Course director(s): Michael Musalek (Wien, Austria)
08.30 - 12.00, Hilton - Salon Bialas

Concluding the literature on definition, pathogenesis, nosological position and treatment of delusions we are confronted with a wide range of opinions. In the first part of the course the various definitory approaches and their value in clinical practice will be discussed. The main focus of second part of the course is dedicated to the manifold results concerning the pathogenesis of delusions, which showed that delusions are caused by complex interactions of various mental, physical and social factors. The choice of a particular delusional theme is determined by gender, age, civil status, social isolation, and special experiences ("key experiences") whereas the incorrigible conviction is based on cognitive disorders and/or emotional derailments and reinforced by social factors. But delusions cannot be longer reduced to psychopathological manifestations once established and therefore persisting. The delusional conviction is a dynamic process which only persists if disorder maintaining factors become active. These disorder maintaining factors are not necessarily corresponding with the delusion's predisposing an triggering factors. In the third part classificatory problems will be raised. Assumptions concerning nosology and classification o delusions have ranged from an independent nosological entity to the attribution to a certain mental disorder, to multicategorical classification models. Previous polydiagnostic studies indicate that delusional disorders are neither a nosological entity nor due to one particular disorder (e.g. schizophrenia) but represent nosologically non-specific syndromes which may occur superimoposed on all psychiatric disorders. Most of the so-called primary delusions (or delusional disorders in a narrower sense – delusions not due to another psychiatric disorder) have to be considered as diagnostic artefacts caused by the use of diagnostic criteria in particular classification systems. The final part of the course will focus on differentialdiagnostics and differentialtherapeutics. As delusions represent nosological non-specific syndromes with a multifactorical pathogenesis modern integrative treatment approaches (including psychopharmacological, psychotherapeutic and socio-therapeutic methods) have to be based on a multidimensional differentialdiagnosis of all the predisposing, triggering, and disorder maintaining factors. In this context the disorder maintaining factors provide the basis for effective, pathogenesis-oriented treatment of the actual symptomatology, whereas the predisposing and triggering factiors prtovide informations for plannimng prophylactic long-term treatment.

Tuesday, April 5, 2005

O-07. Oral presentation: Psychotic disorders I

Chairperson(s): Philip McGuire (London, United Kingdom), Georg Winterer (Mainz, Germany)
08.30 - 10.00, Holiday Inn - Room 7

O-07-01

Intracellular events preceding excitotoxic neurodegeneration - Implications for schizophrenia as a disorder of glutamate neurotransmission

J. Genius, D. Rujescu, H.-J. Möller. *University of Munich Dpt. of Psychiatry, München, Germany*

Objective: Accumulating data indicate that a disrupted neurotransmission might constitute the pathogenetic substrate of schizophrenia. In animal experiments we could demonstrate that mild alterations of glutamate metabolism play a central role, however the exact cellular mechanisms are elusive. To overcome the complexity of whole-animal experiments we established a cell-culture model to further investigate glutamatergic excitotoxicity.

Methods: Hippocampal neurons were isolated from rat embryos and kept in serum-free culture. PC-12. cells were used to obtain different stages of differentiation by NGF-supplementation. superoxide-generation was determined by lucigenin-chemiluminescence. Intracellular calcium was monitored by FURA-2/AM imaging. Glutamate levels were determined enzymatically determined. LDH-efflux, alamar-blue reduction, trypan-blue exclusion and morphological parameters were used to assess viability. Caspase-3 served as an indicator for apoptosis.

Results: NMDA-induced cell death was mainly necrotic and could be enhanced by MK-801. Real-time monitoring of the events following a NMDA-challenge revealed a rapid rise of intracellular Ca++, which triggers excessive and persistent O2.--generation. Oxidative stress itself elicited a glutamate spillover into the extracellular space. We sought to identify the main source of excitoxicity-induced superoxide-generation. -Mitochondria seem to play a minor role, while a NAD(P)H-oxidase with properties different from the phagocytic isoform represents an attractive candidate.

Conclusion: Conventional models of the excitotoxic cascade as a linear sequence of events should be reconsidered. We deliver evidence for a positive feed-back loop between oxidative stress and glutamatergic hyperstimulation which may be responsible for the dramatic effects of even mild oxidative stress. We further suggest to consider non-mitochondrial intracellular sources as the main effectors of excitotoxicity and possible therapeutic targets.

