotic episodes, gender, sociodemographics, drug abuse, estimated duration of prodromal symptoms, duration of untreated psychosis and data on early treatment response: compliance, time to remission, non-remission, relapse, persisting symptoms, type of antipsychotic treatment.

Treatment: Aripiprazole

301. SAFETY OF ARIPIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA GROUPED BY RACE

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Objective: The safety and tolerability profile of aripiprazole in patients with different racial backgrounds was evaluated in this analysis of clinical trial data.

Methods: Pooled data from short-term placebo-controlled studies of aripiprazole for treatment of schizophrenia or schizoaffective disorder were analyzed after grouping patients by race. Of the 1339 patients who participated in these trials, 715 were white, 427 black, 135 Hispanic, 31 Asian, and 31 were classified as Other.

Results: The safety and tolerability profile of aripiprazole in these patient subgroups paralleled that in the overall patient population. In each racial group, the incidence of adverse events with aripiprazole was low and similar to placebo. Among aripiprazole-treated patients, reports of EPS were more frequent in black patients than in white patients, while other EPS-related adverse events (tremor and hypertonia) were reported less frequently in black patients than in white patients. Incidence rates for somnolence and insomnia were similar for black patients and white patients receiving aripiprazole, while nausea and vomiting were lower among black patients than white patients. The plasma concentrations of aripiprazole were similar across all racial groups.

Conclusion: Aripiprazole exhibits a similar favorable safety and tolerability profile in all patients regardless of race.

302. EFFECTS OF LONG-TERM ARIPIPRAZOLE THERAPY ON THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Objective: This study compared the direct long-term effects of aripiprazole and haloperidol on the control of negative symptoms associated with schizophrenia.

Methods: Patients with acute relapse of chronic schizophrenia were randomized to aripiprazole 30 mg/d ($n=861$) or haloperidol 10 mg/d ($n=433$) in this 52-week, multicenter, double-blind clinical trial. Changes in negative symptoms were evaluated from PANSS negative subscale assessments made over the course of the study. A path analysis approach, controlling for the effect on positive symptoms, depressive symptoms, and EPS, was used to estimate the direct effect of treatment on negative symptoms.

Results: Aripiprazole-treated patients showed a significantly greater mean reduction in PANSS negative score from baseline than haloperidol-treated patients (-4.57 vs. -3.59, $P=0.011$). The direct effect on negative symptoms was also significantly greater in the aripiprazole group than in the haloperidol group ($P=0.033$). Among patients with more pronounced negative symptoms at baseline (PANSS negative >24), the mean changes in PANSS negative score from baseline were significantly greater with aripiprazole than with haloperidol (-6.97 vs. -5.25, $P=0.005$). The reduction in negative symptoms following stabilization of acute symptoms was also greater in the aripiprazole group than in the haloperidol group ($P=0.02$).

Conclusion: Aripiprazole was significantly more effective than haloperidol for reducing negative symptoms during long-term therapy of patients with schizophrenia.

303. PARTIAL AGONIST ACTIVITY OF ARIPIPRAZOLE AT D2 AND 5-HT1A RECEPTORS: EVIDENCE FROM IN VITRO BINDING STUDIES

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Background/objective: Published studies provide evidence that aripiprazole has a mechanism of action at D2 and 5-HT1A receptors distinct from other effective antipsychotic drugs. The aim of this study was to provide alternative biochemical readouts to support these published data.

Methods: The study used [3H]arachidonic acid release and [35S]GTPγ S binding assays to estimate the functional profile of aripiprazole at cloned human D2L and native rat hippocampal 5-HT1A receptors, respectively.

Results: Aripiprazole displayed a potent partial agonist activity (pEC50 = 8.13, pm 0.23) in stimulation of [3H]arachidonic acid release in CHO cells stably expressing cloned human D2L receptors; the selective D2L antagonist raclopride blocked this effect in a concentration-dependent way. In comparison, haloperidol, olanzapine, ziprasidone, clozapine, and risperidone did not stimulate D2 receptor-mediated increases in [3H]arachidonic acid release. At the 5HT1A receptor, aripiprazole also stimulated [35S]GTPγ S binding to rat hippocampal membranes with a potent partial agonist profile. Ziprasidone, but not clozapine, risperidone, or olanzapine, displayed a similar potent partial agonist profile to that of aripiprazole.

Conclusion: The present study provides additional support to existing evidence that aripiprazole is a potent partial agonist at D2 and 5-HT1A receptors. Furthermore, the functional profile of aripiprazole at D2 and 5-HT1A receptors was distinct from that of all other antipsychotic drugs tested.

304. ARIPIPRAZOLE IN TREATMENT-RESISTANT SCHIZOPHRENIA: A 6-WEEK DOUBLE-BLIND COMPARISON STUDY VERSUS PERPHENAZINE

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Background: This multicenter study compared the efficacy and safety of aripiprazole with the typical antipsychotic perphenazine in patients with treatment-resistant schizophrenia.

Methods: To confirm treatment resistance, eligible patients initially underwent a period of 4–6 weeks of open-label treatment with either olanzapine or risperidone. Treatment-resistant patients were then entered into a 2–10-day, single-blind, placebo washout phase, before being randomized to aripiprazole, 15 or 30 mg/day ($n=154$) or perphenazine, 8–64 mg/d ($n=146$) for the 6-week, double-blind treatment phase. Efficacy (PANSS and CGI), safety, and quality of life assessments were performed during the study.

Results: Patients treated with either aripiprazole or perphenazine showed improvement in PANSS Total scores from baseline (-9.8 and -10.5 points, respectively) following failure on olanzapine or risperidone therapy. PANSS positive and negative subscale scores, and CGI Improvement scores also showed improvements with both treatments. Overall, 27% of aripiprazole-treated patients and 25% of perphenazine-treated patients responded to therapy, based on CGI-I Score of 1 or 2, or decrease in PANSS Total score. Improvements in the quality of life scale (QLS) total score were greater with aripiprazole than with perphenazine, although the difference was not statistically significant. Fewer aripiprazole-treated patients experienced EPS, ECG abnormalities, or elevations in plasma prolactin levels than perphenazine-treated patients. No clinically significant differences in weight were observed between the groups.

Conclusion: In summary, aripiprazole and perphenazine produced significant improvement in schizophrenia patients resistant to olanzapine or risperidone therapy.

305. EFFICACY, SAFETY, AND TOLERABILITY OF ARIPIPRAZOLE IN PATIENTS WITH SCHIZOAFFECTIVE DISORDER

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Objective: This sub-analysis examines the efficacy of aripiprazole for the treatment of patients with schizoaffective disorder.

Methods: Data were taken from a subsample of patients with schizoaffective disorder who participated in two 4-week, multicenter, randomized, double-blind studies comparing aripiprazole ($n=117$) with placebo ($n=54$). Patients received once-daily treatment with aripiprazole at doses ranging from 15 mg/day to 30 mg/day. Efficacy was evaluated using PANSS and CGI measures. Safety and tolerability assessments included adverse event reports and extrapyramidal symptom (EPS) rating scales.

Results: The mean reduction in PANSS total score from baseline was significantly greater among aripiprazole-treated patients than among those receiving placebo (-12.5 vs. -2.3, $P=0.016$). These reductions in PANSS total score were similar to those observed for patients with schizophrenia enrolled in each of the two trials. Aripiprazole treatment also produced significantly greater improvements in PANSS positive score than placebo (-3.6 vs. -0.7, $P=0.017$). The changes in EPS rating scale scores (Simpson Angus, Barnes Akathisia, and Abnormal Involuntary Movement scales) seen with aripiprazole in this patient population were comparable to those observed with placebo. The overall incidence of adverse events was similar in the two treatment groups.

Conclusion: Data from these 4-week trials show that aripiprazole is an effective, safe, and well-tolerated treatment for patients with acute exacerbation of schizoaffective disorder.

306. EFFECT OF TIME OF DOSING AND FOOD ON ARIPIPRAZOLE PHARMACOKINETICS

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Background: The impact of the time of dosing or a high fat meal on the pharmacokinetics of aripiprazole was investigated in two clinical trials. Time of dosing effect was evaluated in an open-label, parallel group study, in which healthy subjects received a single 20 mg dose of aripiprazole in the morning (AM, $n=16$) or in the evening (PM, $n=16$).

Methods: In the food effect study, subjects received 15 mg aripiprazole in a fasted condition or within 5 minutes of consuming a high-fat breakfast using a two-treatment, three-period, replicate cross-over design ($N = 39$) with at least 21 days washout between each treatment. Blood samples were collected and pharmacokinetic parameters determined for both studies.

Results: Compared to AM dosing, aripiprazole Cmax was lower and Tmax was delayed following PM dosing. However, total exposure (AUC[infinity]) and oral clearance (Cl/F) were not statistically significantly different between groups, so small changes in Cmax are not considered to be clinically relevant. The Cmax or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, were not significantly affected by a high fat meal.

Conclusion: Aripiprazole may be dosed regardless of time of day and without regard to meals.

307. EFFECTS OF SHORT- AND LONG-TERM ARIPIPRAZOLE TREATMENT ON THE EXCITEMENT/HOSTILITY SYMPTOMS OF SCHIZOPHRENIA

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Objective/methods: This analysis examined the effects of aripiprazole, a new antipsychotic with low potential for sedation, on the excitement and hostility symptoms associated with schizophrenia. Changes in the excitement/hostility cluster, derived by factor analysis of PANSS scores, were evaluated using data from short- and long-term studies. Short-term analysis used pooled data from five short-term, multicenter trials from patients with schizophrenia or schizoaffective disorder randomized to aripiprazole ($n = 885$) or placebo ($n = 405$). Long-term data were from a 52-week study comparing aripiprazole ($n = 853$) with haloperidol ($n = 430$) in patients with schizophrenia.

Results: In the short-term studies, the excitement/hostility factor score showed a mean increase (i.e. worsening) of 1.29 points with placebo compared with a mean decrease of 0.94 points with aripiprazole ($P < 0.001$). Analysis of the two fixed-dose studies that included haloperidol arms showed that both aripiprazole and haloperidol treatment significantly improved excitement/hostility scores compared with placebo (aripiprazole, -1.17; haloperidol, -1.11; placebo, $+1.48$; $P < 0.001$). In the 52-week study, the excitement/hostility score decreased by 2.56 and 2.43 points from baseline with aripiprazole and haloperidol treatment, respectively, during the first 8 weeks of therapy. This effect was maintained throughout the 52-week trial.

Conclusion: Aripiprazole was more effective than placebo and comparable to haloperidol for reduction of the excitement and hostility symptoms associated with schizophrenia.

309. BROAD EFFECTIVENESS TRIAL WITH ARIPIPRAZOLE

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Objective: The aim of this study was to evaluate the overall effectiveness (efficacy, safety, tolerability) of aripiprazole in patients with schizophrenia or schizoaffective disorder treated in a general psychiatric practice setting.

Methods: In this multicenter open-label study, patients for whom a switch or initiation of antipsychotic medication was indicated were randomized (through a centralized randomization system) in a 4:1 ratio to aripiprazole (10–30 mg/day) or standard of care (SOC) for 8 weeks. Efficacy, safety, tolerability, and dosing data were collected at regular assessments during the study. In all, 1599 patients were randomized to treatment (aripiprazole,$N = 1295$; SOC,$N = 304$).

Results: Overall, 53% of the patients responded to therapy with aripiprazole, as determined by CGI scores. The majority of patients, and a high proportion of caregivers, have rated aripiprazole as much better than their previously administered medication. Adverse event reports for aripiprazole to date show a similar incidence to that in placebo-controlled studies. In general, events have been mild-to-moderate in severity and time-limited, and no unexpected serious adverse events have been reported.

Conclusion: This naturalistic study demonstrates the overall effectiveness of aripiprazole treatment for patients with schizophrenia and schizoaffective disorder in the general psychiatric setting. It provides valuable clinical insight into outcomes expected with everyday use.

310. TOLERABILITY AND EFFICACY OF ARIPIPRAZOLE IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA: AN OPEN-LABEL PILOT STUDY

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Objective: The objective of this study was to determine the tolerability and efficacy of aripiprazole in patients with first-episode schizophrenia, a population relatively naïve to antipsychotics.

Methods: Data are presented from 20 patients (mean age 22 years) with first-episode schizophrenia (i.e. occurring 1 year prior to study entry) enrolled in a 28-day, multicenter, open-label, fixed-dose study. Patients were treated with aripiprazole 15 mg ($n = 14$), 20 mg ($n = 5$), or 30 mg ($n = 1$) once daily. Tolerability was assessed at week 2 and week 4, while PANSS and CGI efficacy assessments were performed at baseline and week 4.

Results: PANSS total scores showed robust improvement from baseline at the end of the study across all aripiprazole doses (15 mg/day, -15; 20 mg/day, -14). PANSS positive and negative subscale scores and CGI-Severity score also improved over the study period. The most frequently reported adverse events were anxiety, akathisia, tachycardia, and dizziness. There were no clinically significant QTc or laboratory findings, and minimal change in body weight during the study.

Concluson: Aripiprazole showed symptom improvement and was generally well tolerated in this pilot study, suggesting that aripiprazole may be an important treatment option in patients with first-episode schizophrenia.

311. ACUTE TREATMENT WITH ARIPIRAZOLE DOES NOT PRODUCE CHANGES IN BASAL DOPAMINE OR NORADRENALINE LEVELS IN SUBREGIONS OF THE NUCLEUS ACCUMBENS OR MEDIAL PREFRONTAL CORTEX IN FREELY MOVING RATS

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Background: Atypical antipsychotics, such as clozapine, have been shown to produce preferential effects on the mesolimbic and mesocortical dopamine systems.

Methods: The present study used in vivo microdialysis to compare the effects of the atypical antipsychotic aripiprazole (3, 10 mg/kg p.o.) to those of clozapine (10 mg/kg s.c.) on extracellular levels of dopamine (DA) and noradrenaline (NA) in rat nucleus accumbens (NAcc) core and shell, and medial prefrontal cortex (mPFC). Microdialysis probes were implanted, via guide cannulae (surgical implanted 7 days prior), and were perfused with artificial cerebrospinal fluid (aCSF). Following a 2 h equilibration period 4 basal samples were taken. Drugs were then administered and sampling continued for a further 4 h. Samples were analysed using high performance liquid chromatography with electrochemical detection.

Results: Aripiprazole produced no changes in extracellular levels of either DA or NA in any of the brain regions studied. Clozapine, however, produced a significant ($P < 0.05$) increase in DA levels in the NAcc shell (max $194 \pm 16\%$ of preinjection basal levels) that was significantly greater than that observed in the core (max $141 \pm 17\%$; $P < 0.05$). Clozapine also produced an increase in levels of NA in shell ($717 \pm 106\%$) and core sub-regions ($409 \pm 93\%$). Similarly, an increase in both DA ($689 \pm 170\%$) and NA ($544 \pm 143\%$) was observed in the mPFC.

Conclusion: These data support a preferential mesolimbic/mesocortical action of the atypical antipsychotic clozapine. In addition, the neurochemical mechanism of action of aripiprazole appears to differ significantly from that of clozapine.

312. LONG-TERM EFFECTS OF ARIPIPRAZOLE AND HALOPERIDOL ON AFFECTIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: The long-term effects of aripiprazole and haloperidol on the affective symptoms of schizophrenia were evaluated in this analysis of data from a 52-week study.

Methods: This randomized, multicenter study compared aripiprazole with haloperidol for maintenance of response in 1283 patients with acute exacerbation of chronic schizophrenia. Affective symptoms were evaluated using the PANSS depression/anxiety symptom cluster derived by factor analysis, the PANSS depression item (G6), and the MADRS score.

Results: At week 8, improvements in the PANSS depression/anxiety cluster score and the PANSS depression item score were greater with aripiprazole treatment than with haloperidol therapy. This effect was maintained throughout the study period. At week 52, the mean treatment difference was 0.52 ($P = 0.015$) for the depression/anxiety cluster and 0.14 ($P = 0.027$) for the depression item. The difference in the depression/anxiety cluster was particularly pronounced among patients in the upper tertile after stratification by baseline scores (treatment difference 1.10, $P = 0.02$). Analysis of MADRS scores produced similar results. Among patients with pronounced depressive symptoms at baseline (MADRS>16), the reductions in MADRS score were significantly greater with aripiprazole than with haloperidol (6.0 vs. 3.5, $P = 0.029$).

Conclusion: Long-term therapy with aripiprazole is more effective than haloperidol for reduction of affective symptoms in patients with schizophrenia, as measured by changes in MADRS and relevant PANSS items scores.

Treatment: Clozapine

313A. INVOLUNTARY TREATMENT WITH CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Objective: Some psychotic patients with lack of insight are unable to comply with necessary medical treatment. We wanted to assess the effects of involuntary treatment with clozapine.

Method: Retrospective chart review of all consecutive cases of involuntary treatment with clozapine in our hospital.

Results: Seven treatment-resistant psychotic patients with long-standing illnesses were eligible for involuntary treatment with clozapine. They were given a choice between oral or intramuscular injection treatment with clozapine. One patient was given one injection (without any adverse drug reaction) during the first week and decided to return to oral intake. He recovered so much that he was able to convince the commission for complaints to stop involuntary treatment. He subsequently relapsed. Another severely paranoid patient started with injections, which were given during 4 days. Clozapine had to be discontinued because of further psychic and somatic deterioration and infiltrations at the injection sites. 5 patients chose to take clozapine orally and remained on it. All seven patients were scored with CGI at the beginning and the end of the acute treatment phase (median 6 weeks) and at last observation (median 12 months) whether on or off clozapine. CGI-S improved from mean 6.3 (severely ill) to 4.1 and finally 4.1 (moderately ill). These differences were highly significant ($t(6) = 6.58$, $p=.001$ and $t(6) = 4.21$, $p=.006$, respectively). CGI-I was mean 2.3 and finally mean 2.0 (much improved). Three patients were able to move from a closed to an open ward. Three patients became voluntarily compliant with clozapine.

Conclusion: Involuntary treatment with clozapine may be feasible and effective in treatment-resistant psychotic patients who refuse treatment with clozapine.

Treatment: Olanzapine

313B. IM OLANZAPINE OR VELOTAB FOR ACUTELY DISTURBED/AGITATED PEOPLE WITH SUSPECTED SERIOUS MENTAL ILLNESSES: A COCHRANE SYSTEMATIC REVIEW

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Background/Objective: People presenting with agitated or violent behaviour thought to be due to severe mental illness may require urgent pharmacological tranquillisation. Several preparations of olanzapine, an antipsychotic drug, are now being used for management of such agitation. The aim of this study is to estimate the effects of intramuscular or oral-velotab compared with other treatments for controlling aggressive behaviour or agitation thought to be due to severe mental illness.

Methods: The Cochrane Schizophrenia Group's Register (August 2003), was searched. This was supplemented by hand searching reference lists, contacting industry and relevant authors. Selection criteria: Randomised clinical trials comparing oral-velotab or intramuscular olanzapine to any treatment, for people with severe mental illnesses were included. Data collection and analysis: Studies were selected, assessed and data extracted. Binary outcomes are reported where possible. The number needed to treat/harm statistic was also calculated where possible. For continuous outcomes, non-skewed data was reported using a weighted mean difference.

Results: Two separate studies of IM Olanzapine were found comparing IM Olanzapine to placebo and IM Olanzapine to IM haloperidol. Fewer people on olanzapine IM required additional benzodiazepines, but did require greater anticholinergic medication. When compared to active comparators, there was no statistical difference between those on either drug for the outcome of continued agitation.

Conclusion: Further replication of these interventions is required, at arms length from company funding, avoiding an a priori change in the excited component of the PANSS as the main outcome at tow hours. We also look forward to seeing the Agitated Behaviour Scale, devised by the company for these trials, used more widely.

314. RAPID ONSET OF ABSORPTION WITH OLANZAPINE ORALLY DISINTEGRATING TABLETS

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Objective: A clinical perception exists suggesting more rapid onset of action with olanzapine orally disintegrating tablet (ODT) versus olanzapine standard oral tablet (SOT). Olanzapine bioavailability data were evaluated to assess early plasma concentration time profiles for olanzapine ODT versus SOT.

Methods: In three crossover bioequivalence studies of olanzapine ODT (5, 10, or 20 mg) versus SOT (1×5 mg, 2×5 mg, 4×5 mg), approximately 20 healthy subjects received single-dose ODT and the corresponding dose of SOT (≥ 13 days between treatments). Olanzapine plasma concentrations, AUC and Cmax values were evaluated to assess bioequivalence. Early onset of absorption was assessed using comparative absorption profiles.

Results: Olanzapine ODT and SOT were bioequivalent based on AUC and Cmax. Overall, plasma concentration–time profiles and absorption rate constants were nearly identical between formulations. Nonetheless, with 5 mg olanzapine, 79% of ODT vs. 0% of SOT patients had measurable olanzapine concentrations at 15 minutes. Significantly more subjects receiving ODT had higher plasma concentrations over the first hour vs. SOT (e.g. 63% vs. 10% ≥ 1 ng/mL at 45 minutes). These small early concentration differences became indistinguishable before reaching Cmax.

Conclusion: Olanzapine ODT yields a more rapid onset of absorption than SOT as significantly more subjects given ODT achieved slightly higher olanzapine concentrations immediately after administration. The small differences are likely attributable to more rapid onset of ODT GI absorption. These differences do not change the conclusion of bioequivalence. The relevance of earlier onset of absorption to clinical treatment has not been tested.

315. SWITCHING FORENSIC SCHIZOPHRENIA OUTPATIENTS FROM LONG-ACTING INJECTABLE ANTIPSYCHOTICS TO OLANZAPINE: AN OPEN-LABEL NATURALISTIC STUDY

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Objective: To examine what impact switching forensic schizophrenia outpatients from long-acting antipsychotics to olanzapine may have on risk factors for violence.

Methods: Seven forensic schizophrenia patients and 18 schizophrenia control patients receiving long-acting antipsychotics participated. Fourteen weeks of open-label therapy with olanzapine was initiated the evening of the base-line visit (the day the patient was to receive their injectable antipsychotic). Patients were initially prescribed olanzapine at a dose of 10 mg/day. Subsequent doses could be adjusted on the basis of individual clinical status within the range of 5 to 20 mg/day. Clinical scales included the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI). Forensic scales included the Buss–Durkee Hostility Inventory (BDHI) and the HCR-20.

Results: There were no statistically significant differences between the forensic schizophrenia and the schizophrenia control groups on the PANSS, CGI or BDHI at baseline or at the end of the 14-week trial. The two groups did differ on the HCR-20 at baseline and end-point with the forensic group having significantly higher scores in both instances. Furthermore, within group analyses

for the forensic group revealed that total scores on the and the HCR-20 did not change over the 14-week trial.

Conclusion: This 14-week trial suggests that forensic schizophrenia patients can be safely switched from long-acting injectable antipsychotic medications to olanzapine without experiencing a worsening of symptoms. The mean final dose of olanzapine was 13.33 and 12.69 for the forensic and schizophrenia control groups respectively.

316. SAFETY AND EFFECTIVENESS OF OLANZAPINE IN MONOTHERAPY VERSUS CONVENTIONAL ANTIPSYCHOTICS IN THE INPATIENT TREATMENT OF ACUTE SCHIZOPHRENIA: A MULTIVARIATE ANALYSIS OF A NATURALISTIC STUDY

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Objective: This study investigated the safety and effectiveness of olanzapine, when used in antipsychotic monotherapy, compared to conventional antipsychotics in the treatment of patients with schizophrenia hospitalized due to an acute psychotic episode.

Methods: Prospective, comparative, nonrandomized, open-label, observational study. Data included safety assessments with an EPS questionnaire and the report of spontaneous adverse events, as well as clinical assessments with BPRS and CGI. Treatment response was defined as a decrease of at least 40% from baseline in BPRS total score plus an endpoint BPRS score lower than 18 or less than 4 on the CGI-S scale. A multivariate methodology was used to more adequately determine which factors influence the effectiveness of olanzapine in monotherapy regarding EPS.

Results: 339 patients treated with olanzapine in antipsychotic monotherapy (OGm) and 385 patients treated with conventional antipsychotics (CG) were included. Treatment emergent EPS, or worsening of previous ones, were statistically significantly higher in the CG ($p < 0.0001$). Responder rate was significantly higher in the OGm ($p = 0.005$). Logistic regression analyses revealed that the only variable associated with treatment emergent EPS and clinical response was treatment strategy (inclusion in one of the treatment groups), with patients in the OGm having 1.5 more times the chance of obtaining a clinical response, and patients in the CG having 5 more times the risk of developing EPS.

Conclusion: In this naturalistic study olanzapine as antipsychotic monotherapy was better-tolerated and at least as effective as conventional antipsychotics in the treatment of acute hospitalized patients with schizophrenia.

317. OLANZAPINE VERSUS RISPERIDONE: RESULTS OF A ONE YEAR RANDOMIZED TRIAL IN OUTPATIENTS WITH SCHIZOPHRENIA WITH PROMINENT NEGATIVE SYMPTOMS

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Objective: To evaluate the efficacy and safety of olanzapine (Olz) compared with Risperidone (Ris) after 1 year of treatment.

Methods: This was a multi-center, randomized, open-label, parallel, dose-flexible, 1 year study of outpatients with schizophrenia with prominent negative symptoms (SANS Global score ≥ 10). Patients were assigned to treatment with an initial dose of at least 10 mg/day Olz$N = 120$) or at least 3 mg/day Ris ($N = 115$). The primary efficacy measure was the SANS Global score. Secondary efficacy measures included the SAPS and CGI-S. The response rate was defined as a 30% of improvement in the SANS Global score. Safety was evaluated by recording treatment-emergent adverse events (TEAEs) and measuring vital signs and weight. Extrapyramidal symptoms were evaluated by using a questionnaire based on the UKU scale.

Results: The mean dose was 12.2($\pm$ 5.8) mg/day for Olz and 4.9($\pm$ 2) mg/day for Ris. At one year, Olz patients showed significantly higher improvement than Ris patients on the SANS Global ($p = 0.015$), the SAPS Global ($p = 0.021$), and CGI-S ($p = 0.008$) scores. The response rate was greater ($p = 0.001$) in the Olz group (69.2%) than the Ris group (48.7%). Significantly more ($p = 0.03$) Ris patients (7.3%) experienced sexual dysfunction than Olz patients (1.6%). Incidence of treatment emergent EPS, or worsening of the previous one, were statistically significant higher ($p < 0.001$) in the Ris group (50.4%) than the Olz group (28.9%).

Conclusion: Long-term treatment with Olz was associated with significantly better improvement in psychopathology as compared

to Ris in outpatients with schizophrenia and prominent negative symptoms.

318. ADOLESCENT AND YOUNG ADULT PATIENTS WITH PSYCHOSIS TREATED WITH OLANZAPINE: SAFETY RESULTS FROM TWO SAMPLES

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Objective: To compare safety results from two samples of olanzapine-treated young patients with psychosis.

Methods: I. Analysis from a 6-month open-label trial of olanzapine (5–20 mg/day) in patients (12–21 years) with DSM-IV diagnosis of schizophrenia; responders only were treated beyond Week 6. II. Retrospective chart review of olanzapine-treated psychotic inpatients (13–20 years; primarily with ICD 10 schizophrenia).

Results: I. 100 patients entered the trial, 96 patients (mean age 15.9 years) were treated with olanzapine, 80 patients reached Week 6; 34 of 60 responders completed the 6-month observation period. Mean length of treatment (mean maximum dose = 16.7 mg/day) was 97.2 days. Three patients had serious adverse events (SAEs, infection ($N = 1$); rehospitalization ($N = 2$)); 4 patients discontinued for non-serious AEs. Most common treatment-emergent AEs were weight gain ($N = 28$; 29.2%) and increased prolactin ($N = 24$; 25.0%). Leukopenia was documented in 6 patients (6.3%). Mean weight gain was 5.1kg; mean change in Simpson–Angus score was −0.2 (entire sample, LOCF up to Week 6). II. 24 patients (mean age 17.2 years) were treated at a mean maximum dose of 16.7mg/day for a mean period of 60.8 days. There were two discontinuations (lack of efficacy, weight gain), no serious AEs. Weight increase was observed during (primarily typical) neuroleptic premedication and olanzapine treatment (2.9 vs. 3.7 kg/month). There were no clinically relevant changes in hepatic enzymes and leukocytes. EPS rate reductions were found ($p < 0.001$).

Conclusion: Mean daily doses of olanzapine in these samples were similar to those used in adults. Few patients in either study discontinued olanzapine treatment due to an adverse event.

319. ZYPREXA ZYDIS AND IMPROVEMENT IN AGITATION AND MEDICATION ADHERENCE IN NON-COMPLIANT PATIENTS WITH SCHIZOPHRENIA

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Background: Rapid reduction of agitation and improved medication adherence were assessed in 85 acutely ill non-compliant patients with schizophrenia treated with orally disintegrating olanzapine tablets (Zyprexa Zydis).

Methods: Longitudinal effects of Zyprexa Zydis on agitation were assessed using Positive and Negative Symptom Scale-Excited Component (PANSS-EC). This post hoc analysis of 6-week olanzapine treatment examined medication adherence for correlation with clinical psychopathology ratings. Association between previously derived PANSS factors and Rating of Medication Influences (ROMI)—compliance and ROMI-non-compliance subscores was investigated using a multiple regression analysis.

Results: Agitation, measured by PANSS-EC, was significantly reduced at 1 week and beyond ($p < 0.001$). Most ROMI improvement occurred within 1 week of treatment. A significant correlation between PANSS-EC and ROMI-compliance occurred at all time points during active treatment ($p < 0.05$). Regarding relative influence of different PANSS domains on compliance, 1-week ROMI-compliance correlated most strongly with PANSS-hostility/impulsivity; ROMI-non-compliance, with PANSS-positive.

Conclusion: Zyprexa Zydis rapidly reduced agitation (PANSS-EC) in non-compliant patients with schizophrenia. Effective resolution of acute agitation was associated with greater patient acceptance of medication treatment that may help to establish a more enduring therapeutic alliance. Improvement in comorbid hostility and psychosis contributed to improved treatment attitude.

320. A COMPARISON OF THE REDUCTION OF AGITATION IN SCHIZOPHRENIC PATIENTS TREATED WITH OLANZAPINE VS. ZIPRASIDONE IN A 28-WEEK DOUBLE-BLIND STUDY

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Background: Management of agitation in acutely ill patients with schizophrenia is an important treatment goal. An analysis of reduction in agitation from treatment with olanzapine vs. ziprasidone was performed in a *post hoc* analysis of a multi-center, randomized, double-blind, parallel, 28-week study of in- and outpatients with schizophrenia. Akathisia and anxiety were also examined due to symptom overlap with agitation.

Methods: Reduction in agitation, anxiety, and akathisia was assessed in patients treated with olanzapine 10–20 mg/day ($N=277$) vs. ziprasidone 80–160 mg/day ($N=271$). We performed repeated measures analyses of the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC), Barnes Akathisia Rating Scale (Barnes), and Hamilton Anxiety Rating Scale (HAMA) totals and individual item scores.

Results: Significantly greater improvement on the PANSS-EC was observed with olanzapine vs. ziprasidone by week 2 of active treatment ($p<0.05$), and this difference persisted to week 28 with the exception of week 5 ($p=0.121$). A significant therapy effect for olanzapine over ziprasidone was found for PANSS-EC ($p=0.0003$) as well as for all individual PANSS-EC items: excitement, hostility, tension, uncooperativeness, and poor impulse control; for all 4 Barnes individual items; for HAMA total; and for individual HAMA items for tension and insomnia. Mean modal doses of olanzapine and ziprasidone were 15.1 mg/day and 114.8 mg/day respectively.

Conclusion: Olanzapine was superior to ziprasidone in reducing agitation and anxiety. Akathisia scores were higher in the ziprasidone-treated group. Patients with these symptoms may require higher levels of care.

321. IMPROVEMENT OF COMORBID DEPRESSION WITH OLANZAPINE VERSUS ZIPRASIDONE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Objective: This multi-center, randomized, double-blind, 24-week study assessed efficacy of olanzapine (OLZ) compared with ziprasidone (ZIP) in improving depressive symptoms in schizophrenia or schizoaffective disorder.

Methods: Patients with ≥ 16 on the Montgomery–Asberg Depression Rating Scale (MADRS) were randomized to 6 treatment arms: 10, 15, or 20 mg/day OLZ ($n=202$) or 80, 120, or 160 mg/day ZIP ($n=192$). The primary efficacy measure was the Calgary Depression Scale for Schizophrenia (CDSS). Treatment differences were tested using analysis of variance (ANOVA) for LOCF changes on quantitative scales; Fisher's exact test was used for categorical variables.

Results: At study end OLZ-treated patients showed significant improvement (p=.017) in depressive symptoms on the CDSS, which was not evident at 8 weeks. OLZ also provided greater improvement on the MADRS ($p<0.001$), PANSS total ($p=0.008$), and positive ($p=0.008$), negative ($p=0.049$), and cognitive ($p=0.003$) subscales. Extrapyramidal symptoms (EPS) development was minimal with either treatment. Adverse events that occurred significantly ($p\leq 0.05$) more often were decreased appetite, aggravated psychosis, influenza, and migraine symptoms with ZIP, and were increased appetite, peripheral edema, and weight gain with OLZ. Between-group differences in QTc intervals, fasting glucose, and cholesterol were not significant, but triglycerides were elevated with OLZ (p=.016). Differences in weight changes were significant (OLZ, +3.53 kg, and ZIP, −1.65 kg, $p<0.001$).

Conclusion: Patients suffering from significant comorbid depression in schizophrenia or schizoaffective disorder may experience greater symptom improvement with OLZ treatment.

322. CLINICAL STATUS OF PATIENTS WITH SCHIZOPHRENIA IN A NATURALISTIC SETTING

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Background: Antipsychotic response is becoming more important than ever due the wider range of options. This observational study aims to assess and compare effectiveness of olanzapine versus other antipsychotics (APs).

Methods: According to the participating psychiatrists, 1072 Brazilian schizophrenic outpatients initiating or changing an antipsychotic were allocated in two groups: olanzapine and others APs.

Results: A total of 72% patients received olanzapine. All patients were followed for a period of 6 months and comparisons regarding psychopathologic and functional status were made between the two groups. Olanzapine treated patients had a significant improvement of total, negative, and depressive symptoms in CGI. Patients on olanzapine had their number of hospitalizations decreased significantly from the third month compared with baseline conversely to risperidone and typicals treated patients. Regarding body weight, olanzapine did not differ from the other antipsychotics on body mass index.

Conclusion: Data from a naturalistic setting are consistent with findings based on clinical trials. Compared with both risperidone and typicals treated patients, olanzapine treated patients showed better clinical outcome in a real world.

323. OLANZAPINE FOR TREATMENT OF THE SCHIZOPHRENIA PRODROME: 2-YEAR RESULTS OF A RANDOMIZED PLACEBO-CONTROLLED STUDY

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Objective: This 2-year, multisite, randomized, parallel, double-blind, controlled study is the first to assess the long-term efficacy of an atypical antipsychotic, olanzapine (Olz), versus placebo (Plc) in both delaying/preventing conversion to psychosis and reducing prodromal symptoms.

Methods: Sixty patients (mean age = 17.7 years; 65% male) (Olz, $n = 31$; Plc, $n = 29$) meeting Criteria of Prodromal Syndromes (COPS) received olanzapine (5, 10, or 15 mg/day) or placebo for year 1 and no treatment for year 2. Between-group comparison of the conversion-to-psychosis rate was the primary efficacy outcome.

Results: Twenty patients converted to psychosis by year 2 according to the Presence of Psychosis Scale (33% overall conversion rate). Fifteen patients converted in year 1 (10/29 on Plc and 5/31 on Olz) ($p = 0.139$). Olanzapine converters, compared with placebo converters, were less compliant (number of days: 79% vs. 93%). At the end of year 1, positive Scale of Prodromal Symptoms (SOPS) scores decreased significantly from baseline among olanzapine-treated patients ($p = 0.002$; LOCF). At the end of year 2, lack of treatment resulted in increased SOPS positive scores. Safety analysis found no between-treatment differences for incidence of EPS in year 1. Changes in weight and sitting pulse were higher for olanzapine versus placebo (8.8 vs. 0.3 kg and 9.0 vs. − 0.2 bpm, respectively).

Conclusion: Our study suggests that olanzapine may reduce the conversion-to-psychosis rate and appears effective in treating prodromal symptoms, which rebounded when the treatment was stopped. Future studies need larger samples with higher ratios of true positive prodromal patients.

324. PRELIMINARY PHARMACOKINETIC AND TOLERABILITY PROFILES OF OLANZAPINE 20, 30, AND 40 MG/DAY

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Objective: To characterize the steady-state pharmacokinetics and assess the tolerability of 3 higher doses of oral olanzapine (20, 30, and 40 mg/day) among patients with psychiatric disorders.

Methods: Thirty-seven stable inpatients with schizophrenia, schizoaffective disorder, or bipolar mania were treated with olanzapine 20 mg/day for 10 days then were randomized to 10 days of double-blind treatment with olanzapine 20 mg ($n = 12$), 30 mg ($n = 11$), or 40 mg ($n = 14$) daily. For an additional 10 days, 30 mg patients received olanzapine 40 mg/day (30 – 40 mg); all other patients remained on their same dose. To obtain pharmacokinetic data, a 7-day olanzapine washout period followed. Steady-state pharmacokinetics were computed using standard noncompartmental methods and various tolerability measures were obtained during double-blind treatment.

Results: Olanzapine pharmacokinetics appeared linear for doses of 20, 30, and 40 mg/day, with olanzapine plasma concentrations continuing a dose-proportional increase. Doses of up to 40 mg/day of olanzapine were generally well tolerated. Two patients (40 mg) discontinued because of an adverse event (akathisia, depressed mood). The most frequently reported adverse events were increased weight (20 mg, $n = 2$; 30 – 40 mg, $n = 3$; 40 mg, $n = 2$) and sedation (20 mg, $n = 3$; 30 – 40 mg, $n = 2$; 40 mg, $n = 2$). Four patients (40 mg) reported treatment-emergent akathisia (3 of 4 not confirmed by Barnes Akathisia Scale scores). No clinically important changes were observed in QTc intervals, laboratory parameters, or treatment-emergent EPS. Five patients (20 mg, $n = 3$; 30 – 40 mg, $n = 2$) experienced weight increase >7% from baseline.

Conclusion: In general, the pharmacokinetic and tolerability profiles of olanzapine 20, 30, or 40 mg/day in patients with psychiatric disorders were consistent with the known profiles of standard dose olanzapine (5 – 20 mg/day).

325. OLANZAPINE VERSUS PERPHENAZINE IN THE TREATMENT OF SCHIZOPHRENIA: A DOUBLE-BLIND STUDY

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Objective: In this study the main objective was to compare olanzapine with a conventional neuroleptic agent perphenazine with regard to efficacy and safety. The design was a randomized, double-blind, parallel, multicenter study.

Methods: The series included 46 patients fulfilling the DSM-IV criteria for acute schizophrenia or chronic schizophrenia with acute symptoms. The psychiatric and physical status including clinical laboratory tests were evaluated to ascertain the inclusion and

possible exclusion criteria. After a screening and wash out-period for previous neuroleptic treatments of 2 to 9 days the patients were treated for 26 weeks with either olanzapine (5 to 20 mg per day) or perphenazine (8 to 32 mg per day). As instruments of measuring clinical efficacy and eventual adverse effects of the treatment the PANSS, BPRS, CGI, UKU-ConSat, UKU-Sife-Effect-Scale, Barnes akathisia, and Simpson–Angus Scales were applied. One half of the patients completed the entire study in both treatment groups. The main reasons for drop-outs were non-compliance and inefficacy. Adverse side-effects did not constitute a significant reason for the discontinuation of the drug treatment.

Results: In completers, no differences were found in any efficacy or sife-effect ratings between the groups.

Conclusion: The findings indicate that olanzapine and perhenazine exhibit a rather similar pattern of treatment efficacy as well as safety profile in schizophrenic patients with acute overt psychopathology.

326. COMPARISON OF OLANZAPINE TO OTHER ATYPICAL ANTIPSYCHOTICS IN PREVENTING RELAPSE IN PATIENTS WITH SCHIZOPHRENIA

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Objective: Compare time to relapse on olanzapine compared with other atypical antipsychotics in patients with schizophrenia and explore some clinical reasons for relapse.

Methods: Three double-blind studies, comparing olanzapine to risperidone (28 weeks), olanzapine to ziprasidone (28 weeks), and olanzapine to quetiapine (24 weeks), were included in these analyses. Response was defined as 20% or 30% improvement in PANSS-total at 8 weeks. Relapse was defined as 20% or 30% worsening on PANSS-total and a CGI-severity ≥ 3 after 8 weeks in responders. Four sets of pairwise comparisons for response-relapse were conducted and labeled 20–20, 20–30, 30–20 and 30–30. Reasons for discontinuation were examined at 30–20.

Results: The percent of patients achieving 20% or 30% improvement in PANSS-total at week 8 was similar between olanzapine and each of the comparator drugs. Olanzapine-treated patients were significantly less likely to relapse than risperidone-treated patients at both criteria for response and relapse (p□0.001, OR relapse with risperidone ranged from 2.86 to 4.55). Olanzapine-treated patients also relapsed less than ziprasidone-treated patients at 20–20 and 30–20 ($p<0.01$), but not at 20–30 and 30–30. OR for relapse with ziprasidone ranged from 1.79 to 2.33. Olanzapine-treated patients relapsed less than quetiapine-treated ($p<0.02$) patients at all defined levels of response and relapse except 30–20. OR for relapse with quetiapine ranged from 3.85 to 7.14. Analysis of relapsers at 30–20 showed no significant differences in reasons for discontinuations between olanzapine and the other atypicals.

Conclusion: Olanzapine was better at reducing relapse in patients with schizophrenia than risperidone, ziprasidone and quetiapine using multiple definitions of response and relapse.

327. OLANZAPINE FOR REDUCES CUE-ELICITED COCAINE CRAVING AND RELAPSES IN SCHIZOPHRENIA

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Background/Objective: Individuals with schizophrenia and cocaine-dependence have intense craving early in recovery that may play a role in the high substance abuse relapses common in this population (Carol et al., 2001; Smelson et al., 2002). These studies highlight the need to develop pharmacological anticraving interventions to augment the traditional psychosocial treatments. While open label studies suggest that atypical neuroleptics may be useful for treating schizophrenia and cocaine dependence (Smelson et al., 2002), more double-blind studies are needed.

Methods: We conducted a 6-week double-blind trial comparing olanzapine and haloperidol for reducing substance abuse relapses and craving in individuals diagnosed with schizophrenia and cocaine dependence, believing that those in the olanzapine group will have better outcomes. Subjects were administered random urine toxicology screens along with a weekly cue-exposure procedure to prime patients with cocaine cues and study the acute anticraving effects.

Results: Individuals treated with olanzapine ($n=16$) showed fewer positive urine toxicology screening for an illicit substance (12.5%) compared to those in the haloperidol group (40%) ($n=15$), and less cue-elicited craving on the energy (0.01) and sick (0.05) dimensions of craving. This difference in craving reduction was greater for the study completers. Olanzapine was also well tolerated in this subgroup of individuals with schizophrenia and cocaine dependence in doses as high as 20 mg daily.

Conclusion: Olanzapine appears to be an effective adjunctive treatment for decreasing cocaine craving and preventing relapses among individuals with schizophrenia and cocaine dependence.

Acknowledgment: This study was supported by an investigator-initiated trial from Eli Lilly.

328. GENDER DIFFERENCES IN RESPONSE TO OLANZAPINE TREATMENT

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Background: Olanzapine is a novel antipsychotic, whose efficacy and tolerability in schizophrenia treatment has been well established during various controlled and randomized clinical trials. Hovewer, there is still need to confirm these results in unselected populations and long-term treatment.

Methods: In our study efficacy and safety of olanzapine treatment (mean dose 10,3 ± 0,2 mg/d) in 120 schizophrenic outpatients (ICD-10; M = 63, *F* = 57) was monitored during a one-year naturalistic study. Mean duration of olanzapine treatment at the baseline was 15,2 months (range 3–48). We compared the response to olanzapine in male and female subgroups and searched for a possible relationship between the severity of obsessive–compulsive symptoms and a subjective response to this novel antipsychotic. On the basis of the existing data we hypothesized a better general treatment response in female subgroup and a greater severity of obsessive–compulsive symptoms in male subgroup. Visits were carried out on a 3-monthly basis. They included assessment of psychopathological symptoms (Positive and Negative Syndrom Scale, Calgary Depression Scale for Schizophrenia, Yale Brown Obsessive–Compulsive Scale) and subjective well-being on neuroleptics (SWN scale).

Results: Mean reduction of the severity of obsessions ($p = 0{,}20$, Mann–Whitney 2-tailed test) and improvement in selected variables of subjective response to olanzapine (subscales of the SWN scale: regulation of emotions-p = 0.02; self-control-p = 0.44) were greater in the male subgroup.

Conclusion: The results may indicate that factors affecting the response to olanzapine are more complex than expected.

329. EVALUATION OF THE EFFECT OF ORALLY DISINTEGRATING OLANZAPINE TABLETS ON COOPERATION IN NON-COMPLIANT PATIENTS IN CLINICAL PRACTICE

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Objective: To evaluate the effect of the orally disintegrating olanzapine (Zyprexa®VeloTab™) 5–40 mg within 24 hours on cooperation in non-compliant patients in clinical practice.

Methods: 548 patients with agitation and/or non-cooperative behaviour entered a prospective observational study. Agitation and cooperation at baseline and after 24 hours were assessed with the Agitation Calmness Evaluation Scale (ACES) and a visual analogue scale, respectively. Analyses were done on available data.

Results: Psychiatric diagnoses included schizophrenia (57.5%), bipolar mania (14.6%), and other diagnoses (25.6%). In 207/490 patients (42.2%) only olanzapine was added to the existing medication, while in 57.8% olanzapine was combined with other drugs. The median olanzapine dose was 20 mg (range 2.5–40 mg). 182/275 patients (66.6%) were non compliant on previous medication. Baseline cooperation was markedly lower in the non-compliant when compared to the compliant subgroup (3.1 (95%CI 2.8–3.5)) and (5.8 (95%CI 5.2–6.4)). Cooperation improved significantly in both groups, but more markedly in the non-compliant group 1.5 (95%CI 1.2–1.8) and 0.9 (95%CI 0.6–1.2). The mean cooperation score was also lower in agitated (ACES baseline: 3.6 (95%CI 3.4–3.9)) than in non-agitated patients 4.5 (95%CI 3.6–5.4).

Conclusion: Non-compliant patients are markedly less cooperative, but show a larger beneficial effect of orally disintegrating olanzapine (Zyprexa®VeloTab™) than compliant patients. The findings indicate that agitation and cooperation are associated with each other.

330. EEG SLOWING, SLEEPINESS AND TREATMENT RESPONSE IN PATIENTS WITH SCHIZOPHRENIA DURING TREATMENT WITH OLANZAPINE

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Background/Objective: Olanzapine, like clozapine, induces slowing of EEG. During clozapine treatment the EEG-slowing increases with clozapine serum levels, it might predict treatment response and is related to side effects e.g. sedation. As olanzapine and clozapine share many pharmacological properties we investigated if slowing of EEG is related to the treatment outcome and the

prevalence of sleepiness in patients with schizophrenia during treatment with olanzapine.

Methods: 93 patients (mean age 26.4 ± 7.6, 51 females) underwent EEG examination. All recordings were visually evaluated by the same rater (W.J.), who was blinded to clinical data. The results were categorized used standardized form and compared with Fisher exact test, two-tailed.

Results: Among patients treated with monotherapy a moderately EEG-slowing (theta) was found in 65.4% of patients with none or partial treatment response ($n=26$) and in 75.0% of patients with good treatment response ($n=28$) (ns). The pronounced EEG-slowing (delta) was present in 34.6% and 50.0% of patients, respectively (ns). Both groups didn't differ either in the prevalence of sleepiness 30.8% vs 21.4%, respectively (ns). Among patients treated with polytherapy theta activity was present in 81.3% of patients treated in combination with other antipsychotic ($n=16$), but only in 31.8% of patients treated in combination with a benzodiazepine ($n=22$). It was similar as in a group of patients without pharmacological treatment 28.7% ($n=129$).

Conclusion: These results show the limited usefulness of single EEG performed during treatment with olanzapine. Therefore, if it is possible the patients should be investigated before and after the beginning of pharmacological treatment.

331. OLANZAPINE TREATMENT OF FIRST EPISODE PSYCHOSIS AFTER ZERO DUP

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Background/Objective: It remains controversial whether the interval between onset of psychosis and the beginning of antipsychotic medication treatment (duration of untreated psychosis, DUP) influences subsequent outcome of treatment. We report the short term efficacy of olanzapine in the treatment of psychotic patients after zero DUP and compare outcome to historical samples receiving similar treatment after usual DUP.

Methods: The sample consisted of ten consecutive subjects who had been diagnosed as prodromal using the Structured Interview for Prodromal Syndromes, became psychotic while assigned to placebo in a randomized trial, were treated with open label olanzapine 5–20 mg per day, and gave some efficacy data post-baseline. Patients were rated using the PANSS at baseline and at nine visits over 12 subsequent weeks.

Results: The mean modal olanzapine dose was 13.5 mg/d over a mean 10.5 weeks of completed treatment. Baseline PANSS total scores (minimum = 30) were 91.6 ± 8.9, and PANSS LOCF change scores at endpoint were −33.9 ± 23.6, yielding an average possible improvement of 55.0%. This average possible improvement is higher than those in two previous usual DUP first episode samples treated with olanzapine (43.6% over 12 weeks, $N=126$, Lieberman et al. Am J Psychiatry 2003 160:1396–1404; 49.0% over 6 weeks, $N=58$, Sanger et al. Am J Psychiatry 1999 156:79–87).

Conclusion: Although numerous caveats apply, these data support the possibility that antipsychotic treatment after zero DUP may be associated with better short term outcome than treatment after usual DUP. Treatment at zero DUP may require longitudinal monitoring after patient identification during a putatively prodromal phase.

Treatment: Quetiapine

332. THE USE OF QUETIEPINE IN PATIENTS WITH MEDICATION-INDUCED MOVEMENT DISORDERS

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Background/Objective: Quetiepine has been now known to have very low risks of extrapyramidal side efficts while providing good efficacy in psychosis. In this study, our objective was to demonstrate not only low EPS profile but also to possibly show quetiepine as a treatment for patients with eps while maintaining or improving clinical efficacy of psychosis.

Methods: Twenty-two patients with Schizophrenia and eps were studied in an assessor-blinded prospective, parallel switchover study comparing Quetiepine to original antipsychotic treatment. EPS was assessed by clinical and instrumental examinations and psychopathology was assessed using the PANSS. Follow-up assessments were conducted monthly to 4 months.

Results: At four months, Quetiepine showed a significant difference in rigidity ($p=0.007$) and akathisia ($p=0.004$) when compared to the original antipsychotics. Quetiepine also showed

nonsignificant improvement in tardive dyskinesia (by instrumentation) and overall parkinsonism score (Simpson Angus Scale). PANSS scoring showed an improvement in both negative and positive symptom total scores.

Conclusion: Quetiepine showed dramatic improvement in antipsychotic-induced movement disorders. This supports the literature that this medication has very low risk of EPS but perhaps more importantly for those patients that have been afflicted by EPS, targeting improvement in these side effects. Quetiepine also demonstrated efficacy in alleviating psychotic symptoms.

333. MECHANISM OF ACTION OF QUETIAPINE IS VIA MODULATION OF DOPAMINE AT THE D2 RECEPTOR

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Objective: To review the multiple pharmacological mechanisms responsible for the actions of quetiapine.

Methods: This is a review of published literature.

Results: Quetiapine, an atypical antipsychotic, interacts with multiple neurotransmitter receptors with a greater affinity for 5-HT_2 than D_2 receptors. Quetiapine binds loosely to the striatal D_2 dopamine (DA) receptor and is readily displaced by endogenous DA; transient occupancy is thus observed in positron emission tomography studies even at higher therapeutic doses. Furthermore, quetiapine's 5-HT_2 antagonist properties maintain enhanced DA tone in nigrostriatal and tuberoinfundibular DA pathways critical for the prevention of extrapyramidal symptoms (EPS) and prolactin elevation. In addition, through a combination of D_2 and 5-HT_2 blockade, quetiapine reduces activity in the overactive mesolimbic DA pathway, resulting in the control of the positive symptoms of schizophrenia, and, as a partial agonist of 5-HT_{1a}, increases DA tone in the underactive mesocortical pathway, resulting in beneficial effects on the negative and cognitive symptoms observed in patients with schizophrenia.

Conclusion: Quetiapine possesses a unique mechanism of action, allowing normal DA activity in regions of the brain that are dependent on intact dopaminergic transmission while blocking or enhancing DA transmission in regions of the brain that are overactive or underactive. This mechanism of action could explain quetiapine's antipsychotic effect and lack of hyperprolactinaemia and dose-related EPS.

334. THE EFFECT OF QUETIAPINE ON DIFFERENT DOMAINS OF COGNITION AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: The pharmacological and clinical profile of quetiapine is the promising factor in the treatment of negative symptoms and cognitive deficit in schizophrenia.

Methods: In the open, randomized 6 month study we compared the effect of quetiapine on negative symptoms and cognition. We studied the group of schizophrenic patients using typical antipsychotics ($N = 51$), 26 subjects continued in the previous treatment and 25 patients were switched to quetiapine flexibly dosed from 150 mg/day to 750 mg/day. Before and at the end of the trial patients were investigated by the battery of cognitive tests focused on attention (CPT II, Stroop test), executive functions (WCST), verbal memory (AVLT) and visuomotor performance (CFT). The analysis was performed as the change in study parameters form the baseline within both groups.

Results: Quetiapine treated patients in comparison with the control group improved in negative symptoms, attention, executive functions detected by WCST and visuomotor performance ($p = 0.05$). The body weight decreases in quetiapine treated patients (-1.8 kg). We found no differences in the change of positive symptoms, EPS scales and vital signs.

Conclusion: Our data indicate that quetiapine is safe and effective in the treatment of negative symptoms and the core dimensions of cognitive deficit in schizophrenia.

335. SWITCHING TO QUETIAPINE IMPROVES SYMPTOMS AND IS WELL TOLERATED IN PATIENTS WITH SCHIZOPHRENIA INADEQUATELY RESPONSIVE TO OR INTOLERANT OF OLANZAPINE

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Objective: To assess the clinical benefit of quetiapine in a subgroup of patients from the SPECTRUM (Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication)

study, who switched from olanzapine due to inadequate response or intolerance, including weight gain.

Methods: Multicentre, open-label trial comprised a 1-week cross-titration period; quetiapine was increased to 400 mg/day and previous therapies were withdrawn. Quetiapine was then increased to 750 mg/day for 11 weeks.

Results: Patients ($n=66$) previously treated with olanzapine (mean final dose, 18.1 mg/day) received quetiapine at a mean modal dose of 470 mg/day. A total of 71.2% patients completed the study; 22.7% withdrew (ITT population, $n=62$). Significant decreases from baseline in PANSS total (-15.4), positive (-4.4), negative (-4.8) and general pathology (-6.4) scores were recorded at Week 12. Depressive symptoms significantly improved in the overall population (CDSS -2.45) and the 34 patients who had clinically significant depression at baseline (CDSS -4.3). Furthermore, 51% and 38% patients had >20% and >30% reductions, respectively, in PANSS total scores; 54% had improved schizophrenia symptoms (CGI score). 66% patients switched from olanzapine showed clinical benefit with quetiapine. Quetiapine significantly improved parkinsonian and akathisia symptoms, with reductions in SAS and BAS scores of -1.4 and -0.4, respectively. Only 3% patients withdrew due to AEs, with the most common being somnolence (21.2%), asthenia (12.1%) and anxiety (10.6%).

Conclusion: Patients switched to quetiapine, after showing an inadequate response or intolerance to olanzapine, demonstrated improvements on all efficacy measures; quetiapine was also well tolerated.

336A. SUCCESSFUL SWITCHING TO QUETIAPINE IN PATIENTS WITH SCHIZOPHRENIA INADEQUATELY RESPONSIVE TO OR INTOLERANT OF HALOPERIDOL

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Objective: To evaluate the effect of quetiapine in a subgroup of patients from the SPECTRUM (Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication) trial, who switched from haloperidol (mean dose 6.2 mg/day) due to an inadequate response or intolerance.

Methods: Multicentre, open-label, non-comparative trial included a 1-week cross-titration period (quetiapine was increased to 400 mg/day and previous antipsychotic withdrawn) followed by 11 weeks' flexible dosing (up to 750 mg/day).

