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Centre for Psychiatry
Justus Liebig University School of Medicine
Giessen, Germany, EU

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Abstract Book

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Am Steg 22
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INFORMATIONS ABOUT THE CONFERENCE

Organiser:

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Chairman: Prof. B. Gallhofer, M.D., Ph.D.

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Conference
Centre for Psychiatry
Main Lecture Theatre, Main Building
Am Steg 22
Giessen

Conference Dinner (Friday, 1st of March)
Museum of Mathematics
Liebigstrasse 8
Giessen

POSTER ABSTRACTS

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SESSION A

assessment – social – cues – EEG – scales

Assessing multimodal integration dysfunctions in schizophrenia: Beta oscillation change as potential neural marker for semantic integration

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Patients with schizophrenia are found to have impairments in multimodal semantic integration. For example, during the online processing of gesture, which incorporates audio-visual information, patients with schizophrenia show different brain activation patterns in comparison to healthy controls [1]. In the current study, we aim at elaborating the processing difference of multimodal semantic inputs between patients with schizophrenia and healthy controls by investigating the time and frequency domain of Electroencephalography (EEG).

In an EEG study with healthy controls, twenty subjects were displayed with videos with an actor performing co-speech gestures (G) and corresponding speech-only (non-G) sentences. For gesture condition, EEGs are time-locked to the semantic integration point upon which the meaning of a gesture coincides with its corresponding word (s); for the speech-only condition we adopted the latency of the integration point based on the integration word (keyword) from the G condition. We epoched the 1000 ms interval before (Pre) and after (Post) the integration point. Fast Fourier Transformation (FFT) was carried out to give the mean voltage density of a frequency band of each epoch of interests.

With regard to the Post (0-1000 ms) epoch, we observed a power suppression of both alpha (7-13 Hz) and beta (14-30 Hz) frequencies by directly comparing G vs. nonG conditions. Additionally, when comparing the voltage density change (Post-Pre), we found again, a suppression of power in beta band for the G vs. non-G conditions.

The power suppression of both frequency bands may indicate action observation [2]. With regard to power change, given that actions are observed in both the Pre and Post epochs for the gesture condition, we reason that the beta suppression may reflect some sort of integration cost of both visual and audio semantic information [3].

For patients with schizophrenia, in an up-coming study, we hypothesize that they show alpha and beta suppression for gesture against speech-only conditions for a direct comparison of the post-integration interval because they are intact with action observation. However, given that they may be impaired in the semantic integration of multimodal inputs, beta power change (Post-Pre) may be equal across the two experimental conditions.

References:
[1] Straube et al., in press, Human Brain Mapping
[2] Quandt et al., 2012, Neuropsychologia
[3] Bastiaansen et al., 2010, J Cogn Neurosci

Gaze cueing in schizophrenia using static vs. dynamic cues - preliminary results

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Gaze cueing can be used to operationalize joint attention which is a prerequisite or an early cognitive step of theory of mind processing. We use gaze cueing paradigms to untangle elementary cognitive processes which contribute to the well known theory of mind deficits in schizophrenia. Previous research revealed that, in principle, persons with schizophrenia show gaze cueing effects comparable to those seen in healthy persons. However, effects were much weaker and much less consistent across additional influencing factors in schizophrenia patients, compared with healthy controls. In particular, gaze cueing deficits in schizophrenia can be observed using stimulus onset asynchronies outside the optimal range for gaze cueing effects which is centered around 300ms. Therefore we aim at identification of factors enhancing or attenuating gaze cueing. A review of the literature on gaze cueing shows that presenting the cues in a static vs. dynamic fashion may be such a factor. Presenting gaze cues dynamically, i.e. changing the direction of a gaze stimulus during a single experimental trial, may be more effective in attracting attention to the cue compared to presenting the cue statically, i.e. presenting a gaze stimulus with a specific direction, unchanged during the trial. Although both modes of cue presentation were used in published studies we have found no study comparing the presentation modes directly, i.e. introducing presentation mode as an experimental factor with levels 'static' vs. 'dynamic'.

To fill this gap we have carried out a study with experimental factors 'mode' (representing mode of cue presentation: dynamic vs. static), 'congruency' (representing validity of cue direction relative to position of the target stimulus: congruent vs. incongruent), 'type' (contrasting social gaze cues with non-social arrow cues) and 'SOA' (stimulus onset asynchrony: 100ms vs. 300ms). Here, we report on results from preliminary samples (healthy controls: n = 23; schizophrenia patients: n = 11), analysing separately for both groups as weel as both SOA.

Within healthy controls, dynamic cue presentation produced a significant overall reduction in cueing performance during 300ms SOA. During 100ms SOA an interaction between factors modus and congruency could be confirmed, showing that dynamic cue presentation especially has delayed reactions to incongruent trials. Main effect 'congruency' was significant for both SOA. Within schizophrenia patients, the only significant effect was main effect 'congruency' for 100ms SOA. This preliminary results show that dynamic cue presentation seems to disturb cue processing. Confirmation of effects relating to schizophrenia requires completion of the sample.

Validation of a german translation of the Social Functioning Scale (SFS) [1]: a scale to measure social functioning in schizophrenic patients

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The Social Functioning Scale (SFS) is one of the best rated and most cited scales to survey self-reported social functioning. But to our knowledge a german version of the SFS does not exist. For better comparability within international studies we validated a German translation of the Social Functioning Scale (SFS).

The study was conducted in two different steps. In the first step a retest design, 31 students of Anglistics completing both the English and the German versions of the SFS, was employed to identify if the German version of the SFS is an adequate equivalent to its English original. The second step aimed at the validation of the German translation. For this purpose data of 475 healthy subjects and 30 patients diagnosed with schizophrenia were investigated.

Our data confirmed that the german version is an adequate translation of the original scale. Postulated associations between the SFS and other measures for the assessment of functioning, including the Soziale Aktivität Selbstbeurteilungs-Skala (SASS) and the Disability Assessment Schedule 2.0 (DAS 2.0), were found for the healthy subjects. Furthermore a non-significant relationship between the SFS and the Global Assessment of Functioning (GAF) in the anticipated direction (positive) was found for the patient group. There was a significant negative association between the patients' negative symptoms and the SFS. No significant relationship between positive symptoms and the SFS was found. Internal consistencies of the SFS subscales and the scale as a whole were calculated for the healthy subjects and were smaller than those identified for the original English version. By use of a principal component analysis for the seven SFS subscales a two-factor-solution explaining 54% of the variance was proposed for the healthy subjects.