O-07-02

The impact of neurotransmitters on adult neural stem cells derived from mouse hippocampus

J. Benninghoff, A. Gritti, H.-J. Möller, D. Rujescu, A. Vescovi. *Dept. of Psychiatry LMU University of Munich, München, Germany*

Based on general consensus, schizophrenia is based on an imbalance of different neurotransmitter subsystems causing complex neuroplastic changes. To study the impact of different neurotransmitters such as serotonin, dopamine, norepinephrine, glutamate, and GABA on neurogenesis, we established primary cultures from adult mouse hippocampi. In our in-vitro model, we cultured the neurospheres in serum-free medium containg b-FGF and EGF as growth factors. These stem/progenitor cells gave rise to differentiated neural cells such as astrocytes, oligodendrocytes and neurons. In-vitro we were able to show that these cells express key proteins of their protein synthesis, e.g. tryptophan hydroxylase (TPH). In addition, we screened for receptors and transporter molecules by RT-PCR, which revealed 5-HT1A and 5-HT2C, DRD2 and NMDA receptor subtypes and dopamine and norepinephrine transporter. Next, we looked into the chemoattraction and found a strong chemoattraction by 5-HT versus dopamine in our in-vitro model. Taken together, our results make a case for the neurotransmitter driven influence on the cumbersome process of neurogenesis. Basic research may help us in the future to elucidate this process and looking for corresponding findings in

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humans, which in turn may also lead to refined treatment strategies for psychiatric illnesses such as psychosis.

O-07-03

Neuronal dysfunction in patients with schizophrenia and their association with psychopathology

S. Karch, C. Mulert, L. Jäger, M. Teutsch, I. Herrmisson, H.-J. Möller, U. Hegerl. *University of Munich Clinical Neurophysiology, Munich, Germany*

Objective: Schizophrenia seems to be associated with anatomical deficits especially comprising frontal and temporo-parietal regions as well as abnormal interactions between them. These modifications may cause varying cognitive deficits including decreased attentional processes. We thought to examine differences in time course as well as location and extent of neuronal activation during a cognitive task between schizophrenic patients and controls and correlate functional data with intensity of symptoms. EEG and functional MRI data were collected simultaneously in order to hold constant vigilance and habituation during acquisition.

Methods: Up to now we examined eight patients with schizophrenia and eight healthy controls. We used an oddball paradigm in which subjects were required to press a button when an infrequent tone is presented in a series of frequent tones of a different pitch. The discrimination between the two stimulus categories produces the positive-going P300 component.

Results: Preliminary data indicate that we could replicate findings of previous P300 studies for healthy participants revealing a P300 component mainly in midline fronto-parietal regions just as BOLD activations mainly in frontal, especially SMA/cingulate cortex, insula and middle prefrontal gyrus, and temporo-parietal brain structures. Schizophrenic patients showed a decreased P300 amplitude and reduced BOLD response in a widespread network of different cerebral areas indicating pathological processes in many cerebral regions. There was a correlation between PANSS paranoid symptoms and BOLD response in ACC/SMA region.

Conclusion: The study could show that a differential analysis of cerebral activity evoked by a cognitive paradigm allows a specific assignment of psychopathological phenomenons to distinct brain regions.

O-07-04

Instability of cortical signal processing in schizophrenia - A combined Event-Related fMRI- and MEG-Study

G. Winterer. *Johannes Gutenberg-Univ. Hospital Mainz, Dept. of Psych, Mainz, Germany*

Objective: Cortical dysfunction is considered a fundamental characteristic of schizophrenia. Recent electrophysiologic evidence points to a fundamental instability of signal processing in cortical microcircuits resulting from reduced phase-synchronization, i.e., an increased stimulus-related variability ("noise") of single trial responses in the spatial and time domain. Moreover, increased noise was found being associated with risk for schizophrenia and with the Val108/158Met polymorphism of the COMT-gene which has been itself described to be associated with risk for schizophrenia and prefrontal function.

Methods: 12 clinically stable schizophrenic patients and 16 matched controls were investigated. We used both functional magnetic resonance imaging (fMRI) and whole-head 256 sensor magnetoencephalography (MEG) during identical task conditions, i.e., a visual 2-choice reaction task, to measure with higher topographic accuracy prefrontal noise in schizophrenia and its relationship to more traditional measures of "activation". Event-related BOLD-responses were subjected to an analysis of residual noise variance and independent data dimension (independent component) analysis (ICA) in the medial prefrontal cortex. MEG-data were analyzed with a recently developed current density source analysis beamfomer technique: Synthetic Aperture Magnetometry (SAM) and co-registered to structural images in Talairach space.