Results: Patients ($n=43$) received quetiapine at a mean modal dose of 501 mg/day. The mean change in PANSS total score was -32.5; with changes of -8.0, -8.6, and -15.7 on the positive, negative and general psychopathology subscales. 71% patients had a>20% reduction and 66% patients had a >30% reduction in PANSS total score. 66% patients had a CGI score <3 and 70% demonstrated clinical benefit. Furthermore, depressive symptoms improved (mean CDSS decrease -5.06 by Week 12), particularly for the 19 patients clinically depressed at baseline (mean CDSS decrease -8.9). Parkinsonism and akathisia symptoms also improved significantly: mean changes of -4.8 (SAS score) and -0.8 (BAS score) by Week 12. In total, 8 patients withdrew, only 2 (4.7%) due to AEs. AEs reported by >4% of patients included somnolence (16.3%); constipation or dizziness (both 9.3%); dry mouth or weight gain (both 7.0%); and anxiety or tachycardia (both 4.7%).

Conclusion: Quetiapine was well tolerated and showed significant improvement in the symptoms of schizophrenia in patients who switched from treatment with low-dose haloperidol due to an inadequate response or intolerance.

336B. CLINICAL RESPONSE AFTER SWITCHING FROM TWICE TO ONCE DAILY QUETIAPINE IN FIRST EPISODE SCHIZOPHRENIC PATIENTS—SUPPORT FOR THE "TRANSIENT D2 OCCUPANCY" MODEL

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Background: Quetiapine is an effective antipsychotic drug with a low EPSE profile. In vivo receptor imaging studies reveal transiently high striatal D2 occupancy, and suggest this may be sufficient for clinical efficacy. One previous report in $n=10$ first episode schizophrenic patients suggests once daily dosing of quetiapine is effective in treating psychosis.

Methods: We report $n=13$ (6M,7F)first episode patients studied before, and after switching to once daily quetiapine.

Results: 33 patients treated first line with quetiapine (standard titration to BD dosing)were rated prospectively with standard instruments. 13 patients were switched to once daily quetiapine (mean dose 370 mg, 95% CI 271–467). Switching took place at various times after starting treatment, ranging from 6 weeks ($n=5$)–20–30 weeks ($n=5$). 11 patients switched due to sedative side effects, and 2 due to low dosing and convenience. Results are for baseline (before switch) and 6 weeks after switching. Mean PANSS total (baseline) was 73, and after 40($p=0.004$); mean PANSS positive (baseline) was 17, and after 10 ($p=0.025$), mean PANSS negative (baseline) was 18, and after 10 ($p=0.028$), mean GAS (baseline) was 52 and 74 ($p=0.02$).

Conclusion: Switching to once daily quetiapine did not result in symptomatic or functional deterioration within 6 weeks. This

supports the proposal that transient occupancy of D2 receptors is sufficient for antipsychotic efficacy. Clinical improvement may reflect better compliance with once daily dosing, or a surrogate for overall improvement in quality of life and functioning, with a return to vocation, employment and more ''normalised'' lifestyles.

337. THE EFFECTIVENESS OF QUETIAPINE VERSUS OLANZAPINE IN IMPROVING NEGATIVE SYMPTOMS OF PATIENTS WITH SCHIZOPHRENIA

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Objective: To examine the effectiveness of quetiapine versus olanzapine in improving negative symptoms of patients with schizophrenia.

Methods: Forty inpatients with DSM-IV schizophrenia were treated in a public inpatient clinic and were randomly assigned to quetiapine or olanzapine. Nineteen patients received 300–800 mg/day quetiapine and 21 patients received 5–20 mg/day olanzapine for 12 weeks. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS) total score and subscales, the Scale for the Assessment of Negative Symptoms (SANS) total score and subscales and Clinical Global Impression-Scale (CGI-S) and were obtained at study entry and at Weeks 1, 2, 4, 8, and 12 by raters blinded to treatment.

Results: Both quetiapine and olanzapine showed a significant reduction in PANSS total score ($p < 0.001$), Positive Syndrome Scale ($p < 0.001$), Negative Syndrome Scale ($p < 0.001$) and General Psychopathology Scale ($p < 0.001$) from entry to endpoint. Both the SANS total score ($p < 0.001$) and subscales: attentional impairment ($p < 0.001$), avolition-apathy ($p < 0.001$), alogia ($p < 0.001$), affective flattening and blunting ($p < 0.001$), as well as the CGI-S ($p < 0.009$) were significantly reduced by quetiapine and olanzapine from entry to endpoint.

Conclusion: Despite the relatively small sample size, our study suggests that quetiapine and olanzapine improved negative symptoms as well as other clinical measures in patients with schizophrenia.

338. RESTORATION OF FRONTAL ACTIVATION DURING A TREATMENT WITH QUETIAPINE: A fMRI STUDY OF BLUNTED AFFECT IN SCHIZOPHRENIA

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Background/Objective: Blunted affect describes the impaired emotional functioning that is often characteristic of schizophrenia and is associated with poor prognosis, prolonged hospitalisation and poor social functioning. Previous studies have shown a lack of prefrontal activation in patients with blunted affect. The objective of this study was to investigate the change in cerebral activation related to emotional information processing in patients with schizophrenia and blunted affect during treatment with the atypical antipsychotic quetiapine.

Methods: Cerebral activation was examined using functional magnetic resonance imaging (fMRI) in 12 schizophrenia patients with blunted affect. Imaging was conducted before and 5.5 months after initiation of quetiapine treatment (mean dose 529 mg/day) during the passive viewing of a 'sad' film excerpt. Random-effect analyses (paired-sample t-test) were used to determine treatment effect. Improvement in blunted affect was documented using change in the Bells Negative Factor (NEGFT) score from baseline.

Results: Before quetiapine therapy, viewing of the 'sad' film excerpt resulted in activation of the midbrain (pons and medulla). Following quetiapine therapy a significant prefrontal activation (BA 9, 10 and 11) was noted. The NEGFT composite score decreased significantly from 33+1.4 points at baseline to 20+1.53 points at study end ($p < 0.0001$).

Conclusion: During quetiapine treatment of patients with schizophrenia an improvement was reported in their blunted affect, which may reflect an improvement in emotional functioning. fMRI results showed a trend towards restoration of frontal activation in these patients.

Treatment: Risperidone

339. EFFICACY AND SAFETY OF LONG-ACTING INJECTABLE RISPERIDONE IN PATIENTS WITH SCHIZOPHRENIA

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Objective: Open-label trial to investigate the maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia or other psychotic disorders switched directly from any oral or depot antipsychotic to long-acting risperidone without an oral risperidone run-in period. A subgroup analysis on schizophrenic patients was performed.

Methods: Adult patients stable on their antipsychotic regimen for ≥ 1 month received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) every 2 weeks for 6 months. The previous regimen was continued concomitantly during the first 3 weeks of injectable risperidone.

Results: Among 119 patients included in this evaluation, 91 had paranoid schizophrenia, 10 each had disorganised or undifferentiated, 2 had catatonic and 6 had residual. More than half of the patients were switched from atypical antipsychotics. Reasons for switching were lack of efficacy (33%), side effects (31%) and non-compliance (34%). At endpoint, mean scores for total PANSS, negative and general psychopathology subscales and disorganised thought and anxiety/depression factors were significantly ($p < 0.05$) reduced from baseline. Of the initially stable patients, 24% had a $\geq 20\%$ improvement in total PANSS score from baseline to treatment endpoint. Patient satisfaction assessed using a 5-point scale improved significantly from baseline. EPS improved significantly from baseline. No unexpected treatment-emergent adverse events were recorded.

Conclusion: This Switch to Risperidone Microspheres (StoRMi) trial subgroup showed that injectable long-acting risperidone maintained efficacy and may even improve PANSS scores over previous antipsychotic therapy. Treatment was well tolerated, with high levels of patient satisfaction.

340. LONG ACTING RISPERIDONE SIGNIFICANTLY REDUCES THE NEED FOR INSTITUTIONAL PSYCHIATRIC CARE

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Methods: In an ongoing international multi-center trial on treatment with long-acting risperidone (Risperdal Consta®) a health economy analysis was performed on the population from Sweden ($n = 92$) with regards to their need for institutional care before and during treatment. Each subject was their own control and mean duration of treatment with long-acting risperidone was 43 months. Number and length of episodes of institutional care was reported during treatment with long-acting risperidone and for the same period before start with long-acting risperidone. The results were also analysed with respect to changes of number of available institutional beds.

Results: Overall there was a reduction from 136 episodes before treatment start of long-acting risperidone to 85 during treatment. Total number of institutional care was reduced from 6635 days to 2404 ($p = 0.006$). Both number of episodes and length per episode were significantly lower during treatment with long-acting risperidone. Counted in patient year, the reduction was almost 21 days per patient. Even if the reduction of available institutional beds are taken into account, the results still remains statistically significant. When taking into account cost of medication and cost for institutional care, treatment with long-acting risperidone 25 mg every two weeks is expected to yield net savings of over 6300 Euro per patient year.

Conclusion: This study has shown that a switch to long-acting risperidone reduces both the number and the duration of institutional psychiatric care episodes in patients with schizophrenia, which reslts in overall cost-savings associated with this illness.

341. TREATMENT OF ACUTE SCHIZOPHRENIC EXACERBATIONS WITH RISPERIDONE

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Objective: To evaluate the efficacy and tolerability of risperidone in acutely exacerbated schizophrenic patients.

Methods: Prospective multicenter observational study. Acutely exacerbated schizophrenic inpatients were observed at baseline and on day 1, 3, 7, 14 and 28. Efficacy was assessed using the Brief Psychiatric Rating Scale (BPRS), BPRS agitation and hostility subscores, Clinical Global Impression (CGI) and CGI of change (CGI-C). Adverse events were assessed at each visit.

Results: 245 patients (48% male, mean age 41 years, paranoid schizophrenia in 72%) were enrolled. Mean observation time was 26 days. Mean daily doses of risperidone were 2.2 mg/day at the day of admission, 2.9 mg/day at day 1 and 4.5 mg/day at endpoint. Benzodiazepine comedication was frequently used. Total BPRS improved from 66.0 to 38.3 (-27.8, $p < 0.0001$ vs. baseline). BPRS agitation and hostility subscores decreased from 12.0 to 6.2 and 11.4 to 6.1 ($p < 0.001$, respectively). A statistically significant improvement in BPRS agitation and hostility subscores was observed at day 1 and maintained throughout the study. CGI

improved significantly (6.4 to 4.8, $p < 0.001$), and 79.2% of the patients were rated as very much or much improved in the CGI-C. Adverse events were reported in 15.9%, and 2.9% of the patients discontinued treatment with oral risperidone due to an adverse event. The incidence of extrapyramidal symptoms was low (7.8%).

Conclusion: Treatment of acutely exacerbated schizophrenic patients with oral risperidone was effective with a fast onset of action. The doses used in this study correspond well to recently recommended doses for risperidone in acute treatment.

342. DEPOT (LONG ACTING INJECTION) RISPERIDONE FOR SCHIZOPHRENIA: A COCHRANE REVIEW

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Background/objective: Risperidone is the first new generation antipsychotic drug available as a long acting injection. The aim of this study was to examine the clinical effects of depot risperidone for people with schizophrenia.

Methods: We searched the Cochrane Schizophrenia Group's Register (December 2002), references of all included studies, and contacted industry and authors. Studies were selected if they were randomised clinical trials comparing depot risperidone with other treatments. Data collection and analysis: Two reviewers independently inspected citations and extracted data. Outcome measures with more than 50% droupout were excluded from analysis. For dichotomous data, relative risk (RR), 95% confidence interval (CI) and, where appropriate, the number needed to treat (NNT), were calculated on an intention-to-treat basis.

Results: One study ($n = 400$) compared depot risperidone with placebo but 56% of people did not complete the three-month study. Attrition was higher for the placebo group. Severe adverse events were common (13% to 23%) more so in the placebo group. Poor reporting makes these difficult to interpret. Movement disorders were equally common in both groups (RR 2.38 CI 0.73 to 7.78). One study ($n = 640$) compared depot risperidone against oral risperidone for stable people with relatively mild illness. No difference between the depot and oral group noticed. Overall compliance was good. Adverse effects were poorly reported but over half of both groups reported some adverse effect.

Conclusion: There is no reliable data to support the claim that depot risperidone is beneficial for people with schizophrenia. Well designed and reported, randomised studies are needed to fully assess this new preparation.

343. UK EXPERIENCE: DIRECT SWITCHING TO A NEW LONG-ACTING INJECTABLE FORMULATION OF RISPERIDONE IN PATIENTS SUFFERING FROM SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

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Objective: Open-label trial (StoRMi) to investigate the maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia and other psychotic disorders switched directly from oral or depot antipsychotic. A subgroup of patients from the UK was assessed.

Methods: Adult patients stable on their antipsychotic regimen for 1 month were switched to long-acting risperidone without an oral risperidone run-in. They received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) every 14 days for 6 months. The previous regimen was continued concomitantly during the first 3 weeks of injectable risperidone.

Results: Among 119 patients, 90 had schizophrenia, mostly paranoid, and 19 had schizoaffective disorder. Mean total PANSS was 61.3 at baseline. More than 50% of patients were switched from conventional depot antipsychotic. Most patients were switched for lack of efficacy (44%), side effects (42%) and non-compliance (26%). The overall dropout rate was 27%. At endpoint, mean scores for total PANSS, positive subscale, negative subscale, general psychopathology subscale and disorganised thoughts factor were significantly ($p < 0.05$) reduced from baseline. Of all patients, 32% had a 20% improvement in PANSS score from baseline to treatment endpoint. More patients were 'not ill' (CGI) at endpoint (19%) than at baseline (7%). GAF and patient satisfaction improved significantly from baseline. EPS improved significantly from baseline. No unexpected adverse events were noted.

Conclusion: Not only did long-acting injectable risperidone treatment maintain the existing degree of improvement, it was also associated with further reduction in symptomatic measures.

344. ORAL RISPERIDONE COMBINED WITH ORAL LORAZEPAM IS AS EFFECTIVE AS STANDARD IM CARE IN ACUTE PSYCHOTIC PATIENTS

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Objective: To investigate whether oral risperidone plus oral lorazepam is as effective as conventional intramuscular (IM) neuroleptic treatment with or without lorazepam in emergency treatment of acute psychotic patients.

Methods: Patients were free to choose either oral risperidone combined with lorazepam or standard IM treatment. Patients unable to choose were not included in the trial. Oral treatment consisted of a single dose of 2 mg risperidone, preferably liquid, and 2.0–2.5 mg lorazepam. Standard IM treatment consisted of a conventional IM neuroleptic with or without 2.0–2.5 mg lorazepam. Patient response was assessed at 1, 2 and 24 hours. The primary outcome measure was the percentage of subjects with treatment success (at least much improved on CGI Global Improvement or asleep) 2 hours after treatment initiation.

Results: Of 226 patients from five European countries, 121 received oral treatment and 105 received standard IM care. There was no difference between treatment groups concerning age (mean, 41.0 years), gender (54% male), race (>90% white), diagnosis (61% schizophrenia), baseline CGI (mean, 4.0) and psychiatric history. Oral risperidone plus oral lorazepam was statistically significantly non-inferior to standard IM care (66.9% vs 54.3% treatment success rate; $p = 0.0003$). The incidence of extrapyramidal symptoms was significantly smaller in patients receiving oral risperidone plus oral lorazepam (1.7%) than in patients receiving standard IM care (9.5%, $p = 0.014$).

Conclusion: Oral risperidone combined with oral lorazepam is as effective as conventional neuroleptic IM in the treatment of acute psychosis.

345. SAFETY AND EFFICACY OF LONG-ACTING RISPERIDONE IN SCHIZOPHRENIA: A 12-WEEK OPEN-LABEL STUDY IN STABLE PATIENTS SWITCHED FROM ORAL ANTIPSYCHOTIC TREATMENT

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Objective: To assess the safety and efficacy of long-acting injectable risperidone (Risperdal Consta™) in stable patients with schizophrenia who were switched from oral antipsychotic medications.

Methods: After a 4-week run-in period, patients who had been taking haloperidol ($N = 46$), quetiapine ($N = 45$), or olanzapine ($N = 50$) received 25–50 mg of long-acting risperidone every 2 weeks for 12 weeks.

Results: At least one injection of long-acting risperidone was received by 141 patients and 137 had at least one post-baseline Positive and Negative Syndrome Scale (PANSS) assessment. Long-acting risperidone was well tolerated. Adverse events were rated as mild or moderate and the most frequently reported were insomnia (16%), headache (15%), psychosis (11%), and agitation (11%). EPS-related adverse events were reported in 8% of patients. Extrapyramidal Symptom Rating Scale total and subscale scores remained low throughout the study. Hyperprolactinemia was reported in 10 patients (7%). No other clinically relevant laboratory abnormalities or significant ECG changes, including QTc prolongation, were reported. Symptom improvements, as measured by mean changes in PANSS total scores from baseline, were observed at week 4 and throughout the 12-week treatment. PANSS total scores were significantly reduced at week 8 (-2.5, $P < 0.01$) and week 12 (-3.9, $P < 0.001$). At endpoint, 37% of patients were rated as clinically improved (>20% decrease in PANSS total scores).

Conclusion: Symptomatically stable patients with schizophrenia experienced significant clinical benefits with good overall tolerability when switched from oral antipsychotics to long-acting risperidone.

346. PATTERNS OF RISPERIDONE PRESCRIPTION: A UTILIZATION STUDY IN SOUTHWEST FRANCE

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Objective: To describe the patterns of prescriptions associated with risperidone in naturalistic clinical practice.

Methods: We analyzed 500 prescription forms randomly selected from the social security insurance database in Aquitaine (Southwest France).

Results: The prevalence of co-prescription was 42.5% for antidepressants, 46.4% for benzodiazepines, 26.6% for other neuroleptics, 21.8% for mood stabilizers and 19% for anticholinergic drugs. The high prevalence of co-prescribed antidepressants (59.3% SSRIs) may be explained by the frequent co-morbidity of mood disorders in schizophrenia, and by the fact that risperidone was prescribed in naturalistic conditions in disorders other than schizophrenia.

Conclusion: The high level of concomitant drug prescription in patients treated with risperidone illustrates the gap between clinical trials and utilization in naturalistic settings. The association antidepressant-risperidone has been insufficiently studied for efficacy or safety, and has to be explored further from both a pharmacological and clinical point of view.

347. RESULTS OF DIRECT SWITCHING TO LONG-ACTING INJECTABLE RISPERIDONE IN PATIENTS WITH SCHIZOAFFECTIVE DISORDERS

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Objective: Open-label trial (StoRMi) to investigate the maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia and other psychotic disorders switched from any oral or depot antipsychotic without an oral risperidone run-in supplementation period. A subgroup analysis in patients with schizoaffective disorder (DSM IV) is reported.

Methods: Adult patients stable on their antipsychotic regimen for 1 month received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) every 14 days for 6 months.

Results: Among 119 patients, 58 were male and 61 were female. Most patients were switched from conventional depot and atypical antipsychotics. Of patients who discontinued the study early (30%), only four dropped out for adverse events and seven for insufficient response. At endpoint, mean scores for total PANSS, positive subscale, negative subscale, general psychopathology subscale, disorganised thoughts factor, hostility/excitement factor and anxiety/depression factor were significantly ($p < 0.05$) reduced from baseline. Many patients (36%) had a 20% improvement in total PANSS score at treatment endpoint. More patients were 'not ill' (CGI) at endpoint (13%) than at baseline (4%). GAF and patient satisfaction improved significantly from baseline. EPS scores improved significantly from baseline. No unexpected adverse events were seen.

Conclusion: Long-acting injectable risperidone provided further relief and even improvement of symptoms over a 6-month period in schizoaffective patients who had been considered stable at trial entry.

348. PROGRESS OF STORMI: DIRECT SWITCHING TO LONG-ACTING INJECTABLE RISPERIDONE IN THE FIRST 1000 PATIENTS

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Objective: To investigate maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia and other psychotic disorders switched directly from any oral or depot antipsychotic. This open-label, single-arm, multicentre (22 countries) study was designed to yield subgroups of patients with similar characteristics, such as diagnosis and previous medication.

Methods: Subjects were aged ≥ 18 and stable on their previous antipsychotic regimen for ≥ 1 month. Unlike previous Phase III studies, subjects were switched directly without an oral risperidone run-in. They received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) every 14 days for 6 months.

Results: Of the first 1000 patients, most were men (62%) and Caucasian (90%). Mean age was 40 years (17–100 years) and mean BMI, 27.3 kg/m2. Diagnoses included schizophrenia (82%, of which 75% paranoid), schizoaffective disorder (12%) and schizophreniform disorder (2%). About one-third of patients were hospitalised at trial start. Physicians mostly switched from the previous treatment for non-compliance (35%), side effects (32%) and lack of efficacy (30%). Patients were mainly switched from conventional depot and atypical antipsychotics. Mean baseline PANSS subscale scores were: total, 72; positive, 15; negative, 21; general psychopathology, 36. Mean total ESRS score was 6.8.

Conclusion: STORMI is one of the largest trials of direct switching from any neuroleptic to a long-acting injectable antipsychotic in patients with schizophrenia and other psychotic disorders and will allow investigation of treatment results in patients according to various baseline characteristics (previous antipsychotic, reason for switching, underlying diagnosis).

349. RISPERIDONE LONG-ACTING INJECTION: PROGNOSTIC INDICATORS FOR EARLY DISCONTINUATION

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Background: To date, only efficacy trials have been conducted on risperidone long-acting injection (RLAI) and most appropriate utilisation of this drug in everyday practice remains unclear.

Objective: This six month follow-up study aimed to investigate prognostic indicators for early discontinuation of RLAI.

Methods: Consecutive sampling was conducted for adult patients with a psychotic disorder commenced on RLAI (22/08/02–21/01/03), whose injection was dispensed by one of three hospital pharmacies in a South London NHS Trust. Prescription data was collected prospectively and clinical data retrospectively.

Results: 81/88 (92.0%) eligible patients were included of which, 29 (35.8%) had treatment refractoriness. Thirty (37.0%) patients discontinued within 6 months, most commonly due to insufficient clinical response (15/30, 50.0%) and patient refusal (11/30, 36.7%). Patients with a preceding oral antipsychotic were more likely to discontinue RLAI than those with a preceding depot; treatment refractoriness weakly confounded this relationship (summary adjusted OR: 2.68, 95%CI: 0.95–7.53, $p=0.061$). After adjusting for preceding antipsychotic type, patients with treatment refractoriness were no more likely to discontinue than those without (summary adjusted OR: 1.55, 95%CI: 0.59–4.11, $p\backslash=0.376$). Sociodemographic factors (gender, ethnicity, age, marital status), illness duration, clinical indication for RLAI commencement and maximum dose were non-predictive of discontinuation.

Conclusion: For this first wave of patients commenced on RLAI, many had treatment refractoriness. Nevertheless, RLAI discontinuation is high in the early months but then tapers off. Preceding antipsychotic type is a stronger prognostic indicator than treatment refractoriness for RLAI discontinuation. Large prospective studies comparing RLAI with other depots are required.

350. OBESE PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: EFFICACY OF INJECTABLE LONG-ACTING RISPERIDONE

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Objective: The StoRMi (Switch to Risperidone Microspheres) open-label trial investigated the maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia and other psychotic disorders switched directly from oral or depot antipsychotic. Results in an obese subgroup population are reported.

Methods: Adult patients (BMI 30 kg/m2) stable on their antipsychotic regimen for 1 month were switched to long-acting risperidone without an oral risperidone run-in. They received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) every 14 days for 6 months.

Results: Among 119 patients, 87 had schizophrenia, mostly paranoid, and 24 had schizoaffective disorder. At baseline, mean weight and BMI were 98 kg and 33.6 kg/m2, respectively. The majority of patients were switched from conventional depot and atypical antipsychotics. Most patients were switched for lack of efficacy (31%), side effects (40%) and non-compliance (35%). At endpoint, mean scores for total PANSS, negative subscale, general psychopathology subscale, disorganised thoughts factor and anxiety/depression factor were significantly ($p<0.05$) reduced from baseline. Mean weight remained stable during the 6-month study period. 31% of patients had a 20% improvement in total PANSS score from baseline to treatment endpoint. More patients were 'not ill' (CGI) at endpoint (15%) than at baseline (6%). GAF and patient satisfaction improved significantly from baseline. EPS improved significantly from baseline. No unexpected adverse events occurred.

Conclusion: Obese patients benefited from long-acting injectable risperidone treatment similarly to schizophrenic patients in general. The level of patient satisfaction was very high.

351. EFFICACY OF RISPERIDONE ORAL CONCENTRATE ON ACUTE PSYCHOTIC SYMPTOMS

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Background: There is an increasing need for fast resolution of acute psychotic symptoms in psychiatric hospitals due to very short hospitalisation times. The aim of this study was to assess

effectiveness of Risperidone Oral Concentrate (ROC) on different acute psychotic symptoms.

Methods: Open label, non-randomised, 1-week naturalistic study of psychiatric inpatients. Acute psychotic symptoms, EPS and other spontaneously reported side effects were assessed using 5-point Visual Analogue Scale at a Baseline, 2, 4 and 7 days.

Results: 260 out of 262 inpatients completed the study. Males were 33.6% and females 66.4%. Mean age was 37.3 ± 15.7 years and average duration of illness was 6.8 ± 7.3 years. Patients were suffering from different forms of schizophrenia in 91.6% and other diagnoses in 8.4% of cases. ROC statistically significantly decreased severity of the core acute symptoms such as agitation, hallucinations, delusions and mania by at least one point comparing to the baseline within 4 days. Fifty percent or more decrease in symptoms severity by the end of the week was observed in 92.4% of patients with agitation, 78.6% with hallucinations, 78.8% with mania and 64.0% with delusions. Mean dose of ROC used through the study was 4.4 mg. It was used as antipsychotic monotherapy in 73% of patients. Frequency of spontaneous reported adverse events was 8%. They were mild and moderate in intensity and similar to those observed in other Risperidone studies.

Conclusion: Risperidone Oral Concentrate effectively treats acute psychotic symptoms.

352. YOUNG PATIENTS (18–30 YEARS) WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: RESULTS OF DIRECT SWITCHING TO LONG-ACTING INJECTABLE RISPERIDONE (STORMI TRIAL)

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Objective: To investigate maintained efficacy and safety of long-acting injectable risperidone in younger patients with schizophrenia and other psychotic disorders switched from oral or depot antipsychotic without oral risperidone run-in.

Methods: Patients aged 18–30 stable on their previous antipsychotic regimen for ≥ 1 month received long-acting risperidone injections (25 mg, increasing if necessary to 37.5 mg or 50 mg) for 6 months.

Results: Among 119 patients, 101 had schizophrenia, mostly paranoid, and 11 had schizoaffective disorder. More than half were switched from atypical antipsychotics. Main reasons given for switching were lack of efficacy (21%), side effects (24%) and non-compliance (47%). 70% of patients completed the 6-month treatment period. Only six patients discontinued early for adverse events, 11 for insufficient response. At the endpoint, mean scores for total PANSS, positive subscale, negative subscale, general psychopathology subscale, disorganised thoughts factor and anxiety/depression factor were significantly ($p < 0.05$) reduced from baseline. Of all patients, 32% had improvement in total PANSS score from baseline to treatment endpoint. More patients were 'not ill/borderline ill' (CGI) at endpoint (31.5%) than at baseline (5.9%). GAF and patient satisfaction improved significantly from baseline. No unexpected adverse events occurred. EPS improved significantly from baseline.

Conclusion: These subgroup results showed that long-acting injectable risperidone was efficacious in younger patients already stable. All PANSS subscale scores were significantly improved compared to baseline, indicating that this treatment may be beneficial for younger patients ensuring compliance and thereby continuity of treatment. It challenges the notion that 'stability' should be a final treatment outcome.

353. EFFICACY AND TOLERABILITY OF RISPERIDONE AFTER SWITCHING FROM DIFFERENT ANTIPSYCHOTICS

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Objective: To evaluate the efficacy and tolerability of risperidone after switching from different antipsychotics.

Methods: Prospective multicenter observational study. Adult outpatients who were switched to oral risperidone due to lack of efficacy and/or tolerability of their previous antipsychotic medication, were followed for 3 months. Efficacy was assessed by the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression of Change (CGI-C) and the Global Assessment of Functioning (GAF).

Results: 1150 patients were enrolled (54.5% female, mean age 45 years). The most frequent diagnoses were paranoid schizophrenia (48.2%), other subtypes of schizophrenia (20.9%) and delusional disorder (8.6%). 78.9% of the patients were switched from conventional neuroleptics (mainly Haloperidol, $n = 314$), 14.9% from atypical antipsychotics (mainly olanzapine, $n = 156$). Reasons for switching were lack of efficacy (91%) and lack of tolerability (67.5%). The mean risperidone dose at endpoint was 3.8 mg/day. Mean BPRS total scores improved significantly from 62.1 ± 16.1 to 36.9 ± 13.5 at endpoint ($p < 0.0001$). Global functioning (GAF) also improved significantly (44.3 to 63.3, $p < 0.0001$). 88 of 1150 patients (7.7%) had at least one adverse event. Extrapyramidal symptoms were reported in 2.1% and somnolence in 0.6%.

Conclusion: The switch from conventional and atypical antipsychotics to oral risperidone in patients with schizophrenia

and other psychotic disorders was associated with a significant improvement in psychotic symptoms and global functioning. Tolerability was good after switching to recommended doses of risperidone.

354. DIRECT SWITCH FROM ATYPICAL ANTIPSYCHOTICS TO LONG-ACTING INJECTABLE RISPERIDONE IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

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Objective: The StoRMi (Switch to Risperidone Microspheres) trial was designed to investigate the maintained efficacy and safety of long-acting injectable risperidone in patients with schizophrenia or other psychotic disorders switched from oral or depot antipsychotics without an oral risperidone run-in. This subgroup analysis assessed patients switched from atypical antipsychotics.

Methods: Adult patients stable on their antipsychotic regimen for 1 month received injections of long-acting risperidone (25 mg, increasing if necessary to 37.5 mg or 50 mg) at 14-day intervals for 6 months.

Results: Among 119 patients, 89 had schizophrenia, mostly paranoid, and 22 had schizoaffective disorder. Patients were switched from risperidone (78%), olanzapine (19%) and quetiapine (5%). Most patients were switched for non-compliance (53%). Of patients who discontinued the study early (36%), 12 dropped out for adverse events and nine for insufficient response. At endpoint, mean scores for total PANSS, negative subscale, general psychopathology subscale, disorganised belief factor and anxiety/depression factor were significantly ($p < 0.05$) reduced from baseline. 31% of patients demonstrated a 20% improvement in total PANSS from baseline to treatment endpoint. At endpoint, 13% of patients were rated 'not ill' on CGI vs 2% at baseline. GAF improved significantly from baseline. EPS improved significantly from baseline. Unexpected adverse events were not reported.

Conclusion: Although patients were regarded as stable at trial entry, significant improvements were achieved with long-acting injectable risperidone switched from prior atypical antipsychotics. Patients and clinicians were provided with a new treatment modality that can improve quality of maintenance treatment, resulting in potential for symptom remission.

Treatment: Ziprasidone

355. ZIPRASIDONE VS RISPERIDONE IN SCHIZOPHRENIA: 52-WEEK RANDOMIZED, DOUBLE-BLIND COMPARISON

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Objective: To compare the efficacy and tolerability of ziprasidone 40–80 mg BID and risperidone 3–5 mg BID in acute exacerbation of schizophrenia or schizoaffective disorder.

Methods: In an 8-week, randomized, double-blind trial, primary efficacy evaluations were PANSS Total and CGI-S scores; secondary variables included PANSS Negative Subscale score, BPRS Total and Core scores, and Global Assessment of Functioning (GAF). Primary efficacy analyses were based on evaluable patients (≥ 14 days of treatment). Completers could enter a 44-week, double-blind continuation study.

Results: On the basis of a predetermined equivalency criterion, evaluable ziprasidone ($n = 124$) and risperidone ($n = 132$) patients demonstrated equivalent efficacy improvements in primary and secondary measurements. Ziprasidone had a significantly lower mean Movement Disorder Burden Score (MDBS) and lower incidences of prolactin elevation and weight gain $\geq 7\%$. In the 44-week continuation, ziprasidone ($n = 59$) and risperidone ($n = 76$) groups exhibited comparable, sustained improvement in efficacy variables from baseline of the 8-week study. MDBS and incidences of prolactin elevation and weight gain $\geq 7\%$ remained lower with ziprasidone.

Conclusion: Patients receiving 52 weeks of double-blind ziprasidone or risperidone demonstrated comparable symptom improvement. Patients on ziprasidone had a lower movement disorder burden and lower incidences of prolactin elevation and clinically significant weight gain.

356. CLINICAL EFFICACY AND QUALITY OF LIFE IN A CLINICAL TRIAL COMPARING OLANZAPINE AND ZIPRASIDONE

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Objective: To examine changes in clinical severity and health-related quality of life (QOL) in patients with schizophrenia treated with either olanzapine or ziprasidone during a 28 week randomized clinical trial, and to assess the association between clinical changes and changes in QOL.

Methods: Schizophrenic patients enrolled to receive either olanzapine or ziprasidone in a 28-week randomized, double-blinded study. Efficacy was assessed using the Positive and Negative Symptom Scale (PANSS). Quality-of-life was assessed using the Short Form 36 (SF-36) and the Heinrichs-Carpenter Quality of Life Scale (QLS). Analysis of Variance (ANOVA) models were used to evaluate changes from baseline on clinical and QOL scales. The relationship between changes in PANSS total, factor, and subscale scores to changes in the QLS and SF-36 scales and subscales was assessed using Pearson correlations.

Results: The mean change in the PANSS total was -35.7 for olanzapine and -26.0 for ziprasidone ($p<0.001$). Olanzapine patients demonstrated significant improvements from baseline compared to ziprasidone patients on the SF-36 'General Health', 'Role-Emotional', and 'Social Functioning' scales. Olanzapine patients also demonstrated improvements on the QLS dimensions of 'Intrapsychic Foundations', and 'Common Objects and Activities'. All correlations between changes in clinical measures and the SF-36 subscales were significant ($p<0.001$), with inverse correlations ranging from $-.15$ to $-.39$. Similarly, the PANSS and the QLS showed significant inverse correlations on all comparisons ($p<0.0001$), ranging from -0.31 to -0.60.

Conclusion: This study demonstrated superior efficacy and QOL improvements for olanzapine. Reductions in clinical severity were associated with improved health-related quality of life.

357. OVERVIEW OF ZIPRASIDONE TOLERABILITY IN OLDER PATIENTS

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Objective: To evaluate the tolerability of ziprasidone in patients 355 years.

Methods: The ziprasidone phase 2/3 clinical development program was reviewed for incidences of treatment-related AEs, clinically significant laboratory abnormalities, and QTc prolongation in subgroups of patients aged 355 and 365 years. Incidences were compared to those for all patients in the database and for patients of all ages treated with other antipsychotics.

Results: Among ziprasidone-treated patients, AEs were comparable for the 355 and all-patient populations (49% versus 49.9%). Discontinuations due to treatment-related AEs were comparable for both ziprasidone populations (14.6% versus 13.8%), as were incidences of clinically significant laboratory abnormalities (49% versus 56%). The incidence of moderate-to-marked QTc prolongation was comparable to previous data presented on all patients; no patient 355 exhibited QTc 3500 msec or 325% increase over baseline. Similar results were observed in patients 65 years. Ziprasidone was associated with lower incidences of EPS, akathisia, and clinically significant laboratory abnormalities than risperidone or haloperidol.

Conclusion: Ziprasidone was well tolerated in older patients with schizophrenia or schizoaffective disorder. The incidence of overall AEs and clinically significant laboratory abnormalities was similar to that of the all-patients population, and comparable to or better than that seen with other antipsychotics.

358. EFFECT OF ZIPRASIDONE DOSING ON DISCONTINUATION IN SCHIZOPHRENIC PATIENTS

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Background/Objective: Optimal dosing is critical to ensure long-term medication adherence among patients with serious mental illness. We examined the characteristics of patients initiating ziprasidone therapy and the effects of initial dosing on discontinuation, using integrated medical and pharmacy claims data.

Methods: Patients with a diagnosis of schizophrenia and a ziprasidone claim between March 2001–June 2002 who were continuously enrolled for at least 6 months before and 3 months after initiation of ziprasidone were stratified by initial daily dose (40 mg or less vs. 80 mg or more). The risk of discontinuation was examined during the follow-up period using multiple logistic regression.

Results: The mean age was 36 years ($n=921$); 58% were female. The prevalence of medical comorbidities was high (31.4% with hypertension, 13.9% with diabetes). A reduced annualized rate of psychiatric hospitalization was observed after initiation of ziprasidone (1.19 vs. 0.79, $P<.0001$). Compared with doses of 80 mg/day or more, an initial dose less than or equal to 40 mg/day was associated with a two- to fivefold increased risk of discontinuation in 3 of 4 monthly follow-up periods analyzed ($P<.05$), with a trend toward significance in month 5 ($P=0.0981$).

Conclusion: Patients initiating ziprasidone therapy have a high degree of medical comorbidity, and an initial dose of at least 80 mg/day appears to improve medication adherence.

359. HIGH-DOSE ZIPRASIDONE IS ASSOCIATED WITH MARGINAL ADDITIONAL QTC INCREASE

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Objective: To characterize the QTc effects of oral ziprasidone and haloperidol at 3 steady-state dose levels.

Methods: After tapering and washout of existing antipsychotic therapy, subjects with schizophrenia or schizoaffective disorder were randomized to escalating doses of ziprasidone (40, 160, and 320 mg/day) or haloperidol (2.5, 15, and 30 mg/day) administered over 16 days to attain steady-state dose levels. ECGs were collected at baseline (drug-free condition) and during study drug administration on steady-state days 4, 10, and 16, at estimated T_{max} and 1 hour before and after. Samples for pharmacokinetic measurements were collected at estimated T_{max}, and telemetry was performed throughout the high-dose period.

Results: Mean ziprasidone ($n=25$) concentrations increased ~ 6-fold across the 40–320 mg/day dosage range, reaching 327 ng/mL at the 320 mg/day dosage level. Mean DQTc from baseline was 4.5 msec at 40 mg/day, 19.5 msec at 160 mg/day, and 22.5 msec at 320 mg/day. For haloperidol ($n=23$), mean DQTc was − 1.2, 6.6, and 7.2 msec at the 3 respective dose levels. No abnormal telemetry findings or QTc 3500 msec was observed.

Conclusion: At twice the recommended daily dose, oral ziprasidone showed marginal QTc increase from 160 mg/day, with no cardiovascular symptoms or QTc 3500 msec.

360. OPTIMAL DOSING OF ORAL ZIPRASIDONE: CLINICAL TRIAL DATA

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Objective: To elucidate optimal dosing of oral ziprasidone through analysis of clinical trial data.

Methods: We analyzed pooled efficacy (BPRS Total score), discontinuation, and AE data from 4 fixed-dose, placebo-controlled trials in which patients received ziprasidone 40 to 160 mg/day, and reviewed dosing and discontinuation data from 3 flexible-dose (maximum 160 mg/day), active-comparator trials of ziprasidone.

Results: In analyses of placebo-controlled trials, early and sustained improvement was demonstrated with doses 3120 mg/day ($P<0.01$ at Week 1; $P<0.05$ at Week 6). Doses = 80 mg/day were not associated with significant changes until Week 3. Improvement was generally dose related. Discontinuation rate within the first 14 treatment days was lower with doses of 120 and 160 mg/day (5.2%) than with doses of 40 and 80 mg/day (11.5%). The incidence of AEs was comparable across dosing groups. In the 3 flexible-dose trials, mean daily dose during flexible periods was 123 to 137 mg; discontinuation due to inadequate response was less common in the 2 studies allowing faster titration.

Conclusion: The superior, more rapid BPRS Total score improvement observed in placebo-controlled trials and dosing results from short-and long-term, flexible-dose studies support the titration of ziprasidone to 3120 mg/day in patients with acute schizophrenia.

Side Effects

361. LONGITUDINAL EFFECT OF OLANZAPINE ON FASTING SERUM LIPIDS: A RANDOMIZED, PROSPECTIVE, 4-MONTH STUDY

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Objective: To compare lipid profiles of schizophrenic patients treated with conventional antipsychotics or risperidone to those of patients switched to olanzapine.

Methods: Patients were randomized to 2 treatment groups: remain on current conventional antipsychotic or risperidone therapy ($N=27$) or switch to olanzapine 5–20 mg/day, ($N=27$). Fasting mean serum total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL), and triglycerides were collected monthly.

Results: Prior to randomization, all mean serum lipid levels were at, or exceeded, the upper limit of normal at baseline except for HDL. In patients switched to olanzapine, there was no significant within-group change baseline to endpoint in total cholesterol ($p=.69$) or triglycerides ($p=.81$). Moreover, these changes were

comparable to those in patients continuing on conventional antipsychotics or risperidone (between-group: cholesterol, $p = 0.69$; triglycerides, $p = 0.28$). Visit-wise results revealed increased cholesterol and triglyceride levels within the first month among patients switched to olanzapine, which returned to baseline by months 2 and 3, respectively.

Conclusion: Previous studies, mostly short term, usually found moderate triglyceride increases during olanzapine treatment; a minority also found cholesterol increases. Our four-month study found an initial rise in fasting serum lipids in patients switched to olanzapine that returned to pretreatment levels, and endpoint lipid levels were not significantly different from those in patients remaining on conventional antipsychotics or risperidone.

362. SWITCHING TO QUETIAPINE FROM OTHER ATYPICAL ANTIPSYCHOTICS IMPROVES SEXUAL DYSFUNCTION: PRELIMINARY RESULTS OF AN OPEN-LABEL STUDY

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Objective: To evaluate the effect of switching to quetiapine in patients with schizophrenia presenting with disturbing sexual dysfunction while treated with atypical antipsychotics.

Method: Multicenter, open-label, prospective study in patients with schizophrenia with subjectively disturbing sexual dysfunction who were previously treated with risperidone or olanzapine monotherapy. During a 6-week run-in period, patients received either risperidone or olanzapine and sexual dysfunction, amenorrhea and gynecomastia were evaluated using the UKU side effects rating scale. If the side effects persisted, patients were switched to quetiapine, and evaluation of sexual dysfunction, amenorrhea and gynecomastia was repeated after 3 months. Exclusion criteria included patients possibly in menopause or andropause, and those receiving concomitant medication known to alter sexual functioning.

Results: Preliminary results are available for 17 (15 male) of 30 subjects. Nine patients were initially treated with olanzapine (mean dose 21.9 mg/day) and eight with risperidone (mean dose 2.8 mg/day). A sexual desire problem was identified in 82% (14/17) of patients and improved after switching to quetiapine (mean dose 578 mg/day) in all patients. An orgasm problem was identified in 35% (6/17) of patients and gynecomastia in 35% (6/17) of patients; both problems improved in all patients after switching to quetiapine. Erectile dysfunction was identified in 59% (10/17) of patients and improved in 80% of cases. Amenorrhea was present in one female and corrected on switching to quetiapine treatment.

Conclusion: Results of this preliminary analysis suggest that sexual dysfunctions in patients treated with risperidone or olanzapine can be improved on switching to quetiapine.

363. DO ATYPICAL ANTIPSYCHOTICS DIFFERENTIALLY AFFECT BONE MINERAL DENSITY?

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Objective: Previous studies have indicated that classical neuroleptic treatment can affect bone mineral density(BMD), possibly as a result of prolactin elevation. The new generation antipsychotics differ in their propensity for hyperprolactinaemia. We therefore investigated the effect of risperidone, olanzapine and clozapine on BMD.

Methods: In 79 consecutive patients with schizophrenia spectrum disorder (male 53, female 26) and in age-matched controls (male 15, female 26) BMD was measured by ultrasound echography of the calcaneus. In addition prolactin levels were obtained in part of the patient population (male 28, female 16). Medication-treatment in the male-group consisted of risperidone (19), olanzapine (20), clozapine (14); in female group risperidone(8), olanzapine (11) clozapine (5). Mean treatment duration was over 18 months in all patients.

Results: In the male patient group BMD differences were: risperidone < clozapine < controls < olanzapine (0.524; 0.575; 0.583; 0.592 g/cm2). For the female group BMD differences were: risperidone < olanzapine < controls < clozapine (0.480; 0.527; 0.551; 0.587 g/cm2). These differences did not reach statistical significance. Prolactin levels, for men and for women respectively, were significantly higher for the risperidone group (805 and 1900 mU/L) as compared to olanzapine (217 and 401 mU/L) and clozapine (137 and 353 mU/L).

Conclusion: The lower ultrasound values found in risperidone-treated patients together with the concurrent higher prolactin levels suggest that risperidone may differ from non-prolactinelevating antipsychotics in its effect on bone mineral density. These data need to be confirmed in a larger population.

364. ARIPIPRAZOLE IS NOT ASSOCIATED WITH INCREASED DIABETES RISK: A LONG-TERM MODEL

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Background: Previous studies suggest an association between some of the newer antipsychotics and diabetes.

Methods: We used randomized clinical trial data ($N = 306$) to compare the projected risk of diabetes for patients on aripiprazole and placebo. The risk from baseline for diabetes at 7.5 years of maintenance treatment was estimated using a logistic regression model with risk factors for each individual patient, at baseline and 26 weeks. ANCOVA was used to compare the risk between treatment arms.

Results: At week 26, the observed changes in risk factors from baseline (SE) for placebo were: fasting plasma glucose (FPG) = 4.89 ± 2.96 mg/dL, high density lipoprotein (HDL) = − 2.41 ± 1.71 mg/dL, blood pressure (SBP) = − 3.93 ± 2.15 mmHg, and body mass index (BMI) = − 0.49 ± 0.30 kg/m2. The changes for the aripiprazole group were: FPG = 0.61 ± 2.33 mg/dL; HDL = − 3.51 ± 1.35 mg/dL; SBP = − 5.31 ± 1.70 mmHg; and BMI = − 0.54 ± 0.23 kg/m2. The change between treatment arms was not statistically significant (MANOVA, $p = 0.75$). After 26 weeks of therapy, the estimated changes in diabetes risk at 7.5 years were an increase of 6.42% ± 3.15% for placebo, and a decrease of 0.33% ± 2.48% for aripiprazole ($p = 0.10$), suggesting that aripiprazole does not increase the long-term risk for developing type 2 diabetes.

Conclusion: As patients with schizophrenia are at higher risk for diabetes than the general population, it is reassuring to have antipsychotic therapy that would not elevate this risk in these vulnerable patients.

365. THE LONG-TERM EFFECTS OF DEPOT ANTIPSYCHOTICS OR CLOZAPINE ON SEXUAL FUNCTIONING

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Background: The prevalence of sexual dysfunctions in patients with long term treatment with antipsychotics has hardly been studied and the available findings are not consistent. We therefore examined sexual side effects in patients who had been treated at least for six months with classical depot antipsychotics or clozapine.

Methods: In a target population of about 200 patients treated with classical antipsychotics or clozapine for more than half a year, 35 patients (21 classical, 14 clozapine) could be included. The patients were interviewed using the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), an interview based upon the UKU side effects rating scale (Lingjaerde et al., 1987; Knegtering and Castelein, 2001). The ASFQ includes semi-structured items assessing improvement or worsening of sexual functioning attributed to the use of antipsychotics.

Results: Libido reduction was reported in 33% of the patients in both treatment groups. There was a trend of less detrimental effects of classical antipsychotics on erections, orgasm and ejaculation compared to clozapine. The sample-size of the study was small, for this reason the identified differences between the groups did not reach statistical significance.

Conclusion: As the frequency of reported sexual dysfunctions in this long-term study is in line with reports in short-term studies, this study supports the hypothesis that sexual side effects do not subside over time. Definite conclusions of clozapine inducing less sexual side effects than classical antipsychotics cannot be drawn, due to the small sample-size and possible selection bias, but extending the study is warranted.

366. RETROSPECTIVE ASSESSMENT OF RISK FACTORS FOR TREATMENT EMERGENT GLUCOSE ABNORMALITIES DURING RANDOMIZED, DOUBLE-BLIND CLINICAL TRIALS OF MEDICATIONS FOR TREATMENT OF BIPOLAR DISORDER

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Background: We retrospectively examined a large database pooled from multiple randomized, double-blind clinical trials of medications for treatment of bipolar disorder.

Methods: Non-fasting glucose values were used to identify patients as exhibiting treatment emergent diabetes (TED, two non-fasting glucose values ≥ 200 mg/dl during the study, an endpoint non-fasting glucose value ≥ 200 mg/dl, new clinical diagnosis of diabetes, or addition of anti-diabetic medications). Individuals without repeated glucose values ≥ 140 mg/dl were considered to have normal glucose tolerance (NGT). Patient demographics and diabetes risk factors (age ≥ 45 years, body mass index (BMI) ≥ 25

kg/m2, hypertension, ethnic background, and elevated random glucose) were assessed in 1900 patients (olanzapine $n=1247$, haloperidol $n=170$, divalproex $n=105$, or placebo $n=378$).

Results: TED was present in 1% of patients with a median time to TED of 59 days. Comparing entry characteristics, the group of patients identified with TED ($n=20$) were more obese (BMI 36.0 ± 8.4 vs. 27.8 ± 6.6 kg/m2; $p<0.001$), had higher mean non-fasting glucose levels (137.6 ± 39.0 vs. 95.5 ± 15.3 mg/dl; $p<0.001$), and had a significantly greater percentage of patients with hypertension (35% vs. 13.4%, p=.013) and a non-Caucasian ethnicity (55% vs. 22.5%, p=.002) than the NGT cohort ($n=1897$). Significantly more patients with TED had at least 2 baseline risk factors for diabetes compared to the NGT cohort (95.0% vs. 38.2%, $p<0.001$); and all TED patients had at least one baseline diabetes risk factor.

Conclusion: In olanzapine monotherapy clinical trials for the treatment of bipolar disorder, the short-term risk factors for diabetes in patients overlapped those of the general population.

367. HOW VALID ARE RETROSPECTIVE EPIDEMIOLOGICAL STUDIES IN EVALUATING DIFFERENTIAL RATES OF DIABETES MELLITUS ATTRIBUTED TO ANTIPSYCHOTICS?

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Background/Objective: Although antipsychotics can cause glucose dysregulation and Diabetes Mellitus (DM), the relative risk is unclear. As DM is increasingly prevalent in the general population, with many causes, it is important to distinguish between a spurious and causal association with antipsychotics. Numerous articles in 2002–2003 have investigated the role that antipsychotics might play in the development of DM, but many are retrospective in design. The aim of this study was to critically appraise the quality of retrospective epidemiology studies examining antipsychotics as a risk factor for DM in psychiatric patients.

Methods: Embase, HealthStar, Medline, Pre-MEDLINE, PsycInfo were searched between 2002 and 2003, and conference abstracts were hand searched. Studies were checked for (i) adjustment for potential confounders, (ii) adherence to epidemiological principles of association.

Results: 17 suitable studies were identified, accounting for approximately 160,000 patients. We found lack of adjustment for DM family history, exercise, nutrition, and differential screening rates. Few attempted to screen patients for DM at baseline. Their retrospective nature prevented accurate analysis of the temporal relationship between the putative cause (antipsychotics) and effect (DM). The size and direction of the effect was inconsistent across studies.

Conclusion: Few studies accounted for important potential confounders in their analysis of antipsychotics as a risk factor for DM. Their retrospective design limited the confidence with which the association could be made. Well-designed prospective analyses that take into consideration the potential confounders and 'rules' of association are strongly recommended.

368. AMANTADINE FOR WEIGHT GAIN IN OLANZAPINE-TREATED PATIENTS

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Objective: To determine whether amantadine could attenuate weight gain or promote weight loss in patients who gained weight during olanzapine therapy.

Methods: The study included patients with schizophrenia, schizoaffective, schizophreniform, or bipolar I disorders, not manic or acutely psychotic (BPRS total score 45), treated with olanzapine for 1–24 months, and who had gained 5% of their initial body weight. Olanzapine (mean modal dose, 12.4mg/day) was coadministered with double-blind treatment of 100–300mg/day amantadine (Olz+Amt, $n=60$; mean modal dose, 235.6mg/day) or placebo (Olz+Plc, $n=65$). Weight was measured at each visit, and BPRS and MADRS were administered monthly for 16 weeks and again at 24 weeks.

Results: Visitwise analysis of weight showed that weight change from baseline (LOCF) in the Olz+Amt group was significantly different from the Olz+Plc group at Weeks 8 ($p=0.042$), 12 ($p=0.029$), and 16 (primary endpoint, −0.19 ± 4.58kg vs. 1.28 ± 4.26 kg, p=.045). Mean BPRS Total, Positive, and Anxiety Depression scores improved comparably in both groups. The Olz+Amt group had greater improvement in MADRS total score compared with the Olz+Plc group. There were no clinically meaningful between-group differences in safety parameters.

Conclusion: Amantadine was safe, well-tolerated, and promoted weight loss or attenuated weight gain in patients who had gained weight during olanzapine therapy.

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369. ANTIPSYCHOTICS AND METABOLIC IMPLICATIONS

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Background/Objective: Schizophrenic patients chronically treated with antipsychotic medications can gain weight and manifest some important metabolic abnormalities with many potential important medical and psychological consequences (1). Even if a large part of the recent literature in the field claims for a major incidence of those collateral effects in patients treated with atypical antipsychotics (2), the data are far from consistency. Aim of the work: To evaluate the influences of the chronic treatment with one typical (haloperidol) and 3 atypical (olanzapine, clozapine and risperidone) antipsychotics on weight and on different metabolic pathwais in a sample of chronic stabilized schizophrenic outpatients.

Methods: 52 chronic DSM-IV schizophrenics (40M, 12F, age range 18–60 ys) have been evaluated. The following indexes have been assessed: Nutritionale indexes: Body Mass Index (BMI), waist circumference. Metabolic pathwais: Lipidic metabolism, cholesterol, triglyceride), Glucidic metabolism (OGTT; Hb1ac), Homocysteine, Renal function (urea, creatinine), Liver function (ALT, AST, GGT, Bilirubin), A 2 (normal and abnormal) × 4 (antipsychotic treatments) contingengy table has been built for each metabolic index.

Results: No significant differences in the distribution of subjects by nutritional or metabolic indices were found.

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370. RISK FOR AKATHISIA IN PATIENTS WITH RECENT ONSET SCHIZOPHRENIA TREATED WITH RISPERIDONE AND HALOPERIDOL AND ITS ASSOCIATION WITH SUCIDALITY

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Background: Akathisia, a serious adverse effect, afflicts one-third of persons taking conventional antipsychotic medications for schizophrenia. It has been suggested that akathisia is a risk factor for suicide. The purpose of this analysis was to compare incidence and severity of akathisia in patients with recent onset schizophrenia treated with haloperidol ($n=277$) versus risperidone ($n=278$) in a randomized controlled trial and to assess the relationship of akathisia to suicide and suicidal ideation.

Methods: Akathisia was measured using the relevant physician and patient item from the ESRS scale. Incidents of suicidality were recorded on an adverse effects reporting form.

Results: There was no significant difference in akathisia ratings at baseline between the treatment groups. However during treatment, incidence and maximum severity of akathisia were significantly less among risperidone than haloperidol treated patients. Patients who were suicidal during the trial (9.4%, $n=26$, of haloperidol group, three completed suicides, vs. 7.2%, $n=20$ of the risperidone group, no completed suicides) had significantly higher self-reported levels of akathisia at baseline (0.66 sd 0.77, $n=44$) than those who were not (0.39 sd 0.68; $n=508$; $t=2.69$, $p=0.01$) and a trend suggesting higher maximum change on akathisia from baseline (.91 sd 0.77; $n=44$ vs. 68 sd.89; $n=504$, $t=1.65$, $p=0.07$). However there was no significant difference between levels of physician rated akathisia between suicidal and non-suicidal patients ($p<0.48$).

Conclusion: The results suggest that in early episode schizophrenia risperidone is associated with a lower risk for akathisia than haloperidol. Further, feelings of inner restlessness, or self-reported akathisia, predicts subsequent suicidality.

371. EFFICACY, DISCONTINUATION AND SIDE EFFECTS OF ATYPICAL ANTI-PSYCHOTICS IN THE FIRST EPISODE OF PSYCHOSIS

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Background: Patients in their first episode of a psychotic illness are believed to be both more sensitive to both the therapeutic and adverse effects of antipsychotic medication than chronic patients.

Methods: We examined the response to treatment in 33 patients meeting ICD-10 criteria for a first episode of schizophreniform

psychosis. All patients were treated with low doses of an atypical antipsychotic and were assessed with the PANSS and ANNSERS (side effect profile questionnaire) at baseline and 1 and 2 months after initiation of treatment.

Results: The mean total PANSS score at baseline was 73 (*SD = 24*). After 1 and 2 months of treatment it was 61 (*SD = 28*) and 51 (*SD = 18*) respectively. Despite the use of low doses of atypical medication, side effects were evident in 20% of patients at the end of month 1 and 25% at month 2. Overall approximately half the patients had discontinued their original antipsychotic medication after 2 months. This was due to side effects in one third of subjects, lack of efficacy in one third, and disengagement from services in another third.

Conclusion: First episode patients show a good symptomatic response to low dose antipsychotic medication, but a large proportion may require changes in medication during treatment of the acute phase.

