derived sensory gating parameters and significantly reduced correct antisaccades as compared to controls.

Conclusion: Functional deficits mediated by the frontal lobe as reflected by the antisaccade task are present already in the initial prodromal state of schizophrenia, whereas disturbances of the auditory information processing seem to be present to a minor degree in patients at risk to develop a psychosis.

S-11-04

Biology of psychosis vulnerability - positron emission tomography studies in first-degree relatives of patients with schizophrenia

J. Hietala. *Turku University & Turku PET C, Turku, Finland*

Objective: Previous positron emission tomography (PET) imaging studies have convincingly documented a dysregulation of striatal dopamine neurotransmission in neuroleptic-naïve patients with schizophrenia. In addition, early studies with PET and [carbonyl]-11C-WAY100635 suggest altered serotonin 5-HT-1A receptor density in medial temporal cortex and prefrontal cortex in unmedicated patients with schizophrenia.

Methods: There is a good consensus from family, adoption and twin studies that genetic factors play a major role in the vulnerability for schizophrenia. Thus, we explored whether the striatal dopamine dysregulation and 5-HT-1A receptor alterations are shared by first-degree relatives of schizophrenic patients We studied two independent samples of non-psychotic first-degree relatives (FDR) of schizophrenic patients and control subjects with PET and [18F]DOPA as well as [carbonyl]-11C-WAY100635.

Results: Striatal and in particular caudate dopamine dysregulation was seen also in FDRs (increased dopamine synthesis). In addition, preliminary analysis on the 5-HT-1A receptor data suggests an increased hippocampal 5-HT-1A receptor density in FDRs of patients with schizophrenia. More detailed analysis on the relationship of these changes and clinical parameters is underway.

Conclusion: These studies suggest that altered dopamine and serotonin transmission in the brain associates also to psychosis vulnerability. The results may be useful in early detection/ intervention strategies.

S-11-05

MR-spectroscopy in prodromal and first-episode tients with schizophrenia

G. Juckel. *Campus Charite Mitte, Berlin, Germany*

Objective: The interplay of neuronal circuits between cortical and subcortical brain structures as well as within these regions are deeply disturbed in patients with schizophrenia. A valid marker for neuronal integrity is N-acetylaspartate (NAA) which can be measured by proton magnetic resonance (MR) spectroscopy in humans. Patients with schizophrenia are chararcterized by reduced NAA in schizophrenia-relevant regions as hippocampus, thalamus or prefrontal cortex. Our study assumed that patients in the at risk mental state, i.e. the so-called prodromal state of schizophrenia, exhibit first signs of impaired neuronal integrity as measured as reduced NAA in left hippocampus, anterior cingulate cortex and medial prefontal cortex

Methods: In order, to explore a possible continuum of NAA changes from the prodromal phase to the first episde of schizophrenic psychosis, we studied 13 patients in early and late prodromal state of beginning psychosis (in part patients of the European Prediction of Psychosis Study, EPOS), 10 first-episode patients with schizophrenia and 21 healthy controls matched by age and gender. MR spectroscopy (1.5 Tesla, Siemens Magneton Symphony) was performed by using by single voxel technique. NAA was calculated as NAA/creatines rations in the spectrograms.

Results: First trend analyses of the data revealed reduced NAA in hippocampus of schizophrenic patients with first episode. NAA in the hippocampus of prodromal patients was, however, similar and that in the anterior cingulate cortex and in the medial prefrontal cortex was enhanced, both compared to healthy controls.

Conclusion: These tentative results are in line with the findings of the only published study to this issue up to now (Wood et al. 2003, Schizophr Bull 29: 831-43) which reports also no difference concerning NAA in hippocampus, but elevated NAA levels in the dorsolateral prefrontal cortex of prodromal patients. It can be speculated whether increased NAA in prefrontal areas of prodromal patients are a correlate of a compensating reaction to the beginning disease process.

Sunday, April 3, 2005

S-08. Symposium: The impact of genetics on schizophrenia: First schizophrenia genes

Chairperson(s): Dan Rujescu (Munich, Germany), Wolfgang Maier (Bonn, Germany)
14.15 - 15.45, Gasteig - Black Box

S-08-01

Functional candidate genes in schizophrenia: Findings from animal models

D. Rujescu, A. Bender, M. Keck, A. M. Hartmann, F. Ohl, H. Raeder, I. Giegling, J. Genius, R. Greene, H.-J. Möller, H. Grunze. *University of Munich Dept. of Psychiatry, Munich, Germany*

The psychotomimetic effects of noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists such as PCP and ketamine in healthy humans and their ability to exacerbate several psychotic symptoms in schizophrenic patients have promoted a view of schizophrenia as being related to an altered glutamatergic neurotransmission. This prompted us and others to develop animal models for schizophrenia. Attempts to mimic these effects in rats has lead to the recognition of parallels between schizophrenia and molecular, cellular, functional and behavioral abnormalities in these animal models. In our model, chronic, low-dose treatment with the NMDA receptor antagonist MK801 alters the expression of NMDA receptor subunits in a pattern similar to schizophrenia on the molecular level. On a cellular level, the number of parvalbumin- but not calretinin-positive interneurons was selectively decreased, a finding which parallels observations in post mortem brain from schizophrenic patients. On a functional level, recurrent inhibition of pyramidal cells was altered, as postulated from the histological findings. Finally, on a behavioral level, these animals showed cognitive deficits like disturbed working memory, which again parallels findings in schizophrenia. Thus, our pharmacologic model of NMDA receptor hypofunction has a significant potential as an animal model of psychosis-related phenotypes and as a tool in the identification of candidate genes for this disorder. We used a

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functional genomic approach for the identification of hippocampal candidate genes for psychosis-related traits and identified several differentially expressed genes and pathways. These are under investigation in ongoing genetic analyses.

