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

Translational Psychiatry – the way forward to solve the enigma of psychosis?

ROBERT SOMMER AWARD SYMPOSIUM 2010

Robert Sommer Award Symposium

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Abstract Book

Robert Sommer Research Society
Am Steg 22
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Organiser:

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at the Centre for Psychiatry
Justus Liebig University School of Medicine
Chairman: Prof. B. Gallhofer, M.D., Ph.D.

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Venue:

Thursday, 7th October
Centre for Psychiatry
Main Lecture Theatre, Main Building
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Friday, 8th October
Centre for Psychiatry
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Saturday, 9th October
Arnsburg Monastery
35423 Lich

POSTER ABSTRACTS

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Session 2: Social Cognition
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SESSION 1: BRAIN CORRELATES

Correlates of a "split mind" in event-related EEG data

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Introduction: Numerous studies have provided evidence that event-related EEG oscillations at low frequencies in the delta (1-4 Hz) and theta (4-8Hz) band are impaired in schizophrenia. These abnormalities have been linked to cognitive deficits and abnormal neurotransmitter systems. In healthy individuals it appears that event related oscillations arise from a combination of phase-resetting of ongoing oscillations and an increase in power unrelated to ongoing activity. It is unknown which of these processes contribute to the EEG abnormalities observed in schizophrenia and how on-going oscillations influence the generation of new event-related EEG signal in schizophrenia.

Methods: We applied a method recently developed by Martinez-Montes et al. (2008) which employs complex valued time-frequency representations of EEG data to distinguish between the different mechanisms that might contribute to event related perturbations of oscillatory activity (e.g. phase resetting, increase in phase-locked EEG signal, increase in non-phase-locked EEG signal). In addition we tested for interactions between phase resetting and additive event-related EEG signal, as well as cross-frequency interactions.
The EEG data was acquired during an auditory oddball task in 34 male schizophrenia patients and 34 male healthy matched controls (mean ± SD in years; controls 26.33 ± 5.65; patients 25.22 ± 5.46).

Results: In response to target tones, schizophrenia patients showed deficits in increasing mean amplitudes (both phase-locked and non-phase-locked) in the delta and theta band, as well as phase-resetting of on-going delta oscillations. Furthermore, there was evidence of impaired coordination between the ongoing phase of low-frequency oscillations and additive event-related signal in schizophrenia patients within one frequency band, as well as between frequency bands.

Conclusions: The results point to three deficient electrical processes in response to a stimulus in schizophrenia: first, a failure to produce new event-related EEG signal; second, a failure to reset the phase of ongoing oscillations and third, to coordinate ongoing electrical brain activity with new electrical activity. The latter process might be at the heart of the "split mind" in which various mental processes at different time-scales or time-points are not well integrated.

Martinez-Montes, E., Cuspineda-Bravo, E. R., El-Deredy, W., Sanchez-Bornot, J. M., Lage-Castellanos, A., & Valdes-Sosa, P. A. (2008). Exploring event-related brain dynamics with tests on complex valued time-frequency representations. *Stat Med, 27*(15), 2922-2947.

Age effects on habituation and prepulse inhibition of the human startle reflex

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Introduction
Evidence has been accumulating that cognitive deficits, including disturbances in early information processing, form core features in schizophrenia. Given the fact that some of these deficits are not only consistently found in patients with schizophrenia, but also in their first degree relatives, suggests that they might represent endophenotypes for the disease. Deficiencies in both sensorimotor gating and habituation are examples of possible endophenotypes for schizophrenia. Both phenomena can be quantified by assessment of prepulse inhibition and habituation of the human startle reflex. The current study reports on the effect of age on these two paradigms, since there are only a few conflicting studies in literature devoted to that.

Methods
Fourty-eight healthy male volunteers evenly distributed in age from 18-80 years, where tested in a combined PPI and habituation paradigm. Pulse alone and habituation trials consisted of 20 ms of white noise (115 dB), prepulses consisted of bursts of white noise with intensities of either 6 or 15 dB above background (70 dB white noise) with a duration of 20 ms. Stimulus onset asynchrony in prepulse–pulse trials was either 60 or 120 ms, whereas inter-trial intervals were randomized between 10 and 20 s.

Results
No age effects were found on PPI. However a significant effect of age was found on habituation.

Discussion
Other studies have described the age effects on PPI and habituation among healthy volunteers, but with conflicting results:. the results of one study pointed towards an U-shaped function between PPI and age while no effects of age were found on habituation, while in another study no effects of age were found on PPI but increased habituation was correlated with increased age. The current results confirm that PPI is not affected by age, although it does seem to affect habituation

Oxidative stress and schizophrenia: Cause or effect? - In vitro and in vivo analyses of peroxisomal reactions to increased dopamine

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Neurodegeneration is commonly found in schizophrenic patients, albeit still unclear, why it occurs and whether it is a cause of schizophrenia or rather caused by schizophrenia. Although there are numerous studies supporting either theory, it is our belief that the link between both factors could be oxidative stress in the patient's brain caused by excess dopamine (DA), since it is clearly established that an overabundance of DA both in the neuron's cytosol or the synaptic cleft as well the enzymatic degradation of DA through MAO and COMT both lead to the production of reactive oxygen species (ROS). We therefore hypothesize that overabundance of DA in schizophrenia leads to an increase in ROS-production, which over time will lead to oxidative stress and thereby to neurodegeneration.
A key player in the body's antioxidant capacity is the peroxisome. This cell organelle is involved in both enzymatic (e.g. through catalase) as well as non-enzymatic (e.g. through the synthesis of radical-scavenging ether lipids) antioxidant metabolism.
To examine the reactions of peroxisomes we incubated primary cultures of murine cortical neurons and astrocytes (ration ca. 85/15) with different concentrations of DA, whereupon we found an increased abundance of the enzyme catalase as well as a possible redistribution of peroxisomes from the peripheral processes to the somata, with the level of cell death not being significantly increased. This is in accordance with the so-called "atypic neurodegeneration" found in schizophrenic patients.
As the changes were most pronounced in astrocytes we then isolated pure primary cultures of murine cortical astrocytes and incubated these with different DA-concentrations for 24, 48 and 72 h in an attempt to examine whether changes in peroxisomal patterns were specific to neuron-astrocyte interactions.
In a final set of experiments we attempted to increase the DA release in vivo in the brains of wild type male C57Bl6/J mice through i.p. injections of 0.5 mg/kg body weight of the selective NMDAR-blocker MK-801 (dizocilpine).
Animals were injected once every 24 h and sacrificed after 1 h (1 injection of MK-801), 24 h (2 inj.), 48 h (3 inj.) or 72 h (4 inj.). The brains were excised and either fixed and embedded in paraffin for morphological and immunofluorescence analyses or processed for RNA-extraction with subsequent RT-PCRs for the analysis of the expression patterns of various genes involved either in dopaminergic or peroxisomal metabolism.
Our preliminary results support our hypothesis that DA can actually change peroxisomal reactions specifically and only in intact neuron-astrocyte interactions and that these changes become apparent significantly later than the schizophrenia-like changes in animal behaviour observed mere minutes after injection with MK-801.
We therefore uphold our theory that schizophrenia causes oxidative stress and not vice versa and that the direct link is the increased abundance of DA.