372. DOUBLE BLIND PLACEBO CONTROLLED INVESTIGATION OF AMANTADINE FOR WEIGHT LOSS IN SUBJECTS WHO HAVE GAINED WEIGHT DURING TREATMENT WITH OLANZAPINE

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Objective: This study explores whether amantadine added to olanzapine therapy can halt or reverse weight gain in subjects who gained weight taking olanzapine.

Methods: Subjects were 21 adults who had gained weight on olanzapine who consented to a DBPC study of amantadine added to a healthy lifestyle program for weight loss. Olanzapine was continued for treatment of the psychotic disorder. Amantadine was begun at 100 mg qd and titrated up to 300 mg qd when tolerated. At baseline and at 12 weeks anthropomorphic measures, psychiatric status, side effects, fasting bloodwork and vital signs were assessed.

Results: The amantadine group consisted of 12 subjects (5 female) and the placebo group had 9 subjects (4 female). The two groups started at similar weight at baseline ($P>0.08$). Mean baseline weight for the amantadine group was 214.9 lbs (SD = 47.5) and for the placebo group was 213.7 (SD = 47.4). The average follow-up was 76.7 (SD = 17.3) days for the amantadine group, and 87.7 (SD = 3.6) days for the placebo group. By the end of study, significantly more patients experienced weight loss in the amatadine group than control group ($p = 0.02$). The numbers of patients with weight loss, weight gain and no change were 8, 4, 1 in the amatadine as compared to 1, 1, and 7. The average change in weight for the amantadine group was -0.75 lbs ($\pm$ SD = 7.8) and for the placebo group was 8.69 lbs ($\pm$ SD = 11.73) ($p = 0.03$ for the ANCOVA test adjusting for baseline weight using ITT population with last observation carry forward).

373. ORAL GLUCOSE TOLERANCE IN PATIENTS TREATED WITH OLANZAPINE 20, 30, OR 40 MG/DAY

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Objective: To determine whether changes in glucose tolerance are observed during short-term treatment with olanzapine ≥ 20 mg/day.

Methods: Patients with schizophrenia, schizoaffective disorder, or bipolar mania who met entry criteria of fasting blood glucose < 126 mg/dL received olanzapine 20 mg/day for 10 days. Patients were then randomized to 10 days of double-blind treatment with olanzapine 20, 30, or 40 mg/day. For 10 additional days, 30 mg patients received olanzapine 40 mg/day; all other patients remained on their same dose. A 2-hour oral glucose tolerance test (OGTT) was performed at baseline (Day 1) and endpoint (Day 21) of double-blind treatment. Two-hour glucose levels were categorized as follows: < 140 mg/dL = normal glucose tolerance (NGT), 140–199 mg/dL = impaired glucose tolerance IGT), ≥ 200 mg/dL = diabetes (DM).

Results: Thirty patients had both baseline and endpoint OGTTs (20 mg, $n = 10$; 30–40 mg, $n = 9$; or 40 mg, $n = 11$). Mean baseline-to-endpoint change in 2-hour OGTT glucose values did not appear to be dose dependent (20 mg = 4.68 ± 38.37 mg/dL, 30–40 mg = 6.4 ± 21.20 mg/dL, 40 mg = -4.58 ± 33.76 mg/dL). Two patients (20 mg, 40 mg) were categorized as having DM at both baseline and endpoint by 2-hour OGTT glucose values. One patient (20 mg) worsened from IGT to DM and two patients (20 mg, 40 mg) improved from IGT to NGT. The mean area under the glucose curve did not differ significantly between doses.

Conclusion: In this short-term pilot study, no consistent changes were observed in mean glucose excursions or glucose tolerance categories during OGTTs among patients treated with olanzapine 20–40 mg/day.

374. FASTING LIPID PROFILES OF PATIENTS WITH SCHIZOPHRENIA TREATED LONG-TERM WITH OLANZAPINE, RISPERIDONE, OR TYPICAL ANTIPSYCHOTICS

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Objective: To compare fasting lipid profiles of stable, normoglycemic patients with schizophrenia or schizoaffective disorder treated long-term with olanzapine, risperidone, or typical antipsychotics.

Methods: This cross-sectional study included 184 stable, matched (sex, BMI) patients who had been treated continuously for ≥ 1 year with olanzapine (7.5–25.0 mg/day; $n = 67$), risperidone (2.0–7.5 mg/day; $n = 65$), or typical antipsychotics (various agents, doses; $n = 52$). Patients with fasting blood glucose ≥ 110 mg/dL were excluded from the analysis. Blood samples were collected after an 11 ± 1-hour observed fast. Fasting lipids (triglycerides [TG], cholesterol, lipoproteins), glucose, insulin, insulin sensitivity [HOMA-IR]), and predicted 10-year cardiovascular disease (CVD) risk (Framingham model) were compared.

Results: Overall, the 3 treatment groups were well matched. The olanzapine group had significantly higher mean (but not median) fasting TG levels than the risperidone group. However, 3 influential outliers were identified in the olanzapine group; no significant differences when these values were removed. No significant between-group differences were observed in mean cholesterol levels (total, LDL, HDL), LDL particle size, or total cholesterol/HDL ratio. VLDL, apolipoprotein B, and LDL particle concentration were significantly higher during olanzapine than risperidone treatment. No significant differences were seen in fasting glucose, insulin, HOMA-IR, or predicted 10-year CVD risk.

Conclusion: For these stable patients with schizophrenia on long-term antipsychotic therapy, modest but significant differences in fasting TG levels and some qualitative differences in lipoproteins were observed between olanzapine and risperidone groups. The cross-sectional study design and TG outliers limit the interpretation of these findings. Nonetheless, predicted 10-year CVD risk was comparable between treatment groups.

375. THE INCIDENCE OF TARDIVE DYSTONIA AND TARDIVE DYSKINESIA IN PATIENTS ON LONG-TERM ANTIPSYCHOTIC TREATMENT

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Background: Previously we reported about the prevalence of and the risk factors for tardive dyskinesia, tardive dystonia, parkinsonism and akathisia in a cross-sectional study of a cohort of African-Caribbean psychiatric inpatients on the island of Curaç ao[1,2]. We conducted a nine-year follow-up study with this cohort to reveal incidence rates for tardive dystonia and tardive dyskinesia. The incidence of tardive dystonia has never been published.

Methods: During the study period patients were reinvestigated six times in the same way as reported formerly[2]. Tardive dystonia or tardive dyskinesia was defined according to the RD-TD for a persistent case[3]. Two incidence cohorts were defined: first those patients who were free of tardive dystonia (or tardive dyskinesia) at baseline and second those patients who were free of tardive dystonia (or tardive dyskinesia) at baseline and at one-year follow-up.

Results: In the first cohort the mean incidence of tardive dystonia was 0.7% and in the second cohort it was 0.1%. In the first cohort the incidence of tardive dyskinesia at each assessment was 13.5, 10.9, 9.5, 5.5 and 4.9% (mean incidence 9.9%); the corresponding results for the second cohort were 6.1, 3.9, 4.7 and 3.5% (mean incidence 4.9%).

Conclusion: The risk of tardive dystonia is low, but psychiatric patients receiving long-term treatment with antipsychotics remain at risk for tardive dyskinesia.

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376. INCIDENCE OF PRESUMPTIVE TARDIVE DYSKINESIA IN ELDERLY PATIENTS TREATED WITH OLANZAPINE OR CONVENTIONAL ANTIPSYCHOTICS

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Background: Incidence rates of presumptive tardive dyskinesia (TD) were compared in acutely psychotic or agitated elderly patients treated with olanzapine (OLZ) or conventional antipsychotic (CNV) drug therapy.

Methods: Patients without TD were randomized to OLZ (2.5–20 mg/day; $n = 150$) or CNV (dosed per label; $n = 143$) drug

therapy, and underwent a 6-week drug tapering/drug initiation period, followed by reassessment of TD. Patients who remained without TD after six weeks were treated with OLZ or CNV for up to 1 year. The primary analysis was time-to-TD incidence, defined as a rating on the Abnormal Involuntary Movement Scale (AIMS) of either: A) moderate severity in 1 body region or mild severity in 2 or more body regions, or B) moderate severity in 1 body region alone.

Results: Patients in CNV group were at a greater risk for presumptive TD than patients in OLZ group (criteria A or B, $p < 0.05$). Incidence of presumptive TD that persisted for at least 1 month was lower and differed between treatments only for criterion B (moderately severe symptoms; $p < 0.05$).

Conclusion: In elderly patients who are at a greater risk for developing TD, these data revealed a lower risk of developing dyskinetic symptoms in patients treated with olanzapine versus conventional antipsychotics.

377. THE EFFECT OF CLOZAPINE ON FACTORS CONTROLLING GLUCOSE HOMEOSTASIS

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Objective: This prospective study examines the effect of clozapine on factors determining glucose homeostasis.

Method: The sample consisted of all patients commencing clozapine within the South London and Maudsley hospitals during one year. Insulin, growth hormone (GH), insulin-like growth factor-1 (IGF-1), and IGF binding protein-1 (IGFBP-1) were measured in 20 patients (mean age 30.5 yrs (SD: 7.4), 45% female) before, and after, an average of 2.5 (SD: 0.95) months of clozapine treatment. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR).

Results: Patients showed insulin resistance at baseline (mean HOMA-IR level = 3.88, SD = 2.93), which was unaffected by clozapine ($p = 0.37$). Baseline IGFBP-1 was low (3.1 ìg/l, SD = 3.7; expected value >15), indicating long-term insulin resistance. GH ($t = 1.8$, $df = 15$, $p = 0.088$), IGF-1 ($t = 0.58$, $df = 15$, $p = 0.57$), and IGFBP-1 ($t = 1.2$, $df = 15$, $p = 0.24$) were not significantly changed by clozapine treatment. There was no correlation between clozapine blood levels and insulin ($p = 0.5$), GH ($p = 0.7$), IGF-1 ($p = 0.5$), or IGFBP-1 ($p = 0.5$) levels on clozapine.

Conclusion: Patients with treatment resistant schizophrenia show long-term insulin resistance, which may be related to treatment with antipsychotics or the disease process. Clozapine does not alter insulin, GH, IGF, or IGFBP-1 within three months of commencing treatment, suggesting that glucoregulatory changes are secondary to a central effect of clozapine on glucose sensing.

378. METABOLIC SYNDROME: A COMPARISON BETWEEN OLANZAPINE, ARIPIPRAZOLE, AND PLACEBO

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Background: Metabolic syndrome constitutes a set of risk factors for diabetes and coronary heart disease.

Methods: We compared the incidence of metabolic syndrome after 26 weeks in two trials of aripiprazole treatment in patients with schizophrenia. Criteria for metabolic syndrome were based on clinically relevant changes in, and levels of, constituent risk factors, consistent with national guidelines. Survival analysis was performed on the individual studies (Trial 1, $N = 314$; Trial 2, $N = 306$) and on pooled data from both studies.

Results: The pooled analysis showed a cumulative incidence of metabolic syndrome (SE) of 19.2%, 4.0% for olanzapine, 12.8%, 4.5% for placebo, and 7.6%, 2.3% for aripiprazole (log-rank $p = 0.003$). The cumulative incidence for aripiprazole did not differ between the two trials (6.8%, 2.8% versus 8.3%, 3.7%, $p = 0.88$). It did differ significantly between aripiprazole and olanzapine in Trial 1 (log-rank $p = 0.007$), but not between aripiprazole and placebo in Trial 2 (log-rank $p = 0.23$). In Trial 1, the hazard ratio (95% CI) for aripiprazole versus placebo was 0.53 (0.18; 1.54). In Trial 2, it was 0.31 (0.12; 0.77) for aripiprazole versus olanzapine—a 69% relative risk reduction for aripiprazole over olanzapine.

Conclusion: The findings suggest an increased risk for metabolic syndrome among olanzapine patients, and a comparable risk among aripiprazole patients versus placebo. The cardiovascular consequences of antipsychotic therapy warrant consideration by physicians.

379. LONG-TERM WEIGHT EFFECTS OF ARIPIPRAZOLE VERSUS OLANZAPINE

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Objective: This study compared the long-term effects of aripiprazole and olanzapine on weight in patients with acute relapse of schizophrenia.

Methods: A total of 317 patients were randomized to aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day) for 26 weeks in this double-blind, multi-center study. The proportion of patients experiencing significant weight gain (7% increase) from baseline to endpoint was the primary outcome measure.

Results: Among patients remaining on therapy, more olanzapine-treated patients experienced 7% weight gain than aripiprazole-treated patients throughout the study. Mean weight change differed significantly between the groups at weeks 6 and 26; at week 26 there was a mean weight increase of 4.23 kg with olanzapine and a mean weight loss of 1.37 kg with aripiprazole ($P < 0.001$). Differences favoring aripiprazole were also seen for changes in total cholesterol, HDL cholesterol, and triglycerides. The rate of clinical response did not differ between aripiprazole and olanzapine, either acutely (week 6) or in the number of patients remaining in response and on therapy at week 26. The incidence of weight gain and dyslipidemias were significantly lower with aripiprazole than with olanzapine while clinical response was comparable between treatments.

Conclusion: These effects on weight and lipids may lead to a more advantageous long-term metabolic profile in patients treated with aripiprazole compared with olanzapine.

380. EXTRA-PYRAMIDAL SIGNS AND SYMPTOMS (EPS) IN RECENT ONSET SCHIZOPHRENIA: A COMPARISON OF RISPERIDONE AND HALOPERIDOL

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Background: Treatment with second-generation antipsychotics has been associated with fewer extra-pyramidal signs (EPS) compared with older antipsychotics. This advantage could reflect a dose related phenomena. To test this we analyzed EPS for equal doses of risperidone and haloperidol.

Methods: 555 first episode patients were enrolled in a large, multi-national, randomized, controlled, flexible dose (1–6 mg/day) study (risperidone $n = 278$; haloperidol $n = 277$). EPS were rated using the ESRS (Chouinard et al, 1980).

Results: Patients on risperidone experienced less parkinsonism (maximum change from baseline) as compared to those receiving haloperidol (3.01 sd 4.43 vs. 3.92 sd 5.20, $t = 2.20$, $p < 0.03$). This difference was more pronounced amongst patients who had no exposure to antipsychotic drugs prior to enrolling into this study (3.85 sd 4.52 vs. 5.88 sd 5.94; $t = 2.54$, $p < .001$). More importantly, when EPS was examined for identical doses of haloperidol and risperidone, there were 20% to 38% fewer reported EPS with risperidone vs. haloperidol for each dose examined (1–6 mg/day), with differences evident at 1 mg/day (Log Rank 5.27, $p < 0.02$). This was also true when emergent dyskinesia was examined separately using the Schooler and Kane criteria (Log Rank 5.27, $p = 0.02$).

Conclusion: Risperidone was associated with the induction of less EPS than haloperidol in identical doses, even at 1 mg. Furthermore, the effect was not limited to a particular dose of risperidone. Risperidone appeared to have a distinct advantage in terms of reduced propensity to induce EPS, which was most pronounced in never before treated patients. The implications of these findings are considerable.

381. HYPERLIPIDEMIA IN PERSONS USING ANTIPSYCHOTIC MEDICATION

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Background: High serum triglyceride and total cholesterol levels have been associated with antipsychotic medication. We studied the prevalence of hyperlipidemia in subjects with and without of antipsychotic medication in prospective general population based birth cohort.

Methods: The study sample consisted of 5654 members of the unselected Northern Finland 1966 Birth Cohort, who participated in the 1997–1998 clinical excamination at 31 years of age. Blood samples were taken after an overnight fast, and

serum total cholesterol (TC), high density lipoprotein (HDL) and triglycerides (TG) were determined. The sample was analysed in four categories: 1) atypical, 2) typical, 3) atypical and typical (altogether = 45) and 4) no antipsychotic medication ($n = 5609$).

Results: We found high lipid levels in persons with both atypical and typical medication (mean TC 233 mg/dl, TG 162 mg/dl). Mean TC and TG were also high in the subjects with only typical medication (215 mg/dl and 124 mg/dl, respectively). The prevalence of hypercholesterolemia, high LDL-cholesterol and hypertriglyceridemia were high in persons using of antipsychotic medication (31.1%, 20.0% and 22.2%, respectively) compared to persons without such medication (12.2%, 10.2% and 7.0%, respectively).

Conclusion: Lipid levels in subjects with both atypical and typical medication and with only typical medication were high even in young age. As these persons are at special risk for hyperlipidemia, their lipid levels should be regularly monitored, and cholesterol lowering diet, as well as medication, should be considered.

382. TOLERABILITY OF OUTPATIENT ANTIPSYCHOTIC TREATMENT: 6-MONTH RESULTS FROM THE EUROPEAN SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES (SOHO) STUDY

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Objective: The European SOHO study is an observational study of the treatment of schizophrenia. We report on the tolerability profiles of antipsychotics during the first 6 months of treatment.

Methods: The rate of Extrapyramidal Symptoms (EPS), anticholinergic use, weight gain and sexual and endocrine dysfunctions were assessed in 8421 outpatients. Cohorts of patients were defined based on the antipsychotic they started at the baseline visit. Patients who initiated a new antipsychotic without discontinuing their existing antipsychotic medication were assigned to the cohort corresponding to the antipsychotic initiated at baseline.

Results: A higher proportion of patients in the oral (23.0%) and depot (30.3%) conventional antipsychotics, risperidone (23.7%), and quetiapine (13.6%) cohorts experienced more EPS and needed the co-prescription of an anticholinergic than patients in the olanzapine (10.1%) cohort. Patients treated with olanzapine (26.1%) were less likely to have sexual dysfunctions compared to patients in the other cohorts (risperidone: 32.8%; quetiapine: 26.9%; amisulpride: 35.9%; oral typical: 36.8%; depot typical: 33.0%), except for patients in the clozapine cohort (32.9%). Increases in weight and Body Mass Index (BMI) occurred in all cohorts (risperidone: +1.4 kg, 0.5 kg/m^2; quetiapine: +0.6 kg, 0.2 kg/m^2; amisulpride: +1.4 kg, 0.5 kg/m^2; oral typical: +1.1 kg, 0.4 kg/m^2; depot typical: +1.1 kg, 0.4 kg/m^2), but were slightly greater in the olanzapine (2.4 kg, 0.9 kg/m^2) and clozapine (2.3 kg, 0.8 kg/m^2) cohorts.

Conclusion: Antipsychotics clearly have different tolerability profiles. Olanzapine and clozapine seem to be the better tolerated antipsychotic medications.

383. LOW BONE MINERAL DENSITY ASSOCIATED WITH INCREASED PROLACTIN AND AGING IN PSYCHIATRIC PATIENTS TREATED WITH PROLACTIN-ELEVATING ANTIPSYCHOTICS

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Objective: The objective of this study was to determine the prevalence of low bone mineral density in schizophrenia patients treated with prolactin (PRL)-elevating antipsychotics (APD), and to identify factors influencing bone density.

Methods: Schizophrenic patients ($N = 402$), who had been treated with conventional APD or risperidone for 3 months, participated in a 1-day trial to estimate rates of hyperprolactinemia, and associated morbidity. Patients taking PRL-elevating concomitant medications were excluded. Bone density (T-score) was determined by ultrasonography. Bone metabolism was assessed by measuring serum osteocalcin (OCN). Logistic regression was used to determine the effect of age, length of APD treatment, and PRL on T-scores and OCN for both males and females.

Results: The frequency of low bone mass (T-scores ≤ -1) was 20.4% in females and 28.6% in males. Decreased T-scores were significantly associated with increased age for both males ($p = 0.007$) and females ($p = 0.0001$). Length of APD treatment was not significantly associated with T-scores, when controlling for age in either gender. In addition to age, decreased T-scores were significantly associated with increased PRL in males ($p = 0.05$), but

not in females. Increased OCN was significantly associated with increased PRL in both females ($p = 0.03$) and males ($p = 0.05$), with increased age ($p < 0.01$) in females but younger age ($p < 0.01$) in males. In conclusion, decreased bone mineral density was highly prevalent in a chronic psychiatric population treated with PRL-elevating APDs.

Conclusion: Identified risk factors appeared to be increased age and increased PRL for both females and males. Bone demineralization may be a common comorbidity in psychiatric patients treated with PRL-elevating APDs.

384. ZIPRASIDONE VS OLANZAPINE: CHANGE IN CHD RISK DURING A 6-WEEK TRIAL

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Objective: In a 6-week randomized, double-blind trial in schizophrenia, olanzapine was associated with significant increases in triglycerides, low-density lipoprotein cholesterol (LDL), and total cholesterol (TC), while ziprasidone was not. We compared changes in coronary heart disease (CHD) risk in olanzapine-and ziprasidone-treated patients in this trial.

Methods: We analyzed data from participants ¡Ý30 years, using a Framingham data-based algorithm (*Circulation* 1998; 97:1837–1847) calculating percentage risk of CHD over 10 years from age, gender, smoking status, presence or absence of diabetes, high-density lipoprotein cholesterol (HDL), LDL or TC, and blood pressure. Baseline-to-endpoint changes in percentage age-adjusted CHD risk for men and women in ziprasidone and olanzapine treatment groups were compared using ANCOVA.

Results: Mean age was approximately 42 years for each group. In olanzapine-treated men ($n = 55$), risk of CHD increased by 0.8% (baseline, 4.2%), while in ziprasidone-treated men ($n = 44$), risk decreased by 0.2% (baseline, 4.5%) ($P < 0.05$). Olanzapine-treated females ($n = 18$) had a 0.2% decrease in risk (baseline, 3%), while ziprasidone-treated females ($n = 21$) had a 0.4% increase (baseline, 2.5%) ($P =$ NS). Analysis by gender of treatment-associated changes in lipids found significant changes in TC, LDL, and triglycerides in olanzapine-treated men of all ages ($n = 82$) versus ziprasidone-treated men ($n = 69$) ($P < 0.005$); changes in triglycerides in olanzapine-treated women ($n = 32$) versus ziprasidone-treated women ($n = 44$) trended toward significance ($P = 0.09$).

Conclusion: In a 6-week trial, men receiving olanzapine experienced increased CHD risk that was significant versus a decrease among men receiving ziprasidone. Changes in risk did not differ significantly between olanzapine-and ziprasidone-treated women. These results paralleled changes in lipid profile.

385. ANTIPSYCHOTIC DRUGS AND SEXUAL FUNCTION

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Background: Sexual function is an important aspect of human experience, which may significantly contribute to quality of life in patients with schizophrenia (Aizenberg et al., 1995). Antipsychotic drugs can impact upon sexual function.

Methods: A randomised controlled trial compared the impact of atypical versus conventional drugs on sexual function and quality of life in 48 patients with schizophrenia, taking conventional drugs at baseline. The measures used were the self-report Derogatis interview for sexual function (Derogatis, 1997) and Heinrichs QLS (Heinrichs, 1984). Assessments were carried out at baseline and 12 weeks after a switch from conventional antipsychotic treatment to either a conventional or an atypical antipsychotic drug.

Results: A statistically significant increase was found for Derogatis total score at 12-week assessment, compared to baseline, for patients randomised to an atypical antipsychotic drug, compared to patients receiving a conventional agent, using the baseline score as a covariate ($F = 6.684$, $p = 0.014$). No statistically significant changes in quality of life scores were seen over the same time period in either group.

Conclusion: These findings suggest that switching from conventional to atypical antipsychotic treatment results in improved sexual function. No change in sexual function was seen in patients who switched from one conventional drug to another. The improvement in sexual function was not linked to an improvement in measured quality of life.

386. STRUCTURAL BRAIN ABNORMALITIES ASSOCIATED WITH TARDIVE DYSKINESIA IN PEOPLE WITH SCHIZOPHRENIA: A VOXEL-BASED MORPHOMETRY STUDY

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Objective: Structural neuroimaging studies have demonstrated an association between schizophrenia and brain morphological

abnormalities. However, the relationship between such changes in patients who develop tardive dyskinesia (TD) is still uncertain. We aimed to test whether morphological brain abnormalities are present in people with schizophrenia who develop TD, and if so, whether they are different, either in extent or location, from those in people with schizophrenia alone.

Methods: Three groups of right-handed male subjects were recruited. Two groups of 15 each, fulfilling ICD-10 diagnosis for schizophrenia, were identified: one group exhibited orofacial TD and the other had no evidence of this condition. A further 15 normal controls were also recruited. 3-D structural MRI scans were acquired using a T1 weighted MP-RAGE sequence. The two patient groups had comparable duration of illness and were matched for current antipsychotic medications. Their scans were processed using fully automated and operator independent voxel-based morphometry technique within multiple linear regression analysis.

Results: The patients with schizophrenia alone showed regional grey matter reductions in the left superior temporal gyrus ($p < 0.05$ corrected for multiple comparisons over the whole brain). The schizophrenia group with TD showed more extensive grey matter reductions in the left superior temporal gyrus, left hippocampus and bilateral temporal poles.

Conclusion: Our study findings support previous reports that schizophrenia is associated with predominant left temporal lobe changes. However, we also found more extensive morphological changes in patients with both schizophrenia and TD, which supports earlier suggestions that orofacial TD may be a core feature of schizophrenia, often uncovered by antipsychotic medication and ageing.

387. BODY COMPOSITION CHANGES IN PATIENTS WITH SCHIZOPHRENIA

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Objective: Increases in weight, BMI, glucose and lipid levels are important problems in patients with schizophrenia, especially when treated with neuroleptics. These facts motivate the study of body composition variables in more detail.

Methods: 28 patients with DSM-IV diagnosed schizophrenia (10 neuroleptic naïve) and 17 healthy controls were included in the study. There were no significant differences in age, gender, weight or BMI between the two groups. Percentages of body fat (%BF) and intracellular water (%ICW) were measured with a multi-frequency bioelectrical impedance analyser (BIA). Percentage of water in fat free mass (%WFFM) was calculated from BIA and calliper measurement in a three-compartment model.

Results: The mean%WFFM was 69.4 ± 2.6 in patients and 71.5 ± 2.2 in controls ($p < 0.01$). Intra-and extracellular water compartments also differed with mean%ICW 56.4 ± 3.1 in the patients and 58.8 ± 3.2 in the controls ($p < 0.02$).%ICW correlated inversely with duration of disease ($r = -0.38$, $p < 0.05$). Fluid levels tended to be lower also in the neuroleptic naïve patients ($n = 10$) with mean $68.8 \pm 2.5\%$ for WFFM ($p = 0.01$) and $56.8 \pm 2.6\%$ for ICW ($p = 0.09$).%BF was 28.5 ± 8.6 in patients compared to 22.4 ± 9.1 in controls ($p < 0.04$). No difference in%BF was seen between unmedicated patients and controls. Body fat correlated with duration of disease ($r = 0.51$, $p < 0.01$).

Conclusion: A general dryness with lower%WFFM as well as lower proportion of%ICW was found in patients with schizophrenia. These findings appear to be independent of medication status. An elevation in percent body fat was seen in the medicated patients.

388. THE METABOLIC AND CLINICAL EFFECTS OF OLANZAPINE AND QUETIAPINE: PRELIMINARY FINDINGS FROM A RANDOMIZED SINGLE-BLIND TRIAL IN PATIENTS WITH SCHIZOPHRENIA

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Objective: We compared the effects of olanzapine and quetiapine on plasma leptin, lipid, and fasting blood glucose (FBG) levels, and on symptom severity in patients with schizophrenia.

Methods: Twenty two female subjects (age mean: 35.3 ± 14.8) diagnosed per DSM-IV criteria were randomized to olanzapine ($n = 10$) or quetiapine ($n = 12$). Plasma total cholesterol, HDL, LDL, VLDL, FBG and leptin levels were measured and body mass index (BMI) was noted biweekly for 6 weeks. Symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptom (SAPS).

Results: Mean $\pm$ sd olanzapine and quetiapine doses were 20.0 ± 2.0 and 833.3 ± 87.3, respectively. Two cases in the quetiapine group dropped-out at the end of 4 weeks because of lack of response. The percent body weight (7.1% vs 3.7%), plasma leptin (273.3% vs 52.9%), total cholesterol (17.3% vs 8.0%), LDL (31.4% vs 12.2%), and VLDL (8.1% vs 1.7%) changes between week 1 (W1) and week 6 (W6) were greater for olanzapine. While W1-6 changes in the BMI ($p = 0.022$), total cholesterol ($p = 0.005$), LDL ($p = 0.008$), VLDL ($p = 0.047$), leptin ($p = 0.007$), SAPS ($p = 0.005$), and SANS total scores ($p = 0.016$) were significant in the olanzapine group, the significant change produced by quetiapine treatment was limited to the total SANS score ($p = 0.041$).

Conclusion: These preliminary findings suggest that, compared to quetiapine, the metabolic effects of olanzapine might be more pronounced. While both medications seemed to be effective in reducing negative symptoms, only olanzapine seemed to reduce positive symptoms significantly in the first 6 weeks.

389. DEVELOPMENT OF A WEIGHT MANAGEMENT BEHAVIOURAL PROGRAMME FOR PATIENTS WITH SEVERE MENTAL ILLNESS: IMPACT AT 3 YEARS

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Background: Obesity is major physical health concern for psychiatric patients with schizophrenia and bipolar disorder. The evidence base for managing obesity in this population is small.

Methods: Our multi-disciplinary team developed a weight management strategy based on a behavioural intervention. The programme included educating the patient about weight loss and weight management, advising about healthy eating and exercise. Sessions were in groups, weekly, lasting one hour and comprised of an 8-week rotational cycle. Patients (schizophrenia or bipolar disorder) in this study self-referred. All 70 patients who attended the clinic were included in this naturalistic study. Mean BMIs for patients entering the study were 32.5 (SD 5.1). Mean number of sessions attended was 33.69 (SD 34.9).

Results: Patients achieved a mean weight loss of 4.97 kg. (SD 5.5) at a mean rate of -0.25 kg per session (SD 0.3). Weight loss was highly correlated with number of sessions attended ($p = 0.0001$) and appeared to be independent of other factors, including initial BMI or medications, including clozapine.

Conclusion: This naturalistic study demonstrates the long-term value of a weight management programme at 3 years and supports the hypothesis that weight loss can be achieved using a simple behavioural intervention in motivated psychiatric patients. Potentially, weight gain is manageable and this should reduce the need to switch medication and help with compliance.

390. ALTERATIONS OF GLUCOSE METABOLISM UNDER TREATMENT WITH CLOZAPINE VS. AMISULPRIDE

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Background: Alterations of glucose metabolism during treatment with second generation antipsychotics have been recently reported.

Methods: We conducted a prospective investigation (duration of 16 weeks) of patients diagnosis with schizophrenia (ICD-10) who received either amisulpride or clozapine in order to study alterations of glucose metabolism.

Results: So far we included 25 patients. Thirteen of them received clozapine; Five of them were male and eight female. Twelve patients received amisulpride. Seven of them were male and five female. Amisulpride was administered with a mean dose of 489 ($\pm$ 166.3)mg/d and clozapine with a mean dose of 250 ($\pm$ 96.7) mg/d. The BMI in the clozapine group was 25.1 ($\pm$ 4.6) at base line and 25.6 ($\pm$ 4.3) at endpoint. The BMI in the amisulpride group was 29 ($\pm$ 9.8) at baseline and 28.5 ($\pm$ 9) at end point. Our results show that there was no elevation of fasting glucose and of glucose levels after OGTT in the amisulpride group while there were 7 patients in the clozapine group who had elevated fasting glucose and elevated glucose levels after OGTT. We did find a significant increase of HOMA-IR indices in patients treated with clozapine; we did not find increased HOMA-IR indices in patients treated with amisulpride.

Conclusion: These results are preliminary and will be supported by higher numbers of probands until twenty are in each group.

391. FLUMAZENIL TREATMENT OF COMATOSE CLOZAPINE INTOXICATION

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Background: Clozapine overdose may result in intoxication and coma. We treated three cases of coma in clozapine intoxication with flumazenil.

Case Reports: Mr. A, 72 years, was treated regularly with pimozide 6 mg, lithium carbonate 400 mg, acetaminophen 500 mg t.i.d., temazepam 10 mg and lorazepam 1 mg. Erroneous medication dispensing of 100 mg clozapine and 1 or 2.5 mg lorazepam led to coma. Intravenous injection of 0.5 mg of flumazenil showed no effect. Mrs. B, 77 years, was regularly prescribed cisordinol 2 mg t.i.d., prednisolone 10 mg and 5 mg, carbamazepine 200 mg t.i.d. and oxazepam 10 mg b.i.d. Through an error in medication dispensing she ingested 100 mg clozapine, 10 mg oxazepam and 400 mg norfloxazine and fell into a coma. She showed no effect on an intravenous injection of 0.4 mg of naloxone, but she awoke quickly after injection of 0.5 mg of flumazenil and remained alert. 44-year-old Mrs. C suffers from Huntington's disease. Her stable medication was diazepam 2 mg t.i.d., haloperidol 10 mg t.i.d., ibuprofen 200 mg t.i.d. and pantozol 40 mg. Clozapine was titrated in daily steps of 12.5 mg. When reaching a daily does of 175 mg she became comatose. Intravenous injection of 0.5 mg of flumazenil led quickly to full consciousness, but only for 5 minutes. All medications were terminated and she recovered the next day.

Conclusion: Flumazenil was an effective antidote in two of three cases of comatose clozapine intoxication and concomitant benzodiazepine treatment. In the first case the flumazenil dose may have been too low. Flumazenil may antagonize benzodiazepines at the GABA-receptor which is potentiated by the action of clozapine at specific GABA-ergic interneurons.

392. DOES BMI TRULY REFLECT THE PROGNOSTIC SIGNIFICANCE OF WEIGHT GAIN INDUCED BY ATYPICAL ANTIPSYCHOTICS?

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Objective/methods: The aim of this study was to determine the location of antipsychotic-induced weight gain, using BMI, waist to hip ratio (WHR) and visceral fat (IAF) deposition, in first episode, drug naïve patients with schizophrenia ($n = 19$) (BMI = 24.6 kg/m2) and matched controls (BMI = 23.0 kg/m2). Patients ($n = 16$) were re-tested after 6 months of treatment with either olanzapine or risperidone.

Results: At baseline, patients with schizophrenia, had significantly greater WHR (0.84 ± 0.02 vs. 0.91 ± 0.02; $t(18) = 2.8$, $p < 0.008$) and had more IAF (116.8 ± 20.2 cm2) than control subjects (38.0 ± 4.8 cm2) ($t(18) = 3.80$, $p < 0.0001$). Treatment increased BMI (24.6 ± 0.73 vs. 29.4 ± 0.82; $F(2,51) = 3.38$, $p < 0.04$) though did not result in a significant increase in WHR (0.91 ± 0.02 vs. 0.93 ± 0.03; $F(2,51) = 5.86$, $p < 0.005$) or IAF (116.8 ± 20.2 cm2 vs. 131.7 ± 20.9 cm2; $p =$ NS). The increase in IAF did not differ between those given either agent (26.9 ± 12.1 cm2 vs. 18.24 ± 11.44 cm2, respectively; $t(16) = 0.50$, $p < 0.63$).

Conclusion: Therefore, a better of indicator of the prognostic significance of antipsychotic-induced weight gain may be WHR and IAF, as measured by CT scanning as opposed to the BMI.

393. GLYCEMIC CONTROL AND PLASMA LIPIDS IN LONG-TERM TREATMENT WITH ARIPIPRAZOLE

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Background: Aripiprazole is a new antipsychotic agent associated with minimal weight gain.

Methods: The effects of long-term aripiprazole treatment on metabolic parameters were examined in a 26-week study comparing aripiprazole with placebo for prevention of relapse in patients with chronic stable schizophrenia. Glucose, plasma lipid, and glycosylated hemoglobin (A1C) levels were determined from fasted blood samples collected during the study.

Results: Mean changes in fasting plasma glucose levels from baseline to endpoint were minimal with both aripiprazole (0.1 mg/dL) and placebo (2.1 mg/dL). A1C showed similar decreases in the aripiprazole and placebo groups (0.11% and 0.17%, respectively) during the study. Both fasting total cholesterol and fasting LDL cholesterol levels showed small decreases in the aripiprazole and placebo groups, while fasting plasma HDL cholesterol levels increased slightly in the two treatment groups. Fasting plasma triglycerides levels decreased from baseline in the aripiprazole and placebo groups over the 26-week study period (median decrease: aripiprazole, 12 mg/dL; placebo, 4 mg/dL).

Conclusion: In conclusion, long-term therapy with aripiprazole was not associated with adverse metabolic changes. The effects on glycemic control and plasma lipid profile were similar to those observed with placebo.

394. A VALID AND RELIABLE INSTRUMENT FOR MEASURING THE SUBJECTIVE RESPONSE TO ANTIPSYCHOTIC MEDICATION

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Background/objective: Positive and negative experiences with antipsychotic medication are important predictors of medication compliance, response to treatment, outcome of treatment and quality of life. Because of the lack of reliable and valid instruments to measure the subjective response we developed a new instrument, the Subjective Response to Antipsychotic medication (SRA) questionnaire. In this study the psychometric qualities of the SRA-questionnaire were investigated.

Methods: The SRA-questionnaire was completed by 325 patients. All subjects had a DSM-IV diagnosis in the schizophrenia spectrum. At inclusion 74.5% were using atypical antipsychotic medication, 26.5% were using classical antipsychotics. Oral medication was used by 82% of the patients, depot medication by 16% and 4% had oral and depot medication.

Results: A clusteranalyses on the subjective responses revealed 9 clusters: antipsychotic effect, sedation, activation, EPS, being numb, sexual dysfunctions, weight gain, initiative loss, sleep, and a miscellaneous cluster. The SRA-questionnaire has a moderate test–retest reliability and a good internal reliability.

Conclusion: It can be concluded that the SRA is a valid and reliable instrument that can be used for the evaluation drug treatment and development of new antipsychotic medication from the patients' perspective.

Treatment Compliance

396. PROMPTS TO ENCOURAGE ATTENDANCE AT PSYCHIATRIC OUTPATIENT APPOINTMENTS—A RANDOMISED CONTROLLED TRIAL: THE LEEDS PROMPTS STUDY

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Background: Failure to attend outpatient appointments represents failed opportunities to engage people with mental health problems and a waste of resources. 10–30% of people fail to attend psychiatric out patient appointments. A Cochrane systematic review shows that reminder letters may be a simple means of addressing this problem ($n = 200$, 2 RCTs, RR not attending 0.6 CI 0.4 to 0.9). Findings are based on small studies undertaken in one health care system (USA). The PROMPTS study, piloted in Leeds, UK, evaluates effects of an orientation statement letter within the National Health System. Telephone prompting is not clearly effective ($n = 447$, 2 RCTs, RR not attending 0.84 CI 0.66 to 1.07).

Methods: This study was a pragmatic, randomised controlled trial including adults due to attend psychiatric out-patients for the first time. Projected$N = 1000$. They were given 1. Additional prompt letter, in two languages—describing the clinic, clinic procedure, how to get there, suggesting bringing a friend/relative and current medication. 2. Standard care-partial booking service. The outcome measure was clinic attendance. The analysis was by intention-to-treat, cost effectiveness analysis.

Results: Ethics approval has been gained and randomisation started. Accrual of consultants—currently 12 teams provided patient lists; accrual of out patients—currently 100%, no losses to follow up.

Conclusion: Such complete follow up is rare in mental heath evaluation. It is expected that, by January 2004, this will be the largest study of its kind. Pragmatic study designs are possible in all aspects of evaluation of mental health care. These are real world designs with outcomes that have direct application to everyday practice.

397. MEDICATION NON-ADHERENCE: ASSOCIATIONS WITH RESOURCE USE AND COSTS FOR PEOPLE TAKING ANTIPSYCHOTICS

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Background: Non-adherence to antipsychotic medication has long been a concern in the treatment of schizophrenia, primarily because patients who do not adhere to their medication are more likely to relapse (Conley and Kelly, 2001). Previous research suggested that non-adherence leads to more frequent hospital admissions and longer durations of stay. Weiden and Olfson (1995) estimated that improving adherence by 50% would decrease 1-year hospitalisation rates by 12%. The aim of this study was to assess the relative impact of non-adherence and other factors associated with resource use and costs by people with schizophrenia.

Methods: Secondary analyses of data from the 1993 to 1994 UK Psychiatric Morbidity Survey of adults living in institutions. Factors potentially relating to resource use and costs were examined using two-part models.

Results: The odds of not adhering with current antipsychotic medication were over three time greater for those who experience or worry about side effects compared to those who do not. Non-adherence is also one of the most significant factors in increasing external service costs, by a factor of almost three. Non-adherent patients have predicted excess costs annually of approximately £2500 for inpatient services and over £5000 for total service use.

Conclusion: Our study results indicate a strong and significant association between patient experience of side effects and adherence to their antipsychotic medication. Patient reported non-adherence was also significantly associated with a higher level of health service use and costs. Further important factors affecting service use and costs are patient needs and the ability of the system to address them.

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398. CLINIC AND EPIDEMIOLOGY IN USE OF NEUROLEPTIC DEPOT THERAPY IN PSYCHIATRY

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Background/objective: Psychiatric patient often shows an ambivalent relationship with the drug and this lead to an insufficient compliance with a consequent symptomatological relapse so it may be favorable to use long acting depot preparations administered by intramuscular way once every two or four weeks. The aim of this study is to describe the use of neuroleptic depot therapy in the care of psychiatric disorders, and to evidence a possible tight correlation with epidemiological data of the sample and with the different pathologies which the depot therapy is used for.

Methods: The sample consisted of 435 subjects (patients with neuroleptic depot therapy are only 85, patients with oral therapy are 350); the sample was analysed for epidemiological variables, gender, medium age, education, diagnosi and for subtypes and finally for onset.

Results: A great number of males and females fall ill with paranoid schizophrenia, but the disease is more frequent in males and the major part of them are treated with an oral therapy and not with neuroleptic depot therapy. For subjects with depot therapy the medium onset-age is smaller for the feminine gender whereas the medium age of first admission to hospital is smaller for males.

Conclusion: From the collected data emerges a significant correlation between use of neuroleptic depot therapy and psychotic pathology; demographic and epidemiological variables follow tightly the diagnosis and subdiagnosis.

399. PSYCHOPHARMACOTHERAPY COMPLIANCE IN CATATONIC AND PARANOID TYPE OF SCHIZOPHRENIA

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Objective: The aim of this study was to compare psychopharmacotherapy compliance in catatonic with paranoid schizophrenia.

Methods: From a base population of 10569 schizophrenic patients recorded in the Croatian Psychotics Case Register (CPCR), a representative sample of 402 patients (207 males and 195 females) was formed for futher long-term field-clinical–epidemiological follow-up. In this sample there were 59 (14.7%) patients, who were diagnosed at least once in their life as catatonic schizophrenia (ICD and DSM). Every catatonic patient was matched to one with paranoid schizophrenia from the sample, according to residential area, sex and age. The patients were followed up for more than 25

years. The compliance status was assessed in the beginning of the illness and approximately 20 years later.

Results: Age, sex and employment status were not found to be significantly associated with psychopharmacotherapy compliance. Good compliance was recorded more often in patients with catatonic schizophrenia (72.9%; 59.3%) than in group of patients with paranoid schizophrenia (64.4%; 54.2%). In both groups there was a significant drop of psychopharmacotherapy compliance between two observed intervals.

Conclusion: During 20-year follow-up of catatonic and paranoid schizophrenic patients no significant difference in psychopharmacotherapy compliance was found. Variety of different methods (psychosocial interventions, education about illness for patients and relatives, antistigma program, simple drug regiment etc.) should be applied to improve psychopharmacotherapy compliance in patients with schizophrenia.

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400. ADHERENCE TO TREATMENT IN FIRST CONTACT PSYCHOSIS IN SÃO PAULO, BRAZIL

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Objective: There has been growing evidence that compliance to treatment is a key issue in first contact psychosis. The aim of this study is to estimate treatment compliance in a cohort of first contact psychosis in São Paulo, Brazil, and to investigate predictors of compliance.

Methods: Adults (18–64 years), resident in a defined geographic area of São Paulo, included in a first contact psychoses incidence study, were followed up six months after first assessment. At follow-up, information on contact with services, use of medication, and presence of psychotic symptoms was obtained.

Results: Out of 50 subjects included at baseline, 44 (88%) were assessed at 6-month follow up. Eighteen (40.9%) subjects were under some form of treatment, and 17 (38.6%) were taking psychotropic drugs. Fifteen (34.1%) were experiencing psychotic symptoms (delusions and/or hallucinations), of whom only 7 were under treatment. Only insight about psychiatric symptoms showed a trend for association with compliance to treatment.

Conclusion: Effective care for first episode psychosis should be provided by catchment-area based community mental health teams, with outreach programs. Increased public awareness may help acceptance of mental illness and the need of care.

Acknowledgment: Funded by the Wellcom Trust, UK.

Outcome

401. ONE-YEAR OUTCOME IN FIRST-EPISODE SCHIZOPHRENIA

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Background/objective: Describing the early course is still among the major challenges in schizophrenia research. In a study on first-episode patients we aimed at defining predictors of early outcome.

Methods: Forty patients (22 female, 18 male, age 29.0 ± 8.3) with diagnoses of schizophrenia, $n = 34$, schizoaffective disorder, $n = 4$, and schizophreniform disorder, $n = 2$, were examined during their first episode and after 14.1 ± 1.6 months. Well-established instruments were used for assessment, namely SCID, PANSS, SANS, PSE, GAF, and SCS. A semistructured psychiatric interview was applied for information on subjective well-being, compliance with treatment, possible relapse, employment, household duties, intimate and other relationships. Outcome was defined according to criteria from the literature using the above information.

Results: Thirty-four individuals (85%) had been compliant with psychiatric outpatient treatment during the follow-up period, 80% had received regular neuroleptic treatment. During the follow-up period 2 patients had been continuously ill. Relapses had occured in 14 individuals, 6 of whom were fully recovered again at the time of

the follow-up interview. PANSS levels did not differ from remission. Eighty percent of patients were recovered on a syndromal level, 57,5% were rated to be in syndromal and psychosocial recovery. Fifty percent were fully employed at paid work or in vocational or educational training, 27.5% worked part-time. Regression analyses revealed symptom levels on remission and medication compliance during follow-up period to be the single best predictors of follow-up symptomatology.

Conclusion: These results are in accordance with findings from the literature.

402. FIRST EPISODE PSYCHOSIS: DURATION OF UNTREATED PSYCHOSIS AND 'MID-TERM' OUTCOME

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Background: Most studies have shown that a longer duration of untreated psychosis (DUP) adversely influences short term outcome, however it remains uncertain whether this relationship is sustained in longer term studies. We investigated the relationship between DUP and four year outcome for persons with a first episode psychosis. We hypothesized that a longer DUP would independently influence functional and symptomatic outcome.

Methods: Design: Prospective naturalistic follow up study. Setting: An urban community based psychiatric service with a catchment area of 165,000. Participants: Consecutive first presentations with DSM IV psychosis. Main outcome measures: Remission, symptomatology and global functioning.

Results: 171 patients had an average DUP of 18 months and a median of 5 months. The mean duration of untreated mania was 1.5 months, median. 75 months. A longer DUP predicted a poorer functional and symptomatic outcome 4 years later. One unit increase in DUP led to a 2.7 point increase in symptomatology and a 3 point decrease in global functioning. Prodromal length did not influence outcome.

Conclusion: This study extends the findings of short term follow up studies by indicating a link between DUP and mid term outcome. No association between prodromal length and functional or symptomatic outcome was evident.

Acknowledgment: This study was supported by the Stanley Medical Research Institute.

403. FIRST EPISODE OUTCOME STUDY (FEPOS STUDY)—A MEDICAL RECORD REVIEW STUDY OF 704 FIRST-EPISODE PATIENTS TREATED DURING 18 MONTHS IN THE EARLY PSYCHOSIS PREVENTION AND INTERVENTION CENTRE (EPPIC), MELBOURNE, BETWEEN 1998 AND 2000

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Objective: FEPOS study evaluates background, baseline characteristics, evolution and outcome of first episode psychosis patients (FEPP) under non-selected naturalistic conditions.

Methods: 786 FEPP were treated in EPPIC between 1998 and 2000. Data were extracted from medical records (MR) using a specially designed questionnaire.

Results: 704 MR assessed, 82 MR not available for the study. Diagnostic distribution: 66% non-affective psychoses, 28% affective psychoses, 6% non-psychotic disorder. Absence of significant difference in age at admission between male (21.7 yo) and female (21.3 yo). 55% had a positive family history for psychiatric illness. 73% reported a history of substance abuse, 48% of another psychiatric illness, and 70% had experienced trauma. 14% had attempted suicide at least once before treatment. At entry, 60% of patients abused substances and 30% suffered from another co-morbidity, mainly depression (24%). After 18 months of treatment, diagnosis had changed in 45% of the patients, 87% showed a full or partial remission of psychotic symptoms, 40% stopped or decreased substance, and 25% were lost to follow-up. Pre-morbid level of functioning decreased only slightly over the treatment period. Diagnosis, substance abuse and non-compliance were highly predictive for outcome.

Conclusion: Before initiation of treatment, FEPP present a high risk of suicide, substance abuse and other co-morbidities. Early intervention is therefore needed, has a high rate of success in reducing symptoms, and appears to limit the degree of functional deterioration. Treatment of co-morbidity is crucial.

404. SYMPTOMATIC AND FUNCTIONAL OUTCOME AFTER FIRST EPISODE PSYCHOTIC MANIA: IDENTIFYING BARRIERS TO RECOVERY IN AN EPIDEMIOLOGICAL CATCHMENT AREA

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Background: Recent studies have shown that outcome in mania is worse than previously thought. However, they have been conducted in selected samples with restrictive or global measures of outcome. Studies on catchment area populations with broader evaluation of outcome are therefore needed.

Method: Prospective follow up at 6 and 12 months of 87 patients with DSM-III-R first episode psychotic mania admitted in EPPIC between 1989 and 1997. Syndromic and symptomatic outcome was determined with the BPRS, and functional outcome with the QLS and with sub-items of the PAS.

Results: Syndromic recovery was achieved by 90% of patients at 6 and 12 months, but 40% hadn't recovered symptomatically at 6 and 12 months, and still presented anxiety or depression. 66% hadn't returned to their previous functional level after 6 months, and 61% after 12 months. A model composed of functional recovery at 6 months, age, family history of affective disorder and illicit drug use allowed prediction of 12-month functional outcome with success rate of 91%.

Conclusion: While syndromic outcome after a first episode of psychotic mania is good, symptomatic and functional outcome are poor and plateau after 6 months. Developments in early intervention are needed, and should address anxiety, depression, and substance abuse. Psychological intervention should target social initiative and socio-sexual impairment. The role of persistent negative symptoms should be further explored.

405. PREDICTORS OF TREATMENT OUTCOMES IN PREVIOUSLY UNTREATED PATIENTS WITH SCHIZOPHRENIA: RESULTS FROM THE EUROPEAN SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES (SOHO) STUDY

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Background: To identify predictors of outcome, after 12 months of antipsychotic treatment, in 919 patients with schizophrenia who had never previously been treated with antipsychotics, and who initially received olanzapine, risperidone or a typical antipsychotic.

Methods: Data were extracted from the Schizophrenia Outpatient Health Outcomes (SOHO) study, a 3-year, large, prospective, observational study of schizophrenia treatment in 10 European countries. Analyses were adjusted for baseline differences between treatment cohorts (Cohorts were defined based on the drug initiated during the baseline visit) and took into account clinical and socio-demographic factors that may influence outcome. A stepwise selection criterion based on a chi-squared test (difference between the -2 log likelihood of the full and reduced model) was applied in order to remove the terms that did not appear to have a significant influence in predicting the different endpoints.

Results: Baseline predictors of CGI symptom response rates, at 12 months, were: antipsychotic treatment (Odds Ratio: 1.70; 95% CI: 1.11, 2.61), negative (0.79; 0.70, 0.90) and positive (1.13; 1.00, 1.28) CGI symptom scores, hostile behaviour (0.51; 0.34, 0.77), employment status (0.61; 0.43, 0.88), current substance abuse (0.15; 0.05, 0.41), gender (0.91; 0.66, 1.27), EQ-5D VAS (0.99; 0.98, 0.99) and extrapyramidal symptoms (3.65; 1.53, 8.70). Likewise, baseline predictors of EQ-5D VAS, at 12 months, were: antipsychotic treatment (Difference:2.73;95% CI: 0.43, 5.03), gender (-1.31; -2.72,0.10), housing status (2.20; 0.62, 3.79), EQ-5D VAS (0.22; 0.17, 0.27), negative (-2.28; -3.07, -1.48), cognitive (0.85; 0.05, 1.66), and overall (-0.67; $0.-1.90$, 0.56) CGI score.

Conclusion: In this study we found that several baseline characteristics, in particular choice of initial antipsychotic treatment, of patients with first-episode schizophrenia can be important predictors of CGI's and EQ-5D VAS' rates of response.

406. DYNAMIC COGNITIVE CHANGES AND OUTCOME IN RECENT ONSET SCHIZOPHRENIA

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Objective: Although neurocognitive deficits are a major characteristic in recent onset schizophrenia, the predictive value for course of illness and functional outcome is rather limited. Because schizophrenia runs a variable and largely unpredictable course the first few years of the disease, we shifted our attention to dynamic neurocognitive changes and their significance for outcome.

Methods: In this study fifty-eight recent onset patients were tested at inclusion and after four years on a large cognitive battery measuring vigilance, speed of information processing, selective attention, verbal learning, verbal fluency and intelligence. Outcome measures focused on course of illness, hospitalizations and competitive employment. We were interested in changes in cognition and the associations between these changes and several outcome measures.

Results: On average there were no significant changes in cognition. There were however large variations within the patient group, with some patients showing improvement and others deterioration on various cognitive measures. Some of these dynamic neurocognitive changes were significantly associated with outcome, especially changes in intelligence scores. A deterioration in intelligence scores was associated with chronicity and time in psychosis. Competitive employment was predicted by an improvement in intelligence scores and verbal learning.

Conclusion: The question remains whether this association between changes in intelligence scores and outcome reflects a degenerative process, a result of poor social–environmental stimulation or a general learning deficit reflected by the absence of a practice effect after repeated testing.

407. OUTCOME AND ITS PREDICTORS IN SCHIZOPHRENIA BEFORE 35 YEARS OF AGE WITHIN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Background/objective: Follow-up studies of schizophrenia have reported widely divergent rates of recovery and disability. Because these findings are based on samples from particular hospitals or clinics, their generalizability is limited. Only follow-up of an epidemiologically based cohort can establish the prognosis of schizophrenia in the population. We report outcomes of schizophrenia before age 35 years in a longitudinal, population based birth cohort, and test the prognostic significance of selected historical, developmental and illness-related variables.

Methods: All 144 living members of the Northern Finland 1966 Birth Cohort who had psychotic episode were asked to participate in a field study during 1999–2001. Of 92 patients participating, 59 were diagnosed with DSM-III-R schizophrenia. Face to face interviews and case registers were used to rate measures of outcome including clinical clobal impression (CGI), social and occupational functioning (SOFAS), positive and negative symptoms (PANSS), occupational status, psychiatric hospitalizations and neuroleptic medication. Based on available data outcome was categorized as good/moderate or poor, and complete recovery was studied.

Results: While 25 (42%) cases had good/moderate and 34 (58%) had poor outcome, only one schizophrenia case was considered as fully recovered. Mortality was high before age 35 years: Ten cases (9.8%) had died (e.g. by suicide). When compared to good outcome cases, cases having poor outcome had e.g. earlier age of illness onset and more often genetic risk.

Conclusion: Too few patients have favorable outcome of schizophrenia in this relatively early onset group. Some predictors for good and poor outcome can be found.

408. CHARACTERISTICS OF PATIENTS WITH PERSISTENT PSYCHOSIS AFTER FIRST EPISODE

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Background/objective: Early intervention in psychosis has received much attention in recent years and preliminary evidence of it being associated with better outcome is encouraging. Careful follow-up of patients from first presentation should help us identify those at high risk of persistent psychosis. The objective of this study is to identify unique characteristics, if any, of patients with schizophrenia spectrum psychosis that persists for two years by comparing them to those who achieve full remission by one year.

Methods: A total of 130 patients who matched the criteria used to define the sample in this study were admitted to the Prevention and Early Intervention Program for Psychoses (PEPP) as of April 2001. Of these, there are 116 subjects who have baseline, 6, 12 18 and 24 month assessments on rating scales used to determine a clinical outcome. Patients were considered to have a ''persistent psychosis'' if they continued to have a rating of 3 (moderate) or more on one or more global items on SAPS (Scale for Assessing

Positive Symptoms) at all assessment points ($n = 13$). Patients were considered to be "fully recovered" if they showed a rating of 0 on all global items on SAPS at 12, 18 and 24 month assessments ($n = 17$). These two groups were compared on a number of demographic and clinical variables.

Conclusion: The salient findings consist of a statistically significant difference in DUP ($p < 0.05$, 1-tailed) with longer delays in those with persistent symptoms.

