Eur Arch Psychiatry Clin Neurosci (2006) 256 [Suppl 2]
II/1–II/55 DOI 10.1007/s00406-006-2001-3

ABSTRACTS

9th Congress of the German Society for Biological Psychiatry

12–14 October 2006, Munich, Germany

Editor: Prof Dr. Norbert Müller, Munich, Germany

EDITORIAL

Dear colleagues,

It is my great pleasure to welcome you, also on behalf of our society's executive committee, to the 9th Congress of the German Society for Biological Psychiatry, which will take place in Munich from 12–14 October 2006.

The DGBP is a scientific oriented society and our congress aims at illustrating and discussing new developments in research in Biological Psychiatry. The scientific program was designed to promote these themes. Basic research in neuroscience and its transfer to therapeutic methods for our patients will also take important parts in this congress.

Main topics of this year's congress will be psychiatric imaging, psychiatric genetics, the role of immunology and inflammation, as well as clinical studies. These main topics will be reflected in the organisation of plenary symposia and also in the symposia and workshops selected by the scientific committee.

Due to the large number of submitted abstracts for interesting and state of the art workshops and symposia, a part of the scientific program already has to start on Thursday afternoon with workshops and a guided poster session.

The authors of the best posters will be invited to present their research findings within a moderated poster session.

I wish you all a successful course of the congress and lovely autumn days in Munich.

Yours sincerely,
Prof. Dr. Norbert Müller
Munich, Germany

ORGANIZATION/COMMITTEES

Organization

German Society for Biological Psychiatry
(Member of the World Federation for Societies of Biological Psychiatry)
President: N. Müller, Munich
Vice-President: W. Gaebel, Düsseldorf
Secretary: J.-C. Krieg, Marburg
Treasurer: P. Falkai, Homburg

Scientific Committee

N. Müller, Munich
J. Aldenhoff, Kiel
V. Arolt, Münster
K. Bechter, Grünzburg
B. Bogerts, Magdeburg
P. Falkai, Homburg
H. Förstl, Munich
W. Gaebel, Düsseldorf
E. Gouzoulis-Mayfrank, Cologne
A. Heinz, Berlin
F. Holsboer, Munich
J. Klosterkötter, Cologne
J.-C. Krieg, Marburg
W. Maier, Bonn
H.-J. Möller, Munich
W. E. Müller, Frankfurt
P. Riederer, Würzburg
M. Rietschel, Mannheim
H. Sauer, Jena
F. Schneider, Aachen

Congress President

N. Müller, Munich

CONTENTS

Plenary Symposium

PL-01 Immunological mechanisms in psychiatric disorders

PL-01-01
The impact of inflammatory processes on the pathogenesis of schizophrenia
M. Rothermundt (Münster)

Recent research effort has decisively improved the knowledge on etiopathogenic factors of schizophrenia. Several candidate genes could be identified and apart from unspecific indicators an increasing amount of markers for specific inflammatory-immune pathology has been characterized.

Unspecific evidence: An increased risk of intrauterine infection in the second trimenon is associated with an increased risk for schizophrenia. The progressive brain volume reduction in schizophrenic patients which is connected with a poorer prognosis could well base on inflammatory mechanisms. Another unspecific indication of an immune pathogenesis is the fact that immunomodulatory treatment of various somatic diseases (e. g. hepatitis, malignant melanoma) induces symptoms typical for psychotic disorders.

Specific evidence: In the brains of patients with schizophrenia signs of activation of the immunoactive brain cells (microglia, astroglia) have been demonstrated. Centrally as well as in the periphery typical inflammatory patterns of immunomodulators such as cytokines could be shown. In a subgroup of patients infections with neurotropic viruses (e. g. HERV, Borna Virus) were reported. Treatment with anti-inflammatory drugs demonstrated an improvement of symptoms in patients with schizophrenia. In the lecture the specific and unspecific evidence is presented and critically discussed.

PL-01-02
Search for markers of autoimmune/inflammatory processes in postmortem brains of schizophrenics
B. Bogerts, H. H. Bernstein, J. Steiner (Magdeburg)

The remarkable similarity of the time course of schizophrenia over years (characterized by exacerbations, remissions, and stress dependency) with that of several autoimmune diseases argues for similar etiological/pathogenic components. The assumption that neuroimmunological factors may play a role in the etiology of schizophrenic syndromes is further supported by the finding of altered serum and/or CSF levels of interleukin-2, interferon-12, the proinflammatory cytokine TNFa, and S100b in schizophrenics. Direct investigations of autoimmune parameters in brain tissue of patients, however, are nor yet available. We therefore performed in postmortem brains of the Magdeburg brain collection an immunohistological/cytometric study of microglial cells (as indicators of inflammatory cerebral processes) by means of HLA-DR immunohistochemistry and of S100b-expressing cells. In several brain regions HLA-DR immunoreactive microglia cells did not show group differences between patients and normal controls. However, in a subgroup of schizophrenics that died by suicide, HLA-DR cells were highly significant increased in the thalamus. While S100b-positive glial cell densities also were not different between groups, a small subpopulation of neurons that proved S100b-positve was decreased in the schizophrenia patients, especially in patients that committed suicide. The significance of these findings for the autoimmune theory of psychotic disorders is discussed.

PL-01-03
The mild encephalitis (ME) hypothesis – recent aspects
K. Bechter (Günzburg)

In the pathogenesis of affective and schizophrenic spectrum psychoses genes, environment and immune inflammatory mechanisms are involved. Such an interaction is typical for autoimmune diseases. Environmental factors may interact at different levels with preexisting liabilities and/or neurodevelopmental abnormalities. ME hypothesis attempts to explain all these aspects, and provides a framework for understanding the consistent finding of age dependent variance of disease onset in different psychoses, the latter from a similarity with age-related variance of pathogenicity (n diseased to n infected) found in viral infections. Underlying host mechanisms may be changing immune and endocrine function during aging. Neurodegeneration was demonstrated in schizophrenic and in bipolar psychosis interacting with possible preexisting brain volume abnormalities. ME hypothesis and the unitary psychosis concept could merge together to explain psychosis in the individual case. Interestingly diffuse brain atrophy unrelated to focal lesions was recently demonstrated in multiple sclerosis developing slowly during disease course. A similar mechanism may be responsible for the long known parallelism of neurodegeneration and inflammation in general paresis and other CNS infections. Autoimmune mechanisms (eg. epitope spreading, molecular mimicry) may prevail in chronic neurodegenerative types.

PL-01-04
Is an anti-inflammatory therapy an option for psychiatric disorders?
N. Müller, M. Riedel, M. J. Schwarz (Munich)

Recent data underline that an inflammatory process might play a role in the pathophysiology of psychiatric disorders. Proinflammatory cytokines, such as IL-6, IL-1 and TNF-a appear to be elevated at least in the peripheral blood of depressed patients and typically induce 'sickness behaviour', a state similar to depression in an animal model. IL-1 and TNF-a additionally are strong inducers of IDO, an important enzyme for increased serotonin- and trptophan-metabolism. Thus IDO activity may be enhanced in depressed patients through these cytokines. Although IL-6 does not directly act on IDO, its elevated levels in serum may contribute to IDO activation within the CNS by the stimulatory effect on PGE2, which acts as cofactor in the activation of IDO. This fits with a report on the correlation of increased in vitro IL-6 production with decreased tryptophan levels in depressed patients emphasizing the influence of IL-6 on the serotonin metabolism. Due to the increase of proinflammatory cytokines and PGE2 in depressed patients, antiinflammatory treatment would be expected to show antidepressant effects in depressed patients. The role of infection and inflammation in the aetiology of schizophrenia has gained more attention during the last years. A persistent (chronic) infection as aetiological factor in schizophrenia is discussed since many years. Signs of inflammation were observed in schizophrenic brains and the term 'mild localized chronic encephaltis' was proposed. Results of epidemiological studies showed that infection of the CNS in childhood increases the risk of becoming psychotic later on five-fold. Recent research points out that not one single pathogen but the immune response of the mother is related to the increased risk for schizophrenia. Several reports described increased serum IL-6 levels in schizophrenia. IL-6 is a product of activated monocytes and of the activation of the type-2 immune response. Moreover, several other signs of activation of the type-2 immune response are described in schizophrenia, while the type-1 immune response is decreased in the majority of schizophrenic patients. Anti-inflammatory medication, in particular cyclo-oxygenase-2 inhibitors, balances the type-1 and type-2 immune response. Therefore anti-inflammatory medication was hypothesized to have therapeutic effects in schizophrenia, in the meanwhile two studies showed antipsychotic effects of COX-2 inhibitors in early stages of schizophrenia. Regarding the role of the inflammatory process in schizophrenia and major depression, anti-inflammatory therapy should be taken into the focus of further research.

PL-02 Problems of clinical studies: The example 'Kompetenznetzwerke'

PL-02-02
The role of the coordinating centres for clinical trials (KKS) in the planning and conduct of clinical trials
C. Marx (Freiburg)

Clinical trials are conducted within a framework of international and national directives, guidelines, guidances and standards. In contrast to the pharmaceutical industry, investigators and academic institutions often lack the infrastructure and ressources necessary to cope with the administrative burden involved in the conduct of clinical trials according to GCP. In those cases, support can be provided by the coordinating centres for clinical trials (KKS). Founded between 1999 and 2002 within a funding programme of the German Ministry of Education and Research (BMBF), the KKS have established research-oriented supporting structures within university hospitals. The KKS offer a broad range of professional clinical research services. The services include advise and support in the planning, initiation, conduct, analysis and publication of non-commercial and commercial trials and provision of education and training regarding all aspects of clinical trials. The competence and infrastructure of the KKS enables the universities and university hospitals to take organisational responsibilities of the sponsor in non-commercial trials. The involvement of the KKS guarantees their academic and industrial partners the professional conduct of clinical trials according to effectual regulation and standards. The KKS work together within a consortium (KKS network) to provide scientific support for multicentre trials of all phases, to share expertise and to harmonise procedures and templates.

PL-02-03
Clinical studies in schizophrenia – experience from the German research network on schizophrenia
W. Wölwer (Düsseldorf)

The German Research Network On Schizophrenia (GRNS) is a nation-wide network of presently 16 psychiatric university departments, 14 state and district hospitals as well as 6 local networks of psychiatric practices and general practitioners which are collaborating in about 25 interrelated, multicenter projects on schizophrenia research. The GRNS aims to intensify collaboration between leading research institutions and qualified routine care facilities, both within (horizontal network) and between (vertical network) the two levels of research and care, in order to create the scientific preconditions for an optimization of early recognition and intervention, acute and long-term treatment, and rehabilitation of patients suffering from schizophrenia. Several of the studies carried out to accomplish these aims were long-term RCTs comprising treatment periods of up to 2 years, follow-up periods of up to 3 years and up to 13 collaborating centers. Since all these studies were investigator initiated trials, new structures for communication, for entry, storage, monitoring and security of data, and for methodological harmonization across studies had to be established from scratch. Different contributions of centers to patient recruitment and management of studies had to be balanced with funding without compromising the "network idea". While such "internal" difficulties could be managed pretty well, more "external" problems like the adjustment to the (diverse) obligations of the multitude of ethic committees and data security commissioners, or the handling of increasing budget restrictions in hospitals and practices, and last but not least the new legal requirements for drug trials pose(d) difficult problems for a research network with a comparatively restricted funding and small overhead.

PL-02-04
Clinical studies in dementia: Operational experiences made by the german dementia competence network
L. Frölich, O. Peters, I. Heuser (Mannheim)

With regard to the enhanced therapeutic potential in early stages of dementia it appears desirable to detect and treat chronic neurodegenerative diseases as soon as they become clinically apparent. With the aim to use the antidementia drugs Galantamin (Gal, Reminyl©) and Memantine (Mem, Axura©) as efficient as possible, the german dementia competence network (KNDem) has initiated two studies. Within the first one patients with Mild cognitive impairment (MCI) and within the second one patients with Alzheimers disease (AD) were included. The focus of both studies is to elucidate wether the combination therapy, using two different mechanisms of drug action, is superior to the monotherapy with the acetylcholine esterase inhibitor Gal alone. Within the first study (MCI-combi-study) patients with possible AD (amnestic MCI) were recruited. They were randomly assigned to three treatment arms (monotherapy with Gal or combination therapy with Gal plus Mem or Placebo) and it was tested, if cognitive capabilities of MCI patients are altered and if transgression from MCI to AD can be modified. Due to experiences made in earlier initiated MCI-studies with Gal and for security reasons, the treatment within the MCI-combi-study had to be discontinued prematurely. Data, currently processed, will give information about the effect of antidementia drugs on cognition of MCI patients and additionally on the effect of discontinuation of antidementive treatment. In the second study (AD-combi-study) patients with mild dementia syndromes and Alzheimer disease are currently recruited. Within the AD-combi-study it will be tested in two treatment arms, wether cognition and progression of the disease can be influenced positively by early additional dispensation of Mem. This study will be completed in 2008.

PL-03 The genomic revolution in schizophrenia and depression research

PL-03-02
What is the function of the NRG-1 and Dybindin gene for the pathophysiology of schizophrenia?
P. Falkai, E. Parlapani, A. Schmitt, T. Schulze, M. Rietschel (Göttingen, Mannheim)

In the last five years the first risk genes for schizophrenia have been described among them Neuregulin-1 and Dysbindin. Currently major efforts are made to understand the relevant environmental factors interacting with those genes. Furthermore attempts are made to understand the function of them for the pathophysiology of schizophrenia. Current data suggest that the risk haplotype of Neuregulin-1 influences the volume of the hippocampus. Currently published postmortem literature suggests the risk haplotype has an impact on the expression of the isoform of Neuregulin-1. The paper will summarize the evidence for the functions of Neuregulin-1 and Dysbindin within the pathopysiology of schizophrenia.

Symposium

S-01 Prospectives of molecular imaging in psychiatry

S-01-03
How do psychotropic drugs work in our patients' brains? Studies with positron emission tomography
G. Gründer, I. Vernaleken (Aachen)

PET and more recently SPECT have been used extensively to characterize the relationships between occupancy of target molecules in the brain (neurotransmitter receptors and transporters) and plasma concentrations of the respective drug on the one hand and clinical efficacy and side effects on the other hand. PET occupancy measures

have approached the status of surrogate markers that have been proven to be critical in decision making in the development of new psychotropic drugs. It is now widely accepted that determining the appropriate occupancy level for various classes of drugs is vital to streamlining drug development. With new high affinity PET ligands for D2/D3 dopamine receptors such as [18F]fallypride it is now possible to study not only the striatal but also the extrastriatal binding of antipsychotics. Here we present data from [18F]fallypride PET studies on the striatal and extrastriatal D2/D3 binding in relation to plasma concentrations for aripiprazole, clozapine, quetiapine, and ziprasidone, which further elucidate their particular clinical characteristics. Furthermore, in a series of studies with [18F]FDOPA, we characterized the effects of haloperidol treatment on presynaptic dopamine metabolism both in normal volunteers and in patients with schizophrenia. These studies elucidate antipsychotic drug effects beyond simple D2 receptor occupancy.

S-02 Neuroinflammation in neurodegenerative disorders

S-02-01
Neuroinflammation in psychiatric disorders
N. Müller, M. J. Schwarz (Munich)

Different mechanisms promoting an inflammatory process in the CNS may take place in psychiatric disorders. By an animal model of depression it has been shown that psychopathological symptoms during infection and inflammation are mediated by proinflammatory cytokines such as IL-1, IL-6, TNF-a, and IFN-^{3}. The active pathway of these cytokines from the peripheral immune system to the brain is via afferent neurons and through direct targeting of the amygdala and other brain regions after diffusion at the circumventricular organs and choroid plexus. Moreover, there are active transport mechanisms for certain cytokines from the peripheral blood through the blood-brain-barrier. Additionally, it was shown that in a certain percentage of psychiatric disorders the blood-brain-barrier is disturbed, cytokines and activated immune cells can pass into the CNS. Lastely, cytokines are directly produced by and released from glial cells; astrocytes and activated microglial cells contribute to the start and the maintenance of an inflammatory process. Undoubtedly, there is a strong relationship between the cytokine system and the neurotransmitter system, cytokines can directly influence the release of neurotransmitters such as dopamine, noradrenaline, and serotonin. An indirect way to influence the neurotransmitter metabolism by cytokines is the tryptophan/kynurenine pathway, which is controlled by cytokines and influences at least the glutamatergic and serotonergic neurotransmission. For example, in humans, the involvement of cytokines in the regulation of the behavioural symptoms of 'sickness behaviour' has been studied by application of the bacterial endotoxin LPS to human volunteers. LPS, a potent activator of proinflammatory cytokines, was found to induce mild fever, anorexia, anxiety, depressed mood, and cognitive impairment. The levels of anxiety, depression and cognitive impairment were found to be related to the levels of circulating cytokines. The impact of these mechanisms for psychiatric disorders such as depression, schizophrenia, or Alzheimer's disease will be discussed.