Time-Dependent Changes in Gamma Oscillations and Parvalbumin Immunoreactive Cell Density in the CA2/3 Region of the Rat Hippocampus following Sub-chronic Phencyclidine Treatment

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Gamma-frequency oscillations (20-80 Hz) arise from networks of the parvalbumin subset of GABAergic interneurons. These oscillations are prevalent in active hippocampal networks and are important for cognition, learning and memory [1]. In our laboratory, we have consistently shown that a sub-chronic phencyclidine (PCP) dosing regime in adult female rats produces robust, long lasting cognitive deficits, along with decreases in parvalbumin immunoreactive (IR) interneurons in the hippocampus [2-4]. The aim of the current study was to investigate the effect of sub-chronic PCP on gamma oscillations and parvalbumin IR cell density in the CA2/3 region of the hippocampus, at 2 and 8 weeks post-PCP treatment.

In cohort 1, adult female hooded-Lister rats received either sub-chronic PCP (2 mg/kg, n=10) or vehicle (1 ml/kg, n=10) i.p. twice daily for 7 days, followed by 7 days washout. PCP- and vehicle-treated (n=10) rats were sacrificed, 2-8 weeks post-treatment, and their brains were removed for in vitro electrophysiology. Gamma oscillations were induced in horizontal slices of the hippocampus by bath application of kainate (100 nM). Oscillations were measured in both PCP and vehicle-treated animals at 2-5 and 6-8 weeks post-treatment. Power (strength of signal as a function of frequency) was determined as the area under the curve of the power spectra between 20 and 80 Hz. In cohort 2, adult female hooded-Lister rats received either sub-chronic PCP (2 mg/kg, n=16) or vehicle (1 ml/kg, n=16) i.p. twice daily for 7 days, followed by 7 days washout. At 2 and 8 weeks post-treatment, PCP- and vehicle-treated (n=8) rats were sacrificed and their brains were removed for immunohistochemical analysis of parvalbumin IR cell density in the hippocampus.

At 2-5 weeks post-treatment, we observed a significant reduction in gamma oscillations in the CA2/3 region in PCP-treated animals ($P<0.05$ vs. vehicle). In contrast, at 6-8 weeks post-treatment, we observed a significant increase in gamma oscillations in the CA2/3 region in PCP-treated animals ($P<0.05$ vs. vehicle). At 2 weeks post-treatment, we observed a reduction in parvalbumin IR cell density in the CA2/3 region in PCP-treated animals ($P=0.058$ vs. vehicle). In contrast, at 8 weeks post-treatment, parvalbumin IR cell density was unchanged in the CA2/3 region in PCP-treated animals ($P=.751$ vs. vehicle).

In the present study we found a reduction in gamma oscillations following PCP treatment that was paralleled by a deficit in parvalbumin IR cell density, at a similar time point (2-5 weeks post PCP-treatment). In contrast, a time-dependent increase in gamma oscillations was observed (6-8 weeks post PCP-treatment), at which point parvalbumin IR cell density was unchanged. These preliminary studies demonstrate a link between altered gamma-frequency oscillations and abnormalities in parvalbumin interneurons, which may underlie some of the cognitive deficits previously reported in this animal model of schizophrenia.

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Normalizes Sensorimotor Gating Deficits in Chronic Patients with Schizophrenia

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Evidence is accumulating that cognitive deficits form core features in schizophrenia. Several studies have shown improvements of prefrontal cognitive function by α2-agonists in schizophrenia. In the present study it was investigated whether clonidine (an α2-adrenoceptor agonist) could normalize sensorimotor gating deficits in schizophrenia.

Twenty male chronic patients with schizophrenia who were stable on their antipsychotic medication and twenty healthy male volunteers were assessed in an auditory prepulse inhibition of the startle reflex (PPI) paradigm on 5 occasions separated by a minimum of one week: once after oral administration of placebo and once after 25, 50 75 and 150 µg of clonidine.

Patients showed deficient PPI compared to the healthy controls in the placebo condition. Dosages of 25, 50 and 75 ug of clonidine significantly increased PPI in the patients compared to placebo, to such a level that it was no longer significantly different from the healthy controls.

Since even low dosages of clonidine added to the current antipsychotic treatment of the patients were found to normalize their PPI deficits, it suggests that α2-agonists are potent agents to normalize sensorimotor gating deficits in schizophrenia. Since sensorimotor gating deficits are thought to underlie psychotic symptoms, these results have a potentially high clinical relevance.

Regionally localized contraction of brain surface in schizophrenia

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Aims: Morphology of cortical surface is primarily studied via analysis of grey matter 'density' or thickness. Accumulating evidence suggests that distinct set of genetic factors influence brain surface area and thickness [1]. Evolutionary trajectories for these two morphological properties are distinctly different [2]. In addition, postnatal human development shows unique pattern of areal expansion[3]. In schizophrenia, the question of whether regional cortical surface area is reduced has not been addressed so far. Our objective is to test if regionally localised areal contraction can be detected in schizophrenia.

Methods: Participants included 57 patients with schizophrenia receiving medication and meeting *DSM-IV* criteria for schizophrenia and 41 healthy volunteers, matched on age and parental socioeconomic status. Using high-resolution MRI scans, gray-white and pial surfaces were reconstructed. Using a spherical morphing procedure, we mapped areal contraction/expansion across numerous points (vertices) along the cortical mantle. Smoothed cortical maps with accurate matching of morphologically homologous cortical locations on the basis of each individual's sulcogyral anatomy were compared across the two groups. Using total brain surface area as a covariate, we obtained a proportional areal contraction map for subjects with schizophrenia.

Results: Total cortical surface area was significantly reduced in schizophrenia. Regionally localized contraction was seen at homologous locations in both hemispheres, though more pronounced in the left hemisphere. Significant contractions were noted in left superior frontal region, bilateral precuneus, lateral temporal region (bilateral), and inferior parietal region (bilateral) along with left temporo-parietal junction. There were no areas of relative areal expansion in schizophrenia.

Conclusions: Areal contraction map reveals a pattern of morphological changes that are different from cortical thinning maps reported in schizophrenia. This could be related to abnormalities in genetic determinants of cortical surface area in patients with schizophrenia. It is also plausible that an abnormal cortical maturation in schizophrenia is associated with regional differences in normal postnatal areal expansion. Predominant fronto-parietal contraction is likely to be associated with aberrant cortical connectivity.

