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

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2016

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Abstract Book

Robert Sommer Research Society
Am Steg 22
35385 Giessen

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Organiser:

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

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Venue:

Conference
Centre for Psychiatry (old building)
Main Lecture Theatre, Main Building
Am Steg 22
Giessen

Conference Dinner (Friday, 4th of November)
Centre for Psychiatry (new building)
Klinikstr. 36
Giessen

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SESSION A

Elementary Cognitive Processing

Chairs: Trevor Robbins and Jürgen Hennig

A1 - The Effect of Deviance Predictability on Mismatch Negativity in Schizophrenia Patients

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Mismatch Negativity (MMN) is an electrophysiological index of prediction error processing and has been considered an endophenotype marker in schizophrenia. While the prediction error is a core concept in the MMN generation, predictability of deviance occurrence has rarely been assessed in MMN research and in schizophrenia patients.

We investigated the MMN to 12 % temporally predictable or unpredictable duration decrement deviant stimuli in two runs in 29 healthy controls and 31 schizophrenia patients. We analyzed MMN amplitudes and latencies and its associations with clinical symptoms at electrode Fz. With a stimulus onset asynchronicity of 500 ms in the regular predictable condition, a deviant occurred every 4 seconds while it varied randomly in the unpredictable condition. In the traditional random condition we found diminished MMN amplitudes in patients which normalized in the regular deviance condition, resulting in an analysis of variance main effect of predictability and a predictability x group interaction. Deviance predictability did not affect the MMN of control subjects and we found no relevant results with regard to MMN latencies.

Our results indicate that MMN amplitudes in patients normalize to the level of the control subjects in the case of a temporally fixed regular deviant. In schizophrenia patients the detection of deviance is basically intact. However, the temporal uncertainty of deviance

occurrence may be of substantial relevance to the highly replicated MMN deficit in schizophrenia patients.

Literature:

Horacek, M., Kärgel, C., Scherbaum, N., & Müller, B. W. (2016). The effect of deviance predictability on mismatch negativity in schizophrenia patients. Neurosci Lett, 617, 76-81.

A2 - Effective connectivity analysis of audiovisual integration in the superior temporal gyrus during processing of co-verbal gestures in schizophrenia

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The left superior temporal sulcus (STS) is associated with the integration of audiovisual information and is functionally connected to disparate brain regions. Previous studies demonstrated dysfunctional integration of speech and gesture information in patients with schizophrenia for specific gesture types (metaphoric gestures), reflected in aberrant activation of the left STS [1] and lower connectivity between left STS and the inferior frontal gyrus (IFG) [2].

With this study we investigate the specific role of the STS in audiovisual speech-gesture integration processes using Dynamic Causal Modelling (DCM) to identify more precisely possible differences between healthy subjects and patients with schizophrenia. During simultaneous EEG-fMRI data acquisition healthy students (H) (n = 20), patients with schizophrenia (P) (n = 17) and a matched healthy control group (C) (n = 18) were shown videos of an actor performing emblematic or tool-use gestures together with associated person or object related sentences. By means of non-linear DCM we analyzed effective connectivity between the STS, MTG and the occipital lobe (BA19) based on 17 different models grouped together in four model families. In all

models the driving input (C-matrix) was set to the MTG and BA19. Only fMRI data were included in the DCM analysis. In a first step we tested our model space for the H-group to identify a model that fits best our data. Bayesian Model Selection (BMS) revealed a significant winning model with an exceedance probability 79.1% with bilateral intrinsic connectivity between all areas (A-matrix), modulations of both connections to the STS (B-matrix) and modulatory effects of the STS on bilateral connections between MTG and BA19. In a second step we applied the model space to the P- and C-group. The analysis revealed the same winning model as in the H-group (exceedance probability 77.4% in controls and 84.8% in patients). Comparing the summarized DCM parameters, the patients revealed reduced coupling strength from MTG to STS.

In our study we were able to show that audiovisual speech-gesture integration is based on the same core network suggesting similar processing mechanisms in healthy subjects and patients with schizophrenia. However, patients revealed reduced information flow from MTG to STS. These findings provide more specific evidence for dysfunctional neural integration of co-verbal gestures in patients with schizophrenia, which is primarily based on a reduced incorporation of verbal (auditory) input.

Literature:

[1] Straube, B., Green, A., Sass, K., Kirner-Veselinovic, A. and Kircher, T. (2013). Neural integration of speech and gesture in schizophrenia: Evidence for differential processing of metaphoric gestures. Human Brain Mapping 34, 1696–1712.

[2] Straube, B., Green, A., Sass, K. and Kircher, T. (2014). Superior temporal sulcus disconnectivity during processing of metaphoric gestures in schizophrenia. Schizophrenia Bulletin 40:4, 936–944.

A3 - The neural processing of gestures accompanying figurative speech in a narrative context in patients with schizophrenia – Preliminary results from an fMRI study

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Background: Concretism – the inability to understand the abstract or figurative meaning of proverbs and metaphors represents a core feature of thought and language impairments in patients with schizophrenia (e.g. Kircher et al. 2007). Furthermore, patients with schizophrenia tend to misinterpret gestural information. So far, patient studies focused on the integration of speech and gesture on the level of words, sentences or phrases pointing to a dysfunctional involvement of the left inferior frontal gyrus (IFG) in the integration of both modalities (Straube et al. 2013).

The current study aimed at extending previous findings to the investigation of gestures accompanying figurative speech in an ecologically-valid narrative context. We hypothesized, that patients with schizophrenia compared to healthy controls, demonstrate decreased activation in the left IFG for the processing of gestures accompanying figurative information in a narrative context.

Methods: During functional magnetic resonance imaging (fMRI) data acquisition, 10 patients with schizophrenia and 11 matched healthy controls were shown videos of an actor telling a short story that contained many instances of figurative language.

He performed natural gestures while speaking. For analysis, sentences with figurative language in form of similes (e.g., “An X is like an Y”) had been selected from the story. These events were divided into sequences with gesture (language and gesture simultaneously: SimG condition) and without gesture (language only: SimNG condition). Results: In comparison to the healthy control group, the patients showed abnormal activation in left inferior frontal regions, but also in neighbouring regions (e.g. the frontoparietal operculum): Patients with schizophrenia compared to control subjects showed an increased activation for the SimNG condition and a decreased activation for the SimG condition.

Conclusion: In line with our hypotheses, patients differed from healthy control subjects in the neural processing of gestures accompanying figurative speech in a narrative context. The increased neural activation in the left IFG for the SimNG condition suggests that patients need more neural resources than healthy subjects to integrate the abstract meaning of an utterance into a semantically reach environment. In contrast, patients with schizophrenia showed a decreased activation in the left IFG when gestures were used by the actor to illustrate the figurative language. These findings suggest a dysfunction in patients with schizophrenia for the processing of gestures accompanying figurative speech in a narrative context.

Literature:
Kircher, Tilo T. J., Dirk T. Leube, Michael Erb, Wolfgang Grodd & Alexander M. Rapp. 2007. Neural correlates of metaphor processing in schizophrenia. NeuroImage 34(1). 281–289. Straube, Benjamin, Antonia Green, Katharina Sass, André Kirner-Veselinovic & Tilo Kircher. 2013.
Neural integration of speech and gesture in schizophrenia: Evidence for differential processing of metaphoric gestures. Human Brain Mapping 34(7). 1696–1712.

A4 - Increase of set-shifting abilities after illness onset in patients with schizophrenia (results of a 7-16 year follow-up study)

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Background: Set-shifting reflects the ability to be flexible in problem solving, e.g. using feedback to change behavior. Deficits in set-shifting have been established in schizophrenia [1–6] but the long-term progression of the deficits remains unclear. Only few studies have examined the longitudinal stability or progression of set-shifting deficits in people with schizophrenia[6–8], and most with very brief follow-up intervals[6]. The results from these studies are ambiguous, showing either stability of deficits[6,8] or a decline of set-shifting abilities[7]. Only a couple of studies have followed patients beyond the first year and they indicate that set-shifting deficits stabilize after the first year[7,9]. In contrast, data from cross sectional studies comparing patients with first episode schizophrenia with chronic patients supports larger set shifting deficits in chronic patients[2,4,5,10,11].

Hypothesis: Based on the cross-sectional findings, we hypothesize that patients with schizophrenia will show a decline in set-shifting abilities after illness onset.

Methods: In a longitudinal follow-up study, we re-examined 33 patients with schizophrenia and 43 healthy controls 7-16 years after illness onset, on their set-shifting abilities using the Intra-Extra Dimensional Set Shifting Task from Cambridge Neuropsychological Test Automated Battery. We used a univariate ANCOVA in a

preliminary analysis of change scores on Extra-dimensional shift (EDS) errors and total errors (adjusted for stages not completed) with the following covariates: Age, sex, baseline level performance, and the time interval between baseline and follow-up examinations (7-16 years).

Results: We found a significant group difference in change scores of EDS-errors (p=0.025) and total errors adjusted (p=0.049). Patients showed an increase in performance (less errors at FU) when compared to controls who remained relatively stable (mean of EDS-change: patients= -3.2 (SD=10.8) and controls= -0.7 (SD=4.2) and mean total errors adjusted-change: patients= -5.1 (SD=23.3), controls= -1.5 (SD=8.3)).

Conclusion: The results show an increase in set-shifting abilities in the years following onset of schizophrenia compared to relative stability of set-shifting abilities in the healthy control group. Thus the preliminary analysis of our longitudinal study does not support findings of a set-shifting decline after illness onset.

