# ROBERT SOMMER RESEARCH SOCIETY

*Non-profit society for the advancement of research at the*
*Centre for Psychiatry*
*Justus Liebig University School of Medicine*
*Giessen, Germany, EU*


# *ROBERT SOMMER AWARD SYMPOSIUM*

# *2008*

# Robert Sommer Award Symposium

**7th and 8th of November, 2008**

## Abstract Book

**Robert Sommer Research Society**
**Am Steg 28**
**35385 Giessen**

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# INFORMATIONS ABOUT THE CONFERENCE

## Organiser:

Robert Sommer Research Society
Non-profit society for the advancement of research
at the Centre for Psychiatry
Justus Liebig University School of Medicine
Chairman: Prof. B. Gallhofer, M.D., Ph.D.

Adress:
Am Steg 22
35385 Giessen
Germany

## Conference Secretariat:

E. Bauer, Dipl.-Psych.
N. Baer, Dipl.-Psych.
E-Mail: rsrs@psychiat.med.uni-giessen.de
Phone: 0049-641 9945782 or 0049-641 9945776

## Venue:

Friday, 7th November
Centre for Psychiatry
Main Lecture Theatre, Main Building
Am Steg 22
Giessen

Saturday, 8th November
Arnsburg Monastery
35423 Lich

# PROGRAMME
## Friday, 7-11-2008
Centre for Psychiatry

**7.30 Morning Coffee Reception**

**8.00 Welcome**
Welcome address by the patron of the conference
Volker Bouffier esq., Home Secretary of the State of Hesse
OB Haumann, Mayor of Giessen
Stefan Hormuth, President, University of Giessen
Prof. Dr. Manfred Kaps, Vice Dean, University School of Medicine, Giessen

**9.00 *Award Ceremony***
Presentation of the Robert Sommer Award Medal

**9.30 Laudatio: Robin Murray**

**9:45 Laureates' lecture: Shitij Kapur, London**
How antipsychotics work - from receptors to response

**10.30 B r e a k**

**10.40 Morning Session, Chair: Andreas Meyer-Lindenberg**
10.45 Lars Farde
High resolution PET-imaging of dopaminergic biomarkers in relation to cognitive functioning
11.10 Birte Glenthøj
Psychophysiological and cognitive disturbances in antipsychotic-naïve first-episode schizophrenia patients: Relation to dopamine activity
11.35 Robin Murray
Risk Factors for Psychosis: All Roads lead to Dopamine

**12.00 L u n c h B r e a k and P o s t e r S e s s i o n s**
Session 1: Neurotransmitter + Genetics
Session 2: Social Cognition
Session 3: Attention, Gating + Working Memory
Session 4: Reward / Clinical Aspects

## Friday, 7-11-2008
Centre for Psychiatry

**14.30 Afternoon Session I, Chair: Lars Farde**

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Dopamine as incentive: origin of the concept and its role in language and psychosis

15.00 Henrik Walter
Investigating the dopamine hypothesis of schizophrenia with fMRI

15.25 Torgny Svensson
Modes of action of atypical antipsychotic drugs

**15.50 B r e a k**

**16.00 Afternoon Session II, Chair: t.b.a.**

16.05 Chris Frith and Uta Frith
Salience of social stimuli in autism spectrum disorders

16.30 Gebhard Sammer
Neuroimaging of Salience

16.55 Veena Kumari
Neural Correlates and Predictors of Response to Cognitive Behavioural Therapy in Schizophrenia

**17.20 B r e a k**

**17.30 Evening Session, Chair: Torgny Svensson**

17.35 Peter Kirsch
Dopaminergic modulation of reward processing – relations to schizophrenia

18.00 Graham Murray
Learning and motivation in psychosis

**20.00 Dinner Party and Concert at the Arnsburg Monastery**

## Saturday, 8-11-2008

Arnsburg Monastery

**8.15 Morning Session, Chair: Uta and Chris Frith**

8.20 Marcella Rietschel
Common and rare variants in schizophrenia & bipolar disorder

8.45 Tilo Kircher
Effects of Schizophrenia Risk Genes on Brain and Behaviour

9.10 Peter Liddle
The role of oscillations in recruiting the brain for mental processing in schizophrenia

**9.35 B r e a k**

**9.45 Lecture I, Chair: Tim Crow**

Paul Fletcher
Can associative learning models help us to understand the neurobiology delusional beliefs?

**10.30 Lecture II, Chair: Shitij Kapur**

Nancy Andreassen
Progressive Neural Change in Schizophrenia: Does Dopamine Blockade Play a Role?

**11.15 Lecture III, chari: Robin Murray**

Andreas Meyer-Lindenberg:
Neural mechanisms of genetic risk for schizophrenia linked to dopamine signal transmission

**12.00 Presentation of the Poster Awards**

Chair: Petra Netter (speaker of the Poster Award Committee)
Awards will be presented by the Laureate

**12.15 B r e a k**

**13.00 Debate over Lunch, Chair: Bernd Gallhofer**

Topic: The Future of Schizophrenia research is...?
Statements: Nancy Andreassen, Shitij Kapur, Torgny Svensson, Robin Murray

## POSTER ABSTRACTS

**Session 1: Neurotransmitters + Genetics**
**Session 2: Social Cognition**
**Session 3: Attention, Gating + Working Memory**
**Session 4: Reward / Clinical Aspects**

# SESSION 1: NEUROTRANSMITTER + GENETICS

## Genetic analysis of complexin2 – a putative schizophrenia modifier gene

Sabrina Klaus[1], Martin Begemann[1], Sergi Papiol[2], Heidi Friedrichs[1], Katja Ribbe[1], Fritz Benseler[3], Kerstin Reim[3], Joachim Riggert[4], Nils Brose[3], and Hannelore Ehrenreich[1]

[1]Division of Clinical Neuroscience, [2]Department of Neurogenetics, and [3]Department of Molecular Neurobiology, Max Planck Institute of Experimental Medicine, and [4]Department of Transfusion Medicine, Georg August University, Göttingen

Altered expression levels of complexin2 (CPLX2) with consequent deficits in synaptic transmission were suggested to contribute to etiopathogenesis of schizophrenia. Systematic transcriptome analyses of post mortem brain tissue showed decreased mRNA and protein levels of CPLX2 in different brain areas[a]. Published genetic studies from Japan[b] and Korea[c] are contradictory in respect to the role of CPLX2 in schizophrenia. In the present study, sequencing of the coding region of CPLX2 was performed in a large cohort of living schizophrenic patients (GRAS) and healthy controls (N > 1000 per group). Furthermore the 5´ region was analyzed by genotyping of selected SNPs covering this area. Individual SNP analyses showed no differences in the genotypic/ allelic frequencies between patients and controls as well as a lack of gender differences. Further analyses showed three haplotypic blocks with high LD within the CPLX2 gene (87.4 kbp); in the second one we found a significant difference in the distribution of a low-frequency haplotype (defined by SNPs rs1366116 and rs3892909) between cases (2.27 %) and controls (0.90 %) ($p = 0.00069$). This data suggest a small but robust contribution of this gene to the risk of developing schizophrenia. Comprehensive phenotype-genotype analysis based on the GRAS data collection (>3000 data points per patient) might help to define biological subgroups with a potential disease modifier role of CPLX2.

References

[a] Eastwood and Harrison 2005, Sawada et al., 2005
[b] Kishi et al., 2005
[c] Lee et al., 2005

## Dysbindin 1 single nucleotide polymorphismus (SNP) rs 1018381 correlates with cerebral activation in bilateral middle frontal gyrus during working memory task in healthy individuals

Valentin Markov, Axel Krug, Sören Krach, Andreas Jansen, Tony Stöcker, N. Jon Shah, Thomas Eggermann, Klaus Zerres, Jens Treutlein, Marcella Rietschel, Tilo Kircher

Background: Since Straub et al. (2002) implicated an association between genetic variants in dysbindin 1 and schizophrenia numerous studies have reported evidence supporting this association in worldwide populations (Williams et al. 2005). Particularly the minor allele of the dysbindin 1 SNP rs 1018381 is associated with cognitive impairments in patients with schizophrenia and healthy individuals (Burdick et al.2006). Working memory is a part of cognitive domain showing deficits in schizophrenia (Lee and Park 2005). The aim of the present study was to investigate the influence of the dysbindin 1 SNP rs 1018381 on cerebral correlates during working memory task in healthy subjects.
Methods: A sample of 57 healthy volunteers was genotyped for SNP rs 1018381 status. Functional images were measured by use of echo-planar-imaging on a 3T Siemens-scanner. Working memory was assessed by means of the 2-back version of the Continuous Performance Test (CPT). In the fMRI analysis, working memory was modelled as the 2-back condition minus the 0-back condition. The SNP rs 1018381 carrier status was determined and correlated with working memory performance and brain activation.
Results: While there were no effects on performance, risk-allele carriers (N=22) exhibited significantly greater activations of the bilateral middle frontal gyrus (BA 9) compared to non-carriers.
Discussion: Behavioural performance did not differ between groups suggesting a compensational increased activation of bilateral middle frontal gyrus in risk-allele carriers. The data of the current study are in line with results of other fMRI studies demonstrating similar CPT effects in a group of neuregulin1 risk-allele carriers in prefrontal cortex (Krug et al., 2008) and in right anterior cingulate, hippocampus, precuneus and cerebellum (Kircher et al.2008), brain areas which are associated with pathology of schizophrenia. These facts are explicit demonstration of compensatory mechanisms in risk-allele carriers on cerebral activation level in order to perform working memory tasks.

**Prepulse Inhibition – an endophenotype for schizophrenia and its associations to dopaminergic and serotonergic polymorphisms**

Anja Schmitz, Martin Reuter, Nina Alexander, Roman Osinsky, Eva Kozyra & Jürgen Hennig

The inhibition of the startle reflex by a weak prestimulus (prepulse inhibition, PPI) is dimished in schizophrenia and in relatives of schizophrenics. Furthermore it has, as schizophrenia itself, a heritable component, and is therefore suggested to be an endophenotype of schizophrenia. Dopamine function is altered in schizophrenics, and human as well as animal studies suggest that dopamine functioning is also crucial for differences in PPI. Nevertheless, also other neurotransmitters like serotonin seem to play a role in schizophrenia and PPI. Studies regarding the genetic basis of PPI have been rare so far and results of these studies are quite heterogeneous. We therefore investigated the relationship between several dopaminergic polymorphisms (COMT VAL(158)MET, DRD2 TaqIA/ANKK1, DAT1) on the one hand , and a polymorphism within the gene coding for the serotonin transporter (5-HTTLPR) on the other hand, and PPI in 89 healthy female participants. No association between any of the dopaminergic polymorphisms and the PPI could be detected. In contrast, we obtained a significant difference in PPI between carriers of the S-allele of the 5-HTTLPR and participants homozygous for the L-allele, with carries of the S-allele showing a significant stronger PPI. Although various studies suggest that the 5-HTTLPR is not directly associated with schizophrenia, this result is in line with studies investigating the association between the 5-HTTLPR and schizophrenia related traits. In these studies the S-allele is associated with lower scores in schizoid traits as measured by the MMPI in patients and normal controls, and lower intensity of hallucinations in schizophrenics. Implications and further research directions will be discussed.

**Preclinical signs of impairmentin persons at high risk of frontotemporal dementia related to chromosome 3 (FTD3): Preliminary findings in neuropsychological tests**.

