

The World Journal of Biological Psychiatry

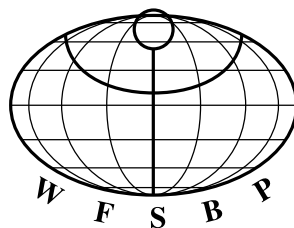
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Supplement 1

World Federation of Societies of Biological Psychiatry

*The Biology of Psychoses
European Congress of Biological Psychiatry
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ABSTRACTS



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Thursday, 13 June 2002

10:00 - 12:00

**SS01 Treatment of cognitive dysfunction in schizophrenia: new research
Sponsored by Janssen Cilag**

SS01.1

Why does cognition matter in schizophrenia?

Michael F Green

University of California, Department of Psychiatry & Behavioral Sciences, Los Angeles, USA

The cognitive deficits of schizophrenia are notable in several respects. For one, they are largely independent of the clinical symptoms of the illness, like positive psychotic symptoms. For another, cognitive deficits appear to reflect vulnerability to the illness, as opposed to the presence of the illness; they are present in unaffected first-degree relatives, as well as people at risk for schizophrenia. Hence, the cognitive deficits are considered to be "core" features of the illness.

Cognitive deficits in schizophrenia are related to the activities of daily living. Meta-analyses revealed associations between key neurocognitive constructs (verbal learning, immediate memory, sustained attention, and executive functions) and aspects of functional outcome. It appears that certain cognitive capacities are necessary for adequate social and vocational outcome. Cognitive deficits may restrict the patient from adapting. Impaired cognition limits what patients can learn in their rehabilitation programs. Two ways of trying to remedy this situation: 1) develop rehabilitation programs with the cognitive deficits in mind, and 2) improve the cognitive deficits (through pharmacological or non-pharmacological means) so that patients can benefit more from their programmes.

SS01.2

Emotional disorders in schizophrenia: a new target for antipsychotics

Oliver Blin, Eric Fakra, Jean-Michel Azorin

University Hospital, Department of Pharmacology and Psychiatry, Marseilles, France

Along with positive and negative symptoms, "emotional deterioration stands in the forefront of the clinical picture" of schizophrenia. Understanding the nature and studying the specificity and intensity of such disturbances is a new field of research. A number of studies have focused on the capacity of schizophrenic patients to perceive and express emotion, essentially through facial emotion recognition and prosodia. Emotional feeling, expression and transmission, ability to communicate and share emotions, are associated with social interaction. We review the diverse advances concerning schizophrenia's emotional disruption. First we explore the numerous studies on psychological assessment of this disturbance, then summarise the anatomical region involved in the generation of emotion, and finally endeavour to draw a parallel with recent functional imagery work. Second-generation antipsychotics such as risperi-

done might improve emotional blunting. More specifically, it has been suggested that risperidone improves emotion recognition. Improving emotional processes in schizophrenia would enable amelioration of sentimental, social and professional life as well as quality of life. As a result, emotional disorders are a new target for antipsychotics.

SS01.3

Treatment of cognitive dysfunction in schizophrenia: new research

Birgitte Fagerlund^{1,2}, T Mackeprang¹, A Gade², R Hemmingsen¹, BY Glenthøj¹

¹ Bispebjerg University Hospital, Department of Psychiatry, Copenhagen, Denmark

² University of Copenhagen, Denmark

Preliminary results of an ongoing longitudinal clinical study examining the profile of cognitive deficits and the effects of antipsychotics on these in drug-naïve, first-episode schizophrenia are presented. Cognitive functions and psychopathology were assessed in 25 first-episode, drug-naïve, schizophrenic patients (plus 25 age and gender matched controls) prior to treatment, as well as after. Patients were randomly allocated to either risperidone or zuclopenthixol for an average of 12.5 weeks. Psychopathology ratings were performed using PANSS (Positive and Negative Symptom Score). Cognitive functions were examined through an extensive test battery focusing on components of attention, executive functions and working memory, including tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) plus word fluency (category and letter), Regard's Figural Fluency test, and Trail Making B. Preliminary results suggest a differential effect on cognitive deficits of risperidone and zuclopenthixol, and underscore the importance of studying the effects of medication on cognitive function at different stages of the disease. This is to enable treatment of patients not only to focus on the psychotic symptoms, but also and optimally on their cognitive function.

SS01.4

Brain activity during cognitive performance in schizophrenia: effects of antipsychotics

Tonmoy Sharma

Clinical Neuroscience Research Centre, Kent, UK

Cognitive dysfunction is an enduring deficit in schizophrenia. It may underpin some of the psychopathology of schizophrenia as well as contribute to the patient's impaired social and vocational functioning. Treatment with atypical antipsychotics has shown that there is a significantly greater improvement in several domains of cognitive function, especially attention and verbal fluency, compared with classical antipsychotics, a result that may be due to the effects of 5HT and other neurotransmitter systems and normalisation of dopamine function by these compounds. Social cognition and learning are probably the domains most likely to have

relevance to functional outcome. It is now possible to map the functional anatomy of neurocognitive improvement with atypical antipsychotics in schizophrenia using functional magnetic resonance imaging and investigate the effects of atypical antipsychotics on social cognition and learning. This presentation will outline new methods of brain imaging and how these methods may allow us to understand the long-term effects of cognitive improvement with antipsychotic drugs in schizophrenia.

SS01.5

Summary & Conclusion: What to expect from atypical antipsychotics on cognitive dysfunction in schizophrenia

Birte Y Glenthøj¹ and Michael F Green²

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² West Los Angeles VA Medical Center, Department of Psychiatry & Behavioral Sciences, Los Angeles, CA, USA

In addition to psychotic symptomatology, schizophrenia is characterized by cognitive deficits, where deficits in the areas of attention, memory, sensory gating, and executive functions are of crucial importance for the developmental course and functional outcome of the illness. Several recent studies have shown that cognitive function is a better predictor of subsequent social function and ability to work than is the presence of psychotic symptoms. Moreover, disturbances in information-processing have been found to form part of the vulnerability for development of schizophrenia. Whereas typical antipsychotics generally are characterized by little effect against cognitive dysfunction in schizophrenia - and/or cognitive side-effects - the atypical antipsychotic compounds improve aspects of cognitive impairments in patients. Several hypotheses have been put forward to explain the mechanisms of the superior effect of atypical drugs, primarily focusing on the high affinity of these compounds for serotonin 5-HT_{2A}-receptors, their limbic selectivity or their different modulation of dopamine D₂- receptors (low affinity/high koff). However, schizophrenia is a heterogeneous disease and patients respond very different to pharmacological treatment. It is therefore imperative that the cognitive function of schizophrenic patients is studied in detail and related to connected disturbances in brain activity and emotional responses in individual patients in order further to ameliorate both the cognitive deficits and the psychotic symptoms. Based on new research, the present symposium will focus on the different disturbances in cognitive function in schizophrenia - and on how these disturbances correlate with biological and emotional disturbances and functional outcome. The aim is to provide the audience with better tools in an up-dated individualized treatment of schizophrenia.

Thursday, 13 June 2002
13:30 - 14:30

PL01

Predicting functional outcome in schizophrenia: lessons from Nebuchadnezzar

Michael F Green

University of California, Department of Psychiatry & Behavioral Sciences, Los Angeles, USA

Schizophrenia is a disease of separate, and largely independent, domains. The cognitive deficits of schizophrenia have little overlap with the more typical clinical features such as positive psychotic symptoms. Since cognition and clinical symptoms are separate aspects of schizophrenia, we expect that they would: 1) follow different time courses across the life span, 2) predict different aspects of outcome, and 3) respond to different treatments. Support exists for all of these predictions.

Cognitive deficits begin long before the clinical symptoms of the illness and they are relatively stable across the life span. These deficits are related to functional outcome, the type of outcome associated with disability in schizophrenia. However, they are not related to clinical outcome (e.g., persisting symptoms). Cognition is related to functional outcome in schizophrenia, but the relationship is probably not direct, and other variables appear to function as mediators for this association. One potential mediator is social cognition.

Social cognition is essentially the interface between non-social cognition and processing interpersonal information. It appears that one aspect of social cognition, affect perception, is a determinant of functional outcome (i.e. vocational and independent living). Also, social cognition appears to be an intervening variable between basic aspects of cognition and functional outcome. Cognition also seems to partially determine how patients cope with stressful life events, which may also be relevant for functional outcome.

There has been considerable optimism about the possibility that newer antipsychotic medications have a beneficial effect on cognition. The field has reached a state of maturity that permits certain inferences to be drawn, and certain limitations to be identified. It appears that the newer antipsychotic medications are better for cognition than standard doses of conventional medications, but that these effects are attenuated at low doses of conventional medications. Newer medications may improve, but clearly do not normalize the cognitive deficits. Little is known about unmedicated performance, but, indirect evidence suggests that newer antipsychotic medications more likely help than harm. The literature is mixed about relative advantages of one newer medication versus another. More substantial cognitive gains may depend on the use of adjunctive, instead of antipsychotic, medications.

**Thursday, 13 June 2002
14:30 - 15:30**

PL02

Imaging neurotransmitters

Marc Laruelle

Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, USA

Several lines of evidence suggest that schizophrenia is associated with two major neurochemical imbalances, an excess of subcortical dopaminergic transmission at the D2 receptor, and a deficiency of glutamate transmission at the NMDA receptor.

Evidence for a dopaminergic excess derives from the D2 antagonism of antipsychotics, and the psychotogenic effects of sustained exposure to dopamine enhancing drugs such as amphetamine. This excess dopaminergic activity has recently been directly confirmed by a number of brain imaging studies that showed elevated F18-DOPA accumulation, elevated amphetamine-induced DA release, and increased occupancy of D2 receptors by dopamine in untreated patients with schizophrenia.

On the other hand, exposure to subanesthetic doses of NMDA antagonists such as ketamine induces a psychotic state, characterized not only by positive symptoms, but also by thought disorganization and negative symptoms, providing a more comprehensive pharmacological model of schizophrenia. Recent data from imaging studies enable bridging the dopamine (DA) and NMDA hypothesis of schizophrenia into one common conceptual framework: 1) under resting condition, DA activity is not markedly disturbed by acute administration of the NMDA antagonist ketamine; 2) under conditions of enhanced DA activity, such as following amphetamine challenge, blockage of NMDA transmission in healthy volunteers results in excess amphetamine-induced DA release; 3) acute administration of mGluR 2 agonists has similar effect on amphetamine-induced DA release. These data suggest that stimulated DA activity is normally under control of a NMDA mediated inhibitory influence. We propose that, in schizophrenia, NMDA receptor hypofunction might be implicated in deficient control of DA cell activity and excess DA release under stressful conditions. This excess DA activity induces sensitization of mesolimbic DA projections and, if sustained, emergence of neuronal loops within cortical-striatal-thalamic-cortical circuits that underlie the psychotic experience.

**Thursday, 13 June 2002
16:00 - 17:30**

S01 New strategies in biological research in schizophrenia

S01.1

Biological basis for risk of illness

Michael Wagner¹, I Frommann¹, C Schröder¹, E Matuschek², R Pukrop²

¹ Department of Psychiatry, University of Bonn, Germany

² Department of Psychiatry, University of Cologne, Germany

Subjects who later develop schizophrenia have cognitive, motor, and social deficits precipitating the onset of disorder. Neuropsychological data may therefore contribute to risk assessment in subjects who present with clinical symptoms possibly indicating the onset of schizophrenia. In an ongoing German multicenter study on early recognition and intervention, subjects suspected to be in a prodromal stage of schizophrenia are assessed with several methods. For this report, the neuropsychological performance of 34 subjects (most of them unmedicated) in presumed prodromal stages was compared with that of a group of matched healthy controls. Subjects in a late prodromal stage (who experienced brief limited intermittent psychotic symptoms or attenuated positive symptoms) had significantly inferior verbal memory, visual motor skills, and working memory. Impairments were less pronounced in early prodromal subjects (reporting basic symptoms like perceptual distortions), but verbal memory was also reduced in this group. Albeit preliminary, these data are consistent with the expectations from high-risk and registry-linkage studies. The follow-up of a larger number of prodromal subjects will allow to examine whether these cross-sectional cognitive impairments also predict a subsequent schizophrenic illness. Supported by the German Research Network on Schizophrenia (BMBF grant 01 GI 9934).

S01.2

Biological basis of reexacerbation in first episode schizophrenics

Wolfgang Wölwer, W Gaebel

Department of Psychiatry, University of Düsseldorf, Germany

This study is a subproject of an ongoing comprehensive study on acute and long-term treatment strategies in schizophrenic first episode patients. Based on the vulnerability-stress-coping (VSC) model the present study aims at (1) a longitudinal assessment of the three components of this model in the course of treatment and (2) an investigation of the relationship of these components with prodromal symptoms and relapses. The questions to be answered will be the predictive power of these components for risk of relapse and outcome after cessation of medication as well as the modifiability of the components by the pharmacological (double blind

medication with either risperidone or haloperidol) and psychological treatment strategies (psychoeducation alone or additional to VSC-oriented treatment modules) used in the randomized long-term treatment study. Assessments take place at inclusion into the long-term treatment study (T0), after 1 year of medication and psychological treatment (T1) and after 1 year of discontinued treatment (T2). Concept, design and first results of patients, who already finished the first year of treatment, will be presented at the conference.

S01.3

Functional magnetic resonance imaging reveals dysfunctions during a continuous performance test in first-episode schizophrenic patients

Frank Schneider, D Braus, U Habel, M Klein, E Meisenzahl, B Müller, MJ Müller, S Ruhrmann, R Schlösser, M Wagner, H Sauer, FA Henn
Department of Psychiatry, University of Düsseldorf, Germany

Neuroimaging is a powerful tool for studying the neurobiological substrates of different cognitive and affective processes in schizophrenia. This project aims to investigate the neural correlates of emotional and cognitive dysfunctions during the initial phase of schizophrenia using fMRI. A multicenter study within the German competence network of schizophrenia is being performed to investigate the pathophysiology of schizophrenia. Eight centers are each carrying out an fMRI paradigm (modified version of the continuous performance test, CPT) relevant for the pathophysiology of the disease. The results presented are part of a longitudinal study aimed at verifying the cerebral correlates of different tasks, with respect to their stability during the progression of illness and their predictive valence regarding the risk of relapse and therapeutic effects of medication. The neurobiological impairments to be described, will be considered individually in relation to psychophysiological and neuropsychological data and the characteristic course of illness. Matched healthy control subjects will also be investigated. fMRI data acquisition relied on a box-car design and an/the EPI technique. The conditions of the CPT were alternating phases of baseline (fixation of letters), and the one-back (reaction on the target letter x) and two-back condition (reaction on each letter when the last but one was the same). Second order analyses (SPM99) for the groups were performed (based on the single subject contrasts). The activation pattern of schizophrenic patients points to a frontal deficit in patients when compared to controls subjected to increasing task demands, i.e. increasing memory load of the CPT (two-back vs. one-back). Currently, the results in first-episode patients concur with previous reports describing a frontal deficit in other schizophrenic patients and suggest a dysfunction present at earlier stages of the disease.

S01.4

Functional brain indicators of negative symptoms

Marcus Streit¹, B Rockstroh²

¹ Department of Psychiatry, University of Düsseldorf, Germany

² Department of Psychology, University of Konstanz, Germany

The objective of this study was to identify neurofunctional correlates of affective disturbances in schizophrenic patients, since those disturbances were expected to be neurophysiologic indicators of negative symptoms. Therefore, neural activity was recorded in the msec time range by means of a 148-Channel Whole Head Magnetoencephalograph (MEG) in schizophrenic patients and healthy controls. To elicit emotional feelings during the MEG recordings pictures from the International Affective Picture System were presented and, additionally, a startle probe was combined with a part of the pictures. First data analyses revealed that the brain responses to the emotional pictures were remarkably different in schizophrenic patients as compared to healthy controls. Healthy subjects showed different MEG responses to different emotional valences at earlier latencies (at about 200 msec) than patients (at about 280 msec). Furthermore, the differences in amplitude between the emotional valences were much greater in controls with the highest amplitudes in response to unpleasant pictures and the lowest in response to neutral pictures. First source reconstructions suggest that orbitofrontal cortex, amygdala and somatosensory cortex might be critical regions for these processes.

S01.5

Molecular- and pharmacogenetics

Wolfgang Maier

University of Bonn, Department of Psychiatry, Germany

Neuroleptics are efficacious in schizophrenia but non-response also occurs in a considerable number of bases. The goal of pharmacogenetics is to predict response and to support the selection of the choice of the most appropriate drug for each patient. Randomised controlled treatment programmes are requested to identify the predictive markers and haplotypes for each drug. How to find predictive markers? The most promising is to focus the search on susceptibility genes and on genes involved in the mechanism of action of the specific neuroleptics; however, only fragmentary knowledge of these pathways is available. Gene expression analyses in model systems using the microarray technique allows to identify new, up to now unknown genes and pathways with modified expression through neuroleptic treatment. We present a research programme with preliminary results aiming at these clinical and preclinical objects.

Thursday, 13 June 2002

16:00 - 17:30

S02 Symptomatology and pathophysiology of atypical psychoses

S02.1

Amino acid metabolism and its relation to the pathophysiology of atypical psychosis

Durk Fekkes, L Pepplinkhuizen

Section Pathophysiology of Behaviour, Department of Psychiatry, Erasmus University Rotterdam, The Netherlands

In a subgroup of psychotic patients suffering from transient acute polymorphic psychoses, diagnosed according to ICD-10 criteria, abnormalities in amino acid metabolism were found. The psychotic episodes of many of these patients are characterized by distorted sensory perceptions and intense emotional states. Plasma concentrations of serine and methionine were decreased, and the concentration of taurine was increased. The determination of plasma amino acid concentrations proved to be useful in discriminating these patients. In remitted patients oral loading with serine induced the characteristic dysperceptions and psychedelic symptoms. Fibroblast experiments suggest that the activities of the serine metabolizing enzymes serine hydroxymethyltransferase (SHMT) and cystathionine β -synthase are increased in these patients. The higher SHMT activity results in an increased conversion of serine into glycine with a concomitant rise in methylene-tetrahydrofolic acid. The latter compound may dissociate into tetrahydrofolic acid and formaldehyde, which may react spontaneously with indoleamines resulting in the formation of so-called β -carbolines. It is hypothesized that one or more of these β -carbolines, of which many have hallucinogenic properties, are involved in the pathophysiology of the acute polymorphic psychosis.

S02.2

The transient acute polymorphic psychoses

Lolke Pepplinkhuizen, D Fekkes,

Erasmus University Rotterdam, The Netherlands

The acute polymorphic psychosis (ICD-10) is a kaleidoscopic, florid psychosis with clear consciousness and complete recovery. When fullblown it is a very characteristic clinical picture, nevertheless hardly recognized and acknowledged as a separate type of psychotic illness outside Europe. (Where it is known as bouffée délirante, cycloid psychosis or degeneration psychosis.) Prominent symptoms can be distorted sensory perceptions, similar to those evoked by hallucinogenic substances (LSD, DMT etc.) From our studies it appears that a catatonic state can induce a psychotic episode. In many vulnerable patients a disturbed one-carbon metabolism, i.p. serine and glycine degradation, can be demonstrated. Feeding these patients during a symptom free period with 7-15 grams of serine induces psychedelic and/or psychotic symptoms. These challenge test have enabled us delineate and study the acute polymorphic syndro-

me clinically and biochemically. The therapeutic and preventive strategies are also different from those of the mood and schizophrenic disorders.