The results offer first support for the validity of the German version of the SFS. But further investigations should aim at an increased sample of schizophrenic patients.

References:
[1] Birchwood, M., Smith, J., Cochrane, R., Wetton, S. & Copestake, S. (1990). The Social Functioning Scale – The Development and Validation of a New Scale of Social Adjusment for use in family intervention programmes with schizophrenic patients. British Journal of Psychiatry, 157, 853-859.

Mismatch Negativity, global functioning and positive symptoms in schizophrenia

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Mismatch Negativity (MMN) is an auditory event related potential in response to auditory deviants among standard tones with a peak amplitude between 100 and 250 ms after stimulus onset. Numerous studies have shown MMN reduction in schizophrenia indicative of early auditory information processing deficits. In contrast, associations between MMN and positive symptoms have been rarely investigated.
In the present study, 45 schizophrenia patients and 15 controls were presented 2400 random tones (standard: 80ms, 78%; duration deviant: 40ms, 22%) while EEG was recorded. The severity of symptoms was evaluated by means of the Positive and Negative Syndrome Scale, Global Assessment of Functioning Scale and the Social and Occupational functioning Scale. MMN amplitudes in schizophrenia patients were attenuated compared to controls and were associated with poor social and occupational functioning. Moreover, we found an association between MMN peak amplitudes and PANSS positive symptoms. Decreased MMN amplitude was related to more severe positive symptoms in patients. Additional to previous results of an attenuated MMN peak amplitude to duration deviants, our study replicates findings of an association between MMN amplitudes, positive symptoms and global functioning in schizophrenia patients.

The influence of eye and arrow cues on the direction of spatial attention and the hemodynamic brain activity

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This fMRI-study examined the neural activity following social (eye) and nonsocial (arrow) cues in 34 healthy participants using an attentional cueing paradigm called Gaze-Cueing-paradigm (Friesen & Kingstone, 1998). In this paradigm gaze stimuli are presented as central spatial cues which bias reactions to peripherally presented target stimuli.
The paradigm provides an opportunity to measure a Theory-of-Mind-precursor known as joint attention which implies events in which one's own attention is redirected according to the attentional focus of a social interaction partner. Therefore it seems appropriate for determining the social functioning deficits commonly observed in schizophrenic patients and for differentiating between social and general cognitive deficits. 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.
The measurement of neural correlates of gaze cueing should help understand the neural processing of spatial attention in the context of social and nonsocial cues. As social cues naturalistic pictures of faces with eyes gazing towards or away from a target stimulus (congruent / incongruent trials) were used and compared to geometric patterns embedding arrows as nonsocial cues. Furthermore two different Stimulus-Onset-Asynchronies (SOAs, 100 & 800 ms) were used. We assumed that the longer SOA would allow for an extended mental processing to take place.
The results show that social and nonsocial cues activate two separate non-overlapping brain areas. Social cues in the long SOA-condition activated mainly occipital-temporal areas, amongst others areas in the superior temporal gyrus and the fusiform gyrus responsible for biological motion and face processing, whereas nonsocial cues activated occipital-parietal areas. In addition the activity was different for short and long SOAs confirming our assumption that a long SOA would lead to more extensive processing. There is also evidence that the activity following social cues occurred faster than the activity following nonsocial cues as there was less difference between short and long SOA for social cues. However there was no significant activity in frontal areas for both cue types.
The results can be seen as a background for examining the neural correlates of social functioning deficits in schizophrenic patients.

Literature:
Friesen, C. K., & Kingstone, A. (1998). The eyes have it! Reflexive orienting is triggered by nonpredictive gaze. Psychonomic Bulletin & Review, 5 (3), S. 490-495.

A brief rating scale for the assessment of individual differences in gesture perception and production

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The use of gesture in everyday life represents an important and ubiquitous tool to underpin the content of a verbal message during interpersonal communication. It has been shown that patients with schizophrenia demonstrate aberrant production [1] and perception of gestures [2] as well as dysfunctions in social perception and empathy [3]. So far, no subjective measures for the categorization of different gesture preferences were developed. Moreover, the potential role of empathy in the process of gesture production and perception is unclear.
First, different statements concerning gesture production and perception in everyday life situations were collected and integrated into a 5-point Likert scale. Second, a representative number of healthy subjects (n=220) were asked to rate the resulting statements on a 12-item scale; empathic traits were measured with the E-scale (Leibetseder et al. 2001). Third, the internal structure was explored in order to identify different gesture components as well as construct validity.
A principal component analysis revealed a four-factor solution reflecting different dimensions of gesture production and perception. Two empathy-related production and perception factors were identified, most likely resembling ‘gesture as help’ and ‘gesture empathy’ dimensions, respectively.
The current investigation yielded excellent psychometric results. Moreover, a distinction between a perceptual and productive factor with and without empathy related components can be supported. For production, empathy seems to be important when gestures are selectively employed as a helping instrument in social communicative situations. On the perceptual level, emotional and perspective taking aspects seem to be related to ‘gesture empathy’.
The psychometrically valid and brief ‘rating scale for the assessment of individual differences in gesture perception and production’ may be of significant interest for psychiatric diseases such as schizophrenia. First preliminary results indicate that the rating scale is a useful and easy tool to assess distinct aspects of communication and social empathy dysfunctions in schizophrenia.