409. CORRELATES OF DURATION OF INITIAL HOSPITALISATION AND TIME TO READMISSION IN SCHIZOPHRENIA: THE WEST LONDON FIRST EPISODE STUDY

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Methods: In a sample of 56 people with first episode schizophrenia, we investigated the correlates of duration of initial hospitalisation and time to readmission within the first year of treatment. The mean duration of initial hospitalisation was 74.77 days (SD 95.13). Following discharge 42.9% were readmitted within the first year. The mean period between discharge and subsequent readmission was 124 days (SD 197.35). The variables examined were derived from assessments at first admission and were related to symptom type, insight, social function, treatment adherence and IQ.

Results: Correlational analysis revealed a significant positive association between duration of initial hospitalisation and severity of the negative syndrome. Examination of individual SANS symptom scores revealed significant correlates to be avolition, anhedonia and asociality rather than core negative symptoms of affective flattening and alogia. A possible explanation for this finding is that avolition, anhedonia and asociality prove difficult to treat even early in the illness, and may be barriers to reintegration back into the community, thus delaying discharge. Time to readmission was negatively associated with current IQ (WAIS-R) and social withdrawal, a subscale of the Social Function Scale. Neither treatment adherence (Compliance Rating Scale), attitudes to treatment (Rating of Medication Influences: ROMI) nor insight (Schedule for the Assessment of Insight) measures at baseline correlated significantly with duration of initial hospitalisation or time to readmission.

Conclusion: These findings suggest that for people with first episode schizophrenia, measures of IQ and social function at initial presentation may have some predictive value regarding early relapse and readmission.

410. DURATION OF UNTREATED PSYCHOSIS AND OUTCOME IN FIRST-EPISODE PSYCHOSIS. PERSPECTIVE FROM A DEVELOPING COUNTRY

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Background/objective: The duration of untreated psychosis (DUP) and its effect on outcome have attracted the interest of a number of researchers over the last two decades. Some authors suggest that longer DUP is predictive of poorer outcome on a variety of measures, while others have been unable to demonstrate such an association. There have not been reports on this issue in a population from the developing world, where schizophrenia may have a different course and outcome.

Method: Forty-eight subjects with first episodes of psychosis were evaluated before initiation of pharmacological treatment and then at three-monthly intervals over a period of 24 months. We first examined the correlation between DUP and symptom improvement as measured on the PANSS. We furthermore performed a multivariate analysis of the effect of DUP and a number of possible confounders to determine the validity of DUP as a predictor of outcome in first-episode psychosis.

Results: DUP showed significant correlation with improvement in PANSS Total and negative subscale scores as well as the PANSS depression factor at 21 and 24 months. Stratification into a group with DUP less than one month and a group with DUP longer than one month showed significant differences between the two groups in terms of the same variables from 18 months onwards. Multivariate analysis found DUP to be the only significant predictor of improvement in negative symptoms at 24 months.

Conclusion: DUP seems to be a significant predictor of clinical outcome in a cohort from a developing country. Early detection strategies may therefore be important tools in reducing the burden of disability in subjects with first episodes of psychosis in this population.

411. BELGIAN SCHIZOPHRENIA OUTCOME SURVEY (SOS)

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Background: SOS compares functional outcome and medical resource use in patients with schizophrenia in Belgium during 2 years following hospitalisation for an acute psychotic episode and being treated with different antipsychotics.

Methods: Patients, >18 and treated with either haloperidol (H), olanzapine(O) or risperidone(R) enter the study at discharge from the hospital and are followed in a naturalistic setting and assessed at baseline, after 3, 6, 12, 18 and 24 months using Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning (GAF), Subjective Well-being under Neuroleptics (SWN) and spontaneous adverse events reporting. Resource use is evaluated (cost, number of hospitalizations, consultations and medication).

Results: The results of the first year follow-up are presented. 323 patients were included (H 32, O 149, R 142). Mean dosages used were H 10 ± 7.8 mg, O 14 ± 6.2 mg, R 4.3 ± 1.9 mg. After one year, the majority of patients continued the same treatment (79%). The drop-out rate was higher with haloperidol (H 25%, O 19% and R 20%). Full time rehospitalisation was significantly longer (mean number of days: H 58.0, O 9.4, R 15.0) and the frequency of emergency visits significantly higher with haloperidol compared to olanzapine(H 29%, O 10% and R 7%). The GAF score improved substantially, although BPRS and SWN scores deteriorated in all groups. EPS was lowest in the olanzapine and highest in the haloperidol group. Weight gain was similar in the 3 groups.

412. REAL-WORLD FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: A GOAL-DIRECTED BEHAVIOUR MODEL

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Background: Real-world, social, occupational and recreational functioning is now considered an important feature in the treatment of schizophrenia. It has been suggested that the remission of positive and negative symptoms is necessary—but not sufficient—if favourable functional outcome is to occur. Indeed, it has been proposed that the role played by the neurocognitive deficits observed in schizophrenia may be the most important aspect of improved functional outcome. We propose that levels of functional outcome may be considered within a model of reduced goal-directed behaviour, incorporating clinical, neurocognitive and behavioural impairment.

Methods: We describe novel methods of time-budget interviewing to elicit patterns of time use and activity participation in two samples, comprising first-episode psychosis ($n = 18$) and chronic schizophrenia ($n = 20$), at baseline and six weeks later. These data were supplemented by objective (actigraphy) and subjective (self-report) information regarding levels of goal attainment. Traditional measures of clinical and neurocognitive status were also employed.

Results: Results of an independent assessment showed a statistically significant reduction in clinical symptoms over the six weeks in the first episode sample (BPRS $t = 2.29$ $p < 0.05$; CGI $t = 3.69$ $p < 0.015$; PANSS $t = 2.87$ $p < 0.05$). However, the clinical improvement in the first episode sample was not matched by any significant improvement in their neurocognitive functioning and patterns of activity participation, despite the actigraphy revealing a 4% increase in levels of raw activity and a 6% increase in time awake. The clinical, neurocognitive and behavioural profile of the chronic sample remained stable over the six-week period.

413. IMPROVEMENTS IN COGNITIVE DEFICITS ARE ASSOCIATED WITH IMPROVED FUNCTIONAL OUTCOMES: RESULTS FROM A LONGITUDINAL OBSERVATIONAL STUDY OF SCHIZOPHRENIA PATIENTS

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Background/objective: Neurocognitive deficits were shown to be associated with poorer functional outcomes. This study examines if *changes* in cognitive deficits are linked to *changes* in functional outcomes in the long-term treatment of schizophrenia patients in usual care, and whether this link is independent of changes in EPS, Positive and Negative symptoms.

Method: Participants were 2144 patients who completed at least 1-year follow-up in the U.S. Schizophrenia Care and Assessment Program, a 3-year observational study of patients with schizophrenia. Cognitive impairment was assessed by the PANSS Cognitive Factor (PANSS Cog). Functional outcomes were measured by the Quality of Life Scale (QLS), the Global Assessment of Functioning Scale (GAF), and the SCAP-Health Questionnaire (SCAP-HQ). Changes were measured from baseline to the end of 1-year follow-up. Statistical analysis employed Pearson correlations, path analyses, and generalized linear models.

Results: Improvements in the PANSS Cog were significantly correlated with improvements in occupational role functioning, social functioning, capacity to engage in activities, participation in the community, GAF, daily activities, employment status, and hourly wages. When adjusting for EPS, Positive and Negative

symptoms, cognitive improvements were significantly ($p < 0.05$) associated with improved GAF, QLS total score, occupational role functioning, and hourly wages.

Conclusion: Improvements in cognitive deficits appear to be associated with improved functional outcomes. Since the PANSS Cognitive Factor was used as a proxy measure of cognition, current findings will require replications with neuropsychological tests. Findings suggest that improving cognitive functioning may become one of the most important clinical targets in the treatment of schizophrenia.

414. NEUROCOGNITION, SYMPTOMS, AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background/objective: The research community has developed a growing interest in the relationship between neurocognitive deficits and functional outcome in psychiatric disorders. A series of studies have shown neurocognition to be a stronger predictor for functional outcome than type and degree of psychotic symptoms for schizophrenic subjects. The study will elucidate the validity of previous findings in schizophrenia, and present new data for the bipolar disorder. Results will indicate to what degree the association between neurocognition and functional outcome is specific for schizophrenia, or a general relationship across the psychotic spectrum.

Methods: As part of a large ongoing study of genetic susceptibility of schizophrenia and bipolar disorder (Ullevål 600), all patients recruited to the study and having completed neuropsychological assessment will be included. Methods comprise subtests from D-KEFS, a PASAT-like task, CVLT-II, Logical Memory (WMS-III), Digit Span and Digit Symbol (WAIS-III), WASI and NART. Functional outcome was measured using the Social Functioning Scale, subjects were diagnosed using the SCID (DSM-IV), and symptoms were rated with the PANSS.

Results: At present (September 10, 2003) approximately 40 subjects have been included in the study. By January 2004 we expect to have data on 100 subjects. Multiple regression analyses will be performed to explore the relative predictive power of symptoms versus neurocognition for functional outcome in schizophrenia as compared to bipolar disorder and controls.

Cognitive Therapy

415. COGNITIVE REMEDIATION AS A TOOL TO IMPROVE REHABILITATION OUTCOMES IN SCHIZOPHRENIA

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Background/objective: There is a growing interest in cognitive rehabilitation of schizophrenia deficits, in particular in what is called 'cognitive remediation', aiming to recover performances by means of progressive training on the compromised functions. A number of studies showed its effectiveness on social/occupational functioning, that also correlated to improvement of specific neuropsychological functions. The aim of the study was to evaluate the efficacy of a program of computer assisted neuropsychological enhancement of individual cognitive dysfunctions in a sample of chronic schizophrenics participating to a cognitive-behavioural rehabilitation program and its influence on personal, social and working functioning.

Methods: Sample consisted in 64 schizophrenic patients (DSM IV), clinically stabilized, who were tested before and after a three months, single blind, placebo-controlled cognitive enhancement with the Brief Assessment of Cognition in Schizophrenia (BACS) battery, the WCST and the CPTax. Psychopathological and functional assessment were performed by means of the PANSS and QLS scales, respectively, at the same times of observation and after six and twelve months. Patients were randomised to placebo or active computer-aided cognitive training with multiple weekly sessions that was added to a standard cognitive-behavioural rehabilitation program.

Results: Preliminary data on 32 patients show a statistically significant improvement of specifically exercise-targeted executive function ($p = 0.01$), sustained attention ($p = 0.01$) and psychomotor performances ($P = 0.003$), only in the active treatment group and a generalization of results also to verbal memory.

Conclusion: These results confirm with a single blind design previous reports of effectiveness of computer-aided enhancement of key cognitive impairments of schizophrenia, considered a limiting step to rehabilitation effects on psychosocial functioning.

416. COGNITIVE BEHAVIOURAL THERAPY IN THE EARLY INITIAL PRODROMAL STATE OF PSYCHOSIS: FIRST RESULTS

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Background: Although the efficacy of cognitive behavioural therapy (CBT) in schizophrenia has been established for persistent psychotic symptoms, little information is available on the effects of CBT in the pre-psychotic phase.

Methods: We developed a comprehensive CBT program for clients in the early initial prodromal state, which is recently evaluated in a randomised, controlled, multicenter trial (RCT). To date more than 1200 persons were screened for inclusion criteria, more than 190 clients fulfilled the criteria and more than 110 gave informed consent to paricipate at the RCT.

Results/conclusion: Early interim analyses indicated that the approach is feasible and has promising treatment effects. However, we have to await the final results of the ongoing trial to judge whether the approach is a effective treatment for persons in the early initial prodromal state.

417. EFFECTIVENESS OF INTEGRATED PSYCHOLOGICAL THERAPY (IPT) FOR SCHIZOPHRENIA PATIENTS: A META-ANALYSIS

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Background/objective: IPT is a manualized cognitive-behaviour group therapy program. Over the past 27 years, research groups in Switzerland, the United States, Canada, Japan, Germany, the Netherlands, Italy, and Spain have conducted 26 independent evaluation studies on IPT using patient samples totalling 1269. The rationale of the present study was to examine the effectiveness of IPT by means of a meta-analytic review.

Review of results: The most salient results indicate favourable mean effects for IPT in comparison to placebo-attention conditions and standard care alone. Moreover, the superiority of IPT continues to increase during an average catamnestic phase of 8.1 months. IPT obtains similar favourable effects in different functional areas (neurocognition, social behaviour, psychopathology) as well as in different assessment formats (expert ratings, self-reports, psychological tests). Furthermore, improvements in neurocognitive functioning correlate significantly with symptom reduction. In the analyzation of different settings, the superiority of IPT in any given therapy or site condition is proved when compared to controls. However, a minimal therapy intensity of two sessions a week would appear to generate additional benefits. The analysis of patient sub samples, as well as of inpatients, outpatients and patients in varying rehabilitation phases, reveals similar favourable effects attributable to IPT. Selecting only high quality studies using RCT and blind-rating standards yields comparable results.

Conclusion: The present meta-analysis corroborates evidence of IPT as an 'empirically validated treatment' according to APA guidelines within multimodal treatment concepts. Further studies of IPT should ideally focus on differential indication and recent research results with regard to social cognition and cognitive remediation approaches.

418. IMPROVING COGNITION WITH COMPUTERIZED TRAINING

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Background: Cognitive dysfunction is a prominent feature of schizophrenia, for example working memory and executive dysfunction, and the extent of cognitive dysfunction has implications for prognosis. For example, a meta-analysis by Green (Am J Psych 153:321, 1996) suggests that cognitive deficits are linked strongly to prognosis and social outcome. Cognitive deficits persist despite pharmacotherapy and psychotherapy which severely limit the recovery of patients with schizophrenia or schizoaffective disorder. Consequently, it appears a matter of priority to focus rehabilitation efforts for patients with schizophrenia on the remediation of cognitive impairment.

Methods: A computer-based training program, RoboMemo (Cogmed Cognitive Medical Systems AB, Stockholm) has been

developed and utilized for children with ADHD (Klingberg et al., J Clin Exp Neurops 24:781, 2002). To improve working memory capacity, verbal and non-verbal exercises are individually performed and trained.

Results: The results showed that training, in comparison with a placebo-group, significantly enhanced performance on a trained visuospatial working memory task, a non-trained visuospatial working memory task, an inhibition ability test and a test thought to measure general cognitive ability and prefrontal functioning (Raven's Progressive Matrices). This implies that a positive training effect is generalized to other settings.

419. NEUROPSYCHOLOGICAL DYSFUNCTION IN PATIENTS WITH SCHIZOPHRENIA: WOMEN PROFIT MORE FROM COGNITIVE TRAINING

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Background: Neuropsychological dysfunctions in schizophrenia, especially in the domains of verbal learning and memory, attentionand executive functioning, have been documented in numerous studies. Most longitudinal data support the idea that neuropsychological functions remain stable throughout the illness. There has been some debate about the effectiveness of cognitive rehabilitation, since cognitive capabilities are important prerequisites for social and occupational integration.

Methods: 64 schizophrenic patients (DSM IV) have been enrolled in our cognitive rehabilitation program immediately after a short period of initial clinical stabilization, 58 (21 females, 22 first-episodes, mean age 29.2 y, SD 7.6 y) completed the program and were neuropsychologically tested before (t1) and after (t2) the four-week program. The assessment of cognitive functioning included: vocabulary (HAWIE-R), auditory verbal learning and memory test (AVLT), figural learning task (DCS), reasoning task (LPS, subtest 3), Modified Wisconsin Card Sorting Task (MWCST), Go-No-Go Task, divided attention task (DA). Clinical symptomatology was assessed with the PANSS, the Calgary depression scale and the GAF.

Results: There was a significant improvement of psychopathological measures in all patients as a group at t2, but looking at sex differences, only women improved significantly on the negative symptom scale. Women performed slightly worse than men in all neuropsychological tests except for the AVLT at t1. After cognitive rehabilitation all patients showed a significant improvement in the performance of the DCS and LPS, women additionally performed better in the AVLT and MWCST. There were no significant differences in the performance of first-episode and chronic schizophrenic patients at t1 or t2.

420. RESPONSE TO WCST REMEDIATION AS A CHALLENGE TO PREDICT PHARMACOLOGICAL AND NEUROCOGNITIVE TREATMENT OUTCOMES IN SCHIZOPHRENIA

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Background/objective: To appreciate the potential of efforts for improving psychiatric care and their impact on opportunities for rehabilitation we examined the utility of a categorization of a schizophrenic sample on the basis of their response to a modified procedure for WCST administration that, through verbalization, has been demonstrated to be useful to remediate the cognitive performance.

Methods: A sample of 90 recent onset to long-term schizophrenic patients treated and clinically responsive to 'atypical' or typical APs, were evaluated along a naturalistic observation. Patients has been divided on the basis of the WCST remediation pattern ('remediators' and 'non remediators') and functional outcome in terms of Global Assessment of Functioning Scale (good outcome if >70).

Results: Interim analysis shows a significant different distribution of subjects responsive to their own AP treatment along cognitive and outcome dissection, with more 'remediators' with better functional outcome the subgroup responsive to 'atypicals' and, vice-versa, more frequent 'non remediators' with better outcome in patients treated with classical AP. Different symptom profiles are seen in the subgroups.

Conclusion: The data suggest the possible utility of the findings from neurocognitive assessment as predictor of AP and, likely, psychosocial treatments. It can be hypothesized that subjects for whom there is room for remediation might report more cognitive enhancement with 'atypical' AP medication. It will be also important investigate the characteristics of not remediating subjects with 'conventional' Aps to see what kind of cognitive profile characterize the treatment outcome of these patients.

421. COGNITIVE BEHAVIOUR THERAPY (CBT) FOR SCHIZOPHRENIA: THE EFFECT OF CLINICAL MODELS AND METHODOLOGICAL RIGOUR

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Background/objective: Evidence based treatment is based on the results mainly from randomised control trials (RCTs). In medication treatments variations in methodological rigour affect the estimated effect sizes but there is no current work on whether these same methodological constraints affect trials of psychological interventions. This study aims to explore the effects of methodological rigour of trials of one preferred psychological treatment, Cognitive Behaviour Therapy for the positive symptoms of schizophrenia.

Method: A measure of methodological rigour (Clinical Trials Assessment Measure, CTAM) was developed based on both a literature search and expert opinion. It had good reliability and validity. The effects of trial methodology and clinical emphasis of treatment was investigated in a database of 18 CBT trials.

Results: There was evidence of a beneficial effect of CBT in a meta-analysis of 18 trials. But in trials where raters were aware of the group allocation the effect size was inflated from approximately 50 to 100%. In methodologically rigorous trials CBT was still advantageous but with a reduced estimated effect size of 0.21. Clinical models which emphasised more behavioural aspects were marginally more advantageous than other models.

Conclusion: Psychological treatment trials that make no attempt to mask the groups to which the participant belongs are likely to have inflated effect sizes. Meta-analyses need to consider these methodological issues carefully particularly when the results will be used to change clinical practice.

Medication Effects on Cognition

422. DISSOCIATING MEDICATION EFFECTS FROM LEARNING AND PRACTICE EFFECTS IN A NEUROCOGNITIVE STUDY OF SCHIZOPHRENIA: OLANZAPINE VERSUS HALOPERIDOL

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Purpose: To contrast the effect of haloperidol and olanzapine on neurocognitive functioning in schizophrenia while controlling for learning and practice effects.

Method: Three groups were recruited: 25 schizophrenia patients (Pt); 9 first-degree family members (FM); 13 normal controls (NC). Repeated assessments prior to treatment randomization was chosen as a method to control for learning and practice effects. Therefore, all subjects were assessed on four occasions within five days on the same neurocognitive battery which consisted of 13 measures focusing on attention and working memory abilities. Patients were then randomized to 56 days of treatment with haloperidol or olanzapine. All subject groups were reassessed on the same neurocognitive measures at Days 28 and 56.

Results: Pts consistently performed worse than NCs. With the exception of three measures, Pts performed significantly worse than FMs. There were no differences between the FM and NC groups on any of the measures. Prior to randomization, overall main effects of time revealed the presence of learning and practice effects on motor tasks, verbal short-term memory, attention, and on a measure of verbal working memory. Reaction time, short-term visuospatial memory, visual working memory, and verbal working memory were resistant to learning and practice effects. There were no changes in performance for any of the four groups (haloperidol, olanzapine, FM and NC) during the 56 day double-blind treatment period.

Conclusion: Once learning and practice effects were controlled, it was observed that olanzapine and haloperidol did not differentially affect performance on measures of attention and working memory in schizophrenia.

423. UNDERSTANDING THE RELATIONSHIP BETWEEN COGNITIVE MEASURES AND FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA

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Background: Cognitive impairments have a significant impact on patient outcome and functioning in schizophrenia, although specific relationships among various domains are not well understood. Relevant data will be available from a large ongoing study of long-acting injectable risperidone, providing an opportunity to explore the relationship between cognitive measures and functional outcomes.

Methods: A prospective study of 320 stable patients with schizophrenia/schizoaffective disorder included measures of working memory, executive function, secondary memory, attention, word list learning, social cognition, simple motor speed and manual dexterity (baseline, 3 months, 6 months). Cognitive results will be correlated with measures of functioning (Strauss-Carpenter Level of Functioning; Personal; Social Performance Scale), quality of life (Schizophrenia Quality of Life Scale), and efficacy (PANSS). Interim data (blinded to dose, 25 vs. 50 mg every two weeks) are now available on cognitive tasks. Interim data on additional patients will be available for presentation at the meeting, along with preliminary data related to functional and clinical outcomes.

Results: Initial data ($n = 60$) showed significant improvements at six months in cognitive functions: simple motor speed (finger tapping test total taps, right mean 11.32, $p < 0.05$), attention (continuous performance test flanker version sum correct neutral mean = 3.25, $p = 0.05$), executive functioning (strategic target detection test: target reaction time mean = − 174.73 msec, $p < 0.01$; total errors mean = − 12.71, $p < 0.02$; non-perseverative errors mean = − 9.70, $p < 0.01$), and verbal memory (working list memory total trial 1, mean = 0.82, $p < 0.03$; total learning mean = 5.74, $p < 0.02$). These results will be correlated with measures of social cognition, efficacy, and functioning to better understand the potential relationship between these variables.

Conclusion: Results suggest that cognitive improvements can occur in stable patients with schizophrenia treated with long-acting risperidone. This study will allow us to prospectively examine the relationship between specific cognitive measures and functional outcome. Limitations include the non-comparative design, while strengths include the large sample size and long treatment duration. Supported by Janssen Pharmaceutica Products, LP.

424. ZIPRASIDONE VS. OLANZAPINE IN SCHIZOPHRENIA: 6-MONTH COGNITIVE DATA

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Objective: To assess the long-term effects of flexible-dose ziprasidone and olanzapine on cognitive functioning in patients with schizophrenia/schizoaffective disorder.

Methods: A 6-month continuation study enrolled 126 patients who responded satisfactorily to ziprasidone or olanzapine in a 6-week, double-blind, randomized trial. Attention, memory, executive-functioning, and verbal fluency domains were assessed.

Results: Significant (within group) mean improvements were seen with ziprasidone (n range, 23–33) and olanzapine (n range, 22–35) in all domains. Ziprasidone produced greater improvement vs. olanzapine on most variables—particularly, Trail Making Test (TMT) Part A = − 32.64 vs. − 10.17 (effect size [ES], 0.60 vs. 0.63; both $P < 0.004$); RAVLT (sum 1–5) = 11.67 vs. 7.77 (ES, 0.97 vs. 0.70; both $P < 0.001$); Delayed Recall = 3.58 vs. 2.15 (ES, 1.06 vs. 0.72; both $P < 0.001$); WCST perseverative errors = − 9.09 vs. − 3.68 (ES, 0.66 vs. 0.33; $P = 0.004$ vs. $P = 0.14$); and Letter Fluency = 4.06 vs. 3.53 (ES, 0.64 vs. 0.36; $P < 0.001$ vs. $P < 0.05$). Olanzapine showed greater improvement than ziprasidone on TMT Part B, Category Fluency, and CPTd'. MANOVA found no significant differences in cognitive performance between groups.

Conclusion: Cognitive performance significantly improved with both agents and was more pronounced with ziprasidone on most tested variables.

425. EFFECT OF OLANZAPINE VERSUS PLACEBO ON THE NEUROPSYCHOLOGICAL STATUS OF PRODROMAL SUBJECTS

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Objective: To present analyses of neuropsychological data collected in the first multi-site, randomized, double-blind, placebo placebo-controlled trial of olanzapine ifor treatment of prodromal phase of schizophrenia. HYPOTHESIS ONE: Subjects who subsequently convert to psychosis will perform at lower baseline levels than subjects who do not convert. Corollary A: Baseline status will relate to conversion proximity. Corollary B: Converters within the olanzapine treatment group will show greater baseline impairment than placebo converters. HYPOTHESIS TWO: Conversion will be accompanied by neuropsychological decline. Corollary: the decline will be mitigated by olanzapine.

Methods: Baseline neuropsychological data were obtained for 60 subjects (mean age 17.7 years, 65% male) meeting prodromal criteriathe Criteria of Prodromal State (COPS). Subjects were randomly assigned to placebo ($n = 29$) or olanzapine 5, 10, or − 15 mg/day ($n = 31$) for one year and no treatment for year two. Non-converters were retested at 6, 12, and 24 months. Converters were retested shortly after conversion and 6 months later.

Results: HYPOTHESIS ONE: Subjects who subsequently convert to psychosis will perform at lower baseline levels than subjects who do not convert. Corollary A: Baseline status will relate to conversion proximity. Corollary B: Converters within the olanzapine treatment group will show greater baseline impairment than placebo converters. HYPOTHESIS TWO: Conversion will be accompanied by neuropsychological decline. Corollary: the decline will be mitigated by olanzapine. Few baseline differences in neuropsychological status are evident between subsequent converters and non-converters.

Conclusion: Mild support for Corollary B exists, with olanzapine-assigned converters showing trends towards weaker baseline performances on several tests.

426. THE EFFECT OF TREATMENT WITH ATYPICAL AND CONVENTIONAL ANTIPSYCHOTICS ON COGNITION FOLLOWING A FIRST EPISODE OF SCHIZOPHRENIA: THE WEST LONDON STUDY

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Background: We examined the effect of treatment with antipsychotic medication on cognitive function 1–3 years following the first episode of schizophrenia.

Methods: Patients were divided into those prescribed atypical ($n=35$) or conventional ($n=25$) antipsychotics throughout the follow-up period and those whose medication had been inconsistent for various reasons ($n=29$). There were no differences between the groups on age of onset, age at testing, duration of untreated psychosis or pre-morbid IQ. Negative, positive and disorganisation syndrome scores at presentation were not different. At follow-up there was a significant improvement in all syndromes for the total sample but no differential effect of treatment grouping. Dyskinesia was more prominent at follow-up in the inconsistent and conventional treatment groups compared to the atypical group. There were no group differences at baseline for any neuropsychological measure. For the total sample, significant improvements were seen in spatial span, spatial working memory and strategy, and Tower of London perfect solutions. There was no change in pattern recognition memory. More patients failed an attentional set-shifting task at follow-up compared to baseline. Significant medication x time interactions were seen for current IQ, spatial span and working memory strategy. This was due to the inconsistent group improving relatively more than the others, an effect that was not explained by the patients who switched to atypical drugs ($n=15$) or by the patients who were overtly non-adherent at follow-up ($n=8$).

Conclusion: Thus in a natural clinical setting, aspects of neuropsychological function improved with treatment but this was not influenced by medication type or regime.

427. NEUROCOGNITIVE EFFECTS OF OLANZAPINE AND LOW-DOSE HALOPERIDOL: A TWO-YEAR TREATMENT STUDY IN FIRST EPISODE PSYCHOSIS

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Background: Patients in the first episode of psychosis manifest severe neurocognitive deficits. In schizophrenia, these deficits are correlated with important indices of outcome and adaptive dysfunction such as occupational skills and quality of life. The treatment of neurocognitive deficits at the onset of psychosis may have a tremendous impact on a patient's lifetime level of functioning.

Methods: In this double-blind study of olanzapine (OLZ) and haloperidol (HAL), 246 (of 263 randomized) first-episode patients were assessed on a range of neurocognitive tests at baseline, including a primary battery comprised of eight neurocognitive tests. Patients were assessed after 24 ($N=126$), 52 ($N=89$), and 104 ($N=46$) weeks of treatment. Standardized scores were developed from each of the measures of the primary battery. The mean modal doses of OLZ and HAL were 10.2 and 4.8 mg/day respectively. The composite score, comprised of measures of verbal fluency, motor functions, working memory, verbal memory and vigilance, improved more following treatment with OLZ than with HAL.

Results: OLZ particularly improved visuospatial working memory and Wisconsin Card Sorting performance compared to HAL. Significant correlations of cognitive change with symptom and side effect change were found with HAL at 104 weeks, but not with OLZ, including correlations with PANSS (total, positive, negative, and general), CGI and EPS. Olanzapine treatment had a significantly greater effect than low-dose haloperidol in improving neurocognitive function in first episode patients.

Concluson: The correlations between neurocognitive change with treatment and clinical changes suggest these factors are independent in patients treated with olanzapine, but not patients treated with haloperidol.

428. OLANZAPINE IN NON-REFRACTORY SCHIZOPHRENIA: EFFECTS ON NEUROPSYCHOLOGY AND PSYCHOPATHOLOGY

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Objective: Evaluate the impact of Olanzapine on neuropsychology and psychopathology in non-refractory schizophrenia.

Methods: Twenty-three (23) non-refractory schizophrenic patients (SCID/DSM-IV) were evaluated in a naturalistic, prospective pilot study with olanzapine (5–20 mg/d). The WAIS-R and WMS-R instruments were applied prior to and after 6 months of treatment, while PANSS was applied every 2 months. Indices for global, verbal, and visual memory, attention/concentration (WMS-R), and global, verbal, and manipulative IQ (WAIS-R) were all analyzed. Psychopathology (evaluated using the PANSS scale) was grouped according to principal components (positive, negative, depressive, cognitive, and excitatory). The results were analyzed using the *t* test [$p < 0.05$].

Results: All 17 patients that concluded the study showed improvements in all neuropsychological indices, with significant improvements in the verbal and global memory indices and the verbal and global IQ indices. There were significant improvements in positive and negative symptoms, in general psychopathology, and in sub-items.

Conclusion: Treatment with olanzapine produced improvements in all psychopathological and cognitive indices. The results also suggest specific effects on verbal memory and IQ.

429. ARTIFICIAL NEURAL NETWORKS (ANN) IN THE STUDY OF THE EFFECTS OF OLANZAPINE ON PATIENTS WITH NON-REFRACTORY SCHIZOPHRENIA

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Objective: Evaluate the impact of olanzapine on the neuropsychological profile of non-refractory schizophrenics previously stabilized with typical antipsychotics, using a computational method based on ANN.

Methods: Schizophrenic patients (SCID/DSM-IV) ($n = 73$) were assessed with a comprehensive neuropsychological evaluation. This evaluation yields eleven parameters covering subcortic-frontal, temporal, and frontal circuits, as well as interhemispheric processing. Twenty-three (23) patients identified as cluster I were selected by a back-propagation-type ANN (previously trained by the research team) participated in a naturalistic, prospective pilot study with olanzapine (5–20 mg/d). They were re-tested after six months of treatment. The same ANN was used to check for possible alterations in neuropsychological profile.

Results: Seventeen (17) patients concluded the trial. The ANN did not recognize 12 of the patients as belonging to cluster I, suggesting a real alteration in their neuropsychological profiles. The ANN recognized 10 patients as belonging to cluster II, characterized by a distinct neuropsychological profile.

Conclusion: In previous studies, cluster I has been characterized by a stable profile and worst neuropsychological performance. Alteration of this profile suggests specific action on the neurofunctional characteristics underlying the schizophrenic condition.

430. IS COGNITIVE IMPROVEMENT WITH ANTIPSYCHOTIC TREATMENT PSEUDOSPECIFIC?

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Background: While cognitive deficits of schizophrenia appear to improve with olanzapine (OLZ) treatment, the relationship between this improvement and other changes in symptoms and side effects (i.e. positive, negative, and extrapyramidal symptoms (EPS)) has not been determined. Cognitive deficits and positive symptoms have repeatedly been demonstrated to be independent dimensions of schizophrenia; however there is substantial evidence that some aspects of cognition are related to negative symptoms or EPS (measured by the Simpson–Angus).

Method: Using post hoc path analyses, we investigated the relationship between cognition, derived from a cognitive battery composite score, and PANSS negative and positive scores as well as EPS. Three double-blind, randomized OLZ versus haloperidol studies were included, resulting in a heterogeneous overall sample (OLZ $N = 311$) including first-episode, early-phase, and stabilized chronic schizophrenia patients.

Results: In the first-episode study, at 24 weeks there was a cognitive effect size of 0.48, with the direct therapy effect accounting for 85.1% ($P < 0.05$) of the LOCF change in cognitive measurements while the other three aspects combined accounting for only 14.9% of the improvement. In two studies (first-episode and early-phase) at 52 weeks, cognitive composite score effect sizes ranged from 0.12 to 1.42, where therapy accounted for more than 81% of improvement beyond baseline. In the third study of stabilized patients, therapy only accounted for 64% (N.S.) of the cognitive effect, with EPS accounting for 27% ($P < 0.05$).

Conclusion: Cognitive treatment effects appear to be autonomous from most other symptoms; it remains inconclusive as to the effect of EPS on overall cognition status.

431. FUNCTIONAL OUTCOMES AND CHARACTERISTICS OF OLANZAPINE COGNITIVE SUPER-RESPONDERS

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Background/objective: Cognitive impairment in schizophrenia is known to have detrimental consequences and olanzapine (OLZ) has been shown to significantly improve cognition in patients with schizophrenia. We hypothesized that there is a differential cognitive response to antipsychotic treatment, with a small portion of patients with schizophrenia improving minimally while others improve considerably. Additionally, we hypothesized that improvement of cognitive deficits during OLZ treatment is a leading contributor to enhanced functional outcomes (acquired occupational skills, quality of life, social problem-solving skills).

Methods: Two double-blind, randomized 52-week studies were analyzed with subjects ($N = 92$) who were either first-episode or within the first five years of the disease. OLZ (mean modal dose = 10.95 mg/day) has been shown to diminish these neurocognitive deficits with some variability.

Results: In this post hoc analysis, we found 22–30% of OLZ-treated individuals to be "cognitive super-responders" defined as 1.0 SD above baseline as measured by a composite improvement score of a cognitive battery. Super-responders ($N = 22$) were characterized as 16–39 years old with a mean age of 23 and approximately 16% males and 10% females. Relationships between these cognitive super-responders and other outcomes, such as functional outcomes, efficacy outcomes, and early discontinuation will be explored.

Conclusion: This characterization of these super-responders will allow us to better understand to role of cognition in improvement of functional outcome.

432. A PLACEBO-CONTROLLED DOUBLE-BLIND INVESTIGATION OF COGNITIVE EFFECTS OF RIVASTIGMINE IN SCHIZOPHRENIA

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Background: Cognitive impairment has the greatest impact on illness outcome in schizophrenia. The most significant challenge in schizophrenia therapeutics, thus, is to develop an efficacious treatment for cognitive impairments. The administration of acetylcholinesterase inhibitors, such as physostigmine and rivastigmine, improves cognitive functions in Alzheimer's Disease, where the loss of cholinergic neurons is thought to be responsible for various cognitive deficits. There are reasons to believe that schizophrenic populations, where the cholinergic system is known to be more intact, may benefit from procholinergic treatment to a possibly greater extent than Alzheimer's disease patients.

Methods: The current study is part of a longitudinal project investigating the cognitive effects of rivastigmine, given as an add-on therapy to antipsychotic-treated patients in a placebo-controlled double-blind design. The study initially involved 40 patients, of which 20 patients (11 assigned to rivastigmine and 9 assigned to placebo) agreed to continued participation, remained on the study drug, and underwent assessment of neuropsychological functions, particularly of executive functioning and working memory, at (i) baseline, and (ii) after12 weeks of treatment with placebo or rivastigmine.

Results: The results revealed a trend (controlling for baseline performance) for improvement in general, with significantly greater improvement seen in spatial working memory with rivastigmine treatment, as compared to the placebo treatment.

Conclusion: Our results suggest that procholinergics can produce cognitive improvement in mild-to-moderately impaired schizophrenia patients. Other procholinergic drugs, such as galantamine, which also act on the nicotine receptors, may produce stronger cognitive enhancement in schizophrenia.

Acknowledgment: This project is funded by the Stanley Research Institute, USA.

433. DOES QUETIAPINE DIRECTLY IMPROVE COGNITIVE FUNCTION?

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Background: There is an ongoing debate about the direct beneficial effect of atypical anipsychotic medication on cognitive function in patients with schizophrenia.

Methods: The present, observational study compared the effects of quetiapine and conventional antipsychotics on measures of executive function, attention, and memory. Subjects were stable outpatients ($N = 33$) with chronic schizophrenia and schizoaffective disorder (DSM-IV) who completed a battery of cognitive tests at the baseline and after 24-week follow-up. Analyses of covariance were performed to compare scores on cognitive measures at the end of the follow-up by treatment group with baseline cognitive function scores used as covariates.

Results: Patients taking quetiapine improved to a greater extent than patients treated with conventional antipsychotics on executive function (Wisconsin Card Sorting Test, $p < 0.01$) and selective

attention (Stroop Color Word Test, $p < 0.001$). Additional differences could be observed for changes in visual working memory between patients receiving low-dose and high-dose conventional antipsychotics. Patients taking low-dose old antipsychotic medication (equivalent with 8 mg haloperidol or less) improved significantly better on visual working memory ($p < 0.03$). No specific association was found between cognitive function and clinical symptomatology or anticholinergic medication.

Conclusion: Long-term treatment with quetiapine appears to have direct beneficial effect relative to conventional antipsychotic drugs on cognitive deficits that are regarded as core symptoms of the disease and have been found to have a critical role in the functional outcome. High-dose conventional antipsychotics seem to worsen these deficits.

434. EXECUTIVE FUNCTION ASSESSMENT OF PATIENTS WITH SCHIZOPHRENIC DISORDER RESIDUAL TYPE IN OLANZAPINE TREATMENT: AN OPEN STUDY

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Background/objective: With the premise that novel 'atypical' antipsychotic (AP) medication could improve cognitive functioning, repeated executive function evaluation by Wisconsin Card Sorting Test (WCST) has been performed on 39 patients with schizophrenic disorder treated with Olanzapine (5–20 mg./day). The primary aim of the study was to assess the effect of Olanzapine on neurocognitive functioning of patients with residual type schizophrenia and dysfunctional outcome. Secondary objective was the evaluation of the drug efficacy to improve symptomatology and quality of life.

Results: After 7 months of treatment patients showed significant improvement of WCST indexes and quality of life with decrease of extrapyramidal signs due to previous AP medications.

Conclusion: Our results show that Olanzapine treatment can improve neurocognitive functioning in term of executive performance. Integrative or more restrictive interpretation of the data is that Olanzapine can permit the possibility of achieving practice effect, otherwise contrasted or worsened by other AP medications. Neurocognitive evaluation, till recently absent from clinical psychiatric treatment planning and implementation, can represent a technique for characterizing dimensions of psychological functioning that are highly impaired in schizophrenia and responsible for difficulties with reintegration into community and independent functioning.

Ethical Issues

435. BASELINE DECISION MAKING CAPACITY IN THE CATIE SCHIZOPHRENIA TRIAL

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Background: Concern about the decision making capacity (competence) of persons with schizophrenia to consent to research participation has led to heated debate and conflicting recommendations. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, a large randomized controlled trial sponsored by the National Institute of Mental Health (NIMH), is now examining the effectiveness of antipsychotic drugs for a broad array of "real-world" patients over 18 months or more. The CATIE schizophrenia trial has implemented procedures to ensure that the competent wishes of research participants are carried out. All prospective subjects were administered the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) and demonstrated adequate capacity before enrolling in the study. The MacCAT-CR consists of four subscales—understanding, appreciation, reasoning, and choice—that reflect the four basic elements of decision making capacity. In CATIE and other studies, the understanding scale was used to determine capacity for research participation.

Method: The MacCAT-CR was completed successfully during screening for all 1493 persons who were randomized in this large-scale clinical trial. Investigators prescreened potential subjects so that only 2% of almost 400 persons who failed screening did so due to inadequate decision making capacity.

Results: Positive correlates of decision making capacity at baseline included education, reading skill, and several other aspects of neurocognition (e.g., executive functioning and verbal learning). Negative correlates included level of negative symptoms. There was no significant association between level of positive symptoms and decision making capacity. Linear regression models augment these findings.

436. FACTOR ANALYSIS OF THE MACARTHUR COMPETENCE ASSESSMENT TOOL—CLINICAL RESEARCH

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Background/objective: Determining the competency of patients with psychosis to consent to research is an issue of growing ethical and clinical concern. Central to this issue is the method of competency assessment. The MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) is a semi-structured interview designed to examine four elements considered central to competence; understanding information, appreciating the information's relevance, reasoning and expressing a choice. Examination of the MacCAT-CR was undertaken to determine its' factor structure quantitatively.

Methods: 111 patients diagnosed with schizophrenia (60), schizoaffective disorder (30) or bipolar (21) completed a standardized version of the MacCAT-CR. There were 61 males and 50 females with a mean age of 37.7 years (SD = 11.4) educated at or above junior high school level. A principal components factor analysis was performed with orthogonal (varimax) rotation to extract factors with an eigenvalue over 1.0.

Results: The resulting six-factor solution explained 62.76% of the total variance. Items loading on the first three factors, accounting for 41.66% of the variance related to three aspects of understanding, immediate recall of semantic information (33.79%), recall of novel factual information (7.47%) and recall of complex concepts (6.12%). The fourth factor related to appreciation of the information (5.67%), the fifth to reasoning (5.09%) and the last to expressing a choice (4.61%).

Conclusion: The results indicate that all elements central to determining competency are assessed with the MacCAT-CR. Interestingly, approximately half of the model's variance is accounted for by immediate recall of information. This suggests neuropsychological evaluation may enhance the standardisation and objectivity of competency assessment.

Violent Behavior

437. TREC-INDIA: RAPID TRANQUILIZATION OF VIOLENT OR AGITATED PATIENTS IN A PSYCHIATRIC EMERGENCY SETTING: A PRAGMATIC RANDOMIZED TRIAL OF INTRAMUSCULAR LORAZEPAM VERSUS HALOPERIDOL PLUS PROMETHAZINE

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Background/objective: The pharmacological management of violence in people with psychiatric disorders is under-researched. The aim of this study was to compare two commonly used interventions for controlling agitation or violence in people with psychiatric disorders to look for specific attributes that either treatment may have to help refine the management of agitation or violence in people with serious psychiatric disorders.

Methods: This pragmatic trial randomized 200 subjects to receive intramuscular lorazepam 4 mg or intramuscular haloperidol 10 mg plus promethazine 25–50 mg mix.

Results: At blinded assessments four hours later (99.5% follow up), 96% of both groups were tranquil/asleep, although 76% given the haloperidol–promethazine mix were asleep compared with 45% allocated lorazepam (RR 2.29, 95% CI 1.59–3.39; NNT 3.2, 95% CI 2.3–5.4).The mix produced faster onset of tranquillisation/sedation and more clinical improvement within the first two hours. Neither intervention differed significantly in the need for additional intervention, physical restraints, numbers absconding, or adverse effects.

Conclusion: Both interventions are equally effective in controlling violent or agitated behavior. However if speed of tranquillisation or sedation is preferred, the haloperidol–promethazine combination has an advantage over lorazepam.

438. A NEUROPSYCHOLOGICAL INVESTIGATION INTO VIOLENCE AND MENTAL ILLNESS

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Background/objective: Previous research has reported cognitive impairment in schizophrenia and antisocial personality disorder, the two mentally disordered groups most implicated in violent behaviour. Until now, studies have focussed on either group exclusively and have been criticised for procedural inadequacies and sample heterogeneity. This study investigated neuropsychological profiles of individuals with antisocial personality disorder and violent and non-violent schizophrenia.

Methods: Individuals who had a history of violent behaviour diagnosed with antisocial personality disorder ($n = 14$) or schizophrenia ($n = 13$), non-violent schizophrenia ($n = 15$) and healthy control subjects ($n = 15$) were compared on a neuropsychological

battery designed to assess general intellectual function, executive function, attention and cognitive processing speed.

Results: Cognitive deficits were more widespread in schizophrenia patients regardless of a history of violence compared to those with antisocial personality disorder, with the latter group displaying significant impairment only in cognitive processing. Violent schizophrenia patients demonstrated greater levels of impairment than non-violent schizophrenia counterparts, specifically in executive functioning.

Conclusion: The findings demonstrate that selective cognitive impairments are implicated in violence in schizophrenia and antisocial personality disorder, implying differences in underlying pathology. Furthermore, cognitive impairment appears more affected by the incidence of schizophrenia than violent history, although there is evidence that a combination of both exacerbates such deficits.

439. ANTICIPATORY FEAR IN VIOLENT SCHIZOPHRENIA AND PERSONALITY DISORDER SUBJECTS: A FUNCTIONAL MRI STUDY

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Background: Incidents of violence in severe mental disorders like schizophrenia and personality disorders are higher than in the general population. Previous research has reported impaired emotion processing in these disorders, and neural circuits involved in emotional processing may underlie violent behaviour.

Methods: This study therefore explored the neural correlates of anticipatory fear, in four groups of men: (i) Personality disorder with history of extreme violence ($n = 13$), (ii) schizophrenia with history of extreme violence ($n = 13$), (iii) schizophrenia with no history of violence ($n = 13$), and (iv) matched controls ($n = 14$).The experimental paradigm involved inducing a state of anticipatory fear in the subjects inside the scanner by repeated presentation of a control condition ('safe') followed by presentation of an activating condition ('shock'). Before going into the scanner, subjects were delivered a mild electric shock by a stimulator in the 'shock' condition off line. The subjects were then instructed that they would receive a similar or stronger shock during the 'shock' condition inside the scanner.

Results: Results in the healthy controls in the shock versus safe conditions indicated activation in the right medial/inferior frontal gyrus, left superior temporal gyrus, and right Insula. In the non-violent schizophrenia patients activation was noted in the bilateral inferior frontal gyrus and left insula. Patients with history of violence did not show any significant areas of activation.

Conclusion: These results indicate abnormalities in the neural circuits underlying the experience of fear in violent schizophrenia and personality disorder subjects.

Acknowledgments: Stanley Research Institute, USA and the Zito Trust, UK.

440. RAPID TRANQUILLISATION FOR AGITATED PATIENTS IN EMERGENCY PSYCHIATRIC ROOMS: A RANDOMISED TRIAL OF MIDAZOLAM VERSUS HALOPERIDOL PLUS PROMETHAZINE [ISRCTN44153243]

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Background: Pharmacological management of aggression has been under researched. Recent studies cannot be applied to most people in middle/low-income countries. The aim of this study was to compare two widely accessible pharmacological treatments for people with aggression/agitation due to mental illness.

Methods: Design: Pragmatic, randomised clinical trial. Setting: Three psychiatric emergency rooms of Rio de Janeiro, Brazil. Participants: 301 aggressive/violent people (151 midazolam, 150 haloperidol/promethazine), Interventions: Open giving of intramuscular midazolam or intramuscular haloperidol plus promethazine. Main outcome measures: Tranquil/sedated at 20 minutes. Secondary outcomes, tranquil/asleep by 40, 60 and 120 minutes; restrained or given additional medication within 2 hours; severe adverse events, another episode of agitation/aggression, needing additional visits from doctor; overall antipsychotic load in first 24 hours, and not discharged by two weeks.

Results: 301 people randomised in 6 months, follow up available for 298 (99%). 134/151 (89%) of people given midazolam were tranquil/asleep after 20 minutes compared with 101/150 (67%)

who received haloperidol/promethazine (RR 1.32, 95% CI 1.16–1.49). By 40 minutes midazolam still had a statistically and clinically significant 13% relative advantage (RR 1.13, 99% CI 1.01–1.26). After one hour about 90% of both groups were tranquil or asleep. There was one important adverse event in each group. One person given midazolam suffered transient respiratory depression and one allocated haloperidol and promethazine had a grande mal seizure.

Conclusion: Both treatments are effective. Midazolam is more rapidly sedating than haloperidol/promethazine. Using haloperidol/promethazine exposes everyone to longer periods of aggression. Adverse effects, and resources to deal with them should be considered in choice of treatment.

441. INFORMATION PROCESSING DEFICIT AMONG SCHIZOPHRENIC PATIENTS WITH EXTREME VIOLENT BEHAVIOR

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Background/Objective: Existence of poor performance in tests of IP among schizophrenic patients is a consistent finding in research literature. Additionally, there is growing evidence that abnormal IP plays an important role in violent non-psychotic behavior. Hypothesis was that IP impairment in violent schizophrenic patients would be more severe than in non-violent schizophrenic patients. The aim of this study was to assess information processing (IP) among extreme violent schizophrenic patients, in comparison to non-violent schizophrenic patients.

Methods: Subjects were 42 schizophrenic patients who were hospitalized in a forensic psychiatric department for murder, attempted murder or extreme violent acts (SH). Age: 34.6 ± 10.7 years, education: 9.1 ± 3.2 years. The second group consisted of 105 male schizophrenic patients (SC) without any violence record who were demographically similar to the first group. IP was measured by a computerized neuro-cognitive battery "CogScan", which included 14 sub-tests: Finger Tapping Test, Inspection time, Motion Perception Test, Simple Reaction Time, Choice Reaction Time, Immediated and Delayed Memory for Pictures, Words and Faces, Stroop test, Digit Symbol Substitution Test (DSST), and Continuous Performance test. Statistical analysis was performed using Student *t*-test.

Results: SH patients were significantly slower in inspection time ($p = 0.000$), but significantly faster in finger tapping test ($p = 0.011$). No significant differences were found in recognition for pictures, words, and faces. However, SH group was significantly less accurate than SC group in working memory (DSST, $p = 0.000$). Significant differences were also found in selective attention ($p = 0.000$), and sustained attention ($p = 0.001$), where SH patients performed worse than SC patients.

Conclusion: Results suggest that schizophrenic patients who manifest extreme violent behavior are significantly more impaired in IP than non-violent schizophrenic patients. Most remarkable are the differences in selective and sustained attention as well as in working memory. Further research is suggested in investigating these impairments as a possible predictor of future violence in schizophrenic patients.

442. BIPOLAR COMPREHENSIVE OUTCOMES STUDY (BCOS): AN AUSTRALIAN OBSERVATIONAL STUDY OF THE TREATMENT AND OUTCOME OF PATIENTS WITH BIPOLAR DISORDER

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Objectives: BCOS is a 2-year prospective observational study of treatment and outcome of patients with bipolar disorder. We present an overview of the naturalistic study design and a description of the implementation and recruitment for this study. There are no previous comprehensive observational studies evaluating the short and long-term management of patients with this disorder in Australia.

Methods: Adult patients with bipolar I (manic, mixed or depressed episode), or schizoaffective, disorder will be enrolled if they: present within the standard course of care; are >/= 18 years; have, at the discretion of the treating psychiatrist, been prescribed a mood stabiliser for the treatment of bipolar disorder; are willing and able to comply with study requirements. It is expected that 240 patients will be enrolled. Outcomes will be assessed across the entire sample population, however, two principal treatment arms will be established at enrollment: (1) patients taking olanzapine—as a mood stabiliser (monotherapy or combined with a conventional mood stabiliser), and (2) patients taking a conventional mood stabiliser (monotherapy or combination therapy-excluding olanzapine). A

range of measures and questionnaires will be used to evaluate clinical, social, quality of life (QoL) and economic outcomes.

Conclusion: BCOS will provide a rich source of information to enhance the understanding of real-life clinical, social, QoL and economic outcomes of patients receiving pharmacological treatment for bipolar disorder in Australia.

443. A PSYCHOPHYSIOLOGICAL INVESTIGATION INTO VIOLENCE AND MENTAL ILLNESS

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Background: Violent behaviour has a strong association with schizophrenia and antisocial personality disorder and impacts on patients' lives as well as on society. The emergence of violence involves a complex interaction between neurobiological and environmental factors. Although developments in the understanding of socio-environmental factors cannot be ignored, advances in prevention and treatment of violent behaviour need to include a full understanding of its neurobiological and cognitive basis.

Methods: This study, therefore, investigated prepulse inhibition (PPI) of the startle response, a psychophysiological measure widely utilised to examine pathophysiology and drug treatments of schizophrenia, in 14 non-violent healthy men, 14 men with schizophrenia but no history of violence, 9 men with schizophrenia and a history of violence, and 9 men with antisocial personality disorder and a history of violence. Neural regions underlying PPI, such as the prefrontal cortex, hippocampus and amygdala, are implicated in both violence and schizophrenia.

Results: The results revealed severe PPI deficits in men with antisocial personality disorder. Men with schizophrenia also showed impaired PPI.

Conclusion: Given the established neural circuitry of PPI from animal and human studies, these observations help to increase current understanding of the neuropsychobiology of schizophrenia and extreme violence. Furthermore, given the sensitivity of PPI to a number of pharmacological manipulations (e.g. disrupted by dopamine agonists and N-methyl-D-aspartate antagonists, and improved by some antipsychotics), the present findings may have implications for developing more effective psychopharmacological approaches to treating mentally ill violent offenders.

Acknowledgment: The study was funded by the Zito Trust, UK.

444. NEURAL CORRELATES OF RIVASTIGMINE TREATMENT IN SCHIZOPHRENIA: AN fMRI STUDY

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Background/objective: Schizophrenia is a disabling psychiatric disorder characterized by multi-faceted cognitive impairment. There is some evidence to suggest that facilitation of central cholinergic activity may form a potential treatment strategy for cognitive impairment in schizophrenic patients. The aim of this study was to investigate the neural correlates of the effects of rivastigmine, a CNS-selective, acetylcholinesterase inhibitor with a very mild side-effects profile, given as an add-on therapy to antipsychotic-treated patients in a placebo-controlled double-blind longitudinal design.

Methods: Twenty-four patients with schizophrenia, stable on antipsychotics and with moderate cognitive impairments, took part. After 1 week on placebo (baseline), all patients entered a double blind protocol and, out of 24 patients, 12 received placebo and 12 received rivastigmine (final sample: 11 patients on rivastigmine and 9 patients on placebo) for the next 12 weeks. All patients underwent functional magnetic resonance imaging (fMRI) during an 'N-back' task involving monitoring of numbers in particular locations on a screen at a given delay from the original occurrence at baseline (prior to drug group allocation) and at 12 weeks after being treated with placebo or rivastigmine.

Results: The results revealed a significant increase in blood oxygenation level-dependent regional brain activity in the cerebellum after rivastigmine treatment, which was not seen in patients who remained on the placebo.

Conclusion: Our observations point to altered neuronal activity in neural regions associated with attention as underlying rivastigmine treatment induced cognitive effects in schizophrenia.

Acknowledgment: The study was funded by the Stanley Research Institute, USA.

Suicidal Behavior

445. SUICIDAL IDEATION IN PATIENTS WITH EARLY PSYCHOSIS

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Objective: The present study aimed to investigate the risk factors of suicidal ideation in early psychosis patients.

Methods: 89 in and out patients with early psychosis and 71 matched normal controls were recruited. A set of comprehensive ratings were used to assess their clinical and psychological profiles: Positive and Negative Syndrome Scale (PANSS), Scale of Assessment of Negative Symptoms (SANS), Montogomery and Asberg Depression Rating Scale (MADRS), Simpson and Angus Scale, Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARNES), Beck Scale of Suicide Ideation (BSS), Beck Hopelessness Scale, Levenson's Internal, Powerful Others and Chance Control Scale (IPC), Brief Reasons for living for adolescents (BRFL-A), Barratt Impulsiveness Scale (BIS-11), Life Event Questionnaire, Future Outlook Inventory, Drug Attitude Inventory (DAI) and Treatment Satisfaction Questionnaire.

Results: The suicidal ideation rate (42%) in patients doubled the rate in normal controls. Suicidal ideation in patients and normal controls shared some common risk factors, including hopelessness ($p = 0.000$), pessimistic future outlook ($p = 0.000$), negative survival and coping beliefs ($p = 0.001$), and history of suicide attempts ($p = 0.002$). Risk factors specific to patients included mild clinical symptoms ($p = 0.001$) impulsive thinking ($p < 0.05$), less endorsement in internal controls ($p = 0.000$), and more endorsement in external controls ($p < 0.05$).

Conclusion: These findings suggested common and specific risk factors of suicidal ideation in patients with early psychosis. Also. It suggested a possible role of psychosis in causing the excessive suicidal ideation, through negative effect of clinical factors and treatment-related factors, additional psychological risk factors, and intensification of mediating psychological risk factors of suicidal ideation.

446. IMPROVEMENT OF SUICIDAL IDEATION AND MEDICATION ACCEPTANCE UNDER TREATMENT WITH ORALLY DISINTEGRATING AND COATED OLANZAPINE TABLETS—RESULTS FROM A PROSPECTIVE MULTI-CENTER STUDY OF ACUTELY ILL PSYCHIATRIC INPATIENTS

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Objective: Study of the treatment of acutely ill patients with olanzapine in psychiatric hospitals. Observation of clinical course, suicidality, and medication acceptance by physicians and nursing staff under treatment with orally disintegrating and coated tablets of olanzapine.