S02.3

The history of the atypical psychoses and the DSM counterparts

FMMA van der Heijden, WMA Verhoeven, S Tuinier, L Pepplinkhuizen, HM Van Praag

Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands

There is a continuing debate about the validity of psychotic disorders that are classified in the European psychiatric tradition but not in the taxonomy of the DSM-IV. Examples are: cycloid psychoses, atypical psychoses, bouffée délirante and (periodic) catatonia. Although apparently rooted in the 19th century the origin of a psychiatric taxonomy and the categorization of psychotic disorders was by no means restricted to this period and several attempts at classification were already made in the 17th and 18th century. The European lines of development of diagnostic concepts will be discussed. In conclusion, some atypical psychoses may form separate nosological entities and transcend the strict borders of the Psychotic Disorders in the DSM and other current taxonomies. The relevance of these potential nosological entities is the supposed alternative treatment strategy that is involved, e.g. maintenance therapy with mood stabilizers. A second possible benefit is the creation of more homogeneous psychotic subcategories with a different pathogenetic and putative genetic background. Reference: Van der Heijden FMMA, Tuinier S, Pepplinkhuizen L, Van Praag HM, Verhoeven WMA. Beyond the mainstream: The heuristic value of the cycloid psychosis. *European J Psychiatry* 2002; in press.

Reference:

Van der Heijden FMMA, Tuinier S, Pepplinkhuizen L, Van Praag HM, Verhoeven WMA. Beyond the mainstream: The heuristic value of the cycloid psychosis. *European J Psychiatry* 2002; in press.

S02.4

Kahlbaum's catatonia and Leonhard's motility psychosis

FMMA Van Der Heijden, S Tuinier, L Pepplinkhuizen, WMA Verhoeven

Vincent van Gogh Institute for Psychiatry, Venray, The Netherlands

Catatonia is an intriguing psychopathological dimension and the discussion about the clinical relevance of catatonic symptoms in psychiatry is continuing for at least 125 years. The debate started from the original description by Kahlbaum and was further elaborated by Kraepelin and Bleuler who incorporated Catatonia in their broad schizophrenia concept. They merely regarded catatonic symptoms as an integral part of schizophrenia. Today's research is focussing on catatonia as a

separate psychopathological dimension as recently revealed by factor analytical studies. This catatonic dimension is identified in about ten percent of newly admitted patients with affective or schizophrenic psychosis. In this presentation the data will be shown of an analysis of 61 patients with catatonic symptoms out of a set of more than 1500 patients with a lifetime diagnosis of psychotic disease. These suggest that, if there would exist a separate catatonic disease entity, this would probably closely resemble the motility psychosis, once thoroughly described by Karl Leonhard and nowadays extensively elaborated by the Wernicke-Kleist-Leonhard group. Furthermore the data from four case studies, concerning an in depth analysis of four patients with episodic catatonic psychoses, give support to the existence of this circular psychotic disease with motor symptoms from the excited pole to the inhibited pole within one episode. Reference: Van der Heijden FMMA, Tuinier S, Peplinkhuizen L, Verhoeven WMA. Catatonia: The rise and fall of an intriguing psychopathological dimension. Acta Neuropsychiatrica 2002; submitted.

Reference:

Van der Heijden FMMA, Tuinier S, Peplinkhuizen L, Verhoeven WMA. Catatonia: The rise and fall of an intriguing psychopathological dimension. Acta Neuropsychiatrica 2002; submitted.

S02.5
Genetic, environmental and neurobiological aspects of cycloid psychoses

Ernst Franzek, (The Netherlands), B Pfuhlmann, G Stöber

Abstract was not available at the time of printing

Friday, 14 June 2002
08:30 - 10:00
SS02 Assessment and management of the acute patient
Sponsored by Eli Lilly

SS02.1
Clinical management of acute mania

Mauricio Tohen, (USA)

Abstract was not available at the time of printing

SS02.2
Clinical management of acute schizophrenia

Bruce J Kinon, (USA)

Abstract was not available at the time of printing

SS02.3
New horizons in the treatment of the acute agitated patient

Allan Young, (UK)

Abstract was not available at the time of printing

Friday, 14 June 2002
10:30 - 12:00
S03 Understanding drug effects on information-processing and psychopathology in schizophrenia
Supported by an unrestricted grant from AstraZeneca

S03.1
Why are antipsychotics anti-psychotic?
Speculations regarding the critical mechanism

Shitij Kapur

CAMH & University of Toronto, Canada

This year marks the 50th anniversary of the accidental discovery of a class of drugs that are now called antipsychotics. Antipsychotics are distinguishable from other major classes of psychotropic drugs, and every antipsychotic blocks dopamine transmission. So, the question arises, how and why does blocking dopamine (a neurochemical intervention) lead to the resolution of psychosis (a mind level phenomenon). It has been proposed by Berridge and Robinson that dopamine has a fundamental role in mediating "saliency" of the environment and its internal representations. Hyperdopaminergia, whatever its origins, may lead to psychosis as it would lead to an aberrant assignment of saliency and to environmental stimuli and their internal representations. The critical mechanism why antipsychotics are anti-psychotic is that they "dampen the saliency" of these abnormal experiences and associations - and by doing so provide a platform for psychological resolution of symptoms. Several animal models of psychosis are consistent with the idea that these drugs dampen the saliency of learnt associations. Thus, they decrease the saliency of symptoms and the symptoms recede to the background of the patient's consideration, do not influence his behaviour and allow her to function - superficially symptom free. However, if the antipsychotics are stopped the dys-regulated neurochemistry re-expresses itself, the dormant ideas and experiences become reinvested with aberrant saliency and a clinical relapse occurs. The implications and limitations of this idea will be explored.

S03.2

Subjective experience and striatal dopamine D2 receptor occupancy in patients treated with antipsychotics

Lieuwe de Haan, (The Netherlands)

Abstract was not available at the time of printing

S03.3

Effects of chronic treatment with antipsychotic drugs on information processing and dopamine D2/D3-receptors in drug-naïve first-episode schizophrenia patients

Torben Mackeprang

Dopaminergic dysfunction and disturbances in information processing in schizophrenic patients are well known. The significance of the dopaminergic system for efficient information processing is also well documented.

In order to examine dopamine D2/D3-receptor conditions and information processing in schizophrenic patients, SPECT scannings ([123I]-epidepride), neuropsychological testing (CPT and reaction time) and measurement of PPI (prepulse inhibition of the startle response) were carried out. Twenty-five drug-naïve schizophrenic patients were examined at inclusion and after 3 months of treatment with the atypical antipsychotic compound, risperidone, or the typical drug, zuclopenthixol.

Results showing the effects of antipsychotic treatment on information processing and D2/D3-receptor occupancy will be presented.

S03.4

Neuronal circuit dysfunction in schizophrenia illuminated by fMRI and MRS

F.A. Henn, G Ende, W Weber-Fahr, M Ruf, DF Braus
Central Institute of Mental Health, J5, Mannheim, Germany

Using matched schizophrenic patients treated with atypical and typical antipsychotic medications MRS spectroscopy was carried out on the anterior cingulate gyrus. The results showed that atypically treated patients had higher levels of NAA than those treated with typical medications. Perseveration errors were shown to correlate with NAA levels ($p < 0.02$). NAA was shown to correlate with time on atypical medication. The longer the patient had been on atypical medication the higher his NAA.

To examine this conclusion in first break never treated patients an fMRI paradigm involving sensory input to auditory and visual systems was used. This input involved no cognitive effort or motivation on the part of the patient. We found that this approach clearly maps deficits in the dorsal visual processing path, thalamus, cerebellum and prefrontal cortex. The first 8 patients examined were treated with atypical medications and were followed for 18 months. The results show a return of prefrontal cortical function compared to the initial measurement made at the time of the first psychotic break.

Friday, 14 June 2002

10:30 - 12:00

S04 Schizophrenia: psychopathology and pathogenetic models

S04.1

The boundaries of schizophrenia concept: results from a polydiagnostic study

Josef Parnas, (Denmark)

Abstract was not available at the time of printing

S04.2

Clinical characteristics of the ICD-10 schizotypal disorders

Peter Handest, (Denmark)

Abstract was not available at the time of printing

S04.3

The misconnectivity hypothesis in schizophrenia: current evidence

Giorgio Innocenti, (Sweden)

Abstract was not available at the time of printing

S04.4

The 'binding process' and the neurodevelopmental hypothesis

Pierre Bovet, (Switzerland)

Abstract was not available at the time of printing

Friday, 14 June 2002

13:00 - 14:00

PL03

The functional neuroanatomy of schizophrenia

Fritz A. Henn, DF Braus
Central Institute of Mental Health, NMR Research Unit, J5, Mannheim, Germany

Structural investigations have suggested that schizophrenia involves a variety of lesions. Assuming that the disorder results from a collection of neurodevelopmental problems which lead to symptom production, the question is, what are the functional correlates of schizophrenic symptomatology?

We used a simple sensory paradigm which involves a visual input and an acoustic input and could demonstrate disturbed thalamic and prefrontal function as well as changes in the dorsal visual processing stream and right acoustic cortex.

These studies demonstrate that early in the disease, without any medication exposure, sensory processing is defective. This involves a task with no performance component and one that is minimally sensitive to attention,

the patients must simply look and listen. The results suggest that there are defects in the connections which mediate the processing of sensory information independent of medication, and these end in a thalamic-dorsolateral-pre-frontal-cortical loop which is functionally impaired.

Friday, 14 June 2002
14:00 - 15:00

PL04

What can we expect from antipsychotic compounds in the future

Jeffrey A Lieberman, (USA)

Abstract was not available at the time of printing

Friday, 14 June 2002
15:30 - 17:00

S05 Neuropharmacology in schizophrenia - a neuroimaging prospective

S05.1

D2 receptor blockade and the new antipsychotics - still necessary and may even be sufficient

Shitij Kapur

Department of Psychiatry and Schizophrenia Program, University of Toronto, Ontario, Canada

The talk will focus on how examining the brain receptors occupied by antipsychotics has enhanced our understanding of how these drugs act and also provided clues for new therapeutic strategies. The talk will review recent data relating the antipsychotic efficacy as well as side-effects of typical and atypical antipsychotics to their effects on the dopamine D2 receptors and serotonin 5-HT₂ receptors as measured in patients in clinical-PET studies. The data argue for a continuing central role for dopamine D2 blockade in the actions of typical as well as atypical antipsychotics. These data show that atypicality (i.e. antipsychotic effect without EPS or prolactin elevation) are largely attributable to appropriate modulation at the D2 receptor level. What then could explain the difference between typical and atypical antipsychotics - it is proposed that a fast dissociation from the dopamine D2 receptors as a molecular property, and an appropriate level of systemic occupancy are key for an EPS-free antipsychotic effect. These findings raise the possibility that a selective D2 blocker can be an atypical antipsychotic? However, several questions remain unanswered. The basis of clozapine efficacy in refractory psychosis remains a mystery. The precise contributions of the other receptors are unclear. Rather than hope for a single molecule that acts on several receptors and hence is the optimal single treatment for the complex illness of schizophrenia, the next generation of antipsychotics should look for specific pharmacotherapies targeted at the specific and separable dimensions (e.g. positive, negative, cognitive, affective) of schizophrenia.

S05.2

Extrastriatal D2 receptors and neuroleptic treatment

Lars Farde

Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Early brain imaging studies of neurotransmission in schizophrenia aimed at quantitation of postsynaptic dopamine receptor subtypes in the striatum. The studies confirmed that antipsychotic drugs occupy D2-receptors to a high degree. Recent advancements of the methodology now allow for examination of low density D2-populations in the thalamus and the limbic and cortical regions that are of central interest in schizophrenia research. The aim of the present study was to test the hypothesis of extrastriatal D2 dopamine receptor selectivity as a mechanism of atypical antipsychotic drug action. The reference radioligand [11C] raclopride and the new high affinity radioligand [11C] FLB457 were used to examine striatal and extrastriatal D2-receptor occupancy by PET in three patients treated with haloperidol and four with clozapine. In patients treated with haloperidol the D2 occupancy was high in all regions examined. In clozapine treated patients the D2-occupancy was low both in the striatum and in extrastriatal regions. The results do not give support for the hypothesis of regional selectivity as the mechanism of action of clozapine. However, despite strong support for the D2-receptor as a target for treatment, most studies indicate that the striatal D2-density is not changed in untreated patients. Two recent PET-studies point to reduced [11C] FLB457 binding rather in the thalamus and the anterior cingulate. The findings are consistent with the reduced cell count and the structural abnormalities reported postmortem and in vivo.

S05.3

Combined dopamine transporter and D2-receptor imaging in schizophrenia: implications for atypical neuroleptics

Eva Meisenzahl, HJ Möller,

Department of Psychiatry, Munich, Germany

Assessment of the striatal D2 receptor occupancy profile of new antipsychotics by IBZM-SPECT can be regarded as a valid tool to predict antipsychotic efficiency combined with risk of development of EPS. Amisulpride belongs to a new generation of atypical neuroleptics which were developed for the treatment of psychotic symptoms without producing typical extrapyramidal side effects. Amisulpride acts antagonistically on presynaptic D2 and D3 receptors with indication for a preferentially presynaptic binding in a low dosage range. In contrast, high doses of amisulpride are supposed to act on postsynaptic dopamine receptors. With IBZM a reliable SPECT-ligand for the postsynaptic dopaminergic receptors has been already established. On the other hand, the new ligand 99mTc-TRODAT-1 with a high specificity for striatal dopamine transporter offers the opportunity to study the presynaptic site of dopamine

synapses. This talk will focus on the examination of the effects of low and high doses of amisulpride on pre- and postsynaptic dopaminergic structures by a combined ^{99m}Tc-TRODAT-1 and IBZM SPECT approach in comparison to other typical and atypical neuroleptics.

S05.4

Serotonergic dysfunction in schizophrenia - implications for antipsychotic drug actions

Johannes Tauscher

Department of General Psychiatry, University of Vienna, Austria

There is considerable evidence for a dysfunction of the serotonergic neurotransmission in schizophrenia. Pharmacological challenge with the partial 5-HT agonist m-chlorophenylpiperazine increased positive psychotic symptoms in schizophrenic patients but not in healthy controls. Several post-mortem studies showed an elevation in serotonin 5-HT_{1A} receptor density in schizophrenia. This was recently confirmed for the first time in vivo. Using PET and [¹¹C]WAY-100635, we could demonstrate increased 5-HT_{1A} binding potential in medio-temporal cortex of patients with a first episode of schizophrenia, who had never received antipsychotic medication. Studies of 5-HT_{2A} receptors in schizophrenic patients to date have mainly involved post-mortem brain samples, and produced conflicting results. In two recent [¹⁸F]setoperone PET studies using ROI-analysis no changes in 5-HT_{2A} receptors were observed in schizophrenic patients. Additional 5-HT_{2A} PET studies have been performed using voxel-by-voxel analysis by the application of SPM. While one found no substantial 5-HT_{2A} receptor changes in the schizophrenic patients, another [¹⁸F]setoperone PET study indicated significant 5-HT_{2A} receptor decreases in the left and right prefrontal cortex in schizophrenic patients. Recent interest in 5-HT with regards to antipsychotic drug action has been fuelled by the fact that novel antipsychotic drugs such as clozapine, olanzapine, quetiapine, risperidone, sertindole and ziprasidone are potent 5-HT_{2A} receptor antagonists and relatively weaker dopamine D₂ antagonists. In addition, 5-HT_{1A} and 5-HT_{2C} receptors seem to contribute to clinical effects of some novel antipsychotics. In particular, there is some preclinical evidence to support a role for 5-HT_{1A} agonism in the antipsychotic action and extrapyramidal side effects of drugs. References: Hashimoto T, Nishino N, Nakai H, Tanaka C (1991): Increase in serotonin 5-HT_{1A} receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. *Life Sci* 48(4):355-63 Newan-Tancredi A, Gavaudan S, Conte C, Chaput C, Touzard M, Verrielle L, et al. (1998): Agonist and antagonist actions of antipsychotic agents at 5-HT_{1A} receptors: a [³⁵S]GTPγ binding study. *Eur J Pharmacol* 355(2-3):245-56. Tauscher J, Kapur S, Verhoeff NPLG, Hussey D, Daskalakis ZJ, Tauscher-Wisniewski S, Kasper S, Zipursky RB (2002): Brain serotonin 5-HT_{1A} receptor binding in schizophrenia measured by positron emission tomography and [¹¹C]WAY-100635. *Arch Gen Psychiatry*: in press Verhoeff NPLG, Meyer JH,

Kecojevic A, Hussey D, Lewis R, Tauscher J, Zipursky RB, Kapur S (2000): A voxel-by-voxel analysis of [¹⁸F]setoperone PET data shows no substantial serotonin 5-HT_{2A} receptor changes in schizophrenia. *Psychiat Res Neuroim* 99 (3):123-135

S05.5

Dopamine stabilizers - beyond the world of simple agonists antagonists

Nicholas Waters, C Sonesson, J Tedroff, S Waters, O Gefvert, T Lundberg, L Lindström, A Carlsson
Carlsson Research AB, Göteborg, Sweden and Västerås Hospital, Västerås, Sweden

In psychiatry and neurology antagonists and agonists with high affinity for dopamine receptors are extensively used. The underlying theory for this use is based on the assumption of either high or low activity of dopaminergic systems. Another hypothesis about underlying causes of psychiatric or neurological illness is relies on the idea that there exists an imbalance in dopaminergic function, either locally or regionally. Such an imbalance may fluctuate over time. Thus, novel treatment strategies could be aimed at pharmacological treatments that are state dependent. To exploit such a strategy we have built a pharmacological assay system, based on functional studies of cortico-striato-thalamic feedback loops, which enable the discovery of compounds that can act as stabilizers of dopaminergic function. Using this assay system we have discovered compounds that display functional stabilization of dopaminergic systems. Thus, dopaminergic stabilizers are compounds that can both enhance and counteract dopaminergic effects, depending on the initial level of dopaminergic activity. Intriguingly these compounds have highly specific effects on dopamine dependent functions via a low affinity mechanism. Preclinical and clinical data describing this new principle will be discussed.

Friday, 14 June 2002

15:30 - 17:00

S06 Craniofacial and other dysmorphologies as indices of cerebro-craniofacial dysmorphogenesis in psychosis

S06.1

Cerebro-craniofacial [dys]morphogenesis in relation to psychosis

John L Waddington

Stanley Foundation Research Unit, Royal College of Surgeons in Ireland, Dublin

Given the intimacy with which the brain and face develop over early pregnancy from common embryological origins, it is well recognised that established neurodevelopmental disorders such as Down's and velo-cardiofacial syndrome are characterised by craniofacial as well as cerebral dysmorphology. In such situations, the topo-

graphy and known developmental biology of craniofacial dysmorphogenesis can be informative as to the nature and timing of cerebral dysmorphogenesis. In the context of developmental models of schizophrenia, a literature on an excess of minor physical anomalies has been complemented by anthropometric techniques which have recently identified subtle quantitative abnormalities of craniofacial morphology. These indicate particular dysmorphology of the anterior [frontonasal] regions of the lower/mid-face and of the palate. There is a particular relationship between morphogenesis of these facial regions and of frontal regions of the brain. As more is known of the developmental biology of the craniofacies than of the brain, such indices can provide more detailed insights into how very early events initiate a process that may be best conceptualised in terms of a lifetime trajectory model of psychotic illness.