Literature:
[1] Ceaser, Goldberg, Egan, McMahon, Weinberger, Gold. Biol Psychiatry. 2008, 64, 782-788.
[2] Jazbec, Pantelis, Robbins, Weickert, Weinberger, Goldberg. 2007, Schizophr Res. 89, 339-349.
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[8] Hoff, Riordan, O'Donnel, Morris, DeLisi. 1992, Am J Psychiatry. 149, 898-903. [9]
[9] Hoff, Svetina, Shields, Stewart, DeLisi. 2005, Schizophr Res. 78, 27-34.
[10] Addington, Addington. 2002, J Psychiatry Neurosci. 27, 188-192.
[11] Albus, Hubmann, Ehrenberg et al. 1996, Eur Arch Psychiatry Clin Neurosci. 246, 249-255.

A5 - Influence of luminance on working memory encoding and its dysfunction in schizophrenia

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Impairments in working memory (WM), the ability to maintain and manipulate information for a short period of time, are a core cognitive deficit in schizophrenia (Sz) that predicts functional outcome. Past research has shown that abnormal perceptual encoding plays an important role in these WM deficits, but the underlying basis of this association is yet to be determined. One possibility in people with schizophrenia is that it may be linked to well documented impairments in processing luminance using the magnocellular pathway. However the relative contributions of the three visual pathways (magnocellular, parvocellular and koniocellular) to WM encoding is unknown as is their role in WM deficits in Sz. Here we hypothesized that 1) there is a differential contribution of parallel visual pathways to WM performance and 2) that abnormalities in these pathways may contribute to WM deficits in Sz.

We investigated whether WM encoding of stimuli defined purely by luminance (i.e preferentially activating the magnocellular pathway) or chromatic (i.e. isoluminant and designed to preferentially activating either the parvocellular pathway or the koniocellular pathway) information would differentially influence WM performance and early visual ERP responses in a delayed discrimination task. We furthermore tested if patients with SZ compared to matched control participants would show a problem in encoding these stimuli into WM. Results of the first experiment

showed that luminance-defined shapes resulted in higher WM accuracy and faster reaction times, which was primarily evident at higher WM loads. Early visual P1 and N2 ERP components responded preferentially to luminance or chromatic stimuli respectively. The 2nd experiment showed that in the patient group both these ERPs were reduced.

Results from these experiments point to the importance of early encoding processes in working memory. In particular, we demonstrated that luminance signals provide an advantage over chromatic signals in working memory processing. Reduced early ERPs in the patient group suggest that visual processing deficits contribute to WM abnormalities.

Literature:
Haenschel, C., & Linden, D. (2011). Exploring intermediate phenotypes with EEG: working memory dysfunction in schizophrenia.. Behav Brain Res, 216(2), 481-495
Haenschel, C., Bittner, R. A., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., Linden, D. E. (2007). Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging.. Arch Gen Psychiatry, 64(11), 1229-1240.

A6 - Neuronal Correlates of Face Detection during Perceptual Uncertainty

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Introduction: Problems in social interactions in schizophrenia might be related to an impairment in processing face information. However the neural mechanisms underlying this perceptual deficit are poorly understood so far. In a recent functional magnetic resonance imaging (fMRI) study, Maher et al. (Maher et al. 2016)compared the brain activity during the processing of faces with different contrast levels between patients with schizophrenia and healthy controls (Maher et al. 2016). While brain activity within core regions of the face-processing network did not differ between patients and controls for high-contrast faces, the authors reported differences between both groups in the fusiform face area (FFA) with regard to face specificity: patients showed, for low-contrast (i.e. noisy) images, less activation differences between face stimuli and tree stimuli than healthy controls. Maher and colleagues, however, did neither assess top-down modulations nor lateralization effects during face detection, although these are crucial topics related to schizophrenia. Therefore, in the present study we set-up a paradigm aimed to examine effects of different contrast levels concerning face detection in order to provide a face detection paradigm for further experiments with schizophrenic patients.

Methods: Brain activity was assessed with fMRI during a face detection task. In this task, we used four different contrast levels of

the stimuli; as control stimuli we used trees. 20 healthy subjects participated in the study. One experimental session had a duration of 30 minutes. Analyzes were performed with SPM12.

Results: Contrasting face stimuli over tree stimuli revealed stable activation patterns in the core network of face perception, e.g., bilateral FFA and occipital face area (OFA). Increasing noise (i.e., decreasing contrasts of the face and tree stimuli) elicited bilateral activation in the lateral prefrontal cortex (inferior frontal gyrus, IFG) and the anterior cingulate cortex (ACC). In terms of lateralization, face stimuli with lower contrasts elicited higher left than right hemispheric activation in OFA.

Discussion: The present paradigm is applicable for investigating brain activation of face detection during perceptual uncertainty. Results show stable activation in left and right FFA and OFA, respectively. Less contrast in face and tree stimuli is associated with higher activation in frontal regions, in particular bilateral IFG and ACC. Hence these regions orchestrate a brain network that subserves processing of indistinguishable stimuli. The challenge now is to investigate if activation patterns or connectivity measures in these regions is altered in schizophrenia.

Literature:
Maher, Stephen; Ekstrom, Tor; Holt, Daphne; Ongur, Dost; Chen, Yue (2016): The Core Brain Region for Face Processing in Schizophrenia Lacks Face Selectivity. In: Schizophrenia bulletin 42 (3), S. 666–674. DOI: 10.1093/schbul/sbv140

A7 - Effects of abnormal perception on Working Memory deficits in Schizophrenia and their impact on cognition and clinical symptoms

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Even when they are not experiencing acute psychiatric symptoms people living with Schizophrenia have problems in everyday life and social interactions. Working Memory (WM) deficits are a cardinal feature of Schizophrenia proposed to underlie many of these day-to-day difficulties. WM dysfunctions in Schizophrenia can already be found in the early encoding phase [1]. Patients also show visual perceptual abnormalities (i.e. lateral inhibition) [2,3]. However, the association between these deficits and their effects on general cognition and on the pathology itself still needs further research.

Here we explore how weak surround suppression (SS) and visual WM are related to clinical symptoms and general cognitive abilities in Schizophrenia. Twelve people with Schizophrenia and twelve matched controls performed both a contrast matching task and a delayed matching to sample WM paradigm which items were designed to stimulate both a weak and a strong SS [4]. We varied WM load by presenting one to three visual objects that were shown sequentially for 300ms each. Both populations also completed the Paired Associate Learning (PAL) to test visual memory and Spatial Working Memory (SWM) tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Patients' clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS). Whereas controls showed a significant difference between weak and strong SS in the contrast matching task, there was no difference in people with Schizophrenia. WM

accuracy was lower and response times were higher in patients compared to controls for all WM loads. People with Schizophrenia performed significantly worse than healthy controls in both PAL and SWM tests. Moreover, both PAL and SWM were highly correlated with WM accuracy in patients but not in controls. Finally, we found a trend of a positive correlation between the negative symptoms subscale of PANSS and WM response times.

Our results confirm weaker SS in people with Schizophrenia compared to healthy controls. This deficit is reflected in patients' poorer performance in a WM task specifically designed to target visual perception in the encoding phase. Additionally, WM behaviour was related to measures of general cognition and negative symptoms. Our results suggest that WM deficits origin in the early encoding phase as they can be linked to visual perceptual dysfunctions. Moreover, these impairments have an impact on general cognitive skills and clinical symptoms which may seriously affect the quality of everyday life of people with Schizophrenia.

Literature:
[1]Contribution of Impaired Early-Stage Visual Processing to Working Memory Dysfunction in Adolescents With Schizophrenia. Haenschel, C., Bittner, R., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., & Linden, D. ARCH GEN PSYCHIATRY. 2007, 64(11), 1229-1240
[2]Weak suppression of visual context in chronic schizophrenia. Dakin, S., Carlin, P., Hemsley, D. Current Biology. 2005, Vol 15 No 20
[3]Visual Perception and Its Impairment in Schizophrenia. Butler, P. D., Silverstein, S., & Dakin, S. BIOL PSYCHIATRY. 2008, 64:40–47 [4]Diminished Orientation-Specific Surround Suppression of Visual Processing in Schizophrenia. Yoon, J.H., Rokem, A.S., Silver, M.A., Minzenberg, M.J., Ursu, S., Ragland, J.D., Carter, C.S. Schizophrenia Bulletin. 2009, 35 (6): 1078-1084

A8 - Influence of Stimulus-Onset-Asynchrony on the neural networks underlying social and nonsocial spatial cueing

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Background: Recent research showed that both gaze cues and non-social symbolic cues such as arrows induce reflexive shifts of attention [1,2]. Using a Posner-like cueing paradigm considerable effort has been made to define the underlying neural systems [3,4]. However, these studies have produced inconsistent results. The aim of the current study was to help clarify these uncertainties by examining the influence of Stimulus Onset Asynchrony (SOA) on the neural networks involved in gaze and arrow cueing.

Methods: 94 subjects (mean age: 32 years; SD= 9.1; range: 21-52) completed a spatial cueing task including naturalistic faces with averted gaze and laterally pointing line-arrow-configurations as cues. Additionally, two SOAs were employed (100 & 800 ms). T2*-weighted EPI was applied during task performance using a 3 T MRI (TR = 2.8 s; TE = 2700 ms; flip angle = 90°; slice thickness = 4 mm; FoV = 192x192 mm; matrix = 64x64 mm; voxelsize = 3x3x3 mm). A brain-wide ROI-to-ROI functional connectivity analysis was conducted using the CONN-Toolbox [5] and the resulting correlation maps were compared between long and short SOA trials.

Results: The results show that length of SOA strongly affected the neural networks involved in gaze and arrow cueing. Long in contrast to short SOA trials increased functional connectivity primarily between frontal, posterior parietal and superior temporal areas. On the contrary, short in contrast to long SOA trials were associated with higher functional connectivity between occipital brain regions.