References:
[1] Matthews, N., Gold, B. J., Sekuler, R., & Park, S. (2011). Gesture Imitation in Schizophrenia. *Schizophrenia Bulletin*, 1–8.
[2] Straube, B., Green, A., Sass, K., Kirner-Veselinovic, A., & Kircher, T. (2012). Neural integration of speech and gesture in schizophrenia: Evidence for differential processing of metaphoric gestures. *Human Brain Mapping*, doi:10.1002/hbm.22015.
[3] Wible, C. G. (2012). Schizophrenia as a disorder of social communication. *Schizophrenia research and treatment*, *2012*, doi:10.1155/2012/920485

A rating scale for the assessment of objective and subjective formal Thought and Language Disorder (TALD)

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Formal thought disorder (FTD) has long been regarded as a core syndrome of schizophrenia. However, patients with other diagnoses, such as mania and depression, also present with FTD. We introduce a novel, comprehensive clinical rating scale, capturing the full variety of FTD phenomenology including subjective experiences.
The 30-item Thought and Language Disorder scale (TALD) is based on a detailed review of the literature, encompassing all formal thought disorder symptoms reported from the early 20th century onwards. Objectively observable symptoms as well as subjective phenomena were included.
Two hundred and ten participants (146 patients ICD-10 diagnoses: depression n=63, schizophrenia n=63, mania n=20; 64 healthy control subjects) were interviewed and symptoms rated with the TALD, TLC, HAMD, YMRS and SAPS/SANS. A principal component analyses was performed for the TALD to differentiate sub-syndromes.
The principal component analysis revealed four FTD factors; objective as well as subjective positive and negative factor dimensions. The correlation analyses with the TLC and the SAPS/SANS FTD sub-scores demonstrated the factor validity for the objective factors.
The scale showed excellent psychometric results, which makes it a practicable, nosologically-open instrument for the detailed assessment of different FTD dimensions. The results strengthen the importance of subjective symptom assessment reported by the patient.

Disconnectivity of the left posterior middle/superior temporal gyrus during processing of metaphoric co-verbal gestures in schizophrenia

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The left posterior middle/superior temporal gyrus (MTG/STG) plays an important role in integrating audiovisual information. Therefore, this area might be functionally connected to disparate brain regions. As compared to healthy subjects it has been previously shown that patients with schizophrenia show similar activation in the left MTG/STG for the processing of gestures in a concrete sentence context (iconic gestures) [1]. However, aberrant activations for the processing of gestures in an abstract sentence context (metaphoric gestures) were found. With this study we test the hypothesis that patients with schizophrenia differ in the functional connectivity of the left MTG/STG for the processing of metaphoric gestures.

During fMRI-data acquisition, 16 patients with schizophrenia (P) and a healthy control group (C) were shown videos of an actor performing iconic (IC) and metaphoric gestures (MP) and associated sentences. A psycho-physiological interaction (PPI) analysis based on the seed region from the previous analysis located in the left MTG/STG [1] has been performed.

For IC and MP gestures we found common positive connectivity of the seed region to the left middle temporal gyrus (MTG) and left ventral interior frontal gyrus (IFG) in both groups. The interaction of group (C>P) and gesture condition (MP>IC) revealed predominantly effects in the bilateral IFG and the left MTG/STG.

Despite considerable communalities, these data suggest aberrant connectivity of the left MTG/STG in particular for the processing of MP gestures in schizophrenia. Reduced connectivity to the left IFG might be the basis of dysfunctional integration of gestures in an abstract sentence context.

Literature:
[1] B. Straube, *Human Brain Mapping*, **in Press.** DOI:10.1002/hbm.22015.

SESSION B
fMRI – cognition – reward

Spontaneous brain activity as an endophenotype for schizophrenia

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The multifarious clinical manifestations of schizophrenia probably covers a large biological heterogeneity. To overcome this complexity in order to improve objective diagnostics and treatment it is necessary to identify biological markers, which in turn will improve our understanding of the relationship between phenotype and genotype. In this study we are investigating the possibility of using the spontaneous or 'resting state' brain activity measured by fMRI as an endophenotype for schizophrenia. Several studies mostly in medicated patients during both activation and resting state have investigated brain activity in terms of functional connectivity within large-scale neuronal networks. Some studies finds reduced connectivity within networks including the Default Mode Network, where others finds increased.[1,2,3,4] In general the results are highly variable possibly reflecting variability in design and analysis strategy.

In a case-control study 41 antipsychotic naive first episode patients and 41 age and gender matched healthy controls were scanned at baseline with fMRI during resting state (instructed to stay awake with eyes closed). 27 patients and 36 controls were re-scanned after 6 weeks. In this period patients where treated with individual doses of the D2/D3 antagonist amisulpride. The fMRI analysis comprises: 1) a seed-based approach with anatomically defined Regions Of Interest (ROI's) corresponding to medial prefrontal cortex, posterior cingulate cortex and ventral striatum on one hand, and ROI's defined using Automated Anatomical Labeling on the other, 2) an approach with ROI's based on networks using Independent Component Analysis (ICA) and 3) a voxel-based approach using ICA to define networks of interest, and subsequently probed for differences across groups and time using a dual regression method.

The ROI based approach with anatomically defined ROI's showed several significant correlations between the regions. However, no significant group differences were detected at baseline or after treatment when corrected for multiple comparisons. The data analysis is ongoing and the results of all of the methods mentioned will be presented at the conference.

So far this study did not show significant group or group-time interactions when properly corrected for multiple comparisons. However, previous results suggest the existence of such effects, mostly in previously medicated patients. This discrepancy may indicate that the effects are truly minor in antipsychotic naive first episode patients. On the other hand comparing this result with the literature emphasises the importance of exploring different analysis strategies in order to validate the methods

used in measuring resting state connectivity. The results of the different strategies mentioned will be compared and explained in detail at the conference.

Literature:

[1] S. Lui et al., *Arch Gen Psychiatry.* **2010**, *67(8)*, 783–792. [2] S. Whitfield-Gabrieli et al., *Proc Natl Acad Sci*. **2009**, *106(4)*,1279–1284. [3] M. Liang et al., *Neuroreport*. **2006**, *17*, 209-213. [4] R. Bluhm et al., *Schizophr Bull.* **2007**, *33*, 1004–1012.