S06.2

Congenital anomalies and risk for psychosis in the PDS study

Alan S Brown, ES Susser, CA Schaefer, RJ Wyatt, M Bresnahan

College of Physicians of Columbia University/New York State Psychiatric Institute, New York, USA

We are examining the relationship between congenital malformations and risk of psychosis, especially schizophrenia and other schizophrenia spectrum disorders (SSD), in the Prenatal Determinants of Schizophrenia (PDS) study. The PDS is a schizophrenia follow-up study of a large birth cohort, consisting of 12,094 offspring of mothers enrolled in an investigation of the impact of developmental risk factors on the offspring. Seventy-one cases of SSD have been diagnosed among the birth cohort members. An extensive database on congenital anomalies in the offspring has been recorded over the first five years of life, and is available. Structural anomalies were diverse and the frequency of each was low. Therefore, anomalies were collapsed into informative aggregates based on theoretical considerations: (i) those structural anomalies potentially 'informative' on the basis of the existing dysmorphology/minor physical anomaly literature; (ii) craniofacial structural anomalies; (iii) structural anomalies of midline development; these were contrasted with the remaining anomalies. Relationships between the topography of congenital anomalies and risk for subsequent psychosis in this dataset are important for understanding the role of early dysmorphic events in the genesis of schizophrenia.

S06.3

Craniofacial abnormalities after gestational irradiation in a primate model of schizophrenia

Lynn D Selemon, DL Gelowitz, PS Goldman-Rakic, P Rakic

Department of Neurobiology, Yale University School of Medicine, New Haven, USA

Anthropometric studies of human schizophrenic pati-

ents have uncovered abnormalities in craniofacial structure, indicating that a developmental disturbance may give rise to brain pathology and craniofacial abnormalities in schizophrenia. In non-human primates, several neuropathologic features of schizophrenia, i.e. reduced thalamic volume, decreased thalamic neuron number, and increased cortical neuronal density, have been replicated by exposure to low-dose, x-irradiation during early gestation (E33- E42). Measurement of craniofacial structure in adult monkeys that were irradiated at E33-E42 revealed reduced head width, inter-orbital distance, and ear width relative to normal adult monkeys. While decreased inter-orbital distance and head width were selectively associated with irradiation during the first trimester, reduced ear width was observed in monkeys irradiated in mid-gestation (E70-81), suggesting vulnerability of ear size to developmental insult over a broader time span. These results support the hypothesis that craniofacial dysmorphogenesis and schizophrenic-like brain pathology may have a common etiology involving disruption of early developmental processes.

S06.4

Velo-cardiofacial syndrome, dysmorphogenesis and psychosis

Kieran C Murphy

Division of Psychological Medicine, Institute of Psychiatry, London, UK

Velo-cardio-facial syndrome (VCFS), the most frequent known interstitial deletion found in man, is associated with chromosomal microdeletions in the q11 band of chromosome 22. Although phenotypic variability occurs, common clinical features include characteristic dysmorphology, cleft palate and high rates of schizophrenia. A core topography of dysmorphology in schizophrenia has repeatedly been described. Several studies report an overall narrowing and elongation of the mid- and lower anterior facial region, with a high palate and reduced mouth width, widening of the skull base and extensive abnormalities of the mouth, ears and eyes. These abnormalities show considerable overlap with the craniofacial abnormalities characterising individuals with VCFS. This observation leads to two possible conclusions (1) The increased rates of craniofacial abnormalities reported in studies of people with schizophrenia may reflect in part the contribution of undetected VCFS individuals and (2) VCFS and schizophrenia may both be associated with similar mechanisms disrupting neuronal migration. As the entire sequence of chromosome 22 has now been determined, the study of VCFS potentially offers a unique opportunity to identify susceptibility genes for schizophrenia in the general population.

S06.5

3D shape analysis of craniofacial dysmorphology in psychotic disorders

Robin J Hennessy, JF Quinn, A Lane, A Kinsella, E O'Callaghan, C Larkin, JL Waddington,

Stanley Foundation Research Unit, Royal College of Surgeons in Ireland, Dublin

One index of an early basis to schizophrenia is the presence of minor physical anomalies, particularly of craniofacial regions. 3D facial landmark coordinates were analysed using geometric morphometrics. There was an overall difference in craniofacial shape ($P < 0.05$) between 169 patients with DSM-III-R schizophrenia (123 male, 46 female; mean age 46.6 years, SD 16.9) and 78 controls (54 male, 24 female; mean age 46.7 years, SD 20.8). Shape differences were visualised using 3D graphics. Patients were characterised by a greater skull base width and a face which was both longer and set further back in its lower aspects. There were no overall differences in craniofacial shape between 70 patients with DSM-III-R schizophrenia (31 male, 39 female; mean age 53.0 years, SD 14.9), 25 patients with schizoaffective disorder (9 male, 16 female; mean age 51.5 years, SD 14.2) and 47 patients with bipolar disorder (20 male, 27 female; mean age 49.8 years, SD 13.8). These findings suggest some homogeneity of craniofacial [dys]morphology across these psychotic diagnoses in terms of specific 3D constructs. These studies were supported by the Stanley Foundation.

Friday, 14 June 2002

17:30 - 19:00

SS03 Dopaminergic mechanisms and the treatment of schizophrenia
Sponsored by Sanofi-Synthelabo

SS03.1

Mechanisms of atypicality: a role of dopamine receptors?

Gavin P Reynolds, (UK)

Abstract was not available at the time of printing

SS03.2

Treatment of schizophrenia: the importance of early intervention

Jeffrey A Lieberman, (USA)

Abstract was not available at the time of printing

SS03.3

Clinical profile of an atypical dopaminergic antipsychotic

Stephen David Martin, (UK)

Abstract was not available at the time of printing

SS03.4

Meta-analysis of safety and efficacy of atypical antipsychotics

Stefan Leucht, (Germany)

Abstract was not available at the time of printing

Saturday, 15 June 2002

09:00 - 10:30

S07A Sensory gating phenomena: from mouse to man - Part I

S07.1

Lecture: Translational human & animal model studies of information processing deficits in schizophrenia

David L Braff

University of California, San Diego, USA

Human and animal model studies of information processing deficits in schizophrenia patients converge along several dimensions. The human studies detail how information processing deficits indexed by prepulse inhibition (PPI) are a central feature of the cognitive dysfunction of schizophrenia, and correlate with thought disorder, distractibility, positive and negative symptoms, and cognitive fragmentation.

Complementary animal model studies of PPI allow us to 1) understand how the forebrain cortico-striato-pallido-pontine (CSPP) neural circuit acts to modulate prepulse inhibition of the startle reflex, 2) provide a powerful tool for assessing neuroleptic antipsychotic efficacy, and 3) illustrate the use of PPI as an endophenotype in genetic studies. This presentation will provide data from the human and animal model studies of prepulse. Methods: All studies cited utilized rapid onset, intense startling stimuli (eg, 115 dB) to elicit a startle response. Prepulses typically blunt or inhibit the startle response when the prepulse precedes the startling stimulus by about 100 msec. Stimulus parameters and data analysis is similar in both human and animal studies.

Results: Results from numerous human and rodent studies will be reviewed. Conclusions: The prepulse inhibition model of characterizing schizophrenia-linked cognitive deficits and neuroleptic efficacy is robust, valid, and allows us to better understand the symptoms, neuropathology, and treatment of schizophrenia spectrum disorders. Major strengths of this model include its cross-species validation. Ongoing studies include animal studies (eg, neurodevelopmental manipulations, knockout mice) and human studies of PPI in a functional MRI environment, and as an endophenotype in genetic studies.

S07.2

Sensory gating deficits in the schizophrenia spectrum and genetic implications

Kristin Cadenhead

University of California San Diego, Department of Psychiatry, La Jolla, CA, USA

The schizophrenia spectrum is a clinically, neurobiologically, and genetically heterogeneous group of disorders. The identification of neurobiological markers in psychiatric genetic research is important because clinical phenotypes are not always reliable or valid descriptors of a genetic diathesis for schizophrenia. Prepulse inhibition (PPI) of the startle response has been shown to be deficient in schizophrenia patients, their first-degree relatives and individuals diagnosed with schizotypal personality disorder. Preliminary correlations and calculations of relative risk within sib pairs and twins suggest that PPI is a heritable trait. Animal studies demonstrate strain differences in PPI and five QTL's have been found to be associated with PPI in inbred mice. The use of phenotypic neurobiological measures to define subtypes within the syndrome of schizophrenia may help to more clearly define the boundaries and neuropathology of neurally-defined schizophrenia and reduce the heterogeneity of an initially clinically defined population.

S07.3

Neurotransmitter modulation of sensory gating

Birte Y Glenthøj, Torben Mackeprang, Birgitte Fagerlund & Ralf Hemmingsen

Bispebjerg Hospital, Department of Psychiatry, Copenhagen, Denmark

Some of the most consistent findings in schizophrenia research have been disturbances in attention and information-processing in patients. Sensory gating refers to the brain's ability to modulate its sensitivity to incoming stimuli. Dysfunction in sensory gating in schizophrenia is believed to be the result of different developmentally and/or environmentally caused disturbances of the limbic and prefrontal cortico-striato-thalamo-cortical circuits involved in information-processing. Psychopathology and disturbances in sensorimotor gating will depend on the primary involvement of distinct parts of these circuits, and on secondary derived time-dependent disturbances of transmitter function. This presentation will focus on sensory gating disturbances as a basis for the understanding of development of transmitter dysfunction, attention deficits, and psychotic symptoms in schizophrenia patients. The hypothetical effects of dopaminergic, glutamatergic, GABAergic, noradrenergic, cholinergic and serotonergic interactions on sensorimotor gating are illustrated and related to our own and others recently presented clinical data on biological changes and information-processing disturbances in drug-naïve first-episode patients. Finally, the implications of the reviewed results will be discussed as a basis for potential new treatment strategies.

Saturday, 15 June 2002

09:00 - 10:30

S08 The role of immunology in schizophrenia - from basic research to therapeutic implications Supported by the German Society for Biological Psychiatry (Group: Immunology in Psychiatry)

S08.1

Immunology, immunogenetics and schizophrenia

Padraig Wright, (UK)

S08.2

Cerebrospinal fluid cytology in schizophrenia

Heikki V Nikkila¹, A Ahokas², K Muller³, K Wahlbeck¹, R Rimón⁴, LC Andersson⁵

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² Department of Psychiatry, Helsinki City Hospital, Helsinki, Finland

³ Section of Clinical Neurosciences, FIOH, Helsinki, Finland

⁴ Department of Psychiatry, Pajjat-Hame Central Hospital, Lahti, Finland

⁵ Department of Pathology, University of Helsinki, Helsinki, Finland

A series of cytocentrifuge studies was undertaken to elucidate the role of immunocompetent cells in schizophrenia by analyzing the mononuclear cell counts and distributions in the CSF samples. Also the concentrations of inflammation markers neopterin and MIP-1 were measured applying RIA- and ELISA -techniques to clarify the possible inflammatory activity.

The finding of the enrichment of macrophages suggests that mobilization of microglia is a potential pathophysiological event in schizophrenia, providing also support to the neuroradiologically demonstrated loss of brain substance without marked gliosis, which is still a controversial topic. The appearance of morphologically atypical lymphocytes reinforces the previous disputable detection of lymphocyte abnormalities in schizophrenia. The constancy of this finding, regarding the duration of the illness or the medication status of the patients, may provide a link to the immunogenetics of schizophrenia.

The negative findings concerning the inflammation markers point out that the aberrations of immunocompetent cells are not a reflection of conventional immunological reactions with inflammatory responses, but rather traces of deviant sequences of programmed cell death during the dynamic plasticity changes of genetically susceptible individuals.

S08.3

S100B may be an indicator for a neuroplasticity in schizophrenia

Volker Arolt, M Peters, M Rothermundt

Department of Psychiatry. University of Münster, Germany

S100B, a calcium-binding protein produced by astroglial cells, can be understood as an indicator of astroglial cellular integrity. It has been shown to be increased to micromolar levels in brain damaging processes. Recently, it has been demonstrated also by our group that S100B levels are significantly elevated in medicated acutely psychotic patients with schizophrenia, however, on nanomolar levels. The study presented here included 26 drug-free patients with acute schizophrenia and 26 matched healthy controls. S100B blood concentrations were determined using a quantitative immunoassay upon admission and after 6 weeks of neuroleptic treatment. Unmedicated schizophrenic patients showed significantly increased S100B levels compared to matched healthy controls. After 6 weeks of treatment, 11 patients showed normal S100B levels while in 15 patients the levels remained increased. These patients showed significantly higher PANSS negative scores upon admission and after 6 weeks of treatment. Continuously increased S100B levels seem to be associated with persistent negative symptomatology. It may be the case that in these patients neuroplastic mechanisms, modulated by S100B, fail to be effective.

S08.4

CSF analysis: comparison between chronic schizophrenic patients and first-episode patients

Barbara Sperner-Unterwieser, U Eder-Ischia, S Eder, D Ortner, N Singewald, B Widner, D Fuchs
Innsbruck University Clinics, Austria

Background: Based on different neurotransmitter hypotheses measurement of several biogenic amines and their metabolites in CSF has been used in schizophrenia research. The results are still controversial. Evaluation of immune parameters in CSF for schizophrenic patients also reveal conflicting results. Two important reasons could be due different diagnostic groups of schizophrenic patients as well as to the influence of antipsychotic treatment.

Aim of the study: Comparison between chronic schizophrenic patients on antipsychotic medication versus antipsychotic naive patients suffering from first-episode schizophrenia.

CSF was analysed for dopaminergic, glutamatergic and serotonergic compounds as well as parameters of immune activation (neopterin, tryptophan and kynurenine).

Results: There was no difference between the two groups in terms of dopaminergic and serotonergic compounds. The most remarkable results were significantly decreased levels of glutamate and neopterin in the group of first-episode patients when being compared to the chronic group.

S08.5

The Th1/Th2 hypothesis of schizophrenia - immunogenetic investigations

Markus J Schwarz, M Ridel, H Krönig, S Sokullu, S Chi-ang, H-J Möller, M Ackenheil, N Müller
Psychiatric Hospital of the Ludwig-Maximilian University of Munich, Germany

Objective: Immunological abnormalities have frequently been reported in patients with schizophrenia. The most prominent findings were elevated antibody titers or decreased in-vitro production of proinflammatory cytokines such as IL-2 and IFN-g. Based on these findings, we have hypothesised a decrease of the Th1-like (cell-mediated) immune system and an increased activation of the Th2-like (humoral) immune system in a distinct group of schizophrenic patients. Following the concept of heredity with a polygenic mode of transmission, we proposed that at least some of the susceptibility genes in schizophrenia may code for immunologically relevant proteins and we performed immunogenetic investigations in schizophrenic patients and healthy control persons.

Methods: We carried out a candidate gene approach in a case-control design (schizophrenic patients n= 160; healthy controls n=160) of genes coding for immunologically relevant proteins, involved in Th1/Th2 balance: IFN-g, IL-4, IL-6, IL-10, IL-12, IL-13.

Results: Homozygosity for the functional IL-13 A4254 polymorphic allele was more frequent in patients compared to controls (p=.009). The IL-10 A1082 allele was more frequent in schizophrenic patients (p=.009). There was no difference in genotype distribution of allele frequency regarding the IFN-g, IL-4, IL-6, or IL-12 gene polymorphisms.

Conclusions: Our findings show the association of the IL-13 A4254G and the IL-10 A1082G polymorphisms with schizophrenia. The IL-13 A4254 allele and the IL-10 A1082 allele are known to be related to increased Th2 activity and altered IL-10 production, respectively. Thus, our findings support the hypothesis of an altered Th1/Th2 balance in schizophrenia and may help to understand the patho-physiology of schizophrenia.

Saturday, 15 June 2002

11:00 - 12:30

S07B Sensory gating phenomena: from mouse to man - Part II

S07.4

Prepulse inhibition of startle in developmental models of schizophrenia

Michael Didriksen

H. Lundbeck A/S, Valby, Denmark

Sensorimotor gating deficits theoretically lead to sensory overload that may underlie some of the symptomatology of schizophrenia. It is widely accepted that schizophrenia is caused by prenatal or early-life events. The last decade, researchers have focused on means by which the neurodevelopmental deficits seen in schizophrenics could be mimicked in animals. These include pre- and neo-natal immune and virus challenge, respectively, prenatal exposure to the mitosis inhibitor (MAM), neonatal hippocampal lesions, isolated rearing and maternal separation. Although using different techniques all these models reflect some of the neurodevelopmental deficits seen in schizophrenia, deficit in prepulse inhibition of the startle response (PPI) being a common feature in all models. Antipsychotics have not been tested in all models, however, both classical and the new generation of antipsychotics can reverse the PPI deficits seen in neonatal hippocampal lesioned, isolated reared and maternal separated animals. The effect of antipsychotics on psychotomimetic-induced PPI deficits is inconsistent thus the non-drug-induced disruptions of PPI may be a more viable approach to identify novel antipsychotics.

S07.5

Acute vs chronic antipsychotic treatment - prepulse inhibition in rats

Bruno Pouzet, M Paabøl Andersen, R Sonne Hansen

H. Lundbeck A/S, Department of Psychopharmacology Psychosis, Valby, Denmark

Dopamine receptor agonists and NMDA receptor antagonists disrupt the prepulse inhibition (PPI) phenomenon in rats which is considered to model PPI deficits observed in schizophrenic patients. Many laboratories have demonstrated that antipsychotics (APs) antagonised these disruptions of PPI. These results are based on acute treatment with APs, which is different from clinical observations since the effects of APs only emerge after weeks of treatment. We investigated the effect of acute versus chronic (21 days) treatment with haloperidol, olanzapine, risperidone, and sertindole on d-amphetamine- or PCP-disrupted PPI in rats. All APs tested dose-dependently reversed the disruptive effect of d-amphetamine after acute treatment, but no reversal effect was observed after chronic treatment. Acutely, there was only minor effect on PCP-disrupted PPI. In conclusion, tolerance develops to chronic APs treatment in the PPI model. Thus, only acute treatment on d-amphetamine-disrupted PPI is predictive for antipsychotic effect.

S07.6

Effects of antipsychotics on prepulse inhibition in drug-naïve schizophrenic patients

Torben Mackeprang

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Background: Disturbances in sensorimotor gating measured by prepulse inhibition of the startle response (PPI) have frequently been reported in medicated and unmedicated schizophrenia spectrum patients and in their relatives, suggesting that the deficit represent a stable vulnerability marker for schizophrenia. Clinical data on the effects of antipsychotics on PPI disturbances are scarce, but from preclinical studies, antipsychotics have been shown to influence PPI.

Methods: First-episode schizophrenic patients never previously medicated with antipsychotics were examined at inclusion and after 3 months of treatment with the atypical antipsychotic compound, risperidone, or the typical drug, zuclopenthixol. Healthy controls were used as a comparison group.

Results: The results confirm deficits in PPI in drug-naïve first-episode patients. No effect of antipsychotic treatment on PPI dysfunction was observed in any of the treatment groups.

Conclusions: The data are the first to show the possible effect of treatment with antipsychotic drugs on PPI disturbances in a longitudinal study of drug-naïve schizophrenic patients. The data do not support any influence of treatment with antipsychotic drugs on sensorimotor gating deficits. Instead, the results point to the impairment in PPI as a stable vulnerability indicator.