Conclusions: Long SOA trials increased functional connectivity within a brain network known to be involved in cognitive control processes [6]. Therefore, these results are in line with the assumption that a longer time interval between cue and target would allow for a deeper and more controlled cognitive processing of the spatial cue [7,8]. The present study emphasizes the importance of SOA for the analysis and interpretation of spatial cueing studies with central gaze and arrow cues.

Literature:

[1] Ristic, J., Friesen, C. K., & Kingstone, A. (2002), 'Are eyes special? It depends on how you look at it', Psychonomic Bulletin & Review, vol.9, no.3, pp. 507-513.

[2] Tipples, J. (2002), 'Eye gaze is not unique: Automatic orienting in response to uninformative arrows', Psychonomic Bulletin & Review, vol.9, no.2, pp. 314-318.

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SESSION B

Emotional and Social Processing

Chairs: Barbara Sahakian and Peter Kirsch

B1 - Impaired emotion recognition in schizophrenia: Neural correlates and emotional bias

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Patients with schizophrenia present with severe deficits in social cognition that have been linked to impaired psychosocial functioning [1]. These social-cognitive deficits are characterized by a negative bias during emotion recognition [2], as well as enhanced activation of the amygdala in response to neutral facial expressions [3].

We conducted two studies in which an affective priming approach was used to investigate the circumstances under which a negative bias occurs in schizophrenia and to investigate the neural basis of such a negative bias. In the first study, a sample of 35 patients with schizophrenia and 47 healthy controls, matched by age and education, completed a combined affective priming and emotion recognition task. In this task, facial expressions (happy, neutral and angry) were preceded by pictures from the International Affective Picture System (positive, neutral, negative). Participants' task was to indicate the emotion of the facial expression.

In the second study that is still ongoing, a modified fMRI-version of the task is used. In study 1, patients with schizophrenia showed deficits in emotion recognition. These deficits were reflected in a general emotional bias in response to neutral facial expressions.

The bias however, was independent of the affective priming. In the current fMRI-sample of study 2 (N = 18 healthy participants),

activation in amygdala and superior temporal sulcus is higher in response to neutral faces that are preceded by a negative scene than to neutral faces that are preceded by a neutral scene. In addition, for participants that show more negative bias during affective priming, activation in Brodmann area 44 and superior temporal sulcus is reduced. Patients with schizophrenia show a general emotional bias in response to neutral facial expressions. This bias might be independent of aberrations in top-down control, as assessed by affective priming, but might be based on disturbances in bottom-up processes, as reflected in enhanced amygdala activation, as well as reduced activation in areas that have been linked to embodied simulation.

Literature:
[1] SM. Couture, Schiz. Bull. 2006, 32[Suppl. 1], S44-S63.
[2] D. Mier, Psych Res. 2014, 221, 195-203.
[3] D. Mier, Psychol. Med. 2010, 40, 1607-1617.

B2 - Dysfunctional amygdala connectivity during humor processing in patients with schizophrenia: an event-related fMRI investigation

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Background: The ability to comprehend and appreciate humor is a key component of successful human interaction. Humor appreciation is reliably associated with activation of mesolimbic reward centers and bilateral amygdala. During the processing of humorous stimuli, the amygdala is thought to coordinate the function of cortical networks relevant for visual salience attribution. In patients with schizophrenia, deficits in humor appreciation have consistently been found in behavioral and functional imaging studies. While previous research suggests that these impairments are related to disturbed Theory of Mind mechanisms and executive dysfunction, the exact nature of humor appreciation deficits and their relationship to amygdala dysfunction in schizophrenia remains unclear. The current study sought to examine the neural correlates of humor processing by investigating differences in regional brain activation and functional connectivity of bilateral amygdala between healthy controls and patients with schizophrenia.

Methods: 18 patients with schizophrenia and 19 healthy controls were studied with functional Magnetic Resonance Imaging (fMRI) during a humor perception task (Falkenberg, Kohn, Schoepker, and Habel, 2012). In this task, a previously validated stimulus set of funny and neutral cartoons was demonstrated in randomized order. In addition, participants were instructed to rate the funiness of each cartoon after presentation. Regional brain activation for funny vs.

neutral cartoons and functional connectivity with bilateral amygdala as seed regions were compared across groups.

Results: Overall, funiness-ratings of humor stimuli were significantly lower in the patient group relative to healthy controls. Reduced activations in patients compared to controls were observed in reward centers (caudate nucleus, insula and midcingulate cortex) and in the Theory of Mind-network, including the temporo-parietal junction (TPJ). However, no significant differences in amygdala activation were found between groups. Functional connectivity analysis revealed a specific pattern of bilateral amygdala-TPJ connectivity for healthy controls. A comparison of amygdala connectivity between groups revealed that patients showed less connectivity between the left amygdala and the right TPJ. This pattern could also be demonstrated using a ROI-to-ROI connectivity analysis with bilateral amygdala as source regions and bilateral TPJ as target regions.

Discussion: We were able to show differences in the neural correlates of humor processing between patients with schizophrenia and healthy controls. Furthermore, our results implicate that humor appreciation deficits in patients with schizophrenia might be influenced by a specific pattern of dysfunctional amygdala-TPJ connectivity. Based on these findings it remains elucidative whether this amygdala-TPJ disconnectivity is a stable trait marker of schizophrenia or can be influenced by specific interventions.

Literature:

Falkenberg, I., Kohn, N., Schoepker, R., & Habel, U. (2012). Mood induction in depressive patients: a comparative multidimensional approach. PLoS One, 7(1), e30016.

B3 - Emotion processing in schizophrenia - a symptom driven data analysis using fMRI and DTI

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Introduction: Negative symptoms are associated with diminished emotional expression and pooreroutcome in schizophrenia (SZ) patients. We investigated the impact of negative symptoms on brain alterations of interrelated brain regions in SZ.

Method: Twenty-one ICD-10 diagnosed patients with SZ and prominent negative symptomsperformed automatic emotion processing of fearful faces during functional magnetic resonance imaging (fMRI) data acquisition. Negative symptoms were correlated with BOLD response to faces and to FA, measured with DTI. Thalamus-seed-based connectivity-map analysis with resting state fMRI data of forty-four separate healthy controls using 7-Tesla high-field fMRI was conducted to clarify the connectivity of thalamic nuclei.

Results: The fMRI data analysis revealed a correlation between negative symptoms and signal changes while processing fearful faces in the bilateral thalami comprising the right anterior dorsal nucleus (AN), the left reticular nucleus (TRN) and mediodorsal nucleus (MD) as well as a small portion of the right caudate nucleus.

The DTI data analysis revealed an association of negative symptoms with white matter integrity indicated by FA encompassing the bilateral fiber bundles within the pyramidal tract (CST) along to the cortico-spinal pathway, located at the height of thalamic region. The associated network obtained from the thalamus-seed-based connectivity map analysis revealed cortical projections encompassing bilateral parietal and frontal areas as well as the bilateral cerebellum. An additional fiber tracking revealed no structural coupling of the thalamus region with the CST.

Discussion: The altered functioning of thalamic nuclei correlated with negative symptoms may explain the altered emotion processing and behavior in SZ patients. The CST finding may also reflect altered thalamo-cortical projections (thalamico-cortical tract) in consequence of the limited resolution getting from the DTI-analysis and, thus also explain the lack of structural coupling of the thalamus and CST finding. The thalamocortical projections indicate that it is more likely that altered WM would be located in the thalamico-cortical tract than the CST.

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B4 - The nucleus accumbens and emotion recognition

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Dopamine is integral not only for motivation and reward, but also for motivational salience, with the nucleus accumbens being the core structure. Aberrations in the dopaminergic system are closely linked to schizophrenia [1], which is associated with impairments in social interaction, cognition and emotion recognition. Our fMRI study investigates the role of the nucleus accumbens for emotion recognition in a novel social jumping-to-conclusion paradigm, which combines emotion recognition and decision making. 46 Subjects looked at pictures of faces expressing two emotions with one of the emotions increasing in intensity over trials. Subjects had to indicate in each trial whether they were certain about the dominant emotion. During the last face with a decision in comparison to the previous faces without a decision, activity in nucleus accumbens was increased bilaterally. Our data suggests an important role of the nucleus accumbens as part of the dopaminergic system in emotion recognition, which is relevant for the understanding and treatment of social-cognitive deficits in schizophrenia.

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B5 - Activity in nucleus accumbens and regions of the mirror neuron system during imitation is linked to schizotypy traits

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Patients with schizophrenia present with vast deficits in social cognition [1]. However, the neural mechanism of these impairments is still unclear. A few recent studies proposed that reduced mirror neuron functioning might be a neural basis for social-cognitive deficits in schizophrenia [2] [3].

The present study aimed on investigating aberrations in regions of the mirror neuron system in healthy participants varying in schizotypy traits. 69 healthy participants completed the schizotypal personality questionnaire (SPQ) and participated in an fMRI-task assessing imitation of facial expressions. In this task, participants either imitated or observed facial expressions of fear and anger, or performed the emotions of fear and anger when prompted by a word stimulus. During imitation, participants showed activation in regions of the human mirror neuron system, namely in Brodmann area 44, as well as in inferior parietal cortex and superior temporal sulcus. Regression analyses revealed positive associations between brain activation and dimensions of SPQ, in particular for “constricted affect” and “lack of close friends”. Specifically, we found a) constricted affect is positively related to activation in nucleus accumbens and BA44 across all task conditions; b) less close friends associate with enhanced activation in nucleus accumbens and BA44 while imitating and observing facial expressions.

Our results show that individuals with more constricted affect and less close friends have increased activation in brain regions linked to

salience processing, as well as in brain regions linked to the human mirror neuron system. These results suggest that aberrations in the dopaminergic system as well as in the mirror neuron system may interact to cause social-cognitive deficits in schizophrenia.