Results: In control subjects, we could demonstrate a non-trivial, complex relationship between BOLD- and MEG-signal which indicated a considerably higher information content of the MEG-signal at comparable spatial localization accuracy. Both MEG-synchronization and desynchronization (decrease and increase of signal variability) were accompanied by an increase of cortical BOLD-responses. In schizophrenic patients, we found increased residual noise variance of the BOLD response that predicted the level of cortical activation in these subjects. In the left hemisphere, residual noise variance strongly correlated with psychotic symptoms. ICA revealed a "fractionized" and unfocussed pattern of activation in patients which correlated with intrasubject reaction time variability.

Conclusion: These findings suggest in conjunction with our previous electrophysioloigical findings that unstable cortical signal processing underlies classic abnormal cortical activation patterns as well as psychosis and abnormal information processing in schizophrenia.

O-07-05

Altered brain activity after standardized emotion discrimination training in patients with schizophrenia: An fMRI study

K. Koch, U. Habel, N. Frommann, M. Klein, N. J. Shah, T. Kellermann, J. Brinkmeyer, W. Wölwer, F. Schneider. *University of Aachen Department of Psychiatry, Aachen, Germany*

Objective: The goal of this fMRI study was to explore the effects of a standardized emotion discrimination training on regional cerebral brain activity in schizophrenia patients. The aim of the training, which lasted 6 weeks and comprised mainly computer-based tasks, was to improve the patients' ability to judge emotions in terms of valence, intensity and situational specificity.

Methods: 20 schizophrenia patients and 10 healthy volunteers have taken part in the study. 10 of the patients participated in the training, the other ten pertained to a waiting control group. Patients with training were scanned before and after the training period; the remaining participants were also scanned twice (T0, T1) with an interscan interval of 6 weeks. Data were collected on a 1.5 T scanner. During scanning, participants had to perform an emotion discrimination task. Data analysis was performed using SPM2. Group analyses were based on a multifactorial ANOVA (p=0.05 FDR corrected).

Results: Results for T0 revealed rather similar activation patterns in both groups. More activation in the training group as compared to the control patient group was mainly found in occipital regions. At T1, however, patients who had participated in the training, showed significant activation in several frontal regions, the left precuneus, the postcentral gyrus/somatosensory cortex and the thalamus which was not detectable in the control patient group.

Conclusion: The training seems to affect brain regions particularly important for emotion discrimination tasks. Thus,

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results point to the specific efficiency of the training in producing task-relevant activation changes.

O-07-06

Gender differences in brain activity in patients with schizophrenia and healthy controls

K. Pauly, U. Habel, T. Kircher, K. Koch, T. Kellermann, M. Klein, N. J. Shah, K. Amunts, N. Seiferth, V. Backes, F. Schneider. *Universitätsklinikum Aachen Psychiatrie und Psychotherapie, Aachen, Germany*

Objective: Cognitive-emotional deficits play an important role in schizophrenia. Negative emotion can exert an impairing effect on cognition, probably differing between patients and controls. Since gender differences have been reported in emotion and cognition the effect of negative emotion on cognition is suggested to be reflected in differential brain activation in females compared to males in addition to differences between patients and controls.

Methods: The cerebral correlates of the interaction of emotion and working memory were investigated with fMRI in 23 schizophrenia patients (14 males/9 females) and 23 matched controls. Participants had to perform an n-back task. Simultaneously, negative affect was induced by odors (rotten yeast). Analysis was based on SPM2 (general linear model).

Results: Negative emotion had a similar impairing effect on the performance of patients and controls revealing no gender differences, but a higher performance in controls. For the emotion-cognition interaction significant hypoactivation emerged in the medial frontal gyrus in patients. Gender specific dysfunctions were also observed: In male patients the frontal hypoactivation included more posterior and lateral areas in contrast to the female sample. Furthermore, male schizophrenia patients demonstrated significantly more activation in temporo-parietal as well as orbitofrontal regions compared to male controls – a difference not found in the comparison of female patients and controls.

Conclusion: Brain activation during negative emotion-cognition interaction differs between schizophrenia patients and controls. These differences may be further subject to gender influences. Cerebral dysfunctions seem to be more pronounced in male patients. Hence, gender may be a relevant factor for future fMRI studies on schizophrenia patients.