S-02-02
Neuroinflammation in MS: The role of neurotrophic cytokines and neurotrophins in autoimmunity of the CNS
R. Linker (Göttingen)

In the recent years, aspects of neurodegeneration gained increasing attentention in understanding the pathogenesis of multiple sclerosis (MS). In particular, neurotrophic factors are involved in the survival of neuronal and glial cells, e. g. during myelin oligodendrocyte glycoprotein induced experimental autimmune encephalomyelitis (MOG-EAE), a model disease of MS. Investigation of MOG-EAE in mice deficient for the survival factor ciliary neurotrophic factor reveals a more severe disease with increased myelin and axonal damage, but an unaltered immune response. In contrast, mice deficient for the related leukemia inhibitory factor suffer from a less severe disease course and display an impaired immune response. The functional relevance of brain derived neurotrophic factor (BDNF) expression by immune cells in autoimmune demyelination is still unknown. Mice with a conditonal deletion of BDNF in myeloid cells or myeloid cells and T-cells display an alleviated first relapse of MOG-EAE and a reduced inflammatory infiltration. Yet, disease severity and the amount of axonal injury in the chronic disease phase are similar to control mice thus supporting the concept of neuroprotective autoimmunity. Our results reveal distinct roles for different neurotrophic factors in maintaining glial and axonal integrity, but also in modulating the immune response in the inflamed CNS.

S-02-03
Neuroinflammation in neurodegenerative disorders
P. Riederer (Würzburg)

Activation of microglia in neurodegenerative disorders like Parkinson's disease and Alzheimer's disease is a consequence of the devastating degenerative processes. Due to this both the communication between neuronal cells and the immune response change. Expression of cytokines has been demonstrated in post mortem brain studies as well as in experimental models of neurodegenerative disorders. Although most of the literature points to cytokines neurotoxic actions more recent work demonstrates also compensatory properties for degenerative neurons. Therefore the contribution of cytokines for inflammatory processes has to be discussed with caution.

S-03 Competence network ADHD in adults

S-03-01
Competence Network on ADHD in adults
M. Rösler, K.-P. Lesch, E. Davids, D. Eich (Homburg/Saar, Würzburg, Essen, Zürich)

The competence network on adult ADHD was founded in 2004. So far eight sites from Germany and two of Switzerland belong to the network. This is about the psychiatric departments of the Universities of Berlin, Essen, Homburg/Saar, Mannheim, Regensburg, Rostock, Würzburg, Zürich and the Psychiatric Policlinic of the University of Basel. These facilities are connected with a number of psychiatrists and child psychiatrists in private practise. The main target of the network is the development of appropriate diagnostic tools and therapeutic methods for the use in adults. The authors report on a multicenter cross sectional case control study performed by the network participants. The results refer to the characteristics of 150 adult male and female ADHD patients. The distribution of ADHD diagnoses and comorbid disorders will be presented as well as results of the examination of different aspects of social adaptation.

S-03-02
Polymorphisms of genes encoding for dopaminergic and synaptosomal proteins and attention deficit hyperactivity disorder (ADHD)
T. Renner, A. Dempfle, M. Romanos, H. Schäfer, M. Gerlach, A. Warnke, K. P. Lesch (Würzburg, Marburg)

Introduction: Recently we detected association between TPH2, a key modulator of the serotonergic system, and ADHD. Further dopaminergic candidate genes, DAT1, DRD2 and DRD4, and genes involving in synaptic transmission like SNAP25 and SYT1 were investigated in this study.

Methods: 103 families with 225 affected children were included. Diagnosis was confirmed according to DSM-IV criteria. Investigated SNPs comprised functionally relevant variants in DAT1, DRD4 and DRD2. SNAP25 and SYT1 variants located in putative transcriptional control regions were genotyped. By using the Pedigree Disequilibrium Test (PDT) SNPs and haplotypes were tested for preferential transmission.

Results: PDT provided no association between neither single variants nor haplotypes of the investigated variants in the dopaminergic genes and ADHD in our sample. Preliminary statistical analysis for synaptic plasticity genes indicates positive association to ADHD.

Discussion: The negative finding in respect to dopaminergic genes could endorse the proposal that subtypes according to DSM-IV criteria comprise genetically heterogeneous entities and a dimensional classification approach of symptoms could be applicable in genetic investigation in ADHD. Genes involved in synaptic transmission are beyond interesting candidate genes in ADHD. Functional analyses of positively associated variants are in process.

S-03-03
Pharmacological differential therapy of adult ADHD
E. Davids, B. Kis (Essen)

Although attention deficit hyperactivity disorder (ADHD) has been officially recognized as persisting into adulthood for more than 25 years, only recently has the condition been studied in adults. There is great syndromatic continuity between childhood and adult ADHD, and thus much of the medication management of adults with ADHD can be based on the experience gained from treating children and adolescents. Stimulant medications remain the treatment of choice and are generally as effective in adults as they are in children. Several extended-release delivery systems that improve convenience and compliance have become available. Further second-line medications are also reviewed. The medications must be finetuned to the needs of the individual patient in regard to the dose and timing of dose that achieve optimal therapeutic benefit. Medication adjustment must be performed by trial and error because no parameter yet identified predicts the molecule or dose that will provide optimal performance. Pharmacologic treatment of comorbid psychiatric disorders is also of permanent current interest.

S-03-04
Anatomical and functional brain imaging in adult Attention Deficit Hyperactivity Disorder (ADHD)
M. Schneider, W. Retz, M. Rösler (Homburg/Saar)

At present, the literature on adult ADHD is somewhat sparse, and so results from imaging have therefore to be considered mainly from the childhood or adolescence perspective. Most work has considered the impairment of executive functions (motor execution, inhibition, working memory), but there is a number of attention networks which have to be discussed when investigating ADHD attention deficits in adulthood. The cerebello-(thalamo-)-striato-cortical network seems to play a pivotal role in ADHD pathology from childhood to adulthood. The core findings in ADHD imaging are alterations in the architecture and function of prefrontal cortex and cerebellum. The dorsal part of anterior cingulated cortex (dACC) is an important region for decision making, and executive control is impaired in adult ADHD. Own fMRI data from adult ADHD patients could affirm the hypothesis of fronto-striatal dysfunction. Dysfunction of basal ganglia is a consistent finding in ADHD, reflecting dysregulation of fronto-striatal circuitry. The cerebellum, and its role in affect and cognition, is also persistently implicated in the pathology of ADHD. Adolescents with ADHD have also significant impairments in their ability to direct and allocate attentional resources. This is associated with bilateral aberrations in the parietal attentional system (Tamm et al. 2006). This indicates that ADHD patients might also have parietal dysfunctions. An overview of actual imaging literature will be given as well as own fMRI data presented concerning dysfunction of fronto-striatal as well as parietal systems in adult ADHD patients.

S-04 New insights in the neurobiological regulation of panic: Focus on genetics, neuroimmunology and neuroimaging

S-04-02
Effects of experimentally induced panic attacks on neuroimmonulogical markers
L. de la Fontaine, M. J. Schwarz, D. Eser, C. Schüle, N. Müller, R. Rupprecht, P. Zwanzger (Münster, Munich)

Neuroimmunological markers like macrophage-migration-inhibitor-factor (MIF) and IL-6 which are functionally related to HPA-axis have been found to be altered in major psychiatric disorders such as depression and schizophrenia. So far, only few studies have been conducted concerning the regulation of immunological parameters in rapid changing psychiatric states such as panic attacks. Experimental panic induction using CCK-4 has been shown to be a very useful tool in anxiety research and serves as a reliable paradigm for neurobiological changes during acute panic.

The current study will investigate the possible influence of CCK-4 induced panic on the neuroimmunological system. Therefore, MIF and IL-6 were determined in a sample of healthy subjects, which underwent experimental panic induction using the CCK-4 paradigm. Panic reaction was assessed at baseline and at five minutes after injection using the API and the PSS score. For measurement of immunological parameters, blood samples were taken 45 and 30 minutes prior to injection, at the time of injection (min 0) and after 5, 20, 60 and 120 minutes. In addition, changes of ACTH and cortisol were evaluated during the challenge. In the presentation, the possible influence of panic on immunological parameters as well as possible interaction between panic regulation, neuroimmunological system and HPA-axis activity will be discussed.

S-04-03
Effect of Rgs gene variation on human panic disorder
C. Hohoff, C. Freitag, P. Krakowitzky, A. Erhardt, J. Fritze, B. Bandelow, R. Fimmers, J. Flint, J. Deckert (Münster, Homburg/Saar, Munich, Pulheim, Göttingen, Bonn, Oxford, Würzburg)

Rgs (regulator of G protein signalling) proteins reduce G protein activity via their GTPase function. Rgs gene variation therefore might lead to variation in GTP mediated neurotransmission. Rgs2 knockout mice show increased neurotransmission and anxiety and Rgs2 was recently identified as a quantitative trait gene for anxiety in mice (PNAS 97:12272–7; Nat Genet 36:1197–1202). In humans different anxiety disorders exist of which panic disorder (PD) is a common form with 48 % heritability. We hypothesized that variations in the Rgs2 and the adjacent Rgs13 gene might effect the development of human PD. Two PD samples (initial sample: 173 patients, 346 controls; replication sample: 144 patients, 313 controls) were genotyped for six Rgs2-SNPs and six Rgs13-SNPs by TaqMan allelic discrimination assays. Association with PD on single marker and haplotype level in the initial sample was replicated only in part in the agoraphobia subgroup (PDA). Exploratory analysis of mutual dependence of genotype effects by stepwise logistic regression however, revealed consistent association of Rgs2-SNP6 and Rgs13-SNP3 with PDA in both samples ($P < 0.05$). Variants of the adjacent Rgs2 and Rgs13 genes may thus play a minor role in the development of human panic disorder. Future studies are necessary to identify possibly functionally relevant variations and the exact relationship to human anxiety.

S-04-04
Volumetric magnetic resonance imaging of limbic structures in panic disorder
A. Erhardt, P. Naumann, G. P. Unschuld, T. Zetzsche, P. Zwanzger, R. Rupprecht, E. Meisenzahl, M. E. Keck (Munich, Zürich)

Panic disorder is one of the most disabling anxiety disorder with a life time prevalence up to 5 % and high number of clinical admissions. The neurobiology of the predispositional and developmental features

of panic disorder are unclear so far. Preclinical and clinical research suggest that several neuroanatomical structures, such as amygdala, hippocampus, prefrontal cortex and hypothalamus are critically involved in the pathophysiology of panic disorders. These neuroanatomical regions are implicated in the modulation of anxiety-related behaviour, fear conditioning and avoidance behaviour. Previous quantitative magnetic resonance imaging (MRI) studies in panic disorder have shown a variety of brain abnormalities, mostly involving the temporal lobes and mainly located in the mesiotemporal area. However, the results are not consistent and besides locus and side specific structural changes, no differences to controls were described in several studies. The aim of the present study was to investigate possible structural changes in the limbic brain loci in 40 patients with panic disorders versus healthy controls. Magnetic resonance imaging scans were performed with 1.5 T Magnetom Vision (Siemens, Erlangen, Germany). The software program "BRAINS" was applied for brain volumetry and segmentation. The data is currently under analyse and first results will be presented.

S-05 Neurobiological aspects of schizophrenia – comparison of adulthood-onset versus childhood-onset

S-05-01
Functional imaging of cognition and emotion processing in schizophrenia patients
F. Schneider (Aachen)

Cognitive and emotional impairments are symptoms in almost every psychiatric disease but they are especially prominent in schizophrenia. As the reliable discrimination of emotions is an important human function in the context of social interactions, these disturbances account for severe impairments of the quality of life in the patients. Furthermore, these impairments appear to be present before the diagnosis of schizophrenia is made. Functional imaging is a well-established method of studying the neurobiological basis of disturbed cognitive and emotional processes. This technique has been used to investigate the neural correlates of these disturbed processes in schizophrenia. Studies in juvenile schizophrenics, early-onset patients and other subgroups of schizophrenia patients have shown stable characteristic dysfunctions in the cerebral networks underlying emotional processes, such as emotion recognition and emotional experience. During working memory demands functional disturbances of regions modulating the interaction between emotion and cognition could be observed. The most consistent findings are hypoactivations in subcortical areas, particularly the amygdala, and in prefrontal areas. The future of neuroimaging studies in schizophrenia will deal with both the assessment of therapeutic interventions and with further improvements of the methods at hand.

S-05-02
Neurobiological aspects of schizophrenia – comparison of adulthood-onset versus childhood-onset
G. Stöber (Würzburg)

Genetic aspects of schizophrenia The hereditary impact in schizophrenia is impressive, as pointed out in family, twin, and adoption studies, though linkage studies have had considerable difficulties in identifying susceptibility loci. Recent meta-analyses pointed to an increasing consistency regarding linkage results at 1q, 2q, 3p, 5q, 6p, 8p, 11q, 14p, 19q, 20q, and 22q. However, there are still discussions whether polymorphisms in positional candidate genes (DISC1, G72/G30, RGS4, dysbindin, neuregulin, GABAA receptor) can be viewed as credible risk factors for schizophrenia. Moreover, the nature of subtypes in schizophrenia and the meaning of heterogeneity in schizophrenia are considered a principal controversy. We addressed these issues in periodic catatonia, which is characterized by qualitative psychomotor disturbances during acute episodes and long term outcome. Two independent whole genome scans mapped and replicated a major disease locus on chromosome 15q15, with evidence for genetic heterogeneity. Parametric linkage and haplotype analyses support the assumption of a single-gene model in this phenotype and transmission in an autosomal dominant mode of inheritance with reduced penetrance. Thus, meticulous clinical differentiation seems to be essential to cope with etiological heterogeneity in schizophrenia and forge ahead a refined nosology of catatonic psychoses.

S-05-03
Neurobiology of childhood-onset schizophrenia: Potential early markers
C. Mehler-Wex, A. Warnke, M. Gerlach, C. Duvigneau (Würzburg, Vienna)

Schizophrenia in children and adolescents differs from adults concerning low prevalence, poor prognosis, markedness of neuroimaging findings already at disease-onset and unspecifity of early symptoms. Thus, the neurodevelopmental hypothesis considers childhood-onset schizophrenia as an own pathogenetic entity. Presently, definitive diagnosis depends on descriptive information only. For a more optimal management at an early stage there is increasing interest in the development of a biological test for the diagnosis of schizophrenia. Investigations until now will be reviewed briefly. Recently, mitochondrial complex I was suggested as a novel marker of schizophrenia in adults (Dror et al. 2002). Increase of complex I activity in platelets of schizophrenic patients was associated with positive symptoms, mRNA and protein levels of the 24- and 51-kDa subunits were significantly higher in schizophrenic patients as compared to healthy subjects. We found an increased mRNA expression of the 75-kDa subunit of complex I in whole blood cells of early-onset schizophrenic patients. This increase appears to be inherent to schizophrenia: it was found in drug-naive patients and was not affected by treatment. Our findings suggest the mitochondrial complex I as a potential peripheral marker of schizophrenia and its involvement in the pathophysiology of this illness.

S-05-04
Antipsychotic induced body weight changes: Clinical observations and potential biological correlates
C. Fleischhaker (Freiburg)

Neuroleptics, and particularly atypical antipsychotics, are frequently associated with substantial weight gain and pharmacologically induced obesity. In many patients, the different atypical antipsychotics lead to varying severities of weight gain depending on the substance. This varying level of weight gain in adults taking different atypical antipsychotics has been shown in various meta-analyses and comparative investigations. However, comparative investigations of atypical antipsychotics in adolescents are to a large extent still lacking. Several examinations with adult patients on weight gain induced by neuroleptics showed that the weight gain caused by antipsychotics is a frequent reason for noncompliance and for the discontinuation of the antipsychotic treatment. This therefore frequently results in a relapse of psychotic symptoms. In several studies, a weight gain was also found in the treatment of children and adolescents with atypical antipsychotics. However, the regularity and severity of weight gain was very different. The existing publications from the field of child and adolescent psychiatry as well as our own clinical experience will be presented. The cause of the weight gain has not yet been systematically examined to any satisfactory extent. However, the causes will be discussed on the basis of varying hypotheses.