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B6 - Cooperative and Competitive Intentions Modulate Theory of Mind Processes in Schizophrenia

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Adaptive behavior during social interaction requires the ability to have a theory about the intentions of other humans, the so-called Theory of Mind (ToM). Functional neuroimaging studies in patients with schizophrenia have revealed aberrant activity in brain regions associated with ToM [1], which may underlie the deficits in ToM abilities found in the disorder [2]. Such impairments may precede the onset of the disorder and predict its outcome, indicating its high clinical relevance.

In this study we investigated the neural basis of ToM during an interactive game where one playing partner played more cooperative whereas another played more competitive. We predicted differential activation of brain areas known to be involved in ToM depending on the playing strategy, and thus the intention of the counterpart, in patients with schizophrenia and healthy controls. During an fMRI-session 19 patients with schizophrenia and 19 healthy subjects played an iterative Prisoner's Dilemma Game (PDG) against fictive opponents and a control condition without a playing partner. The opponents differed systematically in their playing behavior pursuing a cooperative (cooperating in 83.3% trials) or competitive (defecting in 83.3% trials) playing style. We compared regional brain activation between groups and conditions. While performing the task (task>control condition), both groups showed common activation in brain regions associated with ToM abilities (right temporo-parietal junction, precuneus and medial

PFC). Relative to the patients, the controls showed stronger activation in the left inferior frontal gyrus (IFG) in both task conditions and greater activation in a cluster in the basal forebrain extending to the putamen during cooperative vs. competitive interaction. Patients showed greater deactivation in the precuneus and left IFG during interaction with a cooperative vs. a competitive partner than the controls.

Our results show that while patients and healthy controls both share common activation in brain regions associated with ToM abilities, neural responses in these regions were stronger deactivated by the intentions of the interaction partners in the patient group. Patients compared to healthy controls demonstrated a reduced activation in the putamen when playing with a cooperative partner potentially reflecting their impaired ability to decipher social cues.

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B7 - Oxytocinergic Gene Polymorphisms and the Neural Basis of Socially Relevant Fear Conditioning

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The neuropeptide oxytocin plays a crucial role for the processing of socially relevant emotional stimuli as well as for emotional conditioning processes, in which oxytocinergic gene polymorphisms substantially contribute to elucidate individual differences regarding these conditioning processes. Fear conditioning represents an important model for the etiology and maintenance of fear disorders.

This study aims at investigating correlates of acquisition and extinction of conditioned fear considering the role of the oxytocinergic gene polymorphisms CD38 (rs3796863) and OXTR (rs53576). A sample of 57 healthy men took part in a differential socially relevant conditioning paradigm. Neutral facial expressions served as conditioned stimuli (CS), and negative film clips of these persons showing insulting comments as unconditioned stimuli (UCS). On the first day subjects underwent habituation, acquisition and extinction learning. Conditioned electrodermal responses as well as conditioned evaluative self-report measures were assessed. Both, fear and extinction recall were assessed on the following day by functional magnetic resonance imaging (fMRI).

Depending on the oxytocinergic gene polymorphisms, an altered electrodermal activity was found as well as neuronal activation of brain regions related to emotional learning processes. These

findings give first hints to the association of oxytocin-associated individual differences with learning processes, which might be involved in the development, maintenance and therapyin mentaldisorders.

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B8 - Associations between ERPs in reaction to erotic stimuli, DRD2-allele-variation and online-pornography consumption

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Aim of the study was to investigate the reactivity towards erotic stimuli in early and late event-related potentials in association with the D2 dopamine receptor gene Taq1A polymorphism (DRD2/ANKK1) and online-pornography consumption. Reactivity towards positive emotional stimuli - representing the concept of "wanting" (incentive salience, anticipation of reward) - in the LPP have been reported to be associated with variants of the DRD2: DRD2-risk-allele-carriers (A1+) show blunted LPP-amplitudes in response to "wanting"-related stimuli – an effect which is not present in early sensory processing reflected in the EPN. Those results support the hypotheses that "wanting" is associated with dopaminergic neurotransmission, as well as that the LPP is associated with dopaminergic processes - due to motivational salience. The present study investigated the reactivity towards specifically erotic stimuli in the EPN and the LPP in association with DRD2-allele-variation and online-pornography consumption, assuming that it would be related with LPP-reactions.

The reactivity towards erotic words was tested using an emotional Stroop task in N = 71 healthy young males while recording EEG. DNA was extracted from buccal cells and online-pornography consumption was assessed using an online questionnaire.

Results show higher EPN-amplitudes in reaction to erotic words than to neutral ones. Regarding the LPP, reaction to erotic words is mediated by variants of the DRD2. Furthermore, online-

pornography consumption is associated with the LPP-reaction towards erotic, as well as neutral words, and DRD2-allele-variation.

Results are being discussed in regard to reported associations between DRD2-risk-allele carriers and various addictions - and - broadened in regard to online-porn-addiction.

B9 - Severity of illness modulates gaze cueing in schizophrenia

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Introduction: Social dysfunction is a constitutive feature of schizophrenia. It manifests in handicapped everyday life, malfunctioning in face-to-face encounters and impaired social cognition. In social interactions, gaze processing is a fundamental operation because perceived gaze provides an observer with information about internal states of an interaction partner: affective conditions, attentional focus, intentions, or action goals may be inferred from the observed gaze of other's. It is well known that gaze perception, as well as gaze control, is impaired in schizophrenia. Moreover, Langdon et al. (2006) and Akiyama et al. (2008) were the first to demonstrate that schizophrenia may be associated with altered gaze cueing too. In gaze cueing, gaze direction acts as a social spatial cue which triggers spatial attentional processing in a social context. Using a gaze cueing paradigm which uses symbolic spatial cues in addition to gaze cues, social attentional processes can be distinguished from non-social attentional processes. Applying portrait photographs of a person gazing to the left or right as gaze cues as well as arrow cues as non-social cues, oriented accordingly, we previously confirmed that patients with schizophrenia show altered gaze cueing. Here we present results of comparisons between groups of patients with different severity of illness. By means of median splits we divided our sample of patients with schizophrenia into groups of low vs. high severity of illness, according to their PANSS, CGI or GAF rating scores. These comparisons were motivated by differences in the

results of Langdon et al. respectively Akiyama et al., suggesting that duration and possibly severity of illness may have an influence on altered gaze cueing in schizophrenia.

Methods: Subjects: 34 schizophrenia patients (23 male / 11 female; age: 31/33 years); 34 healthy controls (23m/11f; 30/33 years; reference sample). Groups of patients with low vs. high severity of illness: median split according to PANSS, CGI or GAF rating scores. Cues of the cueing paradigm: Photographs of faces with eyes gazing towards vs. away from a subsequent target stimulus (congruent vs. incongruent social cues); compared to symbolic cues, i.e. oriented arrows embedded into geometrical figures. Subjects' response: finger press on target stimuli. Performance measure: reaction time. Cueing intervals (time between cue and target onset; SOA): 100ms (automatic attentional processing), 300ms (controlled attentional processing). An experimental session (600 experimental trials) took about 45 minutes. Statistical analyses: 2x2x2x2 factorial design (grouping factor: low vs. high severity of illness; repeated measures factors: cue type [social/symbolic], cue congruency [congruent/incongruent], SOA [100ms/300ms]).

Results: The repeated measures factors cue type as well as cue congruency show significant interactions with the severity of illness grouping factor. During automatic attentional processing (100ms SOA) low severity of illness was associated with enhanced processing of social cues, whereas high severity of illness was associated with slowed social processing. During controlled attentional processing (300ms SOA) a gaze cueing effect was observed only in the group with high severity of illness. The findings demonstrate that the characteristics of attentional as well as social dysfunctions in schizophrenia depend on severity of illness.

SESSION C

Biological Correlates of Illness

Chairs: Ingrid Melle and Petra Netter

C1 - Evidence that parvalbumin pathology can be rescued by novel drug targets – implications for the treatment of cognitive deficits in schizophrenia

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Cognitive deficits remain an unmet clinical need in a number of neuropsychiatric and neurodegenerative disorders. With an improved understanding of the pathology related to these deficits comes the hope of novel treatment strategies. Current evidence from both clinical and preclinical studies suggests a strong involvement of GABAergic interneurons (particularly the parvalbumin (PV) subset) in regulating cognitive function in vivo. Alongside this are numerous reports of dysfunction of these GABAergic neurons in schizophrenia, with a number of relevant preclinical models recapitulating this deficit [1]. This emerging understanding of the pathophysiology of schizophrenia offers us the potential to identify novel drug targets through which it may be possible to treat the underlying neural dysfunction and potentially alleviate the cognitive deficits. One such target is the Kv3.1 voltage-gated potassium channel. These channels are expressed on PV interneurons, where they confer the ability of the neurons to fire rapidly and accurately, allowing synchronisation of cortical circuits. A recent post-mortem study found reductions in Kv3.1 protein in un-medicated schizophrenia patients [2]. Modulation of this channel may therefore provide a novel target for restoration of cognitive function in schizophrenia patients.

The poster presentation will cover data from behavioural, immunohistochemical, electrophysiological and imaging studies in validated preclinical models aimed at investigating the efficacy of this approach for treating cognitive deficits in schizophrenia. Briefly, we demonstrate that treatment (acute and/or chronic) with: - AUT00206, a novel Kv3.1 modulator (Autifony Therapeutics Limited) significantly attenuated the sub-chronic phencyclidine (scPCP) induced social behaviour deficits. - AUT00206 significantly attenuated scPCP induced deficits in different cognitive domains. - AUT00206 significantly enhanced the power of fast network oscillations in the prelimbic cortex from scPCP treated rats. - AUT00206 significantly reversed the scPCP induced PV deficit, an effect dependent on the presence of AUT00206. - AUT00206 significantly reduced ketamine induced BOLD signal changes in cortical and subcortical regions of the rat brain Taken together these results suggest that the modulation of Kv3 channels on PV neurons by AUT00206 could be an important novel approach for improving cognitive deficits and function in schizophrenia patients.