O-07-07

Relationship between neurological soft signs and verbal fluency with psychopatology in first-episode psychosis

A. Fontalba Navas, M. L. Barrigón Estévez, M. Ruiz Vegilla, M. Anguita Romero, L. Gomis Fletcher. *Hospital Clinico san Cecilio Psiquiatria, Granada, Spain*

Objective: To determine the relationship between Neurological Soft Signs (NSS) and Verbal Fluency (Semantic and Phonetic) in patients with a first-episode psychosis.

Methods: This study includes 27 patients with a first-episode functional psychosis from South Sanitary Area in Granada without antipsychotic treatment or less than 72 hours with treatment. Exclusion criteria were epilepsy or cranial trauma. Psychopatology was measured with PANSS, NSS with Buchanan's Scale and Verbal Fluency with its standard test.

Results: Participants were divided in two clusters, with high or low presence of NSS: NSS+ and NSS-. The patients in NSS+ cluster presented more negative symptoms and less verbal fluency when was compared with NSS- cluster. In the statistical analysis negative symptoms were independently associated with phonetic fluency ($t = -2,4$; $p < 0,05$) and "others" subscale were independently associated with semantic fluency($t = -3,4$; $p<0,05$).

Conclusion: 1. The patients with high presence of NSS in first-episode psychosis present more negative symptoms.2. The patients with high presence of NSS present less verbal fluency3. The phonetic fluency were independently associated with negative symptoms and the semantic fluency with NSS Others Subscale

O-07-08

Central monoaminergic dysfunction in psychiatric disorders as assessed by neurophysiological and neuroimaging techniques

O. Pogarell, K. Tatsch, G. Juckel, C. Hamann, C. Mulert, G. Pöpperl, M. Folkerts, M. Chouker, M. Riedel, M. Zaudig, H.-J. Möller, U. Hegerl. *University of Munich Psychiatry, Munich, Germany*

Objective: Brain monoaminergic function is involved in the pathophysiology of psychiatric disorders. The loudness dependence of the N1/P2 component of auditory evoked potentials (LD) has been proposed as a noninvasive indicator of central serotonergic function, whereas single photon emission computed tomography (SPECT) and monoamine transporter ligands (such as [123I]-iodine labelled ADAM or ß-CIT) can be used to visualize both serotonin (SERT) and dopamine transporters (DAT). The aim of the study was to investigate the relation of LD and SPECT measures in patients with neuropsychiatric disorders and healthy controls.

Methods: Subjects received both neurophysiological and imaging investigations. Evoked potentials were recorded following the application of acoustic stimuli with increasing intensities. The LD of the relevant subcomponents (tangential dipoles) was investigated using dipole source analysis. SPECT was performed according to standard protocols after injection of the respective monoamine transporter radioligands ([123I]-ADAM or [123I]-ß-CIT).

Results: Combined data of SPECT and neurophysiological studies revealed that these measures are correlated, and that LD is associated with both serotonin and dopamine transporter status, which further validates the use of neurophysiological approaches as noninvasive measures of neurochemical brain function and point at interconnections of central monoaminergic systems

Conclusion: Our studies provide evidence of distinct neurochemical dysfunctions in various neuropsychiatric disorders, such as depression, obsessive-compulsive or personality disorders and that a combination of independent monoaminergic measures might be useful for the in vivo assessment of these different aspects of brain neurotransmitter function.

O-07-09

Association between early development at age 1 year and the course of illness in adult schizophrenia - a 34-year follow-up of the northern finland 1966 birth cohort

E. Lauronen, J. Miettunen, J. Veijola, G. K. Murray, M. John, P. B. Jones, M. Isohanni. *University of Oulu Department of Psychiatry, University of Oulu, Finland*

Objective: There is now convincing evidence that children who have delays in neurocognitive and motor development have a small but significantly increased risk of developing schizophrenia. However, once illness develops, the association between these

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markers and the subsequent course of the illness remains poorly understood. The aim is to analyse if the children destined to develop schizophrenia who achieved infant developmental milestones later at about age 1 year also experienced a worse course of illness than early learners.

Methods: The sample included schizophrenia cases by the year 2001 (N=111) in the Northern Finland 1966 Birth Cohort (N=12058). We studied the relationship between neuromotor development and course of illness by using developmental markers at about age 1 (learning to stand, walk, and speak, and attainment of bladder and bowel control). Time spent in psychiatric hospital, ability to work, use of antipsychotic medication, educational attainment, early death, severity of psychotic symptoms and social and occupational functioning were used as markers of the course of illness.

Results: The development at about age 1 did not significantly relate to subsequent course of illness.

