Chairperson(s): Hans-Jürgen Möller (München, Germany), Wolfgang Gaebel (Duesseldorf, Germany)
08.30 - 10.00, Gasteig - Philharmonie

S-43-01

Therapeutic results of early intervention in schizophrenia

J. Klosterkötter, S. Ruhrmann, A. Bechdolf, M. Wagner, W. Maier. *Department of Psychiatry University of Cologne, Köln, Germany*

Objective: There is a whole body of evidence in the literature showing that overt psychosis is preceded by a long course of prepsychotic symptoms. A longer duration of untreated illness was found to worsen the outcome of schizophrenia. Therefore it is necessary to recognise and treat the illness as early as possible.

Methods: We are investigating the effects of early interventions on prodromal symptoms, social functioning and course of the illness. An early and a late prodromal phase based on clinical and ethical considerations were defined. Criteria of an early stage are either basic symptoms or a combination of declined social functioning plus a genetic or obstetric risk.

Results: For the early prodromal phase a psychological treatment program was developed. The late prodromal phase, defined by transient or attenuated psychotic symptoms, is treated with amisulpride in comparison to a psychologically advanced clinical management. Preliminary results of both early intervention programs will be presented.

Conclusion: First results of the intervention studies in the German Research Network Schizophrenia as well as the international standard of knowledge support the applicability of "indicated prevention".

S-43-02

Outcome of acute treatment with haloperidol or risperidone in first episode schizophrenics

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First episode schizophrenics are increasingly seen as a special subgroup under treatment considerations. Based on the literature these patients seem to be very responsive, even to relatively low doses of neuroleptics. On the other side they seem to have an increased risk of extrapyramidal side effects. In the context of the German research network on schizophrenia a randomised, double-blind, prospective 8-week study was performed to compare haloperidol with risperidone. The design guaranteed that the smallest clinically effective dose was used. The patients were hospitalised in different German university hospitals. The main question of the study was whether under the conditions of the first low dose regimen a second generation antipsychotic like risperidone can demonstrate superiority to a classical neuroleptic like haloperidol in terms of efficacy and tolerability. It was hypothesised that risperidone would be superior in the domains of negative symptoms, depressive symptoms and cognitive disturbances as well as with respect to tolerability. The data set is still blinded. The data from the first sample are quite promising. Altogether they demonstrate an almost favourable outcome of the first episode patients are 8 weeks of treatment. The dataset will be unblinded in the coming weeks. Thus the preliminary results of the comparison risperidone versus haloperidol will be available for the presentation at the congress.

S-43-03

Outcome in first episode patients under naturalistic conditions

R. Bottlender. *Psychiatrische Klinik der Ludw, München, Germany*

S-43-04

Schizophrenia: Neuroplasticity and logitudinal neuroimaging evidence

E. Meisenzahl, T. Zetzsche, G. Schmitt, M. Jäger, R. Bottlender, C. Born, M. Reiser, H.-J. Möller. *Psychiatrische Klinik der Ludw, München, Germany*

S-43-05

2 year long-term treatment study comparing risperidol with haloperidol in first episode patients

W. Gaebel. *Heinrich-Heine University Dues, Duesseldorf, Germany*

Objective: In first-episode schizophrenia the advantage of long-term treatment with new atypical compared to (low-dose) typical neuroleptics as well as the indicated duration of maintenance treatment has still to be based on empirical evidence. Accordingly, a multi-center study on long-term treatment strategies in first-episode schizophrenia is currently carried out as part of the German Research Network on Schizophrenia.

Methods: In the first treatment year, the relapse preventive efficacy of maintenance treatment with risperidol vs. (low-dose) haloperidol will be compared (randomized double-blind design). In the second treatment year, relapse rates under continued neuroleptic treatment are compared with those under stepwise drug withdrawal substituting instead prodrome-based early intervention (intermittent treatment; randomized design).