S-06 The amygdala: Neurobiology, genetics, and alterations in psychiatric disorders

S-06-01
Monoaminergic afferents and their targets in the amygdala: Morphological investigations as a basis for functional analyses
E. Asan (Würzburg)

Behavioral tests in rodents indicate a central role of the dense monoaminergic innervation of the amygdala in modulating "emotional" reactions. Peptidergic amygdala systems, in particular the corticotropin-releasing-factor(CRF)-system, are implicated in orchestrating stress- and fear-related behaviour. Our studies on topography and targets of monoaminergic amygdala afferents in rats and mice suggest a complex monoaminergic modulation of amygdaloid information processing. For instance, dense dopaminergic innervation in the lateral central nucleus specifically targets CRF-producing neurons while other monoaminergic afferents are scarce in this subnucleus. In contrast, the lateral nucleus shows dense serotonergic and only scarce dopaminergic innervation. Species and strain differences found in the codistribution of monoaminergic and CRF-reactive fibers point to possible differences in interactions between the systems in different experimental animals. The results present the morphological basis for further studies into specific functions of monoaminergic afferents in the different amygdaloid nuclei, for instance into the possible dopaminergic control of the CeL-CRF system. Species and strain differences indicate that detailed morphological analyses of amygdaloid systems in experimental animals are an indispensable prerequisite for interpretations of functional studies.

S-06-02
Changes in cerebral activation pattern in the course of psychotherapy in patients with borderline personality disorder
S. C. Herpertz, K. Schnell (Rostock, Köln)

Affective hyperarousal is a dominant symptom of borderline personality disorder (BPD) and the main target for dialectic-behavioral therapy (DBT). This pilot study examined whether improved regulation of affective arousal following DBT translates into changes in relevant neural systems.

Methods: Five sequential fMRI scans over a 12-week in-patient treatment program were performed. Six female BPD patients and six controls were included in an event-related fMRI design which induced emotional arousal through standardized images.

Results: BPD data revealed a decreasing hemodynamic response to negative stimuli predominantly in the anterior und posterior cingulate cortices as well as in the insula. DBT responders displayed decrement of HRF modulation in the left amygdala and both hippocampi.

Conclusions: DBT treatment was accompanied by neural changes in limbic and cortical regions resembling those reported on psychotherapy effects in other mental disorders. Since the amygdaloid-hippocampal region is suggested to form an alarm system activated by threatening stimulation, reduction in neural activation by external stimuli in this region might indicate how DBT works in neurobiological terms.

S-06-03
Pathological cerebral activation and gene polymorphisms of the 5-HT neurotransmitter system in panic disorder
J. Deckert, K. Domschke, M. Braun, P. Ohrmann, S. Thomas, B. Jochen, C. Hohoff, A. Kersting, H. Kugel (Würzburg, Münster)

Serotonergic genes have been implicated in the pathogenesis of panic disorder and amygdala function in response to fearful stimuli on the basis of studies in healthy individuals. Brain activation on visual presentation of emotional facial stimuli was therefore investigated in 20 patients with panic disorder by means of fMRI at 3 T. Female and male patients were included, relevant comorbidity were social phobia and depression, medication in half of the patients was with SSRI. Patients were genotyped for the functional –1019C/G 5-HT1A and 5-HTTLPR polymorphisms. In patients homozygous for the 5-HT1A –1019G risk allele (n = 5), fearful stimuli were associated with a decreased activation of right prefrontal cortex regions. Patients homozygous for the 5-HT1A –1019G risk allele or patients carrying the short risk allele of the 5-HTTLPR (n = 13) showed higher amygdala activation in response to happy faces. This exploratory study suggests a role of the functional –1019C/G 5-HT1A and 5-HTTLPR polymorphisms on prefrontal cortex and amygdala activation patterns in response to emotional facial stimuli also in patients with panic disorder. Their effect, however, may differ somewhat from their effect in healthy controls. Possible reasons for these discrepancies will be discussed.

S-06-04
Structural changes of the temporolimbic system in patients with affective disorder and with personality disorder: Potential influences of polymorphisms of the 5-HT system
T. Zetzsche, D. Seifert, G. Schmitt, H.-J. Möller, E.-M. Meisenzahl (Munich)

Both affective disorders and personality disorders were associated with structural brain changes. The results of a structural analysis of the temporolimbic system in patients with major depression (MD) and borderline personality disorder (BPD) according to DSM IV and in matched healthy controls will be presented. A magnetic resonance imaging with a 1.5 T Magnetom Vision was performed. The software program "BRAINS" was applied for brain volumetry of the amygdala and the hippocampus as the "regions of interest". Clinical ratings were performed with established instruments including the Hamilton depression scale. Functional polymorphisms of the 5-hydroxytryptamine (5-HT) 1A receptor gene C-1019 G and the 5-HT transporter (5-HTTLPR) were analyzed for potential association with structural changes of temporolimbic structures in MD and BPD patients. Both similarities and differences regarding structural changes and association with polymorphisms of the 5-HT system were detected between these diagnostic groups. The results will be discussed with respect to the potential pathophysiology of both disorders.

S-07 Pathophysiology, endophenotypes and genetics of schizophrenia

S-07-01
Immun-glutamatergic interaction in the pathogenesis of schizophrenia
N. Müller, M. J. Schwarz (Munich)

A hypothesis bridgeing the gap between psychoneuroimmunological findings and recent results from pharmacological, neurochemical and genetic studies in schizophrenia is presented. In schizophrenia, a glutamatergic hypofunction is discussed to be crucially involved in dopaminergic dysfunction. This view is supported by findings of the neuregulin- and dysbindin genes, which have functional impact on the glutamatergic system. Glutamatergic hypofunction is mediated by NMDA-receptor antagonism. The only endogenous NMDA receptor antagonist identified up to now is kynurenic acid (KYN-A). KYN-A also blocks the nicotinergic acetycholine receptor, i. e. increased KYN-A levels can explain psychotic symptoms and cognitive deterioration. KYN-A levels are described to be higher in the CSF and in critical CNS regions of schizophrenics. Another line of evidence suggests that the immune system in schizophrenic patients is characterized by an imbalance between the type-1 and the type-2 immune responses with a partial inhibition of the type-1 response, while the type-2 response is relatively over-activated. This immune constellation is associated with the inhibition of the enzyme indoleamine 2,3-dioxygenase (IDO), because type-2 cytokines are potent inhibitors of IDO. Due to the inhibition of IDO, tryptophan is predominantly metabolized by tryptophan 2,3-dioxygenase (TDO), which is located in astrocytes, but not in microglia cells. As indicated by increased levels of S100B, astrocytes are activated in schizophrenia. On the other hand, the kynurenine metabolism in astrocytes is restricted to the

dead-end arm of KYN-A production. Accordingly, an increased TDO activity and an accumulation of KYN-A in the CNS of schizophrenics have been described. Thus, the immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia.

S-07-02
Genetics of shizophrenia
W. Maier (Bonn)

After years of frustration the search for genes impacting on schizophrenia is experiencing a period of excitement. Several claims of susceptibility genes could be supported by replications. Thus, there are now at least three very strong candidates: the gene for dysbindin (DTNBP1), the gene for neuregulin-1 (NRG1), and a less well understood gene locus G72/G30 which are likely to influence manifestation of schizophrenia. Other hot candidates as the gene for "disrupted-in-schizophrenia 1" (DISC1), the gene coding for protein kinase B (AKT1), and genes involved in the inositol pathways (PIP5K2A) might also prove as susceptibility genes in the next future. Clinical implications of these findings are not yet fully visible. Yet, first insights are possible: Most of the genetic findings are lacking diagnostic specificity and are also reproduced in bipolar disorder. Strong associations are not only obtained on a diagnostic level but also on a symptom and endophenotype level. The pathophysiological role of these "hot" candidate genes is currently under intensive study.

S-07-03
Endophenotyping & Human Genetics – History & Future
G. Winterer (Düsseldorf)

The past few years have seen a rapid expansion of the application of neuroimaging tools to the investigation of the genetics of brain structure and function. In this talk, 1) the most important steps during the historical developement of this research field will be briefly highlighted, 2) an overview will be given of the present state-of-research and 3) an outlook will be provided of how neuroimaging will be successfully applied in the future.

S-07-05
Genetic variants of neuregulin and dysfunctional cerebral activation in schizophrenia
J. Gallinat (Berlin)

Introduction: The neuregulin 1 gene is among the few candidate genes to have been implicated in schizophrenia susceptibility. About five single nucleotide polymorphisms (SNPs) and two microsatellite polymorphisms were found to be associated with this disease in several populations. However, the functional and pathogenic role of the genetic variants of neuregulin is largely unknown. Neuroelectric activity (EEG) and brain metabolites (proton magnetic resonance imaging; H-MRS) have been determined in schizophrenic patients and healthy controls. Genetic variations of the neuregulin 1 gene were found to be associated with slow EEG activity as well as cerebral glutamate concentration in healthy controls and schizophrenic patients. The results indicate a functional role of neuregulin variations in the human brain. Moreover, the findings are in line with recent evidence that neuregulin is crucial for central glutamatergic neurotransmission.

S-08 Startle modification in schizophrenia and depression: Animal models and human models psychoses

S-08-01
Startle Response in animal models of depression
G. Juckel, C. Winter, M. Pilhatsch, B. Vennström, M. Bauer (Bochum, Berlin, Stockholm)

The startle response is well-suitable to study emotional processes and reagibility in animal and humans. Thus, the startle response is changed in patients with affective disorders, especially depression. To characterize animal models of depression, the startle response can be easily used. In the presentation, animal models dealing with genetic variants of the HPA axis and the thyroid system will be presented. Thyroid hormones play one of the key roles in the pathogenesis and course of affective disorders. They act via 4 thyroid hormone receptors today known ((TRa1 und 2, TRb1 und 2). A transgenic mouse mutant with a mutation of the TRa1 receptor (knock-in in TRa1 gene locus) exhibit a very low binding of thyroid hormones at the receptors and a significant anxious and depressive phenotype, which is fully reversible after substitution with T3. Startle response experiments were carried out to characterize this animal model of depression further on.

S-08-02
Behavioral alterations in postnatal hypoxia: An animal model for obstetric complications in the pathophysiology of schizophrenia
A. Schmitt, P. Falkai (Homburg, Göttingen)

As risk factors for the development of schizophrenia, obstetric complications connected with hypoxia have been identified. Here, we investigated in an animal model whether a postnatal mild hypoxia elicits behavioral changes comparable to schizophrenic symptoms in humans. From postnatal day 4 to 8, we imposed mild hypoxia (11 % O2, 89 % N2) to 30 male SD-rats and their mothers during 6 hours per day. The control group received normal air in the same environment. Prepubertal and in young adulthood, prepulse inhibition of acoustic startle reflex (PPI) was tested. PPI is a valuable test for pre-attentional symptoms. Between PD 99 and 124, subgroups of hypoxic and control rats were treated with oral clozapine. Preliminary results revealed, that mild postnatal hypoxia reduced PPI only after puberty. Chronic treatment with clozapine antagonized the PPI changes induced by hypoxia. The early postnatal period in rats which is comparable to intrauterine human brain development may be a vulnerable period of rat brain development. The behavioral changes measured in adult rats after postnatal hypoxia as well as the ability of clozapine to antagonize these changes support the hypothesis that hypoxia is involved as a substantial factor in the pathophysiology of schizophrenia. Underlying neurobiological alterations in the brains will be discussed.

S-08-03
Effect of subchronic administration of clozapine on prepulse inhibition in inbred mice with different hippocampal NMDA receptor densities
R. Wolf (Magdeburg)

The hypo-glutamatergic hypothesis of schizophrenia is based on the phencyclidine-(PCP)-induced psychosis in mentally healthy humans and on studies with schizophrenic patients demonstrating deficits in post mortem hippocampal N-methyl-D-aspartate (NMDA) receptor gene expression. Furthermore, schizophrenic patients displayed reduced prepulse inhibition (PPI) in comparison to normal controls and this loss of sensory motor gating can be restored by treatment with antipsychotic drugs. Accordingly, this study compared two inbred mouse strains CPB-K and BALB/cJ with considerable differences in hippocampal NMDA receptor densities utilizing the sensorimotor gating paradigm. (1) CPB-K mice, known to have lower levels of hippocampal NMDA receptor densities, displayed significant lower PPI in opposite to BALB/cJ mice. (2) Subchronic treatment over 4 weeks

with the atypical antipsychotic drug clozapine (5 mg/kg, i. p. daily), displayed no significant effect on PPI levels in the CPB-K and the BALB/cJ mice groups. In summary, (1) this study confirmed our working hypothesis: lower levels of hippocampal glutamatergic receptor densities correspond to lower sensorimotor gating in CPB-K mice; (2) on the other hand, subchronic antipsychotic treatment with clozapine did not elevate low PPI levels in CPB-K mice. Therefore, an extension of our experiments will concentrate on other antipyschotic drugs.

S-08-04
Startle modification and attentional orientation in human hallucinogenic model psychoses
E. Gouzoulis-Mayfrank (Köln)

Rationale: Deficits of Prepulse Inhibition of the startle reflex (PPI) and spatial orienting of attention, particularly blunted Inhibition of Return (IOR), have been shown in patients with schizophrenia. However, the relation of these deficits to different psychotic syndromes remains to be elucidated. Pharmacological challenges with hallucinogens in healthy humans are used as models for psychosis. The NMDA antagonist model (ketamine) is a model for undifferentiated psychoses with positive and negative symptoms, whereas the serotonin model (LSD, dimethyltryptamine = DMT) is a model for psychoses with predominantly positive symptoms.

Methods and Results: Fifteen healthy subjects participated in a randomized, double-blind, cross-over study with DMT and S-ketamine. Overall, we found an increase of PPI after S-ketamine, but not after DMT, and a blunting of IOR after both hallucinogens.

Conclusions: Blunted IOR and both positive and negative symptoms are tightly interrelated. However, deficits of PPI do not seem to be directly related to psychotic experience. The implications of these results for the hallucinogen model psychosis strategy and for our understanding of the significance of cognitive abnormalities in schizophrenia are discussed.

S-09 Modulators of neuronal growth in psychiatric disorders

S-09-01
Role of NGF and BDNF in animal models of psychiatric disorders
R. Hellweg (Berlin)

The neurotrophins NGF and BDNF have pleiotropic effects in vivo. Performance in a complex maze was better in wild-type than amyloid-overexpressing mice (APP23) modelling Alzheimer's Disease. Other than in wild-type, hippocampal BDNF levels decreased on training in APP23 mice. Mouse strains have been generated that under- or overexpress glucocorticoid receptor (GR). GR ± mice demonstrate increased helplessness after stress exposure, a behavioral correlate of depression in mice. We analyzed these mice for NGF and BDNF contents in brain areas suspected to be involved in stress adaptation. Our data indicate a contribution of altered BDNF and NGF levels to the predisposition for depressive behaviour in the GR ± mouse, but argue against an eminent role of the serotonergic system in this animal model for depression. The olfactory bulbectomy in rodents has been proposed as a different animal model for depression. These mice demonstrated significantly increased BDNF, but regular NGF levels in hippocampus and frontal cortex. In these brain regions bulbectomy also caused a reduction of the serotonin turnover. With respect to the BDNF hypothesis of depression – predicting decreased BDNF levels in depression related brain areas – olfactory bulbectomy in mice seems to be an animal model for agitated depression rather related to serotonergic dysfunctions.