Saturday, 15 June 2002

11:00 - 12:30

S09 Microarray evaluation of gene expression in schizophrenia and affective disorder

S09.1

Microarray analysis: basic principles

Vibeke S Catts¹, SV Catts², LH Lutze-Mann¹

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Microarray technology is a powerful tool for generating expression data on a large number of genes simultaneously. Though there is interest in applying microarray analysis to the study of psychotic disorders, initial reports have highlighted methodological constraints. The aim of this presentation is to describe the principles of microarray analysis. Experimental considerations related to: RNA isolation; sample matching paradigms; choice of microarray platform; labelling; hybridisation; and, image acquisition and analysis are reviewed. Methodological limitations related to reliability, sensitivity and the differentiation of disease-related changes in gene expression from background biological variability are discussed. The authors conclude that at the current stage of development, microarray analysis is best applied to animal models using specific pharmacological or other experimental challenges, and hypothesis-driven studies of disease-healthy tissue comparisons of specific molecular pathways and their interactions.

S09.2

Gene expression profiling and schizophrenia

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Dysfunction of the dorsal prefrontal cortex underlies many of the cognitive symptoms of schizophrenia. To understand the fundamental molecular mechanisms that contribute to this dysfunction, we have been using cDNA microarrays to perform transcriptional profiling of approximately 10,000 genes in brain samples obtained at autopsy from the prefrontal cortex of subjects with schizophrenia. The levels of gene expression in ten patients were directly compared to those in ten matched control subjects. Our analysis has revealed three major categories of transcriptional abnormalities: (1) genes involved in presynaptic function, including vesicle fusion and release; (2) genes involved in selected elements of post-synaptic signaling, particularly inhibitory G-protein coupled pathways; (3) genes involved in specific

metabolic functions such as ubiquitin and selected amino acid metabolism and mitochondrial membrane transport mechanisms. Bioinformatic and statistical analyses have revealed a number of statistical interactions and cellular relationships between many of these affected gene groups. We have also examined the cellular and disease specificity, and potential drug confounds of some of these expression changes using *in situ* hybridization. A novel neurodevelopmental model integrating our major findings is presented.

S09.3

Identifying a series of candidate genes for mania and psychosis using a convergent functional genomics approach

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We are using metamphetamine treatment of rodents as an animal model for psychotic mania. Specific brain regions are analyzed comprehensively for changes in gene expression using oligonucleotide GeneChip microarrays. The data is cross-matched against human genomic loci associated with either bipolar disorder or schizophrenia. Using this convergent approach, we have identified several novel candidate genes - signal transduction molecules, transcription factors, metabolic enzymes - that may be involved in the pathogenesis of mood disorder and psychosis. In addition, we have extended the studies to look at the effects of mood stabilizing agents - lithium and valproate - on gene expression profiles in our animal model. It is anticipated that this work will provide a better understanding of the pathophysiology of mood disorder, psychosis, and stimulant abuse, as well as provide novel targets for the development of pharmacological agents.

S09.4

Multiplex three dimensional mapping of brain gene expression

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³ Department of Biomedical Engineering, University of California, Davis, USA

To facilitate high throughput 3D imaging of brain gene expression, a new method called voxelation has been developed. Spatially registered voxels (cubes) are analyzed, resulting in multiple volumetric maps of gene expression analogous to the images reconstructed in biomedical imaging systems. Using microarrays, 40 voxel images for 9,000 genes were acquired from brains of

both normal mice and mice in which a pharmacological model of Parkinson's disease (PD) had been induced by methamphetamine. Quality control analyses established the reproducibility of the voxelation procedure. The investigation revealed a common network of co-regulated genes shared between the normal and PD brain, and allowed identification of putative control regions responsible for these networks. In addition, genes involved in cell/cell interactions were found to be prominently regulated in the PD brains. Finally, singular value decomposition (SVD), a mathematical method used to provide parsimonious explanations of complex data sets, identified gene vectors and their corresponding images that distinguished between normal and PD brain structures, most pertinently the striatum.

Saturday, 15 June 2002
14:00 - 15:00

PL05

From functional genomics to molecular receptor dynamics of psychotropic drugs

Svein G Dahl, Olayiwola Adekoya, Erik Hjerde, Aina W Ravna, Ingebrigt Sylte

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The complete sequencing of the human genome marks the start of a new era in biological science, with focus shifting from sequencing to functional mechanisms of gene products. The amino acid sequence of all proteins encoded by a genome can be deduced from the DNA sequences of the genes. However, knowing the amino acid sequence of a protein is not the same as knowing its function. Knowledge about their 3-dimensional molecular structure is crucial in order to understand the functional mechanisms and identify new proteins as potential targets for drug discovery.

In addition to effects on gene expression, most of the currently used therapeutic drugs either have enzymes or membrane proteins as their molecular targets of action. These membrane proteins include ion channels and transporters of small molecules, and receptors that convey signals from one side of a membrane to the other. Membrane proteins are thus involved in a variety of cellular processes and have a large potential as targets for new drug discovery. Detailed structural information is still lacking for the majority of membrane proteins since their association with membrane constituents make NMR spectroscopic and X-ray diffraction determinations difficult. Molecular modelling by biocomputing is a methodological alternative to experimental structural studies of membrane proteins, but has to be based on experimental structural information in addition to computational techniques.

Molecular modelling using bioinformatics and structural information on related proteins may thus predict 3-dimensional protein structures from amino acid sequences. We have used combination of bioinformatics and experimental techniques to model membrane proteins

from two different classes, secondary transporters of the sodium:neurotransmitter symporter family (SNF transporters), and G-protein coupled receptors (GPCRs). The protein models have been used to examine ligand-protein interactions and signalling/transport mechanisms, and to design experimental site-directed mutagenesis studies. The studies have provided information about

- Structural determinants for receptor selectivity among serotonergic G-protein coupled receptors.
- Molecular mechanisms underlying signal transduction and drug mechanisms of G-protein coupled receptors.
- Drug binding sites in G-protein coupled receptors and secondary transporter proteins.
- Mechanisms of membrane transport by secondary transporter proteins.
- The molecular dynamics of drug-receptor and drug-transporter interactions.

These studies have thus provided new insight into the detailed molecular mechanisms of two important classes of membrane proteins, receptors and transporters, which may be of value in the discovery and development of new pharmaceuticals.

Saturday, 15 June 2002
15:30 - 17:00

S10 The neuropsychiatry of affective disorder: from clinical symptoms to genes

S10.1

The Danish PET/depression project

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Previous positron emission tomography (PET) studies of patients with major depression have suggested that dysfunction of regions of the limbic system and the frontal lobes in close connection with the basal ganglia is involved in the pathophysiology of major depression. By means of PET and radioactive water we determined an index of the neuronal activity by mapping the cerebral blood flow distribution of 42 unselected in-patients suffering from moderate to severe depression and 47 healthy controls controlling for age and gender. The PET maps were coregistered to magnetic resonance images of the anatomy of the brain. The Functions-of-interest analysis revealed that the patients had a highly significant increased activity of the hippocampus and the cerebellum compared to the healthy controls even when correcting for age, gender, and the influence of antidepressant medication. A Regions-of-interest analysis confirmed these results and showed a strong negative correlation between the degree of psychomotor retardation of the patients and the blood flow to the dorsolateral and supraorbital prefrontal cortices. The total Hamilton score was correlated with the blood flow to the hippocampus.

Our main finding is increased blood flow to the hippocampus, even when controlling for a number of confo-

unders. This is in accordance with a rapidly expanding literature suggesting an important role for this structure in major depression.

S10.2

The Danish PET/Depression Project: cognitive function in major depression and normal subjects

Raben Rosenberg, B Ravnkilde, P Videbech

Institute for Basic Psychiatric Research, Dept of Biological Psychiatry, Psychiatric Hospital in Aarhus, Risskov, Denmark

The primary purpose of this study was, with a focus on cognitive functioning, to describe neuropsychological aspects of patients suffering from major depression in comparison to healthy controls by means of neuropsychological assessment, and to correlate the results from the cognitive assessment with regional cerebral blood flow (rCBF) obtained from PET scanning of the two groups. Forty in-patients and forty-nine control subjects were included in the study. The study confirmed the current notion that depressed patients suffer from widespread cognitive impairments. We were able to rule out any major effects of age, gender and education on the cognitive deficits in question. The influence of medication on performance could not be entirely controlled, but did not seem to be of great importance and the dysfunctions were not correlated to severity of depression or psychomotor retardation. Contrary to controls, cognitive functions of the depressed patients did not correlate with rCBF in specific regions of their brains in more than a few instances. Our results suggest that the brain of patients with major depression may need to operate in compensatory ways to cope with task demands, and that this compensation should be ascribed to the biological and psychological changes evidently implicated in the disease.

S10.3

The nitric oxide pathway as a potential antidepressant target

G Wegener, (Denmark)

Abstract was not available at the time of printing

S10.4

A genome wide scan for risk alleles for bipolar affective disorder on patients from the Faroe Islands

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Due to relatively few founders, limited population size, sparse immigration, population bottlenecks and genetic drift, the population on the Faroe Islands could be sufficiently homogenous with respect to disease mutations, risk alleles and related haplotypes to greatly facilitate the genetic mapping of disease genes. The present study searched for allelic association, haplotype and chromosome segment sharing among distantly related bipolar patients and controls from the Faroe Islands by genotyping more than 510 microsatellite markers. Preliminary results suggest possible risk loci on chromosomes 1, 2, 3, 6, 7, 10, 12, 14, 16, 17, 18, 20, 21 and 22. Additional genotypings have supported the risk loci on chromosomes 10q26, 12q24 and 22q, while the other regions presently are being further investigated.

Saturday, 15 June 2002

15:30 - 17:00

S11 Antipsychotics: new treatment strategies

S11.1

Metabotropic glutamate receptors: potential new targets in psychopharmacology

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Glutamate is the major excitatory neurotransmitter in the central nervous system and produces its effects via interactions with two classes of receptors, ligand-gated ion channels (ionotropic, iGluR) and G-protein coupled receptors (metabotropic, mGluR). Despite the abundance of glutamate and its receptors in the brain, at present very few marketed drugs produce their therapeutic effects via glutamatergic mechanisms. Recent progress suggests that this will likely soon change. As an example, this lecture will review data, which point to a potential role for mGluR 2/3 receptor agonists in the treatment of anxiety disorders and of schizophrenia. Success in developing subtype selective agents for different metabotropic receptors raises the possibility that the field will soon be in a position to enter a 'post-monoamine' era in which there will be many opportunities to explore a variety of novel glutamate receptor based approaches to the treatment of psychiatric and neurological disorders.

S11.2

Functional antidopaminergic effects of muscarinic ligands

Anders Fink-Jensen

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Current antipsychotic compounds have dramatically improved the treatment of schizophrenia, but substantial efficacy limitations remain; therefore, the development of novel antipsychotic compounds with different

action mechanisms is needed. Acetylcholine is a neurotransmitter that binds to nicotinic receptors and muscarinic receptors. Muscarinic receptors are G protein-coupled receptors and five subtypes (m1-m5) have been cloned and sequenced. Muscarinic receptor antagonists can induce psychotic symptoms in healthy persons and exacerbate psychotic symptoms in schizophrenic patients, whereas selective muscarinic receptor ligands with partial agonist modes of action at m1/m4 receptor subtypes (xanomeline) or m2/m4 receptor subtypes (PTAC and BuTAC) exhibit antidopaminergic efficacy and antipsychotic potential in preclinical trials. In accordance with these results, it has been reported that the m1/m4 muscarinic receptor agonist xanomeline, as well as acetylcholinesterase inhibitors, improve both cognitive deficits and psychotic symptoms in Alzheimer's patients. Even though the basic pathologies of schizophrenia and Alzheimer's Disease are different, similarities in the pattern of regional brain dysfunction, symptomatology, and cognitive deficits exist, indicating that these compounds may also be efficacious in schizophrenic patients. In conclusion, muscarinic receptor partial agonists may be a novel pharmacological approach to the treatment of schizophrenia.

S11.3

Targeting AMPA receptors for the treatment of schizophrenia

Mo Shahid

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A substantial level of both clinical and animal data supports the concept of reduced ionotropic glutamate receptor function in the pathophysiology of schizophrenia. Consequently it has been argued that pharmacological upregulation of glutamatergic neurotransmission may have therapeutic utility in the treatment of this disease. Ampakines(r), a class of compounds that allosterically increase the functional activity of glutamate AMPA receptor subtype, have been shown to enhance central glutamatergic function. Evidence will be presented to show that Ampakines(r) display a psychopharmacology supportive of a novel approach for the therapy of schizophrenia.

S11.4

Development of GlyT1-selective glycine reuptake inhibitors

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Hypofunction of the NMDA system may underlie some symptoms in schizophrenia. Glycine is an obligatory co-agonist at the NMDA receptor complex. Raising extracellular glycine by inhibiting the glycine transporter 1 (GlyT1) could facilitate NMDA receptor activation and provide a novel therapy for schizophrenia. A new generation of potent and selective GlyT1 inhibitors have been identified with favourable CV safety, toxicity, and PK/PD properties. A series of collaborations helped characterise the properties of the series. Systemic administration results in GlyT1 occupation in brain (ex-vivo autoradiography) and an increase in extracellular glycine in rat PFC (in vivo microdialysis). GlyTI inhibitors enhanced the increase in NMDA dependent neuronal activity observed following, stimulation of the VTA. These effects were reversed by the non-competitive MK-801. Acute administration of GlyT1 inhibitors reduced hyperlocomotion seen in rats with a neonatal lesion of the ventral hippocampus, a neurodevelopmental model of schizophrenia, and in DA transporter knock-out (DAT-KO) mice. GlyT1 inhibitors are now being evaluated by development teams.

Saturday, 15 June 2002

17:00 - 18:30

SS04 Bipolar disorders - redefining treatment paradigms Sponsored By Eli Lilly

SS04.1

The spectrum of bipolar disorder or mood stabilization: the future?

Hagop S Akiskal, (USA)

Abstract was not available at the time of printing

SS04.2

The management of acute mania with atypical antipsychotics

Mauricio Tohen, (USA)

Abstract was not available at the time of printing

SS04.3

Treatment algorithms

Willem Nolen, (The Netherlands)

Abstract was not available at the time of printing

Sunday, 16 June 2002

09:00 - 10:00

S12 Basic mechanisms of ECT

S12.1

The neurobiology of ECT: the road ahead

Tom G Bolwig

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ECT has an anticonvulsant effect. This is evidenced by the fact that the seizure threshold increases over a series of ECT and has been shown to be necessary for the therapeutic effect of ECT. Animal studies have, m demonstrated that electroconvulsive seizures induce expression of immediate-early genes, followed after hours by an increased expression of genes for neuropeptide Y (NPY). The regions of particular relevance are the hippocampus, especially the gyrus dentatus, and a variety of cortical areas. NPY is highly effective in inhibiting epileptic seizures and must therefore be considered of relevance for the anticonvulsant effect of ECT. In humans patients undergoing ECT have been shown to have an increase in NPY in the cerebrospinal fluid. NPY thus has a role in the development and effectiveness of ECT. Recent studies further pointing to the role of the hippocampus are the demonstration of increased neurogenesis (formation of newborn cells) in the hippocampus following ECS. The neurogenesis has a dose ? response related pattern and show maintenance for extended periods of time. It is therefore not a transient phenomenon. Also suppression of neurogenesis via irradiation may be reversed by electrically induced seizures.

Conclusion: both the seizure-inhibiting effect of ECT especially in the hippocampus, and the finding of neurogenesis in that particular region give clues to an understanding of the working action of ECT in humans.

S12.2

ECT, Lithium and topiramate share the same target: the hippocampal neuropeptide Y system

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Although electroconvulsive therapy (ECT) has been in clinical use for more than 50 years, its therapeutic mechanism of action has not been identified. Specifically, our work has focused on the significance of neuropeptide Y (NPY), which was proposed to act as an endogenous anticonvulsant and also to play a role in the pathogenesis of affective disorders. We have investigated the state of NPY neurotransmission in brains from animal models of depression, e.g. maternally deprived animals and Flinders sensitive "depressed" rats and also investigated how ECT and other antidepressant or moodstabilising treatment modalities interact with the NPY system in these rats, compared to healthy rats. Our findings show that hippocampal NPY neurotransmission is compromised in 'depressed' rats and that both

ECT, lithium and Topiramate treatment tend to normalise this measure. Our results are in line with our hypothesis that (1) altered brain NPY plays a role in the pathogenesis of affective disorders, (2) one therapeutic effect of ECT is to enhance hippocampal NPY neurotransmission.

Supported by the Swedish Medical Research Council #10414, NAMI Research Institute-Stanley Foundation Bipolar Network, and Karolinska Institutet.

S12.3

Neuropeptide Y and seizures

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Neuropeptide Y (NPY) is a 36 aminoacid polypeptide which is abundantly and widely expressed in the CNS. The synthesis of NPY is prominently increased following seizures of various types, including electroconvulsive stimulation (ECS). This has been suggested to be a compensatory anti-seizure response. Consistent with this concept, exogenous NPY inhibits seizures in vitro and in vivo. Mice deficient in NPY develop more severe seizures than normal mice. Conversely, rats overexpressing NPY in the hippocampus are more resistant to seizures. Increased inhibition has been implicated in the therapeutic effect of ECS in psychiatric illness and, consequently, increased NPY synthesis induced by ECS might be involved in the working mechanism of ECS. Whether future NPY agonists might be useful in psychiatric diseases responsive to ECS remains to be studied. Epileptic seizures are another obvious potential therapeutic target for future NPY active drugs. NPY exerts its biological effects via at least 4 different receptors in the brain (Y1, Y2, Y4, Y5). At present, it is not clear what receptors are necessary for anti-epileptic effects. The Y5 receptor is one likely candidate. For instance, mice lacking Y5 receptors show no effect of NPY or Y5 agonists in vitro epilepsy models. In addition, peptides with selective affinity for Y5 receptors inhibit seizures in some in vivo models, including kainic acid induced seizures, and the selective Y5 receptor antagonist CGP71683A blocks the effect of NPY. In other epilepsy models there is also evidence for involvement of Y2 receptors. It will be important in future studies to determine the antiepileptic target receptors conclusively to allow the drug industry to develop potential new NPY agonistic drugs with anti-seizure effects.

Sunday, 16 June 2002
09:00 - 10:00
FC01 Neurophysiology

FC01.1

Deletion in the alpha7-like nicotinic receptor gene: a risk factor for p50 sensory gating deficit

Florence Thibaut, G Raux, E Houy, S Louchart, F Bonnet-Brilhault, M Petit, T Frebourg, D Campion
Service Hospitalo-Universitaire de Psychiatrie - CHU C. Nicolle et CH du Rouvray, Rouen, Unité INSERM EMI 9906. IFRMP - Université de Rouen - France

Abnormality in the P50 auditory-evoked potential gating is an endophenotype associated with schizophrenia. The alpha 7 nicotinic acetylcholine receptor (nAChR) is involved in this sensory gating deficit. Two related alpha 7 genes (CHRNA7 and CHRAN7-like) resulting from a partial duplication (from exon 5 to 10) are present in the human genome. Two types of variation, a large one and a -2 base-pair deletion in exon 6 may affect the CHRNA7-like gene. We developed a simple multiplex PCR assay on genomic DNA, allowing the quantification of the number of exons 6 and the distinction of all possible exons 6 genotypes. Genotyping of 70 schizophrenics (DSM IV) and 77 controls showed that carrying at least one -2 bp deletion of exon 6 did not constitute a risk factor for schizophrenia. In contrast, the distribution of genotypes differed significantly between subjects with normal and abnormal P50 ratios, with an over-representation of genotypes carrying at least one -2 bp deletion of exon 6 among subjects exhibiting an abnormal P50 ratio. We thus conclude that the -2 bp deletion within the CHRNA7-like gene may be risk factor for P50 sensory gating deficit.