Results: By July 2004 159 first episode patients (ICD-10. F20) have been included in the long-term study. Hitherto, no relapse (corresponding to the predefined criteria) was observable in the first treatment year under regular treatment conditions. On average, psychopathological symptoms were moderate after acute treatment and decreased steadily. Drug side-effects measured with various scales were low, and although compliance on average was high, about 65% of the patients dropped out during the first study year. Regarding the second year about 15% were not eligible for drug discontinuation and about 25% chose the converse treatment as assigned.

Conclusion: Treatment in first episode schizophrenia is effective under both neuroleptics however these patients are at high risk for treatment drop-out. This emphasizes the need for a special support program. Additionally, various long-term treatment strategies should be provided to take patients preferences into account.

Tuesday, April 5, 2005

S-46. Symposium: Neurophysiological indicators of vulnerability to schizophrenia – endophenotypes of the disease

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Chairperson(s): Anke Brockhaus-Dumke (Köln, Germany), Dorien Nieman (Amsterdam, Netherlands)
08.30 - 10.00, Holiday Inn - Room 1

S-46-01

Raw eeg and erp in twins discordant for schizophrenia

M. Weisbrod. *Department of Psychiatry, Univ of Heidelberg, Heidelberg, Germany*

Objective: Raw EEG characteristics and event related potentials (ERP) are genetically controlled. Both, brain-wave patterns and ERPs - like the P300 and the N400 component - are altered in schizophrenic patients and their relatives and, therefore, constitute potential genetic markers. The aim of this study was to find out if and which brain-wave and ERP characteristics reflect genetic markers for schizophrenia.

Methods: Raw EEG, P300 elicited by an auditory oddball paradigm and N400 elicited employing a semantic priming paradigm with directly (i.e. lemon – sour) and indirectly (i.e. lemon – sweet) prime-target pairs, were recorded in monozygotic and dizygotic twin pairs discordant and concordant for schizophrenia and in healthy monozygotic and dizygotic twin pairs.

Results: In comparison to healthy pairs, monozygotic index pairs showed a systematic reduction of within-pair EEG concordance. This reduction was especially high in concordant pairs. P300 amplitudes were reduced in the affected as well as the non-affected twins of discordant pairs. Moreover, P300 amplitudes were higher in non-affected monozygotic twins of discordant pairs than in non-affected dizygotic twins. In addition, affected twins of concordant pairs elicited smaller P300 amplitudes than the affected twins of discordant pairs. Were was no group difference in respect to the N400 component. However, N400 amplitude did not differ between the indirect and the non-related condition in controls and non-affected twins of discordant pairs whereas N400 amplitude in the affected twins was smaller in the indirect compared to the non-related condition.

Conclusions: Our results suggest that the development of EEG abnormalities is not homogeniously driven by genetic factors, and represents genetic factors which are not sufficient for the development of schizophrenia. P300 amplitude reduction reflects genetic vulnerability in a narrow sense. Unfocused spreading of activation in semantic networks seems not to be a suitable genetic marker.

S-46-02

Is the P300 wave an endophenotype for schizophrenia?

E. Bramon, C. McDonald, R. Croft, P. Sham, S. Frangou, R. Murray. *Institute of Psychiatry London, London, United Kingdom*

Objective: We assessed the usefulness of the P300 wave as endophenotype for schizophrenia by means of a meta-analysis of the literature on relatives as well as our own family study.

Methods: Meta-analysis: We conducted a systematic search for articles published between 1983 and 2003 that reported P300 measures in non-psychotic relatives of schizophrenic patients and in healthy controls. Meta-regression analyses were performed using a random effects model. The pooled standardised effect size (PSES) was calculated as the difference between the means of the two groups divided by the common standard deviation. Local study: We examined the P300 wave with a standard two-tone oddball paradigm in 30 patients with schizophrenia, 40 of their non-psychotic relatives and 40 unrelated healthy controls using linear mixed models that account for family clusters in the data.