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Baseline brain perfusion in schizophrenia revisited: An arterial spin labelling study

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Several studies have demonstrated the existence of changes in brain metabolism or perfusion in schizophrenic patients using PET or SPECT in the past. Recent advances in magnetic resonance techniques such as CASL (continous arterial spin labelling)[1] offer superior spatial resolution and allow repeated monitoring of perfusion levels by avoiding ionizing radiation. The purpose of this study was to investigate the capacity of CASL techniques in detecting baseline brain perfusion changes in schizophrenia.

A sample of 31 right-handed schizophrenic patients was matched to 62 controls in sex, age, and date of study. Resting state perfusion was measured while participants lay in the scanner with closed eyes for 8 min.

In patients, relatively increased baseline perfusion was detected in the posterior cingulate and prefrontal cortex (postcentral gyrus), and in the basal ganglia (effect sizes between 3.5 and 4.5 ml/100gr/min). Changes were more marked in the striatum, i.e. caudate nucleus and putamen, while spared the pallidum and the capsula interna. No significant increases were found in the control group compared to the patients.

Arterial spin labelling techniques offer sufficient resolution to identify anatomical structures involved in perfusion changes associated with medicated patients, and may be applied to monitor the evolution of perfusion patterns during different phases of the illness and over the course of treatment.

Literature:
J.J. Wang, *Radiology* 2005, *235*, 218-228.

SESSION 2: SOCIAL COGNITION

Gaze cueing effects in schizophrenia

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Gaze cueing refers to an attentional cueing paradigm in which gaze stimuli were presented as central spatial cues which bias reactions to peripherally presented target stimuli. Gaze cueing is a specific example of shared or joint attention which implies phenomenons in which one's own attention is redirected according to the attentional focus of a social interaction partner. Joint attention, in turn, can be regarded as a prerequisite or an early cognitive step in theory of mind processing. It is well known that schizophrenia is associated with dysfunction in attention as well as social cognition, especially theory of mind. Moreover, schizophrenic patients show reduced brain volumes in the area of the superior temporal sulcus, a brain area which is related to gaze perception as well as theory of mind. Based on these considerations, it is plausible to assume that schizophrenia is associated with deficiency in gaze cueing. Despite this obvious assumption, there are only few studies into gaze cueing and joint attention in schizophrenia. Regarding this issue, differences between schizophrenic patients and healthy controls were reported by Langdon et al. (2006) using portrait photographs with different head directions as well as Akiyama et al. (2008) using pictographical drawing of eyes with different gaze directions as cues. To further clarify this issue we carried out two gaze cueing studies including, in total, 48 schizophrenic patients and 51 healthy controls. We used portrait photographs with eyes gazing towards or away from a target stimulus as respectively congruent or incongruent cues as well as portraits with unaverted gaze serving as neutral cues. We compared these social gaze cues to non-social cues composed of geometrical drawings embedding arrows. Study 1 used short cueing intervals (100 and 300ms) whereas study 2 used longer cueing intervals (300 and 800ms). Over all, in both groups reaction times to targets preceded by congruent cues were significantly shorter compared to incongruent cues. However, effect sizes in the schizophrenia group were half to third of the effect sizes in healthy controls. No substantial differences between groups were found after 300ms cueing interval, in neither study. Both studies revealed that cue type, i.e. social vs. non-social, impinges on spatial cueing in healthy controls only. In study 1, using 100ms cueing intervals, a benefit of congruent social cues compared to non-social cues was observed in this group. In study 2, using 800ms cueing interval, only healthy controls showed significantly longer reaction times after social cues as compared to non-social cues. These findings confirm deviant social cue processing in schizophrenia.

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Langdon,R., Corner,T., McLaren,J., Coltheart,M., Ward,P.B. (2006) "Attentional orienting triggered by gaze in schizophrenia", Neuropsychologia, Vol.44, pp.417-429.

Self-other discrimination in schizophrenia is associated with awareness of illness

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The term “schizophrenia” embraces a group of syndromes that are characterized – among other symptoms – by reduced self-awareness. While there is accumulating evidence for altered self-information processing in schizophrenia from auditory and tactile modalities, surprisingly little is known about their visual self-recognition, which has been suggested to be an indicator of higher-order self-awareness. Clinically, the most important consequence of impaired self-awareness in schizophrenia is lack of insight and unawareness of illness, affecting at least 50% of patients.

Here we address the question whether or not visual self-other discrimination differs between healthy subjects and patients with passivity symptoms. Twenty patients with schizophrenia and twenty age-matched controls were included. We used a video-morphing design where subjects had to indicate when they recognize the person, the video is transforming into. We included the own face, an unfamiliar, a familiar and an average face into the videos. Patients’ symptomatology and awareness of illness were rated using the PANSS and the SUMD, respectively.

Results indicated no evidence for a reduced visual self-other discrimination in patients. However, patients had more difficulties in identifying unfamiliar faces. Patients with higher insight scores responded slower when watching videos morphings in all conditions compared to patients with poor insight. Higher insight was also associated with reduced likeability of one’s own face on pictures.

Self-face recognition in schizophrenia seems to be related to other measures of higher order self-awareness, including insight into the disorder and evaluation of one’s own face.

Theory of Mind (ToM) in patients with schizophrenia

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Introduction: Theory of Mind (ToM) - the ability to infer mental states - is a complex cognitive function that requires integration of information from many sources. There is evidence that schizophrenia patients are impaired in ToM functioning. Imaging studies investigating the neural correlates of these abilities in healthy controls suggested a "social" brain network encompassing the superior temporal gyrus (STS), the temporoparietal junction (TPJ), the medial prefrontal cortex (MPFC) and the anterior cingulate cortex (ACC). In this study we used the "moving shapes" paradigm, which has been shown to successfully activate the neural ToM network in imaging studies. We hypothesized impaired clinical performance and differential activation patterns in ToM regions of the brain in patients with schizophrenia as compared to controls.

Methods: 14 patients with schizophrenia and 13 healthy controls were included in the study. The ToM paradigm consists of 9 silent animated movies presenting triangles displaying random (RM; baseline), goal-directed movement (GD) and ToM sequences. The movies were presented in a blocked fMRI design. Oral descriptions of the movies were recorded after fMRI and evaluated using standardized criteria.

Results: Behavioral data revealed that schizophrenia patients performed significantly worse than controls in the use of ToM-related vocabulary and length of descriptions. Functional activation patterns related to ToM vs. baseline videos showed significant activations in temporo-parietal-occipital cortex as well as in the medial and inferior lateral PFC both in patients and controls. Group comparisons revealed significantly stronger activations in the inferior frontal gyrus, the STS, the ACC and the insula in patients. Controls did not show any areas of greater neural activation compared to the patient group.

Discussion: Results of our study replicate behavioral performance differences between schizophrenia patients and healthy controls. Neuroimaging findings reveal a stronger activation in schizophrenia patients as compared to controls in areas that are closely associated with the neural ToM network. This need to increase the blood flow during ToM task performance could be considered as compensatory and might be a result of the reduction of gray matter volume in prefrontal brain areas as well as of disintegrity in white fibers connecting the crucial brain areas needed for ToM functioning in schizophrenia.