Anders Gade and FReJA research group

Department of Psychology, Copenhagen University; Memory Disorders Research Unit, Copenhagen University Hospital, Copenhagen, Denmark; and Frontotemporal Research in Jutland Association (FReJA)

Background. We have studied a large kindred in Jutland with autosomal dominant frontotemporal dementia linked to chromosome 3, the only such family yet known (Gydesen et al., Neurology 2002, 59:1585-94). The early phenotype is not yet known, and we studied well subjects at risk of developing the disease to detect early signs. Methods. At risk subjects between 40 and 70 years of age and spouses were invited to participate in neuropsychological assessment performed without knowledge of status. 38 family members and 20 spouses participated. Some participants have not yet been haplotyped, and we report preliminary results from comparisons of 20 test measures in 3 groups of well-matched subjects: 11 high risk subjects, 16 low risk subjects, and 19 spouses. Results. T-tests without corrections for multiple comparisons showed: 1) No significant differences between the two control groups. 2) A total of 8 significant differences ($p<.05$; two $p<.01$) between high risk subjects and controls, all with high risk subjects impaired. Trail Making B was impaired relative to both control groups, and significant differences between high risk subjects and one control group (but not both) were found in cognitive estimations, letter-number sequencing (a measure of working memory control), design fluency, immediate (but not delayed) story recall, and one further test. Conclusion. This pattern of subtle impairment is indeed compatible with predominantly frontal involvement. We want to confirm these preliminary results in the full data set and replicate them in further cross-sectional and longitudinal analyses in a planned follow-up. At present, our results indicate that overt symptoms may be preceded by many years of subclinical impairment.

Correspondence: A. Gade, Department of Psychology, University of Copenhagen, 5 Oster Farimagsgade, DK-1353 Copenhagen K, Denmark. Anders.Gade@psy.ku.dk

**Support for the contribution of the NRG1 gene (8p12-p21) to the risk for schizophrenia: Case-control association study in a German population based on the GRAS Data Collection *(Göttingen Research Association for Schizophrenia)***

Papiol S[1], Begemann M[2], Klaus S[2], Friedrichs H[2], Ribbe K[2], Krampe H[2], Stawicki S[2], Benseler F[3], Sperling S[2], Hannke K[2], Nave K-A[1], Ehrenreich H[2]

[1]Neurogenetics Department, [2]Division of Clinical Neuroscience and [3]Molecular Neurobiology Department, Max Planck Institute of Experimental Medicine, Hermann-Rein-Strasse 3, D-37075 Göttingen, Germany.

Schizophrenia is a multifactorial disease with a strong genetic background. Previous studies have shown that the NRG1-locus is associated with an increased risk to develop schizophrenia in different ethnic groups around the world. In the present study the possible role of NRG1-locus to develop schizophrenia was explored with the aid of the data collection of GRAS (*Göttingen Research Association for Schizophrenia*). Using DNA samples of 883 schizophrenic patients from this Data Collection and 880 healthy controls, genetic markers mapped to the genomic area covering the original Icelandic Core Haplotype of risk ($HAP_{ICE}$) and its surrounding regions were analyzed. A new haplotype, named $HAP_{GER}$, was found to be increased in schizophrenic patients, with an associated OR=2.21. $HAP_{GER}$ partially overlaps both $HAP_{ICE}$/$HAP_{SCO}$ and $HAPB_{IRE,}$ described as high risk haplotypes in respective populations. These results confirm that the NRG1-locus is associated with an increase risk to develop schizophrenia. The GRAS data collection, containing comprehensive information on sociobiographic, psychopathological, neuropsychological, neurological and other clinical data for each schizophrenic patient, will now provide a fantastic opportunity to identify putative phenotypes associated with $HAP_{GER}$ and/or other NRG1 genetic variants. This world-wide unique source of phenotypic data together with genetic data analysis will ultimately help generate new hypotheses regarding the pathogenesis of schizophrenia and genotype-phenotype relationship.

## The Data Collection of GRAS (Göttingen Research Association for Schizophrenia): Multi-Center Cross-Sectional Schizophrenia Study

Katja Ribbe, Heidi Friedrichs, Constanze Hilmes, Martin Begemann, Martin Fungisai Gerchen, Mohammad Ghorbani, Stefan Gutwinski, Kathrin Hannke, Sabrina Klaus, Henning Krampe, Richard Leppert, Andreas Mielke, Sergi Papiol, Swetlana Sperling, Sabina Stawicki, Maren Stödtke, Julia Sowislo, Christoph Szuszies, and Hannelore Ehrenreich

Division of Clinical Neuroscience, Max-Planck-Institute of Experimental Medicine, Göttingen

The objective of the GRAS (Göttingen Research Association of Schizophrenia) data collection is to identify biologically meaningful subgroups in the broad spectrum of schizophrenias. The project aims at precisely and comprehensively characterizing over 1,000 patients diagnosed with schizophrenia according to DSM-IV criteria. This "data bank of living and potentially accessible patients" includes epidemiological, sociodemographic, psychopathological, neuropsychological, neurological, and further clinical information as well as family history. Most importantly, genotype analyses, targeting genes of particular interest to GRAS, will allow define specific subgroups of patients based on biological criteria. These subgroups will undergo a comprehensive phenotype screening based on the information collected in the data bank. It is hypothesized that patients who share a certain genotype also share several clinical and neurocognitive features. Common characteristics identified in these subgroups, in turn, will initiate further prospective studies, using e.g. imaging or pharmacological challenges. For these prospective follow-up studies, candidate patients out of the 1,000 will be contacted again and asked for further study participation.

## Decreased Frontal 5-HT2$_A$-Receptor Binding in Antipsychotic-Naive Schizophrenic Patients

Hans Rasmussen, David Erritzoe, Bjorn Ebdrup, Bodil Aggernaes, Bob Oranje, Rune Andersen, Jan Kalbitzer, Jakob Madsen, Lars Pinborg, William Baaré, Claus Svarer, Henrik Lublin, Gitte M Knudsen, Birte Glenthoj.

INTRODUCTION: Post-mortem investigations and the receptor affinity profile of atypical antipsychotics have implicated the serotonin$_{2A}$ (5-HT$_{2A}$) receptor in the pathophysiology of schizophrenia. Most post-mortem studies point towards lower cortical 5-HT$_{2A}$-binding in schizophrenic patients. However, molecular imaging studies of 5-HT$_{2A}$ binding report conflicting *in vivo* results, often restricted by limited sample sizes, or from inclusion of schizophrenic patients who were not antipsychotic-naïve. Furthermore, the relationship between 5-HT$_{2A}$-binding and psychopathology is unclear.
AIM: The purpose of this study was to assess in vivo brain 5-HT$_{2A}$ receptor binding in a large sample (n=30) of first episode, antipsychotic-naïve schizophrenic patients and in age and gender matched healthy controls. Moreover, we explored whether the 5-HT$_{2A}$ receptor binding was related with psychopathology.
METHODS: In vivo brain 5-HT$_{2A}$ receptor binding was measured using [F-18]altanserin with Positron Emission Tomography (PET) in a bolus-infusion approach. The binding-potential of specific tracer-binding was used as the outcome parameter. Psychopathology was assessed using the Positive and Negative Symptom Rating Scale (PANSS).
RESULTS: Schizophrenic patients had significantly lower frontal cortical 5-HT$_{2A}$ -binding ($t=-2.16$, $df=61$, $p<0.05$) as compared to healthy controls. There was a significant negative correlation ($r=-0,571$, $p=0.007$) between frontal 5-HT$_{2A}$-binding and positive psychotic symptoms, but only so in the male patients.
CONCLUSION: Our results suggest that frontal 5-HT$_{2A}$ receptors are involved in the early stages of schizophrenia, and point towards gender-differences in the involvement of the 5-HT$_{2A}$ receptor in schizophrenia.

**Dopaminergic Modulation of Working Memory in Schizophrenia: Evidence for D1 receptor involvement**

Roesch-Ely, D[1]., Weinreich, M. [1]; Kaiser, S. [1] ,Pfueller, U. [1] , Mundt, C. [1], Weisbrod, M.[1,2]

[1] Department of Adult Psychiatry, University of Heidelberg, Germany, [2] Department of Adult Psychiatry, SRH-Klinik, Karlsbad-Langensteinbach, Germany

Background: Evidence shows modulation of dopaminergic D1 receptor subtype in cognitive processes like working memory (WM). This function is impaired in schizophrenia. Although dopaminergic stimulation may improve this deficit, the selective effect of dopamine sub-receptors is not well investigated. Aim of the study was to examine whether adjuvant therapy with dopamine agonist pergolide improves working memory in comparison to placebo in schizophrenic patients. Subjects: 28 partially remitted patients with schizophrenia were included in the study. Method: A double-blind, randomised, placebo controlled design was used. Because there is no D1 agonist available for human research we used a substraction design comparing a dopamine agonist with mixed D1 and D2 agonistic properties (pergolide) to placebo under adjuvant -therapy with amisulpride (antipsychotic with predominant D2 antagonism). With this design the D2-component of pergolide can be antagonized by amisulpride and a D1 agonistic effect can be suggested, as well as protecting patients against a psychotic re-exacerbation. WM was assessed using an auditory WM task. Results: 25% of patients (N=7) did not complete the trial, N=13 took Pergolide and N= 8, Placebo. Non-parametric Mann-Whitney U-Test showed that patients treated with pergolide showed better number of recalled tones (p=.02) than patients treated with placebo (difference from baseline). Conclusions: Patients taking pergolide show better performance as those taking placebo, pointing to a beneficial modulation of D1 receptor on auditory working memory in schizophrenia.

## Oxidative stress and schizophrenia - In vitro analysis of peroxisomal reaction to dopamine and haloperidol in primary neocortical cultures

Phillip Grant, Barbara Ahlemeyer and Eveline Baumgart-Vogt

Institute of Anatomy and Cell Biology II, JLU, Giessen

Ever more studies into the pathogenesis of various psychiatric disorders such as schizophrenia suggest a possible disequilibrium of reactive oxygen species (ROS) and the endogenous antioxidant enzymes and scavengers known as oxidative stress. This oxidative stress is, however, also found in patients or laboratory animals treated (predominantly) with typical neuroleptics, such as haloperidol, wherefore the exact link between oxidative stress, psychotic disease pathomechanisms and antipsychotic pharmacological treatment is still unclear. It is believed that the common factor between schizophrenia, typical neuroleptics and oxidative stress is likely to be the catecholamine dopamine, the metabolism of which is believed to be altered in patients suffering from schizophrenia and is also known to form ROS by autoxidation. Neuroleptics are also linked to the dopaminergic system, as HAL for example is a potent blocker of the dopamine D2-receptor.

The two organelles mainly involved, amongst other things, in ROS metabolism are mitochondria and peroxisomes. Although the issue of cause and effect is far from clear, many studies on patients suffering from the aforementioned or other diseases of the brain show signs of pathological peroxidation of neuronal membranes as well as reduction of metabolites of very long chain fatty acid beta-oxidation, another of the main functions of peroxisomes. It is therefore well established, that diminished peroxisomal function is connected to the onset of oxidative stress.

The most common marker for the localization of peroxisomes in morphological or cell culture studies is catalase, an enzyme endogenous to peroxisomes and commonly found in eukaryotes. Its function is the decomposition of hydrogen peroxide to water and oxygen, thereby protecting the cell from oxidative damage. Catalase is known, however, for having the highest turnover rates in all enzymes and is therefore not present in equal amounts in all cells and tissues. The brain is - with the exception of during early stages of ontogenesis - one of the organs known to express very low levels of catalase, whereof most is found in various glial cells and only extremely low levels in neurons. Catalase is therefore highly unsuitable as a marker for peroxisomes in the brain.