The neurophysiological correlates of working memory consolidation – an fMRI pilot study in healthy subjects

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Working memory (WM) dysfunction is an important cognitive deficit in patients with schizophrenia. Converging evidence from behavioral and neuroimaging studies indicates, that WM is already disturbed during the initial encoding of information. WM encoding can be further subdivided into a number of cognitive processes including WM consolidation, the transformation from a fleeting perceptual into a durable mnemonic representation. Behavioral studies indicate that WM consolidation is impaired in patients with schizophrenia. However, little is known about the neurophysiological underpinnings of WM consolidation. The aim of the current pilot study is to study the neurophysiological correlates of WM consolidation in healthy subjects using functional magnetic resonance imaging (fMRI) in preparation for a study in patients with schizophrenia.
30 healthy volunteers performed a visuospatial change detection task. During encoding, three rectangular bars of different orientation were displayed. We used a masking procedure with varying stimulus onset asynchrony (SOA) in order to interfere with WM consolidation. Shorter SOAs led to greater drops in accuracy. This was accompanied by reduced activation in a fronto-parietal network which has previously been associated with both WM and selective attention. These results are well in line with notion that the successful consolidation of information into WM requires the allocation of attentional resources during, a process prone to interference. They also demonstrate the close relationship of WM consolidation and selective attention.

Current Methods of Modeling Schizophrenia in Animals

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Current approach in medicine, in general meaning, to tackle with diseases has shifted slightly during the recent years. It becomes maybe the most valuable methodology to create animal models of diseases which could be really rough especially for psychopathologies considering the complicacy of the clinical symptoms and different neuroscientific pathways involved. There are, however, some methods developed which are admitted to modelize at least the main characteristics of psychotic diseases. Specifically talking about the schizophrenia, there have been models based on the manipulation of different neurotransmitter systems, including Dopaminergic, Glutamergic and GABAergic pathways, which are explored to be deficited in different ways, in schizophrenia. During the recent years, however, modelizing morely became to target either the relevant brain area, including neonatal ventral hippocampus, or to create developmental methods like social isolation or prenatal stress syndrome [1].

Besides all these, there are phenotypic models which are only simulating particular types of symptoms involved in schizophrenia. These phenotypic methods are generally based on locomotor activity and social interaction scales, latent inhibition and gating measurements, which is also embracing Prepulse Inhibition (PPI) a commonly used measurement as it comes to schizophrenia. This measurements has been found to be impaired in several neurological and psychiatric disorders, including schizophrenia, bipolar disorder, obsessive compulsive disorder and nocturnal enuresis. The specific methods developed within this outline described in this review. Current methods and future promising potential methods are mostly underlined as the new therapeutic approaches are highly placed on these methods [2].

Literature:
[1] Marcotte E. et al., *Animal models of schizophrenia: a critical review*, Psychiatry Neurosci. **2001** November*;* 26(5): 395–410.
[2] Rehn AE, *Investigating the neurodevelopmental hypothesis of schizophrenia,* Clin Exp Pharmacol Physiol, **2005** Sep;32(9):687-96.

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Double-evidence for altered dopaminergic processing in schizophrenia from functional magnetic resonance imaging

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Schizophrenia is a psychiatric condition, clearly associated with dysfunctions in the dopaminergic system. This dopaminergic dysfunction has been linked theoretically as well as empirically to deficits in reward anticipation, altered salience processing and biases in decision-making. While it was repeatedly demonstrated that patients with schizophrenia show hypoactivation in Nucleus Accumbens (NAcc) during reward anticipation and alterations in the neural correlates of salience attribution, studies are missing that investigate neural correlates of decision-making in schizophrenia.
A sample of 18 patients with schizophrenia and 24 healthy controls, matched for age, gender and education, participated in a functional magnetic resonance imaging study. Participants engaged in a reward-anticipation task and a decision-making task, testing for hasty decision-making.
In concert with earlier studies on reward anticipation in schizophrenia, patients were slower in the reward task and had right NAcc-hypoactivation during reward anticipation. Analysis of the decision-making task revealed no deficit on the behavioral level in the patient group, but again hypoactivation in right NAcc. However, correlation analyses revealed no association between right NAcc-activation or performance measures between the tasks.
The present study replicates findings of NAcc-hypoactivation during reward anticipation in schizophrenia. In addition, it extends the current literature by demonstrating NAcc-hypoactivation in the course of decision-making in schizophrenia. The lack of a correlation of NAcc-activation between tasks suggests independent dysfunction of the dopaminergic system during reward processing and decision-making in schizophrenia.

Where in the brain is the Kraepelinian line of divide?

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Significant nosological uncertainty over Kraepelin's dichotomous description of two major psychotic disorders persists to date. While several observations suggest the existence of overlapping pathophysiological processes in schizophrenia and bipolar disorder, the point of rarity in brain structure and function at which the two disorders differ is elusive. There is an increasing realization that the functional integration (measured using fMRI based connectivity measures), rather than regional specialization in the brain, is likely to be abnormal in psychosis, with several studies in schizophrenia suggesting an inefficient recruitment of distributed brain regions during task performance. The study of cortical gyrification can also provide information about the state of connectivity during early phases of cortical development.

Electrophysiological studies of patients with bipolar disorder schizophrenia suggest that early sensory processing deficits may be specific to schizophrenia (Chen et al., Hamm 2012), with fMRI studies finding converging group differences localized to unimodal regions such as the extrastriate visual association cortex (Curtis et al., 2001; Ongur et al., 2010). On the other hand, paralimbic brain regions constituting large scale brain networks such as the insula and anterior cingulate cortex show prominent but shared structural alterations in the two disorders (Glahn et al., 2008).

We recruited a sample of 20 patients with bipolar disorder with psychosis (BPP) and 40 patients with schizophrenia, in addition to 40 healthy subjects matched in age, gender and parental socioeconomic status to the patient group. We computed the degree centrality, a measure of the number of voxel-to-voxel connections of brain regions, during an executive/working memory task (n-back). Cortical folding was measured using local gyrification index (Schaer et al., 2008). The three groups were compared with each other; in addition we also performed conjunction analyses to identify regions showing common abnormalities across the two disorders. Our findings suggest that 25 to 50% of the connectivity based alterations overlap between the two disorders. For both functional connectivity measure and cortical folding measure, the involvement of unimodal sensory area (lingual/fusiform gyrus) discriminated schizophrenia from bipolar disorder. Patients with schizophrenia showed reduced gyrification (permutation corrected $p<0.05$) and excessive transition of degree centrality in these unimodal association regions (FWE corrected $p<0.05$) compared to bipolar patients with psychosis. Both groups showed a prominent loss of gyrification affecting multimodal brain regions, and shared core-hub architecture while a shift in centrality towards limbic/paralimbic regions.