Effects of context information on emotion recognition in schizophrenia

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Introduction: There is increasing evidence that schizophrenic patients can adequately interpret facial expressions in unambiguous social interaction tasks. However, they seem not to benefit from contextual affective information in more ambiguous situations. The neurocognitive basis of impaired processing of contextual information is not yet understood. Accordingly, the aim of this fMRI study was to investigate how the assignment of emotions to facial expressions is influenced by flanking affective information in schizophrenic patients and healthy subjects.

Methods: The subjects (N=34) were asked to assign predefined emotions (happy, surprised, angry, afraid) to pairs of eyes (Öhman's picture set). They were instructed to ignore simultaneously presented flanking affective pictures. The flanking affective information was established by negative or positive emotion pictures (IAPS), and by negative or positive social interaction pictures (new material which we have pretested on 50 participants), or a neutral picture. In relation to the eye pictures, the flanking pictures represented either congruent or incongruent emotions. Using a mixed model design, pairs of eyes and the neutral context picture were presented in one group. In a second group combinations of eyes and IAPS or social interaction pictures were used. Behavioral and hemodynamic data (fMRI) were recorded during the taskperformance.

Results: The behavioral data showed an effect of facilitation of facial expression perception for congruent affective flanking information compared to incongruent conditions in schizophrenic patients and healthy subjects. In both conditions schizophrenic patients performed less accurate. Supporting the initial hypothesis, intensity ratings were different for congruent and incongruent conditions in healthy subjects but not in schizophrenic patients. This particularly applied to negative facial expression targets. Accordingly, the main fMRI results were related to negative emotion pictures. Patients showed less hemodynamic activation in caudate nucleus and nucleus accumbens and more activation in insula and inferior frontal areas for incongruent conditions.

Conclusions: Affective flanker information showed differential effects in schizophrenic patients and healthy subjects, and for positive and negative facial expression target pictures. The hemodynamic activation patterns include core areas that are vulnerable in schizophrenia and which are associated with dopaminergic brain circuits, reward processing, and emotion regulation. Concluding, the results encourage to study further contextual processing in the framework of social cognition and schizophrenia.

Alteration of the Brain Reward System in Schizophrenia

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The brain reward system is normally activated by salient events. The salience hypothesis suggest, that in schizophrenia a dysregulated dopamine transmission distorts the normal process of contextually driven salience attribution, which leads to aberrant assignment of salience to external objects (delusions) and internal representations (hallucinations). So far, only a few studies have examined the function of the brain reward system in antipsychotic naïve schizophrenic patients, and to our knowledge there are no longitudinal studies on this group of patients. The aim of the current study is to investigate the brain reward system in antipsychotic naïve schizophrenic patients before and after a treatment period of 6 weeks with amisulpride (D2 antagonist, atypical antipsychotic).

The study has currently included 18 antipsychotic-naïve patients with schizophrenia and 16 age and gender matched healthy controls. All participants have been assessed with an fMRI reward paradigm using a variant of the Monetary Incentive Delay task.

Only baseline data will be presented in this preliminary report. During the anticipation phase the antipsychotic naïve schizophrenic patients showed a significantly smaller BOLD response of the ventral striatum compared to the healthy controls regarding cues indicating salient events.

Although our results are still preliminary, they are in line with earlier studies on medication free schizophrenic patients, in which a reduced difference was found between striatal activity elicited by salient and neutral events in the schizophrenic patients compared to healthy controls.

Neural correlates of iconic and metaphoric co-verbal gesture processing in patients with schizophrenia

Straube B., Green A., Sass, K. & Kircher T.

Gestures are a significant component of non-verbal interpersonal communication. In schizophrenia comprehension of gestures is impaired. In this study we investigated the neural correlates of speech and gesture interaction in relation to sentence content and gesture type in healthy subjects and patients with schizophrenia.
Patients with schizophrenia and matched control subjects were presented with short video clips of iconic gestures (related to concrete sentence contents) and metaphoric gestures (related to abstract sentence contents) during fMRI data acquisition.
We found comparable activation patterns between the groups for both gesture types vs. baseline (fixation cross), in predominantly bilateral occipital, temporal and frontal regions. However, in contrast to patients only healthy subjects show more activation in left inferior frontal regions for the processing of metaphoric gestures in comparison to iconic co-verbal gestures and uni-modal control conditions.
Our preliminary results are consistent with the evidence of impaired gesture (Berndl et al., 1986) and metaphor comprehension in patients with schizophrenia (Kircher et al., 2007). Patients with schizophrenia possibly fail to activate left hemispheric frontal areas which seem to be important for the comprehension of metaphoric co-verbal utterances (Straube et al., in press).

Acknowledgements:
This research project is supported by a grant from the Interdisciplinary Center for Clinical Research “BIOMAT” (IZKF VV N68) and the Deutsche Forschungsgemeinschaft (DFG, IRTG 1328).

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Fairness Perception and Willingness to Punish Altruistically in Schizophrenia

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Humans possess evolved cognitive and emotional biases that guide an individual's actual behaviour in terms of cooperation, defection or punishment of unfair behaviour. Empirical evidence suggests that a neural network comprising parts of the frontal lobe as well as limbic structures is involved in economic decision-making[1,2,3]. This network greatly overlaps with those brain structures that are known to be dysfunctional in schizophrenia[4]. Accordingly, we hypothesised that patients with schizophrenia would differ from controls in performance on tasks involving economic decision-making.

Methods: 25 in-patients with schizophrenia (SCHIZ) (7 female, 18 male) were compared with a group of 25 healthy controls (NC), on performance in an Ultimatum Game (UG), where participants had the role of the recipient, and in a Dictator Game with Punishment (DGP), where participants took the role of a third-party player equipped with the ability to punish a dictator for being unfair. Notice that punishment in the DGP is costly for the punisher.
Patients' mean-age was 32.0 (SD ± 6.5), with a verbal IQ (according to the MWT-B a verbal intelligence test) of 101. The control group did not differ significantly from the patient group with a mean age of 32.9 (SD ± 6.9) and a verbal IQ of 107. Subjects in both groups had an educational level of 10 years of education as minimum.
Patients' psychopathology was measured using the Positive and Negative Syndrome Scale. In addition, sensitivity towards injustice we measured using the Justice Sensitivity Scale, comprising three different perspectives (victim, observer, perpetrator).
Subject's ability to make inferences about another person's state of mind was tested by a computer version of the Reading Mind In The Eyes Test.