Results: 456 patients with schizophrenia, schizotypal and delusional disorders (80.3%) and mood disorders (17.3%) were followed up for a mean duration of 17.0 ± 12.7 days. Patients were characterized by psychomotor excitement (61.0%), suicidality (41.2%), hostility (28.3%), and psychomotor inhibition (26.5%). Mean final dose was 16.8 ± 7.8 mg/day for coated and 18.2 ± 7.7 mg/day for disintegrating olanzapine. 50.9% of patients received dosages of ≥ 20 mg olanzapine/day (maximum final dose was 60 mg/day). Benzodiazepines (58.6%) and other antipsychotics (26.3%) were most frequently used as concomitant medication. Clinical parameters were subject to descriptive analyses and showed significant CGI improvements at final observation compared to baseline (i.e. 10.5% vs. 57.5% rated markedly ill). At baseline, 240 patients had suicidal ideation as assessed by MADRS item 10 (rating of suicidal thoughts and plans). Scores of 189 patients (41.5%) improved and worsened in 2 patients (0.4%) only. No patient with distinct suicidal plans were documented after two weeks treatment compared to baseline (6.6% of patients). Nursing Assessment of Medication Acceptance (NAMA) showed statistically significant improvement with regard to medication attitude, compliance, ingestion and nursing burden, favouring those patients treated with orally disintegrating olanzapine. Only 3 patients (0.7%) discontinued due to adverse events.

Conclusion: Suicidal ideation and low medication acceptance of severely ill patients improved under acute treatment with olanzapine.

447. SUICIDAL IDEATION CHANGES IN OLZ- OR HAL-TREATED SCHIZOPHRENIA PATIENTS

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Objective/methods: We examined, from a large, randomized, double-blind study, a subset of 935 patients with schizophrenia, schizoaffective, or schizophreniform disorders and baseline suicidal ideation (mean = 1.59) for underlying clinical factors affecting

suicidal ideation, thus potentially associated with the 2.5 times greater rate of suicide attempts during haloperidol (HAL) vs. olanzapine (OLZ) treatment (5–20 mg/d).

Results: Seven out of 40 items on the Montgomery–Åsberg Depression Rating Scale (MADRS) and Positive and Negative Syndrome Scale (PANSS) had a correlation >0.20 with MADRS suicide Item 10 (MADRS-10) and were used for factor analysis. We evaluated change from baseline (LOCF) for MADRS-10 and associated factors, testing for between-treatment differences. Significantly lower MADRS-10 scores were observed in OLZ-treated (0.73, $N=490$) vs. HAL-treated (1.00, $N=194$) patients ($p=0.001$) with 6-week data. Two factors accounted for 62% of the variance; MADRS-10 loaded on one factor (associated with sadness, inner tension, depression) with a 0.37 coefficient and the other factor (associated with pessimism, guilt) with a 0.44 coefficient. Both factors significantly improved with OLZ vs. HAL ($p<0.001$).

Conclusion: In patients with schizophrenia with baseline suicidal ideation, this and related MADRS and PANSS clinical factors were reduced further with OLZ compared with HAL.

448. DEVELOPMENT IN SUICIDE-RATES FOR PATIENTS WITH SCHIZOPHRENIA FROM 1981 TO 1997 IN DENMARK. A NESTED CASE-CONTROL STUDY BASED ON LONGITUDINAL REGISTERS

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Introduction: Risk of suicide is much higher among patients with schizophrenia and related disorders than in the general population. The general population suicide rates in Denmark were reduced by 56 percent during the period from 1980 to 1997. Previous studies have raised concern if the reduction in number of psychiatric beds was associated with increased mortality by suicide. The aim of the study was to investigate the development in suicide risk among patients with schizophrenia.

Methods: Data from four longitudinal Danish registers were linked. A nested case-control design was used including 21,167 persons who committed suicide in the period 1981–1997. Each person was matched with up to 20 controls yielding 423,126 controls. Data were analyzed with conditional logistic regression. The analyses evaluated the relative risk of suicide for persons who had received inpatient treatment for schizophrenia, other psychosis within the schizophrenia spectrum and schizophrenia spectrum disorder during the period 1981–1997. The relative risk was adjusted for social and demographic risk factors of suicide in the general population.

Results: The reduction in suicide rate among patients with schizophrenia and related disorders was similar to the reduction in the general population. The risk of suicide was highest the first year after first admission.

Conclusion: The reduction in suicide rate among patients with diagnosis of schizophrenia and related disorders may be facilitated by better psychiatric treatment or by factors which they share with the general population such as less access to suicidal means or better treatment of suicide attempts.

Substance Abuse

449. CANNABIS ABUSE COMPARED AMONG PARANOID VS. NEURODEVELOPMENTAL PROFILES OF SCHIZOPHRENIC PATIENTS

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Background/objective: Several authors have described associations between cannabis abuse and schizophrenia. More than 60% patients with a first schizophrenic episode have abused cannabis (Allebeck et al., 1993). Other authors suggested that schizophrenia includes different subtypes or dimensions which could indeed constitute distinct entities, from clinical and/or neurobiological perspectives. The aim of this study was to examinewhether specific schizophrenic subtypes are associated with cannabis abuse.

Methods: We studied 83 ($n=83$) schizophrenic in-patients (DSM IV criteria) admitted in different In-patients units of a psychiatric hospital. Patients were measured for a variety of neurodevelopmental markers: neurological soft-signs (NES), obstetric complications (Lewys and Murray) and minor physical abnormalities (Waldrop). They were also administered two short neuropsychological frontal performance tests (TMT a and b) and a psychopathological scale (PANSS). Finally, we also gathered retrospective information on premorbid use and abuse of cannabis, alcohol and other substances, family history, date of onset of the illness and demographic data. Using latent class analysis (LCA) as described earlier (Castle et al., 1998), two subtypes emerged: i.e., neuroedevelopmental and paranoid. We compared both subtypes for cannabis use and the remaining independent variables using, first, a nonparametric univariate approach and, secondly, a multivariate regression analysis to adjust for potential confounding factors.

Results: As described earlier, following Castle's model of LCA two latent schizophrenia subtypes emerged from our sample:

neurodevelopmental ($n = 50$) and paranoid/schizoaffective ($n = 33$). 60.6% of patients in the paranoid group had used cannabis premorbidly compared to 36% of those amongst the neurodevelopmental. This difference was univariately statistically significant with an Odds Ratio (OR) of 2.7 (IC 95%: 1.1–7.5; $p = 0.02$). Finally, after adjusting for all potential confounders controlled for in the study, we found that patients who had premorbidly abused cannabis were 2.9 times more likely to be in the paranoid group than in the neurodevelopmental group (OR = 2.9, 95% CI: 1.1–7.9; $p = 0.035$).

Conclusion: In our sample, cannabis abuse is specifically link to a group of schizophrenic patients with a paranoid/schizoaffective profile rather than to the group with a "neurodevelopmental" profile.

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450. SUBSTANCE MISUSE AMONG FIRST-CONTACT PSYCHOSIS IN SÃO PAULO, BRAZIL: A PRELIMINARY ANALYSIS

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Background: People with severe mental illnesses have high rates of substance misuse. Recent work in Brazil has found lower prevalence of such comorbidity. The aim of the present study is to estimate the prevalence of substance misuse among first-contact psychosis.

Methods: All adults (18–64 years) resident in a defined catchment area who had had a first contact with any mental health service due to a psychotic episode were eligible. Psychiatric diagnosis was carried out with the SCID-II. Alcohol misuse was assessed with the AUDIT and drug misuse was assessed with the South Westminster Schedule (SWS).

Results: Seventy three subjects were included, of whom 40 (54.8%) women. Forty eight (64.9%) had a diagnosis of schizophrenia spectrum disorder. Fifty five (75.3%) subjects used alcohol in the previous 12 months, and 12 (16.4%) scored above the AUDIT cut-off point for alcohol misuse. Twenty one (28.8%) subjects used illicit or non-prescribed drugs in the previous 12 months, and 10 (13.7%) scored above the cut-off point for drug misuse in the SWS. The prevalence of any substance misuse was 24.7% (95% confidence interval: 15.3 to 36.1). Men were twice as likely as women to misuse substances ($p = 0.03$).

Conclusion: Prevalence of substance misuse among first-contact psychosis in São Paulo seems to be similar to those found in centres from developed countries, and higher than that for people with severe mental illnesses in São Paulo. Family control over chronically mentally ill people may play a role in decreasing substance misuse.

Acknowledgment: Funded by the Wellcome Trust, UK.

451. FOLLOW-UP OF COMORBID SUBSTANCE USE IN SCHIZOPHRENIA: THE WEST LONDON FIRST EPISODE STUDY

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Background: Comorbid substance use in schizophrenia is common, and associated with more severe illness and poorer clinical outcome, but data are limited on frequency and impact of substance use in first-episode schizophrenia in the UK.

Methods: We obtained alcohol and drug use data on 75 patients at initial presentation to services (baseline) and at follow up (median 13.5 months).

Results: Comparing those with and without lifetime substance use at baseline, there were no significant differences in follow-up measures of social function, symptom profile or severity of illness. Neurocognitive assessments (IQ, memory and executive function) were available at baseline and one-year follow-up for a sub-sample of 65 patients. There were no significant interactions between change in neurocognitive performance measures over time and baseline drug or non-drug use, except for spatial working memory (SWM). The absence of a drug use history at baseline was associated with a significantly greater improvement in SWM performance over the follow-up period. The proportion of smokers in the sample rose from 59% at baseline to 64% at

follow-up. However, while 28% reported lifetime problem drinking at baseline, only 16% had this problem at follow-up. Further, while 62% reported lifetime cannabis use at baseline, and 28% were currently using the drug, this latter figure had fallen to 19% at follow-up.

Conclusion: The findings suggest that the prevalence of both alcohol misuse and cannabis use in schizophrenia may diminish in the period following first presentation to psychiatric services, in the absence of specific interventions for this problem.

452. SUBSTANCE MISUSE IN SCHIZOPHRENIA: DOES IT AFFECT COMPLIANCE AND OTHER OUTCOME MEASURES?

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Background/objective: Despite the high comorbidity of substance misuse and schizophrenia, few large scale British studies have looked at symptom profile and outcome in this population. The aim of this study was to use data on substance use among subjects with schizophrenia collected in a randomised controlled trial, validated for the purpose of this study, to see if there are differences between substance users and non users on a variety of outcome measures.

Method: 1. A sample of subjects in the CuTLASS study were interviewed using the SCID to determine whether SCID-diagnosed substance misuse disorders corresponded to substance misuse categories generated in the CuTLASS study from casenote review. 2. Substance users were compared with non users on a variety of outcome measures.

Results: 1. Two CuTLASS categories, no substance use and major substance use, could be validated against SCID diagnoses; the third category, minor use, could not be validated. 2. Substance misusers were more likely to be young men. There were no significant differences between users and non users for positive and negative symptoms, quality of life, number of previous hospitalisations, extrapyramidal side effects or medication compliance. Drug users were younger at age of first treatment than non users. Alcohol users had more depressive symptoms than non users. Substance users had more negative attitudes towards prescribed medication, although this effect disappeared when age and gender were controlled for. Non compliance was associated with more severe psychopathology, and a worse quality of life.

Conclusion: Substance misuse did not seem to confer the adverse outcomes that previous studies suggest.

453. CANNABIS USE AND PSYCHOSIS IN ADOLESCENTS AND YOUNG ADULTS

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Background: Adolescents are at higher risk of both developing psychosis and using cannabis. Moreover, several epidemiological studies suggest that cannabis use increases the risk of psychosis, especially in individuals with an established vulnerability to psychotic symptoms. The aim of the present study was to investigate this relationship in a population-based sample of adolescents and young adults.

Method: Data from the Early Developmental Stages of Psychopathology (EDSP) study were analyzed. In a longitudinal design, 2436 adolescents and young adults aged 14 to 24 were studied. Substance use and psychotic symptoms were investigated at baseline and at follow-up 3 years later. Logistic regression analyses were conducted to investigate the interaction-effect of cannabis use and pre-existing vulnerability to psychosis.

Results: Cannabis use at baseline increased the risk of psychotic symptoms at 3-year follow-up, even after adjusting for use of other drugs (OR = 1.80, 95% CI: 1.35, 2.39). The effect of cannabis was much stronger in those with an established vulnerability to psychosis at baseline (risk difference, 16%; additive interaction $\div^2 = 0.036$). Also a dose–response relationship was observed in frequency of cannabis use. Reported psychotic symptoms at baseline did not predict cannabis use 3 years later.

Conclusion: Cannabis use increases the risk of developing psychosis. Particularly young adults with an established vulnerability to psychosis seem to be susceptible to this risk-enhancing effect. The effect of cannabis on psychosis is independent of the use of other drugs or alcohol. There is no evidence that adolescents start using cannabis to self-medicate their symptoms.

454. CANNABIS AND MULTIPLE SUBSTANCE ABUSE RAISE THE SERUM CONCENTRATIONS OF THE NEUROTROPHINS NGF AND BDNF IN DRUG-NAIVE SCHIZOPHRENIC PATIENTS

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Background: Neurotrophic factors are known to play a crucial role in growth, differentiation and maintenance of function in neurons during development and adult life. In schizophrenic patients a deficiency of nerve growth factor (NGF) with respect to neurodevelopment was postulated (1).

Methods: We examined serum-NGF concentrations in 109 drug-naïve schizophrenic patients.

Results: We found normal NGF concentrations compared to controls ($n = 61$) when no substance abuse prevailed, but significantly raised NGF with associated former cannabis or multiple substance abuse. This possibly represents an endogenous repair mechanism of damaged neurons in vulnerable brains (2). Likewise we examined 130 sera of drug-naïve schizophrenic patients for BDNF and again found differences between the groups.

Conclusion: We thus concluded that neurotrophins may play a role in the origin and outcome of schizophrenia at least with respect to drug intake.

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455. DRUG ABUSE IN FIRST EPISODE NON-AFFECTIVE PSYCHOSIS

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Objective: to study the degree, to which patients with first episode psychosis abuse drugs and the relationship between baseline characteristics and drug abuse.

Methods: From the TIPS (early Treatment and Intervention in Psychosis) study, 281 patients of the ages 18–65, with first episode non-affective psychosis have been included during 1997–2001. All patients were assessed at start of treatment on variables such as diagnosis, premorbid functioning, symptom profile, social functioning, quality of life, abuse of drugs/alcohol and neuropsychology. We used the Clinician rating scale to assess drug abuse.

Results: Sixty-two% did not use any drugs, 15% used drugs without any social, economical or work-related side-effects. Fifteen% were abusing drugs and 8% had severe drug-dependence. Abusers were significantly more often abusing alcohol. They were more often males and had less meaningful activities, including work, during the last year before start of treatment. Abusers had, however, more friends during early and late adolescence and during the last year before start of treatment, but poorer school functioning during the same periods. No differences were found for duration of untreated psychosis, diagnosis, global functioning, or for level of symptoms at start of treatment.

Conclusion: Drug abuse is a severe problem for first episode psychosis patients. Premorbidly drug abusers appear to be more extroverted, which might expose them to drugs more than usual.

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456. CANNABIS USE ADVERSELY AFFECTS P300 EVENT-RELATED POTENTIAL LATENCY IN RECENT-ONSET SCHIZOPHRENIA

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Background: Cannabis use in patients with schizophrenia has been associated with lower treatment compliance, more positive symptoms, higher re-hospitalisation rates, and more unfavourable course and outcome of the disease process. Event-related potentials (ERPs) are studied in schizophrenia to gain insight into information processing abnormalities that may constitute a core deficit of this disease.

Methods: The current study investigates the effect of cannabis use on the P300 ERP in schizophrenia patients. Forty-four patients with recent-onset schizophrenia were assessed with the P300, mean age was 21 years. Cannabis use was rated with self reports of the patient, reports of parents or other primary care takers and staff.

Results: Five patients used cannabis 2–3 times a week, one patient used once a day, two patients once a month and one patient once a week. P300 latency was delayed in the cannabis using patient group compared to the noncannabis using patient group at all three electrode locations Fz: $z = -1.9$, $p < 0.05$; Cz: $z = -2.25$ $p < 0.03$ and Pz: $z = -2.2$ $p < 0.03$.

Conclusion: Our preliminary results show a relationship of cannabis use and P300 latency in young patients with recent-onset schizophrenia. Cannabis may slow information processing by producing cell toxicity or disruption of brain messenger coordination.

457. SUBSTANCE USE DISORDERS IN SUBJECTS WITH SEVERE MENTAL DISORDERS ADMITTED TO PSYCHIATRIC HOSPITALS IN SÃO PAULO, BRAZIL

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Objective: To estimate the prevalence of substance use disorders and cigarrette smoking among individuals with severe mental disorders living in São Paulo and who had been admitted to psychiatric hospitals.

Methods: The study had a cross-sectional design. One hundred and three subjects with severe mental disorders, living in defined catchment areas of São Paulo who had been consecutively admitted to psychiatric hospitals between 01/02/2000 and 30/06/2000 were included. Subjects were interviewed with standardised questionnaires to assess psychiatric symptoms, social adjustment, use of alcohol, tobacco and illicit drugs.

Results: Ten (9,7%) subjects fulfilled criteria for alcohol dependence and seven (6,8%) for drug dependence in the previous year. The 12-month prevalence of alcohol or substance use disorders was 13,6% (95% CI: 7.6–21.7%). Men, those with a diagnosis of schizophrenia and poor social adjustment showed higher rates of comorbidity. Smoking was strongly associated with substance use disorders. Comorbidity was associated with the absence of informal caregivers. The 12-month prevalence of smoking was 63.1% (95% CI: 53.0–72.4%). Characteristics associated with tobacco use were higher number of previous psychiatric admissions and a diagnosis of substance use disorder.

Conclusion: These results confirm the low prevalence of comorbidity due to substance use disorders among individuals with severe mental disorders found in a previous Brazilian study and underscores the importance of tobacco use among these subjects.

Acknowledgments: Funded by FAPESP and CAPES, Brazil.

458. SUBJECTIVE REASONS FOR CANNABIS USE AND PRODROMAL SYMPTOMS IN RECENT-ONSET SCHIZOPHRENIA AND A GENERAL POPULATION

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Background: Cannabis use at age 18 is related to developing schizophrenia, also after correcting for poor interpersonal social integration during adolescence and psychiatric illness at age 18, although the odds ratio decreased after this correction (Zammit et al., 2002). This supports both a causal explanation of the found relationship, as well as it suggests that patients may have used cannabis to self-medicate prodromal symptoms.

Methods: To further investigate the self-medication hypothesis, we interviewed 29 patients with a recent-onset of schizophrenia on reasons for cannabis use before the first psychosis, and a general population of 40 cannabis users for comparison. A list of reasons for use was presented to patients (mean age 22.5 years ± 2.7 years) with a history of cannabis use, and to the controls (23.4 years ± 2.3).

Results: After age 17, but before the first psychotic episode, patients (vs. controls) had smoked per year a median of 297 joints (vs. 437), range 0–2267 joints (vs. 3–3357). The reasons for use and the percentages of patients (vs. controls) who reported to have used cannabis for those reasons are: boredom 66% (vs. 38%, $p < 0.05$), feeling tense 52% (45%), feeling empty inside 41% (8%, $p < 0.01$), to belong to a group 38% (28%), to make contact with others more easily 38% (5%, $p < 0.01$), to forget problems (at school, at home) 31% (37.5%), feeling depressed 31% (13%).

Conclusion: Thus, before the first psychosis patients have used cannabis significantly more often than controls for social and coping reasons, which supports the self-medication hypothesis.

459. PREVALENCE OF SUBSTANCE MISUSE AND STABILITY OVER TIME AMONG PEOPLE WITH SEVERE MENTAL ILLNESS IN SÃO PAULO, BRAZIL

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Background: In developed countries, prevalence of substance misuse among individuals with severe mental illnesses is high. Data on such comorbidity in less developed countries are scarce. The aim of the present study was to investigate the stability of substance misuse among people with severe mental illness in a large urban centre of a developing country.

Method: A 1-year follow up study was carried out in São Paulo, Brazil. Subjects were residents of a defined geographic area who had had any contact with mental health services over a three-month period and a diagnosis of functional psychosis. Standardised instruments were used to assess use of alcohol, illegal and non-prescribed drugs. Criteria for substance misuse were assessed with the SCAN.

Results: At baseline, 192 subjects were included in the study, 102 (53.1%) were male and 113 (58.8%) had a diagnosis of schizophrenia. Prevalence of any substance misuse was 10.4% (95%CI: 6.5 to 15.6). At follow up, 149 (77.6%) were re-assessed, and prevalence of substance misuse was 8.7% (95% CI: 4.7 to 14.5). Six out of 13 subjects continued to fulfil criteria for alcohol misuse, and 3 more subjects also fulfilled such criteria. Two out of 7 subjects continued to fulfil criteria for drug misuse and 3 more subjects fulfilled such criteria.

Conclusion: Prevalence of substance misuse was lower than those found in developed countries at baseline and at follow-up. Lack of social policies for those suffering from severe mental illnesses and cultural factors must play a major role.

Acknowledgment: Funded by FAPESP, Brazil.

460. CANNABIS USE PRIOR TO PSYCHOSIS ONSET IS RELATED TO PRESERVED NEUROCOGNITION AT 10 YEAR FOLLOW-UP

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Background: There is presently considerable interest in the relationship between cannabis use and the subsequent development of mental illness.

Methods: Participants in the Manchester first episode psychosis cohort were recruited between 1987 and 1989. As part of their clinical assessments recorded during index admission, they were asked to indicate their use of cannabis on a three point scale (none; less than weekly; at least weekly) during the two year period leading up to their admission. Whenever possible this information was cross-referenced with material provided with one (and sometimes two) informant(s).

Results: At index admission, in comparison to non-users, cannabis users evinced significantly more positive psychotic symptoms, fewer neurological soft-signs, and better pre-morbid adjustment. At 10-year follow-up, there were minimal differences between groups in respect of symptomatic outcome, and only modest differences in respect of functional outcome. However, the cannabis users significantly out-performed the non-users on eight out of nine neurocognitive assessments encompassing spatial skills/memory, recognition memory for faces, verbal fluency and card sorting.

Conclusion: Although we can only speculate as to the role of substance abuse in the precipitation of psychotic illness, our results suggest that the follow-up neurocognitive signature of pre-morbid cannabis users is distinguished by a relative preserving of function and an under-representation of the so-called 'deficit' state.

Acknowledgment: This project has been supported by a grant from the Stanley Foundation.

461. METABOLITE ALTERATIONS IN BASAL GANGLIA ASSOCIATED WITH RESIDUAL SYMPTOMS OF ABSTINENT TOLUENE USERS: A PROTON MRS STUDY

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Background: Long-term toluene abuse causes a variety of psychiatric symptoms, including residual symptoms that are reminiscent of the symptoms in schizophrenia. However, little is known about abnormalities at the neurochemical level in the living human brain after long-term exposure to toluene.

Methods: To detect neurochemical changes in the basal ganglia of subjects with a history of long-term toluene use, proton magnetic resonance spectroscopy (^{1}H MRS) was performed in 12 abstinent toluene users and 13 healthy comparisons with no history of drug abuse. N-acetylaspartate (NAA), creatine plus phosphocreatine (Cr+PCr), and choline-containing com-

pound (Cho) levels were measured in the left and right basal ganglia.

Results: The Cho/Cr+PCr ratio, a marker of membrane metabolism, was significantly increased in the basal ganglia of toluene users in comparison to that of the control subjects. Furthermore, the increase in the Cho/Cr+PCr ratio was significantly correlated with the severity of residual psychiatric symptoms.

Conclusion: These findings suggest that long-term toluene use causes membrane disturbance in the basal ganglia, which is associated with residual psychiatric symptoms that persist even after long-term abstinence from toluene use.

462. THE IMPACT OF SUBSTANCE USE DISORDERS ON RECOVERY AND RELAPSE RATES, AND SERVICE USE, IN FIRST-EPISODE PSYCHOSIS

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Background: Individuals with schizophrenia and other psychotic disorders are at greater risk of developing substance use disorders (SUD) compared to the general population, and there is evidence that SUD can adversely affect the course of psychotic disorders, and that remission of SUD results in greater clinical stability. However, most studies to date have recruited patient samples with chronic psychotic conditions and have not adequately controlled for potential confounding factors, such as illness duration, demographic variables, and non-compliance with treatment, which makes it difficult to interpret the findings.

Methods: The present study utilizes a prospective design to follow-up patients ($N = 126$) presenting with a first-episode of DSM-IV psychotic disorders for a period of 15 months. Patients were recruited from three sites in Melbourne, and clinical interviews were undertaken with standardized research instruments to evaluate clinical functioning and mental health service during the follow-up period. We are evaluating the impact of SUD on recovery and relapse rates, and service use, in this sample.

463. COMORBID SUBSTANCE ABUSE IN RECENT-ONSET SCHIZOPHRENIA: BRAIN MORPHOLOGY AND NEUROPSYCHOLOGICAL EVALUATION

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Background: Subtle changes in brain morphology and neuropsychological impairment are a common finding in patients with schizophrenia. High rates of comorbidity with substance abuse are recognized in schizophrenia also. Nevertheless there is still few knowledge about the relationship of substance abuse, schizophrenic disorder, cognitive dysfunction and brain pathology.

Methods: In a prospective design we studied 100 patients with recent-onset psychosis consecutively admitted to our hospital. 89 patients were diagnosed as schizophrenia or schizoaffective disorder. The patients received standardized psychopathological evaluation (BPRS, SANS, AMDP, MADRS, CGI, GAF), neuropsychological investigation (e.g. TMT-A/B, WCST, Digit Span, Verbal Fluency, Corsi Block Tapping) and cerebral MRI including volumetry of selected brain regions (amygdala, hippocampus, lateral and third ventricle, gyrus temporalis superior, gyrus cinguli).

Results: 32 of 89 patients reported drug abuse (Europ-ASI), in 24 patients THC (22 patients) and/or amphetamines (4 patients) could be detected in urine. Compared with nonabusers the sample of substance abusers was younger, predominantly male and had lower socioeconomic status. Depression was less in abusers than in nonabusers at admission. There was a negative correlation between THC-concentration and hostility-suspiciousness or activation (BPRS). Substance abusers showed a reduced asymmetry-index of the superior temporal gyrus ($p = 0.035$) and displayed better results in TMT-B ($p = 0.017$) and WCST ($p = 0.022$, total errors).

Conclusion: There was evidence that substance abuse and not abnormalities of neurodevelopmental processes (brain morphology and cognitive dysfunction) may serve as a main risk factor for developing schizophrenia in a subgroup of individuals.

Viruses

464A. DIFFERENTIAL EXPRESSION OF RNA ENCODING HERV-W ENVELOPE AND ASCT2 IN THE BRAINSTEM OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Neurons in the upper brainstem have, in animal studies, been shown to be the target of a number of infectious agents after both intracerebral and intranasal inoculations. Our previous findings of elevated transcription of HERV-W related genes in *postmortem* brain tissue from individuals with schizophrenia may be secondary to exogenous infections. Therefore, it is of interest to quantify the transcriptional activity of the genes encoding HERV-W envelope and ASCT2 in tissue from this brain region. ASCT2 is a sodium-dependent amino acid transporter involved in cycling of glutamine between astrocytes and neurons. ASCT2 was recently shown to be a functional receptor for an HERV-W encoded envelope protein. The presence of transcripts encoded by rubella, VZV, HSV-1/2, measles virus, enteroviruses, influenza A virus and Japanese Encephalitis virus was investigated by PCR in sections of the upper brainstem obtained from The Stanley Consortium Brain Collection. Real-time PCR was used for quantification of levels of mRNA encoding HERV-W envelope and ASCT2 in this same material.

Results: We could not detect any viral transcripts in any of these individuals. In the group of individuals that had suffered from schizophrenia there was a significant correlation ($p = 0.0053$) between elevated transcription of the genes encoding HERV-W envelope and ASCT2. In the control group no such correlation was seen.

Conclusion: The present findings indicate an aberrant transcriptional activity of certain HERV-W loci affecting the transcriptional activity of the ASCT2 amino acid transporter. In the upper brainstem, persisting viral transcripts could not be detected in this material.

Sex Differences

464B. SEXUALLY DIMORPHIC COVARIATION OF 3D CRANIOFACIAL SHAPE WITH COGNITIVE FUNCTION

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Background: Over embryogenesis, the face and brain evolve as one developmental unit. This accounts for craniofacial dysmorphogenesis in disorders of early brain development, including schizophrenia, with cognitive deficits in adulthood. Little is known of how craniofacial morphology covaries with cognitive ability among the general population.

Methods: 3D laser surface scans of the face were obtained for 93 volunteers [36 male, 57 female] to resolve 24 3D anatomical landmarks. Subjects were assessed using Trail Making Tests A and B [TrA and B], a cognitive test of spatial attention, visuomotor tracking and processing speed, and the Controlled Oral Word Association Test, a cognitive test of verbal fluency. Covariance of shape was analysed with geometric morphometrics using multiple linear regression of cognitive measures onto principal components of shape variation, with significant shape models visualised using 3D graphics.

Results: Among males, TrA was associated with facial shape [$R2 = 0.39$, $P < 0.001$] while TrB and verbal fluency were not. Among females, verbal fluency was associated with facial shape [$R2 = 0.21$, $P < 0.05$] while TrA and TrB were not. Among males, TrA was associated with facial shape asymmetry [$R2 = 0.22$, $P < 0.05$] while TrB and verbal fluency were not. Among females, verbal fluency was associated with facial shape asymmetry [$R2 = 0.19$, $P < 0.05$] while TrA and B were not.

Conclusion: Sexually dimorphic covariance of cognitive performance with facial shape may reflect the intimacy of early cerebral-craniofacial development over the period when gender-specific topography and asymmetries are established.

Acknowledgment: These studies were supported by the Stanley Medical Research Institute.

465. FEMALES EXHIBIT LOW FREQUENCY-SPECIFIC SUPERIORITY FOR DISCERNING REALITY IN A MALE VOICE

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Background: In schizophrenia, auditory verbal hallucinations may be experienced with varying reality. Reality can be defined as the quality of having actual existence which, in auditory psychophysics, may correspond to the detection of natural sound object characteristics, including spectral detail.

Methods: Forty healthy subjects (20 female) were studied. Digital filters were applied to hallucination-like speech, uttered by a male voice, in two conditions: high-pass (remove frequencies below a set level) and low-pass (remove frequencies above a set level). In a 2 alternative forced-choice design, each unfiltered stimulus was paired with its filtered equivalents. Subjects listened and decided which voice sounded 'real'; the unfiltered stimulus was the target.

Results: Accuracies for identification of the unfiltered target were analysed by ANOVA. A 'gender' by 'filter' interaction was significant [$P = 0.002$]. This was due to better performance by the female than male subjects in the high-pass condition [$P = 0.007$] and better performance within the female subjects in the high-pass than low-pass condition [$P = 0.003$]. On the other hand, there was no difference between genders in the low-pass condition and no difference within the male group between conditions.

Conclusion: We found that for females, but not males, the presence of low, not high, frequencies in a male voice was most important in the perception of that voice as being real. In schizophrenia, hallucinated voices are typically male and female patients may be more likely to experience auditory hallucinations than males. Normal gender differences might contribute to variation in this clinical picture.

466. AGE AT MENARCHE IS NOT ASSOCIATED WITH SCHIZOPHRENIA AMONGST DANISH TWINS

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Background/objective: Estrogen has been implicated in the sex differences in age of onset in schizophrenia, and menarche (the age of first period) has been proposed to be associated with age of onset. We attempted to test this in a Danish population-based sample of twins.

Methods: The material consisted of a cohort of 15,392 female twins from the Danish Twin Register. These data were linked to the Danish Psychiatric Central Register in order to study menarche as a risk factor for schizophrenia, and also to study possible correlations between menarche and age of onset. Data were analysed using Poisson regression. Menarche was collected by a questionnaire mailed to all twins in the Twin Register. For validation of the register data, the association between menarche and age of onset was tested in a sample of personally interviewed twins.

Results: In 57 twins diagnosed with schizophrenia the menarche was known. No association between menarche and schizophrenia risk was found, nor was there any correlation between menarche and age of onset. In the interviewed sample of 27 twins, age of onset was assessed through a personal SCAN interview. There was no relationship to age of onset, nor any relation to total GAF scores.

Conclusion: This study did not support any relationship between menarche and age of onset of schizophrenia or schizophrenia risk. Our study, however, is limited by a relatively small sample size.

467. SEX DIFFERENCES IN EMOTIONAL REACTIVITY TO DAILY LIFE STRESS IN PSYCHOSIS

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Background/objective: The expression of schizophrenia has been reported to differ between the sexes. The current study investigates whether these sex differences in clinical expression are reflected in an underlying mechanism that may be causally related to psychosis, namely increased stress-sensitivity in daily life.

Methods: 42 patients (22 male–20 female) with psychotic disorder in a state of clinical remission, were studied with the Experience Sampling Method (a structured diary technique assessing current context and mood in daily life) to assess (1) appraised subjective stress related to daily events and activities, and (2) emotional reactivity conceptualised as changes in both negative affect (NA) and positive affect (PA) in relation to the subjective stress.

Results: Multilevel regression analyses revealed that females reported a significant increased emotional reactivity to daily life stress compared to males, reflected both in an increase in NA and a decrease in PA.

Conclusion: These results suggest that gender differences are not limited to the characteristics of psychosis, but are also reflected in underlying etiological mechanisms. Furthermore, these results strengthen the hypothesis that females are more susceptible to a schizo-affective subtype of schizophrenia.

Social Behavior

468. SOCIAL "CASEMIX" AND SOCIAL OUTCOMES—ASSOCIATIONS OVER ONE YEAR: A REPORT FROM THE SOHO STUDY PAN-EUROPEAN SAMPLE OF SCHIZOPHRENIA OUTPATIENTS

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Background: Casemix is a term used to describe the mix of cases presenting to a health system (i.e. the range and type of patients a hospital or health service treats). Casemix is also used as a generic term to describe scientifically developed grouping mechanisms used to categorise hospital stays or patient treatment episodes to facilitate scientific planning and management of healthcare. In epidemiological studies, casemix can refer to patient characteristics that comprise treatment cohorts under study.

Methods: Croudace et al. (2002) described a latent structure approach to the development of casemix groupings based on latent class analysis of unordered categorical indicators of social characteristics. This method was applied to the SOHO study Pan-European sample to derive a categorical social casemix variable that 1) summarised social characteristics of SOHO patients, and 2) could be used to adjust outcome comparisons for imbalance between known prognostic factors between treatment cohorts. We present graphical summaries of social outcomes (frequency of social contact) recorded on four occasions during the first year of the SOHO study, stratified by social casemix group. These plots enable us to compare social outcome trajectories between (social) casemix groups and treatment cohorts. This approach may be used by other cohort studies of psychiatric patients where associations among social factors and outcomes are of interest.

Reference

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469. SCHIZOTYPY AND SOCIAL SKILLS: PERFORMANCE VERSUS DISTRESS

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Background: Among the clinical manifestations of schizophrenia, significant impairments in social functioning have been consistently reported. More specifically, social isolation, impairments in social competence, deterioration in interpersonal close relationships and communication-deficits are recognized as characteristics frequently displayed by patients. According to the continuum hypothesis, subjects from a nonclinical population with a biological–genetic liability to schizophrenia may to some degree show impairments similar to patients. A liability to schizophrenia may be expressed as schizotypal personality traits, such as referential thinking. The aim of our study was to examine the relationship between schizotypal personality traits and social skills in a nonclinical, nonstudent sample from the general population.

Methods: The Schizotypal Personality Questionnaire (SPQ) was used for assessing schizotypal traits on the positive, negative and disorganised dimensions. Social skills were evaluated using the Scale for Interpersonal Behavior (SIB). The SIB measures the frequency of engagement in specific social behaviors as well as the experienced distress it is accompanied by. Thirty subjects completed the SPQ and the SIB.

Results: Frequency of specific social behaviors did not correlate with dimensions of schizotypy. However, distress during social behavior correlated significantly with the positive and negative schizotypy dimension ($r = 0.48$, $p = 0.007$ and $r = 0.66$, $p < 0.001$ respectively).

Conclusion: These findings show that both positive and negative schizotypy are significantly related to distress during social interactions. We propose that healthy subjects scoring high on positive and/or negative schizotypy may need more effort to survive in a social environment due to subtle deficits in cognitive-emotional processing and hence may be faced with discomfort in social interactions.

470. MEASURES OF COPING ABILITIES OF SCHIZOPHRENIA PATIENTS

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Methods: Coping Inventory for Stressful Situations (Endler and Parker 1990) was used to measure task-, emotion- and avoidance-oriented coping styles in 148 schizophrenia patients and 174 nonpatient controls. Scores of greater than median reflect a participant's preference for one, two or three coping strategies.

Results: The following coping patterns were identified: task (T), emotion (E), avoidance (A), task-emotion (TE), task-avoidance (TA), emotion-avoidance (EA), higher than median in three coping styles (h-TEA) and lower than median in three coping styles (l-TEA). In addition, these coping patterns were grouped into favorable (T, A, TE, TA, h-TEA) and unfavorable (E, EA, l-TEA) coping modes. Schizophrenia patients used both E and TA coping patterns 2.3 times more often than nonpatient controls, whereas T and EA coping patterns were used significantly less frequently by patients

than controls ($chi^2 = 29.1$, $df = 7$, $p < 0.001$). Coping patterns of schizophrenia patients are significantly associated with symptoms' severity (PANSS), side effects, emotional distress, awareness, quality of life, self-constructs and social support. Established logistic regression model ($R^2 = 0.43$, $chi^2 = 87.4$, $df = 14$, $p < 0.001$) correctly classified 80.9% of patients with unfavorable ($N = 69$) and 86.1% with favorable ($N = 79$) coping modes (83.7% for whole sample). The sensitivity of the model was 80.9% and the specificity 86.1%. Unfavorable coping is associated with obsessiveness and autistic preoccupation, while favorable coping—with quality of life, depression, self-efficacy and social support.

Conclusion: Thus, coping patterns and modes are a valid presentation of coping abilities of schizophrenia patients. Further studies should attempt to investigate stability or changes in coping patterns and modes over time.

471. SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA: SIBLING BOND, COPING PATTERNS AND FEAR OF POSSIBLE HEREDITY

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Background: Research in family burden and family resources in schizophrenia has tended to emphasize parent–child relationship. However, siblings are crucial parts of schizophrenic patients' social network. We aimed to investigate the specific psychological aspects of being a sibling of a person with schizophrenia.

Method: 16 siblings between the ages of 16 and 55 years (mean age 31 yrs.) and their affected relative were recruited in a psychiatric hospital setting. In tape-recorded semi-structured interviews, we explored how siblings perceived the patients' psychiatric illness, the impact of the illness on self and family system, and the role in illness management. The concordance between the two psychologists who independently read the transcribed interviews and identified themes were 0.92–0.94.

Results: A unifying theme was an emotional sibling bond characterized by feelings of love, sorrow, anger, envy, guilt and shame. The major categories linked to coping were avoidance, isolation, normalization, care giving and grieving. The siblings described concerns of the impact of a family history of psychiatric illness, a fear of becoming mentally ill, and reflections on being a carrier of "bad genes". Our findings support earlier findings of coping patterns, but provide a model that includes awareness of genetic vulnerability as an important part of siblings' subjective burden.

Conclusion: Results indicate that schizophrenia in the family has profound long-term psychological impact. Based on the findings, we have recently designed and carried out a six-hour psychoeducational program for siblings of schizophrenic patients.

Quality of Life

472. HOW SHOULD WE MEASURE COMMUNITY FUNCTIONING

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Background: In assessing schizophrenia, there is a great appreciation for the complexity of constructs such as cognition and symptomatology. However, the assessment of community functioning is relatively new and not as well developed. The multifacted nature of the construct of community functioning is frequently neglected. Often times a global index of function is used which provides no information regarding specific areas of strength or weakness. On the other hand, specific measures are lumped together as if they measure the same construct. Furthermore, the method of assessment (e.g. self-report, observation of performance), may not be distinguished. In this study, different dimensions of community functioning assessment were related in a sample of people with psychiatric disabilities (primarily schizophrenia and schizoaffective disorder).

Methods: Eighty one participants completed global and specific measures of community functioning. The global assessments included a self report and informant version of the Independent Living Skills Inventory. The specific measures included knowledge, performance and application versions of a Test of Grocery Shopping Skills.

Results: The results indicate that the strongest relationships existed among the different forms of the specific assessment, particularly knowledge and performance accuracy, $R = 0.63$. The global assessment, particularly the informant version, was most closely related to the knowledge version of the specific measure, $R = 0.41$.

Conclusion: Overall, there were few relationships among the measures. Community functioning should be viewed as a multidimensional construct. Work needs to be done to further distinguish the constructs, and must consider distinctions in assessment content as well as assessment method.

473. THE REVISION AND PSYCHOMETRIC RE-VALIDATION OF THE SCHIZOPHRENIA QUALITY OF LIFE SCALE

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Background/objective: The original SQLS was a 30-item self-completion questionnaire comprising 3 domains (Psychosocial, Energy/Motivation, Side Effects). Changes made following further developmental work to address the development of atypical antipsychotics, cross-cultural adaptation and translation resulted in a number of revisions culminating in the 47-item SQLS-R3. The objective of the current study was to assess the psychometric properties of the SQLS-R3.

Methods: Two hundred and three patients with a diagnosis of schizophrenia completed the SQLS-R3. Over half the patients also completed the Short Form-36 (SF-36), the EuroQol 5 Dimensions (EQ-5D), Psychosis Evaluation Tool for Common use by Caregivers (PECC) and the SQLS-R3 for a second time.

Results: The combined results of exploratory and confirmatory factor analysis (SEM) resulted in a 2-factor, 33-item measure, which was renamed the SQLS-R4. Internal consistency reliability, as well as convergent and divergent validity of the two remaining domains (Psychosocial 20 items; Vitality 13 items) in addition to the calculated total score was found to be excellent. The sensitivity/discriminant validity of both domains and the total score was very good in relation to both disease severity measured by the PECC and type of antipsychotic medication, the latter degree of sensitivity not matched by the SF-36. Both domains and the total score also displayed good test–retest reliability.

Conclusion: The validated 33-item, 2-domain SQLS-R4 is a disease specific health-related quality of life (HRQOL) measure that can be used in clinical practice and research.

474. CHANGES IN HEALTH RELATED QUALITY OF LIFE ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT IN PATIENTS WITH SCHIZOPHRENIA—RESULTS FROM THE IC-SOHO OBSERVATIONAL STUDY

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Objective: To describe 6-month health related quality of life (HRQoL) and functional status results from patients participating in the Intercontinental Schizophrenia Outpatients Health Outcomes (IC-SOHO) study.

Methods: Outpatients ($n = 7658$) with schizophrenia, >/= 18 years, entered this prospective, long-term (3-year), non-interventional, observational study. Psychiatrists, at their discretion, enrolled patients into two treatment arms: initiated/changed to olanzapine, and initiated/changed to non-olanzapine. Patient HRQoL was self-assessed using the EuroQoL EQ-5D questionnaire, including the Visual Analogue Scale (VAS). Other measures included clinical (Clinical Global Impression Severity CGI-S) and functional (social, employment and residential) status. Multivariate comparisons of patients treated with olanzapine, risperidone, quetiapine or haloperidol (monotherapy only) were performed. Baseline, 3 and 6-month findings are described.

Results: At baseline, HRQoL was generally low across the sample; total EQ-5D and VAS scores of 0.62 ± 0.30 and 50.8 ± 22.2, respectively. Moreover, 43% of patients had no social interactions in the 4 weeks prior to enrollment and 68% were experiencing problems with their usual activities. Following 6 months, improvements in total EQ-5D and VAS scores were greater for patients in the olanzapine group compared with haloperidol or risperidone, and comparable to quetiapine. Patients in the olanzapine group were also involved in more social activities compared with haloperidol, risperidone or quetiapine. Improvements in employment and housing status were comparable across the atypical antipsychotics.

Conclusion: Our results show that antipsychotic treatment improves HRQoL and functional status of patients with schizophrenia. We found that olanzapine was superior to haloperidol and risperidone, and comparable to quetiapine, for patient HRQoL measures.

475. PATIENTS' SUBJECTIVE RATING OF MENTAL HEALTH IMPROVEMENT ON CLOZAPINE

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Background: The subjective experience of patients with schizophrenia, receiving antipsychotic medication has been a neglected research area.

Methods: In a randomised controlled trial comparing the impact of new atypical antipsychotic drugs versus clozapine, 67 out of 136 patients with schizophrenia were randomised to receive clozapine. Baseline and 12 week assessments included the PANSS, DAI, and the Kemp Compliance scale.

Results: The greater percentage improvement in total PANSS scores in patients randomised to clozapine was statistically significant when compared to the atypical group at 12 weeks ($p < 0.05$). Patients' subjective rating of their mental health improvement since commencing clozapine treatment correlated significantly with actual percentage improvement in PANSS scores from baseline to week 12 ($p < 0.01$). Significant correlations were also observed between the patients' subjective rating of their mental health improvement and both DAI score and the g12 PANSS insight item ($p < 0.05$). In a regression analysis, DAI score at week 12 explained 26% of the variance in patients' subjective rating of mental health improvement with clozapine. Percentage PANSS improvement explained a further 8% of the variance.

Conclusion: Patients in an RCT of clozapine versus atypicals were able to subjectively rate their own improved mental health status, validated by objective improvement on the PANSS. This was predicted by drug attitude as measured by the DAI. Subjective reports are a useful and valid outcome measure in drug treatment trials.

Acknowledgment: This study was funded by NHS R and D Health Technology Assessment.

476. QUALITY OF LIFE IN SCHIZOPHRENIA: THE IMPACT OF PSYCHOPATHOLOGY, DRUG ATTITUDE AND SIDE EFFECTS

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Background: Quality of life (QOL) is now seen as key outcome variable in schizophrenia. Factors deemed relevant in this context include severity of symptoms, antipsychotic-induced side effects, sociodemographic variables, and patient's subjective response to medication.

Method: In the current cross-sectional study eighty patients with a schizophrenic disorder according to ICD-10 criteria who had a duration of illness over 1 year and whose discharge from an inpatient unit had been at least 6 weeks earlier were investigated. Apart from the registration of demographic data, various rating scales were used: the Positive and Negative Syndrome Scale, the St. Hans Rating Scale for Extrapyramidal Syndromes, the Udvalg for Kliniske Undersogelser Side Effect Rating Scale, the Drug Attitude Inventory, and the Lancashire Quality of Life Profile.

Results: More than half of all patients indicated to be satisfied with their life in general. The specific areas of subjective dissatisfaction, which were most commonly noted in the present sample concerned partnership and mental health. The depression/anxiety component of the PANSS, parkinsonism and a negative drug attitude negatively influenced the patients' QOL, while cognitive symptoms and employment status correlated with higher QOL.

Conclusion: Our results highlight the importance of recognizing the complex nature of QOL in schizophrenia patients. They suggest that special attention should be paid to patients who experience anxiety and depressive symptoms or parkinsonism, to those who are unemployed, and to those with negative feelings and attitudes towards antipsychotics.

477. AFFECT IMPAIRMENT AND QUALITY OF LIFE IN SCHIZOPHRENIA

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Background/objective: Assessment of impact of schizophrenia on life of patients and efficacy of treatment is important task and foundation of illness management. Flat affect is one of major component of schizophrenia. Treatment of severe mental disorders should attempt to optimize Quality of Life (QOL) for the individual patient. Little is known about influence of affect flattening on QOL in patients suffering from schizophrenia. The purpose of the pilot study was to examine whether affect impairment interferes with QOL for patients with schizophrenia.

Methods: The sample was comprised of 21 (12 male, 9 female) patients, diagnosed according to DSM-IV. Mean age was 29 years, range from 18 to 35 years. Mean age of onset of psychosis was 21.2 years, range from 17 to 26 years. For all patients two previous episodes of illness were confirmed. Patients were in remission, on maintenance antipsychotic therapy. An independent clinician made ratings with PANSS, CGI, and the affective flattening section of Scale for Assessment of Negative Symptoms (SANS). The patients rated QOL 100-items questionnaire.

Results: Initial findings indicate that affect impairment in our sample correlates negatively with all domains of the QOL (Spearman $r = 0.47$, $P < 0.001$). It was specifically high in the domains of social contact, psychological distress and coping.

Conclusion: QOL is multidimensional concept that ought to be corresponding to clinical situation and field-tested. Impairment of affect could be responsible for false positive QOL ratings in

schizophrenic patients. Therefore, QOL instruments should not be used alone without integrating it with an evaluation of all dimensions of illness.

478. QUALITY OF LIFE IN PATIENTS WITH PARANOID SCHIZOPHRENIA TREATED WITH TYPICAL AND ATYPICAL ANTIPSYCHOTICS

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Objective: To compare quality of life (using Heinrichs quality of life scale (QLS)) in schizophrenic patients taking typical and atypical antipsychotics.

Methods: QLS was used in order to assess the quality of life in 100 patients with paranoid schizophrenia, according to DSM-IV-TR criteria. Before inclusion, all patients were treated with typical or atypical antipsychotics for a period of at least three months, and were in state of remission. First assessment (baseline) was made upon the inclusion. Second assessment was made after six months of continuous treatment with typical (haloperidol, flufenazine) or atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine).

Results: At baseline, patients treated with atypical antipsychotics showed significantly higher level of social activity. At second assessment, patients treated with atypical antipsychotics showed significantly higher level of social activity, intimate relationships and active acquaintances.

Conclusion: Patients treated with atypical antipsychotics showed significantly higher level of social activity, intimate relationships and active acquaintances on QLS. Duration of continuous treatment and compliance are important factors in improvement of quality of life of schizophrenic patients.

Reference

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479. QUALITY OF LIFE IN FIRST-EPISODE PSYCHOTIC PATIENTS: A STUDY OF ITS RELATIONSHIP WITH INSIGHT

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Background: The concept of quality of life (QOL) in psychotic patients has aroused increasing attentions in recent years. However, few studies addressed the QOL of first-episode psychotic patients in the period of untreated psychosis. Apart from symptomatology, the correlation between QOL and the insight of patients remained unclear.

Methods: This study made a cross-sectional assessment on fifty-three first-episode psychotic patients (mean age 21.4 years old) when they first presented to the psychiatric service. Their QOL was assessed with the Chinese version of MOS 36 item Short Form Health Survey (SF-36) and the World Health Organization Quality of Life Measure, abbreviated version (WHOQOL-BREF(HK)). Insight of the patients was assessed with the Scale to Assess Unawareness of Mental Disorder (SUMD).

Results: Patients who were classified as having unimpaired insight according to their SUMD global score were found to have significantly poorer QOL in the General health and Role limitation due to emotional problems scales of SF-36 than those with impaired insight ($p < 0.05$). The SUMD awareness scores of patients were found to have more significant correlations with various QOL domains ($p = 0.01$ to 0.03) than the SUMD attribution scores. Both depression scores and SUMD awareness scores were found to be significant predictors of QOL, but they accounted for only a small proportion of the variance in regression analysis.

Conclusion: There was an inverse correlation between level of insight and QOL in first-episode psychotic patients. The aspect of symptom awareness was more important than symptom attribution in accounting for the correlation.

480. A COMPARISON OF THE DETERMINANTS OF SUBJECTIVE AND OBJECTIVE QUALITY OF LIFE IN SCHIZOPHRENIC ILLNESS

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Background: Conceptually quality of life is a broad term and consists of a sense of well-being, life satisfaction and access to resources and opportunities.

Methods: A subjective quality of life measure, the Lancashire quality of life scale(Oliver, 1991)was compared with an objective measure, the Heinrichs quality of life scale (Heinrichs et al,1884) in 75 subjects entering a randomised controlled trial comparing conventional and new atypical antipsychotics and clozapine.

Results: A significant correlation was found between the two scales ($r = 0.386$ $p < 0.01$). Determinants of subjective and objective quality of life were explored using multiple regression analyses. The main determinants of subjective quality of life were depression measured on the Calgary Scale, insight(Birchwood Scale) and non neurological side-effects, which together explained 44% of the variance $p < 0.01$. Depression was responsible for 34% of this variance. In contrast, the main determinant of objective QLS were PANSS negative score and PANSS total score. These two together explained 51% of the variance with PANSS negative accounting for most 46% of this $p < 0.01$.

Conclusion: The choice of subjective or objective quality of life measures is likely to reflect different dimensions of outcome,reflecting the underlying psychopathology of schizophrenia as opposed to measuring a discrete construct. A value judgement must therefore be made as to which of these measures best encapsulates what is meant by quality of life in schizophrenic illnesses.

481. QUALITY OF LIFE IN FIRST EPISODE PSYCHOSIS

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Background: Quality of life (QoL) is a central issue in the study of psychotic disorders, but few studies have evaluated QoL in first episode patients (FEP). How well do instruments developed for chronic patients apply to FEP, how does FEP describe their subjective quality of life, and what is the relationship between subjective QoL and clinical status in the early treatment phase?

Methods: The TIPS study included consecutive FEP from four Scandinavian health care sectors over four years. QoL was measured with the Lehman Quality of Life Interview (L-QoLI). At start of treatment, 282 patients completed full L-QoLI interviews.

Results: The L-QoLI differentiated well between different subgroups of FEP, and in factor analyses the factor structure found in studies of other patient populations was reproduced. There was a low degree of association between objective and subjective QoL, and between clinical measures and QoL. Age, marital status, drug abuse, depressive symptoms and the duration of untreated psychosis were significant predictors of subjective QoL.

482. ARE THERE DIFFERENCES IN THE COURSE OF SUBJECTIVE QUALITY OF LIFE BETWEEN DISCHARGED AND NONDISCHARGED PSYCHIATRIC PATIENTS?

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Background: Although quality of life (QOL) assessment has become an accepted method for evaluation of treatment efficacy, little is known about changes in the levels of QOL during hospitalization of severe mentally ill inpatients. This naturalistic prospective study compares QOL scores between discharged and nondischarged cohorts of psychiatric patients.

Methods: 162 inpatients with DSM-IV diagnoses of schizophrenia, schizoaffective, and mood disorder were examined at admission and 20 weeks later using standardized measures of QOL, clinical symptoms and psychosocial resources. The relationship of length of stay with clinical and QOL outcomes, psychosocial factors, and diagnosis was examined. Regression analysis was used to identify QOL indicators for discharged and nondischarged patients.

Results: 40/162 patients (24.7%) showed improved life satisfaction. The discharged cohort showed significant improvement in general activities and QOL index, while the nondischarged cohort demonstrated dissatisfaction with social relationships and stability in QOL index at followup. General psychopathology, emotional distress and task-oriented coping were indicators of QOL level for discharged patients, while social support and self-efficacy were the best QOL indicators for those with prolonged hospitalization. Discharged schizophrenia patients were three times more likely to report improved life satisfaction than those who remained hospitalized, while schizoaffective/mood disorder subjects did not reveal that difference.

Conclusion: Thus, in addition to positive shifts in clinical and psychosocial factors, subjective QOL ratings improved at discharge for schizophrenia but not schizoaffective or mood disorder patients.

483. PREDICTION OF QUALITY OF LIFE CHANGE IN SCHIZOPHRENIA PATIENTS: A 16 MONTH FOLLOW UP STUDY

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Background: Little is known about changes over time in quality of life (QOL) and their determinants in schizophrenia patients.

Methods: In a naturalistic longitudinal design, 148 schizophrenia patients were assessed at hospital admission and again after 16 months. We investigated changes in QOL, psychopathology (PANSS), emotional distress (TBDI), side effects, insight, stress process related factors such as coping styles, self-efficacy, self-esteem, social support, and relationships between these variables.

Results: Satisfaction with QOL improved significantly during the follow-up period and was associated with reduction in distress, depression and paranoid symptoms, side effects, awareness, and increased self-efficacy, self-esteem, task-and avoidance-oriented coping styles, and family support scores. The impact of changes in severity of depression and paranoid symptoms on changes in levels of QOL did not remain significant when scores for distress, side effects, and self-constructs were partialled. Conventional versus atypical antipsychotics, age, education, age of onset, number of admissions, duration of disorder and of last hospitalization were not associated with changes in satisfaction with QOL. The results of this naturalistic, longitudinal study provide support for the hypothesis that fluctuations in satisfaction with QOL over time are associated with changes in primary or stress process related factors rather than in secondary or psychopathology related factors.

Conclusion: We present our findings in the framework of the distress/protection model (Ritsner et al., 2000, 2003) of QOL and identify implications for treatment of schizophrenia.