FC01.2

No P50 gating defect in un-medicated schizophrenic patients

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Objective: With the purpose of comparing a new mixed modality paradigm with the P50 gating paradigm, the standard double click paradigm was examined in un-medicated patients.

Method: Subjects: 17 un-medicated, male, schizophrenia spectrum patients and 17 age-matched healthy men. Paired click stimuli were delivered with an inter stimulus interval of 500 ms and inter train interval of 8.5 s.

Results: The patients had a mean P50 gating (1-S2/S1 x 100) of 49% (std 27), a mean S1 (peak-to-peak amplitude) of 4.7 microV (std 2.6), and a S2 of 2.2 microV (std 1.2); the controls had a P50 gating of 51% (std 27), S1 of 4.0 microV (std 2.3) and S2 of 2.1 microV (std 1.7). The differences were not significant. No effect of diagnosis was found in r.m ANOVA of the N40, P50 and N100 amplitudes at the two stimulus conditions.

Conclusion: Only a few studies have examined un-medicated patients (drug-free period more than 1 month) and the sample sizes are small. Our results do not replicate the original finding of P50 gating defects in un-medicated patients and they do not support the P50 gating defect as a phenotype marker of schizophrenia.

FC01.3

N 100 aberrations in patients with prodromes of psychosis

Stephan Ruhrmann, A Brockhaus, I Tendolkar, A Wiencke, B Canata, R Pukrop, J Klosterkötter,
Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

Early recognition of psychosis in the prodromal state is one of the most important issues in schizophrenia research. To establish a valid prediction a multidimensional approach including neurobiological variables seems necessary. The N100 is of interest because this event related potential has shown to be decreased in schizophrenia. N100 was evoked by an auditory paradigm with standard and deviant sounds. Eleven prodromal patients, nine never medicated schizophrenia patients and 39 healthy controls were included in a first analysis. Recordings of Fz/F3/F4, Cz/C3/C4 were computed. Schizophrenia patients elicited significantly lower N100 amplitudes than controls. Across all electrode sites prodromal patients showed a constant 'in-between' pattern of amplitudes with marked smaller deflections than healthy controls and larger deflections than schizophrenia patients. Statistically, differences between the patient groups were not significant. Compared to controls there was a trend for lower amplitudes for prodromal patients in C4. The pattern observed in this preliminary analysis was in line with our expectations and may indicate that aberrations in neurophysiological information processing is already present in prodromal patients. Data will be presented based on a larger sample size.

FC01.4

Prepulse inhibition in patients with memory disorders

Anne-Mette Hejl¹, T Mackeprang², BY Glenthøj², G Waldemar¹

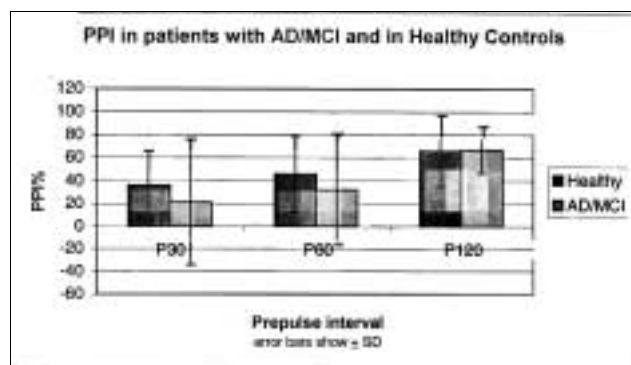
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The aim of this study was to identify possible disturbances of sensorimotor gating of the eye blink startle response in patients with mild Alzheimer's disease (AD) and in patients with Mild Cognitive Impairment (MCI). Prepulse inhibition (PPI) of the startle response, as an operational measure of sensorimotor gating was studied in 13 patients with AD, 18 patients with MCI, and 48 healthy controls. The startle-inducing stimulus was a 40 ms 115 dB burst presented alone or briefly after a pre-

pulse stimulus (85 dB noise burst, 20 ms in duration), at 30, 60, or 120 ms intervals.

No significant differences in PPI were observed between patients and healthy controls. However, the variation for the data of the interval of 30 ms was significantly higher for the AD/MCI group ($P=0.002$) compared to healthy controls. Furthermore, facilitation of the magnitude of the startle response was seen more often in AD/MCI patients than in healthy controls (29%/13%, NS). The explanation for the variation in PPI in patients with AD or MCI will have to await further investigations.



Sunday, 16 June 2002

09:00 - 10:00

FC02 Early and acute psychosis: symptoms and treatment

FC02.1

Opus-project: a randomised controlled trial of integrated psychiatric treatment in first-episode psychosis - clinical outcome improved

Merete Nordentoft, P Jeppesen, P Kassow, M Abel, L Petersen, A Thorup, T Cristensen, J Øhlenschläger, P Jørgensen, Bispebjerg Hospital, Psychiatric Department, Copenhagen NV, Denmark.

Objective: A two-site randomised controlled trial of integrated treatment of patients 18-45 years old with a first time diagnosis of schizophrenia spectrum disorder was conducted in Copenhagen and Aarhus, Denmark.

Method: The treatment consists of modified assertive community treatment, psycho-educational treatment in McFarlanes multifamily groups and social skills training. Inclusion of patients started 1 January 1998. After a three-year period, 600 patients were included in the study. Patients were assessed comprehensively (SCAN-interviews and other validated instruments) at baseline and at 12-month follow-up by independent researchers.

Results: One-year follow-up interviews with the first 341 patients were completed with 82 percent of the patients. At follow-up assessment significantly more patients allocated to psychosis team remained in treatment and expressed satisfaction with care as compared with patients in standard treatment. The integrated treatment improved both positive and negative symptoms more

than standard treatment after one year. The integrated treatment also demonstrated trends toward lesser time spent in hospital, more people stayed out of hospital, more people living independently and fewer homeless people. Significantly more patients in integrated treatment resumed education. Results of one-year follow-up of all 600 patients will be presented.

Conclusions: The integrated treatment improved core psychopathology and some domains of social functioning.

FC02.2

RCT of integrated psychiatric treatment versus standard treatment

Pia Jeppesen, M-B Abel, L Petersen, A Thorup, T Christensen, J Øhlenschläger, P Jørgensen, M Nordentoft H:S Bispebjerg Hospital, Psychiatric Department E, Copenhagen, Denmark

Objective: To examine whether improved compliance with drugs is associated with the effect of integrated psychiatric treatment (IT) on clinical symptoms in first-episode psychosis.

Method: A total of 582 patients with a first episode of schizophrenia spectrum disorder were randomised to IT or standard treatment (ST). IT consisted of assertive community treatment, antipsychotic medication, psychoeducational family treatment, and social skills training. Improvement in clinical symptoms (SAPS, SANS), used dosages of antipsychotics, and compliance with drugs (ROMI) was measured at one-year follow-up.

Results: Regarding the first 341 patients showed that patients in the IT group improved significantly more in positive and negative symptoms compared to patients in the ST group.

Conclusion: IT improved core psychopathology compared to ST. Results regarding the total cohort of 582 patients will be presented including the effect on medication compliance.

Declaration of interest: The Danish Ministry of Health, Danish Ministry of Social Affairs, Danish Medical Research Council, Copenhagen Hospital Corporation, and Aarhus County.

FC02.3

Duration of untreated psychosis in first episode psychosis

Merete Nordentoft, M-B Abel, P Jeppesen, L Petersen, A Thorup, J Øhlenschläger, T Christensen, P Jørgensen H:S Bispebjerg Hospital, Psychiatric Department E, Copenhagen, Denmark

Objective: International interest in early psychosis continues to grow rapidly in both clinical settings and in the research literature. In research there is controversy on key issues such as whether early intervention actually improves outcome.

Method: In the Danish OPUS project 582 patients first episode psychosis patients were included and interview-

ed at baseline with SCAN, SAPS, SANS, IRAOS, PAS and other validated instruments. Analyses of information from baseline and one year follow-up interviews with the first 341 patients will be presented. One-year follow-up interviews were conducted with 80 percent of the patients.

Results: Among young patients with first episode psychosis included in the OPUS project, duration of untreated psychosis was related to poor premorbid function, low global functioning, poor clinical outcome and loss of contact with relatives.

Conclusion: The ideal research design for testing the hypothesis of a positive effect of early detection and intervention is a randomised controlled trial, which cannot be conducted for ethical reasons. Studies using quasi-experimental design and natural studies indicate that early intervention can improve outcome in schizophrenia. Long duration of untreated psychosis is associated with social isolation and loss of social functioning.

FC02.4

Premorbid IQ and schizophrenia: increasing cognitive reduction by episodes

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² Department of Psychiatry, Lund University, Sweden

In order to test the hypothesis that acute schizophrenia episodes have a negative impact on cognitive function, 35 consecutive non-abuse schizophrenia outpatients (age < 60) were enrolled in this study. All subjects for whom grades from the 9th year of the Swedish school system were available, had to complete a comprehensive computerised neuropsychological test session. Symptoms were rated by PANSS and GAF, previous episodes were tallied, and medication was logged. A premorbid cognitive score was calculated on the basis of school characters and validated by comparison with academic career and current cognitive performance ($r = .56$). Half had college level studies or higher, and the overall school grades for the group were above average. PANSS (Sum = 59) and GAF (59) ratings as well as medication (M = 230 CPZ units) suggested a moderate symptom level. Two patients had no neuroleptic drugs, 16 had atypical and 17 had conventional neuroleptics. Vocabulary was intact. On average, patients had lost 1 standard deviation (SD) in most cognitive tests but response time slowing amounted to 3.5 SD. There were no differences in cognition between drug types and no correlation with CPZ dose. The number of previous episodes was positively correlated with reaction time prolongation and negatively correlated with short-term verbal memory, consistent with a previous study suggesting that acute episodes cause specific cognitive reduction.

Sunday, 16 June 2002

10:30 - 12:00

S13 Dopaminergic sensitization: the wind of psychotic fire

S13.1

Endogenous sensitization of dopamine systems in the pathophysiology of psychosis

Marc Laruelle, (USA)

Abstract was not available at the time of printing

S13.2

Brain derived neurotrophic factor triggers behavioural sensitization by controlling the responsiveness of dopaminergic neurons

Olivier Guillin, (France)

Abstract was not available at the time of printing

S13.3

Do patients with schizophrenia inherit a liability of dopamine function?

Jim van Os, (The Netherlands)

Abstract was not available at the time of printing

S13.4

The interaction between drug abuse and genetic predisposition in precipitating psychosis

Robin M Murray, (UK)

Abstract was not available at the time of printing

S13.5

Cognitive neuropsychiatric models of persecutory delusions

Nigel J Blackwood

Institute of Psychiatry, London, UK

People with persecutory delusions view ambiguous data in the social domain as self-relevant, jump to conclusions on the basis of insufficient information and attribute negative events to external personal causes. We present data from fMRI investigations of these social cognitive processes in subjects with active persecutory delusions. The potential contribution of dysregulated dopamine transmission to the documented abnormalities in the deluded state will be discussed.

Sunday, 16 June 2002

10:30 - 12:00

S14 Preclinical models of psychiatric diseases

Sponsored by Neurosearch

S14.1

The neurodevelopmental model of schizophrenia

BK Lipska, [Daniel R Weinberger](#)

National Institute of Mental Health, NIH, Bethesda, MD, USA

We studied in the rat the effects of neonatal damage to the hippocampus, a region implicated in schizophrenia. Excitotoxic lesions lead in adulthood to the emergence of abnormalities in dopamine related behaviors, enhanced sensitivity to glutamate antagonists, deficits in sensorimotor gating and latent inhibition, impaired social behaviors and working memory problems. Our molecular and electrophysiological data suggest that aberrant development of the prefrontal cortex in the context of early damage to the hippocampus may be a critical factor in the onset of the syndrome. Thus, neonatal damage to the hippocampus of the rat appears to reproduce a broad spectrum of aspects of schizophrenia. In this study, we hypothesized that transient inactivation of the ventral hippocampus with tetrodotoxin (TTX) early in development (PD7), with no discernable anatomical changes in the hippocampus, may be sufficient to disrupt normal maturation of brain regions relevant to schizophrenia. The overall characteristics of behavioral changes and their temporal pattern were reminiscent of the disturbances associated with the permanent lesion. Neonatally TTX-infused rats displayed in adulthood motor hyperactivity in response to stress, amphetamine and MK-801. Analogous TTX infusions in adult animals did not alter these behaviors. These data suggest that transient loss of ventral hippocampal function during a critical time in maturation of intra-cortical connections permanently changes development of neural circuits mediating certain dopamine- and NMDA-related behaviors. These results represent a potential new model of aspects of schizophrenia without a gross anatomical lesion.

S14.2

Prenatal methylazoxymethanol exposure as a model of schizophrenia

[Peter Flagstad](#), M Didriksen

H. Lundbeck A/S, Valby, Denmark

Recent work has shown that administration of MAM to rats at gestational day (GD) 17 results in anatomical abnormalities analogous to what is observed in the brains of schizophrenics. We have examined the consequences of such prenatal perturbation and found deviation in various behavioural and neurochemical measures. The MAM treated rats are slightly hyperactive in an open field test, reacts stronger to stress (saline injection) and psychotomimetics (amphetamine and PCP). In a forced swim paradigm, the MAM rats show escape behaviour

for a prolonged period of time and fail to exhibit adaptation, a behavioural deficit parallel to what is observed in rats with PFC deficits (e.g. DA depletion). The findings also include deficits in cognitive functions, both on prepulse inhibition and in a reversal learning paradigm. Aberrations in neurochemistry (dopamine, noradrenaline, serotonin and metabolites) are quantitatively small, but multivariate analysis shows a distinct pattern separating the MAM rats from the controls. Altogether the findings support the relevance of the model for schizophrenia research.

S14.3

Postnatal anoxia in rats as a new animal model of schizophrenia

[Karin Sandager-Nielsen](#)¹, [J Scheel-Krüger](#)¹, [MB Andersen](#)²

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The 'neurodevelopmental' hypothesis of schizophrenia states that an insult early in development may cause disturbances in cerebral function, which later on may give rise to onset or illness. Epidemiological studies have reported an association between lack of oxygen as a result of birth complications and development of schizophrenia in adult life. A putative new animal model has been developed where male rat pups are exposed to 6 minutes of anoxia on postnatal day 9. Postnatal anoxia resulted in impaired sensory gating, as measured by Pre-Pulse Inhibition. Furthermore, rats exposed to anoxia as pups displayed retarded acquisition of a DNMT test and impaired Object recognition. Finally, a significant negative correlation existed between prefrontal cortical N-acetylaspartate, a measure of neuronal integrity, and striatal dopamine activity, as measured by HVA. This correlation was not found in the sham group, indicating a dysfunctional regulation exerted by the prefrontal cortex on subcortical dopamine activity. Thus, exposing rat pups to anoxia may share some phenomenological similarities with the human symptomatology.

S14.4

Functional monoamine interactions in new models of depression

[Jørgen Scheel-Krüger](#), GM Olsen, P Weikop

Department of Behavioural Pharmacology and Microdialysis, NeuroSearch A/S, Ballerup, Denmark

PET studies have shown that depression may be associated with a reduced activity in medial prefrontal cortex (mPFC). The mPFC represent also a key structure by its afferent and efferent connections to brain structures associated with emotions, reward and stress: the amygdala, hippocampus and the hypothalamic-pituitary-adrenal system. The mPFC control impulsiveness and working memory within the emotional system. The monoaminergic systems show also several mutual interacti-

ons. These interactions have been studied in microdialysis in rats following administration of specific and mixed monoamine re-uptake inhibitors, including citalopram, venlafaxine. An important role was found by noradrenaline re-uptake after venlafaxine mediated by α_1 stimulatory and α_2 inhibitory receptors on serotonin release in hippocampus and dopamine, noradrenaline in mPFC. Hippocampal serotonin release is controlled by 5-HT_{1A} receptors. These results combined with the forced swimming test for antidepressant drugs underline the significance for neurotransmitter interactions for current antidepressant treatments.

Sunday, 16 June 2002

10:30 - 12:00

S15 Psychosis: differential diagnosis and biological tools

S15.1

Prevalence, diagnosis and treatment of bipolar depression

Hans-Jürgen Möller

Ludwig-Maximilians-University, Department of Psychiatry, München, Germany

Although the prevalence of psychotic depression is not very high and the diagnosis is very clearly described in traditional textbooks as well in the modern diagnostic algorithm of ICD-10 and DSM-IV, psychotic depression is a category of great clinical interest. It has to be questioned whether it is a clinically and biologically defined entity of its own, in comparison to non-psychotic depression, or whether it is only a certain special expression of a severe depression. Psychotic depression is an interesting bridge between affective disorders and non-affective paranoid hallucinatory psychosis, with schizo-affective psychosis possibly being in the middle of this bridge. Psychotic depression has to be subdivided into unipolar psychotic depression and bipolar psychotic depression, thus including the full spectrum of affective psychoses. From a clinical point of view, it is well known that psychotic depression does not respond as well to drug treatment as non-psychotic depression, and often leads to severely treatment refractory cases. Therefore from a treatment aspect, the presentation will especially focus on the combination of antidepressants with neuroleptics. Acute bipolar depression should be seen as a separate entity under diagnostic and treatment aspects, and should not be mixed up with unipolar depression. The suggestions of various guidelines and consensus papers, especially in US American and Canadian psychiatry, have a strong tendency against antidepressants in bipolar depression: they prefer monotherapy with mood stabilisers and, in the case of co-medication with mood stabilisers and antidepressants in severe depression, to withdraw the antidepressant as early as possible. The intention of this restrictive use is to avoid the risk of mania and of rapid cycling induced by antidepressants. However, the risk of suicidal aspects, which are as prominent in bipolar depression as in unipolar

depression, has apparently been widely neglected in the discussion of the optimal treatment regimen for bipolar depressive patients. Furthermore, the fact that most of the mood stabilisers have not proven their antidepressant efficacy in an adequate and sufficient way, while there is a large body of clinical experience on an equal efficacy of antidepressants in both unipolar and bipolar depression, leads to the problem of undertreatment of bipolar depression if only mood stabilisers are administered. This is not only related to the prolongation of the suffering of the depressed patient, but also to the risk of depression-related suicidal behaviour and of chronicity of depressive symptoms. The fact that the selective serotonin reuptake inhibitors, and possibly some other modern antidepressants, apparently have only a low risk of inducing a switch to mania should support the view that antidepressants still have their place in the treatment of acute bipolar depression. In co-medication with a mood stabiliser, therapy with a modern antidepressant seems to be a safe and effective therapy in bipolar depression. This position will be exemplified by the results of several studies on psychiatric inpatients treated in the Department of Psychiatry of the University of Munich as well as by data from studies being performed at the Munich centre of the Stanley Foundation.