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C2 - The Cacna1c genetic rat model for affective disorders: Behavioral phenotypes and inflammatory markers

Braun, M.D.[1], Kisko, T.M.[1], Kayumova, R.[1], Raithel, C.[1], Hohmeyer, C.[2], Rietschel, M.[2], Witt, S.H.[2], Schwarting, R.K.W.[1], Garn, H.[3], Wöhr, M.[1]

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The neurobiological mechanisms ultimately resulting in the outbreak of affective disorders, i.e. major depressive disorder and bipolar disorder, are not fully elucidated yet. Genetic and environmental risk factors contribute critically to their etiology to varying degrees, but the exact pathophysiological pathways how these risk factors influence brain structure and function remain to be uncovered. Important genetic factors include the novel, yet well-established risk gene Cacna1c, while maltreatment and beneficial environment are among the most relevant environmental conditions that specifically act in windows of opportunity during early development.

Here, we used the newly generated Cacna1c rat model to study its role in affective disorders. Firstly, behavioral phenotypes displayed by Cacna1c heterozygous (+/-) rats and wildtype littermate controls were compared in a sex-dependent manner. Secondly, Cacna1c +/- rats and wildtype littermate controls were exposed to post-weaning social isolation as a model for maltreatment or social plus physical enrichment to study the effects of beneficial environments on inflammatory markers.

Our results show that Cacna1c +/-s rats are viable, yet the average number of rat pups born per litter is smaller for Cacna1c +/- than for wildtype females, with genotypes being evenly distributed among the offspring. Interestingly, Cacna1c +/- females displayed less maternal licking and grooming behavior, while nursing behavior did not differ between genotypes. Consistent with the idea that low levels of maternal licking and grooming result in an anxious phenotype, offspring of Cacna1c +/- females emitted more isolation-induced ultrasonic vocalizations (USV) in the first week of life, as compared to offspring of wildtype females. In addition, Cacna1c +/- pups emitted fewer isolation-induced USV than wildtype littermate controls. No genotype differences were seen in body weight gain, body temperature regulation, and somatosensory reflexes, with both genotypes following a normal early developmental pattern. In adulthood, exploratory behavior in the open field was reduced in both male and female Cacan1c +/- rats. Finally, the measurement of cytokine levels revealed that post-weaning social isolation mostly increased proinflammatory markers, while social plus physical mainly led to opposite effects. Such changes were most prominently seen in wildtype littermate controls, with relatively minor environmental effects being evident in Cacna1c +/- rats.

Together, our findings indicate that Cacna1c is involved in the regulation of behavioral phenotypes with relevance to neuropsychiatric disorders and that the responsivity to environmental changes at the level of inflammatory markers is reduced in Cacna1c +/- rats. Funding by Deutsche Forschungsgesellschaft (DFG), Project FOR 2107.

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C3 - Knockdown of the psychiatric susceptibility gene Cacna1c affects mitochondrial resilience against glutamate-induced oxidative stress in neuronal cells

Michels, S.[1], Ganjam, G.K.[1], Martins, H.[2], Braun, M.D.[3], Kisko, T.M.[3], Schwarting, R.K.W.[3], Wöhr, M.[3], Schratt, G.M.[2], Culmsee, C.[1]

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Background: Several genome wide association studies have identified CACNA1C as one of the strongest genetic risk factors for affective disorders [1,2]. It has recently been shown that the main SNP rs1006737 is associated with increased mRNA expression of CACNA1C [3]. However, its role in disease pathogenesis is still largely unknown [4]. CACNA1C codes for the α1C subunit of CaV1.2, which is the major L-type voltage-gated calcium channel in the brain, and underlies key neuronal functions such as dendritic development, cell survival, and synaptic plasticity [5]. Furthermore, mitochondrial dysfunction is also linked to psychiatric disorders and associated with the deregulation of intracellular calcium levels [6].

Methods: We investigated the effects of both siRNA-mediated knockdown of Cacna1c gene expression and plasmid-mediated protein overexpression on mitochondrial function combined with glutamate-induced oxidative stress in immortalized mouse hippocampal HT-22 cells. Therefore, we analyzed cell viability and mitochondrial parameters using real-time impedance measurements (xCELLigence), colorimetric and luminescence-based

assays (MTT, ATP), and flow cytometry with different fluorescent dyes (AnnexinV/PI, MitoSOX, TMRE, Rhod-2, BODIPY).

Results: We found that the downregulation of Cacna1c mRNA levels significantly protected the neuronal HT-22 cells from glutamate-induced cell death. In addition, glutamate challenged HT-22 cells transfected with Cacna1c siRNA showed reduced lipid peroxidation and mitochondrial ROS formation, and also displayed diminished rise in mitochondrial Ca2+ levels compared to control. Moreover, loss of mitochondrial membrane potential upon glutamate treatment was attenuated in Cacna1c siRNA transfected cells.

Conclusions: These results are in accordance with emerging evidence suggesting L-type calcium channel antagonists as an approach to innovative pharmacotherapy of mood disorders [7,8]. However, the molecular mechanisms underlying the effects of Cacna1c regulation on mitochondrial performance in neurons and the link to the development of mood disorders remain to be elucidated.

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C4 - Sex Differences in Juvenile Social Play Behavior and 50-kHz Ultrasonic Vocalizations of Cacna1c Haploinsufficient Rats Modeling Affective Disorders

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In juvenile rats, the rough-and-tumble play period is an important time for the development of social behavior and communication abilities. During social play, rats emit high numbers of 50-kHz ultrasonic vocalizations (USVs). Studies using playback as well as devocalization have found that 50-kHz USVs are an important component of the rat's social behavior repertoire, serving various communicative functions in regulating social interactions, for instance as social contact calls. Such 50-kHz USV presumably also reflect a positive affective state ("rat laughter"). If rats are unable to communicate properly during play the rate of play significantly decreases, and without sufficient play during the critical juvenile period the risk for developing severe social impairments increases. Therefore, rough-and-tumble play and the concomitant emission of 50-kHz USV appear to be ideal readouts for assessing behavioral deficits in social behavior and communication with relevance to affective disorders, such as major depression and bipolar disorder. A recently implicated gene in several affective disorders is the novel yet well-established risk gene Cacna1c. Using a newly developed genetic rat model, we investigated rough-and-tumble play and 50-kHz USVs of juvenile male and female wild-type (+/+) and heterozygous (+/-) Cacna1c rats. Results indicate that in males there

are no significant differences in play behavior. However, in females, there is a highly significant difference between Cacna1c+/+ and Cacna1c+/- rats, with Cacna1c+/- rats spending more time playing and specifically pinning more than female Cacna1c+/+ littermate controls. Based on this finding it is hypothesized that female Cacn1c+/- rats also show a significantly increased number of 50-kHz USVs, especially during the pinning sequences of play. These results suggest that Cacna1c is implicated in behavioral phenotypes and changes in social development relevant to affective disorders.

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Seffer D, Rippberger H, Schwarting RKW & Wöhr M (2015). Pro-social 50-kHz ultrasonic communication in rats: Post-weaning but not post-adolescent social isolation leads to social impairments - phenotypic rescue by re-socialization. Frontiers in Behavioral Neuroscience, 18, 666-673.

C5 - Post-weaning social isolation leads to ultrasonic communication deficits, cognitive impairments and microRNA-dependent alterations of neuronal plasticity in rodents: Implications for autism

Seffer, D.[1], Rippberger, H.[1], Valluy, J.[2], Bicker, S.[2], Aksoy-Aksel, A.[2], Lackinger, M.[2], Sumer, S.[2], Fiore, R.[2], Wüst, T.[3], Metge, F.[4], Dieterich, C.[4], Schratt, G.[2], Schwarting, R.K.W.[1], Wöhr, M.[1]

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Rats are highly social animals and rough-and-tumble play during adolescence has an important role for social development. Post-weaning social isolation, i.e. separation from conspecifics during this phase, is known to induce behavioral phenotypes and changes in neural development relevant to neuropsychiatric disorders like autism. Ultrasonic vocalizations (USV) are an important component of the rat's social behavioral repertoire and serve as situation-dependent affective signals with important communicative functions. High-frequency 50-kHz USV are produced in appetitive situations such as rough-and-tumble play and induce social approach behavior, indicating that they serve as social contact calls [1,2].

Here, we tested if social isolation impairs approach behavior in response to pro-social USV by means of our highly standardized 50-kHz USV radial maze playback paradigm. Male rats were housed in one of the following conditions: group housing, short-term isolation (24 hours), or long-term isolation (28 days). While group-housed and short-term isolated rats displayed approach behavior in response to pro-social 50-kHz USV, post-weaning long-term isolation led to pronounced deficits, with rats rather displaying avoidance behavior. Importantly, such deficits could be reversed by one additional week of peer-rearing and were not observed after post-adolescence long-term isolation, indicating a critical period for social development during adolescence [3]. At the neurobiological level, post-weaning isolation, also resulting in poor novel object recognition as expected, led to an increase in an alternative E3 ubiquitin ligase Ube3a transcript, Ube3a1, in the hippocampus; a key regulator of activity-dependent synapse development and plasticity. The increase in Ube3a1 RNA expression following post-weaning isolation was paralleled by elevated levels of microRNA 134, with Ube3a1 knockdown increasing dendritic complexity in the hippocampus in wild-type controls. Ube3a1 RNA knockdown, however, failed to induce dendritic complexity when the miRNA cluster 379-410, including miR-134, was missing, demonstrating that the Ube3a1 function is microRNA-dependent [4].