Conclusion: While the trajectory of neurocognitive development during early life is altered in those who develop schizophrenia, after the onset of illness these same factors appear unrelated to the course of the illness.

O-07-10

Length of first hospitalization and relapse in psychoses - The Northern Finland 1966 birth cohort study

J. Miettunen, E. Lauronen, J. Veijola, M. Isohanni. *University of Oulu Dept. of Psychiatry, Oulu, Finland*

Objective: To find out if the length of the first hospitalization is related to the time to relapse, when possible confounders have been taken into account.

Methods: The sample included all hospital treated cases with psychosis by the year 1997 (N=153) in the population based Northern Finland 1966 Birth Cohort (total sample size 10,934). We studied the relationship between the length of first hospitalization and if the patient was rehospitalizated inside two years from discharge. Possible confounders included in analyses were sex, diagnosis (schizophrenia or other psychoses), onset age for psychosis and familial risk (parental psychosis).

Results: Even after taken into account possible confounders, a short first hospitalization (less than one month) predicted rehospitalization in two years (adjusted odds ratio 3.03; 95% CI 1.44-6.39). Schizophrenia diagnosis was also statistically significant risk for relapse in two years (OR 2.29; 1.08-4.86) in this group of psychotic patients.

Conclusion: Although causality is difficult to study, there may be a group of schizophrenia patients who are treated for too short period, and in which too short hospitalization may lead to inadequate improvement in patient's psychiatric status.

Tuesday, April 5, 2005

O-08. Oral presentation: Psychotic disorders II

Chairperson(s): Michael Musalek (Wien, Austria), Gerd Laux (Wasserburg am Inn, Germany)
14.15 - 15.45, Holiday Inn - Room 7

O-08-01

How ill are persons at risk for psychosis? A comparison with first-episode schizophrenia and non-psychotic affective disorder

F. Schultze-Lutter, S. Ruhrmann, H. Picker, A. Wieneke, E.-M. Steinmeyer, J. Klosterkötter. *University of Cologne FETZ, Dept. of Psychiatry, Cologne, Germany*

Objective: Most often used ultra-high risk (UHR) criteria for studies of the initial prodrome of psychosis rely on attenuated and/or transient psychotic symptoms or recent decline in functioning in plus a risk factor for psychosis. In addition, cognitive-perceptive basic symptoms have been proposed. Yet, despite the definition of putatively prodromal subjects in terms of psychopathology, their need for treatment is often evaluated only in relation to transition-to-psychosis rates.

Methods: Psychopathological data of 146 putatively prodromal individuals as assessed with the Schizophrenia Prediction Instrument, Adult version (SPI-A) and the Structured Interview for Prodromal Syndromes (SIPS) is compared to that of 146 first-episode schizophrenia and 84 non-psychotic affective disorder patients.

Results: Putatively prodromal individuals suffered to the same degree or even more than patients with affective disorders from self-experienced cognitive, perceptive, proprioceptive and stress tolerance disturbances in the SPI-A as well as attenuated positive, disorganised, general and certain affective symptoms in the SIPS. Furthermore, they even report as severe emotional deficits, cognitive impediments and body / perception disturbances as the schizophrenia patients.

Conclusion: The fact that putatively prodromal individuals suffer to a degree that is comparable to that of patients with an affective disorder and partially equals that of first-episode schizophrenia patients underlines their need for treatment regardless of their potential risk for psychosis.

O-08-02

Family psychoeducation in schizophrenia: Health and social outcomes. Prospective Follow-up field study

L. Motlova. *Charles University Prague Psychiatric Center, Praha 8, Czech Republic*

Objective: Family intervention supplementation to standard treatment could reduce the relapse rate and enhance quality of life of patients with schizophrenia. This study assessed the influence of a short-term, clinically based, and profesionally led family psycho-education program on a one-year relapse rate and quality of life.

Methods: A total of 120 patients were recruited upon discharge from two psychiatric hospitals in Prague: (1) Site A (N = 86), where family psychoeducation is offered to all patients with schizophrenia, schizoaffective disorder, and acute psychotic episode with schizophrenic symptoms; and (2) Site B (N = 34), where no such program was offered.

Results: Compared to nonparticipants, psychoeducation participants had a shorter average length of rehospitalization stay (5.89 days, vs.17.78 days, p = 0.045) in a one-year follow-up after discharge. The probability of rehospitalization during a one-year follow-up was higher for patients from the site that did not provide psychoeducation.

Conclusion: A shorter average length of rehospitalization of psychoeducation participants, a high turnout of first-episode

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