In the light of these observations, we infer that across the two psychotic disorders, overlapping abnormalities in the structure and function involve the multimodal brain regions and to some extent the limbic/paralimbic cortex, while schizophrenia specific

defects will be restricted to unimodal sensory processing areas. The Kraepelinian line of divide, if it exists, is unlikely to be too far from the unimodal sensory processing regions.

Altered judgment of physical and social causality in patients with schizophrenia: an fMRI study

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Background: Causality is a fundamental aspect of human cognition, as representations of cause-and-effect-relations provide a basis for successful interactions with our environment. In experimental research, physical causality has been investigated using animations of collision events [1]. Causality has been less extensively studied in a social context; however, motion perception and social cognition are likely to contribute to the impression of an interaction between two animated objects perceived as living “entities” [2]. In both physical and social context, spatio-temporal stimulus characteristics play an important role for the impression of causality. Previous research shows an altered perception of physical causality in patients with schizophrenia (specifically, patients with delusions and desorganisation symptoms), as compared to healthy controls [3]. We aim to assess differences and commonalities in neural correlates of causal judgments in patients with schizophrenia and healthy controls, in both physical and social context.
Methods: Eighteen patients with schizophrenia spectrum disorder (2 female) and eighteen matched (with respect to age, gender, education and handedness) healthy control subjects participated in the study. During fMRI-Data acquisition, subjects judged causal relationships (Causal/Non-Causal, C) in two types of animated videos: A blue ball colliding with a red ball (P; physical condition, instruction: “Did the blue ball cause the red ball to move?”), and a blue ball passing the red ball and then straying off the track (S; social condition; “Did Mrs. Red cause Mr. Blue to move?”). In both video types, stimulus-parameters (angle and time delay) were varied equally. A control task was also implemented (judgment of movement direction in the same videos, D).
Behavioral results: Generalized estimation equations analyses (GEE) were conducted to assess interaction effects of group(SZ/HC), task(C/D), stimulus(S/P), and spatio-temporal parameters (angle and time delay) on response (causal/non-causal). SZ and HC show different response patterns with respect to causality, as opposed to direction judgments. We also found context-specific differences: Compared to HC, SZ show more causal judgments in the physical context and less causal judgments in the social context. GEE-analyses further revealed that spatio-temporal stimulus-characteristics contribute less to causal judgments in the SZ, compared with the HC group, in both physical and social context.
fMRI results: We found large overlaps in neural activations in both groups for causality, compared to direction judgment, in a fronto-parietal network. Furthermore we found specific overlaps for social>physical causality judgments in right temporo-

parietal areas previously related to social cognition and motion perception. Despite these large overlaps, groups differed in neural response with respect to task. Specifically, an increased BOLD-response in the SZ group in the left superior frontal gyrus was found for causality, as opposed to direction judgments.
Discussion: Behavioral results show that perceptual cues (space and time; [4]) are less relevant for causal judgments in patients with schizophrenia than in healthy controls. The increased response in the frontal cortex in the SZ group here might reflect altered (i.e. cognitive/interpretational) judgment strategies, in terms of a lower cue sensitivity which leads to an "over/under-interpretation" of causal relations in physical/social contexts, respectively.

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Is normalization of brain reward disturbances associated with Dopamine D_2/D_3 receptor blockade in patients with schizophrenia?

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Background: Various symptoms in schizophrenia are linked to dopamine disturbances and a dysfunction of the brain reward system. Many studies have been done in medicated patients.
We plan to examine how reward processing abnormalities are related to striatal dopamine D_2/D_3 binding potential (BP) and psychopathology in antipsychotic-naïve first-episode schizophrenia patients. We will explore how these disturbances are modulated by D_2/D_3 receptor blockade with amisulpride.
Previously we have, in the same cohort, demonstrated that alterations in reward processing are fundamental in patients with schizophrenia, and are seen prior to any treatment. Data additionally demonstrated an association between clinical improvement in positive symptoms and normalization of reward processing after treatment with amisulpride.[1, 2]

Methods: The study is designed as a 6 week longitudinal study of antipsychotic-naïve patients with schizophrenia and matched healthy controls. The participants are examined at baseline and at 6 weeks follow up with an extensive battery of assessments, including structural and functional Magnetic Resonance Imaging (fMRI) and Single Photon Emission Computed Tomography (SPECT). After baseline examinations the patients are treated with flexible doses of amisulpride according to their clinical condition.
In order 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 BP of dopamine D_2/D_3 receptors in the striatum.

Results: Currently we have both SPECT and fMRI data from 30 patients at baseline, 24 at follow-up and 24 healthy controls.

Conclusion: Data collecting is nearly finished, and data from baseline and follow up will be presented.

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SESSION C
treatment – sensory gating – neurotransmission – cognitive remediation

Volumetric Changes in the Basal Ganglia after Antipsychotic Monotherapy: a Systematic Review

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Introduction
Exposure to antipsychotic medication has been extensively associated with structural brain changes in the basal ganglia (BG). Traditionally antipsychotics have been divided into first and second generation antipsychotics (FGAs and SGAs) however, the validity of this classification has become increasingly controversial. To address if specific antipsychotics induce differential effects on BG volumes or whether volumetric effects are explained by FGA or SGA classification, we reviewed longitudinal structural magnetic resonance imaging (MRI) studies investigating effects of antipsychotic monotherapy.

Material and Methods
We systematically searched PubMed for longitudinal MRI studies of patients with schizophrenia or non-affective psychosis who had undergone a period of antipsychotic monotherapy. We used specific, predefined search terms and extracted studies were hand searched for additional studies.

Results
We identified 13 studies published in the period from 1996 to 2011. Overall six compounds (two classified as FGAs and four as SGAs) have been investigated: haloperidol, zuclophentixol, risperidone, olanzapine, clozapine, and quetiapine. The follow-up period ranged from 3-24 months.
Unexpectedly, no studies found that specific FGAs induce significant BG volume increases. Conversely, both volumetric increases and decreases in the BG have been associated with SGA monotherapy.