Taken together, post-weaning social isolation led to ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity. The finding that environmental factors affecting social behavior and cognition alter Ube3a has important implications, particularly since loss of UBE3A is the leading cause for the neurodevelopmental disorder Angelman syndrome and UBE3A duplications are among the most frequent copy number variations associated with autism.

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C6 - Heritability of glutamate levels in the anterior cingulate and left thalamus assessed with MRS: A twin study

Legind, C.

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Altered glutamatergic neurochemistry is found in frontal and thalamic areas of both patients with schizophrenia and in prodromal subjects1,2. A variety of genes contribute to the heritability of schizophrenia¬, and some are involved in the glutamate homeostasis3. But no heritability estimate of glutamate levels has to our knowledge been proposed. The present study is the largest twin study to investigate heritability and group differences of glutamate along with other brain metabolites in a schizophrenia population. Participants were recruited by combining the Danish Twin Register and The Danish Psychiatric Central Research Register. 21 monozygotic (MZ) proband (diagnosis in the schizophrenia spectrum) pairs, 16 dizygotic (DZ) proband pairs, 22 MZ HC pairs and 19 DZ HC pairs were included along with 11 twins included without their sibling. 3T [1H]-MRS was used to obtain spectra from anterior cingulate cortex (ACC) and left thalamus (thal) for assessment of glutamate (Glu), N-acetyl aspartate (NAA), choline (Ch), creatine (Cr) and myo-inositol (mI). Spectra were analyzed using LCModel. ACE model, including A (additive genetic), C (common environmental) and E (unique environmental), factors was estimated by Structural Equation Modeling in OpenMx. The best fitting model (either AE or CE) was based on the Akaike Information Criterion. Glu in AC had a heritability estimate A of 36%; for NAA A was 9% in AC and common environment C was 26% in thal; for Ch A was 43% in AC and C was 52% in thal; for Cr C was 26% in AC and 33% in thal.; finally mI had A of 38% in AC. A significant correlation between schizophrenia

liability and metabolite concentration was found for NAA, Ch and Cr in AC.

We found no effect of group for Glu by ANOVA, only for NAA and Cr in AC. Post hoc analysis showed a significant difference between NAA in HC and MZ healthy co-twins (0,029) and HC and probands (< 0,000); and for creatine between HC and MZ healthy co-twins (0,014), and HC and probands (<0,000). Significant heritability of Glu in AC of 36%, is a novel finding, and suggests Glu as a possible endophenotype for schizophrenia. For the other metabolites Ch levels were found to be both heritable and correlated to schizophrenia liability, and NAA as well as Cr were present in probands and MZ healthy co-twins to a higher degree than the HC group. The results indicate a genetic component influencing these metabolites in relation to schizophrenia.

Literature:
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[2] Kegels et al., 2012
[3] Ripke et al., 2014

SESSION D

Diagnosis, Treatment and Prediction

Chairs: Robin Murray and Markus Leweke

D1 - Cognitive patterns and microstructural organization of white matter in first-episode antipsychotic naïve schizophrenia patients – Preliminary results

Jensen, M.B., Raghava, J.M., Mandl, R.C.W., Rostrup, E., Nielsen M.Ø., Jensen, M.H., Glenthøj, B.Y., Ebdrup, B.H., Fagerlund, B.

Rasmus Rasks Vej 8, 2.tv. 2500 Valby Denmark

Background: The close relation between cognition and the white matter microstructure (WMM) of the brain is well known in healthy people, and has been studied in schizophrenia as well. Most studies, however, are limited to one or more white matter tracts and a limited number of cognitive measures. Aim: The aim of the study was to explore the relationships between multiple cognitive measures and the complete cerebral WMM, and examine if these relationships differ between schizophrenia patients (PT) and healthy controls (HC).

Method: This is part of a prospective longitudinal study of 54 initially antipsychotic-naïve first-episode schizophrenia patients and 54 matched HC. Cognition was assessed with Cambridge Neuropsychological Test Automated Battery, Brief Assessment of Cognition in Schizophrenia, four subtests from Wechsler Adult Intelligence Scale, 3rd ed., and Danish Adult Reading Test. Structural connectivity was measured with diffusion-weighted imaging on a 3 Tesla MR scanner. Image processing was performed using FSL library of tools and fractional anisotropy (FA) maps were calculated and skeletonized. The DTI derived parameter map (FA) and cognition variables were corrected for age and gender. The FA maps were also corrected for motion. We used partial least squares (PLS) correlation analysis to correlate skeletonized FA maps with

cognitive scores, in order to identify and differentiate correlation patterns within and between groups.

Results: From the PLS analysis (combining patients and controls) one significant latent variable (LV1; p=0.001) was found. Within this LV, a number of variables, comprising measures of intelligence, memory, attention and executive functions, were positively correlated with FA, with patients having more cognitive measures associated with FA than was the case for HC. Two variables, both measuring set-shifting were positively correlated with FA for HC and negatively correlated for PT. For sustained attention, both signal detection and latency were positively correlated with FA for PT and HC.

Discussion: This explorative analysis identified a pattern of cognitive variables associated to FA. The differential relationship between FA and set shifting of PT and HC is intriguing and needs further examination in relation to more specific fiber tracts. The positive correlation between both signal detection and latency with FA may be due to a speed-accuracy trade-off made by PT and HC. This study will guide further hypothesis-driven analyses, regarding which cognitive measures to examine more closely in relation to specific fiber tracts.

Literature:

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Voineskos, A. N., Felsky, D., Kovacevic, N., Tiwari, A. K., Zai, C., Chakravarty, M. M., … Kennedy, J. L. (2013). Oligodendrocyte genes, white matter tract integrity, and cognition in schizophrenia. Cerebral Cortex, 23(9), 2044–57.

D2 - Immediate and long-term effects of cognitive remediation for patients suffering from depression and schizophrenia

Trapp, W.

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Objective: Neurocognitive deficits that persist despite antidepressive treatment and affect social and vocational functioning are well documented in Major Depressive Disorder (MDD) and in schizophrenia. Cognitive training approaches have proven successful in ameliorating these deficits in schizophrenia, but very few studies have been conducted in unipolar depressive patients by now. Whether cognitive deficits are serious predictors of clinical outcome is less clear – neither in schizophrenia nor in MDD.

Method: 60 schizophrenia and 40 MDD patients were included, thirty of the schizophrenia and twenty of the MDD patients that received twelve sessions of cognitive training for a total of four weeks (three sessions per week), were compared to thirty/twenty patients receiving standard drug and non-drug (cognitive behavioural, occupational, sports, relaxation and music therapy) treatment. For most of the patients, who could be traced over a period of two years after the end of the cognitive remediation intervention, time until first relapse and length of hospital stay were determined retrospectively from their medical records.

Results: Cognitive remediation significantly improved problem solving, memory, working memory and attention with high effect sizes in the schizophrenia group. Less, but still significant improvements could be found for verbal and nonverbal memory, working memory and executive function in the MDD group.

Employment status, allocation to treatment group and post test cognitive performance was linked with further clinical course.

Conclusions: These results provide preliminary evidence that cognitive remediation interventions can be successfully applied in MDD and schizophrenia patients and has positive effects on further clinical course.

Literature:
Trapp W., Landgrebe M., Hoesl K., Lautenbacher S., Gallhofer B., Günther W., Hajak G. Cognitive remediation improves cognition and good cognitive performance increases time to relapse--results of a 5 year catamnestic study in schizophrenia patients. BMC Psychiatry. 2013;13:184
Trapp W., Engel S., Lautenbacher S., Gallhofer B., Hajak G. Cognitive remediation for depressive inpatients: Results of a pilot randomized controlled trial. The Australian and New Zealand Journal of Psychiatry. 2016; 50: 46-55.

D3 - Modulating structural connectivity in Ultra High Risk patients by means of psychological interventions: Design, evidence and perspectives

Kristensen, T.D.[1,2,3], Mandl, R.[2,6], Jepsen, J.R.M.[2,5], Rostrup, E.[4], Glenthøj, L.B.[1,2,3], Nordentoft, M.[1,2,3], Glenthøj, B.Y.[2,3], Ebdrup, B.H.[2]

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2. Centre for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, DK-2600 Glostrup, Denmark
3. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
4. Functional Imaging Unit, Department of Diagnostics, Rigshospitalet, University of Copenhagen, DK-2600 Glostrup
5. Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark, University of Copenhagen
6. Neuroimaging Research Group, University Medical Center Utrecht, Nl

Background: Neuroscience has provided increasing evidence of the plasticity of the brain and the possibility for specified training regimens to alter functional connectivity. However, it is not evident to what extend active training regimens can alter structural connectivity as measured with diffusion weighted imaging. Furthermore, the relevance of such training-related alterations and associations with cognitive functioning is still unclear. Here we perform a systematic review focused on the evidence for non-pharmacological modulation of the structural connectivity of the cerebral cortex, and discuss the relevance of using structural connectivity as a biological outcome measure in psychiatric intervention studies. The results of this systematic review will be used to refine the hypotheses for our primary study, where we

investigate potential change in structural connectivity as a result of a specialized psychological intervention in patients at ultra-high risk of psychosis (UHR). In this ongoing large clinical randomized controlled trial (the FOCUS trial), we evaluate the effect of neurocognitive and social cognitive remediation in patients at UHR for psychosis. The FOCUS trial enrolls a total of 126 help-seeking patients aged 18-40 and matched healthy controls. Primary outcome on structural connectivity will be assessed with diffusion-weighted imaging parameters, such as fractional anisotropy (FA), using whole-brain voxelwise tract-based spatial statistics (TBSS), fiber-based analysis as well as network analyses.