S-08-02

Genetic association studies in schizophrenia

M. Gennarelli. *Genetic Unit, IRCCS Centro S., Brescia, Italy*

Objective: Although schizophrenia is a genetic disorder with estimates of risk heritability of around 80%, the identification of susceptibility genes, which act in concert with epigenetic processes and environmental factors, remains an uphill struggle. Genetic association studies have focused initially on the neurochemical theories of schizophrenia detecting, as putative functional candidates, dopamine and serotonin system-linked genes. The feasible association with DRD3 and 5-HT2A receptor genes implies most likely an involvement of other neurotransmitter pathways. A role of glutamatergic signalling in the pathogenesis of schizophrenia has been suggested by the recent identification of five susceptibility genes (NRG1, DTNBP1, COMT, RGS4, G72), alltogether implicated in interlinked processes at glutamate synapses. These promising results come from positional approach and animal models data confirmed with the genetic association studies. Thus, these studies are useful to confirm the role of "candidate" genes based on map or pre-clinical findings but represent the more direct method to test other "candidate" aetiopathological hypotheses. Additional susceptibility genes are emerged from this approach, such as those linked to brain development (BDNF, GDNF, GSK-3β) and to cytokine network (IL-1, TNFa, IL-10). It was only to be expected, these association studies are characterised by a constellation of replica and nonreplica of data because they suffer of some notorious limitations. New methodological strategies are in progress to overcome these limitations improving the reliability of these studies.

S-08-03

Linkage studies in schizophrenia: New findings promise new insights

M. Owen. *Dept. of Psychological Medicin, Cardiff, United Kingdom*

Objective: Genetic epidemiological studies suggest that individual variation in susceptibility to schizophrenia is substantially genetic. However, like other common disorders, the mode of transmission is complex and probably reflects oligogenic inheritance against a polygenic background.

Methods: Genomic approaches to schizophrenia are becoming increasingly feasible as data from the genome project accumulate and technology improves. Attempts to identify genes for schizophrenia have been based on several approaches; systematic linkage studies, association studies and studies of chromosomal abnormalities associated with the disorder.

Results: As larger samples have been studied, a number of relatively convincing linkages have been reported. Moreover analysis of these chromosomal regions has revealed evidence in favour of several positional candidate genes. This evidence now strongly implicates DTNBP1 and NRG1 as susceptibility genes for schizophrenia, while the data for DAO, DAOA, DISC1 and RGS4 are promising. However, there are reasons to remain cautious pending the results of further genetic and biological studies.

Conclusion: The positive findings potentially converge upon abnormalities in glutamatergic neurotransmission in schizophrenia, for which evidence from a number of other sources has already been adduced. However, there are other possible explanations and more work is needed to elucidate pathogenic mechanisms.

S-08-04

The impact of first schizophrenia genes: Focus on dysbindin

W. Maier. *Department of Psychiatry, Univ, Bonn, Germany*

The first disposition genes for schizophrenia were identified and replicated in 2002 and 2003: for dysbindin, for neuregulin1, and for G72/G30. These major break-through became possible after genome-wide linkage analyses delineated candidate regions (among them intervals on chromosome 6p, 13q, 8p) which were likely to cover disposition genes. Linkage disequilibrium mapping in these regions was able to identify these three genes. Further candidate regions affirmed in recent metaanalyses, are under intensive study in order to identify additional disposition genes. Although disposition genes are identified, the search for pathogenic mutants is more difficult than expected. Up to now, only associations between haplotypes in these genes and the disorder are replicated, but the pathogenic mutant is not identified for any disposition gene. Yet, genotype-phenotype relationships can also be explored for at-risk haplotypes in disposition genes. We report the first associations between at-risk haplotypes of the dysbindin gene (DTNBP1) and brain structure and function in schizophrenia.

Sunday, April 3, 2005

S-17. Symposium: Recent directions in cognitive and experimental research on delusions

Chairperson(s): Frank Laroi (Liege, Belgium), Steffen Moritz (Hamburg, Germany)
16.15 - 17.45, Holiday Inn - Room 1

S-17-01

Experimental psychology of delusions

T. Kircher. *Klinik für Psychiatrie u. Psychotherapie, RWTH, Aachen, Germany*

Objective: The present study investigated whether a failure of self-monitoring contributes to core syndromes of schizophrenia.

Methods: Three groups of patients with a DSM IV diagnosis of schizophrenia (n = 27; with either prominent paranoid hallucinatory or disorganization syndrome, or without these symptoms) and a matched healthy control group (n = 23) were drawing circles on a writing pad connected to a PC monitor. Subjects were instructed to continuously monitor the relationship between their hand movements and their visual consequences. They were asked to detect gain changes in the mapping. Self-monitoring ability and the ability to automatically correct movements were assessed.

Results: Patients with either paranoid-hallucinatory syndrome or formal thought disorder were selectively impaired in their ability to detect a mismatch between a self-generated movement and its

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