In this study we therefore present our newly established method of detecting peroxisomes in brain tissues and cultured primary neurons through the peroxisomal biogenesis protein Pex14p (peroxin 14 protein). Hereby we can compare peroxisomal distribution in the brains of healthy controls and patients suffering from schizophrenia as well as measure changes in catalase expression and compare these to the

numerical density of peroxisomes. We also performed studies regarding the aforementioned proteins Pex14p and catalase on primary cultured mouse cortical neurons, which had been treated with either haloperidol, dopamine or a vehicle and thereby analyze the effects these substances have on catalase expression and peroxisomal proliferation.

## SESSION 2: SOCIAL COGNITION

### Dissociation of relevance and salience in emotional processing. A perfusion imaging study

Roberto Viviani[1,2], Andrea Horn[3], Hanna Lo[2] and Eun-Jin Sim[2]

[1]Univ. of Bern, CH, [2]Univ. of Ulm, [3] Univ. of Fribourg, CH

When taking a decision, emotional information, if present, is integrated into cognitive processing. However, the mechanisms of this integration are not well understood. Here, we study the neurobiological correlates of a task in which participants have to form a sentences from a set of randomly arranged words, leaving out one word in the process. Two possible sentences can be formed in each trial. If the two alternatives are emotionally laden, normal individual spontaneously avoid the emotionally negative choice, excluding the negative word even if it is more salient than the positive word that is used in the sentence (positive bias). First, we show that the inhibition of the negative choice does not vary with differences in working memory capacity. Second, we show that the positive selection bias has a neurobiological correlate in two regions, normally deactivated during the execution of a cognitive task: the ventral medial prefrontal cortex, and the left temporoparietal junction. We conclude that inhibition of the negative choice in the face of negative salience is a process that runs parallel to the central executive and discuss the role of the identified regions in terms of monitoring functions such as those present in visual attention.

## Self-Other discrimination in schizophrenic patients

Christine Heinisch[1,2], Martin Brüne[1]

[1]LWL-Universitätsklinik der Ruhr-Uni-Bochum, Psychiatrie, Psychotherapie, Psychosomatik und Präventivemedizin, [2]International Graduate School of Neuroscience, Bochum

Self-face recognition has been suggested to be an indicator of higher-order self-awareness. Recent studies into the neuronal network indicate that the visual pathway of recognising one's own face differs from the one involved in recognising others.
It is assumed that self-face processing is dysfunctional in schizophrenia and this deficit could be related to altered self-awareness in schizophrenia. The most important manifestation of impaired self-reflection in schizophrenia is unawareness of illness,
Here, we address the question how schizophrenic patients with passivity symptoms, whose self-awareness is compromised, differ in a self-other discrimination task from healthy subjects. Our behavioural task consists of videos where the own, a familiar or unfamiliar face transform into each other and the participants have to press a button when they recognize the face the video is transforming into. Combining behavioural tests with EEG we expect a deeper understanding of the neural network involved in self-recognition and awareness of illness in patients.
Results indicate that healthy subjects show an advantage over patients to recognize faces during a self-other discrimination task compared to other-other discrimination. By contrast, schizophrenic patients do not differ between self-other discrimination and other-other discrimination tasks. Notably, they respond to more trials when their own face is included in the video, while they often do not even recognize that the video is changing when other faces transform into other faces.
Further analyses will focus on differences between healthy subjects and schizophrenic patients in EEG activation in parietal regions. Given the known importance of inferior parietal lobule (IPL) function in self-awareness, it is predicted that IPL function is impaired in individuals with schizophrenia who lack awareness of their illness

## Functional magnetic resonance and diffusion tensor imaging study of Theory of mind deficits in a Japanese sample of schizophrenia patients

Katja Koelkebeck[1/2], Kazuyuki Hirao[2], Teruyazu Saze[2], Jun Miyata[2], Ryousaku Kawada[2], Patricia Ohrmann[1], Jochen Bauer[1], Anya Pedersen[1] & Toshiya Murai[2]

[1] Department of Psychiatry, University of Muenster, Albert-Schweitzer-Strasse 11, 48149 Muenster, Germany , [2] Department of Neuropsychiatry, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Introduction: Functional MRI-studies have shown that certain brain areas are less activated in schizophrenia patients as compared to healthy controls during performance of Theory of Mind (ToM)-tasks. ToM describes the ability to infer other's thoughts and intentions by e.g. behavior. Furthermore, by diffusion tensor imaging (DTI), structural deficits have been found showing a reduction of fractional anisotropy (FA) of white fibers in ToM-related brain areas, especially the superior temporal junction and the basal temporal regions. In our study we combine a sophisticated ToM-paradigm first used by Abell et al. (2000) with functional Magnetic Resonance Imaging (fMRI) and DTI in a sample of schizophrenia patients. We hypothesize that a reduced activation pattern during ToM-task performance is related to a reduction of white matter integrity of ToM-relevant brain areas. This is an innovate approach and has not been performed for ToM-tasks.
Methods: So far, 11 schizophrenia patients and 12 healthy controls participated in the study and were assessed in a 3 T scanner. The fMRI-paradigm comprises short video animations of moving geometrical shapes acting in social, sometimes ToM-related patterns. Moreover, DTI has been applied. Psychopathology (PANSS) and neuropsychological data were assessed and behavioral ToM-data were recorded and rated.
Results: Study results indicate differential activation patterns in schizophrenia patients as compared to healthy controls in cortical areas related to the proposed ToM neuronal network. Schizophrenia patients seem to activate certain brain areas more extensively than healthy controls, e.g. the anterior cingulated cortex and the temporal lobes. First analyses of white matter tracts indicate that schizophrenia patients show lower FA-values in the left arcuate fasciculus and right deep white matter of the temporal lobe.
Discussion: Though there are only few findings on functional imaging of social perception in schizophrenia patients, the overactivation of several brain areas related to the ToM-network in schizophrenia during the fMRI task seems to be in line with previous findings of other research groups. The findings might hint on compensatory activation of ToM-related brain areas. Also, analyses of white matter fibers indicate structural abnormalities of schizophrenia patients. Thus, our findings in schizophrenia patients do not only display functional but also structural deficits in mentalizing networks. Detailed analyses of correlation between these deficits will further elucidate the neurobiological basis of these findings.

## Neural Correlates of Affective Theory of Mind in Schizophrenia I: Differences to Healthy Controls

Daniela Mier[1], Carina Sauer[1], Stefanie Lis[2], Christine Esslinger[1], Bernd Gallhofer[2] and Peter Kirsch[1,3]

[1]Division for Imaging in Psychiatry, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, [2]Centre for Psychiatry and Psychotherapy, University of Giessen, [3]Mannheim School of Medicine, University of Heidelberg

Most studies investigated emotion recognition and Theory of Mind (ToM) separately. The aim of our first study was to develop a new affective ToM task that investigates emotion recognition and affective ToM within one experiment. This task leads to an high overlap of activation in the superior temporal sulcus (STS) and the inferior frontal gyrus, areas known to belong to the human the mirror neuron system and the right amygdala during emotion recognition and ToM, but also to higher activation in areas of the mirror neuron system and the left amygdala during ToM as during emotion recognition.
In schizophrenia deficits on different levels of social cognitions are known. Studies with functional imaging found deviations in amygdala and STS activation during the processing of facial stimuli and hypoactivation in frontal areas during ToM. But until now there are only few studies investigating affective ToM in schizophrenia by means of functional imaging and no study that investigates different levels of social cognition within one design. We studies 16 schizophrenia-outpatients and 16 matched healthy controls with the affective ToM task. Schizophrenia patients had a deficit in emotion recognition and a more prominent deficit in affective ToM. Region of interest analysis of functional brain imaging data revealed no difference between groups during ToM, but a hyperactivation in the schizophrenia group in the left amygdala and right superior temporal sulcus during emotion recognition and the processing of neutral facial expressions. These results point to the fact that schizophrenia patients have altered processing of faces per se and that these changes on basic levels of social cognition can lead to disturbances in higher order social cognitions as ToM.

## Neural Correlates of Affective Theory of Mind in Schizophrenia II: Relations between Theory of Mind, Emotion Recognition and Negative Symptoms

Carina Sauer[1], Daniela Mier[1], Stefanie Lis[2], Christine Esslinger[1], Bernd Gallhofer[2] & Peter Kirsch[1,3]

[1]Division for Imaging in Psychiatry, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, [2]Centre for Psychiatry and Psychotherapy, University of Giessen, [3]Mannheim School of Medicine, University of Heidelberg

There is a great amount of evidence that schizophrenia patients show deficits in affective components of Theory of Mind (ToM) and emotion recognition and that these deficits even persist in remission. On a neural basis, these deficits are often associated with alterations in the activation of the social cognition network, especially in amygdala and superior temporal sulcus (STS). Both emotion recognition and Theory of Mind seem to be related to schizophrenic pathology, particularly to negative symptoms. However, until now the neural basis of this relationship is widely unknown.

Therefore fMRI data from 16 remitted schizophrenia outpatients were acquired while performing an affective Theory of Mind, an emotion recognition, and a neutral face processing task (for details of the sample see the poster by Mier et al.). Schizophrenic pathology was assessed with the SAPS/SANS rating scales.

Behavioural data showed a significant negative correlation between the global rating of negative symptoms and both affective ToM and emotion recognition. Moreover, there was a trend for a negative correlation between flat affect and ToM. The fMRI data analyses revealed no significant correlation between brain activation and the global SANS rating of negative symptoms, but negative correlations were found between flat affect and activation of the left amygdala and the right STS during ToM, emotion recognition, and neutral facial processing.

The association of negative symptoms with deficits in affective ToM and emotion recognition seems to be independent from alterations in the social cognition network. However, schizophrenia patients with an increased flat affect show a reduced activation of the social cognition network during affective ToM, emotion recognition and facial processing. This reduced activation could account for the trend of greater ToM impairments in patients with an increased flat affect, but appears to have no effect on emotion recognition and neutral face processing performance. In summary, this hypoactivation of the social cognition network in patients with flat affect may be the neural basis for deficits in higher order social cognition like affective ToM, but does not seem to play a role in more basal social cognitions like emotion recognition or neutral face processing.