Methods: The systematic review is performed in accordance with PRISMA-guidelines in the electronic databases PubMed and EMBASE. Longitudinal intervention studies published in peer-reviewed journals, with human participants aged 18-60 years are included. Interventions must be non-pharmacological, and any type of active training regimens are included. Duration of interventions is between 1 week and 1 year. The primary outcome is task-associated significant changes in structural connectivity from baseline to follow-up, as measured with diffusion-weighted imaging parameters.

Results Review: Database search delivered 2037 hits. 19 eligible studies have been identified. Final results will be presented at the conference, including characteristics of subjects, studies, interventions, DWI-methods, outcomes and risk of bias. FOCUS-trial: initiation was April 2014. To date the FOCUS-trial has included 75 patients and is expected to complete inclusions in 2017.

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D4 - Multimodal neuroanatomical markers predictive of 7 to 16 years outcome in antipsychotic naïve, first-episode schizophrenia patients

Baruël Johansen, L.[1,2], Ebdrup, B.H.[1], Baandrup, L.[1], Klærke, L.[1], Nielsen, M.Ø.[1], Fagerlund, B.[1], Glenthøj, B.Y.[1], Baaré, W.[2]

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[2]Danish Research Centre for Magnetic Resonance (DRCMR), Copenhagen University Hospital Hvidovre, Denmark

Background: Individuals diagnosed with schizophrenia constitute a heterogeneous group as evidenced by the considerable difference in the course of illness and functional outcome between individual patients[1]. There is a need for reliable biomarkers predictive of long-term outcome in order to identify sub-types of schizophrenia patients, and thereby paving the way to more effective and individualised treatment strategies. In this study we will investigate to which extent baseline magnetic resonance imaging (MRI) derived structural biomarkers, are predictive of long-term clinical and functional outcome in first-episode antipsychotic naïve patients who have been followed-up for 7 to 16 years.

Methods: Our research group has collected comprehensive multimodal data in two ongoing longitudinal studies in a total of 64 initially antipsychotic-naïve, first-episode schizophrenia patients and 61 age and gender matched healthy controls. Patients and controls were included at the time of their first psychotic episode[2,3], before receiving any antipsychotic medication, and re-assessed from 2014 to 2016 corresponding to a follow-up period of 7 to 16 years. We will use baseline high-resolution T1-weighted images to

extract measures of cortical thickness, surface area, gyrification and volume, and subcortical volumes. Clinical and functional outcome at long-term follow-up will be assessed with semi structured interviews including the Present state Examination (PSE), the Positive And Negative Syndrome Scale (PANNS), the General Assessment of Function (GAF-F) and register-based data such as antipsychotic medication use and number hospital admissions. Multivariate models and multiple regression analyses will be used to examine the association between neuroanatomical measures and outcome variables.

Results: The re-recruitment and collection of 7- to 16-year follow-up data from patients and controls was finalised in July 2016 and image analyses are currently being carried out. Extraction of register-based data is ongoing.

Conclusion: We expect that the study will provide critical new insights that will inform and improve neuropathological models of schizophrenia in general and strengthen the neurobiological subtyping of schizophrenia patients in particular. Ultimately, the project will contribute to improve clinicians' ability to identify new treatment targets and to develop personalized treatment strategies.

Literature:
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D5 - The influence of individual risk and protective factors on brain structure in psychotic and affective disorders – a transdiagnostical study

Engelen, J.[1], Meier, F.[1], Bröhl, H.[1], Heinen, J.[1], Sauder, T.[1], Dietsche, B.[1], Dannlowski, U.[2], Krug, A.[1], Kircher, T.[1]

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Background: Child maltreatment is a risk factor for psychiatric disorders such as schizophrenia or major depression. Its consequences on brain structure, like for example smaller hippocampal volumes are present in patients and healthy individuals. On the other hand there are protective factors against psychiatric disorders such as secure attachment, social support and resilience. We examine the influence of protective and risk factors on brain alterations independent of diagnoses.

Method: The first 800 participants of DFG-FOR 2107 were used for this study. After excluding invalid datasets, our sample includes healthy controls (HC; N=347) and patients with major depression (N=255), bipolar disorder (N=37), schizophrenia (N=34) and schizoaffective disorder (N=21) who were deeply phenotyped. Individual risk factors and protective factors were gathered via the Childhood Trauma Questionnaire (CTQ), Resilience Scale (RS-25), Social Support Questionnaire (FsozU) and Parental Boding Instrument (FEB). All participants underwent structural Magnetic Resonance Imaging using a 3-Tesla Siemens scanner. Results ROI-analysis revealed smaller volumes of right amygdala (rAmy) and right hippocampus (rHipp) in patients than in HC (0.05, FWE-

corrected). Further transdiagnostic analysis in patients and HC showed negative correlations of both rHipp and rAmy volumes and childhood maltreatment, while positive correlations of rHipp and rAmy volumes and social support as well as resilience could be found. In line with these results, the positive FEB-subscales maternal and paternal care correlated positive with rHipp and rAmy volumes, while negative FEB-subscales maternal and paternal overprotection correlated negative with rHipp and rAmy volumes (all analyses at a significance level of 0.01; correlation of maternal overprotection and hippocampal volume at a significance level of 0.05).

Conclusion: The structural brain changes between patients and HC are in line with the literature. Risk and protective factors independently of diagnoses enhance these brain alterations. Independent of diagnoses, childhood maltreatment is associated with reduced rHipp and rAmy volumes, while protective factors showed the opposite effect on these brain structures. These results point to the importance of common neurobiological findings in psychotic and affective patients as well as in HC and their relation with etiological factors.

Literature:
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D6 - Lateralization and Schizophrenia: can fMRI data be of use for diagnostic questions in psychiatry?

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Introduction: Schizophrenia (SZ) is a severe mental condition encompassing positive (delusions, formal thought disorder) and negative symptoms (apathy, cognitive impairments). At the neural level, the positive symptoms of SZ have been proposed to originate from an aberrant or dysfunctional asymmetry in the hetero-modal cortex (Crow, 2008). In line with this hypothesis, brain imaging studies have found alterations in the hemispheric specialization of task-specific neuronal activity patterns (lateralization) between patients with SZ and healthy control subjects. These differential activations seem to be localized mainly in the frontal cortex, and additionally in posterior cortex regions functionally related to language and higher-order cognition. By contrast, especially the perceptual aspect of positive SZ symptoms (e.g., hallucinations) has been proposed to originate from a disturbed integration of perceptual with cognitive processes, i.e., this hypothesis assumes disrupted connectivity between brain regions and is taking to account the complex interplay and feedback connections between "lower-level" (sensory-perceptual) and "higher-level" (cognitive/language) information processing systems (e.g. Adams, 2012). These two hypotheses although of crucial relevance particularly for clinical imaging research, have not yet been tested in concurrence by means of functional brain imaging, which is partly due to general issues in reproducibility and reliability of neuroimaging and especially functional magnetic resonance imaging (fMRI) data. We need paradigms that reliably capture distinct

aspects of human brain function, particularly fundamental ones like hemispheric lateralization. Aim and

Methods: We conducted a replication study using a well-known fMRI-paradigm designed to investigate lateralization mechanisms. The task requires lexical vs. spatial decisions on similar 4-letter single word stimuli, with lexical decisions triggering left-lateralized and spatial decisions evoking right-lateralized neuronal activity, while anterior cingulate (ACC) connectivity, found to correlate with the changes in activity, was initially proposed as the mechanism underlying lateralization (Stephan et al., 2003). Running two fMRI-sessions on the same group of (n=16) participants, we additionally assessed the Test-Retest-Reliability of the paradigm by means of Intra-Class-Correlation coefficient (ICC).

Results: Our results show a high test-retest reliability for baseline contrast results but no sufficient reliability for results from differential contrast (i.e., those of main interest). Furthermore, we were not able to replicate the connectivity finding on our data, thus cannot confirm the hypothesis of anterior cingulate (ACC) coupling changes as the single mechanism underlying lateralization.

Conclusion: Altogether our results are re-opening the question of neural mechanism(s) accounting for functional asymmetries in brain activity. We propose a change in the design to rule out confounding effects on measured BOLD-signals. Considering lack of information on the robustness of most imaging results in the current literature, we conclude in not recommending to use fMRI data for psychiatric diagnoses.

Literature:

Crow, T. J. (2008). The 'big bang' theory of the origin of psychosis and the faculty of language.

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D7 - Reducing acute psychosis-proneness through positive psychological intervention - implications for schizophrenia prevention?

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The personality framework of schizotypy has been shown to be an excellent predictor for the development of clinical schizophrenia. Hereby research indicates that yet healthy persons at ultra-high risk for schizophrenia as well as healthy offspring of schizophrenia patients share high values in negative/disorganized schizotypy but low positive schizotypy or psychosis-proneness. Vice versa, healthy individuals with extremely high positive schizotypy and repeated psychosis-like experiences are characterised by values in negative/disorganized below the population average, while schizophrenia patients are high in both positive and negative/disorganized schizotypy.

Albeit that schizotypy is a relatively stable organisation of traits, it is subject (as all traits are) to intra-individual variation; referred to as acute or state schizotypy. Since acute positive (unlike negative/disorganized) schizotypic states are highly amenable to environmental influences and are increased in consequence of, e.g., perceived psychosocial stress or psychotomimetic substances, it was our goal to show, that these states could also be actively reduced through directed manipulation based on positive psychology.

We present results from 2 independent studies, including a 12-month follow-up from study 1, showing that an easy-to-perform intervention based on positive psychology, can significantly and

sustainably reduce positive schizotypy compared to a placebo-condition. Furthermore, our results show very high response-rates to said intervention, with responsiveness to the intervention increasing significantly with disorganized schizotypic traits.

Considering the aforementioned interplay of all schizotypic facets regarding the development of schizophrenia, the special importance of the negative/disorganized facet for the factor of "Krankheitswert" as well as the found positive correlation between disorganized schizotypy and response to our intervention, we consider the usefulness of our findings for schizophrenia prevention.