Results: Acceptance rate of unfair offers in the UG was significantly higher in the patient group compared to controls, but both groups' acceptance rates decline with the degree of unfairness of the offers. In the DGP, the punishment-investment by the third-party increased with the degree of unfairness of the proposed offer in both groups at a comparable level. Both groups tended to induce equity between the dictator and the recipient.
Regarding the differences in justice sensitivity there were no significant differences between the groups. Looking at the victim perceptive and the perpetrator perspective according to the justice sensitivity scale the SCHIZ group scored even marginally significantly higher than the NC. Acceptance rate of offers in the 7:3 split-condition correlated significantly with scores on the perpetrator perspective of the justice sensitivity scale in a negative way.
There were no differences in empathic perspective taking according to the Reading Mind In The Eyes Test.

Discussion: Patients with SCHIZ do not behave profoundly different from healthy controls as one would expect according to their assumed malfunctioning in theory of mind abilities and difficulties in social interactions. Notwithstanding Patients with SCHIZ seem to be less sensitive towards the recognition of unfairness according to the results from the UG by accepting significantly more unfair offers. The fact that the patient group punishes unequal shares analogous to the NC and feel comparably concerned about injustice towards another person lead to the assumption that patients with SCHIZ are still capable of empathising with others.

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SESSION 3: THERAPY

Neural Correlates of Cognitive Behavioural Therapy Effects on Positive Symptoms in Patients with Schizophrenia.

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The use of cognitive behavioral therapy (CBT) in treatment of schizophrenic disorders routine is scarcely implemented in routine care. By now there is a good evidence for its effectiveness. However, research on the neural correlates of the effects of CBT in treatment of psychotic disorders is still missing.
Preliminary results of a multicentre fMRI study on the neural basis of CBT effects in patients with psychosis will be presented.

In this study eighty schizophrenia patients from the POSITIVE clinical trial and eighty healthy subjects were recruited at six German university hospitals (Bonn, Duisburg-Essen, Düsseldorf, Frankfurt, Cologne, Tübingen). After nine months of therapy (either with CBT or Supportive Therapy), patients and controls were re-examined enabling the study correlates of cerebral reorganization processes.
Differences in brain activation relating to phenomena of premature reasoning (Jumping-To-Conclusions-Task, JTC) and biased attribution (self- vs. external reference of emotional events, Attributional-Bias-Task, AB) were analyzed.

The JTC-task showed activations in key areas for decision making (prefrontal and inferior parietal networks). Activation in these areas diminished significantly in patients with chronified psychosis.
The comparison of brain regions of both groups in the AB-task also revealed significant decreased activation in the medial superior prefrontal cortex and middle temporal gyrus of patients with schizophrenia compared with healthy subjects.

The preliminary data analysis of the still blinded treatment arms shows significantly increased activations in relevant brain areas after nine months of psychotherapy.

These results suggest that there are neuroplasitic chances present due to relearning strategies in psychotic patients with schizophrenia. This is an encouraging finding, hopefully giving rise to a more widespread application of CBT in schizophrenia.

Regional brain changes in initially antipsychotic-naïve first-episode schizophrenia patients treated with quetiapine: Relation to dose and psychopathology

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MRI studies have shown progressive brain alterations in the course of schizophrenia. Whereas first-generation antipsychotics have been associated with striatal volume increases, the effects of second-generation antipsychotics (SGA) on striatal volumes are unclear. Neuroprotective effects of SGAs have been suggested on hippocampal volumes, whereas ventricular enlargement may be associated with clinical outcome. Dose-dependent volumetric effects of individual SGAs have been scarcely investigated.
In this study, we examined structural brain changes in initially antipsychotic-naïve first-episode schizophrenia patients after six months of mono-therapy with quetiapine.

High-resolution 3D T1-weighted magnetic resonance imaging scans were obtained on a 3 Tesla scanner at baseline and after six months in 22 antipsychotic-naïve first-episode schizophrenia patients and 28 age and gender matched healthy control subjects. Baseline and follow-up brain images were analyzed using tensor based morphometry (TBM). Voxel-wise group comparisons were performed with SPM5. Small volume correction was performed for the striatum, hippocampus and ventricles, using a FDR-correction ($p<0.05$) to control for multiple comparisons. Additionally, volumetric estimates were derived and analyzed. Effects of medication, including dose-dependent effects, and associations with psychopathology (PANSS-scores) were assessed.

Patients had significant striatal and hippocampal volume loss over the six months treatment period. The striatal volume loss was most pronounced with low quetiapine doses and less apparent with high doses. Conversely, hippocampal volume loss appeared more pronounced with high quetiapine doses than with low doses. Clinically, higher baseline positive symptoms were associated with more striatal and hippocampal volume loss over time. Although patients' ventricles did not change significantly, ventricular increases correlated with less improvement on negative symptoms.

Progressive regional volume loss in quetiapine-treated first-episode schizophrenia patients may be dose-dependent and clinically relevant. The mechanisms underlying progressive brain changes, specific antipsychotic compounds and clinical symptoms warrant further research.

Stability of Prepulse Inhibition and habituation of the Startle Reflex in Schizophrenia: A 6 Year Follow-up Study of Initially Antipsychotic Naïve, First-Episode Schizophrenia patients

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Deficits in information processing appear core features in the pathogenesis of schizophrenia. Prepulse inhibition of the startle reflex (PPI) and habituation are operational measure of early information processing. Impaired PPI in schizophrenia has been replicated in many studies and are generally regarded as an endophenotype for schizophrenia. The results on habituation in schizophrenia are inconsistent. There is growing evidence that second generation antipsychotic can improve PPI in chronic schizophrenic patients. However, in an earlier study, we reported that neither a three months treatment with zuclopenthixol (first generation antipsychotic) nor with risperidone (second generation antipsychotic) improved the PPI deficits of antipsychotic naïve, first-episode patients with schizophrenia. Furthermore, the follow-up periods of prior studies had a maximum of 6 month; therefore the stability of PPI and habituation over long time has been deduced from cross-sectional studies. The current study is a 6 year follow-up investigation of that original study, i.e. a 6 year follow-up investigation of schizophrenic patient that were drug-naive at baseline.

At baseline, 25 drug-naive first-episode schizophrenic patients and 23 healthy controls matched for gender and age, participated in the project. Three PPI measures (SOA 30 msec, 60 msec. and 120 msec.) and habituation were examined at baseline, after 3 month of randomized antipsychotic treatment and after 6 years. 16 patients and 17 healthy controls were re-examined at the 6 year follow-up.

Patients had PPI deficits compared to healthy controls at baseline. At the 6 years follow-up, no significant group differences were found and the PPI60 (SOA 60 msec.) had improved significantly in the patients. Furthermore, PPI60 in healthy controls decreased over the same period. Patients habituated significant less than healthy controls and habituation was stable in both patients and healthy controls.

The present results support the notion that PPI deficits are fundamental trait markers of schizophrenia that are already present at an early stage in the development of the disease. However, the deficits seem to diminish over time. Since PPI in matched healthy controls decreased over the same period as PPI increased in patients it is likely that the increase was caused by disease related factors such as disease process, clinical state, or medication.