484. QUALITY OF LIFE OUTCOMES OF SCHIZOPHRENIA: FINDINGS FROM THE SHA'AR MENASHE LONGITUDINAL STUDY OF QUALITY OF LIFE

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Methods: This longitudinal naturalistic study of quality of life (QOL) and related factors was conducted on two cohorts of patients with severe mental disorders (SMD). The first cohort included data concerning 339 adult inpatients consecutively admitted to Sha'ar Menashe Mental Health Center. Participants met DSM-IV criteria for schizophrenia, schizoaffective, major depression or bipolar disorder. At the follow up evaluation performed 16 months later, 199 of 339 patients (58.7%) were available for examination. The second cohort included adult outpatients who met DSM-IV criteria stabilized on atypical (risperidone, olanzapine, $N=78$) and typical antipsychotic agents ($N=55$), they were followed for 12 months. Each patient was assessed using standardized measures of psychopathology (PANSS), quality of life (the Quality of Life Enjoyment and Satisfaction Questionnaire), insight, medication side effects, tolerability, distress, self-esteem, self-efficacy, coping, expressed emotion, and social support. In addition, the Quality of Life Scale for rating the schizophrenic deficit syndrome, the Tridimensional Personality Questionnaire, and the Pittsburgh Sleep Quality Index were employed.

Conclusion: Based on the obtained findings, *a distress/protection model* of QOL was developed (Ritsner et al., 2000). Stress process related (psychosocial) factors rather than psychopathology affect subjective QOL of SMD patients. Different coping strategies may reduce the negative influence of specific symptoms and related distress on the subjective QOL of schizophrenia patients. Temperament factors substantially influence satisfaction with QOL in schizophrenia: novelty seeking, reward dependence and harm avoidance are associated with different domains of QOL. Dissatisfaction with QOL is associated with repeated suicide attempts. Atypical antipsychotic agents revealed an advantage in QOL outcomes over typical agents when daily doses, duration of treatment, subjective tolerability and adjuvant antidepressants were controlled.

485. CARE NEEDS OF PATIENTS WITH FIRST-CONTACT PSYCHOSIS IN SÃO PAULO, BRAZIL

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Objectives: The aims of the present study are to describe the Brazilian version of the Camberwell Assessment of Needs (CAN-R), and to estimate needs of care in a sample of first contact psychosis.

Methods: All adults (18–64 years) resident in a defined catchment area of São Paulo who had had a first contact with any mental health service due to a psychotic episode were eligible. Psychiatric diagnosis was carried out with the SCID-I, and needs of care were assessed with the Brazilian version of the Camberwell Assessment of Needs. Each one of the 22 dimensions were rated as no need, met need, or unmet need.

Results: Seventy-two subjects were included, of whom 39 (54%) women. Forty-seven (65%) had a diagnosis of schizophrenia spectrum disorder. All 22 dimensions of the original version of the CAN were maintained in the Brazilian version. Adaptations were related to anchor points for scores of met or unmet needs. Forty-seven (65%) subjects had at least one met and one unmet need, 21 (29%) did not have any unmet need, and only 5 (7%) did not have any need. Psychotic symptoms was the dimension where more subjects (56%) reported met needs, whereas information, intimate relationships, and benefits were the dimensions were more subjects reported unmet needs.

Conclusion: A high proportion of first-contact psychosis in São Paulo reported met and unmet needs. Better community mental health services and social support are necessary to decrease their unmet needs.

Acknowledgment: Funded by the Wellcome Trust, UK.

486. WHAT DOES IT TAKE TO FEEL GOOD? QUALITY OF LIFE AND NEUROPSYCHOLOGICAL IMPAIRMENT IN FIRST EPISODE PSYCHOSIS

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Background: Access to resources, opportunities and a sense of well being are considered to be the essential ingredients for quality of life (Lehman 1988). Aspects of quality of life (QOL) are underpinned by cognitive flexibility and executive functioning (Green, 1996; Addington and Addington, 1999). Whilst a number of studies have investigated the impact of psychosis and neuropsychological (NP) deficits on QOL in established schizophrenia scant attention has been paid to young people who have recently experienced their first episode.

Methods: Forty-one first episode patients completed a range of NP tasks measuring pre-morbid and current IQ, executive functioning and memory. Lehman's QOL Interview which encompasses both objective and subjective QOL was also administered.

Results: Overall the analyses revealed a pattern of different relationships with subjective and objective measures of QOL and specific NP measures. Correlations using the objective measures showed moderate positive associations with the total objective QOL score and current IQ (CIQ) and between social time spent with friends and CIQ, whilst family contact was negatively correlated with attention, memory and CIQ. Alternatively, on the subjective scale, satisfaction with daily activities was positively associated with pre-morbid IQ and satisfaction with social relations was negatively associated with cognitive inflexibility.

Conclusion: One of the implicit goals in early intervention is improved functional outcomes for young people with psychosis, thus deficits in NP and QOL have important implications for treatment and recovery.

487. WELL-BEING SUPPORT PROGRAMME: A MODEL OF CARE FOR PATIENTS WITH SERIOUS MENTAL ILLNESS

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Background: Harris highlighted that, in schizophrenia, 80% of deaths are due to natural causes with mortality rates 1.5 times higher than the general population. Brown found schizophrenia sufferers have a poor lifestyle, high smoking rates, low activity and poor diets. Dixon and Taylor highlighted a high incidence of diabetes in schizophrenia (15%, 9%) and Subramaniam highlighted the need for screening. NICE Clinical Guidance, NSF and the GMS contract have all highlighted physical health as a priority. The Well-Being Support Programme was developed to deliver a more holistic package of care. It offers patients with SMI a dedicated nurse to assess their physical health, side effects and lifestyle. Nurse's role: initial consultation, general health screening, supportive group therapy, lifestyle advice, co-ordination of input from various healthcare professionals. Expected outcomes of the Programme: Improved physical health, Reduced side effects, Weight management, Improved social interaction.

Case Reports: Patient: Features: Result: Male with schizophrenia—57 Overweight, unstable diabetes Lost 21 lbs, diabetes stabilised; Female with schizophrenia—41 Weight gain Lost 18 lbs; Female with schizophrenia—42 Hypertension, anaemia, Weight loss,specialist; hyperprolactinaemia care accessed. Female

with bipolar disorder—54 Sedation, weight gain. Learned to swim, improved Hyperthyroidism, identified self esteem, weight loss.

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488. CHANGES IN QUALITY OF LIFE IN SCHIZOPHRENIC PATIENTS: A COMPARISON BETWEEN EUROQOL AND WHO-QOL

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Background: It has often been postulated that simple, short questionnaires are unable to reflect complex changes in well-being of individuals with chronic psychiatric disorders.

Methods: To investigate these assumptions we included two recently developed instruments to measure quality of life (the WHOQoL-Bref and the EuroQoL EQ-5D) in a randomised control trial (RCT) in which two treatment conditions were compared. Aims of the study were to assess the sensitivity and validity of these quality of life (QoL)-instruments, to establish their relationship and to examine the predictors of changes in QoL. Subjective changes in QoL were measured on three assessments waves in a period of 18 months and compared to objective changes in psychopathology and social functioning in a sample of 76 chronic schizophrenic patients who participated in the RCT.

Results: Results indicated that both WHOQoL-Bref and EuroQoL EQ-5D are capable of detecting changes in QoL over time in physical and psychological well-being. The instruments partly measure the same aspects of QoL, indicated by 50% common variance on total scores. Reduction of positive psychotic symptoms appeared to be the most important factor in improving QoL. The weighted TTO-score of EuroQoL-5D, which is often used as an index in economic evaluations of health care, did however not correspond with these changes, which indicates that it is less sensitive to changes in social and psychological well-being. It's use as the core measure in (economic) health evaluation in the field of psychiatry therefore seems less appropriate.

Schizophrenia/Bipolar Comparison

489. STABILITY VS. INSTABILITY IN DIAGNOSIS AFTER THE ONSET OF PSYCHOSIS AMONG AN EPIDEMIOLOGICALLY COMPLETE POPULATION: THE CAVAN-MONAGHAN FIRST EPISODE STUDY AT 7 YEARS

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Background: In first episode studies there is often diagnostic uncertainty at and after the onset of psychosis. Such stability vs. instability within and across diagnoses is poorly understood and is best addressed in systematically ascertained, epidemiologically complete populations.

Methods: Since1995, 'all' first episode cases of psychosis presenting to the catchment area of Cavan-Monaghan Psychiatric Service, a homogeneous region of rural Ireland, have been entered into the study.

Results: At 7 years, 153 cases [96 male, 57 female] were accrued among a population of 103,054. DSM-IV diagnoses initially and at a 6-month follow-up were compared. Among 25 initial diagnoses of schizophrenia and 5 schizoaffective, all except one suicide retained their diagnosis at 6 months; among 19 with schizophreniform disorder, 11 [58%] changed: 8 schizophrenia, 1 schizoaffective, 1 bipolar, 1 substance-induced; among 11 with brief psychotic disorder, 3 [27%] changed: 2 bipolar, 1 major depression with psychotic features; among 9 with delusional disorder, 3 [33%] changed: 2 schizophrenia, 1 schizoaffective. Among 23 with bipolar disorder, only one [4%] changed to schizoaffective at 6 months; among 31 with major depression with psychotic features, 2 [6%] were changed: 1 schizophrenia, 1 schizoaffective. Among 9 with psychosis NOS, only one [11%] had a different diagnosis, of substance-induced disorder, at 6 months. Other diagnoses were generally stable.

Conclusion: While inception diagnoses appear more stable when symptoms are severe or persistent, more 'transient' or uncertain symptoms do not necessarily converge, indicating a continuum of psychosis.

Acknowledgment: These studies were supported by the Stanley Medical Research Institute.

490. CHOLESTEROL CONCENTRATIONS ARE REDUCED IN VISUAL ASSOCIATION CORTEX IN MOOD DISORDERS BUT NOT SCHIZOPHRENIA

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Background/objective: Low serum cholesterol levels have previously been associated with mood disorders and with suicidal behaviour. Cholesterol forms an integral part of neuronal and glial cell membranes and is a major component of myelin. Cholesterol also plays a vital role in the development, function and stability of synapses. The aim of this study was to quantify brain sterol concentrations in major psychiatric disorders and further to relate these levels to markers of myelin and synapses.

Methods: Samples of visual association cortex were obtained post-mortem from subjects with schizophrenia, bipolar disorder (BPD) and major depressive disorder (MDD) and from controls (all $n=15$). Concentrations of brain cholesterol, its precursors lathosterol, desmosterol and lanosterol and its metabolite 24S-hydroxycholesterol were determined by gas–liquid chromatography. Immunoreactivity for myelin basic protein (MBP), synaptophysin and the SNARE protein VAMP was quantified by ELISA.

Results: Cholesterol levels were lower by 13% in MDD ($p=0.018$) and by 10% in BPD ($p=0.052$) compared with controls. Overall, cholesterol levels were lower in the psychiatric patients who did not die by suicide compared with patients who did (ANOVA, $F=4.264$, $p=0.045$). Cholesterol precursor or metabolite levels did not differ between groups. MBP immunoreactivity was not different between groups. While synaptophysin immunoreactivity was lower by 20% in BPD ($p=0.025$) and VAMP lower by 37% in MDD ($p=0.032$) and by 45% in BPD ($p=0.009$) relative to controls, we found no overall correlation between cholesterol levels and any myelin-or synaptic-associated protein.

Conclusion: Our data suggest that lower brain cholesterol levels may be a common feature of mood disorders.

491. THE SEPTAL REGION IS DIFFERENTLY AFFECTED IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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Background: The septum is a brain midline structure closely related to the hippocampal formation and forming part of the limbic structure. The fornix is an important pathway connecting the hippocampus with subcortical brain regions. Although postmortem and MRI studies indicate a higher frequency of enlarged cava in schizophrenics, nearly nothing is known about structural changes of the septum and the fornix in psychiatric disorders. We found that the volumes of the septal tissue did not differ between patients with schizophrenia, affective disorders and control subjects. However, a subgroup of schizophrenic patients showed enlarged cava volumes, which correlated with larger septal tissue volumes (Brisch et al., 2003).

Methods: Nissl and fiber stained 20 micrometers coronal sections were used in our study. No significant differences were found with regard to the volumes of the fornix between 11 patients with schizophrenia, 9 patients with affective disorders and 10 control subjects. Another aim of this pilot study was to determine the cell numbers and the cell densities in different septal nuclei of psychiatric patients and control cases. Cell countings showed fewer neurons in the nucl. lateralis in affective disorders compared to control cases and a higher cell density in the diagonal band of Broca in schizophrenia. Since both habenula and raphe nuclei show morphological alterations in affective disorders, it may be concluded that affective disorders have a disrupted feedback loop between the septum, the habenula and the brain stem nuclei.

Acknowledgment: Supported by NBL-3 and The Stanley Medical Research Institute.

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492. BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) IN SCHIZOPHRENIA, MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDER—A POSTMORTEM STUDY IN THE HIPPOCAMPUS

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Background: There is increasing evidence of a role for neurotrophins and neurogenesis in schizophrenia and affective disorders, and in the mechanism of action of antidepressant drugs. BDNF is the predominant neurotrophin in hippocampus and is involved in neurogenesis, migration, differentiation, survival, and post-natal neural plasticity. Previous studies report inconsistent changes in hippocampal BDNF in schizophrenia and depression.

Methods: We performed quantitative immunoautoradiography to measure hippocampal BDNF in Stanley Consortium postmortem tissue using a rabbit polyclonal antibody and a ^{35}S-labelled secondary antibody. Formalin-fixed paraffin-embedded sections of anterior hippocampus were studied in subjects with depressive disorder, bipolar disorder, schizophrenia and age and gender matched controls ($n = 15$ per group). Using image analysis software (Bioquant Nova Prime), optical density measurements were taken in hippocampal subfields (Granule cell layer, hilus/CA4, CA3, CA2, CA1 and subiculum) and converted to nCi/g/tissue with ^{14}C standards.

Results: No significant changes in BDNF levels were found in schizophrenia or depressive disorder in any of the subfields. In bipolar patients however, a significant decrease was found in hilus/CA4 subfield. No effect of antipsychotic or antidepressant treatment was observed.

Conclusion: These results are compatible with recent evidence that impaired BDNF function and neurogenesis may be a mechanism of affective disorder.

493. FACTOR STRUCTURE OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) IN SCHIZOPHRENIA, SCHIZOAFFECTIVE DISORDER AND BIPOLAR AFFECTIVE DISORDER

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Background: The Positive and Negative Syndrome Scale (PANSS) is widely used to evaluate the nature and severity of psychiatric symptoms. Although the "pentagon model" factor structure comprising negative, positive, cognitive, excitement and depression factors is widely accepted, several researchers have found this model has inadequate goodness of fit, while others have proposed alternative factor solutions.

Methods: We investigated PANSS ratings for 289 acute inpatients with diagnoses of schizophrenia (153), schizoaffective disorder (72) or bipolar disorder (manic/mixed) (61). Raters underwent extensive training and had excellent interrater reliability coefficients.

Results: A forced five-factor solution with an orthogonal (varimax) rotation on the total sample corresponded to the standard five-factor model. Exploratory analysis however, extracting factors with eigenvalues over 1.0 gave a seven factor solution which included a "motor" factor and separated "anxiety" from "depression", consistent with several previous findings. Preliminary analyses for each diagnosis indicated a seven factor schizophrenia solution, which combined "excitement" with "positive" symptoms, separated "depression" and "anxiety" and formed "uncontrolled behaviour," "depression" and "motor" factors. An eight factor solution for schizoaffective disorder included " social withdrawal", "interpersonal skills" and "depression" in addition to separate "anxiety" and "motor" factors. Bipolar mood disorder had a six factor solution with "negative," "uncontrolled hostility/manic", "positive", "executive cognition", "gross cognitive and motor dysfunction" and "preoccupation" factors.

Conclusion: The results indicate that while a five factor PANSS solution can be extracted, a seven factor solution may better account for the data. Preliminary evidence suggests the PANSS factor structure is variable, dependent upon the diagnostic characteristics of the sample employed.

494. INCIDENCE AND ETHNICITY OF BIPOLAR DISORDER: A COMPARISON WITH SCHIZOPHRENIA

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Background/objective: Several studies have shown an increased incidence of schizophrenia in migrant populations, and there has been some suggestion that the incidence of non-psychotic mania and bipolar disorder might follow a similar pattern. The present study aimed to determine the absolute rates of operationally defined bipolar disorder in 3 geographically defined areas and to investigate previously reported differences in the rate of the disorder between migrant and non-migrant groups.

Methods: Three prospectively ascertained cohorts of first episode psychotic disorder including non-psychotic mania and bipolar disorder were identified as part of the AESOP study and categorised using ICD-10 criteria. Incidence rates of bipolar disorder (cases per 100,000 population per year) were calculated using denominator data from the 1991 census, corrected for under-enumeration and standardised for age across the three centres.

Results: 75 cases were identified across the 3 centres. The age standardised incidence rates for bipolar disorder in London (7.7: 95% CI 5.3–10.0) was over twice that of Nottingham (3.2; 2.0–4.4) and Bristol (2.0; 0.3–3.8). The incidence rates of bipolar disorder in migrant groups in all three centres were significantly inflated compared to whites. The rate ratios in London, Nottingham and Bristol were 5.7 (95% CI 4.6–6.9), 6.8 (5.6–8.4), 12.4 (10.1–15.1) respectively.

Conclusion: Our results demonstrate that like schizophrenia, the risk for bipolar disorder is increased in migrants to the UK compared with the white population. This inflation may be an artefact of initial presentation bias but may also be a true increase attributable to a risk factor common to both bipolar disorder and schizophrenia that is more apparent in ethnic minority groups.

495. AMYGDALA VOLUME IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER FROM MULTIPLY AFFECTED FAMILIES AND THEIR UNAFFECTED RELATIVES

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Background: While there is considerable evidence that schizophrenia is associated with reduced amygdala volume, some recent studies have found this structure to be enlarged in bipolar disorder (BD). As with many structural deviations associated with these disorders, the relative genetic and environmental contributions to amygdala volume deviation is unknown.

Methods: We measured amygdala volume on MRI brain scans of patients with schizophrenia ($n=42$), their unaffected first-degree relatives ($n=57$), bipolar disorder ($n=38$), their unaffected first-degree relatives ($n=52$) and controls ($n=54$). Most of the schizophrenic subjects and all of the bipolar subjects were from multiply affected families.

Results: After controlling for possible confounders, schizophrenia patients had significantly reduced volume of both left amygdala ($B=-107$, $p=0.004$) and right amygdala ($B=-105$, $p=0.03$) compared to controls. In contrast, bipolar patients had a trend for increased right amygdala volume ($B=79$, $p=0.08$) compared to controls. Schizophrenia relatives showed no significant volume changes, but bipolar relatives had a trend for increased volume of the right amygdala ($B=74$, $p=0.08$) compared to controls. Bipolar patients had significantly larger volume of left ($B=92$, $p=0.05$) and right amygdala ($B=144$, $p=0.008$) than schizophrenia patients.

Conclusion: Our data demonstrate that schizophrenia is associated with volume reduction of the amygdala and that this is likely to be linked to the illness process or non-genetic risk factors. In contrast, bipolar disorder is likely to be associated with increased volume of the right amygdala and this volume deviation is a probable manifestation of genetic risk, since it is also apparent in their unaffected first-degree relatives.

496. SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER HAVE DISTINCT BUT OVERLAPPING BRAIN STRUCTURAL PHENOTYPES

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Background/objective: Although schizophrenia and bipolar disorder have traditionally been divided into separate disorders, there is increasing evidence that the two illnesses share features in common, including susceptibility genes. We investigated the relationship between genetic risk and brain structural variation using computational morphometry in patients and their non-psychotic relatives sampled from multiply affected families.

Methods: MRI scans were obtained from 25 patients with schizophrenia, 36 of their unaffected first-degree relatives, 37 patients with bipolar I disorder, who had experienced psychotic symptoms during episodes of illness exacerbation, and 50 of their unaffected first-degree relatives. A measure of genetic liability was calculated for each subject and this score was used to predict regional variation of tissue volume in each set of families.

Results: Genetic risk for schizophrenia was associated with distributed clusters of grey matter volume deficit ($p=0.004$) in left lateral temporal cortex, bilateral frontal cortex, striatum and thalamus, whereas genetic risk for bipolar disorder ($p=0.004$) was associated with grey matter deficit only in right anterior cingulate gyrus and ventral striatum. There was an association between genetic risk and white matter volume reduction in fronto-temporo-parietal regions for both schizophrenia ($p=0.010$) and bipolar disorder ($p=0.011$), which overlapped in left prefrontal and temporal regions.

Conclusion: Our results demonstrate that the brain structural phenotypes of the two major psychotic disorders are characterized by distinct patterns of grey matter deficit. However both types of psychosis display overlapping white matter phenotypes, indicating

that left fronto-temporal anatomical dysconnectivity is a manifestation of genetic liability to psychosis in general.

497. DO SCHIZOPHRENIA AND BIPOLAR DISORDER BELONG TO THE SAME NEUROBIOLOGICAL CONTINUUM? NEUROLOGICAL ABNORMALITY IN HIGH-RISK OFFSPRING FROM BIRTH TO ADULTHOOD

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Background/objective: Schizophrenia and bipolar disorder may potentially belong to the same biological/genetic continuum. If this is true, then offspring born to women with schizophrenia and women with bipolar disorder should be similar to one another on levels and types of neurological abnormality at different ages.

Methods: This question was studied in our prospective investigation of neurological abnormality in offspring born to women with schizophrenia (maximum $n = 28$), bipolar disorder (max $n = 16$), and unipolar depression (max $n = 7$), as well as control women with no history of psychosis (max $n = 88$).

Results: At each of three ages (neonatal, 6 yr and 22 yr), offspring of women with schizophrenia evidenced significantly increased rates of neurological abnormality, compared to normal-risk controls. In contrast, offspring of women with bipolar disorder consistently had somewhat lower rates of neurological abnormality than normal-risk controls, being quite similar to offspring of women with unipolar affective disorder.

Conclusion: The increased neurological abnormality consistently characteristic of offspring of schizophrenic women in early life is consistently missing among offspring of women with bipolar disorder, suggesting that the two disorders belong to separate biological spheres.

Acknowledgments: Supported by the Stanley Medical Research Institute and the Swedish Medical Research Council.

498. CHANGE IN EXTRAPYRAMIDAL-MOTOR SYMPTOMS AFTER SWITCHING SCHIZOPHRENIC PATIENTS FROM CONVENTIONAL DEPOT NEUROLEPTICS TO LONG-ACTING INJECTABLE RISPERIDONE

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Background: To evaluate the change in extrapyramidal-motor symptoms after switching from frequently used conventional depot neuroleptics to long-acting injectable risperidone (Risperdal Consta™), without oral risperidone run-in.

Methods: 12-week open-label prospective multicenter trial. After a run-in period of two treatment cycles on their conventional depot antipsychotic (either haloperidol decanoate, flupentixol decanoate, fluphenazine or zuclopentixol decanoate), symptomatically stable adult schizophrenic patients were switched to long-acting injectable risperidone administered by gluteal injections every 2 weeks. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptom Rating Scale (ESRS) at baseline and end of the 12-week treatment period (endpoint). Adverse events including extrapyramidal symptom-related events were recorded at each visit.

Results: 166 patients (67% male, mean age 42.9 ± 11.6 years) were enrolled. Most patients had paranoid (69.3%) or residual (15.7%) schizophrenia. The modal dose of long acting risperidone was 25 mg in 86% of the patients and 37.5 mg in 14%. The median total ESRS score was 5.0 (range 0–43) at baseline, decreasing to 2.0 at endpoint. Median change in total ESRS was -2.0 ($p < 0.01$ vs. baseline). Scores for Parkinsonism, which was most pronounced at baseline, decreased after switching to long-acting risperidone (4.0 to 1.0, $p < 0.01$). Overall, 5/166 patients (3.0%) experienced an extrapyramidal symptom-related adverse event during treatment with long-acting injectable risperidone.

Conclusion: In this study, extrapyramidal symptoms as measured by ESRS decreased significantly after switching from conventional depot antipsychotics to long-acting injectable risperidone.

500. EVIDENCE FOR A DIFFERENT PATTERN OF PREMORBID INTELLECTUAL FUNCTIONING IN SCHIZOPHRENIA AND BIPOLAR DISORDER: RESULTS FROM A COHORT STUDY OF MALE CONSCRIPTS

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Background: Premorbid intellectual impairment has been consistently described in schizophrenia but little is known about premorbid intellectual and neuropsychological functioning in bipolar disorder or other psychoses. Such information would inform current debate about whether schizophrenia and bipolar disorder are distinct entities or share a common etiology.

Methods: The results of verbal, arithmetic, and visuospatial reasoning tests were obtained from apparently healthy 195,019 male subjects conscripted into the Finnish Defence Forces during 1982–1987 (mean age 19 years). Linkage with the Finnish Hospital Discharge Register data (mean follow-up time 7.1 years) identified those conscripts who had later been diagnosed with bipolar disorder ($N=100$), schizophrenia ($N=621$) and other non-schizophrenic, non-affective psychoses ($N=527$).

Results: There was an inverse linear relationship between general intellectual functioning at age 19 (as measured by summing the results of the verbal, visuospatial and arithmetic tests) and risk of later schizophrenia and other psychoses—the poorer the performance the greater the risk ($p<0.0001$ for linear trend). There was no relationship between general intellectual functioning and later bipolar disorder. Examination of the results for the individual tests demonstrated that poor visuospatial test performance at age 19 was associated with an increased risk for all three disorders: ($p<0.0001$ for linear trend in all categories). The odds ratios (OR) between the lowest and highest of 9 performance categories were 34.7 (95% CI 4.1–296.4) for bipolar disorder, 13.8 (95% CI 5.5–34.5) for schizophrenia and 4.3 (95% CI 2.1–8.8) for other psychoses. In contrast, the higher the score in the arithmetic test at age 19 the greater the risk of bipolar disorder ($p=0.008$ for linear trend). A high score in the arithmetic test was associated with over a 12-fold risk for bipolar disorder. Performance in the verbal test score was not associated with increased risk for psychiatric disorder.

Conclusion: Poor visuospatial functioning in late adolescence appears to be a nonspecific risk factor for functional psychotic illness. Poor general ability was associated with an increased risk for later schizophrenia or other psychosis but, however, high arithmetic test performance was associated with an increased risk for bipolar disorder. These findings provide further support for a nosological distinction between schizophrenia and bipolar disorder.

501. SOCIAL FACTORS AND THE RISK OF DEVELOPING PSYCHOSIS—A NATIONAL COHORT STUDY

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Background: Earlier studies have not been conclusive regarding the effect of social factors on psychosis. Most studies are based on small number of patients including only the parents' occupation as indicator of social class. The aim of the present study is to describe the effects of a broader range of social factors on the risk of developing psychosis in a national cohort.

Method: 1.2 million children/youths in Sweden (born 1968–1979) in family households from the census of 1985 were followed-up in the in-patient register 1991–2000. Multivariate Cox regression analyses of proportional hazards were used to estimate the risk of social adversity during childhood on subsequent hospitalization for psychoses.

Results: Increased age and sex adjusted HRs for schizophrenia (HRs 1.1–3.3) and psychoses (1.1–2.4) were found for children from households with low socio-economic status, rented apartments, unemployment, single adult households, households receiving social welfare and urban residency. The HRs were reduced but still elevated in a model including all the above factors as well as foreign-born parents and hospitalization for psychotic illness in parents.

Conclusion: Increased risks of schizophrenia and psychoses were found for children from less advantaged households thus indicating that social adversity in childhood contributes to the risk of developing schizophrenia.

502. DEFICIENT PREFRONTAL CORTEX CALCIUM-DEPENDENT CONSTITUTIVE NITRIC OXIDE SYNTHASE (CNOS) ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA AND DEPRESSION

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Background: The free radical gas nitric oxide (NO), synthesized by oxidation of arginine, plays a significant role in cortical vasodilation and blood flow regulation in the brain. It is possible that deficient nitric oxide synthase (NOS) activity could contribute to the frontal hypoactivity in schizophrenia and affective disorders.

Methods: We determined the calcium-dependent constitutive NOS (cNOS) enzymatic activity and protein levels of neuronal NOS (nNOS) and endothelial NOS (eNOS) in the postmortem prefrontal cortex (BA 9 region) of patients with unipolar, bipolar,

and schizophrenic disorders and non-psychiatric controls ($n = 15$ for each group).

Results: Protein levels of nNOS and eNOS were not significantly different from the non-psychiatric controls in any of the patient groups. However, cNOS activity was significantly lower in schizophrenic patients (mean $\pm$ S.E. = 19.1 $\pm$ 3.2 cpm/ug/45 min) than in the control group (28.5 $\pm$ 3.4, $P < 0.05$). Trends of lower cNOS activity were found in unipolar (20.3 $\pm$ 2.6, $P = 0.062$) and bipolar patients (20.8 $\pm$ 3.0, $P = 0.079$). Males had significantly higher NOS activity (25.4 $\pm$ 2.20 $n = 36$, $P = 0.01$) than females (17.3 $\pm$ 1.9, $n = 24$). Postmortem interval (PMI) did not affect NOS activity or NOS isoform proteins. However, cNOS activity was significantly correlated with brain pH ($r = 0.28$, $P < 0.05$).

Conclusion: These results suggest that deficient cNOS activity could play a role in the altered blood flow regulation and abnormal neurotransmission in the prefrontal cortex of patients with schizophrenia and affective disorders.

Acknowledgment: Supported by the Stanley Medical Research Institute.

Miscellaneous

504. USING THE INTERNET AS A TOOL IN EPIDEMIOLOGICAL STUDIES

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Background: The Internet has an excellent potential as a tool in epidemiological and clinical studies. Sweden has among the highest Internet penetration in the world and a free access in many public places. This study examines the possibility of collecting health and lifestyle data related to cancer, diabetes, rheumatic diseases and mental health using a Web-based questionnaire.

Methods: 50,000 women (40–60 yrs.) received an invitation letter containing instructions, a personal login, and the web address to the 'Women's Lifestyle and Health Study'. The questionnaire contained approximately 100 questions (and some colour pictures) concerning e.g. physical activity, smoking, alcohol, diet, hormone therapy, self-reported medical conditions, depression and psychotic symptoms.

Results: The study is ongoing. To date, we have a 45% response rate (including one reminder) and aim for an additional 20–25%. Even if the age group in question have less computer knowledge than younger ones, the reaction has been very positive. The Swedish individual national registration numbers and population-based registers guarantee basic information on responders and non-responders. If the probability of responding can be assumed to depend on e.g. age, sex, occupation, social class the analysis can be weighted to control for differential response rate. We further aim to investigate 1) the impact of the order of questions and answer alternatives, 2) how different reminder procedures and socio-economic factors may influence the response rate.

Conclusion: The Internet provides a cost-effective and advantageous substitute for traditional paper questionnaires. We will discuss design, procedure and the data quality improving features.

505. PHYSICAL HEALTH MONITORING IN SCHIZOPHRENIA: THE USE OF AN INVITATIONAL LETTER IN A PRIMARY CARE SETTING

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Background: Schizophrenia is associated with increased risk of physical illnesses such as cardiovascular disease and diabetes mellitus. Physical health monitoring is considered an essential part of the management of those with schizophrenia. This study aimed to establish whether a single invitation letter was an effective tool in increasing the level of monitoring in those with schizophrenia within a primary care setting.

Methods: The study was carried out at an inner London general practice surgery with 9199 registered patients. Thirty patients with a diagnosis of schizophrenia were identified. A baseline level of physical health monitoring was established. Each patient was then sent a letter inviting them to attend the surgery for a health check. The level of physical health monitoring was re-assessed after a period of two months.

Results: The baseline level of physical health monitoring was poor, with only 53% having a BP recording, 30% a screen for diabetes and less than 20% any recording of drug and alcohol use in the previous year. Only 20% of patients responded to the invitation letter. There was a marked increase in the level of physical health monitoring of those who did respond but the small number of respondents limited the overall impact.

Conclusion: The poor response rate and limited effect on the overall levels of physical health monitoring shown in this study suggests that invitation letters may be of limited value in improving the physical health care of those with schizophrenia.

506. USE OF POPULAR MEDIA BY PEOPLE WITH SCHIZOPHRENIA

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Background: In the literature on stigma there is an interest in how mentally ill people are portrayed in popular media. Little is known on the use of popular media by people suffering from schizophrenia.

Methods: In an explorative study we evaluated the use of popular media in 15 schizophrenic patients (5 inpatients, 5 patients in sheltered housing, 5 patients living in the community). Patients were assessed with a semi-structured interview based on current media-theories.

Results: Patients with schizophrenia frequently use many different types of popular media. Apart from leisure gathering news and information is their main focus. Patients in institutions tend to be more passive users and use popular media to combat boredom and fill empty time. This can lead to media dependency. People in the community are more active news gatherers. Media use is also steered by the need to relief negative emotions. Most patients use media as a window on the world and a social comparator. The use of the internet is preferred by younger patients where they look for information which they can explore at there pace. The patients seem to need to use the media on a regular basis and in small blocks to structure their day. Patients are quite sensitive to and aware of the negative image of psychosis portrayed in popular media. This clearly has a negative impact on their self-esteem. These results need to be confirmed in a large study.

507. CAROTID INTIMA MEDIA THICKNESS IN FIRST EPISODE SCHIZOPHRENIA: AN EARLY MARKER FOR CARDIOVASCULAR DISEASE

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Background/objective: Schizophrenia is associated with excess mortality with 60% attributable to physical disease and cardiovascular disease being a major contributor. Evaluation of carotid intima media thickness (IMT) using ultrasound is a validated quantitative method for assessing atherosclerosis. Furthermore a close relationship has been observed between IMT and the incidence of coronary heart disease. We hypothesize that individuals with a first episode of schizophrenia will demonstrate a greater common carotid artery (CCA) IMT than a matched control group. Additionally severity of illness will be positively correlated with IMT.

Methods: 20 individuals with first episode schizophrenia and 20 matched controls had carotid IMT measured with B-mode ultrasonography. The BPRS measured severity of illness.

Results: Individuals with schizophrenia had a significantly higher carotid IMT than controls in the right CCA (0.0624 cm vs. 0.0543 cm) and in the left CCA (0.0668 cm vs. 0.0464 cm). Severity of illness ($r = 0.63$, $p < 0.05$) and cigarette smoking ($r = 0.56$, $p < 0.05$) were positively correlated with total carotid IMT.

Conclusion: Carotid IMT is enlarged in individuals with first episode schizophrenia compared with matched controls. This indicates an increased risk for the development of atherosclerosis in schizophrenia. Smokers and more severly ill individuals appear to be at increased risk. This study highlights the need for rigourous assessment of these individuals at risk in order to institute preventative strategies and therefore reduce morbidity and mortality.

Cognition

508. COGNITIVE FUNCTIONING IN FIRST EPISODE PSYCHOSIS: A TWO YEAR FOLLOW-UP

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Background: Studies with first-episode psychosis samples have demonstrated cognitive impairment similar to that seen in those with an established schizophrenia illness.

Methods: In this study, using a comprehensive battery of cognitive tests, we assessed cognition in 182 individuals who had presented with a first-episode of psychosis to a specialized program and who had been followed for one year. One hundred and twenty-seven of these subjects completed a two year assessment.

Results: Although there were statistically significant improvements over the two year period in a range of tasks (e.g. memory,

verbal fluency, executive functioning, information processing) none of the improvement could be considered clinically significant. At both the one and two year follow-up periods there were significant associations between social functioning, negative symptoms and residual positive symptoms and cognition (verbal memory, verbal fluency, visual–spatial tasks, information processing and executive functioning). However, regression analyses demonstrated that after controlling for negative symptoms cognitive impairment accounted for less than 7% of the variance in social functioning. Since first-episode psychosis samples present not only with schizophrenia but a range of schizophrenia spectrum disorders, we also compared the different diagnostic groups on cognition.

Conclusion: Results demonstrated that there were no real significant differences in cognition amongst the different diagnostic groups. Our results suggest that impaired cognition exists in the very early stages of a psychotic illness and that it is a core feature not just of schizophrenia but other schizophrenia spectrum disorders. Secondly, our results offer support that, although related, poor social functioning may be independent of cognitive impairment.

509. PSYCHOSIS AND ALZHEIMER DISEASE: A RETROSPECTIVE STUDY OF SUSCEPTIBILITY

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Background/objective: Growing evidence indicates that many characteristics are shared by Alzheimer Disease (AD) and psychoses suggesting the existence of some shared genetic background. The aim of our research was to acquire more information on the prevalence of psychotic disorders in first degree relatives of AD patients. Our hypothesis was that there is a common genetic background for psychoses and AD.

Methods: The clinical charts of 752 subjects referring to our Center have been considered. Four hundreds and fifty-eight subjects (317 females, 141 males) had a diagnosis of AD according to the NINCDS-ADRDA criteria. The remaining 294 subjects (133 males and 161 females) represented the control sample and were affected by neurological conditions other than AD(e. g. vascular dementia, Parkinson disease).

Results: No significant differences were found in the frequency of positive family history (FH) for psychoses (Schizophrenia, Schizoaffective Disorder, Psychotic Disorder NOS). However, a significant higher frequency of positive FH for dementia in AD patients ($p < 0.003$) was found.

Conclusion: The results from this study do not appear to confirm the hypothesis that AD and psychoses share a common familial susceptibility. Further investigations with more structured assessment of FH are needed to confirm these preliminary results.

510. EVIDENCE FOR A DIFFERENTIAL EFFECT OF DISENGAGEMENT DEFICIT OF ATTENTION IN SCHIZOPHRENIA DURING A VISUAL ORIENTING TASK

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Background: Deficits in preattentive phases of attention are consistently associated with schizophrenia.

Methods: In visual attention, dysfunction in transient early warning system has been suggested. Schizophrenic medicated patients DSMIV ($n = 13$) and healthy controls ($n = 13$) were assessed during a cued target detection task including two fixation conditions that differentially affect attentional engagement. Central fixation was offset either (1) prior to the target (Gap condition) (2) simultaneous with the target onset (No-Gap condition) with five different types of trials (valid, invalid, double-cued, no cued and central). Reaction times (RT) are typically reduced in the Gap condition, known to facilitate attentional disengagement or to act as a warning signal.

Results: Repeated measures of ANOVA showed an interaction between Group, Condition and Gap effect (F4, $96 = 2.79$, $p = 0.03$). Separate analysis of ANOVA in each group, revealed that for the controls, the profile of the different RT for each type of trials was the same during Gap and No Gap condition (e valid and double cued trials different from invalid, no-cued and central trial). This similarity between Gap and No Gap was not present for schizophrenic patients. In the Gap condition, patients showed faster RT for valid trials compared to the other trials while no difference appeared between cued versus uncued trials. Finally, no asymmetrical abnormalities in the schizophrenic group were found.

Conclusion: These preliminary results suggest that schizophrenic patients apparently have a decreased ability to identify and/or use unexpected visual stimuli in condition of disengaged fixation.

Acknowledgments: This research was promoted by CHSA and received financial support by Lilly France and IINSERM.

511. RELATIVE SPARING OF EXECUTIVE FUNCTIONS AND SET SHIFTING ABILITIES IN THE FIRST FIVE YEARS OF SCHIZOPHRENIA

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Background: Findings about the onset and severity of the cognitive deficits in schizophrenia are controversial. In the context of their neurodevelopmental hypothesis, Panthelis et al. (2003) have recently suggested that functions developing earlier in life (e.g., set shifting abilities) are less likely to show deficits during schizophrenic illness, whereas those that take longer to fully develop (e.g. verbal declarative memory or executive functions) are more likely to be impaired.

Methods: In the search for a possible difference between the severity of cognitive deficits, we held a comprehensive assessment of cognitive functions in a young and relatively well-educated sample. Forty patients with DSM-IV Schizophrenia in the first five years of their illness were included. Sixty healthy subjects served as controls. Z scores were analyzed in a MANCOVA model, followed by Bonferronni correction, where the age, education, and the Wechsler Adult Intelligence Scale full IQ were the covariates. Effect sizes were calculated to reflect the magnitude of any difference.

Results: The magnitude of verbal declarative memory dysfunction on the Wechsler Memory Scale Logical Memory subtest far exceeded set shifting (Trail Making B-A) and response inhibition (Stroop Interference) deficits. They were also greater than executive dysfunction on the Wisconsing Card Sorting Test, although the difference was less striking.

Conclusion: These results are controversial with the view emphasizing executive dysfunction at all phases of the illness. However, they imply a possible differential effect of early and late insults, as suggested by Panthelis et al. (2003).

Reference

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512. EVALUATION OF TRUSTWORTHINESS OF FACES IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: Trustworthiness evaluation on the basis of facial appearance of others plays a significant role in social interaction. Recent evidence from lesion studies and functional neuroimaging research has found bilateral engagement of the amygdala during evaluation of trustworthiness of faces. Because structural imaging studies report that the amygdala is compromised in schizophrenia we examined whether trustworthiness evaluation of faces is also affected in patients with schizophrenia.

Methods: Patients viewed faces and made trustworthiness judgments. Subsequently, their ratings were compared with those of healthy control subjects. We found that trustworthiness ratings of patients were significantly higher than the ratings of healthy controls, $F = 6.30$, $p = 0.017$.

Results: We found no significant difference between patients and controls on a facial recognition task, which we included in the study to control for possible differences in the ability to recognize faces.

Conclusion: The findings are interpreted to suggest that patients with schizophrenia rate faces more trustworthy, possibly due to structural abnormalities of the amygdala.

513. COGNITIVE HETEROGENEITY IN FIRST EPISODE PSYCHOSES AND AT-RISK MENTAL STATES: EVIDENCE FROM CAMEO

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Background: CAMEO is a new Cambridge-based NHS service for people experiencing their first episode of psychosis (FEP), or who may be in an 'at-risk mental state' (ARMS) for psychosis.

Methods: All referrals receive a one-hour neuropsychological battery including CANTAB tests of executive function, memory and attention, all known to be impaired in psychosis. Follow-up assessments, including repeated cognitive testing, occur at 12 and 24 months after referral, and also at 6 months for ARMS cases.

Results: Results from the first year of baseline cognitive assessment are presented. The majority of CAMEO clients show significant impairment in one or more cognitive domains. ARMS cases are younger and have a higher NART-predicted IQ than FEP cases; they show less, though significant, cognitive impairment. However, great heterogeneity of cognitive function is found both within the FEP and ARMS groups, and within individual patients across different neuropsychological tests.

Conclusion: Contrary to traditional group study approaches, we suggest that this heterogeneity should be further investigated with a view to identifying 'cognitive phenotypes' of psychosis. Longitudinal assessment of cognition in the early stages of psychosis may reveal clinically important distinctions between patients experiencing early symptoms of psychotic disorders, which may have previously been obscured by group-based comparisons.

514. LACK OF SELF-SERVING BIAS AND EXCESSIVE INTERNALISING OF BLAME IN THE ATTRIBUTIONAL STYLE OF SCHIZOPHRENIA-PRONE INDIVIDUALS

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Background: People with schizophrenia excessively blame negative events on other people and positive events on themselves, an exaggeration of the normal self-serving bias found in normals which contributes to the maintenance of schizophrenia's core symptom, paranoid delusions. However, the temporal relationship between an exaggerated self-serving bias and the emergence of schizophrenic symptomatology has yet to be identified.

Methods: The present study examined the attributional style of normal people with a relatively high proneness towards developing schizophrenia. Decision-making style for positive and negative events was measured in the 25 highest and 30 lowest scorers on the *O-LIFE* schizotypy scale (from a sample of 251 students) using the *IPSAQ*.

Results: There was a significant interaction ($F = 3.5$, $P < 0.05$) between schizotypy group, type of blame and event-type. Low schizotypes showed a normal self-serving bias, however, rather than display the exaggeration of this bias that has been found in schizophrenia, high schizotypes made similar attributions for negative events and positive events: no significant differences were found between positive and negative events for the amount of internal and external attributions they made. High schizotypes blamed themselves more than others for positive events as did low schizotypes, however, they repeated the pattern for negative events. The schizotypal feature of increased cognitive disorganisation especially correlated with reduced self-serving bias.

Conclusion: These findings suggest that an exaggerated self-serving bias doesnot precede schizophrenia-onset, as low schizotypes showed a greater self-serving bias than high schizotypes, but that an unusual attributional-style consisting of excessive internalising of blame for both good and bad events is nevertheless pre-existant.

515. NEUROPSYCHOLOGICAL DYSFUNCTION AND RELATION TO VARIOUS DIMENSIONS OF SYMPTOMATOLOGY IN SCHIZOPHRENIA

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Background: Impaired neuropsychological functions are consistently reported in schizophrenia, but there is no consistent pattern linking specific deficits with different symptoms of schizophrenia.

Methods: As part of an ongoing study 32 patients with schizophrenia (mean age: 26,4 years), admitted to hospital during the last month, were compared to age matched healthy controls on a battery of neuropsychological tasks; including working memory (Letter–Number Span), selective attention (Stroop), verbal memory (Johns Hopkins Verbal Memory Task), non-verbal memory (Kimura) and phonological and semantic fluency tasks.

Results: Based on PANSS the following symptom dimensions were identified: A cognitive component, depressive symptoms, positive symptoms, negative symptoms and an excited component. The patients performed significantly below healthy controls on all neuropsychological tasks. Working memory, verbal memory and semantic fluency were strongly correlated with the cognitive component ($r = -0.50$, $p < 0.001$, $r = -0.60$, $p < 0.001$ and $r = -0.57$, $p < 0.001$, respectively) and with negative symptoms ($r = -0.50$, $p < 0.005$, $r = -0.42$, $p < 0.05$ and $r = 0.61$, $p < 0.00001$, respectively). Semantic fluency was also correlated with depressive symptoms ($r = -0.35$, $p < 0.05$). There emerged no significant correlations between any of the neuropsychological tasks and neither positive symptoms nor the excited component.

Conclusion: Although preliminary, these results indicate that there are some specific patterns of relations between neuropsychological task performance and the clinical symptomatology of schizophrenia.

516. PROGRESSIVE CHANGES IN THE WORKING MEMORY NEURAL NETWORK IN EARLY-AND MID-ADULTHOOD

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Background: Prefrontal cortex dysfunction has been demonstrated repeatedly in schizophrenia and it has been proposed that deficits in neurocognitive processes reliant on prefrontal cortex are a cardinal feature of the disorder. Working memory deficits in schizophrenia have been shown to be present throughout the course of the illness and are relatively resistant to pharmacotherapy. In normal individuals, studies of age-related changes in the neural network subserving working memory have tended to compare groups of young and old individuals. Although these studies promote understanding of age-related neurocognitive decline in later life, they have limited application in the study of early-and mid-adulthood changes. Valid interpretations of longitudinal functional imaging studies of first episode psychosis require a more complete understanding of normal age-related changes in early adulthood.

Methods: We therefore scanned twenty male, right-handed individuals (age range:19–51) using fMRI while performing the N-back task (periodic task design). The BAMM software suite was used to analyse images. A regression analysis was implemented to identify brain regions where age-related changes were present ($p < 0.01$). All participants were able to perform the task and correctly identified >90% of target stimuli.

Results: There was a significant reduction in activation with age in left prefrontal cortex and right parietal cortex. No areas were identified where activation increased with age. Maintained ability in working memory performance in mid-adulthood is associated with reductions in prefrontal and parietal activation.

Conclusion: Age-related changes in the neural circuitry of working memory are life-long and may therefore interact with the effect of schizophrenia throughout the course of the disorder.

517. THE ABANDONMENT OF CENTRAL EXECUTIVE? FRACTIONATION OF EXECUTIVE FUNCTIONS IN PATIENTS WITH SCHIZOPHRENIA

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Objective: The purpose of this study was to examine the phenomenon of fractionation of executive attention performance in schizophrenia.

Methods: A group of 90 schizophrenic patients (74 men, 16 women) were recruited. Patients were given a set of frontal-executive function sensitive tests to assess initiation, sustained attention, switching and flexibility, impulsivity and disinhbition, strategy allocation and planning. They were also given information subscale and memory subtests of the WAIS-R and WMS-R. We analyzed individual patient's executive attentional performance with the normative data from our laboratory. Summary scores for all specific executive attention components were computed. For each component, participants were classified as having impairment with their test performance below 1.5 standard deviations of the norms of the corresponding test.

Results: The findings showed that there were 27.8% ($n = 25$) cases demonstrated impaired performance in all executive components and 5.6% ($n = 5$) exhibited intact performance in all components. About 18.9% ($n = 17$), 16.7% ($n = 15$), 21.1% ($n = 19$), and 10% ($n = 9$) showed intact performance in 1 component, 2 components, 3 components, and 4 components, respectively. No significant differences were found among the groups in terms of education, gender, and duration of illness. Multiple univariate ANCOVA using age, information and medication as covariates indicated significant differences among the groups in terms of clinical symptoms and non-executive functions.

Conclusion: These findings suggest there is a fractionation of central executive in this clinical group.

518. THE INFLUENCE OF SCHIZOTYPAL PERSONALITY ON MEASURES OF EXECUTIVE FUNCTION IN HEALTHY INDIVIDUALS

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Background: A growing body of research (e.g. Park and Holzman, 1992) suggests that both schizophrenic patients and healthy participants with high scores on schizotypal personality traits (e.g. Peters et al., 1994) show reduced executive functioning. The current research examined the relationships between three aspects of schizotypal personality (positive, negative and disorganised) and performance on a battery of executive tasks assessing attention, working memory, verbal fluency and verbalisable rule learning and reversal.

Methods: Eighty-five healthy participants completed the Schizotypal Personality Questionnaire (SPQ, Raine, 1991) and completed five executive tasks.

Results: Multiple regression analyses revealed no significant relationships between schizotypal personality and four of the five executive measures. However, high scores on the Odd Beliefs and Magical Thinking subscale of the SPQ positive factor significantly predicted fewer correct responses in the rule reversal phase of a categorisation task. Thus, executive disruption was particularly reflected in a pattern of perseverative behaviour. However, the lack of significant associations between schizotypal personality and the other traditional executive measures may have been obscured by the regression procedure, in which power is reduced by multicollinearity. Therefore, the findings will be compared with a more powerful analysis based on the novel statistical technique, partial least squares (PLS, Nestor et al., 2002).

519. SEVERITY OF SCHIZOPHRENIC SYMPTOMS AND NEUROPSYCHOLOGICAL CORRELATES

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Background/objective: Cognitive deficits are recognized as a core characteristic of schizophrenia a long time ago. Kraepelin described cognitive disfunction in dementia praecox in the fifth edition of his textbook (Kraepelin, 1896). Although there is already a vast investigational literature concerning the neuropsychological deficits in schizophrenia, it is yet obscure the exact timing of it appearance, course, nature, and relation with severity of psychotic symptoms. Having these considerations in mind, we decided to evaluate a group of chronic schizophrenic patients with the following aims: 1—to determine the extent and nature of the cognitive deficits in these patients in comparison to aged and gender matched healthy control subjects; 2—to determine if it can be establish a correlation between the cognitive deficits and symptom severity.

Methods: In order to achieve the results we used these instruments: 1—a clinical and demographic interview; 2—the LURIA-NEBRASKA BATTERY, 3—PANSS. The study sample included 12 chronic schizophrenic patients followed on the Psychiatry Consultation of our hospital and the same number of controls who gave their informed consent. All the patients were stabilised.

Conclusion: The results of this study will contribute to better understand the characteristics of cognitive deficits in these patients and its relation to symptomology.

520. COGNITION IN EARLY ONSET SCHIZOPHRENIA (EOS): A 5 YEAR FOLLOW-UP STUDY

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Objective: This is an initial report of the follow-up phase of the Maudsley Early Onset Schizophrenia Project on the first 10 patients re-assessed out of the forty in the initial sample.

Methods: Ten patients (6 boys and 4 girls) with EOS were assessed twice, at the time of onset of psychosis and after a mean interval of 3.8 years. Their mean age at baseline was 17.4 (sd 1.7) years and at follow-up 20.7 (sd 1.5). All patients were still supported by their families. All were unemployed although 4 were attending part-time education. IQ indices were measured by the WAIS-R and memory by the WMS-R. Data were analysed using repeated measure analysis with time as within subject and gender as between subject factors.

Results: At baseline, mean full scale (FIQ), verbal (VIQ) and performance IQ (PIQ) were 95.6 (+13), 103.2 (+13), 103.2 (+10) and 89.9 (+13) respectively. IQ indices a follow-up for mean FIQ, VIQ and PIQ were 103.1 (+13), 102.6 (+12) and 103.2 (+15) respectively. The improvement in the mean PIQ at follow-up was statistically significant. The general, verbal and visual memory scores at baseline were 88.7 (+(21), 86 (+22) and 100 (+20) respectively and at follow-up these were 85.2 (+11), 82.6 (+8 and 101.2 (+16) There was no significant change over time for any memory measure.

Conclusion: In schizophrenia, as in the healthy population, the VIQ>PIQ discrepancy shows fluctuations over time. Memory impairment seems a more stable and enduring deficit.

521. NEUROPYCHOLOGICAL EVALUATION OF PATIENTS WITH TREATMENT RESISTANT AND SUPER TREATMENT RESISTANT SCHIZOPHRENIA: PRELIMINARY RESULTS

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Background/objective: Recently efforts have been made to better define those patients who do not completely respond to clozapine treatment who have been called incomplete responders or super-resistant to clozapine treatment. The Proerta is research project dedicated to the study of treatment resistant schizophrenia and, as general methodology, aims to compare non treatment resistant (NTR), treatment resistant (TR) and super treatment resistant (STR) schizophrenic patients by clinical, genetic, neuroimaging and neuropsychological parameters. The aim of the present study is to compare patients with TR with STR schizophrenia in terms of neuropsychological parameters.

Methods: 10 TR (4 men, 6 women, mean age $33.9 \pm 9{,}5$ y.o) defined by Kane's criteria and 10 STR patients (8 men, 2 women, mean age 34.10 ± 8 y.o) defined by the persistence of positive symptoms after a 6 months trial of at least 300 md/day of clozapine were evaluated at baseline by the following tests: Wechsler Memory Scale Revised, Stroop Test, Verbal and non-Verbal Cancellation Tests, Trail Making Test, Word Fluency, Wisconsin Card Sorting Test, Weschler Abbreviated Scale of Intelligence and Boston Naming Test. The Man Withney test was used for continuous variables and the chi square for dichotomous variables

Results: No differences were found between age and gender distribution among TR and STR patients as well as the different neuropsychological tests.

Conclusion: TR and STR patients seem not to differ in terms of neuropsychological parameters but the present study is limited due to the small sample size.

522. PSYCHOLOGICAL INTERVENTIONS FOR COGNITIVE AND EMOTIONAL DYSFUNCTIONS: A COMPARISON OF DIFFERENTIAL TRAINING STRA

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Background: Dysfunctions concerning social cognition (e.g. affect recognition, emotional reasoning, emotional regulation) as well as impairments concerning cold cognition (e.g. attention, memory and executive functions) are well established in patients with schizophrenia. Although these impairments have a significant relationship with poor outcome of social and vocational functioning, treatment approaches to overcome such dysfunctions are still rare.

Methods: Within this project, two training strategies for social as well as for cold cognition have been newly developed and implemented, which differ in conceptualization by focussing special functions (molecular approach) or an integrated view of functions and copingstrategies (molar approach). Training conditions were also be compared with treatment as usual.

Results: In the two research centers 113 schizophrenic patients finished the study.The results point to specific training effects: social cognition training improved facial affect recognition and understanding of social scenes and had additional positive effects on memory, attention and executive functioning, with the molecular training being most effective in general. The two cold cognition trainings had also specific effects, one improving attention and the other improving verbal memory. Whereas cold cognition training did not improved social cognition.

Conclusion: This points to the necessity of specific training for specific psychological domains with the possibility of different effective approaches within each domain.

523. RELATIONSHIP OF IQ TO NEUROPSYCHOLOGICAL TASKS INVOLVING PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Small samples of chronic or treated patients and the absence of a correlation between multiple neuropsychological tests are the methodological limitations of previous studies on the functioning of dorsolateral prefrontal cortex (DLPFC).

Methods: We studied treated (novel antipsychotics; $n = 36$) and untreated (drug-free, $n = 25$; drug-naive, $n = 19$) schizophrenic patients, according to DSM-IV ($n = 80$) and a control group ($n = 39$). We administered: the Wisconsin Card Sorting Test (WCST), the Self-Ordered Pointing Task (SOPT) and Visual Conditional Associative Learning Task (VCALT) referring to two subregions of the dorsolateral prefrontal cortex (areas 46/9 and 8 respectively) and the WAIS-R. We compared performances on these tests between drug-free, drug-naive and treated patients.

Results: All patients, tested during the acute phase, had a significant worse performance versus controls. The impairment was significant both in treated and untreated schizophrenics. While in the controls the performances on SOPT, VCALT, WCST

and WAIS-R were not correlated among each other, in schizophrenic patients there was a significant correlation between the WAIS-R and the other tests. Patients treated with novel antipsychotics did not show a significant cognitive impairment compared to the untreated patients. Conclusions: a) cognitive impairment is evident since the beginning of schizophrenia; b) novel antipsychotics seem not to affect executive functions c) poor performance on WCST, SOPT and VCALT is a feature of schizophrenic patients who present lower IQ, suggesting that in these patients is not possible to demonstrate specific deficits using selective tests only.