INDEX OF POSTER AUTHORS

Neuroplasticity – between Genes, Environment and Treatment

This year's *Robert Sommer Award Winner:*

Barbara Sahakian & Trevor Robbins

Professor of Clinical Neuropsychology at the Department of Psychiatry, University of Cambridge School of Clinical Medicine

Head of the Department of Experimental Psychology at the University of Cambridge, Director of the Behavioural and Clinical Neuroscience Institute at the Cambridge University

Programme

Thursday, 3-11-2016

13.00 Information desk open

14.00 Welcome Address: Bernd Gallhofer

14.15 Opening Lecture – Chair: Lars Farde

Andreas Meyer-Lindenberg, Mannheim: From psychological research to social prevention in psychiatry: the Robert Sommer legacy

15.00 Symposium I – Chair: Birte Glenthøj

Markus Leweke, Mannheim: Fatty acid ethanolamides in psychosis and related conditions

Marta Di Forti, London: Cannabis use across the EU: a ticket to Psychosis?

16.00 Coffee Break

16.30 Symposium II – Chair: Peter Kirsch

Lars Farde, Stockholm: Contribution of non-genetic factors to dopamine and serotonin receptor availability in the adult human brain

Gebhard Sammer, Giessen: Gaze Cueing: New Insights

17.30 Evening Lecture – Chair: Christos Pantelis

Sir Robin Murray, London: Should psychiatrists be more cautious about prophylactic use of antipsychotics?

Friday, 4-11-2016

8.30 Morning Coffee Reception

9.00 Welcome Addresses

Joybrato Mukherjee, President, Justus Liebig University Giessen

Wolfgang Weidner, Dean, Faculty of Medicine, Justus Liebig University Giessen

Dietlind Grabe-Bolz, Mayoress of Giessen

9.45 Award Ceremony: Presentation of the Award Medal

Laudatio: Andreas Meyer-Lindenberg, Mannheim

10.00 Laureates' lectures:

Trevor Robbins, Cambridge: Translational Models of Schizophrenia: Prospects and Utility

Barbara Sahakian, Cambridge: Improving cognition using modafinil or games in first episode psychosis and schizophrenia

11.00 Coffee Break

11.15 Poster Sessions

A Elementary Cognitive Processing – Chairs: Trevor Robbins and Jürgen Hennig

B Emotional and Social Processing – Chairs: Barbara Sahakian and Peter Kirsch

C Biological Correlates of Illness – Chairs: Ingrid Melle and Petra Netter

D Diagnosis, Treatment and Medication – Chairs: Robin Murray and Markus Leweke

13.00 Lunch Break

14.00 Symposium III – Chair: Robin Murray

Ingrid Melle, Oslo: The polygenetic background of schizophrenia and neurodevelopment

Birte Glenthøj, Kopenhagen: Multimodal abnormalities in schizophrenia patients before and after their first antipsychotic treatment: Insight into the pathophysiology of schizophrenia based on data from four cohorts of initially antipsychotic-naïve first-episode schizophrenia patients

15.00 Symposium IV – Chair: Marta Di Forti

Tim Crow, Oxford: Does schizophrenia arise from XY epi-mutations in male meiosis?

Tilo Kircher, Marburg: Gene Environment Interaction in the Aetiology of the Major Psychoses

16.00 Coffee Break

16.30 Evening Lecture – Chair: Ingrid Melle

Christos Pantelis, Melbourne: Risk and Resilience for psychosis and developmental disorders: Brain maturation, genes and environment

17.15 Presentation of the Poster Awards by the Laureate

Chair: Petra Netter (Speaker of the Poster Award Committee)

19.30 Evening Dinner Reception

20.00 Conference Dinner in the New Building of the Centre for Psychiatry and Psychotherapy Giessen

Saturday, 5-11-2016

8.30 Morning Coffee Reception

9.00 Welcome Addresses

9.30 Symposium I

Andreas Meyer-Lindenberg, Mannheim: A passion for schizophrenia research – the Giessen legacy.

Lars Farde, Stockholm: Non-neuronal brain plasticity

Lars Witteck, Gießen: Bernd Gallhofer as a philanthropist

11.00 Coffee Break

11.30 Welcome Addresses

12.00 Symposium II

Sir Robin Murray, London: Cognitive Heterogeneity in Psychosis: views of an Ex-European

Michael Franz, Kassel / Bad Emstal: Quality of Life in Schizophrenia

Peter Kirsch, Mannheim: Cognitive function in schizophrenia: The social neuroscience perspective

13.30 Closing Remarks: Gebhard Sammer

NOTES

NOTES

HOTELS AND TAXIS

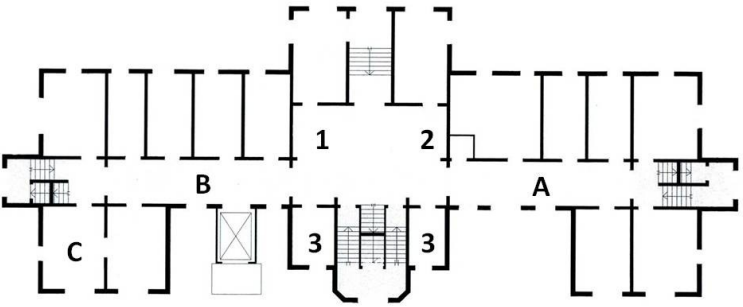
Hotel Altes Eishaus
Wißmarer Weg 45
35396 Gießen
Tel: +49 (0) 641-3890-80
Fax: +49 (0) 641-3013-528
info@Altes-Eishaus.de

Hotel Tandreas
Licher Straße 55
35394 Gießen
Tel: +49 (0) 641-9407-0
info@tandreas.de

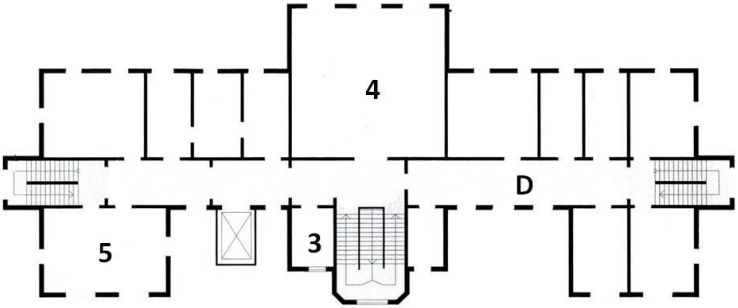
Taxi / Minicar
+49 (0) 641-82082 (Lahn-City-Car)
+49 (0) 641-33337 (Star Taxi & Minicar)
+49 (0) 641-66666 (Unicar Minicar)
+49 (0) 641-42045 (Minicar Planet)

ORIENTATION GUIDE

Ground floor – Main Building



First floor – Main Building



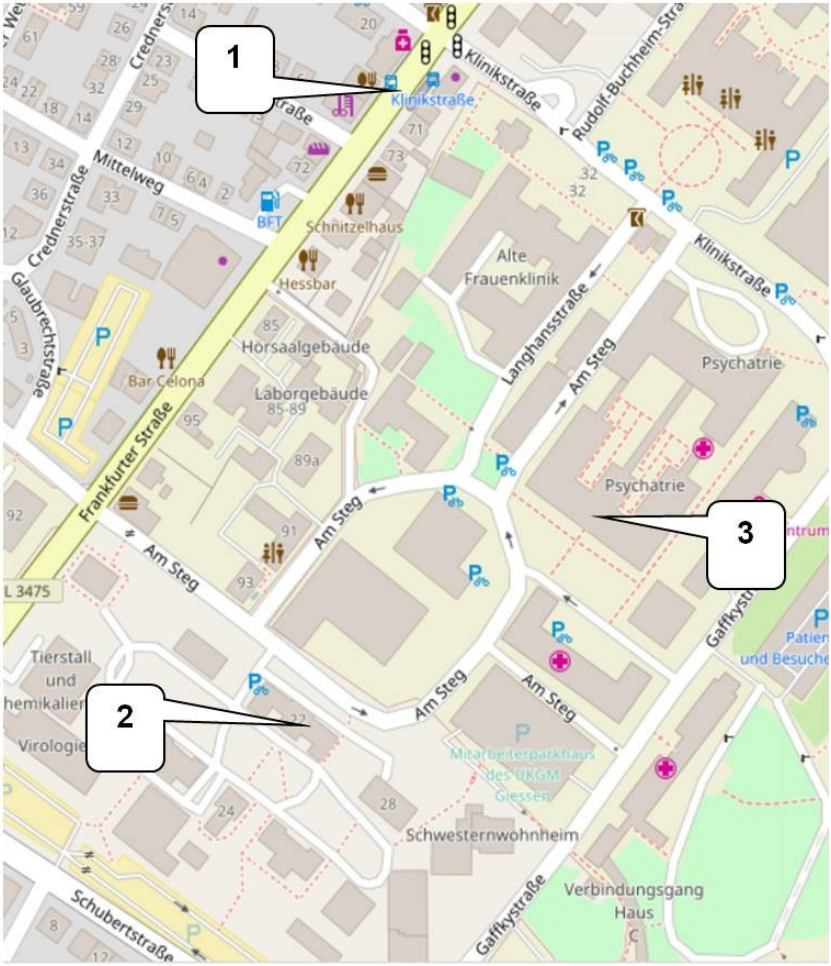
1: Information desk
2: Industrial exhibition
3: Restrooms
4: Main lecture theatre
5: Coffee reception

A: Poster session A
B: Poster session B
C: Poster session C
D: Poster session D

Centre for Psychiatry

Am Steg 22

35385 Giessen



1: Bus Station Klinikstraße

2: Main Building

3: Conference Dinner