Results: Meta-analysis: We identified 11 studies suitable for meta-analysis, including 472 relatives and 513 controls. The P300 amplitude was significantly reduced in patients with a PSES of 0.61 (95% CI: 0.30 to 0.91; $p<0.001$). The P300 latency was significantly delayed in patients with a PSES of -0.50 (95% CI: -0.88 to -0.13; $p=0.009$). There was evidence of publication bias for the P300 amplitude. Local study: The patients showed significant P300 amplitude reductions ($p=0.04$) and latency delays ($p<0.01$). The relatives displayed no P300 amplitude deviances but had significant latency delays ($p=0.02$).

Conclusion: Based on this meta-analysis and our family study, we believe that the P300 amplitude and especially the P300 latency are promising alternative phenotypes for genetic research into schizophrenia.

S-46-03

P300 and eye movement abnormalities in patients at risk for developing psychosis

D. Nieman, L. J. Bour, H. E. Becker, J. R. van de Fliert, N. Plat, M. Niessen, M. C. Klaassen, P. M. Dingemans, D. H. Linszen. *Academic Medical Centre, Depar, Amsterdam, Netherlands*

Objective: To investigate P300 and eye movement abnormalities in patients with a high risk for developing psychosis. P300 and eye movement abnormalities in schizophrenia patients have frequently been reported. Schizophrenia patients tend to perform worse on the antisaccade task than healthy control subjects. In this task, the subject is requested to inhibit a reflexive saccade to a suddenly appearing target and look in the opposite direction. In addition, schizophrenia patients show reduced P300 amplitude and prolonged P300 latency.

Methods: In the present study, antisaccade task performance and P300 were investigated in a group of patients at high risk for developing psychosis ($n=25$), an age- and intelligence matched group of schizophrenia patients ($n=41$) and an age- and intelligence matched healthy control group ($n=14$).

Results: The high risk group showed increased antisaccade error rate (mean error rate=29%) compared to the healthy control group (18%; $t=2.2$, $p<0.04$) and decreased antisaccade error rate compared to the schizophrenia patient group (51%; $t=-3.3$, $p<0.01$). Antisaccade error rate was not related to state factors like symptomatology. Prolonged P300 latency was related to an increased score on the disorganisation subscale of the Structured Interview for Prodromal Syndromes ($r=0.42$; $p<0.05$).

Conclusion: Antisaccade error rate appears to be a trait marker whereas P300 latency may be a state marker. Forty percent of the high risk subjects is expected to develop a psychotic episode in the near future. The value of eye movement and P300 abnormalities as a predictor of psychosis will be discussed. This study is part of the European Prediction of Psychosis Study (EPOS).

S-46-04

Intermediate phenotypes in schizophrenia research: P300 and Theta activity

J. Gallinat, M. Bajbouj, T. Sander, K. Xu, D. Goldman, G. Winterer. *St. Hedwig Krankenhaus, Campus Mitte, Berlin, Germany*

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Objectives: A common functional polymorphism G1947A of the catechol-O-methyltransferase (COMT) enzyme has gained interest in schizophrenia research because of its critically involvement in dopamine catabolism and frontal lobe function. An assumed mechanism of dopamine is the reduction of noise in prefrontal neural networks during information processing. The hypothesis was tested whether a variation of the COMT genotype is associated with prefrontal noise, which is in part reflected by the frontal P300-amplitude.

Methods: The P300-component (auditory oddball) was recorded in 100 schizophrenic patients and 240 healthy controls. Three single nucleotide polymorphisms of the COMT gene were investigated.

Results and Conclusion: We observed a significant effect of G1947A COMT genotype on frontal P300-amplitude. Lower frontal P300-amplitudes occurred in homozygous carriers of the Met allele in schizophrenic patients. This suggests that the amount of noise in prefrontal neural networks during information processing might be in part under genetic control, which is mediated by dopamine. Moreover, new results concerning theta and delta activity, which are important oscillatory components of the P300 amplitude, will be presented.