S-09-02
Nerve growth factor and Brain-derived neurotrophic factor in schizophrenic psychosis
M. Jockers-Scherübl (Berlin)

Neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are important for the development and maintenance of function of neurons. Neurodevelopment is thought impaired in schizophrenia, and vulnerable schizophrenic brains may be more sensitive to toxic influences. Thus, cannabis, often used chronically by schizophrenic patients (and other substances) may be more harmful to schizophrenic brains than to non-schizophrenic brains. In a study with drug-naïve first-episode schizophrenic patients we could demonstrate earlier disease onset and significantly raised NGF-and BDNF serum concentrations in drug-naïve schizophrenic patients with previous long-term cannabis abuse in comparison to schizophrenics without cannabis abuse and cannabis abusers without schizophrenia. Only the combination of schizophrenia and cannabis abuse resulted in the raised neurotrophin serum concentrations, suggesting a potential role as repair marker or marker for neural integrity. The latter hypothesis was underlined by the fact that NGF serum levels in treated and remitted schizophrenic patients returned to "normal" in a prospective study and the previously found differences among the groups no longer existed.

S-09-03
S100B as astrocytic modulator of neuronal proliferation: Insight from cell culture models
G. Ponath (Münster)

Recent studies revealed that astrocytes are able to modulate synaptic transmission. Neuroplasticity and dendritic spine formation is linked to enhanced glutamate-mediated synaptic activity, hence to a rise of intracellular neuronal [Ca2+]i levels. A target protein concerning the regulation of neuroplasticity by [Ca2+]i is S100B, a calcium-binding astrocytic protein. S100B exerts a dual effect on neurons depending on its concentration, i. e., a pro-survival effect on neurons and stimulation of neurite outgrowth at nanomolar doses and a neurotoxic effect at micromolar doses. Binding to the receptor for advanced glycation end products (RAGE) on neurons has been involved in both neurotrophic and neurotoxic effects of S100B. Extracellular S100B activates astrocytes indicated by proinflammatory cytokine expression. It could be shown that astrocytic IL-6 and TNF-α secretion can be upregulated by stimulation with S100B protein mediated by RAGE. Intracellular S100B acts as a regulator of the activation status of astrocytes by counterregulating the astrocyte specific intermediate filament protein GFAP. It was shown that S100B regulates GFAP incorporation into intermediate filaments in astrocytes with a relevant impact on neurite outgrowth and neuronal survival. Our data indicate a general involvement of S100B in autocrine and paracrine neuroplastic processes.

S-09-04
S100B in psychiatric disorders
M. Rothermundt (Münster)

Until recently, astrocytes were regarded as mere supporters of neurons regulating the environmental milieu. New research, however, has demonstrated that astrocytes play a major role in the regulation of neuronal proliferation and differentiation. Since neuronal remodelling appears to be a relevant pathogenic factor in various psychiatric disorders the role of astrocytes needs to be evaluated. S100B, a calcium binding astrocyte-specific cytokine, presents a marker of astrocytic activation. Recent studies showed increased S100B levels in medicated acutely psychotic patients with schizophrenia and drug naïve schizophrenics. A positive correlation between negative symptoms and S100B was described. In a longitudinal approach over 24 weeks a continuously increased S100B concentration was associated with persistency of negative symptoms and deceleration of therapeutic response. In major depression increased S100B concentrations

were found in the melancholic subtype of depression in contrast to non-melancholic types. S100B levels were correlated with therapeutic response and associated with electrophysiological changes in acute disorder and after remission. These findings document a potential role of astrocytes in the pathogenesis of psychiatric disorders. S100B is an adequate marker of astrocyte activity which can be used in psychiatric research.

S-10 Alzheimer's disease: Interaction between neuroinflammation and amyloidpathology

S-10-01
Innate immunity and neurodegeneration
S. Walter, M. Letiembre, Y. Liu, K. Fassbender (Homburg)

Microglial activation, is a key feature in Alzheimer's disease neuroinflammation. The innate immune receptors CD14 and Toll-like-receptor 4 (TLR4) are first-line host defense receptors against invading microorganisms. We showed that CD14 interacts with amyloid peptide aggregates, and that CD14 deficiency or defective TLR4 strongly inhibits microglial and monocytic activation by aggregated amyloid peptide resulting in a significantly lower release of the inflammatory products IL-6, TNFa and nitric oxide. Treatment of primary murine neuronal cells with supernatants of amyloid peptide-stimulated microglia demonstrates that both, CD14 and TLR4 contribute to amyloid peptide-induced microglial neurotoxicity. In addition, stimulation experiments in transfected HEK293 cells allowed us to define that a tri-molecular receptor complex consisting of CD14, TLR4 and MD-2 is required for full cellular activation by aggregated amyloid peptide. The clinical relevance of these findings is supported by an increased expression of CD14 and TLR4 in Alzheimer's disease patients brain tissue. Together, these observations provide evidence for a role of the key innate immune receptors, CD14 and TLR4, in Alzheimer's disease neuroinflammation.

S-10-02
Amyloid peptides stimulate the release prostaglandins in glial cells
M. Hüll, B. Müksch, A. Waschbisch, B. L. Fiebich (Freiburg)

Neuroinflammatory processes involving release and intercellular signalling of interleukins (IL) and prostaglandins (PG) have been suggested to be involved in neuropsychiatric disorders such as Alzheimer's Dementia (AD) or late onset major depression. Microglial synthesis of IL-1, astroglial synthesis of IL-6, and elevated levels of PG-derivates in the CSF are found in early AD. PGs are generated by the enzymatic activity of cyclooxygenase-1 and -2 (COX-1/2). PGs modulate several functions in the CNS such as the generation of fever and the sleep/wake cycle. Among all forms of PGs, prostaglandin E2 (PGE2) is abundantly produced in the brain and strongly involved in neuroinflammation. PGE2 act via four isofoms of endoprostanoid receptors (EP1-EP4) which have divergent and counteracting effects on second messenger systems. Selected EP receptors are present on specialised neuronal populations. Some isoforms of EP receptors have been suggested to inhibit neurotransmitter release under physiological conditions. Under pathological conditions different EP receptor isoforms have been reported either to enhance or diminish neuronal cell death. The presence of EP receptors on glial cells has been shown in vitro while in vivo data are rare. PGE2 can induce the synthesis of IL-6 which can influence mood and has been linked to neuroinflammatory aspects of AD. Here we show that two factors of AD pathology, amyloid b peptides (Ab25-35) and IL-1 strongly modulate PGE2 function. Ab25-35 induces COX-2 mRNA, COX-2 protein synthesis, and a subsequent release of PGE2 in primary astrocytes. Ab25-35 rapidly induces the phosphorylation and enzymatic activation of protein kinase C (PKC) in primary rat midbrain glial cells and in primary human astrocytes from post mortem tissue. PKC inhibitors prevent Ab25-35-induced COX-2 and PGE2 synthesis. While Ab25-35 influences PGE2 production, IL-1 changes PGE2 receptor expression. EP3-receptors are upregulated in astroglial and microglial cells by IL-1 suggesting a novel role of EP3 in the brain under neuroinflammatory conditions. An increase of PGs synthesis and EP receptor expression may modulate the involvement of microglial and astroglial cells in the progression of amyloid pathology. Due to the counterbalancing functions of different EP receptor subtypes, inhibition of selected EP receptor isoforms may be a more focussed intervention in neuropsychiatric disorders than blockade of COX-2.

S-10-03
Activation of the transcription factor PPARg as therapeutic strategy for Alzheimer's disease
M. Heneka (Münster)

Epidemiological evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk for Alzheimer's disease (AD). The mechanism by which this neuroprotection is achieved remains to date unknown. Accumulating evidence suggests that one dimension of NSAID protection is mediated activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARg). PPARg represents a nuclear hormone receptor which regulates insulin sensitivity, suppresses proinflammatory gene transcription and modulates beta amyloid peptide (A^2) processing. Thus, PPARg activation increases insulin sensitivity in target organs including muscle, liver and brain, thereby influencing the energy metabolism of these organs. In microglia and astroytes, PPARg activation inhibits proinflammatory genes through silencing the transcription factors nuclear factor kappa B and AP-1. Moreover, PPARg agonists reduce Ab- and cytokine mediated neuroinflammation and neurotoxicity in vitro and in vivo. NSAIDs, such as indomethacin and ibuprofen reduce immunostimulated Ab production in a PPARg-dependent manner and an acute treatment of APP overexpressing mice with ibuprofen or the specific PPAR g agonist pioglitazone reduced microglial activation, inflammatory gene expression, b-secretase 1 (BACE1) levels and Ab plaque deposition. This anti-amyloidogenic effect is mediated by transcriptional regulation of BACE1 promotor activity via binding to a specific responsive element (PPRE). Mutagenesis of this PPRE abrogated the binding of PPARg to the PPRE, increased BACE1 gene promoter activity, and abolished the A^2 lowering effect of NSAIDs. More recently, epidemilogical studies have demonstrated a reduced risk to develop AD for patients who are on regular PPARg agonist medication. In addition, a 18 month treatment trial using the PPARg agonist pioglitazone has shown a positive effect on cognitive decline in AD patients.Taken together, these data suggest that PPARg activation may represent a novel therapeutic avenue for the treatment of AD patients.

S-10-04
Non-steroidal anti-inflammatory drugs (NSAIDs) as modulators of amyloid production in Alzheimer's disease
S. Weggen (Mainz)

NSAIDs have been considered for treatment or prevention of Alzheimer's disease (AD) since more than two decades. This approach was derived from epidemiological studies and from observations that the causative amyloid pathology is accompanied by a secondary inflammatory response. However, recent findings have demonstrated that NSAIDs possess additional anti-amyloidogenic activities that provide an alternative explanation for their protective effects. Most notably, some NSAIDs were shown to selectively lower cellular production of the Abeta42 peptide, a key agent in familial and sporadic forms of AD. In contrast to conventional gamma-secretase inhibitors, these gamma-secretase modulators effectively suppress Abeta42 production while sparing processing of NOTCH and other gamma-secretase substrates. Importantly, the Abeta42-lowering activity is not related to inhibition of cyclooxygenases but rather involves direct interaction with gamma-secretase or its substrates. We propose that future drug development efforts should focus on the improvement of Abeta42-lowering molecules without COX activity, which could provide a potent means to prevent both amyloid pathology and secondary inflammatory reactions while avoiding clinical side-effects associated with inhibition of COX and gamma-secretase.

S-11 Advances in the neuropathology of psychoses: Hippocampal findings

S-11-01
Modulatory effects of NRG-1 on structure and function of the hippocampus in patients with schizophrenia
T. Kircher (Aachen)

Linkage studies have identified a significant association of the Neuregulin (NRG1) gene with schizophrenia, but its functional implication in the disorder is largely unknown. First, the function of the NRG1 gene will be reviewed. Secondly, its implication in schizophrenia will be discussed and genetic meta analysis presented. Thirdly, data on first episode patients with schizophrenia and control subjects will be presented. All subjects performed a letter n-back task while brain activation was measured with functional Magnetic Resonance Imaging (fMRI). Neuronal signal changes were compared between groups of patients with and without the most consistently confirmed at-risk allele (SNP8_221533) from the Islandic haplotype. Group comparison within the patients during working memory load (2-back vs. 0-back) revealed that those without the at risk allele showed greater activations in a network comprising the left parahippocampal gyrus, superior frontal gyrus, lateral temporal lobe, precuneus and the right anterior cingulate. Brain regions, such as the hippocampus, are differentially affected in those patients carrying the genetic at risk status in the NRG1 gene.

S-11-03
Does disturbed adult neurogenesis contribute to hippocampal pathologies found in endogenous psychoses?
A. Reif, S. Fritzen, M. Finger, K.-P. Lesch (Würzburg)

Based on animal studies it has been suggested that reduced hippocampal adult neurogenesis (AN) is implicated in the etiopathology of depression, and that the AN contributes to the mechanism of action of anti-depressants. Data from human postmortem brain is still lacking. The initial step of AN (neural stem cell proliferation, NSP, which can be used as an approximate measure of AN) can be determined by immunohistochemistry using antibodies against the nuclear antigen Ki-67. As AN cannot be measured in humans, we investigated whether NSP is altered in hippocampal tissue of patients suffering from bipolar affective disorder, major depression or schizophrenia as compared to controls. The tissue used (n = 15 sets of hippocampal slices for each group) was provided by the Stanley Foundation. Per brain, 7 sections of the anterior hippocampus were processed for Ki-67 immunohistochemistry. Anti-depressant treatment did not result in an increase of NSP. Importantly, significantly reduced NSP was found in schizophrenia, but not in depression. These results fit well with recent data from animal studies demonstrating that the disruption of candidate genes like PAS3 results in both schizophrenia-like symptoms and reduced AN. Together, these findings provide evidence that reduced AN may contribute to the pathogenesis of schizophrenia, but not depression.

S-11-04
Hippocampal pathology in animal models of schizophrenia
A. Schmitt, P. Falkai (Homburg)

In animal models, postnatal hippocampus lesion induces schizophrenia-related behavior in early adulthood and supports the impact of neurodevelopmental disturbances. However, pathophysiological processes are not mirrored by this model. Other animal models of obstetric complations, e. g. sectio caesarea or postnatal hypoxia in rats, have shown hippocampus-related behavioral alterations in young adulthood, such as disruption of prepulse inhibition of acoustic startle response. In our animal study we investigated the impact of postnatal hypoxia on the glutamate pathway. After chronic postnatal hypoxia (11 %O2, 89 %N2), we investigated receptor binding and gene expression of subunits of the NMDA (N-methyl-D-aspartate) receptor. NR2A subunit was downregulated by chronic hypoxia only in CA3 region of hippocampus (by 25.3 %), whereas NR2C was upregulated in the same region (29.8 % $p < 0.05$). Hypobaric hypoxia in adult rats is known to induce delayed neurotoxicity in the hippocampus. Therefore, reduced NR2A expression or increased NR2C expression may be viewed as a consequence of cell injury or NMDA receptor hypofunction. The question remains open, whether our hypoxia paradigm may be neurotoxic, reduce neuropil or induce astrogliosis. Additional studies using stereological cell counting are warranted to elucidate these mechanisms.

S-12 Neuropsychology, functional neuroanatomy and biochemistry of major depression

S-12-01
Neuronal correlates of executive dysfunction in severe major depression
S. Grimm, G. Northoff, J. Beck, C. Schmidt, P. Boesiger, D. Hell, H. Boeker (Zuerich)

Major depression can be characterized by co-occurrence of emotional and cognitive symptoms. We investigated patterns of neural activity in ventral prefrontal cortex during emotional and cognitive stimulation in 29 healthy and 20 depressive subjects using functional magnetic resonance imaging (fMRI). Subjects' executive functions were tested with the Intradimensional/Extradimensional (ID/ED) Attentional Set-Shifting task. Analysis focused on patterns of hyper- and hypoactivation in prefrontal cortex and the correlation between psychopathological symptoms, neuropsychological symptoms and neural activity. Data shows severely impaired executive functions as well as abnormal patterns of neural activity in prefrontal cortex in depressive subjects.

S-12-02
Neural correlates of emotional attention in major depression
F. Bermpohl (Berlin)

Using functional magnetic resonance imaging, we aimed at investigating emotional stimulus processing and its attentional modulation in patients with major depression. Emotional and neutral cues were presented prior to emotional and neutral pictorial stimuli (International Affective Picture System), in order to direct the subjects' attention to the emotional content of the pictorial stimulus. For control, half of the pictorial stimuli were not preceded by expectancy cues. Compared to healthy subjects, patients with major depression showed larger BOLD responses to emotional stimuli in brain regions associated with emotion perception. Healthy subjects, on the other hand, showed stronger attentional modulation of emotional stimulus processing. Our findings suggest both altered emotion preception and modulation in major depression.

S-12-03
Prefrontal spectroscopy findings and brain activity in major depression
M. Walter (Magdeburg)

Recent work on cortical functional alterations associated with major depressin (MDD) underlined the involvement of prefrontal cortices including ventromedial prefrontal cortex (VMPFC) and anterior cingulate (ACC). In these regions, higher baseline activities and altered excitability, including weaker functional deactivations, indicated as negative BOLD responses (NBR) in functional magnetic resonance imaging (fMRI), were discussed to be related to changes of emotional behavior and subjective emotional experience. These neuronal effects seem to be closely related to gabaergic and glutamatergic transmission. We tried to investigate this relation of altered BOLD responses and metabolite concentrations in the prefrontal cortex by measuring local concentrations of glutamate and glutamine relative to creatine. Results suggest that altered glutamate concentrations in MDD patients may acount for observed changes of prefrontal brain activity.