524. EMOTIONAL MEMORY, THE AMYGDALA AND THE BASIS OF MOOD CONGRUENT DELUSIONS

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Background/objective: We set out to investigate a model of delusion formation that suggests that in the context of affective disturbance excessive/abnormal emotional enhancement of stimuli (mediated by the amygdala) leads to biased recall and hence delusional beliefs. We hypothesised that groups with mood congruent (MC) and mood incongruent (MI) delusions would differ in amygdala structure and function (measured by the Cahill emotional memory test).

Methods: We measured amygdala volumes in 43 first-episode psychosis subjects with delusions (MI = 15, mixed = 13, MC = 15) and 43 controls.

Results: There was a nonsignificant trend in mean total amygdala volume (Control>MI>mixed>MC). We found a significant group x gender interaction for left amygdala volume ($F = 2.47$, $p = 0.068$) and a significant group x gender interaction for L–R asymmetry ($F = 5.32$, $p = 0.002$). We therefore examined amygdala volumes and L–R asymmetry in men and women separately and combined the mixed and MC group for increased power. In MI females the left amygdala was significantly larger than in controls and the MC/mixed group ($p < 0.05$) and there was significantly greater L–R asymmetry ($p < 0.02$). In males there was an opposite nonsignificant trend towards greater L–R asymmetry in controls compared to the deluded groups.

Conclusion: Preliminary results in our investigation of emotional memory suggest that both of these groups show reduced emotional enhancement of memory compared to controls but the MI group shows least emotional enhancement. These findings lend support to our model of delusion formation linking affective disturbance to abnormalities in amygdala structure and function and suggest that this may operate differently in men and women.

525. ACTIVE INHIBITION AND LATENT INHIBITION IN SCHIZOTYPY

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Background/objective: Latent inhibition (LI) has often been used to assess the ability of schizophrenic patients, and those high on measures of schizotypy, to screen out irrelevant information. However this task can be administered only once and it has proved difficult to develop a reliable within-subjects version of the task. Active inhibition (AI) is the term used to describe the ability of a person to inhibit distracter items that are presented 200–300 ms before ('previewed') the rest of the items in a visual search task (Watson and Humphreys, 1997). In such a search task the target is hard to find amongst the distracters, however if the distracters can be inhibited then the target is easy to find. The difference in performance when these distracters are previewed versus when they are not is an index of the subject's ability to actively inhibit these items. We hypothesized that this ability to screen out items in the preview task may be related to the ability to screen out irrelevant information in the latent inhibition task.

Results: As hypothesized, AI was strongly correlated with the learning score for the pre-exposed participants on a between-subject LI task, but did not correlate with the learning score for the non pre-exposed participants. However, whilst we replicated previous findings showing reduced LI with increasing schizotypy (using the O-LIFE) we found no relationship between schizoptypy and AI.

Conclusion: Therefore, whilst AI appears to have some relationship to LI our study has not established any relationship so far to measures of schizotypy.

526. REDUCED APPRECIATION OF SOCIAL CONTEXT IN SCHIZOPHRENIA IMPAIRS THE PERCEPTION OF COMPLEX MENTAL STATES

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Background/objectives: Previous evidence for reduced context processing and poor social cognition in schizophrenia suggests that these individuals fail to use *social contextual* information effectively when making mental state attributions. This study investigated whether poor context processing impairs the ability to discriminate

basic emotions from complex mental states when judging the meaning of facial expressions.

Methods: Vignettes describing social situations were read to participants who then judged the meaning of a visually presented facial expression following each vignette. Story-face pairs were designed to be discrepant in affective valence so that mental state judgments could be interpreted as reflecting the dominance of either situational context or visual information in the faces. Control subjects' ($n = 60$) judgments were influenced by story contextual information: faces depicting basic emotions (e.g., anger, surprise, fear, sadness) were interpreted as other emotions or complex mental states (e.g., determined, puzzled, hope) according to the situation described in vignettes.

Results: However, preliminary findings in schizophrenia ($n = 8$) show reduced context processing for angry faces when the situation suggests a complex mental state. That is, when controls judged an angry face as 'puzzled' according to the social context, schizophrenia subjects instead perceived 'anger'; schizophrenia subjects also interpreted angry faces as 'feeling pain' when the social context cued 'determination'. Interestingly, the schizophrenia group performed like the control group in using contextual information when vignettes described a situation that was predictive of a basic emotional state (e.g., fear, anger, disgust).

Conclusion: The ability to infer 'higher order' mental states may be compromised by poor social context processing in schizophrenia.

527. NUMBER AND TYPE OF PATIENT NEEDS AND COGNITIVE FUNCTIONING IN SCHIZOPHRENIA

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Background/Objective: Cognitive impairments may hamper social functioning and may be related to higher level of patient health care and social needs. We thus hypothesie that cognitive deficits are related to patients needs in the social functioning area.

Methods: Cross-sectional study with 63 outpatients (DSM-IV criteria for schizophrenia). Patients were administered the Camberwell Assessment of Needs (CAN) questionnaire and a neuropsychological battery that included the MMSE, Stroop test, TMTA and TMTB, WAIS sub-scales, WCST, FAS (verbal fluency), TAVEC (Spanish version of the California Verbal Learning Test), and CPT. The CAN assesses the presence of needs and unmet needs in 22 areas (accommodation, food, looking after home, self-care, daytime activities, physical health, psychotic symptoms, information, psychological distress, risk to self, risk to others, alcohol, drugs, company, intimate relationship, sexual expression, child care, education, telephone, transport, money and social benefits).

Results: Sixty-four percent of patients were male and mean age was 44 years (sd 10). Mean number of unmet needs were 1.86 (sd 1.78). Level of unmet needs were related to executive functioning (TMTB, WCST). Needs most related to cognitive deficits were education, transport, use of telephone and administration of money. Education needs were related to attention, memory and overall impairment (MMSE); use of telephone needs were related to attention and overall impairment; transport needs were related to attention, executive functioning and psychomotor speed; and administration of money needs was related to working and verbal memory.

Conclusion: Level and type of patient unmet needs are related to specific areas of cognitive deficits.

528. COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: THE PSYCHOMOTOR COMPONENT

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Objective: In this study we compare a design using psychomotor tasks with some commonly used neuropsychological tests for the assessment of cognitive functions in schizophrenia.

Methods: 30 in-patients and 30 matched controls were recruited. The neuropsychological battery consisted of five tests: the Rey Auditory Verbal Test (RAVLT), the Continuous Performance Test (CPT), the Trail Making Test (TMT) part A and B, the Letter–Number Sequencing test (LNS) and the Wisconsin Card Sorting Test (WCST). Three writing tasks were administered on a personal computer and a digitizer using a pressure-sensitive pen: simple lines differing in orientation and 24 figures differing in familiarity and complexity had to be copied, furthermore circles had to be connected with a line of 10 mm from the centres of two circles with a diameter from 0.25 to 0.50 cm. Mean effect sizes (d) were calculated in differences between z-scores. A linear regression analysis was performed using the indices of the psychomotor tasks as predictors of the performance on the neuropsychological tests.

Results: All writing tasks showed mean effect sizes that equal or exceed the average difference across tasks (0.89) as opposed to the neuropsychological tests that showed differences below this mean impairment. Linear regression revealed that the writing tasks could

predict a significant part of the scores on the WCST and the CPT in patients.

Conclusion: Psychomotor retardation shows to be an important deficit in schizophrenia, not measured by the commonly used neuropsychological tests**,** although psychomotor retardation declares partially the poor performance on some of these tests.

529. ATTENTIONAL BIAS TO FACIAL EXPRESSIONS AND PSYCHOLOGICAL RESPONSIVITY IN FIRST-EPISODE PSYCHOSIS

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Background: Patients with schizophrenia often show deficits in the perception of emotional facial expressions. Although biased attention to threat-related stimuli such as negative emotional facial expressions has been demonstrated in schizophrenic patients, attentional bias to facial expressions in relation to physiological responsivity has not been studied in first-episode psychosis.

Methods: In this ongoing study, we want to examine the attentional and psychophysiological disturbances of inpatients with a first-episode psychosis during performance of an emotional interference task. During this task the subjects viewed picture-pairs of faces with emotional expressions (angry–neutral, happy–neutral, neutral–neutral), after which they had to respond to non-facial target stimuli. Before (5 min) and during the task heart rate, skin conductance level, breathing rate and blood pressure were measured continuously. So far, 11 first-episode patients (mean age: 23 years, sd: 4; 10 males) and 11 healthy controls (mean age: 25 years, sd: 6; 10 males) were evaluated.

Results: The patients responded significantly slower to all task conditions (angry, happy or neutral) compared with controls, but no significant difference was observed between target appearance on the same side as the emotional face versus the opposite side. Whereas the controls responded with a significant reduction of heart rate, and significant increases of breathing rate, and systolic and diastolic blood pressure, the patients did not show significant changes in the physiological parameters.

Conclusion: These initial data only show limited support for biased attention to emotional faces in first-episode psychosis, which was not accompanied by significant changes in autonomic nervous system activity.

530. THEORY OF MIND IN PATIENTS WITH SCHIZOPHRENIA, NON-PSYCHOTIC RELATIVES AND SCHIZOTYPAL INDIVIDUALS

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Background: It has been proposed that certain psychotic symptoms associated with schizophrenia reflect a deficit in the ability to appreciate other people's mental states (theory of mind) (Frith, 1992). Recent evidence suggests that subtle alterations in theory of mind may also be present at lower levels of the psychosis continuum (Janssen et al., 2003). We investigated theory of mind skills in patients with schizophrenia, non-psychotic relatives and individuals with schizotypy.

Methods: The study included 39 patients diagnosed with psychosis, 34 first-degree relatives, 40 subjects scoring high (>75-percentile) on schizotypy according to the CAPE positive dimension scale, and 53 normal controls. Theory of mind was assessed using the hinting task (Corcoran, Mercer and Frith, 1995). This task examines the ability to infer the real intentions behind indirect speech.

Results: The scores on the hinting task were dichotomised (0:no mistakes; 1:one or more mistakes). The results were expressed in OR's using logistic regression. There was a significant association between schizophrenia and failure on the hinting task (OR: 4.6; 95%CI 1.7–12.9). The first-degree relatives had intermediate values between patients and controls, although the association was not significant (OR:1.9; 95%CI 0.8–4.6). For the individuals with positive schizotypy, the chance of failing the hinting task was not different from that of controls (OR:0.8; 95%CI 0.4–1.8).

Conclusion: Patients with schizophrenia had difficulty in monitoring and understanding the thoughts and intentions of other people. The first-degree relatives, but not the individuals with positive schizotypy, showed subtle alterations in theory of mind.

531. MENTAL REPRESENTATIONS IN SCHIZOPHRENIA: RELATIONSHIP TO PREMORBID ADJUSTMENT AND SYMPTOMS

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Background: Mental Representations (MR) have been defined as cognitive–affective schemata of self and others. Individuals with schizophrenia have been found to show deficiencies in MR. The present study examined the association of MR, premorbid adjustment, insight and symptoms.

Methods: Sixty-one subjects with DSM-IV schizophrenia/schizoaffective disorder were assessed using the Premorbid Adjustment Scale (PAS), the Positive and Negative Syndrome Scale (PANSS) and six measures of MR, including the four subscales of the Bell Object Relations and Reality Testing Inventory (BORRTI), the Differentiation-Relatedness Scale (DRS), and the Human Representations Variable (HRV) of the Rorschach Comprehensive System (RCS).

Results: Factor analysis of the MR measures revealed three factors that accounted for 74.3% of the MR variance. Factor 1 (25.4%) emphasized characteristics of "self" and displayed a tendency toward significance with negative symptoms ($r = -0.226$, p=.085). Factor 2 (24.9%) emphasized characteristics of "others", but was unrelated to symptoms or premorbid adjustment. However, factor 3 (24.0%), which emphasized characteristics of "interpersonal relations", was significantly related to positive symptoms ($R^2 = 0.191$, Adjusted $R^2 = 0.177$, $F(1, 56) = 13.22$, $p = 0.001$) and to premorbid adjustment ($r = -0.352$, $p = 0.007$). Age at onset of psychotic symptoms, duration of illness, age, and gender were not related to MRs, nor level of insight.

Conclusion: These results suggest that MRs are multidimensional and may be of utility in assessing psychopathology that reflects both premorbid adjustment and positive symptoms. These findings support results obtained with other methods of investigation in suggesting that positive symptoms in schizophrenia relate to difficulties in understanding interpersonal relationships between self and others.

532. COGNITION, METACOGNITION AND INSIGHT IN FIRST-EPISODE SCHIZOPHRENIA: THE DIFFERENTIAL CONTRIBUTION OF DISAGREEMNT VERSUS UNAWARENESS TO POOR INSIGHT

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Objective: The aim of this study was to explore the neuropsychological basis of poor insight in first-episode schizophrenia.

Methods: Sixty first-episode patients and a comparison group of 50 chronic patients were assessed with the Scale of Unawareness of Mental Disorder (SUMD) and the meta-cognitive version the Wisconsin Card Sorting Test (WCST) developed by Koren et al. (2000). In an attempt to distinguish between patients whose poor insight is primarily due to *unawareness* ("I don't have any problem" and "my doctor doesn't think I have one either") and those whose poor insight appears to stem from *disagreement* ("I don't have a problem" but "my doctor thinks I have one"), we asked our subjects not only about their own opinion about what they have, but also about what they believe their doctors think they have.

Results: Contrary to our hypotheses, insight into illness was not correlated with neither the conventional scores from the WCST or with the new free-choice metacognitive measures. On the other hand, metacognitive performance had significant correlations with patients' insight into what their doctors' believe they have. In addition, metacognitive measures were able to differentiate between patients who were classified as *disagreement-type* from those who were classified as *unawareness-type*.

Conclusion: These results suggest that deficits at the metacognitive level may play a mediating role between basic neurocognition and poor insight in schizophrenia. Moreover, they suggest that more attention should be paid to the differential contribution of *unawareness* versus *disagreement* to poor insight in schizophrenia.

533. THE IMPACT OF FAMILY HISTORY OF SCHIZOPHRENIA AND RELATED DISORDERS ON NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIA PATIENTS

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Objective: To examine the impact family history of mental illness has on neurocognitive functioning in persons with schizophrenia.

Methods: Seventeen schizophrenia patients and 13 healthy normal controls (NC) participated in this study. All subjects were examined on 13 neurocognitive measures examining attention and working memory. The Family Interview for Genetic Studies (FIGS) was used to determine the presence or absence of a first degree family history of schizophrenia and related disorders. The patient

group was then stratified into family history positive (FH+; $n=6$) and family history negative (FM-; $n=11$) groups.

Results: There was a statistically significant effect of group on ten of 13 measures (simple reaction time, grooved peg board, visuospatial memory, digit span forward and backward, digit span distractability test, Stroop color–word test, visual memory span forward, letter number sequencing, and the D2 Test of Concentration). With the exception of the visual memory span forward test, post hoc analyses revealed that FH-patients performed significantly worse than the NC group on the remaining nine measures. A comparison of the FM+ group with the NC group revealed that they only differed on four of 10 measures: the grooved peg board, digit span forward, Stroop color-word test, and the D2 Test of Concentration. There were no differences in performance between the two FH groups.

Conclusion: FH-patients were impaired on many more measures compared to NCs than were FH+patients. Therefore, sporadic cases of schizophrenia may show greater neurocogitive impairment compared to genetically mediated cases.

534. THE NATURE OF IMPAIRED VERBAL LEARNING AND MEMORY IN ADOLESCENTS WITH SPECTRUM DISORDER SCHIZOPHRENIA

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Background/objective: Recent evidence suggests that verbal learning and memory are among the most severely compromised cognitive domains in schizophrenia. However, few studies have investigated memory in adolescents with schizophrenia. Because earlier age of onset has shown an association with poorer cognitive function this is an important group to investigate. Also, early age of onset may reflect a high genetic loading and adolescents may display clear marker deficits. Thus, the aim of the study was to investigate the nature of verbal memory in adolescents with schizophrenia spectrum disorders.

Methods: Twenty-one inpatients (mean age:15,4 years, mean IQ: 89) and a group of age-matched healthy controls were compared on various measures of verbal learning and memory.

Results: Preliminary data analyses indicate that the schizophrenia group show an impaired rate of acquisition and deficient retrieval. The patients are also more vulnerable to proactive interference than controls. Storage processes, however, appear to be preserved. No between-group difference was found on a frequency of occurrence task, presumably reflecting intact automatic memory processes. On tasks of phonological and semantic fluency the patient group expose impaired performance relative to controls. With regard to immediate short-term memory no difference between the groups was found on the digit span forwards. However, on tasks with a stronger working memory component, i.e. digit span backwards and a serial supra-span task, patients performed poorer than controls.

Conclusion: Taken together these results indicate that there is a specific pattern of impaired and preserved verbal memory functions in adolescents with schizophrenia.

535. TIME PERCEPTION DYSFUNCTION IN PSYCHOMETRIC SCHIZOTYPY

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Background: Time perception dysfunction has been demonstrated in patients with schizophrenia. The aim of this study was to investigate whether time perception was disturbed in people with schizotypal personality trait and whether this was related to specific dimensions of schizotypal personality.

Methods: A total of 101 non-clinical subjects completed SPQ (the Schizotypal Personality Questionnaire, Raine, 1991) and the temporal bisection task with two interval ranges (400/800 msec, 1000/2000 msec). Individuals with total SPQ score below and above 1 standard deviation and individuals close to the group mean were compared. The relationship between bisection data and schizotypal dimensions (cognitive/perceptual, interpersonal, and disorganization) was also explored.

Results: The results showed that high SPQ scorers judged durations significantly longer, relative to low SPQ low scorers in the 1000/2000 bisection condition. Within schizotypy dimensions, both cognitive/perceptual and interpersonal dimensions were significantly associated with the longer duration judgement.

Conclusion: The results of this study indicated that schizotypy was associated with a decreased internal clock speed. Further research into patients with schizophrenia is required to determine whether the pattern of results obtained is comparable.

536. EFFERENCE COPY MECHANISMS IN HUMANS AND THE EMERGENCE OF DELUSIONS AND SELF-DISTURBANCES IN SCHIZOPHRENIA

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Background: Feed forward mechanisms are important for movement control (Wolpert et al., 1995, von Holst and Mittelstaedt, 1950) and may contribute to the identification of self-produced actions by attenuating the sensory consequences of self-produced actions (Frith et al., 2000). Impaired forward mechanisms may underly pathological states such as delusions of influence or passivity experiences in schizophrenia. These patients have difficulties in distinguishing their own from an alien hand carrying out movements under ambiguous experimental conditions (Leube et al., Consciousness and Cognition, in press).

Methods: In our study, patients with schizophrenia and a control group opened and closed their hand slowly and continuously (0.5 Hz). This movement was filmed with an MRI compatible video camera and projected online onto a screen, viewed by the subject while BOLD contrast was measured with fMRI. The temporal delay between movement and feedback was parametrically varied (0–200 ms). In each trial, subjects judged whether there was a delay or not.

Results: In the contol group there was a positive correlation between the extent of the temporal delay and activation in the right posterior superior temporal cortex (pSTS) and a negative correlation in the left putamen. A second analysis addressed the neural correlates of subjective judgement under conditions of uncertainty. This contrast showed a differential activation in the cerebellum (Leube et al., Neuroimage, in press).

Conclusion: These results support the assumption of a forward model implying that predictions generated in motor areas attenuate sensory areas in healthy subjects. They also suggest that conscious detection of small temporal deviations is based on signals generated in the cerebellum. We hypothesize that the prediction of forward models is corrupted in schizophrenic patients so that the sensory consequences of self-produced movements are not attenuated (i.e. the movement sensitive areas in the temporal lobe). Thus the sensory consequences of self-produced movements are at risk being misclassified as externally generated.

537. SYMPTOMATOLOGY AND SOCIAL INFERENCE: A THEORY OF MIND STUDY OF SCHIZOPHRENIA AND PSYCHOTIC AFFECTIVE DISORDER

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Background: Theory of Mind (ToM; often referred to as mentalising) is the ability individuals have to correctly determine the intentions and behaviours of others. There is evidence that patients with schizophrenia have deficits in ToM capabilities. It is unclear whether these are symptom or diagnosis specific.

Methods: Using the Hinting task (Corcoran et al., 1995) the performance of patients with schizophrenia, affective psychoses and healthy controls was compared in order to investigate the hypothesis that a deficit in ToM skills is associated with particular psychotic symptoms, regardless of diagnosis.The task was administered to 15 patients with a DSM-IV diagnosis of schizophrenia, 15 patients with psychotic affective disorder and 15 healthy controls. Severity of current psychopathology was measured using the Krawiecka standardized scale; IQ was estimated via the Quick test.

Results/conclusion: The patients with schizophrenia performed significantly worse than the affective and control group. However, across both psychotic groups, poor performance on the Hinting task was found to be significantly related to the presence of positive symptoms (but not negative features) and specifically related to delusions and hallucinations. These findings remained when covariance for several potentially confounding variables was applied.Patients with schizophrenia performed less well on this ToM task than the psychotic affectives and control group. Positive symptomatology was linked to poor performance and further supports the notion of symptom-related difficulties in the ability of schizophrenics to infer the mental state of others.

538. ASSESSING EXECUTIVE FUNCTIONING IN SCHIZOPHRENIA WITH THE COGTEST

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Background: Cogtest (Cogtest plc, London) is a computerized neurocognitive test battery of 16 subtests currently being used in over 300 organizations across 16 countries. It is designed for use with a variety of clinical populations and in clinical trials. The platform allows for accurate recording of reaction time data, enhanced standardization relative to examiner administered tests and is easily adapted for implementation in functional neuroimaging environments. Its internet data capture and web reporting facilities make it unique amongst current cognitive test providers. Additionally, its multiple parallel forms make it amenable to repeated testing sessions across time. One subtest, The Strategic Target Detection Test (STDT), probes executive functioning in a manner similar to the paper-and-pencil 'cancellation' tests or the 'cross-out' subtest of the WAIS-III. The subject is not told in advance which of the stimuli is the 'target' and must therefore learn which is the correct target by observing feedback and modifying future responses. The target stimulus also changes after a criterion number of consecutive correct responses, similar to the WCST.

Methods: We administered the STDT to acutely ill inpatients with schizophrenia (Scz) and adults with attention deficit hyperactivity disorder (ADHD), in addition to a healthy comparison group.

Results: Preliminary data reveals that Scz patients have longer reaction times for correct responses [$F(2,14) = 12.98$; $p = 0.001$] relative to both the comparison and the ADHD group.

Conclusion: These results suggest that the Cogtest is useful in characterizing the executive dysfunction of schizophrenia patients.

539. RECOGNITION WITHOUT FAMILIARITY: USING ROCS TO STUDY THE FACE RECOGNITION MEMORY DEFICITS IN SCHIZOPHRENIA

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Objective: The aim of the experiment was to explore the effects of two types of encoding instructions, superficial versus deep encoding, on recognition memory for faces in schizophrenia.

Methods: The effect of level of encoding on familiarity and recollection, the two distinct memory processes involve in recognition decisions, was studied. The paradigm used was first developed by Jacoby (1991), it is a process dissociation framework for dissociated the contributions of familiarity and recollection. Subjects were tested during two sessions: 1) a study phase in which they were asked to make judgements on 16 non-familiar faces expressing one or the other of a set of two emotions. According to the conditions, they were made judgements about gender (superficial encoding) and about the perceived honesty (deep encoding) of a face; 2) the second session was a test phase. Two types of recognition tests were used: on the inclusion test, subjects are instructed to endorse as old all faces studied earlier, on the exclusion test, subjects are instructed to exclude faces which emotion has changed. Dual-process signal-detection model was used to estimate recollection and familiarity. The ROCs obtained are linear for schizophrenics and curvilinear for controls.

Results: The primary finding is that schizophrenics unlike controls use principally recollection and not familiarity.

Conclusion: We can conclude that one of the origin of the recognition memory dysfunction in schizophrenia is a problem of emergence, retrieval or used of the feeling of familiarity, probably due to a disruption of hippocampique system and temporal lobe interaction.

540. INTELLECTUAL IMPAIRMENTS ARE A MARKER OF VULNERABILITY TO SCHIZOPHRENIA BUT NOT BIPOLAR DISORDER

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Objective: This study addressed the hypothesis that schizophrenia and bipolar disorder are separate disorders by examining the neuropsychological performance of schizophrenic, bipolar and unaffected individuals from families in which the disorder appears to breed true, and from families where there is a history of both schizophrenia and bipolar disorder and a further group of healthy subjects.

Methods: DSM-IV diagnoses of probands were confirmed using the OPCRIT symptom checklist. The diagnostic status of unaffected relatives and controls was confirmed using the SADS-L. All participants underwent a neuropsychological test battery including the NART, and Wechsler Abbreviated Scale of Intelligence (WASI). Statistical analysis was conducted corrected for the presence of current symptoms.

Results: NART IQ was impaired most in schizophrenic subjects and their well relatives compared to controls. Current FSIQ was however impaired in schizophrenic subjects, their well relatives, both bipolar groups and showed a trend to reduction in the unaffected subjects from mixed, but not purely bipolar families. Performance and verbal IQ were also reduced in all affected subjects but only unaffected subjects who were from schizophrenic or mixed families showed. IQ decline, estimated by WASI FSIQ-NART IQ discrepancy, was greatest in schizophrenic subjects, but was present in all patient groups. 'Premorbid', current, performance and verbal

IQ all appear to be reduced in schizophrenic subjects and their well relatives. However, current, performance and verbal IQ are reduced in all patients. No intellectual measures appear to be associated with a genetic liability to bipolar disorder.

Conclusion: This study suggests that while the expression of psychosis itself causes deficits in IQ, it is a liability to schizophrenia alone which appears to be associated with reductions in well relatives. These findings suggest the presence on one or more genes for schizophrenia which are also associated with increased liability to intellectual impairment.

541. INFORMATION PROCESSING IMPAIRMENT IN VERY EARLY ONSET SCHIZOPHRENIA: A PILOT STUDY

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Background/objective: VEOS is a rare disorder, defined as schizophrenia with an onset of psychosis in pre-adolescent years. Existence of poor performance in tests of IP among adult schizophrenic patients is a consistent finding in research literature. However, there is no empirical evidence of impairment of IP among children diagnosed as VEOS. Hypothesis was that IP impairment in VEOS patients would be more severe than among healthy children. The aim of this study was to assess information processing (IP) in very early onset schizophrenia (VEOS).

Method: Subjects were 15 VEOS patients (6 girls and 9 boys; average age of 14.6 ± 3.3 years) and 47 healthy children (22 girls and 25 boys age: 14.8 ± 3.5 years). IP was measured by a computerized neuro-cognitive battery-"CogScan", which included 15 subtests: Tapping Test, Inspection time, Motion Perception Test, Simple Reaction Time, Choice Reaction Time, Immediated and Delayed Memory for Pictures, Words and Faces, Stroop test, Time-Accuracy Tradeoff, Digit Symbol Substitution Test (DSST), and Continuous Performance test. Statistical analysis was performed using t-test.

Results: Significant differences between VEOS and control group were found in all sub-tests of IP exept Inspection time: motion perception ($p = 0.001$), finger tapping test ($p = 0.009$), simple reaction time ($p = 0.004$), choice reaction time ($p = 0.02$), time-accuracy tradeoff ($p = 0.001$), selective attention (Stroop: neutral latency, $p = 0.045$; and accuracy $p = 0.05$) and sustained attention (CPT, $p = 0.032$). Significant differences between VEOS and control group were found only in some of the memory sub-tests: immediate recognition for pictures ($p = 0.000$), and faces ($p = 0.024$), and working memory (DSST, $p = 0.000$). Delayed recognition for pictures, words, and faces was preserved.

Conclusion: Children with VEOS were significantly impaired in input, processing and output stages of IP. VEOS children were found to have a significant impairment in motion perception, selective and sustained attention, immediate picture and face recognition, and in working memory as compared to healthy children. The differences between groups can be partially explained by the use of antipsychotic agents. Our preliminary results suggest that further investigation of IP impairment in VEOS patients is certainly warranted.

542. DEVIATIONS IN AUDIOVISUAL INTEGRATION PROCESSES IN SCHIZOPHRENIC PATIENTS AND HIGH-RISK-POPULATIONS-EXPERIMENTAL STUDIES

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Background/objective: We investigated audiovisual integration processes in 18 schizophrenic patients by using the McGurk effect. Studies on language processing with healthy participants show that humans make use of visual information of lip movements to understand spoken language. A prominent phenomenon to demonstrate the power of these inter-modal information processing is the McGurk effect. When participants listen to incongruous audiovisual speech they often report hearing illusory phonetic segments that are presented neither acoustically nor visually.

Methods: We replicated prior results of our group that schizophrenic patients give fewer illusory answers. In a second step we evaluated if a psychometrically defined high-risk-population shows deficits in audiovisual integration as well.

Results: There were no differences compared to persons without vulnerability. Either deficit in integration ability are not a marker of schizophrenia vulnerability or the deficit was to weak to find significant differences. For this reason we retested the high-schizotypes by using a paradigm with temporal asynchrony in visual and auditory information onset to heighten cognitive demand. Interestingly, high schizotypes showed not weaker but stronger modality integration.

543. NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

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Background: Schizophrenia has been known as the most intriging psychiatric disorder for its major complexity and, nowadays, is seen as a clinical condition that must be studied in several stages and levels.

Methods/results: This study is a contribution to analise the relationship between deficits and syndromes. Its based in a neurocognitive and syntomatologic evaluation of a sample of thirty one subjects with Schizophrenia diagnostic. The synthomatologic evaluation with the Positive and Negative Syndrome Escale allowed the subset of patients in syndromes. The Wechsler Adult Intelligence Scale allowed the evaluation of intellectual abilitys in both syndromes (Verbal I.Q. ¨C $p = 0.93$; Manipulative I.Q. ¨C $p = 0.068$; Global I.Q. ¨C $p = 0.136$). The sustained attention was evaluated by the Toulouse-Pieï®n ($p = 0.194$). The memory as evaluated by the Wechsler Memory Scale ($p = 1{,}551$). The Wisconsin card Sorting Test allowed the evaluation of executive functions thru the indexes% Mistakes ($p = 0{,}643$),% Persevering Answers ($p = 0{,}901$),% Persevering Mistakes ($p = 0{,}802$),% Non-Persevering Mistakes ($p = 0.036$),% Conceptual Answers ($p = 0.867$), and% failures in Sustained Behavior ($p = 0.534$) C the scores obtained in% Failures in Sustained Behavior and Number of Persevering Mistakes also allowed the evaluation of working memory in both syndromes.

Conclusion: This study indicates that the cognitive deterioration seems to be an inherent feature of the Schizophrenic process, particularly in what refers to the sustained attention and working memory deficits.

544. INEFFICIENT AUTOMATIZATION OF WORKING MEMORY PROCESSES IN SCHIZOPHRENIA

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Background/objective: Practice generally improves performance, reflecting a shift from controlled to automatic processing. Behavioral automatization appears to be intact in schizophrenia patients. However, while controls reduce brain activity in working memory regions following practice, patients do not (Jansma et al., Schizophr.Res.49:S178–S179, 2001). The degree of neurophysiological automatization appears to predict performance decrement when a second task is added, suggesting that processing-capacity is coupled to the ability to reduce claims on neuronal resources with practice (Ramsey et al. Brain 2003, in press). We tested whether failure of neurophysiological automatization in schizophrenia predicts reduced information processing-capacity.

Methods: Eleven patients and twelve controls performed a Sternberg task with two conditions (novel and practiced targetset) during fMRI. Afterwards the task was repeated, alone and concurrently with a second task. The difference in performance on the Sternberg task (single vs. dual) represents information-processing capacity, and the practice-induced difference in brain activity represents neurophysiological adaptation.

Results: With practice, patients improved performance comparable to controls. As a group, patients were impaired on the dual-task ($p < 0.007$), but some performed normal whereas others performed very poorly. When comparing all patients to all controls, reduction of brain activity after practice did not differ. However, practice-effects on brain activity in the five poor performing patients was significantly enhanced.

Conclusion: These results suggest that practice-effects on activity varies strongly in patients, and that it is associated with processing-capacity and possibly with strategy of task execution. The group of patients is currently expanded to examine which clinical and/or neuropsychological measures distinguish the two groups.

545. EXECUTIVE PREDICTORS AND PATTERNS OF CHANGE IN INSIGHT FOLLOWING COGNITIVE REMEDIATION THERAPY

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Background: Theories of insight in schizophrenia suggest that impairments result from either deficits in executive function or an avoidant coping style. It has been hypothesised that these routes may operate independently and may vary between patients. Recent advances in therapies to improve cognition may have an impact on insight and may enable us to test the proposed theoretical relationships between executive function and insight.

Methods: This study uses a large battery of executive functioning tests and investigates the relationship between cognitive improvements and increased insight following cognitive remediation therapy (CRT). 85 people with a diagnosis of schizophrenia were assessed on a range of executive function and symptom measures and were randomly assigned to receive either CRT or treatment-as-usual. Participants were re-assessed after three months (for the therapy group this was immediately after the cessation of therapy).

Results: Three executive principal components were extracted from the baseline data: (i) verbal working memory, (ii) response inhibition, and (iii) cognitive flexibility, the first two of which were significantly correlated with insight. Hierarchical and k-means cluster analyses were conducted using executive components and PANSS insight, and differential baseline associations between executive components and insight were found between clusters. For the whole sample, only improvement in the cognitive flexibility factor was predictive of increased insight three months later.

546. CONTRASTS IN NEUROPSYCHOLOGICAL TEST PROFILES BETWEEN PATIENTS WITH SCHIZOPHRENIA AND RECURRENT NON-PSYCHOTIC DEPRESSION

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Background/objective: Patients with schizophrenia show neuropsychological deficits in a broad range of functions. A common finding is that type and degree of impairment varies across individuals. Conclusive reports regarding the selectivity of impairment remain scarce. To assess selectivity it is of interest to examine to what degree patients with schizophrenia present different or similar neuropsychological test profiles to patients with major depression. In order to distinguish what is unique to schizophrenia and depression respectively, but not attributable to psychosis as such, schizophrenia patients were compared to non-psychotic depression patients.

Methods: 53 patients with schizophrenia, 45 with recurrent non-psychotic major depression, and 50 normal controls were assessed with a comprehensive NP test battery and clinical instruments.

Results: Test scores were grouped into 7 neurocognitive factors. MANOVA revealed significant group differences in test profiles. Post hoc comparisons showed that schizophrenic patients performed significantly below normal controls on all 7 factor, whereas depression patients were significantly impaired on 2 factors. When controlling for IQ-differences between groups, 5 of the 7 factors upheld discriminating power. Thirty-eight percent schizophrenia patients performed deviant (a threshold of 1.5 SD from the mean of normal controls) in less than 2 domains and were classified as cognitively unimpaired, whereas 17% were characterized as severely impaired.

Conclusion: The schizophrenia group is characterized by significant deficits across a wide range of NP functions, whereas only a mild and selective disturbance is apparent in the non-psychotic depression group.

547. PERCEPTION OF COGNITIVE IMPAIRMENT IN PATIENTS WITH PSYCHOSIS

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Objective: Despite there is a growing interest in the assessment of the subjective perception of cognitive impairment in patients with psychosis there is a lack of standardized instruments specifically designed to evaluate such type of construct. The aim of this study is to present the characteristics and psychometric properties of a scale for measuring cognitive impairment as reported by patients with psychosis.

Methods: The new GEOPTE scale gathers information from two sources: the patients subjective perception of his deficits and that of the informant or caregiver. It consists of 15 items, 7 for basic cognitive functions and 8 for social cognition. The scale was applied to 107 patients with a diagnosis of psychosis (according to DSM-IV), and gathered general clinical data, overall clinical impression, mood and degree of insight.

Results: The GEOPTE scale presented an excellent internal consistency (Cronbachs Alpha: 0.84 for patient and 0.87 for informants). Factorial analysis identified two factors, which explained a total variance of 39%. The first factor was related to basic cognitive function items and the second to social cognition items. As regards the validity of the construct, the grading on the scale is closely related to Overall Clinical Impression, degree of insight and depressive symptoms.

Conclusion: The GEOPTE scale for measuring social cognition in psychosis has an excellent psychometric behavior both in the degree of internal consistency and in the correlation with overall clinical variables, mood and degree of insight.

548. EXECUTIVE CONTROL AND MOTOR FUNCTION IN SCHIZOPHRENIA

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Background: An influential hypothesis about the cognitive decifit in schizophrenia proposes a deficit in the working memory (WM) component of maintaining context information necessary to guide appropriate task behavior (Servan-Schreiber and Cohen, Psychol Review, 1992). An alternative hypothesis proposes a deficit in the WM component of exerting control over ongoing information processing in the brain (Baddeley, 1996, Q J Exp Psychol).

Methods: We tested these alternatives with a four-choice motor cuing task in which we minimized demands on WM maintenance and maximized the active control of WM over ongoing processing. We measured the Electroencephalogram (EEG), the Electromyogram (EMG) and behavioral indices during task performance in 16 schizophrenia patients and 16 healthy controls. From the EEG we derived the Contingent Negative Variation (CNV) and the Lateralized Readiness Potential (LRP) as indices of general and selective motor preparation.

Results: The behavioral results showed that patients used cue-information to control their task performance to a lesser extent than controls. The CNV and LRP during the cue-probe interval showed that one reason for this is that patients use cue-information to a lesser extent than controls to prepare cognitive and motor functions in advance of the probe. The LRP and EMG to the probe, however, also suggest that patients differ from controls in motoric functioning independent of the task.

Conclusion: We conclude that the task performance decrement in the patients is related to a deficit in executive WM control over motor activation and to more general differences in motoric function.

549. CHANGE BLINDNESS AND SCHIZOTYPY

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Background/objective: Change blindness refers to the phenomenon that large changes in a visual scene may go undetected if the observer's attention is not focused upon the area of the change. Peripheral interest changes (as defined by psychological rather than physical factors) are harder to detect than central interest changes. This ability to screen out irrelevant information may be related to the phenomenon of latent inhibition (LI). As LI has often been shown to be altered in schizophrenic patients and in those high on measures of schizotypy, we hypothesized that similar effects may be observed in measures of change blindness. That is those with high schizotypy scores would have a smaller difference in RT scores between peripheral and central interest changes, compared to those with low schizotypy scores.

Methods: Forty-five non-psychotic participants completed the O-LIFE measure of schizotypal traits (Mason, Claridge and Jackson, 1995) and a change blindness test.

Results: Poor gating, characterised by a smaller difference in RT scores between peripheral and central items, was significantly associated with Cognitive Disorganisation, but not with traits characteristic of positive or negative schizotypy.

Conclusion: Further research now needs to establish the relationship of performance on this task to schizophrenic symptomatology and to other measures of gating (LI, PPI, etc.).

550. EFFECT OF AGE ON A THEORY OF MIND TASK IN HEALTHY SUBJECTS: IMPLICATIONS FOR SCHIZOPHRENIA

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Background/objective: The study of developmental changes in Theory of Mind (the ability to understand the intentions of others; ToM) in healthy individuals may reveal important information about the biological underpinnings of social function and identify a marker of social function useful for schizophrenia research. In order to determine if age related changes occur in social cognition, performance on a ToM task was examined in healthy individuals of different ages.

Methods: This was a cross sectional study in twenty healthy subjects using the "Reading the Mind in the Eyes" ToM task (Baron-Cohen et al., 2001), a mental state and gender recognition task.

Results: There was no ceiling effect on task performance. A negative correlation was found between subject age and performance on recognition of both mental state ($r = -0.73$, $R2 = 0.54$, $p < 0.001$) and gender ($r = -0.56$, $R2 = 0.31$, $p < 0.025$). The data on mental state identification have since been replicated (Phillips et al., 2002; Maylor et al., 2002). This study is the first to demonstrate a decline in gender identification with increasing age.

Conclusion: This finding suggests that in healthy individuals ToM may decline with age. A similar decline in ToM, whether due to normal aging or other process, may account for the decline in social function of a subset of schizophrenia patients. Given it's lack of ceiling effect in healthy individuals, the "Reading the Mind in the Eyes" task may be sensitive enough to detect a decline in ToM in these schizophrenia patients. If so, this task could be a powerful probe for studying social function in schizophrenia patients.

551. DYNAMIC ARCHITECTURE OF WORKING MEMORY IN SCHIZOPHRENIA

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Background/objective: Deficits of working memory in schizophrenia are frequently reported. The retrieval of information from a memorized list depends on the serial position of the item to retrieve (architecture) and this architecture varies with the memorization period (dynamic). In this study, we investigate the dynamic architecture of working memory in schizophrenia.

Methods: For this purpose, we tested seven schizophrenic and ten healthy control subjects in recognition tasks with verbal, iconic or spatial stimuli. A list of four stimuli was presented in each trial, followed by a probe stimulus after a delay of 0.5, 5 or 10 s. The probe stimulus had equal chance of being part or not of the memorized list. When it was part of the list, it had equal chance of being from any serial position. The subjects were asked to determine whether or not the probe was part of the list of memorized stimuli.

Results: We analyzed the effect of serial position and delay on the percentage of correct responses (%C) and on reaction time (RT). These experimental factors affected the%C similarly in patients and controls. In contrast these factors (serial position and delay) affected the RT in controls but not in patients. A similar pattern of results was found for all types of stimuli.

Conclusion: These results indicate that the deficits in working memory in schizophrenia are related to disturbances of the dynamic architecture of working memory rather than to general deficits. Furthermore schizophrenia patients have the same disturbance of working memory in verbal, iconic and spatial processing.

552. AUTOMATIC PROCESSING OF FACIAL EMOTION IN SCHIZOPHRENIA

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Background: It is assumed that people spontaneously evaluate any incoming stimulus as pleasant or unpleasant. The evaluative response appears to structure perception and to have direct links to emotional states.

Methods: To investigate the automatic processing of face valence a sequential priming task based on emotional face stimuli was administered to schizophrenia patients with a flat affect expression, schizophrenia patients suffering from anhedonia, schizophrenia patients not suffering from anhedonia or flat affect, and healthy controls. The Scale for the Assessment of Negative Symptoms (Andreasen, 1989) was applied to evaluate affective symptoms and categorise patients into groups.

Results: Schizophrenia patients without affective negative symptoms exhibited reversed priming effects similar to that of healthy subjects. In contrast, flat affect patients and anhedonic patients showed only a prime effect due to negative facial valence. In the flat affect patient group, negative prime faces facilitated the evaluation of target faces, whereas in the anhedonic patient group negative prime faces tended to inhibit the evaluation of subsequent target faces.

Conclusion: The present findings support the idea that chronic schizophrenia patients extract automatically the valence of emotional facial expression but they also suggest processing differences between schizophrenia patients as a function of affective symptoms.

553. A NEUROPSYCHOLOGICAL STUDY ON MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA

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Background/objective: Despite strong evidence for a genetic component to susceptibility of schizophrenia, the nature of the genes involved and the traits they transmit are yet to be determined. One way of approaching this is by looking at the inheritance of pathophysiological processes mediating between the genotype and the clinical expression of the disease. It has been previously suggested that genetic predisposition to schizophrenia can also be expressed as a liability to cognitive impairment.

Methods: We examined 9 pairs of monozygotic twins discordant for schizophrenia on current/premorbid IQ, and on executive processes, and compared their performance to 17 pairs of age and sex matched controls. IQ was assessed by the WAIS-IIIUK, which in addition to global full scale, verbal and performance IQs, can also provide indexes on more refined domains of cognitive function. Premorbid IQ was assessed using the NART. Executive processing was examined by administering tests assessing verbal fluency, abstract thinking, sustained attention and mental flexibility.

Results: Both the ill and well twins showed lower levels compared to controls on current IQ, working memory, processing speed, and verbal fluency. In addition, the ill siblings were also

impaired on mental flexibility and on sustained attention. Neither the ill nor the well siblings were impaired on measures assessing verbal comprehension, perceptual organization, abstract thinking and premorbid IQ. The ill siblings performed worse in relations to their well siblings on processing speed and on sustained attention.

Conclusion: Our data suggest that intelligence, working memory, processing speed and verbal fluency constitute inherited risk factors for schizophrenia.

554. AGE OF ONSET LINKS TO VERBAL LEARNING AND MEMORY IMPAIRMENT

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Objective: Schizophrenia patients have often severe impairments in their cognitive functions. The earlier the illness outbreaks the more severe the cognitive deficits are likely to be. Familial effects on this association are not known. We set out to study whether the age of onset has an effect on attention and working memory, verbal learning and memory, and verbal and visuospatial ability functions among families with schizophrenia patients.

Methods: Of schizophrenia patients and their first-degree relatives identified from nationwide registers, 234 patients and 232 healthy relatives were interviewed and neuropsychologically tested. The effect of age of onset on the neuropsychological test performance was examined by linear mixed effects analysis with familywise models. Age, sex, and duration and chronicity of the illness were controlled for, and to adjust for familial loading, the number of affected first-degree relatives was included in the models.

Results: Impairment in verbal learning and memory functions was significantly associated with the earlier age of onset. Such association was not found for working memory or intelligence. Adjustments for the illness factors or familial loading did not eliminate the effect of the earlier age of onset on verbal learning and memory.

Conclusion: Early age of onset links to verbal learning and memory impairment in schizophrenia. In patients with early onset, these cognitive functions in particular should be taken into account in the neuropsychological evaluation and efforts of remediation.

555. VISUAL BINDING IN SCHIZOPHRENIA

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Background: The binding problem is the general question of how any kind of distributed information is integrated in the brain to ultimately result in coherent action and perception. Theoretical and empirical data indicate that synchronized correlated activity in the gamma frequency band (30–80 Hz) may serve as a temporal code for the integration of neural activity (Singer and Gray, 1995). We (Phillips and Silverstein, in press) have argued elsewhere that dysfunctional binding may represent a core disturbance which underlies the multiple cognitive deficits in schizophrenia and the disorganization at the level of signs and symptoms.

Methods: We examined visual binding in acute and chronic schizophrenia ($N=72$), non-schizophrenia psychotic disorders ($N=35$) and non-psychotic psychiatric disorders ($N=25$). Acute schizophrenia patients were tested at admission and after discharge from an inpatient unit to relate changes in symptomatology to cognitive functioning. The test battery consisted of visual closure and visual size perception tasks, which represent robust psychophysical paradigms of binding mechanisms in vision.

Results/conclusion: The results suggest that disorganized schizophrenia patients were more impaired in the visual closure task but showed more accurate performance in the visual size perception task. In addition, hierarchical regression analyses indicated that reduction in disorganized symptoms were the only significant predictor for improved performance in the visual closure task during remission of symptoms in acute schizophrenia patients. These data support the hypothesis that schizophrenia is characterized by dysfunctional binding which may be related to the disorganization of thought and behavior.

556. THEORY OF MIND AND SCHIZOPHRENIA: AN EXPERIMENTAL STUDY

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Background: Patients suffering from schizophrenia have impaired ability to represent their own and other people's mental states. This ability is known as meta-representation or Theory of Mind (ToM). The lack of awareness of illness is not specific for

psychiatric patients and can be found also in neurological patients. Tegner and Marcel asked anosognosic hemiplegic patients about their performances with their paralized limbs. The patients described their limbs as normal. However, if the authors asked the same patients, "If my arm were paralyzed, could I shuffle a pack of cards?" some of the patients responded "Of course not". These results show that in some cases, the passage from a first person to a third person perspective can change the patient's awareness about his/her illness.

Methods: Thirty-seven DSM-IV-TR paranoid, severely delusional schizophrenic patients participated in the study. We performed the SAPS and the SANS and a clinical interview in which the subjects described their delusions. Each patient was asked if he/she considered reasonable the content of his/her delusions. Then the interviewer asked each patient if the same content was considered reasonable by the interviewer.

Results: All patients stated that the content of their own delusions were reasonable (first person question). When they were asked if the interviewer could consider reasonable their own delusions (third person question) the 20% of them answered no.

Conclusion: These results show that some delusional patients suffering for schizophrenia, gain access and modify their own mental states.

557. SPATIAL WORKING MEMORY AND SPATIAL/TEMPORAL WORKING MEMORY IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA

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Background/objective: Schizophrenia is a disabling illness with a peak age-of-onset during late adolescence and early adulthood. Both adolescents and adults typically present with an array of cognitive deficits and clinical symptoms. One cognitive domain that has been described as a potential trait marker for schizophrenia is impairment in working memory (WkM). Impaired WkM appears to be persistent throughout the course of the illness and is relatively resistant to psychopharmacologic interventions. Patients with schizophrenia demonstrate a reduction in the amount and duration of information that they are able to store in WkM and saturate their storage capacity earlier than matched controls. The purpose of this study is to utilize both behavioral and psychophysiological (i.e., eye tracking) measures to study spatial WkM and spatial/temporal WkM in children and adolescents with schizophrenia spectrum disorders.

Methods: Patients with a schizophrenia spectrum disorder (schizophrenia, schizoaffective, schizophreniform) were recruited from the both the inpatient psychiatric unit and outpatient clinic at the University of Minnesota. The patients and healthy volunteers have undergone a diagnostic assessment using the K-SADS, as well SANS/SAPS, BPRS-C, Premorbid Adjustment Scale, and Age-of-Onset Timeline. All subjects are between eight and nineteen years of age. Two oculomotor delayed response tasks (O-DRT) were utilized to assess spatial WkM and spatial/temporal WkM. The first task measures spatial WkM as a function of delay (2, 8, or 20 sec) and response mode (recall or recognition). The second task is identical to the first, except that the subject is to recall the temporal order of three dots that are sequentially displayed. The dependent variables are spatial accuracy, saccadic response times, and performance on a verbal distractor task.

Conclusion: The preliminary results are intriguing and show age-dependent differences between patients and controls. These findings will be discussed within a neurodevelopmental model for schizophrenia.

558. WORKING MEMORY CONTROL IN SCHIZOPHRENIA

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Background: Deficits in Working Memory are viewed as core cognitive abnormalities in schizophrenia.WM consists of distinct neurocognitive mechanisms: (1) the encoding of important information, (2) the maintenance of that information in WM and (3) the use of that information in the control of motor activation. The role of these mechanisms in WM dysfunction in schizophrenia is still unclear and no studies have been performed that investigated all of these mechanisms with a single paradigm.

Methods: We administered three versions of the Continuous Performance Test (CPT), in which we manipulated the amount of pre-stimulus information, to a schizophrenia group and a control group. We used behavioural measures and event-related brain potentials (ERP's) to investigate selective stimulus encoding and working memory control of motor activation as a function of pre-stimulus information. We investigated selective stimulus encoding with selection related ERPs and WM control of motor activation with the Contingent Negative Variation (CNV) and the Lateralized Readiness Potential (LRP).

Results/conclusion: The results indicated that patients with schizophrenia have problems with selective stimulus encoding and with the WM control of motor activation. These problems can be seen in terms of primary and secondary deficits. For example, is the observed deficit in motor activation a primary deficit or a secondary deficit caused by deficient selective stimulus encoding?

559. THE SUBJECTIVE COGNITIVE IMPAIRMENTS SCALE: DEVELOPMENT OF A SELF-REPORT MEASURE OF SUBJECTIVE DAILY-LIFE COGNITIVE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: A 31-item self-report questionnaire named the Subjective Cognitive Impairments Scale (SCIS) was developed to assess schizophrenic patients' self-perceived cognitive functioning in daily life. It was developed based on the premise that impairments detected by objective cognitive assessments only partially correspond to patients' complaints about their cognitive functioning in daily life, and this mismatch in turn impinges on treatment planning and efficacy.

Methods: Thirty patients with schizophrenia were interviewed and asked to describe their cognitive impairments encountered in daily life. Their responses were analyzed and classified into five domains including attention, memory, executive functioning, cognitive speed, and language comprehension and expression. The face validity of the SCIS was confirmed by a group of experts consisted of psychiatrists and clinical psychologists. The SCIS was administered to normal controls and patients.

Conclusion: The preliminary pilot data showed that none of the participants misunderstood and misinterpreted the items. Further analysis will be performed to confirm the factor structure and validity of the questionnaire.

560. FACIAL AFFECT RECOGNITION IN SCHIZOPHRENIA: SPECIFIC DEFICITS AND RELATIONSHIP WITH SYMPTOMS

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Background/objective: Disturbances in the processing of emotional material are a hallmark of schizophrenia. These problems in emotional processing may contribute to social dysfunction. In the present study, we tested the hypothesis whether schizophrenia patients show emotional processing deficits, if this deficit is emotion-specific and if this deficit is limited to facial affect recognition or whether biases are also present in verbal material.

Methods: 34 patients with schizophrenia were compared with 25 healthy matched control subjects on facial and verbal emotional processing tasks. There were no differences in age, sex, years of education and a verbal measure of intelligence.

Results: Patients with schizophrenia made more errors in recognizing fear on a degraded facial affect recognition task, $F = 22.15$, $p < 0.00$. In contrast, schizophrenic patients were better in recognizing anger in degraded faces compared to controls, $F = 10.51$, $p = 0.002$. These differences between the two groups remained the same after correction for non-emotional face recognition. There was a negative correlation between the severity of symptoms and the correct recognition of fear. Subtle biases in the processing of emotional verbal material were also observed.

Conclusion: We suggest that patients with schizophrenia demonstrate specific affective processing abnormalities that are mainly limited to the processing of threat-related information.

561. FUNCTIONAL CORRELATES OF TRAINING OF FACIAL AFFECT RECOGNITION IN SCHIZOPHRENIA

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Background/objective: We were recently able to demonstrate an amelioration of impairments of facial affect recognition in schizophrenia patients using the newly developed "Training of Affect

Recognition'' (TAR, Frommann et al. 2003, Psychiatr Res 117: 281–284). The present study investigates correlates of training effects in regional cerebral activity using fMRI.

Methods: Using a pre–post control group design, two groups of schizophrenia patients (Sz, $2 \times n = 10$) were compared with a non-patient group (N, $n = 10$). One group of patients received 12-sessions of TAR, which is especially designed to restore and compensate impairments in facial affect recognition. The other group of patients with schizophrenia received treatment as usual (TAU). Before and after the 6 weeks treatment period (T0, T1), fMRI measurement was performed on a 1.5 T scanner using EPI. Non-patients and healthy controls were also assessed twice with an interscan interval of 6 weeks. During scanning, subjects had to perform an emotion discrimination task using the standardized Pictures of Facial Affect series.

Results: At T1, an improvement in facial affect recognition resulted under TAR, but not under TAU. According to ongoing analyses of the fMRI data with SPM99, patients receiving TAR demonstrated significantly increased cerebral activity, particularly in inferior frontal and cingulate gyrus. For patients under TAU, the T1 vs. T0 variances in these structures were markedly smaller, if detectable at all.

Conclusion: Accordingly, the concurrent use of remediation strategies and fMRI may be a valuable tool for further investigation into the neurobiological substrates of emotional dysfunctions and their appropriate treatment.

562. COGNITIVE PREDICTORS OF SKILL ACQUISITION ON INTERPERSONAL PROBLEM SOLVING IN PATIENTS WITH SCHIZOPHRENIA

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Objective: The aim of the study was to evaluate the relationship between interpersonal problem solving ability, clinical features and cognitive functions, and determine the predictors of benefit from social problem solving training in 63 patients with schizophrenia.

Methods: We administered BPRS, WCST, Digit Span Test, Continious Performance Test and the Assesment of Interpersonal Problem Solving Skills (AIPSS). Only BPRS-positive symptoms subscale was related to AIPSS on linear regression analysis. After the completition of the pretesting, the patients were randomized to either problem solving training ($n = 32$) or control groups ($n = 31$). Patients in training group received 6 weeks problem solving training in group modality, and those in control group were treated as usual. We readministered AIPSS at the end of six weeks.

Results: There were significant changes from pretest to posttest on AIPSS total score, receiving skills, and processing skills subscores in training group than control group. WCST-number of correct answers emerged as the only predictor of change on AIPSS. We also found a correlation with CPT score and change on AIPSS sending skills.

Conclusion: Our findings suggest that skill acquisition on social problem solving was related with cognitive flexibility and sustained attention.

563. PATTERNS OF PREMORBID FUNCTIONING IN FIRST EPISODE PSYCHOSIS: A TWO YEAR FOLLOW-UP

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Background: It is well established that an individual's level of premorbid functioning is a robust predictor of both outcome and course of schizophrenia. Recently, distinct patterns of functioning during the premorbid period have been identified and it may be that persons with these patterns may also differ in their outcome.

Methods: Using the Cannon-Spoor Premorbid Adjustment Scale (PAS) we assessed premorbid adjustment in a sample of 200 subjects who had presented with a first-episode of psychosis to a specialized program and who had been followed for one year. One hundred and sixty-three of these subjects completed a two year assessment. Using cluster analyses we identified four patterns: stable-good, stable-intermediate, poor-deteriorating and deteriorating. At the one and two year assessments positive and negative symptoms, depression, substance misuse, number of relapses, social functioning and cognitive functioning were assessed.

Results: Relative to the stable-good group, the deteriorating and poor-deteriorating groups had significantly more positive symptoms at 1 year ($p < 0.001$) and significantly more negative symptoms ($p < 0.0001$) and significantly poorer social functioning ($p < 0.0001$) at both 1 year and 2 years. Using a comprehensive battery of cognitive tests only verbal fluency differentiated between the groups with the stable-good group having a superior performance.