S15.2

Bi-polar psychosis

Jose Luis Ayuso Gutierrez, (Spain)

Abstract was not available at the time of printing

S15.3

Schizophrenia

Wolfgang Fleischhacker, (Austria)

Abstract was not available at the time of printing

S15.4

Epileptic psychosis and its diagnosis by cerebral spect

Carlos Roberto Hojaj

The Melbourne Clinic, Australia

For some years now the Cerebral Spect has been presented as a tool that could indicate a brain anomaly (pathology or just a dysfunction). A correlation from data Spect and psychiatric disorders would be desirable in terms of diagnosis and progressing treatment. Among those psychiatric illnesses that could benefit from a Spect analysis the Epileptic Psychosis looks the more promising. Several studies show areas of hypoperfusion in temporal lobe (right and/or left). Many studies have been contradicted by negative results, not giving to the Spect the reliability is needed in Biological Psychiatry. Considering the high complexity of brain functioning and the multiple interactions between the neurosystems, more recent researches try to establish a correlation not with a specific disease, but with cluster of

symptoms (syndrome). In order to test Cerebral Spect as an objective tool for the diagnosis of Epileptic Psychosis (CID-10: Organic Personality Disorder: Limbic Epilepsy), 14 patients receiving such diagnosis were divided in two syndromic categories: a first one with predominantly mood features (simple partial seizures: consciousness not impaired and mood features), and a second one with consciousness disturbances and psychotic symptoms (complex partial seizures with impairment of consciousness and psychotic symptoms including automatisms). Just after the clinical diagnosis the patients were submitted to Cerebral Spect. The results are presented as well as a discussion on the validity of Cerebral Spect as a diagnostic tool in Biological Psychiatry.

Sunday, 16 June 2002
12:30 - 13:30

PL06

Schizophrenia: from hypofrontality to genetic causation

Daniel R Weinberger

National Institute of Mental Health, NIH, Bethesda, MD, USA

Studies of prefrontal neurocognition and functional neuroimaging of prefrontal information processing consistently reveal abnormalities in patients with schizophrenia. The earliest of these studies came from a landmark collaboration between Neils Lassen in Copenhagen and David Ingvar in Lund. Since their seminal observations of "hypofrontality" in patients with schizophrenia, numerous other reports of physiologic dysfunction of prefrontal cortex have appeared, and prefrontal dysfunction is taken as a constitutive manifestation of schizophrenia. Recently, abnormal prefrontal information processing has been associated with genetic risk for schizophrenia and has been the target phenotype for identifying the first genetic mechanism of susceptibility to this illness. Both the physiologic abnormalities and the cognitive deficits referable to prefrontal cortex are predicted by a cellular measure in dorsolateral prefrontal cortex (DLPFC) - low N-acetyl aspartate (NAA) signals from MR spectroscopy. In pharmacologic imaging studies, patients manifest excessive dopamine release induced by amphetamine, an abnormality also predicted by low NAA in DLPFC. These findings suggest that abnormal function of the working memory cortical system (associated with negative symptoms) and abnormal responsivity of dopaminergic neurons (associated with positive symptoms) represent emergent properties of specific DLPFC neuronal pathology. Abnormalities of prefrontal information processing also are found in unaffected individuals who are genetically at risk for schizophrenia, suggesting that genetic polymorphisms affecting prefrontal function may be susceptibility alleles for schizophrenia. One such candidate is a functional polymorphism in the COMT gene that markedly affects enzyme activity and

that appears to uniquely impact prefrontal dopamine. COMT genotype predicts performance on prefrontal executive cognition and working memory tasks. fMRI confirms that COMT genotype affects prefrontal physiology during working memory. Familybased association studies have revealed excessive transmission to schizophrenic offspring of the allele (val) related to poorer prefrontal function. These various data provide convergent evidence that the COMT val allele increases risk for schizophrenia by virtue of its effect on dopamine-mediated prefrontal information processing - the first plausible biologic mechanism by which a specific allele affects variation in normal human cognition and risk for mental illness.

Friday, 14 and Saturday, 15 June 2002
12:00 - 13:00

POSTER SESSIONS

P01 Affective disorder - clinical studies

P01.1

Reduced volumes of the habenular complex in depression

Karin Ranft, D Krell, P Danos, S Diekmann, B Bogerts, B Baumann, H-G Bernstein

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The habenulae are important relay nuclei linking the limbic forebrain to the midbrain and certain aminergic brain stem nuclei. Theoretical considerations and experiments with animals have led to the assumption that the habenular complex might be involved in psychiatric diseases (schizophrenia and depression). We examined habenular volumes in postmortem brains of 15 schizophrenics, 10 patients with depression and 15 matched controls. Furthermore, we counted the number of neurons in the medial habenular complex of 17 schizophrenics, 12 depressives and 15 controls. It was found that in depression the volume of the habenular complex is significantly reduced (by about 20%) in comparison to controls, whereas in schizophrenics the volume of this area did not differ from controls. Also, a reduction in the number of habenular neurons was revealed in depression. Hence, we identified the habenula as another brain region which shows pathomorphological alterations in depression.

Supported by Graduiertenkolleg of the DFG and Stanley-Foundation.

P01.2

Actual tendencies in the use of mood stabilizers in an Spanish sample of bipolar patients

Carlos López Conesa, V Fabregat Navarro, R López Velasco, C Ventura Fuentes, M Bel Villar

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Objective: Evaluation of the use of mood stabilizer drugs for bipolar outpatients.

Method: Retrospective assessment (years 1999 and 2000) of case-histories for a sample of 69 bipolar outpatients, using DSMIV criteria, performed in a Spanish mental health center.

Results: 1) 87% of the patients have received lithium at some point in her illness, and 13% have never received lithium. 2) 62% were on lithium at the moment of our examination, and 38% were on anticonvulsants. 3) 62% were controlled on mood stabilizer monotherapy, and 38% on polytherapy.

Conclusions: 1) Lithium therapy is still the first line treatment for bipolar disorder, as seen in other European studies. 2) the use of anticonvulsants is the second option and is only used as first line treatment in a very short group of patients (13%). This is a major difference with USA where anticonvulsants are increasingly used as a first line treatment. 3) the combination of mood stabilizer drugs in 38% of the patients is less than in other studies, but is a reliable option despite the risk of more adverse effects and less compliance.

References: Robert M. Post, M.D.; Mark A. Frye, M.D.; Kirk D. Denicoff, M.D. Beyond lithium in the treatment of bipolar illness. *Neuro-psychopharmacology*. 19:206-219, 1998.

P01.3

Bright light therapy as an antidepressant modality

Giuseppe Tavormina

Studio di Psichiatria, Provaglio di Iseo, Italy

Background: Bright light therapy (L.T.) is the recommended treatment for SAD; in addition, L.T. have new applications, as an antidepressant modality.

Materials & methods: Eight patients between 26 and 51 years old (three of these patients were pregnant) were included in this naturalistic study about L.T., with the following diagnosis (meeting the DSM-IV diagnostic criteria): Major Depression, Recurrent Depression, PAD, Depression in Bipolar Spectrum, Social Phobia, Bulimia crisis. The following rating scales were adopted in determining the effect of the L.T.: the 'HAM-A' for PAD; the 'Zung SDS' for all type of depressions; the 'LSPS' for social phobia; the 'BS' for bulimia crisis. Three between not-pregnant began the L.T. as add-on therapy to drugs because their symptoms was not well controlled.

Results: All the patients obtained very good results (the rating scales presented a final score clear-cut). Any treatment-emergent adverse events were not reported.

Conclusions: In this naturalistic study L.T. confirmed its efficacy with several new applications, and above all its tolerability and safety for all patients but especially during pregnancy.

P01.4

Venlafaxine utilization in mood disorders with resistant depressive symptoms.

Giuseppe Tavormina

Studio di Psichiatria, Provaglio di Iseo, Italy

Objective: To assess clinical efficacy, and also tolerability, of Venlafaxine in mood disorders with resistant depressive symptoms, administered to patients with an only partial clinical results with others antidepressant (switching from them).

Materials & methods: A total of 13 outpatients were included in this open-label, naturalistic study, meeting the DSM-IV diagnostic criteria for Major Depression and Depression in Bipolar Disorders. These patients, all taking others antidepressants (AD), did not reach a satisfactory mood balance after a valuation of at least ten weeks of therapy. The rating scales 'Zung SDS' and 'GAS' were adopted in determining the effects of their therapy, before and after the ten weeks of therapy with the others AD, and before and after six weeks of Venlafaxine treatment. Tolerability was assessed, during clinical interviews, by registering treatment-emergent adverse events.

Results: Very good results were obtained, put in evidence by the rating scales. Only two patients needed to stop the therapy after ten days for side effects (nausea; tenseness).

Conclusions: In this naturalistic study, despite the methodological limitations, Venlafaxine demonstrated its considerable efficacy vs. others antidepressants for remission of resistant depressive symptoms.

P01.5

Mood or anxious diseases of the significant others of patients with mood or anxious diseases

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² Consultant of Psychiatric Rehabilitation Center - Sarnico (BG - Italy)

³ Social Service Office for Minors - Bologna (Italy)

⁴ Centro Studi Psicologi Associati - Roma (Italy)

Background: All the Significant Others (S.O.) of 264 adult patients with mood and anxious spectrum disorders have been taken into consideration in this multi-centre, naturalistic, statistical, study; with the aim to value in what percentage the same diseases could be present in the S.O. of the patients.

Methods: The respective S.O. of these patients have been valued, for the same diagnosis and diagnostic criteria, as our knowledge of them becoming from patients' clinical interviews or others reliable data.

Results: The data obtained merits must be noted: the 44% of the patients chose own S.O. with a similar disease; only the 14% chose own S.O. with any mental disease. The 13% of the patients did not have any S.O. and in the 27% he cases the health of S.O. was unknown.

Conclusions: All the S.O. of the patients in this study presented with high percentage a similar disease to the

patients. All that could suggest to us to take into a consideration, for a preventive aim, to counsel the patients to assess of own partner's mental health status. Furthermore, eventual studies could demonstrate if the disease of S.O. would precede couple life or instead begin from a difficult interpersonal relation.

P01.6

Pindolol and the acceleration of the antidepressant response

Per Plenge, ET Møllerup

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Background: It has been suggested that treatment with selective serotonin reuptake inhibitors (SSRIs) in combination with pindolol, a partial agonist at the 5-HT_{1A} receptor, may produce a fast antidepressant response. However, inconsistent results have been obtained in clinical studies with combination of the two drugs. Some studies, most using paroxetine, show an acceleration of the antidepressant response whereas studies with other SSRIs find no marked latency reduction.

Methods: Five different SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are present in use. In patients either receiving a first dose of SSRI, or in steady state treatment with the drugs, the free SSRI concentration in plasma was estimated using pharmacokinetic data for the individual drugs. Results: The SSRIs all inhibit 5-HT uptake with marked selectivity, although the drugs are quite different in chemical structure. Due to this, the drugs differ markedly regarding protein binding, distribution volume and affinity for the 5-HT transporter (5-HTT). The 5-HT uptake inhibition obtained with clinically relevant doses therefore differs markedly among the SSRIs, both regarding onset of effect and in the steady state situation. A table showing the 5-HTT-blockade obtained both after the first dose of SSRI and in the steady state situation will be shown in the poster. Conclusions: To accelerate the antidepressant response of SSRI drugs with pindolol it is a prerequisite that the 5-HT reuptake is strongly inhibited in the 5-HT projection areas as early as possible after onset of treatment. Only paroxetine (and venlafaxine) are able to fulfil this condition already after the first dose, probably explaining why only studies using paroxetine, consistently have found an accelerating effect of pindolol.

Friday, 14 and Saturday, 15 June 2002

12:00 - 13:00

P02 Psychopharmacology - animal experiments

P02.1

Repeated administration of the neurotensin analogue NT69L induces tolerance to its suppressant effect on conditioned avoidance behaviour

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Although acute neurotensin receptor stimulation exerts diverse behavioural effects that resemble those seen after administration of antipsychotic drugs, data on effects after repeated exposure to neurotensin receptor agonism is relatively sparse. In the present study, we investigated potential antipsychotic-like effects of acute and repeated administration of NT69L, a novel neurotensin(8-13) analogue with CNS-penetrating ability. In similarity with the classical antipsychotic drug haloperidol, NT69L dose-dependently (0.08 - 0.31 mg/kg, s.c.) suppressed conditioned avoidance responding (CAR), a pre-clinical assay with a high predictive validity for antipsychotic activity. However, repeated treatment with NT69L (0.08 - 0.31 mg/kg, s.c., twice daily for 7 days) completely abolished its effect on this behaviour. In contrast, the suppressant effect of haloperidol on CAR was still present after up to 21 days of daily treatment (0.04 - 0.16 mg/kg, s.c.). These findings clearly support the notion that acute neurotensin receptor stimulation induces antipsychotic-like effects. However, the present results also suggest that this beneficial antipsychotic-like effect of neurotensin receptor stimulation may be abolished, or at least profoundly reduced, after repeated exposure to neurotensin receptor agonists.

P02.2

Anti-psychotic profile of the A_{2A} receptor agonist CGS 21680 in monkeys

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It has been hypothesised that the adenosine A_{2A} receptor agonist CGS 21680 may have a potential as an antipsychotic with an atypical profile. Studies in rats have shown effects of CGS 21680 very similar to those of clozapine. The aim of the present study was to explore the antipsychotic potential and side effect profile of CGS 21680 in a non-human primate. Apomorphine-induced arousal in *Cebus apella* monkeys was used as a model for psychosis. The monkeys have been sensitised to extrapyramidal side effects (EPS) corresponding to EPS liability of antipsychotics in the clinic. CGS 21680 significantly decreased apomorphine-induced arousal in doses of 0.01, 0.025 and 0.05 mg/kg. No EPS were observed, neither when CGS 21680 was administered alone nor when it was administered in combination with apomorphine. At 0.05 mg/kg CGS 21680 produced vomiting and slight sedation when administered alone while the two lower doses did not produce side effects. In conclusion CGS 21680 showed an antipsychotic effect in an apomorphine-model in *Cebus apella* monkeys with no production of EPS suggesting an atypical antipsychotic profile of adenosine A_{2A} receptor agonists.

P02.3

The M1/M4 agonist xanomeline inhibits amphetamine behavior in monkeys

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³ Neuroscience Research Division, Eli Lilly Research Laboratories, Indiana, USA

Xanomeline is a muscarinic M1/M4 preferring receptor agonist with little or no affinity for dopamine receptors. The compound exhibits an antipsychotic-like profile in rodents without inducing extrapyramidal side effects (EPS) at therapeutically relevant doses and reduces psychotic-like symptoms in patients with Alzheimer's disease. In the present study, we investigated the effects of xanomeline on behavior induced by d-amphetamine and apomorphine in *Cebus apella* monkeys. Xanomeline inhibited d-amphetamine-induced motor unrest, stereotypies and arousal as well as apomorphine-induced stereotypies and arousal in drug naive *Cebus apella* monkeys. Xanomeline did not induce EPS but caused sedation and emesis in some monkeys at high doses. In EPS-sensitized *Cebus apella* monkeys, xanomeline did not produce EPS at the dose range used in the dopamine agonist study (0.5-3.0 mg/kg). When xanomeline was tested at 4.0 mg/kg, moderate dystonia was seen in two out of three monkeys.

In conclusion, xanomeline inhibits d-amphetamine- and apomorphine-induced behavior in *Cebus apella* monkeys at doses that do not cause EPS. These data further substantiate that partial muscarinic receptor agonists may serve as a new tool in the pharmacological treatment of psychosis.

P02.4

Dopamine D3 receptor and tardive dyskinesia in a highly susceptible non-human primate

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Tardive dyskinesia (TD) is a severe adverse effect of traditional neuroleptics, which occurs in 20% of schizophrenic patients. Susceptibility to TD and other extrapyramidal symptoms (EPS) seems to be a genuine genetic trait, but the underlying mechanisms are unknown. Knockout of the D3 dopamine receptor (DRD3) in mice produces locomotor disturbances mimicking EPS and in humans the ser/gly polymorphism in position 9 of the DRD3 gene has been associated with TD. *Cebus apella* monkeys are at least five times more susceptible to EPS than humans and readily develop syndromes very similar to acute and tardive dyskinesia in humans making these monkeys the favored animal model to study EPS. We assessed whether the postulated human trait/genotype association between

high susceptibility to TD and the gly9 DRD3 allele can be supported by sequencing and comparing the DRD3 gene of *Cebus apella* to that of humans and other species. We found that *Cebus* monkeys are monomorphic with respect to gly9 supporting the notion of an association between this allele and liability to TD. We furthermore identified additional amino acids potentially implicated in susceptibility to TD.

P02.5

Lack of spermine effect on d-cycloserine activity in scopolamine learning impairment in rats

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Department of Pharmacology, K Marcinkowski University of Medical Sciences in Poznan, Poland

NMDA receptor agonists such as glycine (GLY) and a selective and partial agonist at the GLY binding site D-cycloserine (CS) has been shown to enhance the performance of spatial learning in rats. Furthermore CS was effective in reversing the scopolamine (SCO)-induced learning deficits of rats. The present study was designed to evaluate the effects of activation of the GLY and polyamine (PA) sites of the NMDA receptor on SCO-induced (5 mg/kg, i.p.) memory deficits of rats in radial maze. Spermine (SPM) (5 mg/kg, i.p.) was used as a PA site ligand of the NMDA receptor. Prior to maze task male Wistar rats received i.p. injections of saline (SAL), SAL+SCO, SCO+SPM, SCO+CS (30 mg/kg, i.p.) or combination SCO+CS+SPM. The number of arm choices, running times and choice latencies were analysed. The administration of SCO+CS significantly attenuated the all parameters of SCO-induced maze learning impairment. The combine treatment with SCO+CS+SPM did not change the effect produced by SCO+CS leading to control values. Concluding, it can be assumed that GLY-modulation of the NMDA receptor site is involved in facilitation the learning tasks after following systemic application of SCO, however the exact role of PA in these processes needs further studies.

P02.6

Effect of dopamin D3 receptor ligands on locomotor activity in rodents

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Regarding the role of the dopamine D3 receptor in the regulation of motor activity of rodents it is hypothesized that its stimulation or blockade leads to hypo- or hypermotility, respectively. We compared the effects of D3 antagonists with various selectivity over D2 receptors on motor activity in mice and rats. Locomotion was measured in photocell activity cages during 30 min periods. U-99194A (5-10-20 mg/kg sc.) caused robust hypermotility in both species, SB-277011 showed stronger effects

in mice (15-22.5-30-45 mg/kg p.o.) than in rats (13.5-20-30 mg/kg p.o.). The actions of nafadotride (0.1-0.3-1-3 mg/kg ip.) differed even more sharply: it caused hypomotility in mice, while in rats it slightly increased the motor activity. The agonist compounds 7-OH-DPAT and PD-128907 decreased the motor activity in rodents at the dose of 0.1 mg/kg sc. However, only U-99194A inhibited the hypomotility induced by either agonist; nafadotride and the more selective antagonist SB-277011 were ineffective.

The results suggest that agonist-induced hypomotility may not be a D3 receptor mediated response, nevertheless, the D3 receptor may play a role in the hypermotility evoked by the antagonist compounds.

P02.7

5-HT_{1A} agonist and D₂/D₃ antagonist activities confer on SSR181507 atypical antipsychotic profile with additional anxiolytic/antidepressant properties

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SSR181507, a D₂/D₃ antagonist and 5-HT_{1A} agonist, was shown to be active in schizophrenia models (active avoidance and apomorphine-induced climbing in mice, d-amphetamine-induced hyperlocomotion in rats). However, it did not produce catalepsy, and blocked haloperidol-induced catalepsy in rats: this was likely due to its 5-HT_{1A} activity, as co-administration with SL88.0338 (selective 5-HT_{1A} blocker) produced catalepsy, and reversed anticataleptic effects. SSR181507 behaved as a partial 5-HT_{1A} agonist, producing minimal serotonergic syndrome (forepaw treading in rats), and greatly attenuating the 8-OH-DPAT syndrome. These data suggest that, in the clinic, SSR181507 should possess antipsychotic activity in the absence of extrapyramidal signs. SSR181507 was also active in anxiety/disinhibition and depression models: it disrupted passive avoidance in a step-down procedure, reduced separation-induced vocalisation in guinea pig pups, and delayed the onset of paradoxical sleep. SL88.0338 antagonised these effects, demonstrating a role for 5-HT_{1A} receptors. The present results suggest that in addition to its atypical antipsychotic activity, SSR181507 should also display anxiolytic/ disinhibitory and antidepressant activities.