S-12-04
Neuroanatomical and biochemical correlates of the default-mode network in major depression
G. Northoff (Magdeburg)

Patients with major depressive disorder (MDD) show higher signal intensities in the subgenual/pregenual anterior cingulate (Cg25/PACC) and the ventromedial prefrontal cortex (VMPFC) during emotional tasks. Together with other areas like the posterior cingulate cortex (PCC), these regions have been subsumed under the default-mode network showing negative BOLD responses (NBR) related to a variety of tasks. This led us to hypothesize that higher signal intensities in MDD may be due to abnormal NBR. Using fMRI, we therefore investigated 20 medication-free patients with acute MDD during both emotional picture perception and judgment. As hypothesized, MDD patients showed significantly decreased NBR in both emotional tasks in Cg25/PACC, VMPFC and PCC which, unlike in healthy subjects, were no longer parametrically modulated by their abnormally negative subjective emotional perception. In sum, we show lower NBR in MDD revealing for the first time abnormal activity in the default-mode network in this psychiatric disorder.

S-13 Neurobiological Correlates of Negative-Schizophrenia

S-13-01
The Question for neuropathology in negative symptoms
P. Falkai (Göttingen)

Is there a neuropathology in negative symptoms? Prof. Dr. med. Peter Falkai, Klinik für Psychiatrie und Psychotherapie, Universitätsklinikum Göttingen, 37075 Göttingen Since the introduction of the term "Schizophrenia" as a disease, negative symptoms have been a core feature of it. Since then leading psychiatrists like Emil Kraepelin have tried to unravel the structural basis of this symptom domain. Meanwhile we know that negative symptoms constitute of a cognitive and an affective syndrome. The paper summarizes recent evidence connecting the neuropsychological deficit of schizophrenia with structural and functional brain abnormalities.

S-13-02
Social cognition and social competence in schizophrenic patients with negative syndrome
M. Abdel-Hamid, G. Juckel, M. Brüne (Bochum)

There is good empirical evidence that patients with schizophrenia spectrum disorders are impaired in several neurocognitive functions such as attention, memory, task switching and executive planning. More recently, several studies have shown that selective social cognitive deficits, i. e. independent of other cognitive impairments, may contribute to the psychopathology associated with schizophrenia. Social cognition embraces such diverse abilities as emotion recognition, face processing and "theory of mind" or mental perspective taking. Cognitive malfunctioning varies within the schizophrenia spectrum. One of the most unequivocal finding is that patients with predominant negative symptoms are the most severely impaired in tests tapping into neurocognitive functioning and social cognition. However, since over time there is a general cognitive decline in negative schizophrenia, including general intelligence (IQ), most study results are confounded by lower IQ in the patient group when compared with healthy controls. Here, we present findings from a study into social cognition in normal IQ patients with schizophrenia. Results suggest that even in a subgroup of patients with normal IQ and negative syndrome social cognition is compromised and predicts impaired social competence best.

S-13-03
Reward system dysfunction in schizophrenic patients – Effects of typical and atypical antipsychotics
F. Schlagenhauf (Berlin)

It was often hypothesized that negative symptoms are associated with a dysfunction of the mesolimbic dopaminergic reward system. We used functional magnetic resonance imaging (fMRI) to assess the blood oxygen level dependency response in the ventral striatum of unmedicated and medicated schizophrenics and matched healthy control subjects during reward anticipation. Compared to healthy controls, unmedicated schizophrenics showed reduced ventral striatal activation during the presentation of reward-indicating cues, which was inversely correlated with the severity of negative symptoms. Schizophrenics treated with atypical neuroleptics showed ventral striatal activation in response to reward-indicating cues, but schizophrenics treated with typical neuroleptics did not. In unmedicated schizophrenic patients, a high striatal dopamine turnover may interfere with neuronal processing of reward-indicating cues by phasic dopamine release, thus contributing to negative symptoms as such as loss of drive and motivation. Significant blunting of ventral striatal activation was not observed in patients treated with atypical neuroleptics, which may reflect the improved efficacy of these drugs in treating negative symptoms.

S-13-04
Dopamine and cognition in schizophrenia: New insight from PET studies
I. Vernaleken, G. Gründer (Aachen)

Molecular imaging, genetics as well as behavioural and animal data suggest a linkage between cognition and dopamine transmission. However, impaired cognitive performance is a major problem in the treatment of schizophrenia. New positron emission tomography (PET) results will be presented that illustrate the dopaminergic modulation of 'prefrontal' cognitive functions. Using D2/3 and D1 receptor ligands, changes of intrasynaptic dopamine concentrations can be estimated. Furthermore, FDOPA PET provides the possibility to measure parameters for dopamine synthesis capacity, storage capacity and presynaptic loss. In schizophrenia especially the dopamine storage capacity and to a lesser extent the dopamine synthesis capacity is disturbed. Furthermore, the presynaptic dopamine elimination is elevated two-fold in striatum, the largest biochemical difference in brain of schizophrenics yet reported. Cognitive Performance is correlated with striatal dopaminergic turn-over in patients suffering from schizophrenia and in healthy controls. However, the direction of correlation is inverted in schizophrenia. Furthermore, antipsychotics can severely affect cognition and dopamine-transmission. Treatment related changes of cognition appear to be dependent on the baseline dopamine turn-over. These data provide new insights in the pathophysiology of cognitive impairments in schizophrenia.

S-14 Presidential memorial symposium Manfred Ackenheil – Pharmacogenetics

S-14-01
Pharmacogenetics of response to antidepressants
W. Maier (Bonn)

Currently, the selection of an antidepressant drug for an individual patient is still a matter of "trial and error". Pharmacogenetics holds the promise to fill this gap of knowledge. DNA-sequence variations as the most important source of interindividual differences present as strong candidates for determining individual drug response. Up to now, consistent evidence for genetic variants predicting the clinical response is growing only slowly. Recently, new enthusiasm emerged from major studies demonstrating a modest predictive power of variants of genes involved in synaptic transmission. However, independent replications are still needed. In particular, it remains obscure if contributing genetic variants of response is substance-specific or

common to all antidepressants. A more focussed approach might circumvent these difficulties: (a) focus only on prospective studies with standardized monotherapy; (b) use of specific neurobiological target systems for measurement of outcome and candidate genes impacting on these prespecified target systems; e. g., reestablishment of feedback control in the HPA system might be used for outcome measurement and genes coding for synaptic transmission and HPA-regulating proteins as candidates. We report on a study programme on 150 patients treated with citalopram or mirtazepin, addressing most of these difficulties in unipolar depression (e. g., substituting diagnostic and psychopathological measures by neurobiological phenotype characterisation; highly standardized treatment programme for exclusion of interfering effects). In this study we identified several variants of HPA-related genes and of other genes relevant for synaptic transmission (e. g., COMT, 5-HT-2A) as modifiers of neurobiological phenotypes and outcome measures.

S-14-02
Metabolic disturbances under psychopharmacological therapy: role of pharmacogenetics
P. Zill, M. Riedel, I. Spellmann, R. Musil, A. Douhet, S. Dehning, N. Müller, H.-J. Möller, B. Bondy (Munich)

The inter individual variability of drug response is a major problem in clinical practice and drug development, which can lead to therapeutic failure or adverse effects in patients. There is growing evidence that not only pharmacokinetic factors might predispose to adverse effects, but also genetic variations in drug targets. Moreover the existence of comorbid disorders, as for example the metabolic syndrome, characterized by elevated abdominal obesity, triglycerides, blood pressure, fasting glucose, which has been suggested to be associated with schizophrenia and depression is supposed to have an impact on the incidence of side effects after psychopharmacological treatment. In own studies with 210 schizophrenic patients we found that polymorphisms in the 5-HT2C receptor- (–579C/T), β-adrenergic receptor- (β2 arg16 gly) and ghrelin- (leu72met) gene seem to be involved in weight gain during neuroleptic treatment. The 5HT2C –597 C/T and a β2-adrenergic receptor polymorphisms (arg16 gly) might also be involved in glucose and lipid metabolism. These results suggest that characteristics of the metabolic syndrome are among the common side effects, but these findings have to be replicated in further prospective studies. Knowledge from these studies will ultimately lead to the individualization of psychiatric drug treatment, as well as to future treatment strategies.

S-14-03
Large scale association study on short-term response to haloperidol
D. Rujescu (Munich)

Haloperidol is highly efficient in the treatment of acute psychosis, especially when severe symptoms predominate. This study investigates the association of response to short-term haloperidol treatment with 120 microsatellites and 200 SNPs in various candidate genes selected based on their role in neurotransmission. One hundred patients with acute psychosis (schizophrenia, schizoaffective, brief psychotic, and substance-induced psychotic disorder) were treated with haloperidol for up to 28 days. Diagnosis was established by applying the SCID I and II interview. Patients were assessed at baseline and on days 3, 7, 14, 21and 28. Improvement and response were measured by using the Positive and Negative Syndrome Scale. Haloperidol plasma levels were also obtained. We will present, for the first time, data on this ongoing large-scale association study on response to haloperidol. Genotyping of further 400 SNPs is under way.

S-15 Addiction treatment: From bench to bedside

S-15-01
Neurobiological background of recent addiction treatment strategies
F. Kiefer (Mannheim)

Alcohol addiction is a chronic disorder that develops on a genetic, psychosocial and environmental background. Whereas alcohol withdrawal treatment is widely accepted as a pharmacotherapeutic domain, anti-craving and relapse prevention treatment in clinical practice up to now is mainly based on psychosocial and psychotherapeutic interventions. However, there is growing interest in the interaction of psychotherapy with drug therapy since it has been shown repeatedly that pharmacological treatment is efficacious in the reduction of craving and risk of relapse in abstinent alcohol dependent patients. Drugs have been developed on the basis of knowledge of the biological mechanisms of alcohol dependence. The talk will present the neurobiological background of anti-craving treatment, will interprete very recent data from clinical trials and will translate these results into relevant information for clinical "bedside" treatment.

S-15-02
Dopaminergic transmission – genetic and epigenetic findings in patients with alcohol dependence
S. Bleich, D. Bönsch (Erlangen)

Background: Recently it has been shown that alpha synuclein levels are increased in alcohol-dependent patients. This increase was significantly associated to craving. Based on these observations, the present study analyzed two polymorphic repeats within the NACP gene and its epigenetic regulation.

Methods: We analysed the alcohol-dependent patients of the Franconian Alcoholism Research Studies (FARS). Epigenetic DNA methylation was done within the promoter region of the alpha synuclein gene to determine changes of the gene regulation.

Results: We found highly significant longer alleles of NACP-REP1 in alcohol- dependent patients compared to healthy controls (Kruskal-Wallis test, $\gamma 2 = 99.5$; $df = 3$, $p < 0.001$). Additionally, these lengths significantly correlate with levels of expressed alpha synuclein mRNA ($\gamma 2 = 8.83$; $df = 2$, $p = 0.012$). Furthermore, we observed a significant gene specific DNA promoter hypermethylation within the alpha synuclein gene.

Discussion: Since hypermethylation of DNA is an important epigenetic factor in the down regulation of gene expression these findings may explain the reduced value of craving under alcohol drinking conditions. The present results further point to a novel approach for a genetic determination of craving.

S-15-03
The relevance of comorbid addictions for the treatment of alcohol dependence
T. Hillemacher, K. Bayerlein, N. Thürauf, J. Kornhuber, S. Bleich (Erlangen)

Various studies have described the comorbidity between alcoholism and other types of substance abuse including nicotine dependence. Epidemiological investigations have shown that the prevalence of alcoholism in smokers is estimated to be 10 times higher than in nonsmokers. Furthermore, recent studies suggest that ethanol and nicotine may share neuropathophysiological pathways and both interact with the dopaminergic reward system. Also, smoking has been identified as a factor that influences relapse rates in alcohol dependent patients. We investigated a possible association of nicotine dependence and alcohol craving evaluating both – obsessive and compulsive behaviour. Spearman correlation analysis revealed a significant association between the extent of alcohol craving and the FTND score especially for the compulsive subscore of the OCDS. These results could be confirmed using general linear models. Our findings show that the severity of nicotine dependence is associated with higher compulsive

(not obsessive) craving in alcohol dependent patients. These results point towards shared pathophysiological mechanisms in compulsive alcohol craving and nicotine addiction and may help establishing a more individualized therapy in patients suffering from both, alcohol and nicotine dependence.

S-15-04
Leptin serum levels and craving in alcohol dependence
T. Kraus, S. Bleich, H. Frieling, A. Schanze, J. Wilhelm, W. Sperling, J. Kornhuber (Engelthal/Erlangen, Erlangen)

Objective: Recent studies have described an association of leptin serum levels and craving in alcoholic patients. Aim of the present study was to prove evidence of an association between leptin serum levels and craving data. A large sample size and a power-based statistical analysis should be used.

Subjects and methods: 156 male and 33 female patients were included suffering from alcohol dependency, admitted for detoxification treatment. Leptin serum levels were measured using a commercial ELISA kit. The Obsessive Compulsive Drinking Scale (OCDS) was used to assess alcohol craving on admission.

Results: For both genders, Spearman's correlation revealed significant results. These findings could be confirmed using a multiple linear regression models (males: $r = 1.881$, $t = 4.338$, $p < 0.001$; females: $r = 6.160$, $t = 5.793$, $p < 0.001$) with a power of 1.00.

Conclusions: In contrast to previous results, describing an association only in female patients, this power-based analysis shows an association of leptin levels with alcohol craving in both, females and males.

WS-01 Workshop

WS-01 Multimodal neuroimaging in psychiatry

WS-01-01
Relevance of multimodal neuroimaging for a better understanding of psychopathological phenomena
T. Dierks, C. Lehmann, W. Strik, D. Hubl (Bern)

One prominent psychopathological phenomenon is auditory verbal hallucinations (avh). It has been suggested that interaction between frontal and temporal speech-related areas might contribute to pathogenesis of avh. In a previous fMRI study we found evidence that directly speech related brain are involved in the generation of avh. These cortical areas are known to be inhibited during internal speech in normal subjects, whereas in hallucinating patients we demonstrated a co-activation of primary auditory cortex during internal speech. Furthermore it has been postulated that alterations in connectivity between frontal and temporal speech-related areas might contribute to pathogenesis of avh. We used MR diffusion imaging to assess the directionality of cortical white matter (wm) tracts and could demonstrate that patients with hallucinations have significantly higher wm directionality in the lateral parts of the temporoparietal section of the arcuate fasciculus compared with control subjects and nonhallucinating patients. Our findings suggest that during inner speech, the alterations of white matter fiber tracts in patients with avh lead to abnormal coactivation in regions related to the acoustical processing of external stimuli. This abnormal activation may account for the patients' inability to distinguish self-generated thoughts from external stimulation.

WS-01-02
Towards specific fMRI imaging of distinct neural events using trial-by-trial coupling of EEG and fMRI
C. Mulert, L. Jäger, C. Seifert, G. Leicht, S. Karch, M. Moosmann, O. Pogarell, H.-J. Möller, U. Hegerl (Munich, Munich, Bergen)

While conventional fMRI does not allow to differentiate between distinct neural processes in the millisecond range, this is possible with EEG. Trial-by-trial combination of EEG and simultaneous fMRI offers neuroimaging with both high spatial and high temporal resolution. We present data demonstrating different BOLD-reponses to distinct components of event-related potentials.

WS-01-03
Combination of Near-Infrared Spectroscopy (NIRS) with EEG: New developments
A. Fallgatter (Würzburg)

Near-infrared spectroscopy (NIRS) is an optical imaging technique perfectly suitable for the investigation of auditory paradigms, since virtually no noise is involved in the measurement. We conducted a simultaneous NIRS-ERP measurement to investigate the cortical correlates of auditory sensory gating. Sensory gating refers to the ability of cerebral networks to inhibit responding to irrelevant environmental stimuli, a mechanism that protects the brain from information overflow. The reduction of the P50 amplitude (an early component of the event-related potential/ERP in electrophysiological recordings) after repeated occurrence of a particular auditory stimulus, is one means to detect and quantify gating mechanisms. Results of the multi-channel NIRS recording indicate a specific activation of prefrontal and temporo-parietal cortices during conditions of increased sensory gating (dual-click trials). Combining the hemodynamic data (NIRS) with an electrophysiological index of the quality of the gating process (gating quotient Q) revealed a positive correlation between the amount of sensory gating and the strength of the hemodynamic response during dual-click trials in left prefrontal and temporal cortical areas. The results indicate that prefrontal and possibly temporal regions of the left hemisphere are crucially involved in the process of auditory sensory gating.