Discussion
Induction of striatal volume increases is not a specific feature of FGAs. Except for clozapine treatment in chronic patients, volume reductions are not restricted to specific SGAs.
The current review adds brain structural support to the notion that antipsychotics should no longer be classified as either FGAs or SGAs. Future clinical MRI studies should strive to elucidate effects of specific antipsychotic drugs.

The effects of treatment with a dopamine D2/D3 receptor antagonist on P3a and P3b amplitudes in drug-naïve schizophrenia

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Background

Successful information processing requires efficiency at preattentive automatic levels in order to allocate resources to novel and/or salient stimuli and inhibit responses to redundant or irrelevant stimuli. (Grillon et al., 1990). These processes can be examined quantitatively in event related potentials (ERP) studies. In ERP P3a reflects the automatic orienting of attention towards novel or deviant stimuli (Escera et al., 2000) and P3b reflects the orienting and subsequent response towards "salient" stimuli (Polich, 2007). Early sensory information processing deficits, such as selective attention deficits have consistently been associated with schizophrenia (SZ). However the majority of these studies have been conducted in medicated and inhomogeneous groups of SZ patients which make it difficult to determine if attentional deficits can be considered as stable endophenotypic markers for SZ or should be considered as deficits that change with medication or with progress of the disease. The aim of the present study was to investigate the above mentioned electrophysiological parameters of selective attention in a large group of antipsychotic naïve, first-episode patients with schizophrenia. A further aim was to investigate the effects of a subsequent 6 weeks treatment of these patients with a dopaminergic D2/D3 receptor antagonist (amisulpride)

Methods

Drug naïve first-episode schizophrenia patients were tested in a selective attention paradigm and re-tested after 6 weeks of amilsulpride treatment. The patients were matched on age, gender and parental social-economic status with healthy subjects who, similarly as the patients, were tested at baseline and 6 weeks follow-up, however without receiving any treatment. The study is still ongoing, but currently we have recruited and analyzed data of 47 patients at baseline and 26 at follow up, as well as of 47 controls at baseline and 36 at follow-up.

Results

Unexpectedly and in contrast to our previous studies, neither a significant main effect of group was found in P3a and P3b amplitudes at baseline, nor at follow-up. However, a significant first order interaction was found between group and treatment, indicating that where the P3a amplitude of controls dropped significantly between baseline and follow-up, the amplitude of patients remained unaltered. In addition a significant effect of gender was found on the P3a amplitude, indicating higher amplitude in females than in males, as well as a higher drop in P3a amplitude in females than in males from baseline to follow-up. A gender effect was also found on

the P3b amplitude, with women scoring higher amplitudes than males irrespective of group and time (treatment). However neither males nor females showed a significant difference in P3b amplitude between baseline and follow-up. No group differences were found in the latencies of the ERPs, neither at baseline nor at follow-up.

Conclusion

In the present preliminary data we did not observe the usual found group differences at baseline in P3a and P3b between unmedicated SZ patients and healthy controls. However, we did observe a lack of retest effect on P3a in the SZ group but at the current preliminary stage of data-analysis we cannot conclude whether this effect is due to D2/D3 antagonism or not.

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Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)—a suitable endophenotype of schizophrenia

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The concept of schizotypy or "psychosis proneness" captures individual differences in perceptual, cognitive, and affective experiences that may relate to a range of psychotic disorders. The concept is an important way to assess the contribution of pre-existing psychological and genetically based biological features to the development of illnesses such as schizophrenia (so called endophenotypes).

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) is a widely used multi-dimensional measure of the construct and consists of four scales which mirror several groups of psychotic symptoms: Unusual Experiences (UnEx; positive symptoms), Cognitive Disorganization (CogDis; cognitive symptoms), Introvertive Anhedonia (IntAn; negative symptoms), and Impulsive Nonconformity (ImpNon; impulsive and antisocial symptoms). For the purpose of evaluating the suitability of schizotypy as an endophenotype of schizophrenia the current version of the O-LIFE was translated into German: its psychometric properties (including re-test reliability and construct validity) were examined in a large sample (n > 1200) and compared to those of the English original.

The German version was both highly reliable and consistent with the original. The study aimed to show that schizotypy as measured by the O-LIFE can indeed be regarded as an endophenotype of schizophrenia in terms of genetic associations regarding relevant dopamine-related candidate polymorphisms of schizotypy [i.e., Val158Met-polymorphism of the COMT gene, uVNTR of the MAOA gene, Taq1A-polymorphism of the DRD2 gene, VNTR of the SLC6A3 (DAT) gene]. We also wanted to compare the genetic associations of the O-LIFE to those published using other operationalizations of schizotypy.

Our results show a large number of significant associations and borderline-significant trends between the O-LIFE sub-scales and a range of genes, thereby supporting using the O-LIFE in the search for endophenotypic markers.

Literature:
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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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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 examine 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.

100 Patients suffering from schizophrenia or schizoaffective disorder will be included in two hospitals (clinics for psychiatry and psychotherapy in Giessen), 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.

Preliminary results of selected tasks indicate an effect of CRT on social functioning, quality of life, psychopathology and cognitive functions in the treatment group (n=23, TAU: n=19).
For example, treatment patients rated themselves better in scales like interpersonal communication, competence in daily activities and cognitive ability compared to baseline and TAU. There seems to be no effect of CRT on the assessment of psychotic symptoms – neither self nor external. Regarding depressive symptoms both groups tend to rate themselves less depressive compared to baseline – with more improvements for the treatment group. On verbal, numerical, and spatial memory tasks like Digit Span, Memo-Test, delayed recall, and Spatial Span we found no effect of CRT. However, the treatment group seems to benefit from CRT in problem solving tasks (WCST completed categories, SOC problems solved in minimal moves) by reaching faster a pre-episodic level compared to TAU patients who even treatment group performance after one year.

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.

Chronic Olanzapine reverses the cognitive but not the neuronal deficits in the sub-chronic phencyclidine model - relevance to schizophrenia

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Schizophrenia is a chronic psychiatric disorder characterised by positive, negative and cognitive symptoms. Deficits in cognition are one of the central features in schizophrenia and are currently an unmet clinical need. Although the exact cause remains elusive there is substantial evidence for neuronal dysfunction in the brains in patients with the disorder.