S-46-05

Abnormalities of auditory information processing in patients at risk for psychosis

A. Brockhaus-Dumke, F. Schultze-Lutter, R. Pukrop, I. Tendolkar, J. Klosterkötter, S. Ruhrmann. *University of Cologne Psychiatry and Psychotherapy, Köln, Germany*

Objective: As part of a multidimensional approach to the early recognition of psychosis, sensory gating indices, mismatch negativity (MMN) and P300 reflecting different aspects of auditory information processing were investigated for their qualification as a neurobiological at-risk indicator of psychosis.

Methods: P50 and N100 gating (double click paradigm), MMN (3-tone oddball paradigm, duration and frequency deviants) and the P300 (2-tone oddball paradigm) were examined in 66 patients at risk, 37 patients with schizophrenia free of neuroleptic treatment, and 44 controls. The prodromal state was defined by a high-risk cluster of basic symptoms obtained from the data of the Cologne Early Recognition Study (Klosterkötter et al. 2001).

Results: Sensory gating resulted in P50 ($p < .05$) and N100 amplitudes ($p < .01$) and the N100 gating score ($p < .003$) were significantly reduced in patients with schizophrenia. Similarly, MMN amplitudes ($p < .05$), P300 amplitudes ($p < .001$) and P300 latencies ($p < .001$) showed a significant amplitude reduction res. latency prolongation in patients with schizophrenia. The ERP parameters of patients at risk lay in between controls and patients with schizophrenia.

Conclusion: Our results show deficits in auditory information processing in patients with schizophrenia – extended to a sample of neuroleptic-free patients. The sample of patients at risk is heterogeneous as regards the outcome 'first-episode psychosis' and time until transition (50% risk to develop a psychosis within 2 years after assessment). In patients at risk, early stages of information processing (P50) seem to be affected to a minor degree compared to later stages reflecting automatic processes such as stimulus evaluation (N100) and comparison with a memory trace (MMN) as well as higher cognitive processes (P300).

Tuesday, April 5, 2005

S-55. Symposium: Endophenotypes for molecular genetic studies in schizophrenia

Chairperson(s): Dan Rujescu (Munich, Germany), Florence Thibaut (Rouen, France)
14.15 - 15.45, Holiday Inn - Room 1

S-55-01

Theory and practice in quantitative genectics: The use of endophenotypes in detecting QTLs for schizophrenia

D. Posthuma. *Department of Biological Psych, Amsterdam, Netherlands*

S-55-02

Genetic variations underlying electrophysiological endophenotypes in schizophrenia

F. Thibaut. *INSERM EMI 9906, IRFMP, Facult, Rouen, France*

Objective: Twin and adoption studies, as well as familial clustering, have supported a genetic aetiology for schizophrenia. A model involving numerous interactive genes with minor effects interacting with environmental factors is hypothesized. The complexities of the genetics of schizophrenia and the lack of precise phenotype definition have made classical genetic studies quite unproductive.

Methods: Alternative genetic strategies have been used such as the endophenotype strategy. As suggested by previous studies, abnormal sensory gating, measured by the P50 paradigm, could be an endophenotype predisposing to schizophrenia. In addition, we have measured simultaneously three electrophysiological paradigms in schizophrenic patients, non schizophrenic first-degree relatives and normal controls: P50 inhibition, antisaccade paradigm and smooth pursuit. We have evaluated the concordance rates among these 3 markers.

Results: We have shown a significant association between the presence of at least one -2 bp deletion located within exon 6 of the alpha7-like nicotinic receptor subunit gene and the P50 sensory gating deficit in the general population. We have also reported a significant association between the promoter -194C polymorphism of the nicotinic alpha7 receptor (CHRNA7) gene and a normal P50 sensory gating. The concordance rates among the three electrophysiological markers will be reported.

Conclusion: A recent study has reported polymorphisms located in the core promoter region of the CHRNA7 gene as risk factors for the sensory gating deficit. This -194C allele polymorphism is probably in linkage disequilibrium with other causal variations for the P50 sensory gating deficit. The three different paradigms measure different aspects of central inhibition.

S-55-03

Genetic analyses using eye movement disturbances as endophenotypic marker in schizophrenia

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