WS-01-04
The functional role of regional zerebral glutamate: Combination of magnetic resonance spectroscopy and EEG
J. Gallinat, A. Heinz, F. Schubert (Berlin)

Brain waves reflect collective behaviour of neurons and provide insight into distributed network processing. Frontal and hippocampal theta oscillations (4–7Hz) have been linked to cognitive tasks, and animal studies have suggested an involvement of glutamatergic neurotransmission in integrative frontal-hippocampal processing. Human evidence for such relationships is lacking. Here we studied the associations between glutamate concentrations in the hippocampal region, measured by 3-tesla proton magnetic resonance spectroscopy (1H-MRS), and EEG theta activity during an auditory target detection paradigm. A robust relationship between hippocampal glutamate and frontal theta activity during stimulus processing was found. Moreover, frontal theta oscillations were related to response speed. The results suggest a functional coupling between the frontal cortex and hippocampal region during stimulus processing, and support the idea of the hippocampus as a neural rhythm generator driven by glutamatergic neurotransmission. These preliminary data show for the first time a relationship between in vivo measured glutamate and basic cerebral information processing in humans.

WS-02 Neurobiology of aggressive and impulsive behavior

WS-02-01
Neurobiology of suicidal behavior and aggression associated phenotypes
T. Bronisch (Munich)

Suicide seems to be exclusively confined to men considering the phylogenesis. Suicide needs as a prerequisite self-reflection, i. e., the individual has to differentiate between an observing and an experiencing ego. From the topographical-anatomical point of view suicidal behavior as a genuine human property may be located in the phylogenetic youngest area of the brain, i. e., the forebrain and – more distinct – the prefrontal cortex (PFC). Other areas such as amygdala, thalamus, basal ganglia, Hippocampus as well as the midbrain are certainly also involved. Heterogenous psychiatric disorders like depression, schizophrenia, substance-related disor-ders, anxiety disorders and personality disorders increase the risk of suicidal behavior. A diathesis for suicidal behavior may result from impaired control of impulsivity and aggression which may in part be determined or mediated by neurobiological mechanisms. Recently it was postulated that a serotonergic deficit in the ventral prefrontal cortex could predispose to impulsive and autoaggressive behavior in stressful life events. A series of neurobiological studies showed a dysregulation of the HPA system. Placebo controlled studies point to the decrease of hostile and impulsive behavior as well as negative affectivity and to the increase of affiliative behavior and of recognition of positive affectivity in patients and healthy subjects by SSRIs. Controlled clinical trials show that antidepressants and lithium significantly reduce suicidal behavior. A serious problem in the treatment of suicidal patients is that suicidal behavior cannot be sufficiently predicted and controlled. This may be due to increased impulsivity with overshooting autoaggressivity. Empirical studies demonstrate that impulsivity and aggressivity only poorly respond to pharmacological treatment or psychotherapy. Many patients lack sufficient insight into the necessity of a long-term treatment after a suicide attempt.

WS-02-02
Genetics of aggressive and impulsive behavior
D. Rujescu, A. M. Hartmann, B. Schneider, A. Schnabel, A. Thalmeier, K. Maurer, H.-J. Möller, I. Giegling (Munich, Frankfurt)

Risk of suicide-related behavior is determined by a complex interplay of sociocultural factors, psychiatric history, personality traits, and genetic vulnerability. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution. Neurobiological studies have shown that serotonergic dysfunction is implicated in suicidal behaviors. We have initiated a large scale case control association study which comprises of 250 suicide attempters and 1900 healthy volunteers and investigated the role of a comprehensive set of serotonergic candidate genes in this behavior. Since both, aggression related traits and serotonergic activity are partially heritable and correlate inversely variations in genes of the serotonergic system might then account for variations in aggression-related behavior. Thus, we also investigated the relationship between serotonergic genes and anger and aggression. Additionally we conducted a large-scale gene expression analysis using cDNA-microarrays to identify new candidate-genes for suicide. We found several genes to be differentially expressed in the orbitofrontal cortex of suicide completers. Cross-validation experiments using quantitative RT-PCR validated 9 genes so far. These genes were genotyped as well to look for associations with suicide-, anger- and aggression-related behavior.

WS-02-03
Hippocampal volume and aggressive behaviour in patients with borderline personality disorder
T. Zetzsche, S. Tabrizi, N. Koutsouleris, H.-J. Möller, E.-M. Meisenzahl (Munich)

In patients with borderline personality disorder (BPD) disturbances of aggression and impulse control are frequently observed. The hippocampus is part of the limbic system, which is involved in the control of these types of behaviour. The intention of our study was to investigate potential structural changes of hippocampal formation in BPD patients and to evaluate if these are related to aggressive and impulsive behaviour. Twenty-five female and right-handed BPD patients (DSM IV) and 25 healthy control subjects matched according to sex, age, handedness and educational status were examined. MRI scans were performed using 1.5 T Magnetom Vision. The software program "BRAINS" was employed for segmentation and volumetry of the hippocampal formation. Established instruments were used to evaluate impulsive and aggressive behaviour. We detected a hippocampal grey matter volume reduction that was more pronounced in BPD patients with multiple hospitalizations. Hippocampal volume of the left hemisphere was inversely correlated with lifetime history of aggressive behaviour. Our study confirms previous results indicating a volume reduction of the hippocampus in BPD patients. Furthermore, this structural change might facilitate aggressive behaviour. It has to be clarified in subsequent studies whether reduction of hippocampal volume is a trait or risk factor for increased aggression.

WS-02-04
Neurobiology of aggressive and impulsive behavior
S. C. Herpertz (Rostock)

Reactive aggression is likely to occur in rather young, emotionally unstable, impulsive individuals, particularly those with borderline personality disorder. Distortions in social perception may contribute to aggression in these individuals. In contrast, instrumental aggression predominantly occurs in psychopathic offenders. Increasing amount of evidence indicates that differences in psychopathology between these subtypes are accompanied by specific differences in neurobiological functioning. Neuroimaging data suggest, that the amygdala and the orbital frontal cortex modulate the neural circuitry mediating reactive aggression. The amygdala increases reactive aggression by responding to unconditioned and learnt threat or anger stimuli. Damage to orbitofrontal and medial frontal cortical structures is associated with increased risk for the display of reactive aggression probably due to its function of regulating the subcortical neural systems. In psychopaths, reduced amygdala functioning has been hypothesized to be the most significant biological factor underlying emotional detachment and instrumental aggression. However, although psychopaths show considerable evidence of amygdala dysfunction, the direction of change is inconsistent.

WS-03 New insights into the pathophysiology of the spectrum disorders Tourette syndrome, OCD, and ADHD using multi-modal voxel-based MRI and SPECT

WS-03-01
New insights into neuropsychiatric disorders using voxel-based multimodal MRI
T. Peschel, K. Müller-Vahl, H. Emrich, J. Großkreutz (Hanover)

Recent technical developments have made it feasible to comprehensively assess brain anatomy in neurological and psychiatric populations. Three different sensitive MRI methods which can detect macroscopic as well as microstructural cerebral alterations in vivo will be presented: (i) voxel-based-morphometry (VBM), an objective whole-brain method that uses an unbiased approach to characterize differences in gray and white matter volumes, (ii) magnetization transfer

imaging (MTI) which is more sensitive to neuropathological changes than conventional MRI and provides a quantitative measure of macrostructural integrity in vivo, and (iii) diffusion-tensor imaging (DTI) which is suitable to study the microstructural integrity of white matter pathways and cerebral tissue. Furthermore, by the use of statistical parametric mapping (SPM), it is possible to study the whole brain in an exploratory fashion without having to make a priori assumptions about the structures to be investigated. We will show that these methods can detect the underlying neuropathological hallmarks in patients with different neurodegenerative diseases in vivo, and that they have the potential for multi-site studies in large patient samples to link neuropathological abnormalities with clinical characteristics in vivo.

WS-03-02
Structural alterations in attention deficit hyperactivity disorder as assessed by voxel-based multimodal MRI
N. Buddensiek, T. Peschel, S. Bents, M. Ohlmeier, H. M. Emrich, J. Großkreutz, K. R. Müller-Vahl (Hanover)

Background: According to data from neuroimaging studies there is evidence for an involvement of fronto-striatal circuits in the pathophysiology of attention deficit hyperactivity disorder (ADHD). However, influence from comorbidities and medication effects due to heterogenous study populations have produced conflicting results regarding the extent of morphological alterations. The aim of the study was to further investigate the structural abnormalities in a homogenous population sample of male ADHD patients.

Methods: 25 adult, male, unmedicated patients without comorbidities and 25 male, age-matched control subjects were investigated using three different MRI techniques: voxel-based morphometry (VBM), magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) analyzed on a voxel-by-voxel basis using SPM2 (1.5 T neuro-optimized GE-scanner).

Results: Compared with controls, alterations in the anterior cingulate gyrus, the thalamus, the neostriatum, the orbitofrontal as well as the dorsolateral prefrontal cortex were detected in ADHD patients.

Conclusions: Our findings suggest an involvement of fronto-striatal pathways and the mesocortical-mesolimbic system in the pathophysiology of ADHD. Due to the study design, influences from comorbidities, gender, medication and age can be excluded.

WS-03-03
Changes of dopaminergic and serotonergic neurotransmission in Tourette syndrome and obsessive compulsive disorder
G. Berding, K. Müller-Vahl (Hanover)

Increased dopaminergic neurotransmission has been hypothesised to play a role in the pathophysiology of Tourette syndrome. This was based on increased dopamine receptor binding observed at post mortem, beneficial effects of dopamine antagonists on tics in vivo and detrimental effects of dopamine agonists. Accordingly, we found increased specific radiotracer binding to striatal dopamine transporters in Tourette patients. However, clearly increased binding was detected only in about half of the patients. This subgroup was clinically characterised by an increased frequency of self-injurious behaviour and a lack of impulse control. Obsessive compulsive disorder has been related to an impaired serotonergic activity. This is substantiated by reports of a decreased level of serotonin metabolites in the cerebrospinal fluid and an improvement of symptoms seen during SSRI therapy. Correspondingly, we found decreased specific radiotracer binding to serotonin transporters of the hypothalamus midbrain region in Tourette patients with obsessive compulsive behaviour. Moreover, a negative correlation between the severity of obsessive compulsive symptoms and the degree of transporter binding was detected. Our results exemplify, that changes in neurotransmission function may be primarily related to specific neuropsychiatric symptoms, rather than to the presence of a complex clinical syndrome.

WS-03-04
Involvement of fronto-striatal pathways in Tourette syndrome with and without comorbid ADHS and OCD
K. R. Müller-Vahl (Hanover)

Background: Despite strong circumstantial evidence that the pathophysiology of Tourette syndrome (TS) involves disturbances of the basal ganglia and cortical frontal areas, inconsistent findings from TS imaging studies have provided conflicting results. The aim of the study was to investigate the degree of myelinization, axonal density, white (WM) and gray matter volumes (GM), and the integrity of micromolecular structures in TS.

Methods: 19 adult, male, unmedicated patients without comorbidities and 20 male, age-matched control subjects were investigated using three different novel MRI techniques: voxel-based morphometry (VBM), magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) (1.5 T neuro-optimized GE-scanner).

Results: Using these different MRI techniques we found highly consistent results in "TS only" patients with alterations in the medial frontal gyrus (including a reduction of frontal WM), in the putamen bilaterally, the left caudate nucleus, the cingulate gyrus, and different parts of the corpus callosum.

Conclusions: Our findings strongly suggest an involvement of fronto-striatal pathways in the pathophysiology of TS. It will be discussed whether results in "TS only" patients differ from those in TS patients with comorbid ADHD or OCD to answer the question whether TS, ADHD and OCD represent a spectrum disorder or distinct entities.

WS-03-05
The pathophysiology of obsessive-compulsive disorder: Evidence by voxel-based multimodal MRI
T. Peschel, J. Großkreutz, N. Buddensiek, A. Glahn, H. Emrich, K. Müller-Vahl (Hanover)

Background: Available data from functional neuroimaging studies is consistent in identifying alterations involving frontosubcortical circuits in obsessive-compulsive disorder (OCD). The results of structural studies have been notably heterogeneous, probably as a consequence of different patient selection and the diversity of methods adopted to delineate regions of interest.

Methods: 16 adult, male, unmedicated patients without comorbidities and 20 male, age-matched control subjects were investigated using three different MRI techniques: voxel-based morphometry (VBM), magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) analyzed on a voxel-by-voxel basis.

Results: Compared with control subjects, patients with OCD showed significant ($p < 0.05$ corrected) differences in brain morphology in the anterior cingulate cortex, cerebellum, the ventral striatum, the globus pallidus internus, paralimbic areas as well as the dorsolateral prefrontal and orbitofrontal cortex.

Conclusions: The findings of our study identified specific parts of the frontostriatal system that were altered in patients with OCD. The data of this homogenous study sample further define the structural brain alterations in OCD and may contribute to constraining the prevailing biological models of this disorder. Correlations of anatomical changes with relevant clinical variables will be discussed.

WS-04 Pathophysiological basis of disturbed working memory in neuropsychiatric disorders

WS-04-01
Working memory dysfunctions in psychiatric disorders: diagnostic value, genetic factors and compensatory neuroplasticity
O. Gruber (Homburg (Saar))

In schizophrenia but also in other psychiatric disorders, e. g. in bipolar affective disorder and in attention-deficit/hyperactivity disorder, working memory impairments are considered to be core deficits and potential endophenotypic markers. In this introductory talk, recent

findings of experimental neuropsychological, genetic and structural neuroimaging studies of working memory dysfunctions in major psychiatric disorders will be summarized. Overall, these studies reveal a remarkable heterogeneity within diagnostic groups regarding the presence or absence of working memory deficits. Nevertheless, there is preliminary evidence that specific dysfunctions of verbal and visuospatial working memory may be associated with genetic polymorphisms that impact on the serotonergic and dopaminergic system, respectively. Furthermore, recent investigations using voxel-based morphometry indicate that in psychiatric patients without manifest working memory deficits neuroplastic changes may occur in brain areas underlying specific working memory functions and may thus compensate for possible disturbances of these functions due to pathophysiological processes.

WS-04-02
Amygdala hyperactivity as pathophysiological correlate of working memory deficits in bipolar affective disorder
O. Gruber, B. Krauss, C. Braeman, I. Henseler, H. Scherk, P. Falkai, M. Rietschel (Homburg (Saar), Mannheim, Göttingen)

Recent evidence suggests that deficits of working memory may be a promising neurocognitive endophenotype of bipolar affective disorder. In the present fMRI study we assessed specific subcomponents of verbal working memory in euthymic bipolar patients. 14 euthymic bipolar patients and 14 healthy controls performed two modified versions of the Sternberg item-recognition task, one under single-task conditions and the other under articulatory suppression. These two tasks had been repeatedly demonstrated to activate two different brain systems that underlie the articulatory (rehearsal) and the non-articulatory component of verbal working memory. Bipolar patients showed a trend towards reduced performance in the articulatory rehearsal task. During performance of this task, only bipolar patients revealed a (presumably compensatory) co-activation of the prefronto-parietal network that is associated with the non-articulatory component of verbal working memory. Furthermore, in contrast to healthy control subjects bipolar patients exhibited additional activations of the amygdala during performance of both types of working memory tasks. The present results thus suggest an impairment of the articulatory rehearsal mechanism in euthymic bipolar patients which may be related to the abnormal amygdala activations observed in these patients.

WS-04-03
Compensatory hyperactivations as markers of latent working memory dysfunctions in obsessive-compulsive disorder
I. Henseler, S. Kraft, C. Krick, W. Reith, P. Falkai, O. Gruber (Homburg, Homburg/Saar)

Prior studies indicated that OCD is associated with deficits in working memory (WM), but the findings are inconsistent. This inconsistency could be explained by the ability of some patients to compensate for disturbances in WM. To test this hypothesis we investigated selected patients with OCD and healthy controls during performance of different WM tasks with fMRI. 11 OCD patients and 11 controls matched for WM performance were investigated during performance of a spatial and two verbal WM tasks which had been previously proven to reliably activate different domain-specific networks of WM. In each of the WM tasks, patients activated the same set of brain regions as did the healthy controls. Yet, direct statistical comparisons between groups revealed significantly enhanced brain activation in OCD patients both during the two verbal tasks (left inferior frontal junction area (IFJA), left frontal opercular cortex and middle third of the left inferior frontal gyrus) and during the spatial WM task (left IFJA). The present data support the notion that WM is dysfunctional in OCD by providing evidence that even those patients, who do not show a deficit in behavioral performance, exhibit abnormal activations in regions known to underlie WM. These hyperactivations may allow those patients to compensate for latent WM dysfunctions and may thus serve as markers of such dysfunctions.