**Mentalising in schizophrenia:**
**The role of clinical symptomatology and neurocognition in understanding other people's thoughts and intentions**

Mona Abdel-Hamid, Caroline Lehmkämper, Claudia Sonntag, Georg Juckel, Irene Daum, and Martin Brüne

*Background*: A wealth of studies have demonstrated that patients with schizophrenia are impaired in reflecting upon their own and other persons' mental states. This cognitive capacity has been termed "mentalising" or "Theory of Mind" (ToM). Here, we used a novel five-factor model of the PANSS to test the hypothesis that the presumed selectivity of ToM deficits in schizophrenia depends on the predominating symptoms. We predicted that ToM impairments would be non-selective in neurodevelopmental subtypes with pronounced negative (NF) or disorganized symptoms (DF), whereas selective ToM impairment would occur in patients with predominant positive symptoms (PF).
*Methods*: We recruited 50 patients diagnosed with schizophrenia or schizoaffective disorder and compared premorbid intelligence, executive functioning, ToM and psychopathology with 29 healthy controls.
*Results*: Patients performed more poorly on tasks involving executive functioning and ToM abilities. Using median split procedures in the patient group for each of the novel PANSS factors we found that high vs. low scorers on the PANSS-PF differed significantly in ToM performance when executive functioning was co-varied out, whereas executive functioning had a major impact on ToM task performance in the NF and DF groups.
*Conclusions*: This study lends further support to the assumption of differential associations of ToM deficits with neurocognitive functioning in different subgroups of the schizophrenic phenotype.
Keywords: Schizophrenia, heterogeneity, theory of mind, PANSS five-factor model, selective impairment

**Schizophrenic patients don't use emotional expressions of faces to adapt their behaviour in a Gambling-Task**

Schönwetter[1], T., Gallhofer[1], B., Kirsch[2], P., Lis[1], S.
[1]Centre for Psychiatry, JLU-Giessen, [2]ZI Mannheim

Introduction: Impairment of social functioning is a core feature of schizophrenia. The ability to represent the mental state of another subject in a particular situation forms the basis to adapt the own behaviour according to a particular situation and social counterpart, i.e. for a successful social interaction. Prior experience with a certain subject as well as cues within a particular situation like the emotional expression of a face form part of this complex process to develop a 'Theory of Mind' (ToM).
Gambling tasks constitute experimental paradigms that might be well suited to simulate social interactions. The aim of the present study was to investigate with help of a modified trust-game whether schizophrenic subjects are able to use emotional expressions of the faces of a virtual social counterpart to guide their behaviour.
Methods: 16 schizophrenic patients and 16 healthy controls matched according to age, sex and education participated in a modified version of the trust game. Subjects had to achieve a maximum gain in 72 trials with four different virtual counterparts. In each trial, they had to hand over a part of their account to the particular partner who could increase or decrease the gain. Two partner played fair, but the other two unfair. The payback of one fair and one unfair partner could be predicted for each trial by the emotional expression of the face ranging from angry to happy. In contrast, one fair and one unfair partner played with an uniform neutral face.
Results: In contrast to their healthy controls, schizophrenic patients were not able to predict the fairness of the partner by the variation of the emotional expression and adapt their behaviour accordingly. However, they were able to differentiate between the emotional expressions and judged the fairness of the behaviour of their partners comparable to their healthy controls.
Conclusions: Schizophrenic patients show deficits in the usage of correctly recognised emotional expressions to guide their behaviour in social interactions. The measurement of behaviour in virtual social interactions might help to identify factors that underly impairments of social functioning in everydays life.

**Different Patterns of Gambling Behaviour in Schizophrenia and Borderline-Personality Disorder : The effects of fairness and emotional expression in a modified Trust-Game**

Hagenhoff[1], M., Franzen[1],N., Schmidt[1], A., Scheibel[1], N., Schönwetter[1], T., Gallhofer[1], B., Kirsch[2], P., Lis[1], S.
[1]Centre for Psychiatry, JLU-Giessen, [2]ZI Mannheim

Introduction: Impairments of social functioning are observable not only in subjects suffering from schizophrenia, but subjects with Borderline personality disorder as well. The aim of the present study is to analyse whether the patterns of impairments in social cognition are distinguishable between both psychiatric disorders with help of the analysis of behaviour in a virtual social interaction paradigm. We present first results from an ongoing study.
Methods: 16 schizophrenic patients, 10 patients with Borderline Personality Disorder and 16 healthy controls participated in a modified version of the trust game. Subjects had to achieve a maximum gain in 72 trials with four different virtual counterparts. In each trial, they had to hand over a part of their account to the particular partner who could increase or decrease the gain. Two partners played fair, but the other two unfair. The payback of one fair and one unfair partner could be predicted for each trial by the emotional expression of the face ranging from angry to happy. In contrast, one fair and one unfair partner played with a constant neutral face.
Results: Healthy subjects differentiate their stake between fair and unfair counterparts only if they show no variation of the emotional facial expression. Schizophrenic patients do not vary their stake between fair and unfair players independently of additional social cues. Patients with Borderline Personality Disorder hand over less of their account to unfair players than to fair players independently of the existence of cues from emotional facial expressions.
Conclusions: The patterns of alterations in behaviour in a virtual social interaction differ between schizophrenic patients and patients with Borderline Personality Disorder. Schizophrenic patients do neither use cues from emotional expression of the faces of the virtual partner nor seem to adapt their behaviour based upon the experience with a particular counterpart. In contrast, Borderline Patients are able to integrate information from both sources to predict the partners behaviour and adapt their own action. However, while the emotional expression constitutes for healthy subjects such a strong cue that they neglect the past experience with the behaviour of their partner, Borderline patients differentiate between fair and unfair players independently of the existence of cues from emotional facial expressions.

**Perception of fairness and altruistic punishment in patients with schizophrenia**

Julia Wischniewski, Georg Juckel, Martin Brüne

Humans possess evolved cognitive and emotional biases that guide an individual's actual behaviour in terms of cooperation, defection or punishment of unfair behaviours. Empirical evidence comes from behavioural observation and brain imaging studies during performance of tasks involving decisions about the distribution of (virtual) goods, suggesting a neural network comprising parts of the frontal lobe as well as limbic structures. Little is known as to what extent differences in character and temperament or psychopathology affects an individual's performance in social exchange games.
Methods: This study, therefore, sought to explore individual differences in acceptance of fair versus unfair offers and in altruistic punishment in patients with schizophrenia (SCHIZ) compared with a group of healthy controls (NC), using an Ultimatum Game (UG) and a Dictator Game with Punishment by a third-party player (DGP).
Results: Acceptance rate of unfair offers in the UG was significantly higher in the patient group compared to controls. In the DGP, the punishment-investment by the third-party increased with the degree of unfairness of the proposed offer in both groups, but the SCHIZ group invested less money in penalising unfair offers than the NC.
Conclusions: Patients with SCHIZ seem to be less sensitive towards the recognition of unfairness and accordingly less harsh in their attitudes to punish unfair behaviour.

## How emotion recognition is influenced by context in healthy and schizophrenic subjects

Ariane Dettbarn[1], Silke Leifheit[1], Harald Gruppe, Stefanie Lis, Bernd Gallhofer, Gebhard Sammer

[1]equally contributed

Recently, cognitive deficits in schizophrenic patients have been supposed to be in correlation with impaired processing of contextual information (Green et al., 2005). Does impaired processing of contextual information serve other deficits observed in schizophrenia? There is evidence that schizophrenic patients can adequately interpret facial expressions in unambiguous social interaction tasks. However, schizophrenic patients seem not to benefit from additional information given in such tasks.
In this study we investigate how the assignment of emotions to facial expressions is influenced by contextual information. Flanking contextual information is established by negative or positive emotion pictures (IAPS), and by negative or positive social interaction pictures (new material), or a neutral picture. Subject's task is to assign predefined emotions to pairs of eyes (Öhman's picture set) and to ignore the surrounding emotional or social pictures.
Behavioral and hemodynamic data were recorded during task performance of both schizophrenic patients and healthy volunteers. When eyes and flanking information represent incongruent emotions, preliminary results on healthy subjects show pronounced differences in dorsolateral prefrontal and superior temporal activation. Currently this paradigm is applied to schizophrenic patients.

**Gesture Imitation and ToM: an fMRI study**

Authors: Mainieri, A. G.; Krach, S.; Green, A.; Straube, B.; Kircher, T.

Our ability to explain and predict the behaviour of ourselves and others by attributing mental states such thoughts, beliefs and desires that are independent from our own is essential in social contexts. Previous studies have demonstrated the implication of premotor, parietal and superior temporal areas in action understanding and mental state attribution in the so called Theory of Mind system (ToM). More recently a relationship between ToM and the Mirror Neuron System (MNS) has been proposed. However, the role of these cortical regions in action understanding and performance (real or solely imagined imitation) remains largely unclear, as well as the relationship between these two systems. In this respect, the aim of the present study was to determine the involvement of the neural correlates of ToM in gesture imitation/observation. In an event-related fMRI fashion, subjects (N=20) watched 90 videos sequences (each of 4 sec length) while being asked to perform either an imitation of the gesture presented or purely an observation. Videos displayed social gestures (which require the attribution of thoughts, beliefs and desires independent from your own – thus mentalizing), non-social gestures (mimes of common actions or events of the physical world) and control gestures (free gestures, without meaning). Preliminary data indicates an activation pattern including the inferior frontal cortex (opercular region), superior parietal cortex, superior temporal cortex and cerebellum. The results are discussed in the light of the embodied simulation theory.

## Deviant neural processing of coverbal metaphoric gestures in patients with Schizophrenia

Green A[1], Straube B[1], Weis S[2], Kircher T[1]

[1]Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany, [2]Department of Neurology, RWTH Aachen University, Aachen, Germany

Schizophrenia includes impairments in social functioning which comprise difficulties in the decoding and interpretation of gestures [1]. In this study we investigated the neural correlates of speech-gesture interaction in relation to sentence content and gesture type in healthy subjects and patients with schizophrenia.
During fMRI data acquisition patients with schizophrenia and healthy controls were presented with short video-clips containing speech with either iconic gestures (related to concrete sentence contents) or metaphoric gestures (related to abstract sentence contents). In both groups comparable activation patterns were found for both gesture types vs. baseline (fixation cross) in predominantly bilateral occipital, temporal and frontal regions. However, in contrast to patients only healthy subjects showed more activation in left temporal and frontal regions for the processing of metaphoric gestures as compared to iconic coverbal gestures.
Our results are consistent with the evidence of impaired gesture [1, 2] and metaphor comprehension in patients with schizophrenia [3]. Patients with schizophrenia possibly fail to activate left hemispheric temporal and frontal areas which seem to be important for the comprehension of metaphoric speech-gesture pairs.

References:
[1] Toomey R, Schuldberg D, Corrigan P, Green MF, 2002. Nonverbal social perception and symptomatology in
schizophrenia. Schizophrenia Research 53, 83-91.
[2] Berndl K, von Cranach M, Grüsser OJ, 1986. Impairment of perception and recognition of faces, mimic
expression and gestures in schizophrenic patients. European Archives of Psychiatry and Clinical Neuroscience
235, 282-291.
[3] Kircher TT, Leube DT, Erb M, Grodd W, Rapp AM, 2007. Neural correlates of metaphor processing in
schizophrenia. NeuroImage 34, 281-289.

## SESSION 3: ATTENTION, GATING + WORKING MEMORY

### Disturbed Functional Connectivity During Working Memory Encoding, Maintenance, And Retrieval In Early-Onset Schizophrenia – An Event-Related Functional Magnetic Resonance Imaging Study

Robert A. Bittner[1,2,4], Corinna Haenschel[1,2,4], Alard Roebroeck[5], Fabian Härtling[3], Anna Rotarska-Jagiela[1,2], Rainer Goebel[5], Wolf Singer[2,4], Konrad Maurer[1,2], David E.J. Linden[6]

[1]Laboratory for Neurophysiology and Neuroimaging, Department of Psychiatry and Brain Imaging Center, [2]Brain Imaging Center, [3]Department of Child and Adolescent Psychiatry, Johann Wolfgang Goethe-University, D-60528 Frankfurt, Germany, [4]Max-Planck-Institute for Brain Research, D-60528 Frankfurt, Germany, [5]Department of Cognitive Neuroscience, Faculty of Psychology, Maastricht University, 6200MD Maastricht, The Netherlands [6]Wolfson Centre of Cognitive Neuroscience, School of Psychology, University of Wales, Bangor, Wales

Introduction: There is converging evidence that working memory (WM) dysfunction in schizophrenia is caused by impairments of both encoding and subsequent processes, e.g. maintenance and retrieval. The neurophysiological abnormalities underlying the impairments of different WM subprocesses remain pooly understood.
Methods: Using functional magnetic resonance imaging, we examined differences in brain activation and functional connectivity during the different stages of a visual WM task in 17 adolescents with early-onset SCZ (age 15 to 20 years) and 17 matched controls. Up to three abstract visual shapes had to be maintained for 12 seconds before comparing them to a test stimulus. Group data were aligned on the basis of the individual cortical anatomy. Activation differences during the different WM phases were assessed with a random effects model. Differences in functional connectivity, derived from the instantaneous influence term of Granger causality mapping, were analyzed using t-tests.
Results: Accuracy was significantly reduced in patients across all WM load conditions. During encoding and maintenance, controls had greater activation in the dorsolateral prefrontal cortex (DLPFC) bilaterally and the left ventrolateral prefrontal cortex (VLPFC). Patients showed stronger activation in a network comprising the eye field (FEF) and the intraparietal sulcus (IPS) bilaterally. Prefontal-parietal connectivity was reduced in patients. During retrieval, activation of the DLPFC, VLPFC, FEF and the IPS was increased in patients. Patients also had stronger prefrontal-parietal connectivity.
Conclusions: Our findings indicate that impairments of encoding and maintenance processes in patients seem to be the consequence of weaker prefrontal-parietal connectivity as a result of reduced prefrontal activation. This seems to lead to stronger activation in attention related areas (FEF and IPS) in patients, which cannot support these processes with the same efficiency under conditions of high WM load. During retrieval, stronger activation and connectivity throughout the frontoparietal network in

patients might point toward greater difficulty of accessing previously stored information.