Conclusion: These results suggest that those who demonstrated poor or deteriorating functioning prior to the onset of acute psychosis have a poorer outcome up to at least two years in terms of symptoms and functioning. However, performance on a range of cognitive tasks did not vary amongst the four patterns of premorbid functioning.

Satellite-Mt Sinai Meeting on Cognition

Oral Presentations

AFFECTIVE SEMANTIC PRIMING IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is a large literature examining semantic priming in schizophrenia with contradictory findings. There is also a plethora of research showing patients with schizophrenia have deficits processing emotion. However, there are few studies that have examined processing of emotional stimuli during language tasks, especially semantic priming.

Methods: We investigated affective semantic priming using a lexical-decision task and four different affective categories of semantically related word pairs: neutral, happy, fearful and sad in patients with schizophrenia and normal controls. There was a 700 ms SOA. The 18 subjects in each group were age and IQ matched.

Results: The controls exhibited significant semantic priming of the neutral and happy prime-target pairs (42.5 ms and 44.1 ms). However, they showed no significant priming of fearful pairs and sad pairs showed an inverse effect (− 4.2 ms), where reaction times to related sad word targets were slowed compared to the unrelated. Therefore, in controls, negative stimuli show reduced or inhibited effects of semantic association. Patients with schizophrenia showed reduced neutral and happy priming (13.4 ms and 20.2 ms). Patients showed a similar degree of priming of fearful stimuli as controls, however, patients showed no priming of sad stimuli (0.2 ms) and not the inverse effect as shown by controls.

Conclusion: The data suggest that patients with schizophrenia are influenced by the alternative categories of emotion differently from controls, especially the sad stimuli. Also, previous studies may not have adequately controlled for the emotional salience of the stimuli when performing semantic priming tasks.

AN EVENT-RELATED fMRI STUDY OF MAINTENANCE BRAIN ACTIVITY IN SCHIZOPHRENIA DURING THE PERFORMANCE OF A VARIABLE LOAD WORKING MEMORY TASK

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Background: Although the aberrant patterns of working memory (WM) activity found in schizophrenic subjects have often been attributed to an impaired ability to maintain information over a delay, few fMRI studies have used methods allowing activity associated with maintenance to be isolated from that associated with encoding and responding.

Methods: In the current event-related fMRI study, stimulus timing and modelling parameters were adjusted to optimize our ability to isolate the activity associated with maintenance from that associated with other task phases. Fifteen schizophrenic subjects and 15 non-patient controls completed a variable load WM task in which 2, 4, 6 or 8 letters were maintained over a six second unfilled delay.

Results: For the 2, 4 and 6 load conditions, the two groups showed similar patterns of activation. In contrast, for the 8 load condition, a reduced extent of activity for the schizophrenic group was observed in the left parietal cortex (BA40), a brain region implicated in short-term storage of verbal information. Within the high load condition, for both patient and control groups, a positive Pearson's correlation between the extent of left parietal activation and accuracy was observed ($r = 0.61$, $p = 0.02$; $r = 0.41$, $p = 0.12$, respectively).

Conclusion: This suggests that increased left parietal cortex activation is associated with greater storage of information. Thus, the reduced extent of left parietal activation observed in the patient group can be interpreted as an information storage deficit. In other words, a reduced storage capacity may underlie the WM deficits seen in schizophrenia.

THE IMPORTANCE OF PREMORBID IQ AND THE RISK, ONSET AND PROGNOSIS OF SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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Background: Longitudinal cohort studies have provided some of the most robust evidence of premorbid risk factors for schizophrenia and affective disorders. Recently published studies include National birth cohorts in the UK, and Scandinavia, and conscript cohorts from Sweden and Israel. The evidence suggests that low IQ is a potent risk factor for schizophrenia. However, other questions remain such as: is the risk uniform across the spectrum of IQ? Does premorbid IQ predict age of onset? Is risk for affective disorders similarly increased and if so, is the size of the risk more or less than in schizophrenia?

Methods: In order to answer some of these questions we critically examine the published literature. Furthermore, we add new data from a previously studied Swedish conscript cohort that has now been re-examined with follow-up data up to the age of 45 years.

Results/Conclusion: The results show that low IQ is a significant risk factor for later schizophrenia and other related psychotic disorders, across the IQ spectrum. However risk for bipolar disorder is not increased. Age of onset and total duration of hospital care over the follow-up period are both unrelated to IQ.

THE BRIEF ASSESSMENT OF COGNITION IN SCHIZOPHRENIA: RELIABILITY, SENSITIVITY, AND COMPARISON WITH A STANDARD NEUROCOGNITIVE BATTERY

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Background: Studies of neurocognitive function in patients with schizophrenia use widely variable assessment techniques. Clinical trials assessing the cognitive enhancing effect of new medications have used neurocognitive assessment batteries that differed in content, length and administration procedures. The Brief Assessment of Cognition in Schizophrenia (BACS) is a newly developed instrument that assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The BACS requires less than 35 minutes to complete in patients with schizophrenia, yields a high completion rate in these patients, and has high reliability. The BACS was found to be as sensitive to cognitive impairment in patients with schizophrenia as a standard battery of tests that required over two hours to administer.

Results: Compared to healthy controls matched for age and parental education, patients with schizophrenia performed 1.49 standard deviations lower on a composite score calculated from the BACS and 1.61 standard deviations lower on a composite score calculated from the standard battery. The BACS composite scores were highly correlated with the standard battery composite scores in patients ($r = 0.76$) and healthy controls (r=.90).

Conclusion: These psychometric properties make the BACS a promising tool for assessing cognition repeatedly in patients with schizophrenia.

SELF-MONITORING IN PATIENTS WITH SCHIZOPHRENIA

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Background: The present study investigated whether a failure of self-monitoring contributes to core syndromes of schizophrenia.

Methods: Three groups of patients with a DSM IV diagnosis of schizophrenia ($n = 27$; with either prominent paranoid hallucinatory or disorganization syndrome, or without these symptoms) and a matched healthy control group ($n = 23$) were drawing circles on a writing pad connected to a PC monitor. Subjects were instructed to continuously monitor the relationship between their hand movements and their visual consequences. They were asked to detect gain changes in the mapping. Self-monitoring ability and the ability to automatically correct movements were assessed.

Results: Patients with either paranoid-hallucinatory syndrome or formal thought disorder were selectively impaired in their ability to detect a mismatch between a self-generated movement and its consequences, but not impaired in their ability to automatically compensate for the gain change.

Conclusion: These results support the claim that a failure of self-monitoring may underlie the core symptoms of schizophrenia.

METACOGNITION: A POTENTIAL BRIDGE BETWEEN BASIC NEUROCOGNITION AND REAL-LIFE PERFORMANCE IN SCHIZOPHRENIA

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Background/objective: While the role of neurocognitive deficits in predicting functional outcome in schizophrenia is generally well established by now, little is known about the potential mechanisms that mediate between basic neurocognition and functioning in real-life situations. The aim of this presentation is to introduce our new approach for neuropsychological assessment and intervention that attempts to close this gap in schizophrenia. The new approach is motivated by the view that the main limitation of current neuropsychological procedures lies in their relying almost exclusively on forced-responding tasks. Consequently, they fail to assess crucial aspects of functioning in naturalistic situations like *self-monitoring* (the process by which subjects routinely assess the accuracy of their knowledge) and *self-directed action* (the degree to which these assessments affect their decision to actually report an answer and at what level of elaboration).

Methods: To address this limitation and increase the ecological validity of current neuropsychological procedures, we adapted paradigms developed in experimental psychology to study metacognition.

Conclusion: We believe that if further validated, the new method would help identify patients who have specific self-monitoring and self-regulation deficits, and would allow for future studies on the effectiveness of therapeutic interventions specifically focused on remediation of deficits at this level. In addition, it will provide an empirical foundation for future studies focusing on the brain systems or neural mechanisms involved in self-monitoring and self-directed action, as well as on atypical medications that potentially target these deficits.

EXPLORING MEMORY CONTROL IN SCHIZOPHRENIA USING A MODIFIED DIRECTED FORGETTING PARADIGM

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Background/objective: Memory impairment is common in schizophrenia. We wished to determine whether problems with memory were more prevalent in deluded schizophrenics than people who had recovered from their delusions. Secondly, we wished to explore whether any memory problems were attributable to a problem of tagging information for salience.

Methods: We used a modified 'directed forgetting' paradigm. Groups of deluded schizophrenics, non-deluded schizophrenics and normal controls were shown lists of words. After each word was presented, participants were instructed that the word was either 'to be remembered' (TBR) or 'to be forgotten' (TBF). Participants were first asked to recall the 'to be remembered' (TBR) words. This was followed by a recognition task, of discriminating previously seen words from novel distracters, and identifying whether the words they recognised had been shown as TBR or TBF words.

Results: There were no differences between deluded and non-deluded participants on any measure. The schizophrenics showed poorer recall than the controls with an excess of intrusion errors but they were equivalent to the controls on recognition. The schizophrenics showed comparable 'directed forgetting' effect to the controls on recognition. However, the schizophrenics were extremely poor at identifying whether the TBF words they recognised had originally been shown as TBF or TBR.

Conclusion: These results indicate that basic judgments of item familiarity may be spared in schizophrenia, and that while they may be able to use information about salience at encoding, they may have problems with the inhibition or tagging of irrelevant material during storage or retrieval.

EVIDENCE OF SEMANTIC DISORGANISATION IN SCHIZOPHRENIA USING A NEW WORD DEFINITION TASK

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Background: Semantic processing deficits are central to cognitive abnormalities in schizophrenia. They have been related to (a) delusions and thought disorder and (b) poor access to and storage of semantic information. However, these are relatively new areas of research and evidence is often inconsistent.

Methods: A new word definition task was used to examine these research questions. 33 schizophrenics, 28 patients with bi-polar disorder and 32 matched normal controls were asked to 'generate' definitions of 120 words. This was compared with a 'recognition' task using the same words: subjects selected the correct word definition from 4 choices: 1 correct, 2 partially correct foils and 1 incorrect.

Results: On the generate task, schizophrenics produced more associative errors (army-navy), opposite errors (shallow-deep), nonsense errors (dusk-cooking), incorrect responses (hasty-uncertainly) and do not know responses than bipolar subjects and normal controls. However, on the recognition task, both the patients with schizophrenia and bipolar disorder choose a greater number of foils compared to controls, and had less correct. Task performance in schizophrenia was significantly correlated with both delusions and thought disorder.

Conclusion: The overall results are interpreted as showing a loosening of normal semantic associations in schizophrenia. We speculate that the data indicate[s] disorganised storage of semantic information, which in turn interferes with efficient access.

COGNITIVE REMEDIATION IN EARLY-ONSET PSYCHOSIS: TREATMENT EFFECTS ONE YEAR AFTER DISCHARGE

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Objective: The aim of the study was to investigate the long-term effects of a cognitive remediation program for adolescents with early onset psychosis, one year after discharge.

Methods: Twenty-seven inpatients were randomly assigned to cognitive remediation or control group. Both groups received a psychoeducational treatment program while in the unit, while only the experimental group received the addition of a 30-hour cognitive remediation program. Twenty-four subjects (cognitive remediation $n = 14$, control group $n = 13$) were included at the one-year follow up. Participants were assessed on cognitive, clinical and psychosocial measures.

Results: Prior to covarying for IQ no significant between-group differences in baseline-follow-up scores were found. However, after covarying for IQ the remediation group showed a significantly greater improvement in early visual information processing ($p < 0.05$). Exploratory within-group analysis demonstrated that the remediation group improved on eight of the 10 cognitive measures and three of the outcome measure, while the control group improved on five cognitive and one outcome measure.

Conclusion: The improvements in the remediation group indicate that the training may have facilitated improvements in some areas of cognition and functional outcome. In particular the training may have favourable long-term effects for early visual information processing. However, since both groups improve the results also suggest that cognition in general improves somewhat over time in adolescents with early onset psychosis. This could indicate that there are elements in the psychoeducational approach employed that are advantageous for cognition and functional outcome. Other intervening factors such as the natural course of the illness, or cognitive maturation may also play a role.

MODAFINIL MODULATES PREFRONTAL FUNCTION IN SCHIZOPHRENIA

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Background: Modafinil is a putative cognitive enhancer. We studied the behavioural and functional anatomical consequences of its acute administration in men with negative symptoms of schizophrenia.

Method: Seventeen stable, right-handed, schizophrenia patients (mean age 38 years), participated in a double-blind, placebo-controlled, cross-over study, receiving either modafinil 100 mg or placebo across two study days (one week apart, order counterbalanced). Functional imaging data were acquired two hours post-administration using a 1.5 T MR system; subjects performing a working memory protocol (the '2-back' versus '0-back' control condition).

Results: Group functional imaging data were analysed using a random effects model in SPM99. In the modafinil vs. placebo comparison we found increased activation solely in the anterior cingulate cortex (ACC), during the 2-back, compared to 0-back condition (Brodmann area 38; $Z = 3.14$). For each subject, we then extracted an estimate of fMRI signal change in ACC, during the 2-back. Differences in signal change and behavioural performance between modafinil and placebo conditions were significantly and positively correlated (rho = 0.42; 1-tailed $p = 0.04$). This correlation reflected increased fMRI signal in the majority of subjects, with concomitant improvement in memory performance in half, and decreased signal in a minority of subjects, most of these exhibiting reduced performance following modafinil administration.

Conclusion: Modafinil modulates ACC function in schizophrenia and may improve cognition in some patients. However, its effects are not uniform in this syndrome and further research is needed to characterise those subjects who may benefit.

Acknowledgment: This study was funded by a project grant awarded by Cephalon UK.

SUBJECTIVE AND OBJECTIVE ASPECTS OF NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

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Background/objective: Cognitive deficits in schizophrenia are often subtle, subjective, and have significant impact on daily functioning and quality of life. The relevance of contemporary models of cognition in schizophrenia, and the role of standard evaluations in identifying cognitive deficits and their impact on daily living remains unclear at the present time. The study was designed to examine the relationship between subjective complaints of cognitive dysfunction, self appraised daily functioning and quality of life, and objective measures of neurocognitive deficits in schizophrenia.

Methods: A convenience sample ($n = 102$) of treated, symptomatically stable, community based schizophrenic patients (DSM IV) completed standardized questionnaires to quantify self-appraised cognitive dysfunction (Subjective Scale to Investigate Cognition in Schizophrenia or SSTICS), daily functioning and quality of life (Sickness Impact Profile or SIP). Subjects' neurocognitive deficits were evaluated at the same time with COGLAB, a computer-assisted self-administered neuropsychological test battery.

Results: There was a significant correlation ($r = 0.72$, $p < 0.001$) between perceived cognitive dysfunction (SSTICS scores) and subjective quality of life (SIP scores). However, four out of the five COGLAB subtests (size estimation, visual tracking, Asarnow's task and Wisconsin Card Sorting Test) did not reveal any significant association with the subjective dimensions; and a weak correlation was noticed with the backward masking task ($r = 0.32$, $p < 0.02$).

Conclusion: Perceived deficits, dysfunction and quality of life are meaningful outcomes for patients, families and clinicians. The onus is on researchers and neuropsychologists to identify the precise nature of cognitive deficits in schizophrenia, and develop appropriate test procedures that are capable of sensitively capturing them.

EXTENT AND LATERALIZATION OF LINGUISTIC PROCESSING IN SCHIZOPHRENIA I: ASSESSMENT OF EFFECTIVE CONNECTIVITY USING CONSTRAINED PRINCIPAL COMPONENT ANALYSIS (CPCA)

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Background: Psychophysiological interactions involve explaining activation in the brain in terms of an interaction between experimental conditions and activity in a region of interest (typically a region early in the information processing stream). Traditionally, this technique involves multiple univariate tests—when activation in a particular brain region can be accounted for by the aforementioned interaction, it is said to be effectively connected to the region of interest. As an alternative to multiple univariate tests, activation maps displaying interconnected systems can be generated. These activation maps display neural systems for which a particular voxel's importance is determined by its connectivity with other voxels. The corresponding statistical analysis typically involves generation of eigenimages, based on principal component analysis.

Methods: We developed an application of Constrained Principal Component Analysis (CPCA) that allowed us to generate eigenimages computed on brain activations constrained to the variability relevant to the psychophysiological interaction between the linguistic vs. nonlinguistic processing, and activation in primary auditory cortex (BA 41 and 42).

Results: The first component resulting from this analysis was characterized by cerebellar-frontal connections that were notably reduced in the patient sample.

Posters

564. SOURCE MONITORING DEFICITS IN SCHIZOPHRENIA: A SIGNAL DETECTION ANALYSIS STUDY

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Background/objective: Source monitoring refers to the set of processes involved in the attribution of an origin to memories and beliefs. A deficit in this function has been observed among schizophrenic patients that could be unable to monitor the initiation of some self-generated thoughts. Source monitoring errors found in schizophrenia consistently involve attribution of self-generated items to outside sources, and different studies found correlations with hallucinations, delusions or negative symptoms. This study aimed to assess internal to external source monitoring attribution biases in schizophrenic patients and their possible correlation with clinical and neuropsychological variables, by means of a signal detection analysis applied to a source monitoring task.

Methods: 55 stabilized schizophrenic patients and 50 normal volunteers were studied with a the 'Source Monitoring Task' (Keefe et al., 2002) and the Brief Assessment of Cognition in Schizophrenia (BACS) a battery testing main neurocognitive functions known to be disturbed in schizophrenia.

Results: Patients with schizophrenia and normal controls differed in source attribution from any internal or external source as concerns d′ (detection sensitivity) with significantly better performance among normal controls. Only schizophrenic patients with active delusions showed a significantly worse b values (response bias), than normal controls.

Conclusion: This suggests a significant difference in the patterns of control of self-non self source attribution errors. b values were significantly correlated to Tower of London performances and verbal memory among schizophrenic patients only. Results from the source monitoring task confirm the hypothesis of an internal–external misattribution bias related to delusional psychopathology and influenced by executive function and verbal memory, as expected.

565. DAILY LIVING TASK PERFORMANCE AND COGNITIVE IMPAIRMENTS IN PEOPLE WITH SCHIZOPHRENIA

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Background/Objective: Attention, memory and executive function have been found to be impaired at various degrees in people with schizophrenia. Little is known concerning how the actual performance of everyday activities of these individuals is affected by cognitive impairments. The purpose of this pilot study was to describe the impact of cognitive deficits on the performance of two daily activities of different complexity levels, in ten individuals suffering from schizophrenia. This study also examined how community functioning is related to the performance of the two daily activites.

Methods: The "Perceive, Recall, Plan and Perform" system of task analysis (PRPP), a two-stage criterion-referenced tool based on information processing theory, was used to describe the impact of cognitive deficits on task related behaviors, while a French version of the Independent Living Skills Survey (ILSS) was used to assess community functioning.

Results: Results from this study suggest that the task related behaviors associated with the ability to perceive and to plan were most affected during both activities. More behavioral errors were observed in relationship to the ability to perceive, to recall, and to plan when performing the more difficult daily living activity. Community functioning was strongly related to the performance of the more challenging daily activity.

Conclusion: In spite of a small sample size, results from this study are consistent with recent findings on the relationship of perceptual and executive impairments and the ability to perform daily tasks as well as community functioning.

566. IMPLICATIONS OF MISMATCH NEGATIVITY DEFICITS FOR COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: OVERVIEW AND INTERPRETATION

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Background/objective: Cognitive impairment in schizophrenia is an important predictor of clinical and social outcome, yet its neurobiological basis is not understood. We explored the correlation between cognitive status and deficits in mismatch negativity (MMN) generation in patients with schizophrenia.

Methods: MMN was recorded using a new stimulation protocol with continuously changing standard stimuli in order to measure the effect of stimulus repetition on MMN, the memory trace effect. Cognitive status of the patient group ($n=28$) was assessed using neuropsychological screening. Healthy participants ($n=20$) served as age-matched comparison group. In patients, MMN amplitude in frontal electrodes as well as the MMN memory trace effect was diminished compared to controls.

Results: While both measures were inversely related to patient's age and disease severity, only the MMN memory trace effect was robustly correlated with the degree of neuropsychological impairment.

Conclusion: The data suggest that ERP measures of short-term auditory plasticity, which are significantly modulated by NMDA-dependent processes, more appropriately characterise the pathophysiological processes underlying cognitive impairment in schizophrenia than static measures of ERP magnitude.

567. COGNITIVE FLUCTUATION IN SCHIZOPHRENIA IS ASSOCIATED WITH LOWER SYMPTOM LEVELS, HIGHER FUNCTIONING AND BETTER QUALITY OF LIFE

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Background: The CANTAB IDED attention-shifting task is conceptually similar to the WCST; successful completion of the crucial, extra-dimensional attention shift (EDS) requires executive function and is impaired in schizophrenia. Poor executive function has been linked to increased negative symptom levels and poor functional outcome in schizophrenia, however the longitudinal associations between these domains remain unclear.

Methods: Assessment on the IDED task occurred at trial entry and at 12, 26 and 52 weeks of a randomised control trial of antipsychotic drugs in schizophrenia ($n = 46$). Patients were also independently assessed on PANSS, GAF and Quality of Life scales at each time point.

Results: Twelve patients consistently failed the EDS, 15 consistently passed it and 19 changed in performance on the EDS over the course of the trial. Patients who showed cognitive change were younger than those who performed consistently poorly. At trial entry, no differences were found in symptom or function levels between those who passed or failed the EDS. However, significantly lower negative symptoms and better quality of life and global function were found in those who showed cognitive change during the trial, than in those who were cognitively stable (either consistently passing or failing the EDS). These differences were greater at one year than at trial entry.

Conclusion: Patients who fluctuate in executive function may be a subgroup of young, high functioning patients who can recover from periods of cognitive dysfunction. Cognitive change may be more important than cognitive performance at any one time-point in predicting clinical and functional outcome.

568. TCL, OR WHO DID WHAT TO WHOM: THETA-ROLES AND SYNTAX PROCESSING IN SCHIZOPHRENIA AND SPD

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Background: Aphasiologists and speech impairment researchers have developed new tests in order to detect with accuracy language impairments in population of patients. One of these tests has been widely used in clinical aphasiology research by D. Caplan and N. Hildebrandt (1988).

Methods: We have translated, adapted, and modified this test, where necessary, in order to assess with accuracy language impairments in schizophrenia and Schizotypal Personality Disorder. We have added to the original tests a specific battery (nine sentences) intended to investigate whether the syntactic structure Delete-F-Bar (DEL-F′) was impaired in such patients. We added this battery because it emerged by aphasic speech reports that such structure was almost certainly damaged in frontal damaged patients. We have termed this test *Test di Comprensione Linguistica* (TCL, *Test of Linguistic Comprehension*) and to date we have used it with the purpose of assessing language impairments in a population of schizophrenic and SPD outpatients (Schizophrenics = 8; SPD = 2). As group of control we have employed ten healthy people without history of psychiatric illnesses matched to our patients' group for sex, age and education.

Results: The results are consistent with heavy impairments concerning language abilities in the schizophrenic and SPD group (t-test patients/controls performed considering all TCL parameters: $t = 7{,}28$, two-tailed $p < 0{,}0001$). Furthermore, a classical double dissociation between wide-ranging Short Term Memory (STM) and specific language-parsing STM emerged.

Conclusion: These results can be seen in the light of specific impairments affecting modular language parsing in schizophrenia and SPD.

569. SOURCE MONITORING DEFICITS IN SCHIZOPHRENIA: HOW PATIENTS IMPROVE RECEIVING ANTIPSYCHOTIC TREATMENT

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Background/objective: Some studies in the last decades investigated and confirmed the role of the Source Monitoring Deficits in schizophrenic patients, in particular those affected by positive symptoms of Schneiderian quality, but limited data are available about its change in response to effective drug treatment. Our study aimed to determine whether antipsychotics were effective in reducing source monitoring deficit and whether changes in this aspect of cognition were related to reduction of delusions.

Methods: Out sample consisted of 32 schizophrenic patients (DSM-IV criteria) who were poor responders to classical antipsy-

chotics and switched to risperidone and then clozapine, respectively, with the aim of obtaining a satisfactory clinical response with a sequential design switch study. Patients were assessed with PANSS, a Source Monitoring Task (Keefe et al., 2002), and a battery including evaluation of cognitive function known to be defective in schizophrenia, the Brief Assessment of Cognition in Schizophrenia (BACS) (Keeefe et al., in press), before and after 8 weeks of drug switching.

Results: A statistically significant reduction of PANSS delusion score and of misattribution of self-generated items to external sources (seen or heard) was found after 8 weeks of treatment (Wilcoxon test for paired dataz = 3.2, $p = 0.001$ and z = 4, $p = 0.0042$, respectively). The source monitoring deficit change was only statistically significant in patients with initial active delusions. monitoring variable change.

Conclusion: Source monitoring change in patients treated with antipsychotics might be used as a biological marker of antipsychotic activity.

570. IMPAIRED TEMPORAL INHIBITION OF IRRELEVANT PROCESSING IN PATIENTS WITH SCHIZOPHRENIA: EVIDENCE FROM ATTENTIONAL BLINK, VISUAL BACKWARD MASKING, AND ATTENTIONAL MODULATION OF PREPULSE INHIBITION

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Methods: The expression of attentional blink (AB) in schizophrenic patients ($n = 23$) was compared to healthy subjects ($n = 24$) in a dual-target rapid serial visual presentation (RSVP) paradigm in which a sequence of discrete stimuli was presented in rapid succession. Target identification accuracy was then correlated with performances in a visual backward masking (VBM) task and measures of prepulse inhibition (PPI). In the VBM task, subjects were required to name a letter which was masked at SOAs 16–83 ms. Prepulse inhibition (PPI) of acoustic startle response was measured for prepulse–pulse intervals of 60 and 120 ms. To investigate the attentional modulation of PPI, subjects were instructed to count either high- or low-tone prepulse and ignore the other prepulse.

Results: Schizophrenic patients showed significant enhancement of AB, greater susceptibility to VBM, and lack of PPI when compared to healthy subjects. The latter two findings may reflect a reduced ability to inhibit transient processing of disruptive stimuli in the patients. Greater AB magnitude in patients was correlated with greater susceptibility to VBM; lower second-target accuracy in the AB task was correlated with weaker PPI in the ignored prepulse (120 ms) condition. In the controls, AB magnitude correlated negatively with VBM susceptibility; first-target accuracy in the AB task correlated negatively with the PPI in the attended prepulse (60 ms) condition.

Conclusion: This pattern of results suggests that enhancement of the AB effect in patients with Schizophrenia may be due to a deficit in the inhibition of irrelevant information processing.

571. RIVASTIGMINE EFFECTS ON PROCEDURAL MEMORY AND ATTENTION IN PATIENTS WITH SCHIZOPHRENIA: PRELIMINARY RESULTS

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Background/objective: Atypical neuroleptics improve cognition in patients with schizophrenia, but some aspects of memory, attention and executive functions remain impaired with regards to normative data. Cholinergic agonists, including acetylcholinesterase inhibitors like rivastigmine, have been shown to improve cognitive impairments in others diseases. The presence of abnormal cholinergic function in schizophrenia provides the rationale to test the effectiveness of cholinesterase inhibitors in treating cognitive impairment in cognitively impaired patients with schizophrenia.

Methods: Thirteen patients (age 28.6 ± 6.7 years; M = 11, $F = 2$) stabilized with atypical neuroleptic underwent neurocognitive evaluations performed with Cambridge Neuropsychological Test Automated Battery (CANTAB) before and after twelve weeks of treatment with Rivastigmine. The posology was administered in function of tolerability of the patients. Beginning at 3 mg/day reaching 6 mg the first month to progressively increase at 9 mg/day. Tasks used were "Stockings of Cambridge" (SOC) which evaluated executive functions and procedural memory and "Rapid Visual Processing" (RVP) which evaluated subtained attention, working memory and visual detection.

Results: The results revealed that patients have improvements in executive functions such as planification after treatment with rivastigmine: they resolved more problems in a minimum of moves

on SOC. We also noted improvement in procedural memory: the patients proceed more rapidly on SOC after initial move. The patients show improvement in subtained attention: they made less error on RVP task in detecting stimuli.

Conclusion: In conclusion, our results suggest that acethylcholinesterase inhibitors may improve some aspects of memory, attention and executive deficits. However, future research with better design on cholinergic agonists need to be further developed.

572. THE EFFECTS OF REPETITION AND DIFFICULTY ON MEMORY AND CONSCIOUSNESS IN PATIENTS WITH SCHIZOPHRENIA

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Background/objective: Patients with schizophrenia suffer from a wide range of cognitive impairments, that contribute to their inability to solve social problems. Also, insight deficits in schizophrenia seem to be multidimensional. The present study was aimed at investigating how and with which efficiency patients with schizophrenia controlled their learning strategies and evaluated their knowledge according to the contextual environment of the task, in this case the repetition of learning (from one to three learning trials) and the instrinsic difficulty of the material to be learned (associated versus non associated word pairs).

Methods: 19 patients and 19 control subjects participated in the study.

Results: Patients with schizophrenia had a general deficit in memory efficiency. However, patients used the same strategies as normal participants did: they allocated more time to the first presentation of the material, and they spent also more time to learn the difficult than the easy pairs. This reflects an intact ability to take into account external cues to improve performance and a preserved awareness. The difficulty and the repetition had the same general effect on retrieval in both groups, except that the patients' performances were allways lower. Patients underestimated their knowledge, but the accuracy of their monitoring in predicting recall, as assessed by Gamma coefficient between Judgments Of Learning and recall performance, remained valid. Subsequently, patients with schizophrenia do not display a general and uniform decline of the cognitive and metacognitive abilities, and some aspects of these domains seem preserved.

Conclusion: These observations have clear implications for cognitive remediation.

573. COMPARATIVE PROFILES OF COGNITIVE DEFICITS IN EARLY ONSET SCHIZOPHRENIA OR PSYCHOSIS AND ADULT ONSET SCHIZOPHRENIA

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Background: The neurodevelopmental hypotheses posit a more severe disease process and course of illness in early onset schizophrenia compared to adult onset schizophrenia. Evidence from retrospective studies supports the presence of more severe cognitive deficits in patients who have experienced en early onset of illness. However, it is unclear whether these more severe deficits are present at the time of illness onset or appear later in the course of the illness due to a progressively deteriorating disease process.

Methods: Deficits of executive functions, attention, and reaction time were examined in two parallel clinical studies including A: Adult onset first-episode drug-naïve schizophrenic patients ($N=25$), and B: Early onset schizophrenic patients ($N=18$) and early onset non-organic psychotic patients ($N=22$) as well as age and gender matched controls ($N=65$). Neurocognitive tests from CANTAB (Cambridge Neuropsychological Test Automated Battery) were carried out.

Results: The results showed a similar level of severity of executive and attentional deficits in the early onset and adult onset patients, with more severe deficits of reaction times in the adult onset patients. The profile of cognitive deficits suggests involvement of putative frontal lobe functions in both early onset and adult onset patients, but with the additional involvement of putative fronto-striatal pathways in the deficits of the adult onset patients.

Conclusion: The results suggest that compared to adult onset patients, early onset patients do not have more severe deficits of executive functions, attention, and reaction at the time of illness onset, but may be a sub-group of patients with progressively deteriorating cognitive deficits.

574. THE COURSE AND CORRELATES OF FORMAL THOUGHT DISORDER IN OLDER PATIENTS WITH SCHIZOPHRENIA

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Background: Impairments in verbal communication in schizophrenia have been reported since the first descriptions of the illness. These communication impairments reflect disturbances in both the amount of language and its coherence. In younger patients with schizophrenia, the severity of disconnection in speech and abnormalities in verbal productivity havce been generally found to be independent of each other. Several studies have examined the course and cognitive functioning correlates of communication disorders in schizophrenia, but none of these studies have examined geriatric patients.

Methods: This was a longitudinal follow-up study of communication disorders and cognitive functioning in older patients with schizophrenia. Patients were seen at baseline and at a follow that ranged from 36 to 72 months. *Subjects*: All participants were schizophrenic patients over the age of 65 ($n = 420$). *Assessments*: Communication disorders were rated with the Scale for Assessment of Thought, Language, and Communication (TLC). Cognitive functioning was evaluated with the Mini-Mental State examination. Communication disorders were divided into those that reflected verbal underproductivity (poverty of speech) and 6 aspects of communication disorder that reflected poorly connected discourse.

Results: There were statistically significant worsening in both poverty of speech ($p < 0.05$) and in MMSE scores ($p < 0.01$) and a significant improvement in disconnected language ($p < 0.01$). There were significant correlations between poverty of speech and MMSE scores at both baseline and follow-up ($p < 0.005$), but not between disconnected speech and either poverty or speech or MMSE scores. Correlations between all variables from baseline to endpoint were statistically significant, indicating that the distributions of scores was stable over time. Further, worsening in MMSE scores was correlated with worsening in poverty of speech, while disconnected language was also uncorrelated with changes in either poverty of speech or MMSE scores.

Conclusion: These data indicate that disconnected speech and verbal underproductivity appear independent in geriatric patients with schizophrenia, similar to previous findings in younger patients. Similar to previous cross-sectional data on older patients, verbal underproductivity and cognitive impairments appear to be related at each assessment point and cognitive decline is associated with increases in poverty of speech. In contrast, the severity of disconnection-related aspects of communication disorder is not predicted by the cognitive impairments measured by the MMSE. These results suggest that communication impairments are persistent into later life, but that the cognitive decline seen in a subset of chronically institutionalized patients is accompanied by reductions in verbal output, but not by changes in coherence of speech.

575. REAL WORLD PLANNING IMPAIRMENTS IN THE DISORGANISATION BUT NOT THE PSYCHOMOTOR POVERTY SYNDROME OF SCHIZOPHRENIA

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Background: Theoretical neuropsychological models propose poor plan formation in the psychomotor poverty syndrome and poor plan execution in the disorganisation syndrome in schizophrenia, yet few studies have compared planning in these groups.

Methods: This study investigated whether qualitative differences in planning occurred in three groups of: (i) Psychomotor poverty schizophrenia ($n = 27$), (ii) Disorganisation schizophrenia ($n = 28$), (iii) normal controls ($n = 28$), well balanced for age, sex and parental socio-economic status. Two tests of planning were administered: (i) Tower of London test (standard planning test), (ii) Virtual planning test (ViP): a novel ecologically valid measure of real world diary planning to achieve a goal of visiting a relative for a party. Differences in plan accuracy, efficiency and speed were explored through repeated measures ANCOVA and logistic regression analyses with current IQ as a covariate.

Results: The disorganisation group demonstrated poor plan efficiency, with greater distracter use in real world planning and more moves above minimum in standard planning, compared to the psychomotor poverty group. Accurate planning (correct activities, perfect solutions and activity omissions) in the disorganisation group was associated with independent contributions from current IQ and working memory. Adherence to goal-related activities in real world planning in all groups and accurate standard planning in all but the disorganisation group suggested that both schizophrenia groups could form plans to govern behaviour.

Conclusion: Inefficient planning in the disorganisation syndrome may contribute to symptom presentation while alternative processes, such as plan and response initiation, may be associated with the psychomotor poverty syndrome.

576. FAMILIAL CO-VARIATION OF PSYCHOSIS PRONENESS AND NEUROCOGNITION IN THE GENERAL POPULATION

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Background: Studies in patients and their relatives have shown that cognitive impairments are markers of familial transmission of liability to psychosis. We examined to what degree the broad distribution of psychosis proneness in the general population shows similar familial continuity with neurocognition.

Method: Interview-based (Structured Interview for Schizotypy-Revised) and self-report (Community Assessment of Psychic Experiences) measures of psychosis proneness (trait 1), as well as a measure of verbal fluency (trait 2-selected because of its high discriminatory power between controls and people with psychotic disorder), were administered to a general population sample of genetically related individuals. Cross-trait, within relative ($n = 425$ individuals) and cross-trait, between relative ($n = 422$ pairs of related individuals pertaining to 64 families) analyses were conducted.

Results: Psychosis proneness was negatively associated with verbal fluency both within and across relatives, with standardised effect sizes of around 0.10–0.15. Results were apparent for both the positive and the negative dimensions of psychosis proneness, but not the disorganised dimension. Effect sizes were in part stronger in men than in women, and the self-report positive dimension was the measure that appeared most sensitive to showing an association with verbal fluency.

Conclusion: Variation in neurocognition is a familial marker of psychosis proneness in the general population.

577. LONGITUDINAL SYMPTOM PATTERNS IN PSYCHOTIC EPISODES ARE RELATED TO NEUROCOGNITION AND OUTCOME

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Background/objective: Longitudinal patterns of psychopathology in psychotic episodes may reveal information on underlying factors and processes. This notion can be tested empirically on symptom courses by utilizing methods of dynamical systems research, such as time series analysis I.

Methods: n the "Schizophrenia Process Study" performed at the University of Bern, Switzerland, symptom courses of 114 schizophrenia spectrum patients were observed using daily ratings of psychopathology (mean duration of observation: 88 days). A 10-item scale for daily symptom assessment was applied (Today's Evaluation of Psychopathology, TEP). The rating scale was composed of three factors: positive symptoms, negative symptoms and anxiety-depression. The courses were analyzed by time series methods using vector autoregression (VAR) which models the day-to-day interrelations between symptom factors (1). Comprehensive neuropsychological assessments were performed at the beginning and at the end of the observed course. Associations between the day-to-day patterns of symptoms, and neurocognition and outcome were calculated.

Results: Results revealed specific relationships between the longitudinal symptom patterns and both outcome and neurocognition. The interactions between positive and negative symptoms were related to outcome. If positive symptoms predicted negative symptoms outcome tended to be unfavorable. In cross-sectional studies, different symptom domains as well as symptoms and neurocogntion are often found to be independent. The results of this study, however, suggest that different symptom domains as well as symptoms and neurocognition are associated if longitudinal patterns of symptoms in indivdual patients are examined.

Reference:

Tschacher, W., Kupper, Z., 2002. Time series models of symptoms in schizophrenia. Psychiatry Research, 113 (1–2) 127–137.

578. MIND READING CARTOONS: A PICTORIAL THEORY OF MIND STUDY IN PEOPLE WITH SCHIZOPHRENIA

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Background: The ability of individuals to correctly determine the intentions and behaviours of others relies on having an intact Theory of Mind (ToM; often referred to as mentalising). It is known that patients with schizophrenia have deficits in ToM capabilities and it is currently unclear whether these are symptom or diagnosis specific.

Methods: Using a pictorial paradigm in which two sets of cartoon joke images were used, a set of physical images (in which no mental state attribution was required for comprehension of meaning) and a ToM set (cartoons in which attributions of either

false belief or ignorance to one or more of the characters were vital for comprehension). 20 DSM-IV classified Schizophrenics were compared to 20 healthy controls. Participants had to explain what they thought the joke was in each image, responses were scored accordingly. Severity of the current psychopathology was measured using the Krawiecka standardized scale; IQ was estimated via the Quick test, and matched between groups.

Results: Patients with schizophrenia were found to perform significantly worse than the controls in both the physical condition ($p>0.05$) and the ToM condition ($p>0.001$). Poor performance on the ToM condition was also found to be significantly related to the presence of positive symptoms and specifically related to the presence of hallucinations (but not delusions as found in our Hinting task study).

Conclusion: The link between positive symptomatology and compromised ToM abilities within the schizophrenic group lends further credence to the argument for symptom-related difficulties in the ability of schizophrenics to infer the mental states of others.

579. NEUROCOGNITIVE PATHWAYS FROM INFANCY THROUGH ADOLESCENCE TO ADULTHOOD IN PSYCHOSIS AND THE GENERAL POPULATION

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Background/objective: Previous studies of development in schizophrenia have examined premorbid measures in terms of risk of developing later disorder; however, such studies have mainly been limited to considering simple diagnostic outcomes—"caseness" or not. We aimed to map the path of neurodevelopment in psychosis over the lifespan by modelling the associations between infant motor development at age 1, adolescent motor performance as measured by teacher ratings for physical education at age 16 and adult executive function at age 32.

Methods: We used these measures as indirect indicators of neurodevelopmental integrity, and investigated their relationships within an epidemiological sample: a case-control study nested in a general population cohort, the Northern Finland 1966 Birth Cohort, comprising 11017 individuals who have been followed from birth up to the present day. Prospectively collected data from each of the three time-points across the lifespan were available on 53 subjects with DSM-IIIR schizophrenia, 19 subjects with other psychoses, and 85 general population control subjects randomly selected from the cohort. We constructed a measure of neurodevelopmental integrity that could serve to compare these differing measures over the three time points by calculating z-scores from the original data.

Results: ANOVA comparing neurodevelopmental integrity revealed a significant main effect of diagnostic group ($F_{(2, 154)}=7.3$; $p=0.01$) and a significant diagnostic group x time of developmental measure interaction ($F_{(4, 152)}=3.1$; $p=0.017$).

Conclusion: These results confirm that individuals with psychosis follow a neurocognitive developmental trajectory that differs from that of the general population.

580. CONSISTENCY OVER TIME OF SEMANTIC ORGANISATION IN PEOPLE WITH SCHIZOPHRENIA

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Background/objective: Semantic memory impairments are well established in patients with schizophrenia (Tamlyn et al., 1992, Clare et al., 1993). Such impairments appear to result from a disorganisation of the semantic network (Goldberg et al., 1998, Elvevag et al., 2002), rather than a loss of semantic representations as seen in patients with Alzheimer's dementia. Previous studies in this field have tended to be cross sectional and there is currently a lack of information pertaining to the stability of these impairments. Therefore, the current study assesses whether semantic category organisation is stable over time.

Methods: 16 participants with a DSM IV diagnosis of schizophrenia completed a card-sorting task (Category Generation Test; Green et al., 1999) in order to assess the organisation of their semantic categories. Participants were asked to sort items from five standard taxonomic categories (e.g. vehicles and fruits) into groups. 69% were found to produce overinclusive or underinclusive categories, showing a disorganisation in their semantic knowledge. This test was then repeated after approximately 12 months.

Results: Analysis revealed very poor concordance across time, with only 4 participants creating the same categories at both time points. Participants who showed semantic disorganisation (i.e. over/underincluded) at baseline did not necessarily replicate this at follow up. Changes in performance could not be accounted for by changes in medication or symptoms.

Conclusion: The results are difficult to interpret in terms of a fixed structure in semantic memory, but suggest that people with schizophrenia are less able to utilise conventional categorisation strategies than healthy controls.

581. SCHIZOPHRENIA PATIENTS WITH COGNITIVE DEFICITS: COSTS AND FACTORS ASSOCIATED WITH COSTS

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Background: Cognitive deficits in patients with schizophrenia affect their quality of life, current and future social functioning, and treatment outcome. Those with the severest deficits are also more likely to consume large amounts of health and social care resources. This study aimed to explore the relationship between costs and cognition.

Methods: 86 patients were recruited to a RCT comparing the cost-effectiveness of cognitive remediation therapy with standard care. Baseline assessments recorded various clinical and social factors and health and social care resources used in the previous 6 months. Structural equation models were used to examine relationships between the costs of those resources and cognition. Cognition was considered both as a single summary measure and as three constituent factors (verbal working memory, response inhibition speed and cognitive flexibility).

Results: Average 6-month costs were £15114. Cognition as a single summary measure was negatively associated with costs (estimated loading -0.393; $c^2 = 124.9$; $p = 0.06$). A separate model with three separate elements of cognition showed that none were individually associated with costs.

Conclusion: Thus interventions may need to improve cognition overall in order to bring about reductions in costs. Furthermore, as 73% of average total health/social care costs consisted of specialised accommodation, improvements in cognition may need to be sufficiently large to affect length of stay in specialised accommodation. Nevertheless, prior understanding of links between cognitive deficits and costs could aid interpretation of the potential impact interventions in this patient group, and indicate how resources could be targeted more efficiently and to those most able to benefit.

582. IS THERE AN ASSOCIATION BETWEEN DURATION OF UNTREATED PSYCHOSIS (DUP) AND NEUROCOGNITIVE PERFORMANCE AT ADMISSION?

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Objective: Does long duration of untreated psychosis (DUP) independently compromise cognitive function? To evaluate this question we examined the relationships between neurocognitive function and DUP.

Methods: Patients were recruited to a study (TIPS) evaluating the effect of an early detection program on DUP for first-episode psychoses in two catchment areas. These were compared to patients in two catchment areas without an early detection program but with identical treatment programs. Median DUP was 10.5 weeks for the entire sample. A total of 301 patients entered the study and 207 completed a comprehensive neuropsychological (NP) test battery. Median time from start of treatment to neuropsychological testing was 108 days; all patients were tested within nine months. Five dimensions were measured with the neuropsychological test battery: Working Memory/Fluency, Executive Function, Verbal Learning, Impulsivity, and Motor Speed.

Results: No significant association was found between DUP and any of the cognitive indices. Strong associations were demonstrated between poorer premorbid school functioning and several neurocognitive deficits.

Conclusion: We did not find that longer DUP is associated with more severe cognitive deficits. Thus, our data contribute to a disconfirmation of the hypothesis that DUP has a neurotoxic effect.

583. WOULD I LIE TO YOU? LIE DETECTION IN SCHIZOPHRENIA

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Background: The ability to detect liars falls at chance level in the general population. Individuals who are overly suspicious and overly vigilant, such as those with paranoid schizophrenia, may have an advantage in the detection of liars.

Methods: We wished to explore whether patients with schizophrenia with predominantly paranoid symptoms ($N = 20$) would be better lie detectors than either healthy controls ($N = 20$) or those patients who were current in remission ($N = 18$). Subjects watched 10 video clips of college students describing a scenario involving a briefcase and an envelope containing $50. All the students claim that they did not take any money from the envelope, but half of them are lying. After watching the video items subjects stated if the person was lying or telling the truth and gave a confidence rating (out of 10). Overall confidence rating was also obtained at the start and end of the session.

Results: Subjects did not differ in their estimation of their lie detection ability overall at the beginning and end of the task. Overall accuracy was also not different between the groups (with most subjects performing at chance level) nor was the number of false positives and false negatives. What did distinguish the groups however, was the number of times the subjects gave a individual item (video) rating of 10. Remitted and controls subjects gave an item rating of 10 significantly fewer times compared to the paranoid group.

Conclusion: These results reflect the tendency of paranoid subjects to be overly confident in their judgements of social situations.

Acknowledgment: This study was funded by a project grant awarded by Cephalon UK.

584. AGE AND THEORY OF MIND IN HEALTHY SUBJECTS: IMPLICATIONS FOR SCHIZOPHRENIA

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Background/objective: The study of developmental changes in Theory of Mind (the ability to understand the intentions of others; ToM) in healthy individuals may reveal important information about the biological underpinnings of social function and identify a marker of social function useful for schizophrenia research. In order to determine if age related changes occur in social cognition, performance on a ToM task was examined in healthy individuals of different ages.

Methods: This was a cross sectional study in twenty healthy subjects using the "Reading the Mind in the Eyes" ToM task (Baron-Cohen et al., 2001), a mental state and gender recognition task. There was no ceiling effect on task performance.

Results: A negative correlation was found between subject age and performance on recognition of both mental state ($r = -0.73$, $R2 = 0.54$, $p < 0.001$) and gender ($r = -0.56$, $R2 = 0.31$, $p < 0.025$). This study is the first to demonstrate a decline in gender identification with increasing age.

Conclusion: This finding suggests that in healthy individuals ToM may decline with age. A similar decline in ToM, whether due to normal aging or other process, may account for the decline in social function of a subset of schizophrenia patients. Given it's lack of ceiling effect in healthy individuals, the "Reading the Mind in the Eyes" task may be sensitive enough to detect a decline in ToM in these schizophrenia patients. If so, this task could be a powerful probe for studying social function in schizophrenia patients.

585. MINI MENTAL STATE EXAMINATION IN CHRONIC SCHIZOPHRENIA SIX YEARS LATER

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Background/objective: In 1997 sixty patients with chronic DSM-IV schizophrenia were assessed with the Mini Mental State Examination (MMSE). Mean age was $54{,}4 \pm 13{,}2$ years, mean duration of illness was $27{,}3 \pm 13{,}2$ years, mean number of previous hospitalizations $11{,}8 \pm 9{,}1$. The aim of this study was to asses the change in MMSE score, in this chronic, institutionalized patient group after six years.

Methods: The same rater as in 1997 (T1) performed the examination in 2003 (T2). 21 patients were lost to follow up: 8 died, 8 were transferred to the nursing homes, 5 refused to participate in a study. There was no difference in MMSE at T1 between the group of patients who were assessed at T2 and those who were not. There were no significant differences in pharmacological treatment at T1 and T2. Mean MMSE at T1 was 27.5 ± 2.8 and 22 ± 5.8 at T2. Patients were divided into two groups: patients older than 60 years at T1 constituted one group, younger than 60 constituted the other. Mean MMSE score at T1 was similar in both groups: 27.1 vs. 27.8; p = ns.

Results: In both groups there was significant reduction in MMSE score between T1 and T2 (Wilcoxon test, $p < 0.005$). The mean reduction in MMSE was -8.4 ± 7.4 in the older and -3.6 ± 4.8 in the younger group (Mann–Whitney test, $p < 0.03$).

Conclusion: Despite many limitation this study points at significant reduction in cognitive function measured by MMSE in a sample of chronic institutionalized schizophrenic patients.

586. INSIGHT CHANGE IN FIRST-EPISODE VERSUS CHRONIC SCHIZOPHRENIA: ITS ASSOCIATIONS WITH CHANGES IN COGNITIVE VERSUS METACOGNITIVE PERFORMANCE

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Objective: The primary aim of this study was to investigate the natural course of insight change in first-episode versus chronic schizophrenia patients. A secondary goal was to assess the unique and joint contribution of cognitive versus metacognitive deficits to the prediction of insight change.

Methods: Sixty first-episode patients and 50 chronic patients were assessed with the Scale of Unawareness of Mental Disorder (SUMD) and the Wisconsin Card Sorting Test (WCST). In addition to the standard administration of the WCST, subjects were also asked to rate their level of confidence in the correctness of each sort and to decide whether they do or do not want each sort to be "counted" toward their performance score on the test. The battery was administered on admission, and then was repeated at discharge, and six months later.

Results: Patterns of insight change over time were distinctly different among the two groups. In the first-episode group there was a mild but steady improvement from admission to six months. However, in the chronic group there were two strongly opposing trends before (improvement) and after (deterioration) discharge. While the strength of associations was moderate at best, in both groups, changes in insight over time were more strongly related to changes in metacognitive rather than in cognitive performance.

Conclusion: These results suggest that the course of insight change may be different in the early versus later stages of the illness, but that independent of the illness stage, it may be better predicted by changes in metacognitive rather than in cognitive performance.

587. EXTENT AND LATERALIZATION OF LINGUISTIC PROCESSING IN SCHIZOPHRENIA II: EFFECTIVE CONNECTIVITY TO PRIMARY AUDITORY CORTEX

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Background/objective: Reduced lateralization of language in schizophrenia may represent a fundamental disease process; it is likely a reflection of both decreased left and increased right hemisphere activity. It has also been proposed that aberrant semantic activation may be a component of this language dysfunction. We predicted that decreased functional laterality would be observed during passive auditory language comprehension in subjects with schizophrenia, and that there would be an increase in the extent and/or magnitude of activity in regions associated with semantic processing.

Methods: We used fMRI combined with an analysis of effective connectivity of primary auditory cortex to investigate. Subjects listened to 30-second blocks of alternating English, reversed English and rest; no response was required. Effective connectivity was assessed by subjective analysis of eigenimages depicting activation produced by a psychophysiological interaction between the language conditions and activation in primary auditory cortex (BA 41 and 42).

Results: Both groups showed activation in the region of the temporo-parieto-occipital junction, a region thought to be involved in semantic processing. The extent and magnitude of this activation was greater in patients than controls, particularly in the right hemisphere. Controls showed bilateral activation of temporal white matter, greater on the right than left; this pattern was suggested in patients but not clearly presented.

Conclusion: These results are consistent with the hypotheses of decreased lateralization and increased semantic activation in schizophrenia.

588. COGNITIVE FUNCTION IN EARLY ONSET PSYCHOSIS

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Background/objective: Studying cognitive functioning in a sample of people with psychosis rather than a single diagnostic group can be seen as an economical research strategy as there appears to be little difference in cognitive function between the psychoses in adults. The present study examines whether cognitive functioning in early-onset psychosis reflects that found in adult-onset psychosis and whether cognitive function in psychosis is similar to that found in schizophrenia.

Methods: Cognitive processes, assessed via a comprehensive neuropsychological battery, were examined in a group of forty-eight, 11–19 year old (mean age 15.85) participants who had experienced psychosis before 16 years of age. The control group ($n = 47$) were matched on gender, age and IQ.

Results: The majority of tests showed no significant difference between the controls and probands. Where there were significant differences, the probands performed better than the controls but on all tests, probands performed lower than age derived norms. Further analysis revealed that type of school made an impact on the results but excluding participants with IQ < 70 or covarying out verbal IQ did not influence results. There were no substantial differences between those with schizophrenia and those with other diagnoses of psychosis nor did medication status. Length of illness or age at onset did not influence the results. However there were significant positive correlations between age at testing and scores on most of the tests.

Conclusion: These findings suggest that early-onset psychosis shows a pattern of static encephalopathy and a neurodevelopmental rather than a neurodegenerative pattern.

Lilly Satellite Symposium

PREDICTORS OF ONSET AND GOALS TOWARD FUNCTIONAL OUTCOMES

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Background: Emerging evidence suggests that the early stages of schizophrenia are a critical window, where optimal intervention may result in attenuation, delay, or even prevention of the onset of psychosis. However, a prodrome is difficult to recognize prospectively because of its nonspecific manifestations. Thus, a more challenging approach is to identify the causal risk factors that may subsequently be eliminated or modified. Possible examples of risk factors may include prenatal, perinatal and postnatal complications, urbanicity, lower level of social and cognitive functioning, cannabis and depression.

Methods/results: A review of the relevant literature indicates that childhood trauma may in some cases be causally related to the development of psychotic symptomatology. The frequency of and distress associated with single psychotic symptoms are also strong predictors of psychosis. Finally, the duration of prodromal symptoms or untreated illness is consistently associated with clinical and functional outcomes.

Conclusion: Although only part of this association is likely to be causal, this evidence suggests that the earlier treatment is initiated in the course of illness, the more likely that there will be recovery of the first episode and improved functional outcomes for patients. Thus, several recently completed and ongoing trials suggest that pharmacological and non-pharmacological interventions may be of benefit in preventing individuals at risk from making a transition to psychosis.

THE FUNCTIONAL HURDLE: CONNECTING THROUGH COGNITION

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Background: Neurocognition is severely impaired in schizophrenia. The relevance of this neurocognitive impairment is clear, as deficits on tests of attention, memory, motor functions, and executive functions are more strongly correlated with outcome than any other aspect of the illness. Patients in the first episode of psychotic illness also demonstrate severe impairments, which may be particularly important as neurocognitive skills may determine success in the areas of occupational and social functioning. Typical antipsychotic medications such as haloperidol have little impact on neurocognitive deficits in chronic patients; however, few data are available on low-dose strategies in first-episode patients. Recent studies suggest that novel antipsychotics, such as clozapine, risperidone, quetiapine, and olanzapine, enhance neurocognitive function in patients with chronic schizophrenia. Olanzapine has been found to be superior to low-dose haloperidol in improving cognition in patients with first-episode psychosis. Since cognitive deficits are so strongly associated with important clinical factors, such as therapeutic alliance, adherence, and long-term social outcomes, it is likely that these treatment-related improvements in neurocognitive function will lead to improved therapeutic relationships and, eventually, improvements in important aspects of the quality of everyday life.

SOHO, LONGITUDINAL EVIDENCE FOR SCHIZOPHRENIA OUTCOMES

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Background: Atypical antipsychotic agents have a proven therapeutic efficacy for both positive and negative symptoms of schizophrenia and a lower incidence of extrapyramidal symptoms when compared to conventional antipsychotic agents. These proven therapeutic advances should correlate to an improvement in health outcomes. A recent study by Namjoshi et al. assessed the clinical and quality-of-life outcomes associated with olanzapine, risperidone, and haloperidol treatment of patients with schizophrenia. The study concluded that olanzapine treatment was associated with better clinical and quality-of-life outcomes compared to haloperidol and risperidone treatment. Results of similar studies suggest that improvement in health outcomes may vary among the atypical agents.

Methods: The European Schizophrenia Outpatient Health Outcomes (SOHO) Study is a ten-country, three-year, prospective, observational study of over 10,000 patients treated with clozapine, olanzapine, risperidone, quetiapine, or typical drugs. Patients could be enrolled just after they initiated or changed any antipsychotic treatment in the outpatient setting.

Results/Conclusion: An early conclusion from this study indicates an ease of use with the initiation of olanzapine treatment in outpatients. The study also concluded that olanzapine treatment was associated with better clinical and quality-of-life outcomes compared to haloperidol and risperidone treatment. The impact of this and other differences from this study on health outcomes requires further examination.