P02.8

Antidepressant drug effects on monoamines in prefrontal cortex and hippocampus

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The medial prefrontal cortex (mPFC) and the hippocampus represent important structures involved in depressive disorders and also substrates for the monoaminergic systems activated by current anti-depressant

drugs. The monoaminergic effects after venlafaxine and citalopram were studied in rats by microdialysis probes located within the mPFC and hippocampus. Venlafaxine inhibits reuptake of 5-hydroxytryptamine (5-HT) and noradrenaline (NE). Citalopram is a specific 5-HT inhibitor. In agreement with previous studies was found a mutual interaction between the monoamines within the mPFC. The effect of venlafaxine on NE was found induced by α_1 stimulatory and α_2 inhibitory receptors influencing not only extracellular NE release but also dopamine (DA) and 5-HT release within the mPFC. The systemic administration of the α_2 antagonist idazoxan (1.5 mg/kg) given in combination with venlafaxine (10 mg/kg) induced thus a further enhancement of NE, DA and 5-HT release. Idazoxane induced a substantial increase of the venlafaxine effect on NE in the hippocampus and also enhancement on 5-HT and DA. Citalopram induced a specific increase of 5-HT within mPFC and hippocampus without major changes on NE and 5-HT. These findings together with effects of 5HT_{1A} and α_1 blockade after WAY 100635 and prazosin will be discussed, since the chronic treatments with antidepressant of various classes induce an α_2 , 5HT_{1A} receptor down regulation favouring an α_1 stimulation of the monoamines.

**Friday, 14 and Saturday, 15 June 2002
12:00 - 13:00**

P03 Schizophrenia - clinical studies

P03.1

EEG reactivity during mental tasks in schizophrenic families

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Objective: To assess whether EEG reactivity indices may serve as markers of genetic liability to schizophrenia.

Method: EEG recordings were obtained from 57 schizophrenic patients, 72 their parents, 44 siblings, and 47 control subjects in rest condition and while performing verbal, arithmetic and spatial tasks. Task-related changes of EEG power in five frequency bands were calculated as follows: (task - rest)/rest.

Results: The patients showed more deviations from controls during the arithmetic and spatial tasks, while their relatives had the most prominent abnormalities during the verbal task. When performing the verbal task, there were augmented depression of alpha-activity over both hemispheres in siblings and that of beta activity in parents. Besides, the patients and relatives groups showed the increase in theta power in the right anterior regions during this task. During the spatial task the patients and parents had augmented delta power in temporal areas, more on the right, and mental arithmetic evoked similar changes in the left frontal region.

Conclusions: The increase in reactivity over the right frontotemporal area during verbal task may be associated with genetic liability to schizophrenia.

P03.2

Glutamate dehydrogenase immunoreactivity in platelets in schizophrenia

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Glutamate dehydrogenase (GDH) immunoreactivity has been revealed in human platelets using polyclonal antibodies raised against human brain readily soluble GDH isoform. The GDH immunoreactivity level was evaluated by ECL-immunoblotting in protein fraction of platelets from controls and patients with schizophrenia. Patients with schizophrenia diagnosed by ICD-10 (F20.x 1, F20.x 2, F20.x 3) with PANSS total score not less than 60 were included (total PANSS score- 95,6±14, PANSS positive subscale-18,6±5,8, PANSS negative subscale-29,6±5,7, PANSS general psychopathology subscale-47,4±3,3). The GDH immunoreactivity level was found to be significantly higher in patient group (n = 23) than in control group (n = 22), (p<0.01). This finding is in consistent with recent discovery that GDH immunoreactivity level is elevated in frontal cortex of postmortem brain in schizophrenia. GDH immunoreactivity level may be a useful marker of glutamatergic system status in patients with schizophrenia. Supported by the Theodore and Vada Stanley Foundation, USA.

P03.3

Decreased volume of the anterior internal capsule in schizophrenia

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Objectives: To clarify the structural correlates of abnormal fronto-thalamic connectivity hypothesized in schizophrenia, volumes of the anterior limb of the internal capsule, which connects the thalamic nuclei with the prefrontal cortex, were measured.

Methods: 53 patients with schizophrenia and 48 healthy comparison subjects were studied. Informed consent was obtained from all subjects. High-resolution 3-dimensional MRI was acquired and volumes of anterior parts of the internal capsule, caudate nucleus, and lentiform nucleus were measured. In addition, white matter concentration was compared using the voxel-based morphometry (VBM).

Results: Compared to the controls, the patients had significantly decreased volumes in the bilateral anterior internal capsule, although volumes of the caudate or lentiform nuclei were not different between the groups. VBM also revealed reduction in white matter concentration of the bilateral internal capsule in the patients.

Conclusions: The volume reduction found in the anterior internal capsule further supports the hypothesis of abnormal fronto-thalamic connectivity in schizophrenia.

P03.4

Mismatch negativity deficits in prodromal and schizophrenia patients

Anke Brockhaus-Dumke, S Ruhrmann, I Tendolkar, A Wieneke, B Canata, R Pukrop, J Klosterkötter, Department of Psychiatry, University of Cologne, Germany

We investigated auditory working memory in schizophrenia patients, persons at risk to develop a psychosis (prodromal patients) and healthy controls. The mismatch negativity (MMN) was recorded using an auditory 3-tone oddball paradigm with frequency and duration deviants. In this preliminary investigation, 20 prodromal (25,9 years ± 5,7; 14 male) and 20 schizophrenia patients (30,6 years ± 7,9; 14 male) were included. MMN for frequency deviants were lowest in schizophrenia patients (Fz: -2,4 m ± 1,3) and highest in healthy controls (Fz: -2,9 m ± 1,0), but these differences did not reach statistical significance. MMN for duration deviants were lowest in prodromal patients (Fz: -2,1 m ± 1,5) and highest in healthy controls (Fz: -3,3 m ± 1,9). Differences between patients and controls reached statistical significance, whereas differences between schizophrenia and prodromal patients did not. These results indicate that already in prodromal patients the MMN as a measure for auditory processing is disturbed as it is shown in schizophrenia patients. Thus, the MMN may be a promising parameter in the early diagnosis of patients suspected to develop schizophrenia.

P03.5

Shared constructs in tests of executive functioning in schizophrenia

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We investigated the potential overlap of two widely used tests of executive functioning in a group of patients with schizophrenia. Both the Stroop test and the Wisconsin Card Sorting Test (WCST) require the ability to inhibit an established response in order to produce a more adaptive strategy as the task demands change. Thirty-eight patients with schizophrenia participated in this study. The Stroop Word-Color condition correlated with the number of categories achieved, conceptual level responses, percentage of correct responses and percentage of perseverative errors on the WCST. Similarly, the Stroop Color condition correlated significantly with the percentage of correct responses on the WCST, as well as the percentage of perseverative errors. Neither the Stroop Word condition, nor the interference score was significantly related to any of the WCST variables. Clinical status (as assessed by the PANSS general score) was related to Stroop, but not WCST performance. These results confirm our hypothesis of a common cognitive process with respect to response inhibition on the two tasks, and also suggest a role of visuo-perceptual skills.

P03.6

Schizophrenia with onset in childhood, adolescence and adulthood

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Aim: To assess prodromal phase and personal/family history of schizophrenics patients with respect to the age of illness onset.

Method: We studied three groups of patients with schizophrenia or psychotic disorder NOS (DSM-III-R or DSM-IV): 16 patients with age of onset <13 years, 38 with onset between 14-17 years, and 12 with onset >18 years. We retrospectively examined the duration and type of their prodromal symptoms, their developmental history and the difficulties presented in their childhood. Obstetric complications, birth weight, gestational age and family history were also assessed.

Results: No differences were found among the three groups regarding family history and obstetric complications. Patients with childhood onset schizophrenia presented more developmental difficulties. The onset in this group was found to be marginally more insidious, with a prolonged prodromal phase. Content analysis also revealed differences in the type of prodromal symptoms among the groups, but similar difficulties in patients' childhood (i.e., adjustment difficulties, poor social skills, oppositional behavior and separation anxiety).

Conclusion: Adolescence and adulthood onset schizophrenia patients appear to share several features in common, but they are quite different from those with childhood onset schizophrenia.

P03.7

Cognitive functions and insight into illness in schizophrenic patients

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The aim of the study was to evaluate cognitive functions of schizophrenic patients and their associations with the insight into illness and course and severity of schizophrenia. Methods: Thirty six inpatients with schizophrenia (18 male, 18 female, mean age 40,9 years) were studied. Neuropsychological tests (Trail Making Test - TMT, Stroop Test, Digit Span and Auditory Verbal Learning Test) were performed. Insight into Illness Scale (IIS) consisting of six items scored 1-3 points was used. Severity of illness (PANSS), intensity of depression (HDRS) and quality of life (WHO Bref) were also evaluated. Control group consisted of 31 (10 male, 21 female, mean age 35,9 years). Results: Only 16 patients (44,4%) scored 9 or less in the IIS. Patients performed significantly worse than controls in all neuropsychological tests, their quality of life was significantly lower. Good insight was associated with better memory tests results and lower positive symptoms intensity. IIS scores

did not correlate with TMT and Stroop test results. Conclusions: Our results confirm the presence of cognitive deficits and frequent insight disturbances in schizophrenia and point to the need of further investigations in this area.

P03.8

Attention disorder in schizophrenia: the role of the parietal lobes

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Objectives: This study analyse the neuroanatomical bases of sustained attention with cognitive task which required the subjects two different types of information processing: automatic and controlled.

Methods: Participants were eleven naive patients with Schizophrenia and ten healthy volunteers. All underwent medical screening, psychiatric interview, neurocognitive evaluation, and neuroimaging exam. The experimental design included four conditions: rest, auditory stimulation by external presentation of clicks (1 per second), and two counting tasks. First, subjects were instructed to mentally count the auditory clicks, and secondly to count forward at an estimated frequency of 1 per second (time estimation). Relative cerebral blood flow (relCBF) was measured by means of PET 15O-water. Results and Conclusions

Results: in this investigation suggest that patients with Schizophrenia activate similar cerebral regions to normals for simple attentional tasks which require automatic processing. However, during controlled tasks requiring additional cognitive effort (working memory and time estimation), the pattern of activation in patients differs with significant less activation in anterior cingulate gyrus, dorsolateral prefrontal cortex, and inferior parietal cortex. Additionally, patients major engaged inferior frontal cortex during the same tasks. The hypofrontality hypothesis and a cognitive compensatory model will be discussed.

Literature References: 1. Carter CS, Mintum M, Nichols T, Cohen JD (1997): Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia: [15O]H2OPET study during single-trial Stroop task performance. Am J Psychiatry December 154(12):1670-1675. 2. Cohen RM, Nordahl TE, Semple WE, Andreasen P, Pickar D (1998): Abnormalities in the Distributed network of sustained attention predict neuroleptic treatment response in Schizophrenia. Neuropsychopharmacology 19(1):36-47.

P03.9

Brain structure: association with the striatal dopamine in schizophrenia

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Even if data are controversial brain structure alterations in schizophrenic patients are discussed in the etiology of the disease. Generally, frontal and temporal changes can be found in post-mortem or in-vivo MRT imaging studies. New metabolic studies with SPECT revealed a dysfunction of the striatal dopaminergic system. The basic level of the dopamine content in the striatal dopaminergic synapse seems to be elevated in schizophrenic patients compared to healthy controls. The aim of our study was to combine the analysis of structural alterations and striatal dopaminergic metabolism in first-episode never treated schizophrenic patients. We used structural MRT and a simultaneous SPECT of the striatal dopaminergic D2-receptor and dopamine transporter (DAT) in 15 drug-naïve inpatients with a diagnosis of schizophrenia according to DSM IV/ICD-10 criteria. Patients got a structural MRT and a combined protocol for a 99mTc-TRODAT-1 / 123I-IBZM-SPECT. Data were analysed according to routines established in our laboratory. Correlations of different brain regions and D2-receptor and DAT binding were calculated and compared to a group of age and gender matched healthy controls. The TRODAT-1 binding to the DAT was significantly reduced in the patient group. A significant inverse correlation was found between the TRODAT-1 binding to the striatal DAT and the volume of left and right ventricle.

P03.10

Treatment-resistant schizophrenia

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The introduction of antipsychotic drugs into clinical practice remains one of the major advances in twentieth century medicine. The efficacy of neuroleptic drugs in both the acute and long-term treatment of schizophrenia has been established in numerous double-blind, placebo-controlled trials. The care of people with schizophrenia that has failed to respond to conventional antipsychotic medication remains a formidable challenge. However the introduction of some new atypical antipsychotic agents, such as: clozapine, olanzapine, seroquel, risperidone heralded a new optimism in this area and prompted an increase in research interest in the pharmacotherapeutic options for such patients. These atypical antipsychotic drugs consistently fail to produce a satisfactory response in a proportion of patients with schizophrenia.

References: 1. Brenner HD, Dencker SJ: Defining treatment refractoriness in schizophrenia, Sch.Bull., 16:355-62 1990. 2. Hirsch SR, Barnes TRE: Clinical use of atypical new antipsychotic neuroleptics, Compr. Psych., 9:633-43,1998.

P03.11

Dissociation of item and context memory in schizophrenia

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We investigated the episodic memory for temporal context information in schizophrenics compared to healthy controls electrophysiologically. Event-related brain potentials (ERPs) were recorded as subjects made recency judgements to word pairs. These pairs were composed of two previously studied words drawn from each of two study lists, ('Old+Old'), one old and one new word ('Old+New'), or two unstudied words ('New+New'). Both groups performed recency judgements at well above chance levels with patients being less accurate. Over left temporoparietal cortex, ERPs to 'Old+Old' and 'Old+New' pairs were more positive-going than those to 'New+New' items. This old/new effect was apparent prefrontally only between 'Old+Old' and 'New+New' pairs. It took a frontopolar maximum in controls, but was lateralized to the right in schizophrenia patients suggesting a different recruitment of the underlying neural generators. Moreover, both old/new memory effects, possibly reflecting neural activity from either prefrontal or mediotemporal regions, were aborted some 300 ms earlier in the patient group. Our findings suggest that schizophrenia patients exhibit a disturbed episodic memory retrieval possibly mediated by the medial temporal lobe which in turn led to impaired, prefrontally based working memory operations involved in the processing of context information.

P03.12

Interhemispheric transfer in schizophrenic patients: evidence of a left hemisphere impairment?

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Background: There is evidence that schizophrenic patients have an abnormal corpus callosum and an abnormal pattern of cerebral asymmetries. We have investigated whether there are corresponding functional abnormalities in callosal interhemispheric transfer (IT) and laterality effects.

Method: 26 medicated schizophrenic patients and 20 matched controls have been tested in a manual simple reaction time (RT) paradigm, i.e. the so called Poffenberger paradigm (Marzi et al., 1999) which consists in a simple unimanual RT task with small unstructured visual stimuli tachistoscopically presented either to the right or to the left visual hemifield. When hemifield of stimulus presentation and hand used for response are on the same side (uncrossed condition) an IT is not required and RT is on average quicker than in the crossed condition in which hemifield and hand lie on opposite sides. This is because in the latter condition the centres receiving the stimuli and those which emit the response are situated on different hemispheres and a callosal extra-step is needed. By subtracting the averaged RT of the uncrossed conditions from the RT of the crossed conditions one obtains an estimate of IT time (Marzi et al., 1991).

Results: IT time was not measurable because of an unexpectedly slow RT to stimuli that had to be processed intra-hemispherically by the left hemisphere, i.e., in the uncrossed right field / right hand condition.

Conclusions: These results demonstrate the existence in medicated schizophrenic patients of a consistent slowing down of visuomotor responses subserved by the left hemisphere. As a general conclusion, the main thrust of the present study is that it extends the evidence for a left hemisphere impairment in schizophrenic patients to a tasks requiring a simple response to unstructured light stimuli.

References: Marzi C.A. (1999): the Poffenberger paradigm: a first simple, behavioural tool to study interhemispheric transmission in humans. *Brain Research Bulletin*, 50: 421-422.

P03.13

Prenatal exposure to analgesics and increased risk of schizophrenia

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Background: We hypothesised a link between prenatal exposure to analgesics and increased risk of schizophrenia

Methods: The relation between second-trimester exposure to analgesics and risk of schizophrenia was examined in 7590 individuals from The Copenhagen Perinatal Cohort born between 1959 and 1961 and followed through The Danish National Psychiatric Register through end of 1999. We used multiple logistic regression analyse to calculate odds-ratio for schizophrenia in exposed and un-exposed.

Findings: Second-trimester exposure to analgesics conferred a significantly elevated risk (odds ratio 4.06 [95

% CI from 1.6-10.2]. The effect was independent of gender and was not attenuated with the inclusion of potential confounders (parental psychiatric morbidity, social status, pregnancy complication scores). Differential effects of pharmacological substances could not be evaluated as mixtures containing several active substances were common. However, tentative data indicate that obsolete substances (for instance pyrazolon derivatives) could have accounted for some of the observed effect.

Conclusion: These findings suggest that analgesic consumption during second trimester of pregnancy is associated with increased offspring risk of schizophrenia (possibly 'sporadic' cases). The study raises concern that subtle developmental disruptions might be associated with second-trimester exposure to certain analgesic substances

P03.14

Brain structure/symptom correlations in first-episode psychosis

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In-vivo imaging studies have consistently found structural brain abnormalities in schizophrenic patients as compared to controls. Results of studies investigating the relationship between brain structure and clinical symptomatology have been less consistent. The present magnetic resonance imaging (MRI) study correlated clinical symptom severity to gray matter volume in 47 patients experiencing their first psychotic episode: 22 females, 25 males, mean age = 20.9 years (SD = 6.3, range = 10-37 years, median = 18.2 year). Patients were diagnosed according ICD-10 criteria: F20, schizophrenia (n = 39); F21 schizotypia (n = 5); F22, paranoid psychosis (n = 1); F28, other non-organic psychosis (n = 2). Clinical symptomatology was registered using the SAPS and SANS. Three-dimensional high-resolution MR-scans of the brain were acquired on a 1.5 Tesla scanner for volumetric analysis. Voxel based morphometry was used to statistical test for gray matter volume/symptom correlations throughout the brain (e.g. voxel by voxel). In this group of mainly first episode schizophrenia patients smaller right (and left) posterior superior temporal gray matter volumes were related to increased severity of overall positive symptoms and specifically disorganized behavior.

P03.15

Polyunsaturated fatty acids involved in schizophrenia modulate neuronal receptor function

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A number of psychiatric diseases are associated with a change in brain lipid composition. Schizophrenia has thus been associated with a decreased amount of polyunsaturated fatty acids (PUFAs) in the brain. Further, epidemiological studies, as well as double blind treatment studies, suggest that the outcome of schizophrenia depends on the amount of PUFAs in the diet. As PUFAs modulate the function of numerous membrane proteins, including GABA channels and dopamine receptors, also in systems where specific interactions have not been shown, we examined whether the effects could be due to changes in the mechanical properties of cellular membranes. A conformational change in a membrane protein that involves a deformation of the surrounding cell membrane will be regulated by changes in the membrane mechanical properties. We show that PUFAs alter the mechanical properties of the plasma membrane of living cells. We further show that other structurally very different compounds that alter cell membrane mechanical properties can mimic the effects of PUFAs on the GABA(A) channel, an abundant and typical neuronal membrane protein. The results suggest that the effects of PUFAs in psychiatric diseases can be due to changes in mechanical properties of cellular membranes.