**Prefrontal activation pattern in N-back-task:**
**The effect of sensory and motor encoding strategies**

Damm[1], M., Gallhofer[1], B., Kirsch[2], P., Lis[1], S.

[1]Centre for Psychiatry, JLU-Giessen, [2]ZI Mannheim

Introduction: It is commonly agreed on that schizophrenic patients show impairments in working memory (WM) tasks. However, the exact nature of the underlying dysfunction is still under debate. Studies reveal different patterns of deficits not only in behavioural parameters as reaction times and error rates but also of cerebral activations as e.g. hyper- and hypoactivations of dorsolateral prefrontal cortex area.
N-back tasks are one of the well established experimental procedures to analyse WM deficits in schizophrenia. Most studies have focused on the sensory aspects of WM, i.e. they have manipulated stimulus features (e.g. visuospatial, verbal stimuli), but have neglected the importance of action related processes.
Two types of N-back tasks can be differentiated depending upon whether a retrospective, sensory encoding or a prospective, motor encoding strategy can be applied for task solving.
Recent data suggest
- that first-episode, never treated schizophrenic patients solve both types of N-back task with a sensory encoding strategy. In contrast, healthy subjects switch to a faster and more accurate motor encoding strategy if the task allows for that
- that the difference in the behaviour of healthy subjects between both types of tasks can be resolved if the usage of a motor encoding strategy is prevented by an experimental manipulation and subjects are forced to store information in a sensory code in WM. This results in a behavioural pattern that mirrors that of the schizophrenic patients.
The aim of the present study was to investigate whether differences in the cerebral activation of dorsolateral prefrontal cortex area (DLPFC) can be shown depending on the use of a sensory or motor encoding strategy.
Methods: 30 healthy subjects were tested using two versions of a 1-back task: the continuous-matching-task (CMT) and the continuous-delayed-response-task (CDRT). In CMT, subjects have to compare the present stimulus with the one presented 1-stimuli back. In CDRT, subjects select a response depending on the stimulus 1-back. CDRT allows response selection to occur prior to information storage in WM, i.e. to store the task relevant information as a mental representation of a future motor act. Contrarily, CMT requires to match stimulus features of the stimulus N-back and the present one, i.e. a sensory encoding. The use of a motor code in CDRT was prevented experimentally by random arrangement of the target buttons. Cerebral activation was measured by fMRI during task solving.
Results: With fixed arrangement of the target buttons CDRT was solved faster and more accurate than CMT. A higher activation of the left DLPFC (BA46) could be observed in CMT compared to CDRT. With random arrangement of target buttons the performance was comparable in both types of N-back tasks. Activation of BA46 increased in CDRT, but not in CMT, when the positions of the target buttons varied between trials.

Conclusions: These results point to a different involvement of the DLPFC depending on the usage of a sensory or a motor encoding strategies: A sensory encoding strategy is accompanied with a higher activation in BA46 compared to a motor encoding strategy. A hyperactivation in schizophrenic patients might result if their cerebral activation during sensory encoding is compared with that of their healthy controls applying a motor encoding strategy. A hypoactivation might become observable if both groups use a comparable sensory encoding strategy. Future studies have to investigate whether this hypothesis holds true.

## Interactions between visual attention and encoding into spatial working memory in schizophrenia: An fMRI study

Mayer J.S.[1,2], Fusser F.[1,2], Maurer K.[1,2], Haenschel C.[1,2,3]

[1] Department of Psychiatry, Johann Wolfgang Goethe University, Frankfurt, Germany
[2] Brain Imaging Center, Johann Wolfgang Goethe University, Frankfurt, Germany
[3] Max Planck Institute for Brain Research, Frankfurt, Germany

Impairments in working memory (WM) are regarded as a core cognitive deficit in schizophrenia. Behavioral findings suggest that reduced WM performance is caused by deficits of both encoding and maintenance processes. In healthy subjects we have previously demonstrated common processing limitations for visual WM encoding and attention in distributed visual, parietal, and premotor regions. In the present study we used functional magnetic resonance imaging to test the hypothesis that visual WM deficits in schizophrenic patients are due to impaired processing capabilities shared by visual WM and attention in these posterior regions. We combined visual search and delayed discrimination of spatial locations and independently modulated the demands on selective attention and WM encoding. Attention was manipulated by the difficulty of the search (difficult vs. easy search), and WM load was varied parametrically (1 or 3 locations). Patients performed worse than healthy controls in all conditions. They showed an increase in reaction time and a decrease in accuracy from WM load 1 to WM load 3 under easy and difficult search. The fMRI analysis focussed on the encoding phase. For patients, preliminary results revealed regions in the posterior parietal cortex (intraparietal sulcus, precuneus) that were reduced in their memory load response (WM load 3 vs. 1) under the condition with high vs. low attentional demand. Thus, deficits in visual WM encoding in schizophrenic patients appear to be a consequence of increased competition for resources shared by visual WM and attention in the posterior parietal cortex.

**Impaired low and high-frequency oscillatory activity during working memory in adolescents with schizophrenia**

Corinna Haenschel[1,2], Robert A. Bittner[1,2], James Waltz[3], Fabian Härtling[4], Konrad Maurer[1], Wolf Singer[2], David E.J. Linden[5], Eugenio Rodriguez[2,6]

[1]Department of Psychiatry, Laboratory for Neurophysiology and Neuroimaging, [2]Max-Planck-Institut for Brain Research, [3]University of Maryland School of Medicine, Baltimore, USA, [4]Department of Child and Adolescent Psychiatry, Frankfurt, Germany, [5]School of Psychology, Bangor, U.K, [6]Universidad Catolica de Chile, Santiago, Chile

Background: Impairments in working memory (WM) are regarded as a core cognitive deficit in schizophrenia. Recent models of cognition in schizophrenia (SCZ) have emphasized the role of dysfunctional oscillatory neural activity in the low and high frequency range. Here we investigated the relationship between impairments in low- and high-frequency oscillations and WM using a delayed discrimination paradigm.
Methods: Fourteen patients diagnosed with early-onset SCZ (EOS, age 15 to 20 years) according to DSM IV criteria and fourteen matched controls participated in a visual working memory experiment. Subjects had to encode up to three abstract shapes that were presented sequentially for
600 ms each. After a delay of 12 seconds they had to compare the memorized shapes to a test shape, which was a match in fifty percent of the trials. 64-channel EEG was acquired at a 500Hz sampling rate. Encoding, maintenance and the retrieval periods were analysed for both evoked and induced oscillatory low (theta and alpha) and high-frequency gamma oscillations using a sliding window FFT.
Results: EOS patients showed significant reductions in the number of successfully encoded objects. Successful memory was predicted by evoked theta, alpha and beta oscillatory activity during encoding in controls but not in patients. During early WM maintenance EOS showed a comparable
increase in induced alpha and gamma activity with higher WM load conditions to controls. In contrast, during the later maintenance phase, induced gamma increased only for WM load 3 in controls, whereas it increased for WM load 2 in patients. Finally, induced theta and gamma
activity were reduced in patients compared to controls during the retrieval phase.
Discussion: Our findings suggest that the behavioural WM deficits in EOS are associated with impaired evoked oscillatory activity during encoding, which suggests that the neuropathology underlying WM dysfunctions is not confined to prefrontal networks. Furthermore, our
data indicate that the cortical storage system reaches its capacity limit at lower loads at longer maintenance intervals in EOS. Deficits in maintaining oscillatory activity in specific frequency bands could thus result in the information overload that may underlie cognitive deficits
and symptoms of schizophrenia.

**Lion-(Tiger)-Stripes:**
**The influence of indirect priming and modalities on semantic processing**

Katharina Saß, Olga Sachs, Sören Krach, Tilo Kircher

Department of Psychiatry und Psychotherapy, RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany

Background: One of the core features of schizophrenia is disorganized thinking and speech, termed formal thought disorder (FTD). A dysfunctional semantic system has been shown to underlie FTD. We investigated the influence of unimodal (word-word) and cross-modal (auditory-word) semantic priming on word recognition and on different semantic distances using a lexical decision task.
Methods: A group of healthy subjects was compared with schizophrenia patients. Four experimental conditions were used: directly related (picture – frame), indirectly related (seatbelt – garage), unrelated (car – bottle) and non-word trials (picture – fubber). Half of the word-pairs were presented unimodal, the other half cross-modal. Stimuli were presented with a short SOA (350 ms) as subjects performed a lexical decision task while brain activation was measured with a 3T Philips MRI system.
Results: For healthy subjects, the results revealed left fronto-tempo-parietal for direct priming and right fronto-parietal signal changes for indirect priming. Modality-independent activation for direct priming was found within the left middle temporal gyrus and within the right insula for indirect priming. The comparison of semantic distances (direct > indirect) showed one region activated modality-independent: the precuneus. The preliminary results of six schizophrenic patients revealed activation of left frontal (direct priming) and bilateral fronto-temporal regions (indirect priming). Common activation for both modalities was found within bilateral fronto-parietal (direct priming) as well as within left temporal regions (indirect priming).
Conclusions: Direct priming is associated with activation clusters corresponding to a large left-lateralized network. Indirect priming recruits right-hemispheric regions, reflecting widespread semantic fields and attentional components. The modality-independent comparison of direct and indirect priming revealed common areas of activation supporting an amodal rather than multiple semantic systems. The activation related to semantic distances underpins the special role of the precuneus. This region is involved in semantic priming and association processing whereas episodic memory contents might be addressed.

**Perceptual and associative salience attribution in antipsychotic-naïve schizophrenic patients – preliminary results from an fMRI study**

C. Eßlinger[1], M. Zink[1], W. Bowl[2], C. Sauer[1], S. Englisch[1], V. Peus[1], D. Mier[1], M. Hoerst[3], N. Tunc-Skarka[3], A. Meyer-Lindenberg[1], P. Kirsch[1]

[1]Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, [2]Centre for Psychiatry and Psychotherapy, University of Giessen, [3]Department of Neuroimaging, Central Institute of Mental Health, Mannheim

Clinical observation suggests that abnormal attribution of salience to usually nonsalient stimuli is a major psychotic symptom in patients suffering from paranoid hallucinatory schizophrenia. Kapur (Am J Psychiatr, 2003) has proposed that dysregulated dopamine release could underlie this abnormal attribution of salience which then leads to the formation of delusions and hallucinations.
We examined eight antipsychotic-naïve patients with schizophrenia or suspected first episode of schizophrenia and seven healthy control subjects with fMRI during a face matching task. Salience of face stimuli was modulated in two ways: associative salience by famousness of the person depicted and physical stimulus salience by presenting the faces in dull versus very bright colours.
Across the whole sample, bilateral amygdala and ventrolateral prefrontal cortex, precuneus and left temporal pole were activated during presentation of famous as compared to unknown faces. During viewing of bright versus dull pictures, there was increased activation of the inferior parietal lobule bilaterally.
When comparing patients and healthy controls, the former showed an increase in activation in the ventral tegmental area (VTA) during viewing of famous as compared to unknown faces, while control persons showed a decrease of activation in the same area. A statistical trend towards an increase of activation in patients versus no change in controls was seen in the left amygdala. No differential effects were observed as a function of perceptual salience.
Although these preliminary results must be interpreted with caution due to small sample size, the increased activation in the VTA in the patients might indicate abnormal dopamine release as a reaction to associative stimulus salience. In healthy controls, novel (unknown) faces elicited a greater salience signal than famous faces; the reversal observed in patients fits with the Kapur hypothesis.