WS-04-04
Dysfunctional activity of the neural correlates of working memory in Parkinson's Disease
E. Kraft, E. Bincer, D. Lule, O. Gruber (Munich, Ulm, Homburg)

Parkinson's Disease (PD) is characterized by motor symptoms. In addition, frequently working memory deficits are present. We used fMRI to assess the verbal and the visuo-spatial domains of working memory in PD under articulatory suppression. 9 patients diagnosed with PD (Hoehn/Yahr stages I–II) underwent fMRI twice while performing a modification of the Sternberg-Item recognition paradigm. fMRIs were carried out after dopaminergic medication had been withdrawn for at least 12 hrs (off-state) and one hour after administration of 200 mg levolopa (on-state). Patients with PD showed during performance of the verbal WM task reduced activity within the left middle frontal gyrus (area corresponding to the dorsolateral prefrontal cortex), right cerebellum and left posterior part of the inferior temporal gyrus. These reduced activities were partly reversibel after levodopa administration. Our findings indicate dysfunctional activity in PD during verbal WM task performance. Further studies should intend to characterize more precisely subgroups of patients with dysfunctional network activity during WM performance and study the predictive value of these dysfunctions to the risk to develop dementia.

WS-05 Structural, functional and neurometabolic changes in affective disorders: Clinical implications and new research results

WS-05-01
Imaging technics in the daily routine diagnostics
M. Gastpar (Essen)

The progress in neuro imaging technics asks for a currant definition, what is used in daily procedures and what is still part of scientific development. This is specially important in spite of the fact, that the health costs are still increasing and have to be restricted by political and budged reasons. Within the catalog of psychiatry diagnostics imaging technics are one of the most expensive tools and therefore guidelines are needed for there reasonable use. Here the recent guidelines of the respective professional societies are presented and discussed. In addition special attention is given to new technics, which are actually just on the door of eventually being used for routine procedures.

WS-05-02
Morphometric brain abnormalities in uni- and bipolar depression: Findings and models
L. Tebartz van Elst (Freiburg)

Introduction: Numerous studies have addressed the issue of morphometric brain abnormalities in uni- and bipolar depression. In this paper we want to review and summarize the respective literature with special focus on uni- and bipolar depression. Also we want to discuss possible models integrating these findings into a more general theory of the neurobiology of depression.

Method: A literature review has been performed in order to identify the respective studies. The results are summarized and presented separately for uni- and bipolar depression.

Results: There are few studies published in the literature with purely negative findings. Morphometric alterations have been reported for many different brain areas including the amygdala, hippocampus, basal ganglia, thalamus, cerebellum, prefrontal and temporal brain areas. Many findings are not reliably replicated and often they are even contradictory in uni- as well as bipolar depression.

Discussion: Analysing brain abnormalities in affective disorder based on a categorical concept results in contradictory and inconsistent findings. Alternative research strategies must be developed in order to improve the quality of the findings.

WS-05-03
Explicit and implicit facial affect recognition in patients with major depression and healthy controls: A functional magnetic resonance imaging study
T. Frodl, J. Albrecht, N. Koutsouleris, J. Scheuerecker, A. M. Rezezika, J. Linn, H. Brückmann, H.-J. Möller, E. Meisenzahl (Munich)

Background: Functional imaging studies have led to the postulation of a putative dysfunction in prefrontal-amygdalar-pallidostriatal-mediothalamic mood regulation circuits in the pathophysiology of major depression. The aim of the present study was to investigate dysfunctions of the mood circuit in patients with depression.

Method: 12 patients with major depression and 12 healthy controls underwent functional and structural MRI using a 1.5 Tesla Magnetom. During the fMRI an explicit facial affect recognition task and an implicit facial affect recognition task were recorded. Each emotion block consists of six images expressing the affect sadness, three of each gender, all derive from a standard set of pictures of facial affect (Ekman and Friesen, 1976), presented sequentially for 5 s. After each emotion block a simple figure discrimination task was shown, which was equally built than the emotion task. Data are analyzed with the software program SPM99.

Results: Enhanced amygdala and anterior gyrus cinguli activity as well as reduced activity in the prefrontal cortices is expected for patients with major depression as compared to healthy controls.

Discussion: F-MRI with a facial affect paradigm is a good tool for studying correlates of mood regulation. It may be clinically relevant, because it might be used as a marker for the clinical outcome.

WS-05-04
MR spectroscopic investigations of neurometabolic changes in depressed patients
G. Ende (Mannheim)

A decreased signal of choline containing neurometabolites in the hippocampus of depressed patients was detected with proton MR spectroscopic imaging (1H MRSI). Following electroconvulsive therapy an increase of this signal was observed. In recent studies we could corroborate the finding of decreased hippocampal choline with 1H MRS. We furthermore observed a decreased glycerophosphorylcholine with proton decoupled 31P RINEPT MRSI. An opposing change of choline containing neurometabolites was observed in the basal ganglia region where an increased choline signal was found in depressed patients. The 31P RINEPT MRSI yielded an increased glycerophospoethanolamine in this brain region in MDD. It can be speculated, that deficits in hippocampal synaptogenesis as predicted by the neurotrophin hypothesis lead to compensatory functional alterations in other regions within the LCSPT circuit. Striatal synaptic and/or membrane alterations (here: possibly an increased membrane turnover) are then reflected in a detectable choline rise.

WS-06 Motor development and cortical excitability in ADHD

WS-06-01
Altered inhibitory brain processes in ADHD
A. Fallgatter (Würzburg)

Deficits in response inhibition are considered as candidate endophenotypes of altered prefrontal brain function in Attention Deficit Hyperactivity Disorder (ADHD). We employed a multi-channel EEG during performance of a Go-NoGo task to assess the electrophysiological basis of response inhibition in healthy subjects as well as in patients with ADHD. The ERP-measure derived from this protocol was termed NoGo-Anteriorisation (NGA) and is characterized by a high interindividual stability, high short- and long-term test-retest reliability and, moreover, is independent from age- and gender. In patients with ADHD during childhood and adulthood the NGA was diminished as compared to age- and sexmatched healthy controls. Furthermore, a three-dimensional source location analysis with LORETA indicated an electrical dysfunction of the ACC in the patient groups. Additionally, disturbances in inhibitory brain functions are also indicated by preliminary double pulse Transcranial magnetic stimulation (TMS) measurements in ADHD patients. These results exemplify the measurement of disease related disturbances in brain function in ADHD with ERPs and TMS. Future studies will show whether such electrophysiological endophenotypes may contribute to the diagnosis of subgroups of ADHD and whether they may serve as endophenotypes to further clarify genetic contributions to the disease.

WS-06-02
Transcranial magnetic stimulation (TMS) in children with Attention Deficit-/Hyperactivity Disorder (ADHD)
J. Buchmann, W. Gierow, S. Weber, S. Herpertz, F. Hässler, J. Höppner (Rostock)

Motor hyperactivity is one of the most outstanding symptoms of attention deficit hyperactivity disorder (ADHD) which might be caused by a disturbed inhibitory motor control. Using focal TMS we tested inter- and intracortical inhibition and fazilitation (iSP, SICI, ICF, LICI) in 18 ADHD children pre- and post medication with methylphenidate (MPH) compared with a sex- and age-matched control group. ADHD children showed both, a decreased motorcortical inhibition (SICI, iSP) and also a decreased motorcortical fazilitation (ICF), which was normalized by MPH (analysis of variance and ANCOVA). Simultaneous Conners-Score reduction by MPH was correlated with improved SICI and iSP duration, not with ICF. A dopaminergic dysregulation responsive to MPH treatment in ADHD seems to be part of the disease's pathophysiology. As underlying physiological mechanism we propose an indirect effect of MPH on the activity of cortical interneurons via a dopaminergic striatal drive within the striato-thalamo-cortical loop modulating the inhibitory motorcortical neuronal circuits.

WS-06-03
Transcranial magnetic stimulation in adults with Attention Deficit/ Hyperactivity Disorder (ADHD)
J. Höppner, W. Gierow, S. Herpertz, F. Haessler, J. Buchmann (Rostock)

Motor system excitability can be investigated in vivo by means of single and paired pulse transcranial magnetic stimulation (TMS). Several TMS-paradigms reflect inhibitory or facilitatory mechanism in the motor cortex: 1. cortical silent period (CSP) the general degree of inhibitory mechanisms within the sensorimotor loop, 2. intra-cortical inhibition (ICI) and facilitation (ICF) the excitability within one motor cortex and 3. ipsilateral silent period (ISP) the inhibitory mechanism between both motor cortices. Hyperactivity is one of the most outstanding symptoms of ADHD, it seems to be reduced in adults. In childhood several dysfunctional patterns of motor system excitability could be demonstrated by TMS experiments. Such investigations were not published for adult ADHD patients. We investigated adults with ADHD and compared them with an age- and sex-matched control group. The investigation was repeated after a stable dose of MPH. While ICI and ICF were not significantly changed in patients, ISP findings in adult patients with ADHD were similar to ISP findings in children and showed a prolonged latency and decreased duration. In contrast to results in childhood, MPH did not improve the deficitary ISP. These data suggest that ISP could be a solid neurobiological characteristic of deficient inhibitory motor control in child- and adulthood ADHD.

WS-06-04
Dysfunction of GABA-mediated inhibitory processes in patients with adult ADHD
P. Eichhammer, B. Langguth, R. Laufkoetter, P. Sand, G. Hajak (Regensburg)

Attention-deficit/hyperactivity disorder (ADHD) is a common, early-onset neurodevelopmental disorder marked by difficulties in organizing tasks, inattention to details, and hyperactivity. While overactivity is usually attenuated over time, other hallmarks of ADHD often

persist into adulthood leading to significant psychosocial impairment. In affected adults, ADHD may account for lower socioeconomic status, poorer academic performance and more frequent divorces as compared to the respective measures in healthy subjects (Wilens & Dodson, 2004). There is ample proof of dysfunctional inhibitory cortical processes which my mediate clinical signs of this syndrome. Transcranial magnetic stimulation (TMS) has emerged a feasible tool to proof distinct parameters of cortical excitability in vivo. Using this neurophysiological technique we studied 24 adult patients with ADHD before and after receiving methylphenidate over a longer time-period. Compared to an age- and sex- matched control sample adult patients with ADHD displayed a significantly prolonged cortical silent period (CSP) which is known to reflect especially GABA-B-mediated inhibitory mechanism, preferentially at the level of the thalamus. Methylphenidate was able to correct selectively theis prolonged CSP additionally pointing to the involvement of GABA-B-mediated effects both in the aetiology and therapy of adult ADHD.

WS-07 Estrogens and Alzheimer's dementia – Recent developments

WS-07-01
Estrogens and Alzheimer's disease – what's new?
C. Behl (Mainz)

Estrogens have been described as effective neuromodulatory and neuroprotective molecules. Neuroprotective activities can be mediated directly by estrogens' interaction with neurotransmitter receptors or indirectly by increasing the expression of neurotrophic factors or even by effects on glial functions. In addition direct biochemical effects of the phenol estradiol has been described indicating that estradiol is also a neuroprotective antioxidant. As convincing as the data are supporting a powerful neurotrophic role of estrogens as inconsistant is the knowledge concerning the clinical situation. In various retrospective studies the application of estrogens in postmenopausal women has been shown to be beneficial to suppress estrogen deficit effects on neuronal functions including memory formation. On the other hand prospective clinical trials employing estrogen in replacement therapy did not support a role for estrogens in preventing memory loss and Alzheimer's disease (AD). As usual many criticisms have been raised with respect to the retrospective and prospective epidemiological and clinical investigations and no clear cut judgement can be drawn currently. Finally it has to be considered that on average women live approximately 40 % of their life after the age of menopause and therefore in an estrogen depletion status.

WS-07-03
Estrogen use and Alzheimer's Dementia: Prevention vs. therapy
C. Luckhaus (Düsseldorf)

Data from basic science studies suggest positive estrogen (E2) effects in CNS regions subserving cognition by neuroprotective, connectivity-enhancing and neurotransmitter-modulatory mechanisms. E2 application in middle-aged healthy women has been shown to positively affect memory tasks that show gender difference. Also, prospective observational studies suggest that E2-containing hormone therapy (E2-HT) in pre- and perimenopausal women reduces the risk for Alzheimer's dementia (AD) by up to 50 %. The recent Women's Health Initiative Memory Study, however, cautioned the notion of universal beneficience of E2-HT, as combined E2 and progesterone treatment in elderly women was associated with an increased incidence of breast cancer, ischemic stroke and all-cause dementia. Also, clinical pioneer studies empolying E2-monotherapy in female patients of advanced age with moderately severe AD could not demonstrate antidementive therapeutic effects. On the other hand, limited data on E2 as an add-on treatment suggested cognitive enhancement also in AD. In conclusion, the benefit of E2 use may largely relate to neuroprotective mechanisms in pre-dementia conditions. E2 may thus have a particular potential for preventive or early interventive strategies. Timing of initiation, type of drug formulation and type of cognitive functions to be treated may be crucial to efficacious E2 use.

WS-07-04
Benefits and risks of postmenopausal hormone replacement therapy
O. Ortmann (Regensburg)

Kaum eine medikamentöse Behandlung ist in den letzten Jahren so kontrovers diskutiert worden wie die Hormontherapie mit Östrogenen und Gestagenen im Klimakterium und in der Postmenopause. Jüngere randomisierte placebokontrollierte Studien wie die WHI und Beobachtungsstudien wie die Million Women Study haben zum Teil neue und unerwartete Ergebnisse erbracht und bekannte Erkenntnisse untermauert. Unbestritten ist die positive Wirkung der Behandlung auf klimakterische Beschwerden, deren Kardinalsymptome Hitzewallungen und Schweißausbrüche sind. Damit assoziierte Symptome können ebenfalls durch die HT positiv beeinflußt werden. Diese Wirkungen konnten eindeutig in placebokontrollierten klinischen Studien belegt werden. Keine andere Therapie ist in der Lage diese Symptome so effektiv zu behandeln. Eine weitere Indikation der HT besteht in der Behandlung der Urogenitalatrophie. Auch hier sind die Ergebnisse aus verschiedenen Studien, die die lokale oder systemische Östrogenbehandlung untersuchten, eindeutig. Der Nutzen der Therapie ist klar erwiesen. Widersprüchlich ist die Datenlage bezüglich des Nutzens der HT im Hinblick auf die Harninkontinenz und Harnwegsinfekte. Die Hormontherapie hat eindeutig positive Wirkungen in der Prävention und Behandlung der Osteoporose. In der WHI wurde erstmals in einer plazebokontrollierten Studie gezeigt, daß auch das Schenkelhalsfrakturrisiko um ca. 35 % reduziert werden konnte. Diese Effekte können sowohl mit Östrogenmonotherapie als auch mit Östrogengestagenkombinationen erzielt werden. Thromboembolische Erkrankungen treten unter einer HT etwa doppelt so häufig auf wie bei Nichtanwenderinnen. Besonders zu berücksichtigen ist diese Nebenwirkung bei Frauen mit einer Disposition für Thromboembolien. Deren Risiko kann beispielsweise bei prothrombotischen Mutationen 15fach erhöht sein. Auch Schlaganfälle treten sowohl unter Monotherapien als auch kombinierten HTs häufiger als bei Nichtanwenderinnen auf. Das Risiko ist um ca. 40 % erhöht. Problematisch ist die Bewertung der Datenlage zu kardiovaskulären Erkrankungen. In der Vergangenheit wurde aufgrund von verschiedenen experimentellen und präklinischen Untersuchungen vermutet, daß Östrogene das Risiko für kardiovaskuläre Erkrankungen (Hypertonie, koronare Herzkrankheit) reduzieren können. Eine Reihe von Beobachtungsstudien haben diese Vermutung bestätigt und den breiten Einsatz der HT unterstützt. Die WHI sowie einige sorgfältig durchgeführte Metaanalysen ergaben allerdings keinen protektiven Effekt auf die koronare Herzkrankheit. Unter einer Östrogengestagentherapie war das Risiko in der WHI sogar geringgradig erhöht. Einige jüngere Untersuchungen weisen darauf hin, daß vaskulär gesunde Frauen möglicherweise von einem frühzeitigen Einsatz einer niedrig dosierten Östrogenbehandlung profitieren. Dies wird derzeit in prospektiven Studien untersucht. Bis zur Vorlage dieser Studienergebnisse sollte die HT allerdings nicht mit dem Ziel der kardiovaskulären Prävention eingesetzt werden. Da die in den Anfangsphasen der HT durchgeführte Monotherapie mit Östrogenen hat zu einem deutlichen Anstieg von Endometriumkarzinomen geführt. Durch einen adäquaten Gestageneinsatz kann die östrogeninduzierte Entwicklung eines Endometriumkarzinoms allerdings verhindert werden. Anwenderinnen einer korrekt durchgeführten kombinierten HT haben im Vergleich zu Nichtanwenderinnen kein erhöhtes Endometriumkarzinomrisiko. Die Monotherapie mit kombinierten Östrogenen führte in der WHI nicht zu einer Erhöhung, unerwarteter Weise sogar zu einer leichten Erniedrigung des Brustkrebsrisikos. Die Ursachen die für diese eher unplausible Beobachtung müssen geklärt werden. Jüngere, sehr sorgfältig durchgeführte Metaanalysen führten zu einer realistischen Bewertung der Datenlage. Eine Monotherapie mit Östrogenen führt auch nach mehrjähriger Anwendung nur zu einer geringgradigen Steigerung des Risikos für ein Mammakarzinom. Demgegenüber führt die kombinierte Therapie mit Östrogenen und Gestagenen zu

einer Steigerung des Brustkrebsrisikos auf ein relatives Risiko von ca. 1,6 bis 2. Das Risiko für kolorektale Karzinome kann durch eine Hormontherapie reduziert werden. Zusammenfassend kann festgehalten werden, daß die HT wichtige Nutzen hat. Die Risiken müssen allerdings bei der Indikationsstellung berücksichtigt werden.