Cognitive remediation in schizophrenia: short and long term effects of computerized training on cognitive performance, cerebral correlates and course of disease

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Introduction: Cognitive deficits are a core symptom of schizophrenia. Though cognitive impairments are of tremendous importance for the functional outcome of the disease, they are hardly influenced by the given psychopharmacologic interventions. Reviews of cognitive remediation therapy (CRT) suggest that these deficits respond to training, although the sustainability of cognitive improvement following CRT has not been sufficiently evaluated so far. This multicentric study is planned to examin the long-time effects of CRT on cognitive functions and their cerebral correlates (fMRT), social functioning and course of disease, also considering the impact of genetical factors on cognitive processes, e.g. working memory.

Methods: 100 Patients suffering from schizophrenia or schizoaffective disorder will be included in two hospitals (clinics for psychiatry and psychotherapy in Giessen and Marburg), as well as 50 healthy controls, matched for age, sex and education. All patients receive treatment according to AWMF-guidelines. The treatment group (n=50) additionally receives CRT using a computerized training program (x-cog®). Cognitive functions (e.g. performance on reaction time tests, CANTAB, WCST, Memo-Test, RWT and Digit span tasks), psychopathology, social functioning, quality of life, sociodemographic aspects, fMRT, reward paradigms and genetical factors (blood samples) will be assessed before, during and after treatment.

Results: Preliminary results of selected tasks indicate an effect of CRT on cognitive functions in the treatment group (n=4, TAU: n=4). For example, perseveration errors (WCST) tend to decrease after treatment associated with an increase of 'number of categories completed'. On the other hand, there is no effect of treatment on measures like Memo-Test, RWT and Digit span tasks so far.

Discussion: Although there are indulgent evidences of positive effects of CRT on cognitive functions, regarding the small sample size these data are only preliminary. For more convincing results more subjects need to be included, and further evaluation of the exalted data is inevitable. Due to our knowledge, there are only a few studies linking long term effects of CRT on cognitive deficits, their cerebral correlates, social functioning and genetical factors. Thus, we anticipate to make a contribution to treatment options of cognitive deficits in schizophrenia.

Serotonin2A receptor blockade and clinical effect in first-episode schizophrenia patients treated with quetiapine

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We have previously reported decreased frontal cortical serotonin2A receptor binding in 30 antipsychotic naïve first episode schizophrenic patients and a relationship with positive symptoms. Until now, no longitudinal studies of serotonin2A receptor in first-episode antipsychotic-naïve schizophrenia patients have reported on the relationship between serotonin2A receptor occupancy and treatment effect after sustained treatment with one atypical antipsychotic compound. Here, we measured serotonin2A receptor occupancy with [^{18}F]altanserin PET in 15 first-episode antipsychotic-naïve schizophrenia patients after 6 months of quetiapine treatment. Moreover, we investigated possible relationships between clinical efficacy, oral dose, plasma levels of quetiapine, and of the active metabolite nor-quetiapine. Significant nonlinear relationships were found between serotonin2A receptor occupancy, quetiapine dose and plasma concentration. The mean quetiapine dose was 383 mg corresponding to a serotonin2A receptor occupancy of 64%. There was a modest effect on positive symptoms up until a serotonin2A receptor occupancy level of approximately 60%. A serotonin2A receptor occupancy level between 60-70% (corresponding to 336-538 mg/day) appeared to exert the optimal treatment effect on positive symptoms. Above a serotonin2A receptor occupancy of 70% no additional serotonin2A receptor associated treatment effect was obtained. Taken together the data points to a therapeutic role of the serotonin2A receptor in the treatment of schizophrenia. Specifically the study indicates a serotonin2A receptor associated therapeutic window on positive symptoms in the range between 60-70% occupancy in antipsychotic-naïve first-episode schizophrenia. Future studies with concurrent measurement of interactions with other receptor systems are warranted.[1]

Literature:

Rasmussen H, Ebdrup BH, Erritzoe D, Aggernaes B, Oranje B, Kalbitzer J, Pinborg LH, Baare WF, Svarer C, Lublin H, Knudsen GM, Glenthoj B. Serotonin2A receptor blockade and clinical effect in first-episode schizophrenia patients treated with quetiapine. *Psychopharmacology* (Berl) 2010.

Are antiserotonergic antipsychotics associated with the development of obsessive-compulsive syndromes in schizophrenia?

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Background: Several epidemiological investigations established that up to 30 % of schizophrenic patients suffer from comorbid obsessive compulsive symptoms (OCS). Within several pathogenetic theories, it has been proposed that atypical antipsychotic agents with pronounced antiserotonergic properties might induce the de-novo occurrence of secondary OCS, but multimodal investigations of large samples are missing. This cross-sectional comparison tested the hypothesis that antiserotonergic antipsychotics are associated with OCS.

Method: We stratified 70 patients with DSM IV diagnosis of schizophrenia/ schizoaffective disorder according to their mode of antipsychotic treatment: clozapine and olanzapine (group I) against aripiprazole and amisulpride (group II). Psychopathology and neuropsychology were compared between groups.

Results: Significant differences in OCS prevalence and severity were found between groups. OCS was found significantly more prevalent and severe in group I. In this group OCS severity correlated with duration of antipsychotic treatment and dosage of clozapine. The neuropsychological assessments revealed more pronounced deficits in group I regarding visuo-spatial perception and memory, impulse inhibition, perseveration and dual-task abilities. These cognitive domains significantly correlated with OCS severity.

Conclusions: Our results support the hypothesized association between treatment with antiserotonergic antipsychotics and secondary OCS. Longitudinal studies are needed to confirm causal relationships. The neuropsychological results indicate a differential profile of cognitive deficits between the two groups and might help to establish a discriminating test battery.

Disturbances in the reward processes in schizophrenia and its relation to dopamine activity: A longitudinal study in antipsychotic-naive first-episode schizophrenia patients

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In this study we plan to examine how reward processing abnormalities are related to striatal dopamine D_2/D_3 binding potentials and psychopathology in antipsychotic-naïve first-episode schizophrenia patients. Furthermore, we will explore how these disturbances are modulated by interventions with a D_2/D_3 antagonist (amisulpride).