## Lack of striatal activation during implicit sequence learning in schizophrenia patients

Anya Pedersen PhD[1], Jochen Bauer MSc[1], Harald Kugel PhD[2], Volker Arolt MD PhD[1], Patricia Ohrmann MD PhD[1]

[1]Department of Psychiatry, University of Muenster, Germany, [2] Department of Clinical Radiology, University of Muenster, Germany

*Introduction*: There is growing evidence for deficient implicit learning in schizophrenia patients. Using functional MRI we examined neural correlates associated with implicit learning in schizophrenia patients as compared to controls.
*Methods:* Nineteen schizophrenia patients and twenty-three healthy control participants were studied with 3 Tesla functional MRI while performing a serial reaction-time task (SRT). In this paradigm the degree of implicit learning depends on participants' profiting from a hidden stimulus sequence measured as a faster responding. Brain activation in sequential blocks and random blocks was contrasted.
*Results:* In controls activation in bilateral putamen, left insula, and right frontal middle gyrus were significantly correlated with the degree of implicit sequence learning. In schizophrenic patients no such correlation was revealed. Moreover, simple motor performance was not related to striatal activation.
*Discussion:* The study revealed a lack of striatal activation associated with implicit sequence learning in schizophrenic patients. This striatal activation pattern observed in healthy subjects is specific for implicit learning. Our results provide further evidence of striatal dysfunction in schizophrenic patients.

**Reduced anterior cingulate and medial-frontal cortex activity during the N200 time window in schizophrenia patients**

K Doege[1], M Kumar[1], D Das[1], A Bates[1], T White[1], PF Liddle[1]

[1] Division of Psychiatry, School of Community Health Sciences, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK

Fronto-central N200 during Go/Nogo (GNG) tasks is a manifestation of conflict monitoring, inhibition and mismatch related processes (Folstein & VanPetten, 2008) often linked to medial-frontal cortex activity. Schizophrenia patients show impairments in those executive functions. The aim of our study was to investigate in schizophrenia patients which EEG frequency components underlie N200 amplitude and which brain areas are associated with amplitude reductions.
*Methods:* 17 male, partially remitted, highly functioning schizophrenia patients (mean = 26.1 years) within their first 5 years of illness and 17 matched healthy controls performed a visual GNG task while EEG from 128 Electrodes (Biosemi) was recorded.
*Results:* Despite equal task performance in both groups, N200 amplitude during correct rejects (CR) and correct hits (CH) trials was significantly reduced in schizophrenia patients. At this time window we also observed reductions in evoked and induced theta and evoked delta during both trial types and in induced delta during CR trials. Evoked oscillations correlated significantly with N200 amplitude. Source localization of N200 in CR trials with sLORETA revealed reduced activity of anterior cingulate (BA 24), cingulate (BA 32), medial frontal (BA6) and superior frontal (BA 8) gyrus in patients. A ROI analysis at these areas during CH trials indicated also significant differences between the two groups.
*Conclusions:* Reduced amplitude of N200 during CR and CH trials in schizophrenia patients is associated with deviant low frequency activity. The medial frontal cortex of schizophrenia patients shows deficient functioning not only during rare no-go-trials but also during frequent go-trials.

**Sensory Gating in First-Episode, Antipsychotic-Naïve Schizophrenia Patients. A Longitudinal Study.**

Bodil Aggernaes, MD; Bob Oranje, PhD; Birte Y. Glenthoj, PhD, MD

Center for Neuropsychiatric Schizophrenia Research. Faculty of Health Sciences. University Psychiatric Center Glostrup, Copenhagen, Denmark.

Introduction: Cognitive deficits appear to be core features in the pathogenesis of schizophrenia. Reduction of the P50 evoked related potential (ERP) in a conditioning-testing task, is generally considered to be a measure of sensory gating. Previous studies have consistently found a robust reduction in the P50 amplitude in response to the testing vs. the conditioning stimulus in healthy subjects. In contrast, schizophrenia patients have generally shown significantly less reduction compared to healthy subjects. In some - but not all - clinical studies improved P50 suppression was found in schizophrenia patients following treatment with atypical antipsychotic compounds, while generally typical antipsychotics have no such effect. Most previous studies, however, used cross-sectional designs and included medicated patients, which might have confounded the results.
Methods: In the present longitudinal study, P50 suppression of 29 antipsychotic-naïve, first-episode schizophrenia patients was assessed and compared to that of 33 age and sex matched healthy controls. P50 suppression was re-assessed after six months, a period during which the patients were treated with the atypical antipsychotic compound quetiapine, while the controls received no treatment at all.
Results: At baseline, the patients showed a significant reduction in the P50-ratio (T/C) compared to controls. Treatment with quetiapine did not restore the deficits in P50 suppression in those 16 patients, who succeeded treatment to follow up.
Discussion: Since the antipsychotic-naïve, first-episode schizophrenia patients showed significantly less P50 suppression compared to the healthy controls, this indicates that P50 suppression deficits are present at an early stage in the development of schizophrenia. Furthermore, since 6 months of treatment with quetiapine did not restore the gating deficits, the current results may indicate that P50 suppression deficits are stable vulnerability indicators.

**Source localization of Sensory gating:**
**Concurrent assessment of EEG and fMRI, preliminary results**

Nikolaj Bak[1], MSc; Birte Y. Glenthøj[1], DMSc, MD; Egill Rostrup[2], DMSc, MD; Henrik Larsson[2] DMSc, MD; Bob Oranje[1], PhD

1 Center for Neuropsychiatric Schizophrenia Research (CNSR), Faculty of Health sciences, Copenhagen University, University Psychiatric Center Glostrup, Glostrup, Denmark, [2] Functional Imaging Unit, Department of Clinical Physiology and Nuclear Medicine, Glostrup Hospital, Denmark.

Keywords: P50, sensory gating, source localization, concurrent EEG-fMRI

Reduced sensory gating appears to be among the core features in schizophrenia. The sources of sensory gating however are largely unknown. The aim of the current study is to identify these sources. To our knowledge this is the first study in which concurrent EEG and fMRI assessment of P50 suppression was performed.
Twenty healthy male volunteers were tested with identical paradigms in two separate sessions: an EEG setting, and an EEG concurrent with fMRI setting. Instead of the classical P50 suppression paradigm an especially constructed paradigm was used for the fMRI environment, in which the auditory stimuli were replaced by weak electrical stimuli. Two interstimulus intervals (ISIs) were used: 500 and 1000 ms.
The preliminary results from the 16 subjects who were analyzed in the EEG setting and 9 from the fMRI setting so far showed significant P50 suppression only in the 500 ms interval, not in the 1000 ms ISI. The contrast between the 1000 ms and 500 ms ISI revealed activation in the temporal region based on the results from the 9 subjects who were analyzed so far in the fMRI setting.
The results indicate that the EEG data between the two settings are compatible. Furthermore the electrical P50 suppression paradigm gives results that are consistent with classical auditory paradigms. The fMRI results suggest that the temporal cortex is involved in P50 suppression.

## Probing a new approach to altered brain function in schizophrenia by combined EEG/fMRI

Helge Gebhardt, Harald Gruppe, Bernd Gallhofer, Gebhard Sammer

In numerous studies, neuropsychological measures showed the greatest differences between patients with schizophrenia and normal controls (Rund et al., 2006). Structural measures (CT, MRI) and cerebral metabolic measures (fMRI, PET, SPECT) less frequently showed clear differences between individuals with schizophrenia and normal controls. Electrophysiological measures (EEG) also showed significant differences (Shagass, 1991).
The candidate areas under discussion to be involved in the pathognomonic processes of schizophrenia are extensively interconnected and function as part of complex circuits, not as discrete brain areas. As a result, altered function can arise somewhere in these networks, in the primarily impaired area or as a secondarily affected structure even far away from the focus of structural or functional disease. For instance, executive function impairment can be associated not only with changes in prefrontal activity but also with alteration somewhere else in the working memory networks - the fronto-striatal circuits or superior parietal areas of the cortex. Thus, a beneficial approach to brain function of schizophrenic individuals should focus on networks rather than on single structures, and should allow a decomposition of functional specific processes within parts of these networks.
Compared to single use of EEG and fMRI, it was shown recently that EEG-constrained fMRI-analysis has the potential to improve the interpretation of brain activation data significantly (Zhongming et al., 2006). The functional specificity of brain areas can be assessed by correlations between ERP-components and BOLD fluctuations.
In several feasibility studies, we investigated the potentiality and limits of simultaneous EEG/fMRI recordings and analysis (Sammer et al. 2005, 2007; Gebhardt et al., in press). Results show, that event related potentials can be used to set suitable limits to the usually seen rather spacious activations patterns e.g. with working memory tasks. In addition, connectivity can be investigated by correlations between ongoing-EEG and distribution of activated voxel (Sammer et al., 2007). Further studies will focus on the effects of schizophrenia on the P300 (Salisbury et al., 1998) and related hemodynamic activation.

## Prepulse inhibition of the auditory startle reflex during simulated acoustic fMRT conditions - preliminary results

Harald Gruppe, Christian Ubben and Bernd Gallhofer

Prepulse inhibition (PPI) of the auditory startle reflex is impaired in schizophrenia. However, it is unclear how far PPI can be used as an indicator for neurobiological changes in schizophrenia because changes in PPI are unspecific in terms of the brain systems involved. Functional MRI (fMRI) during a PPI procedure may clarify that question. But the unquiet background noise of fMRI (EPI noise) which is unavoidable for technical reasons interferes with the acoustic stimuli of auditory PPI. Using tactile stimuli, this problem can be avoided. However, little is known about the correlation between auditory and tactile PPI. Single studies combinig auditory PPI with fMRI have virtually ignored the interference problem. Therefore, 3 studies were designed to compare reactivity as well as PPI of the auditory startle reflex during standard background noise (70 dBA continuous white noise; WN) vs. EPI noise (92 dBA pulsed sound, recorded from our own MR scanner and presented outside the scanner; EPI). Each study varied another aspect of the relation between loudness of prepulses (PP; 1000Hz sinus) and loudness of background noise (BN; WN or EPI) - study 1: identical difference between PP and BN during WN or EPI, PP standard during WN and above standard during EPI; study 2: same as study 1, but PP standard during EPI and below standard during BN; study 3: different differences between PP and BN during WN or EPI and PP standard with identical level during WN or EPI, i.e. PP above WN, but PP below EPI. First results can be presented for study 1 (WN: PP = 74/78 dBA; EPI: PP = 96/98 dBA). Reactivity of the startle reflex was significantly reduced during EPI as compared to white noise. For the 180ms prepulse interval, there was significantly more PPI during EPI. A corresponding trend has been observed for the 60ms and 120ms prepulse intervals. Inspection of the raw data reveals an increased number of blink reactions to the prepulse stimuli during EPI. This effect has to be taken into account in PPI quantification. Results show that auditory PPI can consistently be evoked during fMRI, however, comparability of PPI during standard noise vs. EPI noise seems to be questionable under the conditions implemented in study 1.