N-acetylaspartate (NAA) is present in high concentrations in the CNS and is considered to be a general marker of neuronal loss and/or cellular dysfunction. Numerous magnetic resonance studies have shown reductions in levels of NAA in schizophrenia, with deficits correlated to disease severity. Recovery of NAA levels following acute brain injury and increases in NAA following pharmacological therapy have also been reported. Taken together these studies demonstrate its potential use as a biomarker for assessing restoration of neuronal function following successful treatments.

We have consistently demonstrated that sub-chronic phencyclidine (PCP) treatment in the female rat produces robust cognitive deficits and pathological changes that mimic those reported in schizophrenia [1].

The aim of this study was to investigate the effect of chronic treatment with the atypical antipsychotic olanzapine on cognitive and neuronal deficits in the sub-chronic PCP model.

Treatment Regimes: Adult female hooded lister rats received vehicle (saline 0.9% bi-daily, i.p.) or sub-chronic PCP (2 mg/kg bi-daily, i.p.) for 7 days followed by a 7 day washout period. Animals also received vehicle or olanzapine (1.5 mg/kg i.p.) once daily for 28 days.
Experiment 1: Sub-chronic PCP, Chronic Olanzapine & Cognition:
In a rodent operant reversal-learning paradigm deficits in reversal learning, produced by PCP, were attenuated following both acute and chronic treatment with olanzapine.
Experiment 2: Sub-chronic PCP, Chronic Olanzapine & NAA:
Compared to vehicle, sub-chronic PCP treatment produced significant reductions in NAA, in the frontal cortex ($p<0.05$) and ventral hippocampus ($p<0.05$), with no significant changes in the striatum, dorsal hippocampus or temporal cortex. Chronic olanzapine did not reverse the deficits in NAA in sub-chronic PCP treated animals.

These preliminary findings demonstrate that sub-chronic PCP administration causes cognitive (deficits in reversal learning) and neuronal deficits (reductions in NAA) of

relevance to schizophrenia. Furthermore we found that chronic treatment with the atypical antipsychotic olanzapine can reverse the behavioural but not the neuronal deficits.

This study provides further evidence to suggest that sub-chronic PCP can mimic aspects of the behavioural and neuronal pathology of schizophrenia. Taken together the results suggest that NAA may provide a translational biomarker for assessing the effect of treatment on indicators of normal neuronal function.

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Associations between dopamine D_2 receptor binding, brain structure and psychopathology before and after antipsychotic monotherapy

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This project has examined two separate cohorts of antipsychotic-naive first-episode schizophrenia patients before and after a period of antipsychotic monotherapy. The aim of the project is to investigate to what extend the progressive brain volume changes which are seen in schizophrenia are caused by the illness itself or rather by the dopamine D_2 receptor blockade induced by antipsychotic medication. Furthermore, we will examine D_2/D_3 receptor binding potential (BP_P a potential biomarker for treatment effect.

All subjects underwent structural magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) scans. Clinical rating scales included the positive and negative syndrome scale (PANSS) and the extrapyramidal symptoms rating scale (ESRS). Based on age, gender and socioeconomic status patients were matched 1:1 to healthy controls.
After baseline examinations patients in the ^{IBZM}cohort were treated with amisulpride for 6 weeks. Patients in ^{EPI}cohort were randomised to 12 weeks treatment with either risperidone or zuclopenthixol. Two different ligands were used for the SPECT scans. [^{123}I] IBZM which is suitable for quantifying D_2/D_3 receptors in the receptor rich basal ganglia was used in the ^{IBZM}cohort. [^{123}I]epidepride, which is suitable for quantifying D_2/D_3 receptors in the receptor poor extrastriatal areas was used in the ^{EPI}cohort. MRI analyses will be based on region of interest analyses using the same regions as defined in the SPECT scans.

In the ^{IBZM}cohort 24 patients were SPECT and MR scanned at baseline and follow-up. In the ^{EPI}cohort 21 patients were SPECT and MR scanned at baseline and at follow-up. PANSS and ESRS were assessed at baseline and follow-up. Imaging analyses

iare currently being carried out and results will be presented when analyses have been performed.

The results of this study will provide unique and new insights to the relationship between striatal and extrastriatal D_2/D_3 receptor activity, symptomatology and progressive volumetric brain changes in the early stages of schizophrenia.

Clonidine Normalizes Sensory Gating Deficits in Patients with Schizophrenia on Stable Medication

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Background: Sensory gating deficits are among the core features of schizophrenia. Recently, we reported significantly increased sensorimotor gating following additional administration of single dosages of clonidine to the treatment of stably medicated patients with schizophrenia who, in spite of their medication, showed gating deficits. In the current study we investigated whether this result is generalizable to filtering of sensory information as a whole, by examining clonidine's effect on P50 suppression in the same group of patients.

Methods: In a double blind, placebo controlled, randomized yet balanced cross-over design 20 male schizophrenia patients on stable medication were assessed in a sensory gating paradigm on 5 occasions: once after oral administration of placebo and after single doses of 25, 50, 75 and 150 µg of clonidine. Their results were compared with 20 age and gender matched healthy volunteers, who received no treatment.

Results: Patients showed significant P50 suppression deficits in the placebo session compared to controls. All dosages (except the highest dose) of clonidine significantly diminished these deficits, to such levels that they no longer differed significantly from the healthy controls.

Conclusions: This is the first study to show that even a single low dose of clonidine added to stably medicated patients with schizophrenia not only significantly reduces their P50 suppression deficits, but also normalizes them. The results indicate that α2-noradrenergic agonists are capable of normalizing sensory gating deficits, which has a potentially high clinical relevance for the medical treatment of schizophrenia.

5-HT_{2A} receptor binding is a biomarker of quetiapine associated BMI increase in antipsychotic-naive first-episode schizophrenia patients

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Antipsychotic-induced weight gain is of major clinical importance since it is associated with severe metabolic complications and increased mortality. The serotonin2A receptor system has been suggested to be implicated in weight gain and obesity. However, no previous *in vivo* imaging data have related serotonin2A receptor binding to weight gain before and after antipsychotic monotherapy.