The study is designed as a 6 week case-control follow-up study of 30 antipsychotic-naïve patients with schizophrenia and 30 matched healthy controls. The participants are examined at baseline and at 6 weeks follow up with an extensive battery of assessments, including Single Photon Emission Computed Tomography (SPECT), structural and functional Magnetic Resonance Imaging (fMRI), and neurocognitive- and psychophysiological testing. Patients are further examined with clinical, validated rating scales to measure psychopathology, the level of function, subjective well-being, and side-effects. After baseline examinations the patients are treated with flexible doses of amisulpride according to their clinical condition.
To examine the reward disturbances, fMRI is performed with a variant of the monetary incentive delay task. We use SPECT with ^{123}IBZM (123 labeled iodbenzamid) as radioligand to examine the binding potential (BPp) of dopamine D_2/D_3 receptors in the striatum. 175 MBq ^{123}IBZM is administered over 4 h according to a steady state bolus-infusions-paradigm, and participants are scanned for 2 x 30 min after 3 hours infusion in a two headed Siemens Symbia-scanner. Plasma parent compound is determined by equilibrium dialysis and the BioTrap method.
For the co-registration between MRI and SPECT images Matlab is used. Predefined volumes of interest (VOIs) will subsequently be identified automatically on the MRI image and directly transferred to the co-registered SPECT image.

We have fMRI and SPECT data from 7 patients at baseline, 6 at follow-up and 6 healthy controls so far. Data monitoring and analyses are ongoing and we expect to present a few preliminary data at the symposium.

We expect that blockade of striatal D_2/D_3 receptors will correlate positively with treatment effect on positive psychotic symptoms and decrease in salience abnormality (as measured with fMRI), and to a certain point blockade will correlate negatively with negative symptoms. We expect to find an individual narrow therapeutic window of D_2/D_3 blockade, within which there is a positive effect on the positive symptoms without a negative effect on the negative symptoms.

Augmentation with Pregabalin in Schizophrenia

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Anxiety is a core symptom of schizophrenia which elicits significant subjective burden of disease and contributes to treatment resistance in schizophrenia. Anxious syndromes might be attributed to incompletely remitted delusions, the negative syndrome, depressive episodes, panic attacks, social phobia, avoidance after hospitalization and down-tapering of benzodiazepine medication. Pregabalin, an antagonist at the α2δ-subunit of voltage-gated Ca^{2+}-channels, modulates several neurotransmitter systems and was found to alleviate anxiety in several mental disorders. In schizophrenia, this treatment option has not been evaluated before. Here, we report a case series of 11 schizophrenic patients who suffered from treatment-resistant anxiety and received augmentation with pregabalin. This observational analysis reveals that this strategy was able to significantly reduce scores on the Hamilton anxiety scale; furthermore, we observed improvements of psychotic positive and negative symptoms and mood as assessed by PANSS, SANS and CDSS. After augmentation, both a complete discontinuation of concomitant benzodiazepine (BZD) treatment as well as a dose reduction of antipsychotics could be achieved. We did not observe pharmacokinetic interactions or adverse events.
These observations suggest that treating anxious syndromes in schizophrenia with pregabalin can be effective and tolerable. Further investigations should differentiate schizophrenic sub-syndromes of anxiety and evaluate benefits and risks of pregabalin in comparison to placebo and active competitors.

Keywords: Augmentation, anxiety, combination, mood stabilizer, pregabalin, schizophrenia

SESSION 4: COGNITION

Evaluation of cortex-based alignment for fMRI studies of working memory in schizophrenia

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Background: It has been argued that fMRI findings of reduced activation in patients with schizophrenia, e.g. prefrontal hypoactivation during working memory (WM), may in part be caused by a larger degree of cortical anatomical heterogeneity which would lead to a greater spatial variability of functional activation clusters. This problem may not be addressed properly by standard normalization procedures which align structural and functional data to a volume-based coordinate system, e.g. MNI or Talairach space. Such an approach cannot correct for the hetereogeneity of cortical topology between populations. Here we used a surface-based alignment method, which operates in a cortical coordinate system and aligns brains using the curvature information of the cortex. We investigated the effects of this technique on the strength of cortical activation during WM in healthy controls and patients with schizophrenia. We hypothesized that cortex-based alignment would reduce anatomical variability particularly in patients, resulting in a larger decrease of structural and functional variability in this population.
Methods: We assessed brain activation during the performance of a visual WM task in 17 adolescents with early-onset schizophrenia and 17 matched controls using fMRI. Anatomical scans were segmented, reconstructed and morphed into spherical representations. We then aligned the folding pattern of each cortical hemisphere to a dynamically updated group average through iterative morphing following a coarse-to-fine matching strategy. We mapped the functional data into the resulting common spherical coordinate system and analyzed them across groups and for each group separately using a random-effects GLM. We compared the results with those of a standard analysis in Talairach space.
Results: Our method reliably aligned cortical landmarks in all participants. The overlap of functional activation increased in both groups across the cortical WM network. However, this effect was more pronounced in patients, leading to a larger increase of activation in this group. Accordingly, while prefrontal hypoactivation in patients was still observed after cortex-based alignment, it was less prominent.
Discussion: Our findings indicate that activation differences between patients with schizophrenia and healthy controls are in part the result of a higher degree of anatomical variability in patients. Cortex-based alignment corrects for this confound to

a considerable degree. This method seems to provide more reliable results in fMRI studies of abnormal cognition in schizophrenia.

Activation of dopaminergic brain regions during probabilistic reasoning in the "Jumping to Conclusions" metacognition task in healthy subjects

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Background: Besides other cognitive disturbances, schizophrenia patients show deficits in metacognitive functions, i.e. to critically reflect on and monitoring one's own reasoning. One specific deficit is the so called "Jumping to Conclusions" (JTC) bias, where schizophrenia patients, especially patients suffering from delusions, make decisions on the basis of too little evidence.[1]. Although it has been proposed that the JTC bias is linked to aberrant salience processing [2], so far only one small study investigated the neural correlates of probabilistic reasoning during a JTC task [3] and failed to find activation in regions implicated in salience processing.
Methods: We studied 25 healthy subjects with functional magnetic resonance imaging to identify neural systems active during a JTC task. We used a modified version of the "beads task" that employs a more lifelike scenario with fish jumping from a lake. The task requires a probabilistic decision after a variable amount of data has been requested by the participants. We assessed brain activation over the duration of a trial in a block design analysis and with an event related design specifically at the time point of decision making. Furthermore, to control for motivational aspects during the task, we split the sample and half of the subjects performed a monetary incentive version.
Results: Analysis of tonic activation showed an extended network including the prefronto-parietal executive functioning network as well as medial parieto-occipital regions, partly overlapping with the findings of the former study [3]. During the decision process, activity implicated in the processing of salience, namely midbrain and ventral striatum was detected, as well as in thalamus, medial occipital cortex and anterior insula. There was no increase in activation in these regions in the monetary incentive version.
Conclusions: Executive functions seem to play an important part in the process of probabilistic reasoning. In addition, especially at the point of decision making, dominergic salience regions become phasically active. This finding provides a candidate mechanism that could underlie the behavioral link between delusion formation and the JTC bias in schizophrenia and that could be a neural target for metacognitive therapies. Further studies with delusional schizophrenia patients will have to be performed to substantiate this link.