## SESSION 4: REWARD / CLINICAL ASPECTS

### Salience of cigarettes in smokers depends on dopaminergic responsivity and type of smokers

C. Lujic and P.Netter

Centre for Psychiatry and Department of Psychology, University of Giessen

There is a debate, if the universally observed higher prevalence of smokers among schizophrenics represents the patient´s effort to counteract the cognitive depressant effects of antipsychotics (de Leon, 1996; Barr et al. 2008) or if it derives from the schizophrenia related disturbance of the mesolimbic dopaminergic system known to be associated with reward and addiction. Therefore the present study tries to investigate the role of dopaminergic responsivity and dispositional traits associated with addictive behaviour in healthy subjects thus avoiding the confounding effects of antidopaminergic treatment.
The questions investigated are: 1.Does a dopamine (DA) agonist modify cigarette craving (i.e.the salience of smoking) in nicotine deprived smokers? 2. Is the dopaminergic response as measured by decrease of prolactin (PRL) associated with craving ? 3. Is the dispositional degree of addictive behaviour responsible for the development of deprivation induced craving and how does this interact with the drug effect and the drug response?
Method: 36 male student smokers received 1.25 mg of bromocriptine and placebo in a balanced cross-over design applied 1 week apart. Measures of habitual intensity of smoking motivation (Coveting smoking, Stimulation smoking, Addictive tendencies),were assessed by questionnaires, plasma PRL responses were measured in blood samples collected from an indwelling cannula, and smoking urges after 5 hours of deprivation were obtained by a questionnaire as well as by behavioural measures from a computer choice paradigm.
Results revealed: While neither the dispositional factors of smoking motivation nor the drug itself altered changes in craving, it was reduced by the dopaminergic drug in highly addicted smokers (substitution theory) and increased in lows (incentive motivation theory).
Furthermore, the larger DA induced PRL response was associated with higher craving (confirming a study by Reuter et al.,2002), and craving increased most in persons with high PRL responses + high addictive smoking motivation. It must be concluded, that responsivity of the dopaminergic system may be more relevant in addiction research than the drugs themselves and that interaction with dispositional smoking related personality measures should be taken into account.

**Regional gray matter reductions are associated with lifetime substance abuse diagnosis in first episode antipsychotic-naïve schizophrenic patients**

Bjørn H. Ebdrup[1], William Baaré[2], Henrik Lublin[1], Birte Y. Glenthøj[1]

[1]Centre for Neuropsychiatric Schizophrenia Research, Psychiatric University Centre Glostrup, Copenhagen, Denmark, [2]Danish Research Centre for Magnetic Resonance, Hvidovre University Hospital, Denmark

Background: Two recent meta-analyses indicate only hippocampal volume reduction and ventricular enlargement to be consistently present in first episode schizophrenia, *Vita et al. Schizophr.Res (2006), Steen et al, Br.J.Psychiatry (2006).* Studies in antipsychotic-naïve first episode schizophrenia patients have generally focused on the basal ganglia. These studies tend to find reduced absolute volume caudate nucleus volumes, however, only few studies reach significance, most likely due to small sample sizes.
This study aimed to confirm the presence of reduced hippocampal volumes and enlarged ventricles in 38 antipsychotic-naïve first episode schizophrenic patients as compared to 43 matched healthy controls by means of VBM using a high-dimensional non-linear inter-subject warping. Moreover, reduction in the caudate nucleus was hypothesized. The possible effect of lifetime abuse was examined by categorizing patients into two subgroups; without (n=29) and with (n=9) lifetime (but not current) substance abuse side-diagnosis.
Methods: Patients were diagnosed with SCAN interviews (DSM-IV). Clinical measures included PANSS and Duration of Untreated Illness (DUI). Subjects underwent a high-resolution 3D T1-weighted MRI-scan on a 3 Tesla scanner. Images were analysed using SPM5 and spatial normalized with DARTEL. Small volume correction was performed for hippocampus, caudate nucleus and the lateral ventricles, using FDR (0.05) to control for multiple comparisons.
Results: As hypothesized, patients as compared to healthy controls had significant bilateral reduced hippocampal and caudate volumes. The hippocampal reductions, however, were solely driven by the subgroup of patients with lifetime abuse side-diagnosis, while the caudate reductions were most prominent in the patients with no history of abuse. Ventricles were not enlarged. Differences in global gray or white matter or CSF were absent. Exploratory analyses revealed an association between left hippocampal volume reduction and longer DUI.
Conclusion: Our results support the presence of hippocampal and caudate reductions in first episode antipsychotic-naïve schizophrenic patients. The hippocampal reductions, however, seem to be influenced by lifetime abuse and not specific to schizophrenia *per se*. The latter agrees with the fact that hippocampal changes are observed in various neuropsychiatric disorders, including substance abuse. Caudate volume reductions, on the other hand, might be specific for schizophrenia at the onset of the disorder.

## Wanting but not liking aspects of sensory-specific satiety are affected in schizophrenia

Verena Huth[1], Til Ole Bergmann[2], Dunja Hinze-Selch[3], and Roman Ferstl[1]

[1]Department of Psychology, Christian-Albrechts University Kiel, Germany, [2]Department of Neurology, Christian-Albrechts University Kiel, Germany, [3]Center for Integrative Psychiatry, Department of Psychiatry and Psychotherapy, Christian-Albrechts University Kiel, Germany

Background: Schizophrenia patients show abnormalities in eating behavior increasing the risk for disorders of the metabolic syndrome. They also exhibit disturbances of the reward system, especially in the dopaminergic parts in limbic and orbitofrontal brain areas. Particularly the processing of motivational aspects of reward (*wanting*) is affected, hedonic reward mechanisms (*liking*) seem to be largely intact. Therefore, sensory-specific satiety (SSS) as a mechanism of the regulation of food intake which is associated with orbitofrontal functioning and comprises *wanting* and *liking* aspects was investigated in the present study.
Methods: 27 patients with schizophrenia according to DSM-IV receiving stable neuroleptic medication and 27 healthy subjects matched for age, sex and body mass index (BMI) participated in the study. A SSS paradigm was implemented (1) as well as a computerized stimulus reward association reversal task for orbitofrontal functioning (2).
Results: As expected, schizophrenia patients showed weakened SSS regarding the *wanting* aspect, whereas the *liking* component remained relatively unaffected. The patient group also displayed deficits in the orbitofrontal reversal task compared to control subjects.
Conclusions: These results indicate a diminished motivational aspect of SSS in schizophrenia patients and suggest a higher *wanting* for more food compared to controls. This is fatal keeping in mind the patients' unhealthy nutrition behavior and the preference for foods high in sugar or fat. Impairments in orbitofrontal functioning could be part of the explanation for the affected *wanting* component of SSS in the patient group. Therefore, the results of the present study provide an important contribution to the investigation of the unhealthy food intake and disturbed body weight regulation in patients with schizophrenia.

References:
1: Rolls, E. T. & Rolls, J. H. (1997). Olfactory sensory-specific satiety in humans. *Physiol Behav, 61*(3), 461-473.
2: O' Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J. & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci*, *4*(1), 95-102.

**Appetite regulation in Schizophrenia:**
**preliminary results of a visual cue based fMRI Study**

Grimm, O; Klein, S; Zink, M; Smolka, M

INTRODUCTION: Appetite regulation in schizophrenia is a serious clinical problem due to reduced medication compliance and loss of life quality. Compared to healthy probands, schizophrenics have higher rates of obesity. Typically, weight gain is seen as a result of atypical antipsychotic medication, some of them (e.g. olanzapine) lead to an increase in appetite. However, the correlation between obesity and schizophrenia antedates the availability of atypical antipsychotics, pointing to a much complexer interrelation with the disease process itself. We propose that the study of the appetite dysregulation is not only of clinical importance but may gain insight into pathophysiologiocal processes of the disease itself.

METHOD: In our study we included 16 patients with schizophrenia (ICD-10 criteria) which were on a stable regime of antpsychotic medication and did not shwo a major alteration of mental stability (no CGI change >1) and 16 matched controls (age,gender smoking status). Probands had to fast for 8 hours before the fMRI trial. In a block-design paradigm probands saw images og high-caloric food and scrambled control images. Scanning was done on a 3 Tesla Siemens TRIO, data analysis was done with SPM5.

RESULTS:Healthy probands showed significant stronger activation in parts of the hypothalamus, thalamus, the globus pallidus and the amygdala ($p<0.001$, spatial correction 5 voxel).

DISCUSSION. Patients exhibit a lesser activation of parts of the limbic system and the putamen which is related to reward and appetite regulation. In analogy to drug craving, the underlying pathology in schizophrenia related weight-gain and food-craving seems to be a reduction in the sensitivity of reward processing circuits (e.g. dorsal striatum). Lower activation of the ventral and dorsal striatum is found in obesity (hypothalamus) or drug addiction (basal ganglia).

## Neural correlates of reward anticipation and outcome in patients with schizophrenia – preliminary results

*Stefan Kaiser[1], Joe Simon[1], Stephan Walther[1], Christoph Stippich[2], Matthias Weisbrod[1]*

[1] Department of Psychiatry, University of Heidelberg, [2] Department of Neuroradiology, University of Heidelberg

Previous studies have shown a decreased activation of the ventral striatum during reward expectation in patients with schizophrenia that is associated with negative symptoms and less pronounced in patients treated with atypical antipsychotic drugs. The goal of the present study was twofold: First, we wanted to investigate whether the neural response to rewarding outcomes is also abnormal in patients with schizophrenia. Second, we asked whether differential aspects of negative symptoms correlate differentially with neural activation during reward anticipation or outcome. In an ongoing study 10 patients with schizophrenia have so far performed a probabilistic monetary incentive delay task while undergoing functional magnetic resonance imaging. During reward anticipation subjects with schizophrenia showed mildly decreased activation of the ventral striatum, although all subjects were treated with atypical antipsychotic drugs. During reward outcome, subjects with schizophrenia showed reduced activation in the medial prefrontal cortex superior to the brain regions commonly associated with rewarding outcomes. These results suggest dysfunctional brain activation during both reward anticipation and outcome in patients on atypical antipsychotic drugs. At the meeting data based on a larger sample size will be presented including correlations between anhedonia/apathy scales and neural activation.

## Cognitive Effects of 6-month Quetiapine Treatment in Antipsychotic-Naïve First-Episode Schizophrenic Patients

Rune Andersen[1,2], Anders Gade[2], Birgitte Fagerlund[3], Bob Oranje[1] and Birte Glenthøj[1]

[1]Center for Neuropsychiatric Schizophrenia Research, Psychiatric University Center Glostrup, Denmark, [2]Department of Psychology, Copenhagen University, Denmark, [3]Bispebjerg Center for Child and Adolescent Psychiatry, Copenhagen, Denmark

Studies have found that atypical antipsychotics improve some cognitive deficits in schizophrenia, although it is unclear whether improvements are due to ameliorated cognitive functions, placebo effects, or retest-effects. Very few treatment studies have included both first-episode antipsychotic-naïve schizophrenic and matched healthy controls, and may therefore be confounded by prior medication and retest effects on neuropsychological tasks.

Effects of quetiapine on cognition were investigated in a group of first-episode antipsychotic- naïve patients with schizophrenia (n=24). A comprehensive battery of neuropsychological tests was administered at baseline and after 6 months of treatment with quetiapine (mean dose 519.6 mg/day; S.D. = 297.4). In order to control for retest effects, a matched and untreated healthy control group was also tested at baseline and after 6 months.