Fifteen antipsychotic naive first episode schizophrenia patients were included and investigated before and after 6 months of quetiapine treatment. We examined the relationship between serotonin2A receptor binding as measured with positron emission tomography (PET) and [^{18}F]altanserin and change in body mass index (BMI). Quetiapine was chosen because it is characterized by a moderately high affinity for the serotonin2A receptor and a fast dissociation rate from the dopamine D_2 receptor.
After six months of quetiapine treatment the BMI had in average increased by approximately 7 %, corresponding to an average weight gain of 5.0 kg. We found a significant positive correlation both between neocortical serotonin2A receptor binding prior to treatment and subsequent increase in BMI. At follow-up, the serotonin2A receptor occupancy was significantly positively correlated with BMI increase.

To our knowledge, these are the first *in vivo* receptor imaging data in initially antipsychotic naive first episode schizophrenia patients to show that the cerebral serotonin2A receptor is associated with antipsychotic-induced weight gain.

Sleep, problem solving and procedural learning in schizophrenia

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Unmedicated patients with schizophrenia show altered sleep patterns which are, however, largely normalised with medication. In healthy volunteers sleep has a beneficial effect on problem solving and learning. The question arises whether sleep has a similarly beneficial effect in schizophrenia. We investigated the relationship between sleep parameters, including micro-architectural features such as K-complexes and spindles, and problem solving as well as procedural learning in schizophrenia.
Twenty outpatients with a diagnosis of schizophrenia and 12 healthy controls took part in the study. All patients were on stable medication (15 atypical, 1 typical and 5 both antipsychotics). Participants were randomly allocated to undergo a day or a night interval first. Learning occurred in the morning and evening, respectively, and testing 8 hours later. The learning tasks were (a) Tower of London (ToL), a problem solving task and (b) mirror tracing, a procedural learning task. Patients were given standard diagnostic interviews and both groups completed neuropsychological tests. Sleep EEG, derived from left C3 to earlobe was analysed according to Rechtschaffen and Kales' (1968) criteria adding number of K-complexes and spindles to the variables.
Patients performed less well than controls on all neuropsychological tests but there were no significant group differences with regard to any of the sleep parameters. Compared to controls, patients took longer to complete ToL and the mirror tracing task and made more errors during the latter. Both groups improved with regard to these variables irrespective of type of interval from learning to testing. In patients, a higher number of K-complexes were related to an increased number of solved ToL tasks and fewer mirror tracing errors. Longer SWS was related to faster completion of the ToL both pre and post night interval. In controls, a greater number of spindles were related to a faster completion of the ToL and fewer errors during the mirror tracing task.

The results confirmed previous findings of normalised sleep in medicated schizophrenia patients. We failed, however, to confirm the beneficial effect of a night over a day interval upon consolidation in either group. It is notable that an improved performance is related to K-complexes - thought to indicate intra-cortical activity - in patients whereas it is related to spindles – activity of thalamo-cortical connectivity – in healthy controls. The results suggest altered sleep processes in relation to cognitive performance in schizophrenia.

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Cognitive remediation improves cognition and good cognitive performance increases time to relapse – results of a 5 year catamnestic study in schizophrenia patients

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Background:
Cognitive deficits are stable features of schizophrenia that are linked to functional outcome. Cognitive remediation approaches have been proven successful in ameliorating these deficits, although effect sizes vary considerably. Whether cognitive deficits are serious predictors of clinical outcome is less clear.
Methods:
Sixty patients suffering from schizophrenia were included in our sample, thirty of them received computer-assisted cognitive training, and twenty received occupational therapy. For a subsample of 55 patients, who could be traced over a period of five years after the end of the cognitive remediation intervention, time until first relapse was determined retrospectively from their medical records.
Results:
Cognitive remediation significantly improved problem solving, memory and attention with high effect sizes. Employment status and post test verbal memory performance outperformed all other measures in the prediction of time to relapse, while allocation to treatment group outperformed all other variables in the prediction of verbal memory performance.
Conclusions:
Cognitive remediation of neurocognitive deficits thus makes sense in a twofold fashion: It enhances cognition directly and positively acts on clinical course indirectly via improved neurocognition.

The effect of reboxetine and haloperidol on P50 suppression in healthy volunteers

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Introduction: Disruptions in filtering of sensory information have frequently been observed in patients with schizophrenia. Successful sensory gating prevents sensory overload of higher brain functions by filtering out irrelevant stimuli before they can reach the higher brain areas. Deficits in sensory gating may therefore result in an overload of irrelevant information reaching the higher brain areas, which in turn might contribute to the formation of psychotic symptoms. One well established paradigm to assess sensory gating is P50 suppression. In this paradigm, patients with schizophrenia score significantly lower than healthy controls. In schizophrenia both a reduction in prefrontal dopaminergic activity and an increased noradrenergic activity have been suggested to be involved in the disease. In the current study we aimed to further investigate the involvement of these neurotransmitters using the norepinephrine reuptake inhibitor (NRI) reboxetine and the dopamine antagonist haloperidol, to increase noradrenergic as well as decrease dopaminergic neurotransmitter activity, respectively.
Material and methods: The design of the experiment was a double-blind, placebo-controlled, cross-over study, where a dose of either reboxetine (8 mg), haloperidol (2 mg), their combination or placebo was administered to 21 healthy male subjects at four separate visits with a minimum of two weeks apart. The subjects were thereby tested in The Copenhagen Psychopsysiological Test Battery (CPTB) which, amongst others, measures P50 suppression using electroencephalography (EEG).
Results: As expected, we found a significant reduction in P50 suppression following separate administration of either reboxetine or haloperidol as well as following their combined administration compared to placebo.
Conclusion: The current study aimed to help clarify the neurotransmitter systems involved in sensory gating. Based on the results obtained it seems that both an increased noradrenergic and a decreased DA activity is involved in P50 suppression, as expected. However we did not observe a synergistic effect of the combination of the compounds, which might indicate a ceiling effect or a drug/drug interaction. Since sensory gating in schizophrenia patients is usually found to be reduced compared to controls our results may indicate similar underlying neurotransmitter activity.

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