P03.16

Acute effects of antipsychotics and diazepam on prepulse inhibition of the startle response in healthy human volunteers¹

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Prepulse inhibition (PPI) of the startle response is an informative widely used cross-species operational measure of sensory gating. Dopamine (DA) agonist-induced disruption of PPI is a valid preclinical model for prediction of antipsychotic efficacy, since only clinically effective antipsychotics are able to restore the deficit. N-methyl-D-aspartate (NMDA) antagonist-induced disruption of PPI has, on the other hand, been used to differentiate drugs with an atypical antipsychotic profile from typical compounds, since atypical antipsychotics in contrast to typical antipsychotics are able to reverse the deficit. Whereas a large number of preclinical studies have examined the effects of antipsychotics and other agents on PPI, clinical data are scarce. We have recently in the first longitudinal within-group study on the effects antipsychotics on PPI disturbances in drug-naïve schizophrenia patients failed to demonstrate any effect of chronic antipsychotic treatment. The few existing clinical data on the acute effects of antipsychotics on PPI in healthy humans are contradictory, but generally fail to find any influence. Further clinical studies on the effects of drugs used in the treatment of schizophrenia patients on PPI are needed both to clarify the correspondence between pharmacological effects on PPI in humans and animals, and to examine the effect of these compounds on PPI in the clinic. To meet these problems we studied the effects of different doses of a typi-

cal (zuclopenthixol) and two atypical (risperidone and olanzapine) antipsychotic drugs and of diazepam on PPI in humans.

Methods: Placebo or 2 different doses of risperidone (0.5 mg or 3.0 mg), olanzapine (2.5 mg or 7.5 mg), zuclopenthixol (2 mg or 8 mg), or diazepam (2.5 mg or 5.0 mg) were administered to healthy humans prior to PPI testing.

Results: No significant drug-effects on PPI were observed in any of the treatment groups.

Conclusions: Neither typical, nor atypical antipsychotics or diazepam influenced PPI following acute administration. The different compounds could, however, be differentiated as regards the effects on amplitudes, habituation, and latencies to onset or peak. Future studies must clarify whether the observed differences have any clinical implications.

¹ The study was sponsored by H:S (Copenhagen Hospital Cooperation) Research Council, Copenhagen University Hospital, Bispebjerg, and the Novo Nordic Foundation. MSc Peter Allerup is thanked for assistance in carrying out the statistical analyses

**Friday, 14 and Saturday, 15 June 2002
12:00 - 13:00**

P04 Psychosis - psychopathology

P04.1

Auditive commandatory hallucinations and suicide attempt

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Objective: Determine the frequency of auditory commandatory hallucinations of auto-elimination in recent suicide attempters and establish violence of suicidal method.

Methods: Prospective assessment of patients with recent suicide attempt in respective Program (June-Dec.2001) taking into account demographic aspects and clinical diagnoses according DSM-IV criteria, as well as hallucinatory component (sub-scale 3 PANSS), specifically auditory commandatory for self-elimination, also considering suicidal violence method (ICD- 1 O-OMS).

Results: OF 213 suicide attempters evaluated: 55 males (25.8) and 158 females (74.2), aged between 18 to 80 years old (x:37.5 years); DSM-IV principal diagnoses were: Major Depression Disorder(38.0), Schizophrenia and other psychotic disorders (16.4), Dystimic disorder (15.9), adjustment disorder with depressive symptoms (15.9), others (13.6). Auto-elimination auditory commandatory hallucinations were registered in 39 patients (33.6), with diagnoses of Schizophrenia and other psychotic disorders (60.0), and Major Depressive Disorder with psychotic symptoms (22.2), respectively. About self-harm methods, violent ones were reported in 21 patients (S3.8), while non-violent ones in 18 patients (46.2).

Conclusions: It was not infrequent finding auto-elimination

nation auditory commendatory hallucinations in recent suicide attempters, which seem to be associated to violent methods amongst them. Authors recommend careful assessment of these suicidal components for convenient decisions and adequate handle.

P04.2

Prevalence of psychopathology in medical students at local, private university

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Objective: To establish the prevalence of psychological disorders in medical students from all years of study at local private university for having a profile of mental disease and formulate some recommendations.

Methods: It was a transversal study, as a part of an annual health examination, during summer of 1997, using an instrument Initial Format Assessment and diagnostic criteria for International Classification of Diseases - Chapter V (ICD-10) (Mental World Health - 1989) applied to medical students of a private university in Lima ('Cayetano Heredia') by an equipment of psychiatrists.

Results: It was found any ICD-10 disorder in 80 students of 795, it is to say: 10. 1 psychopathological disorders were more frequent in male than in female students (M/F relationship 2.1/1.0). At first ranked affective disorders with 30.0; second, adaptive disorders: 22.5, followed by personality disorders: 20.0, nearly anxiety disorders: 18.8, then psychotic disorders: 2.5, and finally other disorders: 6.3. Sex affectation was variable for each group of disorders. A seven year of medical school training showed next: anxiety disorders - mostly social phobia - were more frequent amongst student of three first years; students from fourth to seven year presented more frequently affective disorders: in students of fifth year were equally frequent affective and adaptive disorders, while in students of sixth year it was registered a great percentage of personality disorders. Also, it was noticed excessive drinking and smoking as well as academic and vocational problems amongst others.

Conclusion: These findings showed a panoramic scope of psychopathology in medical students and their mental health affectation, which could serve for appropriate and opportune management but also to call attention from university authorities to formulate policies and programs for early detection of mental disturbances and best for their prevention.

P04.3

Mathematical models of diagnostic tactics in psychiatry

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The aim of the research is to identify patterns according to which the diagnosis of mental patients is conducted. As the initial basis of our research the PANSS scale has been applied. The first seven characteristics were

used. This scale was modified so that apart from giving each characteristic its corresponding grade the doctor should analyze the importance scale of this characteristic in the final diagnosis of a patient. The range of this parameter varies within 0 (minimum) to 10 (maximum). We were mainly interested not so much in the importance of the characteristics per se, as in the ways they indicate different tactics of the process of diagnostics. To this end we have made an attempt to build mathematical models of diagnostic tactics in psychiatry. The latter require quantifiable parameters that a) are unique for every doctor and b) represent the pattern of the diagnosis. On this basis new criteria identifying the diagnostic tactics applied by doctors have been formulated. The following criteria were identified: A. Caution/recklessness. This is a static criterion. It is calculated as a normalized sum of correlations between the grade and its importance. A low value of this parameter is interpreted as recklessness. B. Flexibility/rigidity. This criterion is a dynamic one. The parameter is computed as the mean (average) sum of absolute values of differences between the importance embracing all patients. The low value of this parameter is interpreted (indicates) as rigidity. C. Experience/lack of experience. This parameter is also a dynamic one, and it is calculated as an average correlation coefficient between vectors of importance, where each vector corresponds to the importance of characteristics of different patients.

P04.4

Schizophrenia and affective psychoses: symptom distinction in acute episodes

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Objective: A century after introduction of concept of schizophrenia (SCZ), its distinction from affective psychosis (AFF) still remains controversial. The aim of this naturalistic study was to further clarify the differences of symptom pattern between these disorders in acute episodes.

Methods: This was a cross-sectional study of 365 consecutive emergency cases, diagnosed as SCZ or AFF by two different psychiatrists. The presenting symptoms were assessed using a validated checklist. One factor analysis and two logistic regression analyses were performed to determine the discriminative power of individual symptoms, gender and age.

Results: The analyses yielded an eleven item model with 81.1% correct classification rate (Sensitivity = 80.7%, Specificity = 81.4%, Likelihood Ratio = 4.3). The items with the greatest discriminative power were bizarre delusion and gender for SCZ, euphoric or depressed mood and grandiose delusion for AFF.

Conclusions: It appears that affective symptoms are primarily responsible for diagnostic distinction between these two disorders. Similar psychotic symptom pattern is clearly the weaknesses of the diagnostic specificity of SCZ. This suggests a need for a newer and more specific concept of SCZ.

Friday, 14 and Saturday, 15 June 2002

12:00 - 13:00

P05 Ageing, dementia

P05.1

Apolipoprotein E e4 in patients with Alzheimer's disease in Slovak population

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Many studies have found high frequency of Apo E4 in patients with Alzheimer's disease (AD). Our previous studies have found the Apo E4 frequency in very small per cent of these patients (1) In this study we have extended the number of patients.

Methods: Study of 34 patients, all subjects met the ICD-10 criteria for AD. Complete urine exam, biochemic exam of blood, complex hematological exam, cortisol, lipidogram, and hormones of thyroid gland were investigated too. The polymorphism of Apo-E E4 allele was investigated by polymerase chain reaction and digestion with Hae II and Alf III.

Results: The apo E3 allele was found in 55,9 % of all patients, and apo E4 was found in 44,1% of all patients.

Conclusion: The frequency of apo E4 allele was found in 44 % of all patients which is more than in our previous study was found.

P05.2

Accelerated neuropsychological aging of caucasus migrants

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In the series of clinico-biological and neuropsychological studies, involving 3,500 native (Azerbaijanians) and migrant (Russians) population of the Caucasus, we found that the Russian migrants (first and eleventh generations) had an accelerated type of CNS aging in comparison with native people and the Russians living in Russia. The onset of age-related changes in the neuropsychological activity (memory decline, emotional dysfunctions, depressive-hypochondriac state, reduced brain electrogenesis) occurred 5-6 years earlier in the Caucasian Russians compared to native population. The prevalence of various forms of senile dementia was 2 to 3 times higher in Russian migrants. In the latter, the structure of correlations between CNS functioning and neurohumoral regulation indices (noradrenalin, adrenalin, aldosterone, cortisol, and renin contents of the blood) was changed. The type of firm correlations was being formed, that suggested the narrowing of an adaptational range and determined the increase of risk for developing neuropsychological disturbances in the Russian ethnic group.

P05.3

Nervous system aging: national-ethnic features

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We have analyzed age changes of the CNS in two ethnic groups (Russians and Tatars), residing in the Crimea: 950 persons of Russian nationality and 820 persons of Tatar nationality, aged 25 to 85, by using EEG, ultrasound dopplerography of head vessels, Hamilton scale, neuropsychological profile. The onset of CNS age changes (decrease of alpha rhythm frequency, reduction of volumetric blood flow) in the Tatar group was registered 10-15 years later than in the Russian group. At 60-74 years, the frequency of depression among Tatars was 5.2%, among Russians 18%, and Alzheimer frequency among people aged 80 years and over was 3% and 10%, respectively. The slowed type of aging and low frequency of nervous-psychic diseases among Crimean Tatars are explained by the combination of favourable social-environmental (rational nutrition, high physical activity, preservation of national traditions) and genetic factors (extravert personality type, EEG constitutional types).

Friday, 14 and Saturday, 15 June 2002

12:00 - 13:00

P06 Non-Psychotic disorders

P06.1

Adolescent's posttraumatic disorder (PTSD), comorbid panic disorder (PD) and topiromate efficacy

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Child And Adolescent Psychiatry, Kyiv, Ukraine

Objective: Preliminary findings suggest that topiromate is effective in PTSD. However, as over 40% of adolescent with PTSD have comorbid PD and/or depression.

Methods: Inclusion criteria: primary DSM-III-R diagnosis of panic disorder, with or without agoraphobia, 4 or more panic attacks in the 4 weeks prior to screen evaluation; minimum score 18 on the HARM - D and/or HARM - A. Studies utilized a flexible dosing regimen (50 - 100 mg/day). Key efficacy measures included the change from baseline in the CAPS - 2 total score and CGI responder analyses. Presence of baseline comorbid disorder was determined using the HARM - D and HARM - A.

Results: The reduction in the CAPS - 2 total score observed with topiromate was statistically significantly greater than that seen with sertraline at week 10 endpoint (treatment difference - 10.40; 95%; CL - 13.4, - 7.38; P<0,001). A statistically significantly greater proportion of topiromate - treated patients (50%) than placebo treated patients (10%) were defined as treatment responders based on the CGI (much or very much improved) [adjusted odds ratio = 2.30; 95%; CI 1.77, - 2.97; P<0,001].

Conclusions: Topiromate is effective and well tolerated in treatment of PTSD, comorbid PD and/or depressive.

P06.2

Refugees and migrants with social-stress disorders in Moscow

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Since 1994 the therapist and psychotherapist began to act in 'Civic Assistance' Committee (CCA - the first Russian public charity organization which assists to refugees and forced migrants) with the aim to improve the refugees' somatic and mental health and promote their psychosocial rehabilitation. The analysis over 3500 refugees from Chechnya Abkhazia, Tadjikistan is present. In most cases (91%)-the refugees were from Chechnya: married women (very rarely their husbands) in ages 20-60 years with 3-5 children. The other(9%)-refugees of both sexes in ages 40-70 years from the rest of mentioned regions. All of them voluntary asked for psychological help. It was shown that: 12% of refugees suffered from predisease reactions with emotional tension and different psycho-somatic disorders(somatoform, hypochondrical, vegetative dysfunctions); 18%-consequences of affective-shock reactions(in anamnesis) with neurotic states and psychosomatic disorders (above mentioned and chronic somatoform algal disorders); 31%-psycho-adaptive states with neurasthenical, hysterical, anxiolical reactions and all spectrum of psychosomatic disorders; 39%-pathological personality development with the most pronounced psychosomatic disorders. All above mentioned groups of patients nosologically were determined as Social-Stress Disorders (SSD). The different kind of treatment of refugees with mental disorders will be present.

P06.3

Using olanzapine in non psychotic disorders

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Purpose: we want to show our experience in the use of olanzapine in this kind of patients.

Method: we describe the shape of patient to hom we have prescribed olanzapine for a reason different from a psychotic disorder. All of them were attending our psychiatric consulting room for outpatients, and were the consecutive ones that fulfil the criteria for the present study in 18 months.

Results: ten were the patients in our study with next diagnoses: 4 personality disorders which dropped out the treatment in a few days; 3 somatoform disorders which had a great improvement, and 3 patients had anxiety which experimented a slight improvement.

Conclusions: Olanzapine has shown to be usefull in low doses for treating some no psychotic disorders as somatoform disorders which patients had good results

and for anxiety disorders the results were not so good; for personality disorders we dont know it efficacy yet all patients dropped out medication or got lost. No side effects were reported.

P06.4

Psychiatric care for somatic patients in General Hospital

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For last 3 years 4685 General Hospital' patients with different psychosomatic and somatogenic mental disorders were consulted and treated (45,3% men, 54,7% woman) in Department of psychiatry and psychotherapy. 71% of the patients were suffered from the different psychosomatic disorders and 29% - from psychotic disorders. All these patients were suffered from the following somatic disorders: ischemic disease of heart, hypertonia, bronchial asthma, ulcer of stomach, discirculatory encephalopathy, paralytic stroke, different organic diseases of brain, severe burns, surgical operations, struma, pathology of pregnancy, adnexitis, acute somatogenic psychosis. In somatic patients with disorders of psychotic level the persons with psychoorganic syndromes, vessels and senile dementia were predominantly (57,6% cases from all psychotic disorders). In somatic patients with comorbid disorders of non-psychotic level (borderline level) there were predominantly the persons with neurosis-like disorders connected with distress and somatoform disorders(43,1%). The results of psychopharmacotherapy of the General Hospital' patients with mental disorders will be discussed.

P06.5

Neurobiological measures of OCD

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Previous studies have pointed to both the basal ganglia and frontal cortex being involved in the development of obsessive-compulsive symptoms. 20 OCD patients fulfilling DSM-IV criteria for OCD were studied using 18-fluorodcoxyglucose PET scans and quantitative EEG (QEEG). The patients were studied before and after a 12-20 weeks treatment with paroxetine. The patients were followed with clinical monitoring at no specific especially behavioural psychotherapy. Using the Y-BOCS scale we measured severity of symptoms before and after treatment. The patients were studied with PET and QEEG either the same day or with a few days interval. Clinical results: The Y-BOCS score dropped from 30 to 13 and this drop in symptom severity was strongly correlated to a drop in the glucose metabolism in a

number of regions most significantly in the right caudate nucleus and also to some extent in the dorsolateral prefrontal cortex and the anterior singulum. QEEG showed that the patients before treatment had significantly increased activity in the frontal region, and this activity, which was significantly increased compared to a normalised database dropped towards normalisation following treatment. Using these different approaches we were able to substantiate the concept of a disturbance in the frontothalamic circuit activity of which may be voluntarily modified in a normal persons whereas no such modification takes place in untreated OCD. As the effects of paroxetine were striking the serotonin which connections within the frontostriatal thalamic circuit is hypothesised to be a main pathophysiological factor for the development and maintenance of obsessive-compulsive symptomatology.

Friday, 14 and Saturday, 15 June 2002
12:00 - 13:00
P07 Late Abstracts

P07.1

A new treatment paradigm in seasonal affective disorder

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The objective of this study was to evaluate, in patients with Seasonal Affective Disorder (SAD), the remission rate of short-term bright light treatment, followed by citalopram treatment in a double-blind randomised study. Bright light treatment was given for 2 hours each morning for 7 days with careful supervision. Responders to light treatment (a 50% reduction of depression severity), were randomised to citalopram or placebo treatment in a 15 week follow-up period. Non-responders were randomised accordingly. Results showed a response rate of 62.4% and a remission rate of 54%, after one week of light treatment. Remission rates for light responders in the citalopram group increased to 88.1% and remission rates for light non-responders in the citalopram group increased to 80.0%. The overall remission rates at endpoint (15 weeks) for the citalopram groups were 85.0% compared to the 66.7% for the placebo groups ($p < 0.01$). In conclusion, this treatment paradigm yielded a large remission rate for the citalopram groups and represents an alternative treatment option for SAD patients not inclined to light treatment for the whole season.

P07.2

The activation pattern during confirmed rem sleep dreaming

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Object: To characterize the activation pattern during rapid eye movement (REM) sleep with confirmed dreaming.

Method: Positron emission tomography (PET) measures of the distribution of regional cerebral blood flow (rCBF) using repetitive injections of O15-labelled water during polysomnographically verified REM sleep and wakefulness. Dreaming was confirmed immediately after each scan. Successful PET measurements were obtained in 7 subjects in a total of 26 REM sleep dreaming and 15 awake measurements. Images were analyzed using statistical parametric mapping (SPM99).

Results: The most prominent activation during REM sleep dreaming was in the Pons. Other areas involved Limbic structures (the Anterior Cingulate Gyri, the Amygdalae, the Parahippocampal Gyri); and cortical areas (the Superior Temporal Gyri, the Superior Pre-and post-central Gyri, the right Fusiform gyrus). Relative deactivation included the Dorsolateral and Ventrolateral Prefrontal cortices, The Precuneus, and the Inferior Parietal Lobes.

Discussion: The activation and deactivation patterns correlate with well-known dream phenomenology and previous animal experiments. Limbic structures determine the emotional narrative relying on remote memory content, efferent ponto-cortical projections determine sensori-motor, auditory, and visual hallucinations, while the fronto-parietal deactivation is responsible for "negative" symptomatology such as lack of insight, judgement, emotional and volitional control, and orientation. Given that all subjects reported vivid visual dream content it is surprising that a larger part of visual cortex was not activated.

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