At baseline, patients performed significantly worse than controls on measures of intelligence, attentional set shifting, sustained attention, spatial working memory, spatial memory span, processing- and psychomotor speed, verbal and figural fluency, and verbal memory. While patients seemed to improve at follow-up on a number of these measures (within-group tests), they were found to improve significantly only on measures of attentional set shifting and speed of processing when controlled for retest effects (between group tests).

The results suggest that cognitive changes after treatment with quetiapine may mainly be due to retest effects. However, certain cognitive measures are also improved beyond retest effects, which supports some efficacy of quetiapine on cognition. The results emphasize the importance of controlling for retest effects, by including baseline-and follow-up assessments of healthy controls, in order to distinguish retest effects from cognitive amelioration.

## Prooxidative and proapoptotic effects in circulating leukocytes under clozapine therapy

Stefan Löffler[1], Karin Fehsel[2], Klaus Krieger[2], Uwe Henning[2], Christian Luckhaus[2], Ansgar Klimke[1]
[1]Psychiatric Department, Klinikum Offenbach a. M., [2]Neurobiochemical Research Unit, Psychiatric Department, Heinrich-Heine-University Düsseldorf

About 0,8% of patients starting clozapine treatment suddenly develope agranulocytosis (CA) within the first 18 weeks. In these patients clozapine leads to apoptotic break down of neutrophils and their progenitors. In nonCA-patients the initial decrease of these cells is counterregulated at least in part by G-CSF and probably by IL-6. Oxidative stress and expression of pro- and antiapoptotic genes were investigated in leukocytes of 5 CA-patients, 19 nonCA-patients under long term-medication with clozapine and 1 patient at start of clozapine treatment. Increased production of superoxide anion radicals ($O^{2-}$.) and elevated expression of the proapoptotic genes p53, bik und bax were observed in all 25 patients. The percentage of apoptotic leukocytes was enhanced at onset of CA (37%) and at start of clozapine medication (4%) in comparison to controls (sham treated cells; 2%). RT-PCR revealed increased expression of the chaperone hsp27, the detoxifying enzyme NQO-1, the antioxidative protein A1 and of the calcium-binding protein sorcin. In the beginning of the therapy expression of heme oxygenase-1 was elevated too, but in 89% of long term-clozapine patients HO-1 expression was downregulated. Patients under clozapine-treatment have increased IL-6 plasma levels. This cytokine is known to exhibit antiapoptotic effects and regulates proliferation and maturation of progenitor cells in bone marrow. Our results indicate that prooxidative effects and omission of cytoprotective mechanisms may contribute to CA.

## Treatment Resistant P300 Abnormalities in a Large Group of Antipsychotic Naïve, First-Episode Patients with Schizophrenia

Bob Oranje, PhD; Bodil Aggernaes, MD; Birte Y. Glenthoj, PhD, MD

Center for Neuropsychiatric Schizophrenia Research (CNSR), Faculty of Health sciences, Copenhagen University, University Psychiatric Center Glostrup, Glostrup, Denmark.

*Background:* Evidence is accumulating that cognitive deficits form core features in schizophrenia. It has been suggested that treatment with atypical antipsychotics can ameliorate these deficits. However, studies have often been confounded by patients either being medicated or chronically ill, making it hard to differentiate between medication effects and progress of the disease. In addition they frequently suffer from low subject populations, giving rise to power issues. In the present study the influence of a six months treatment period with quetiapine (atypical antipsychotic) was investigated on psychophysiological parameters of selective attention in a large group of first episode, antipsychotic naïve schizophrenia patients and age and gender matched healthy controls.
*Methods:* Thirty-four antipsychotic naïve patients with first-episode schizophrenia and 40 age and sex matched healthy controls were tested in a selective attention paradigm at baseline and at 6 months follow-up. The patients were treated with quetiapine during the period between baseline and follow-up, the controls received no treatment.
*Results:* Both at baseline and at follow-up, the patients showed highly significant reduced P300 amplitudes compared to the healthy controls. No treatment effects were found.
*Conclusions:* The results indicate that deficits in P300 amplitude, and thus attention deficits, are present at an early stage in the development of schizophrenia. Furthermore, the results indicate that a 6 months treatment period with quetiapine does not ameliorate these attention deficits. The results are consistent with the concept that P300 amplitude deficits represent stable endophenotypes for schizophrenia.

## Cognitive improvement of schizophrenia patients: Enhancing cognition while enjoying computer-aided cognitive training

Wolfgang M. Trapp[1], Alexander Hasmann[2], Bernd Gallhofer[3], Ursula Lang[1], Wilfried Guenther[1] and Matthias Dobmeier[2]

[1]Sozialstiftung Bamberg, Department of Psychiatry,St.-Getreu-Strasse 14-18, D 96049 Bamberg, Germany, [2]University of Regensburg, Department of Psychiatry, Universitätsstrasse 84, D 93042 Regensburg, Germany, [3] Justus Liebig University School of Medicine, Centre for Psychiatry, Am Steg 22, D-35392 Giessen, Germany

**Objective**: Two studies examined the effects of computer-aided cognitive training using motivational software that evokes positive emotions in patients suffering from schizophrenia.

**Method**: 40 outpatients and 60 inpatients were included. 20/30 of them received cognitive training, 20/30 received occupational therapy. Before and after treatment, all patients were assessed with a battery of neuropsychological tests measuring executive functions, attention and verbal memory.

**Results**: Enhancing effects on executive functioning level, attention and verbal memory could be found. At the same time, effects on positive and negative symptom level could be observed. Changes in symptom levels and cognitive improvement were uncorrelated.

**Conclusions:** Our findings indicate that cognitive achievement of schizophrenia patients can be improved using pleasant and “game-like” cognitive training tasks. Beside a motivating effect, these tasks may cause more enhanced processing. Furthermore rapid online processing and accurate timing, which is assumed to be inadequate in patients with schizophrenia, might be ameliorated.

## Treatment outcome in Turkish immigrants with mental disorders compared to German patients

Bernd Hanewald

Centre for Psychiatry and Psychotherapy, Giessen

*Background:* Turkish immigrants are an important target group in psychiatric care systems, because they suffer more often and more severely from mental disorders compared to persons of German origin. Several studies report a stronger symptom distress even after treatment in Turkish patients compared to Germans. This could be due to a lack of transcultural competence. In the present study, we compared treatment outcome between Turkish and German patients with mental disorders.
*Methods:* We interviewed patients of Turkish origin and a control group of German patients (matched on age, gender, diagnosis and hospital) in their native language. The data collection took place in three hospitals. Treatment outcome was assessed by self-ratings and doctor-ratings in a prospective manner.
*Results:* Turkish patients not only showed worse treatment outcome at the end of the treatment, but also felt more impaired at the beginning of treatment in comparison to German patients. They showed a stronger symptom distress, a stronger severity of illness and a lower global functioning than German patients.
*Discussion:* Worse treatment outcome in Turkish patients compared to German patients could be explained by cultural and migration-associated characteristics such as pessimistic illness beliefs, use of maladaptive coping styles and migration-associated stressors. These characteristics should be considered in the treatment process. Nevertheless, the stronger impairment at the beginning of treatment in Turkish patients could also have negative effects on treatment success.

**Validation of a Clinical Global Impression Scale forAggression (CGI-A) in a sample of 558 psychiatric patients**

Christian G. Huber, MD; Martin Lambert, MD; Dieter Naber, MD; Alexander Schacht, PhD; Hans-Peter Hundemer, MD; Thomas T. Wagner, PhD; Benno G. Schimmelmann, MD

Objective: Clinical management of aggression depends on the availability of easily administrable measurements allowing reliable evaluation. The present study's aim is to validate a Clinical Global Impression-Severity of Aggression scale (CGI-A).

Method: 558 inpatients with psychiatric disorders and an agitated-aggressive syndrome at baseline were continuously assessed over 5 days using CGI-A and the Positive and Negative Syndrome Scale Excited Component (PANSS-EC). Equipercentile linking, correlation analyses and linear regression were applied.

Results: Relationship between CGI-A and PANSS-EC total score was found to be linear. On a 5-level CGI-A scale, values of 1 to 5 points were found to correspond to PANSS-EC scores of 12.2, 16.7, 21.3, 25.8, and 30.4, respectively (average increase: 4.6). All findings remained stable when only data from patients with schizophrenia spectrum disorders were analyzed.

Conclusions: The CGI-A is proposed as a quickly administrable scale for the assessment of patients' aggressiveness.

**Patterns of depression in putatively high-risk for psychosis subjects**

H. Graf von Reventlow[1,2], S. Ruhrmann[2], M. Heinimaa[3], P. Patterson[4], P. Dingemans[5], S. Özgürdal[1,6], F. Schultze-Lutter[2], G. Juckel[1,6], A. Morrison[7], D. Linszen[5], R. K. R. Salokangas[3], M. Birchwood[4], J. Klosterkötter[2], and the EPOS Group[1,2, 3,4,5,6,7]

[1]Ruhr-University Bochum, Germany, [2]University Hospital of Cologne, Germany, [3]University of Turku, Finland, [4]Academic Medical Centre, Amsterdam, The Netherlands, [5]Early Intervention Service, Birmingham, UK, [6]Charité, Berlin, Germany [7]University of Manchester, UK

Introduction: High rates of depressive symptoms and syndromes have been observed in the early course of non-affective psychoses. Recent analyses even point to depression being a psychopathological dimension in its own right. Albeit the prevalence of depressive disorders in patients putatively at risk for psychosis, not too much is known about severity, type, and so on. Thus, the European Prediction of Psychosis Study (EPOS) investigated more deeply into that field.
Methods: At EPOS inclusion, relevant baseline measures (BDI, BSABS-P, SOPS 3.0, PANSS, SCID I etc) were obtained for 240 subjects putatively at risk for psychosis, with follow-ups for 9- and 18-months.
Results: High levels of sad mood (76.3% in BDI item, mean of 1.25) and clinically relevant current depression (58.1% in BDI total score, mean of 19.9) were reported at baseline. About 40% of the sample fulfilled the criteria of a current DSM-IV affective disorder. Significant correlations of depression were found with PANSS positive and negative scores, SOPS 3.0. suspiciousness and perceptual abnormalities, current level of functioning, among others.
Discussion: The results highly correspond to findings of retrospective studies on the early course of non-affective psychoses, and underline the relevance of depression in early recognition and treatment of psychosis.

## Lack of insight and cognitive dysfunction in schizophrenia

S. Bal[1], S. Loos[1,2], G. Sartory[1], B. Müller[2], J. Wiltfang[2], M. Wagner[3] and S. Klingberg[4]

[1]Dept. Clinical Psychology, University of Wuppertal, [2]Dept. Psychiatry, University of Duisburg-Essen, [13]Dept. Psychiatry, University of Bonn, [4]Dept. Psychiatry, University of Tübingen[4]

Lack of insight represents a core symptom of schizophrenia and accounts to a large degree for the lack of adherence to treatment, frequently encountered in this group of patients. Previous studies in chronic schizophrenia found either deficits of executive function or of declarative memory to be related to lack of insight. In the present study, 27 patients with predominantly positive symptoms were administered a battery of neuropsychological tests and the SUMD (Scale to Assess Unawareness of Mental Disorder). Symptom ratings and scores of test performance were entered into regression analysis with insight scores as dependent variable. Results revealed deficits in declarative memory to be significantly related to lack of insight. The results are consistent with findings of lack of insight in amnestic disorders.

## INDEX OF POSTER AUTHERS

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