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Alpha phase-locking predicts residual working memory performance in schizophrenia

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Background: Working memory (WM) deficits are a core feature of schizophrenia. Recent electrophysiological evidence indicates that the brain systems for visual encoding are especially impaired. However, patients still achieve performance levels clearly above chance, which indicates the existence of residual mechanisms supporting WM encoding. The present study presents evidence that alpha phase-locking of the electroencephalogram is a marker for such residual cognitive mechanism.

Methods: Alpha phase-locking during encoding into WM was compared between 17 patients with early-onset schizophrenia (EOS), and 17 healthy control subjects. Results of phase-locking were correlated with accuracy. A median split based on alpha phase-locking in patients was used to compare accuracy between controls and patients with high and low alpha phase-locking.

Results: Alpha phase-locking increased with WM memory load in both EOS and controls, although alpha phase-locking was generally reduced in EOS. Furthermore, for EOS a positive correlation between alpha phase-locking and performance was obtained. Additionally, patients exhibiting high phase-locking did not differ in performance from controls.
Conclusions: These results provide the first evidence for a relationship between alpha phase-locking and visual WM encoding. This neural mechanism seems to be preserved in some patients with schizophrenia and then allows them to attain normal performance levels.

Literature:
Haenschel et al, Haenschel C, Linden DE, Bittner RA, Singer W, Hanslmayr S. Biol Psychiatry. 2010 epub.

The effect of a genome-wide supported variant in *CACNA1C* on structural and functional correlates of episodic memory encoding and retrieval

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Objective: The alpha 1C subunit of the L-type voltage-gated calcium channel is known to be involved in learning, memory and brain plasticity. Genetic studies implicated *CACNA1C* gene as a susceptibility locus for bipolar disorder, schizophrenia and major depression.
Method: We investigated the influence of the *CACNA1C* single nucleotide polymorphism (SNP) rs1006737 on structural and functional correlates of episodic memory encoding and retrieval. Brain activation was measured with functional magnetic resonance imaging (fMRI) during an episodic memory encoding and retrieval task in 94 healthy individuals who were genotyped for *CACNA1C* rs1006737. In addition, morphometric MRI data was obtained for all subjects.
Results: In the fMRI experiment, while there were no differences in behavioral performance, neural activation –mainly in the superior frontal gyrus and inferior and middle temporal gyrus - was associated with *CACNA1C* genotype during encoding and retrieval. Voxel based morphometry analyses revealed an effect of CACNA1C genotype on local gray matter volume in the right hippocampus.
Conclusions: Our data suggest that rs1006737 influences the neural systems related to memory processes: Brain activations during encoding and retrieval of new material might compensate for structural anomalies in the hippocampus. These findings are in line with results of imaging studies in affective disorder and schizophrenia. It may explain some of the brain activation variation found in these disorders and healthy subjects.

Cognition in first-episode anti-psychotic naive schizophrenic patients: A 2-year follow-up study

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Schizophrenia is associated with deficits in cognitive functions, with estimates ranging from 75-85 %. However, studies on this issue are often carried out in chronic, medicated patients and are therefore compromised by the possible confounding effects of medication. As part of the PECANS project (Pan European Collaboration on Antipsychotic Naïve Schizophrenia) the present study seeks to establish the prevalence and profile of cognitive deficits in first-episode anti-psychotic naïve schizophrenia and relate these findings to psychopathology and effects of medication.

The design constitutes a 2-year longitudinal study with assessment at baseline and follow-ups after 6 weeks, 6 months, 1 and 2 years. First-episode, antipsychotic-naïve schizophrenia patients are included, as well as healthy controls (HC). Data collection began in the fall of 2008, and so far includes 29 patients and 20 HC. The goal is to include 60 patients and 60 HC subjects and monitor and assess their clinical, functional, and cognitive status continuously. The study utilises multiple instruments, including CANTAB (Cambridge Neuropsychological Test Automated Battery) and BACS (Brief Assessment of Cognition in Schizophrenia). Premorbid intelligence is estimated using DART (Danish Adult Reading Test) and current intelligence from 4 subtests from WAIS (Wechsler´s Adult Intelligence Scale). Psychopathology ratings are obtained using PANSS (Positive and Negative Symptom Scale).

The current presentation includes data from the baseline assessment. Cognitive deficits are present in schizophrenia patients at this early stage of the disease. The prevalence and profile of these deficits will be presented in detail.

Cognitive deficits are prevalent in schizophrenia patients from the time of their first episode, before initiation of treatment of antipsychotic medication, supporting the contention that cognitive deficits are core symptoms of schizophrenia.

Behaviour in cognitive tests and cognitive performance of patients with schizophrenia and bipolar disorder

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According to current knowledge bipolar patients show similar cognitive deficits compared to schizophrenia patients, although their "cognitive profile" seems to be less pronounced.
However, neuropsychological tests – such as the Wisconsin Card Sorting Test or the Iowa Gambling Test - may be too unsubtle, especially, when only achievement scores are considered. Perhaps specific deficits for each of the two mental illnesses lead to identical performance scores via different performance paths.

We present first results of an ongoing study examining the performance of bipolar and schizophrenia patients in tests of attention (Continuous Performance Test), problem-solving (Wisconsin Card Sorting Test), memory (Wechsler Memory Scale) and a newly developed computerised task (X- Cog LTP) that requires cognitive flexibility and self management (patients have to change the task's difficulty due to their perceived performance).

Initial results show that both patient groups show only minor differences in their performance in psychometric tests, whereas the computerised task seems to separate better between the two groups.

Memory consolidation during sleep in schizophrenia

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There is evidence of improved memory consolidation, i.e., an increase in recall without further training, during sleep compared to a waking condition. This study seeks to determine whether patients with schizophrenia show a lack of sleep-related consolidation and whether the impairment is related to disturbances of particular sleep phases or other indices. So far, 19 patients with schizophrenia (mean age 42.9 years) and 20 healthy controls (38.5 years) have taken part in this ongoing study. There is a day and night-time condition in a balanced design. Both conditions comprise a learning phase at the beginning and a test phase after 8 hours. A verbal (short prose passage) and a procedural learning task (mirror tracing task) were used. The sleep EEG was recorded by means of a Biopac MP 150. In a preliminary data analysis, patients with schizophrenia showed no improved memory consolidation during the night compared with the day condition. Enhanced prose learning was related to an increased number of sleep spindles whereas improved consolidation of mirror tracing was related to REM sleep parameters.

Functional neuroanatomy of executive functioning in schizophrenia

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The Wisconsin Card Sorting Test (WCST) is one of the most widely used tests to evaluate executive functioning. Impaired WCST performance has most consistently been reported in schizophrenic patients, and performance quality on the WCST is strongly related to shifting functions. In schizophrenic subjects, functional MRI studies reported reduced activation of the prefrontal cortex during WCST performance, and in SPECT studies hypofrontality was described as the most salient activation difference in schizophrenic patients compared to controls. This study has been the first to use event-related functional MRI to investigate activation patterns during different subcomponents of the WCST in schizophrenic patients and in healthy controls.

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