WS-08 Non-pharmacological therapy in depression – News from therapeutic sleep withdrawal and transcranial magnetic stimulation

WS-08-03
Effects of selective REM sleep deprivation on depressive symptoms as related to the ultradian sleep cycle
M. Grözinger, J. Röschke (Aachen, Kiedrich)

Selective REM sleep deprivation (SRSD) is supposed to improve depressive symptoms. A strong challenge is imposed on the generator of the ultradian rhythm when repeatedly prevented from initiating REM sleep. A study on SRSD revealed interesting relationships between the therapeutic effects of two awakening paradigms and their impact on the ultradian cycle. In 10 consecutive nights short awakenings were applied to 27 depressed patients randomly assigned to two groups. In the first awakenings were initiated on every occurrence of REM sleep. In the second an equal number of awakenings was applied during nonREM sleep. The parameters of the ultradian cycles were correlated with the outcome after the treatment period. In the first group the awakenings accelerated the ultradian alternations while they slowed down in the second. In both cases a significant correlation was found between the outcome in HAMD scores after 10 nights and the duration of the first nonREM – REM cycle under treatment. If this duration remained rather unchanged despite the awakenings the outcome of patients was rather good. Our results might indicate that the strength of the cycle generator to resist the awakenings reflects an ability of the system to recover from depression. The procedure might allow a prognosis for sleep deprivation therapy or even be an indicator for the severity of the disease.

WS-08-04
Metabolic alterations after repetitive transcranial magnetic stimulation in patients with unipolar major depression
M. Bajbouj (Berlin)

Neuroimaging studies suggest a specific role of anterior cingulate cortex (ACC) and left dorsolateral prefrontal cortex (DLPFC) in major depression. Stimulation of the latter by means of repetitive transcranial magnetic stimulation (rTMS) as an antidepressant intervention has increasingly been investigated in the past. The objective of the present study was to examine in vivo neurochemical alterations in both brain regions in 17 patients with unipolar major depression before and after 10 days of high-frequency (20Hz) rTMS of the left DLPFC using 3-tesla proton magnetic resonance spectroscopy. Six out of seventeen patients were treatment responders, defined as a 50 % reduction of the Hamilton depression rating scale. No neurochemical alterations in the ACC were detected after rTMS. As compared to the non-responders, responders had lower baseline concentrations of DLPFC glutamate which increased after successful rTMS. Correspondingly, besides a correlation between clinical improvement and an increase in glutamate concentration, an interaction between glutamate concentration changes and stimulation intensity was observed. Our results indicate that metabolic, state-dependent changes within the left DLPFC in major depressive disorder involve the glutamate system and can be reversed in a dose-dependent manner by rTMS.

WS-08-05
Results of pacebo-controlled multicenter trials investigating the antidepressant effect of transcranial magnetic stimulation
U. Herwig, A. Fallgatter, J. Höppner, G. W. Eschweiler, G. Hajak, F. Padberg, A. Naderi-Heiden, M. Spitzer, C. Schönfeldt-Lecuona (Zürich, Würzburg, Rostock, Tübingen, Regensburg, Munich, Vienna, Ulm)

Objective: Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a new treatment option for depression. Respective previous studies were performed with low sample sizes in single centers and reported heterogeneous results.

Method: We performed a randomized double-blind sham-controlled multicenter trial to investigate the efficacy of rTMS as add-on treatment in depression. 127 patients with moderate to severe depressive episodes were included and randomly assigned to real or sham stimulation during three weeks in addition to parallel initiated antidepressant medication.

Results: We neither found a meaningful difference concerning the responder rates of both groups (real and sham each 31 %, primary efficacy variable), nor concerning the decrease of the rating scores in BDI, HAM-D and MADRS.

Conclusion: Our data do not support previous reports from smaller samples indicating an antidepressant effect of rTMS in medicated patients. Preliminary results of an American multicenter trial implied moderate effects in non-medicated treatment-resistant patients that are to be discussed in a common frame with our study. Further exploration of possible efficacy of other stimulation protocols or within selected subpopulations of patients is necessary. At this stage, an application of rTMS as antidepressant treatment is recommended solely in a scientific frame.

WS-09 Functional assessment of central monoaminergic neurotransmission – Clinical and therapeutic relevance in psychiatry

WS-09-01
Preclinical studies on the relationship between loundness dependence of auditory evoked potentials and the central serotonergic neurotranmission
G. Juckel, A. Wutzler (Bochum, Berlin)

A valid indicator of central serotonergic neurotransmission would be useful for various purposes in psychiatry. However, known peripheral serotonergic measures only partially reflect serotonergic function in the brain. Previous findings suggest that the loudness dependence of auditory evoked potentials (LDAEP) is closely related to central serotonergic activity. A study in cats examines the effects of microinjection of a 5-HT1A agonist (8-OH-DPAT) and a 5-HT1A antagonist (spiperone) into the dorsal raphe nucleus (DRN) on AEP recorded epidurally from the primary and secondary auditory cortex in behaving cats. We found a stronger LDAEP only from the primary auditory cortex after 8-OH-DPAT, which inhibits the firing rate of serotonergic DRN neurons, and a weaker intensity dependence after spiperone, which increases serotonergic cell firing, as compared to baseline measurements. In a recent study in rats, we found a close negative correlation between extracellular serotonin levels in the auditory cortex, as measured by in-vivo microdialysis, and the LDAEP recorded epidurally from the same area of the auditory cortex. These results demonstrate that the LDAEP is inversely related to serotonergic neuronal activity and that it may be a promising tool for assessing central serotonergic function in humans (e. g., identifying patients with low serotonergic neurotransmission).

WS-09-02
Central monoaminergic function as assessed by neurophysiological and functional neuroimaging techniques
O. Pogarell, K. Tatsch, C. Mulert, G. Leicht, R. Musil, W. Koch, M. Riedel, H.-J. Möller, U. Hegerl (Munich)

Alterations of monoaminergic neurotransmission have been suggested as pathophysiologically relevant for the development of neuropsychiatric disorders. Therefore the in vivo assessment of monoamine transmitter systems might be of particular scientific and clinical interest. Nuclear medicine (SPECT and iodine-123 radiolabelled IBZM, β-CIT or ADAM) and neurophysiological ("loudness dependence of auditory evoked potentials" – LD) techniques have been used as tools to investigate indicators of monoaminergic anatomy and function in healthy subjects and patients with neuropsychiatric disorders. Combined neurophysiological and SPECT studies revealed that both measures 1) are significantly correlated, 2) provide evidence of distinct neurochemical dysfunctions in different neuropsychiatric disorders, and 3) suggest that monoaminergic variables can be used as predictive tools for the patients' responses to pharmacotherapy. The combination of independent monoaminergic measures might help to comprehensively assess brain neurochemical function in vivo and thus to obtain multiple insights into the physiology and pathophysiology of neurotransmitter systems. There is increasing evidence that either technique provides clinically relevant information on the neurobiological background of neuropsychiatric disorders in terms of diagnostic and therapeutic properties.

WS-09-03
Experimental human challenge studies for central serotonergic system – Investigation of neurophysiological and neuropsychological aspects
C. Norra (Göttingen)

Monoaminergic challenges with the tryptophan depletion test (TDT) enable to conduct clinical studies under acute depletion of central nervous serotonin (5-HT) system. TDT in animal studies suggests an inverse influence on the 5-HT neurotransmission as represented by auditory evoked potentials to stimulus intensity (LD) or startle, while similar effects in humans remain mostly unconfirmed. However, various psychiatric disorders with assumed 5-HT dysfunction correlate to these neurophysiological measures. Studies with volunteers showed only a slight increase of LD with TDT depletion. Regarding auditory sensory gating and processing, TDT led to reduced startle amplitudes, but no change of prepulse inhibition. Short-term effects on mood and cognition will also be presented. Thus, despite strong depletion the findings provide only minor arguments for a 5-HT modulation on auditory neurophysiological measures in contrast to some of the recent neuropsychological data. As opposed to other selective challenges with e. g. SSRI, interactions of TDT with further transmitter systems have to be discussed. Previous animal findings or clinical observations will have to be re-evaluated in respect to the complex neuroanatomy and pharmacology of 5-HT receptors.

WS-09-04
Theta activity of the rostral ACC and loudness dependence of the auditory evoked potential as predictors of treatment response in major depression
C. Mulert, G. Juckel, M. Brunnmeier, S. Karch, G. Leicht, R. Mergl, H.-J. Mölller, U. Hegerl, O. Pogarell (Munich)

Two promising approaches have been introduced for the prediction of treatment response in major depression: One concept is based on the activity in the rostral anterior cingulate cortex (rACC). Subjects with higher metabolic rates respond better to sleep deprivation or antidepressive medication. Another approach is the investigation of the loudness dependence of the auditory evoked potential (LDAEP). Here, a high LDAEP is supposed to reflect low central serotonergic activity. We present the first study comparing both approaches in the same group of patients. Patients with major depression ($n = 20$) were investigated with using both resting EEG and LDAEP before treatment with either citalopram or reboxetine. We found significant differences between responders and non-responders in the rACC in the theta-frequency range (6.5–8 Hz, $p < 0.05$). In the subgroup of patients treated with citalopram we found higher LDAEP-values in responders versus non-responders ($p < 0.05$) and a significant correlation between pre-treatment-LDAEP and improvement in the Hamilton score after treatment ($r = 0.71$, $p < 0.05$). In combining both methods a prediction whether a patient with major depression might be at risk for non-response to a standard therapy as well as a suggestion for a pharmacological approach of choice seems to be possible.

Oral Presentation

V-01 Imaging

V-01-01
Magnetic resonance imaging of the thalamus and adhesio interthalamica in twins with schizophrenia
U. Ettinger, S. Landau, K. Matsumoto, N. van Haren, N. Marshall, T. Toulopoulou, N. Davies, R. Murray, M. Picchioni (London)

Thalamic abnormalities are thought to be central to the pathophysiology of schizophrenia. These abnormalities include altered structure of the thalamus itself and possibly changes to the adhesio interthalamica. However, it is not clear to what extent these abnormalities are determined by the genetic liability for schizophrenia. We used structural magnetic resonance imaging (MRI) to investigate thalamic volume and the presence of the adhesio interthalamica in monozygotic (MZ) twins concordant or discordant for schizophrenia. 123 twins took part: 19 MZ twin pairs concordant for schizophrenia, 15 MZ schizophrenic twins and 16 MZ non-schizophrenic twins drawn from 17 pairs discordant for schizophrenia, and 27 MZ pairs without schizophrenia. Groups were matched for age, gender, handedness, education, parental socio-economic status, and ethnicity. Concordant twin pairs displayed significantly reduced thalamic volume compared to control twins, even when covarying for whole-brain volume, age, and gender. There was a significant linear decrease in thalamic volume indicating control > discordant non-schizophrenic > discordant schizophrenic > concordant. There was no difference across groups in the frequency of the adhesio interthalamica. These findings suggest that volumetric thalamic abnormalities may mark the substantial genetic contribution to the illness in concordant twin pairs.

V-01-02
Mineralocorticoid receptor function in post-traumatic stress disorder
M. Kellner, C. Muhtz, A. Yassouridis, K. Wiedemann, C. Otte (Hamburg, Munich)

The function of glucocorticoid receptors has been extensively studied in patients with post-traumatic stress disorder (PTSD) to further elucidate alterations of their hypothalamic-pituitary-adrenocortical system activity. However, no investigations have characterized whether mineralocorticoid receptors (MR), that mediate its tonic inhibition in the limbic system, are involved as well. Recently, a preclinical study has shown that hippocampal MR increase after psychological stress corticotropin releasing-hormone (CRH)-dependently (Gesing et al. 2001). In two pilot studies, we tested MR function in patients with chronic PTSD and matched healthy controls. In the first study, the effects of the MR antagonist spironolactone on ACTH and cortisol secretion before and after a CRH stimulus were investigated (Kellner et al. 2002). In the second study, subjects received the MR agonist fludrocortisone after pre-treatment with metyrapone and we measured ACTH and cortisol secretion (Otte et al. 2006). Both studies indicated intact, but not enhanced, MR function in PTSD. Limitations of the studies include the small sample sizes, aspects of dosing and timing of the challenges applied, potential masking of MR antagonist effects by concurrent GR activation, and additional affinities of

spironolactone and fludrocortisone for steroid receptors other than the MR.

V-01-03

Dysfunction of the reward system correlates with alcohol craving in detoxified alcoholics

J. Wrase, T. Kienast, B. Knutson, A. Heinz, F. Schlagenhauf (Berlin)

Objective: Alcohol dependence is associated with dysfunction of the brain reward system, so that nonalcoholic reward cues fail to activate the ventral striatum, while alcohol cues continue to activate it. Alcoholics may then crave the effects of alcohol in order to stimulate the dysfunctional reward system.

Methods: 16 detoxified male alcoholics and 16 matched healthy volunteers participated in two fMRI paradigms. In the first one alcohol-associated and affectively neutral pictures were presented, where as in the second one a monetary incentive delay task (MID) was performed. For both paradigms the association with alcohol craving was assessed.

Results: Compared to healthy volunteers, detoxified alcoholics failed to activate the ventral striatum during the expectation of monetary reward. However, alcoholics did show increased activation of the ventral striatum when confronted with alcohol cues. Reduced activation in the ventral striatum during expectation of monetary reward, and increased activation during presentation of alcohol cues were correlated with alcohol craving in alcoholics, but not in healthy controls.

Conclusions: Our results suggest that the reward system in alcoholics is biased towards processing of alcohol cues. This might explain why alcoholics find it particularly difficult to focus on conventional reward cues and engage in other rewarding activities.

V-01-04

Serotonergic genes and adverse childhood environment increase the risk for violent behavior: evidence for gene by environment interactions

W. Retz, A. Reif, P. Retz-Junginger, M. Schneider, J. Thome, K.-P. Lesch, M. Rösler, C. Freitag (Homburg/Saar, Würzburg, Swansea)

The present study aimed to identify the contribution of polymorphisms of the serotonin transporter and MAO-A genes to the development of violence and to test for a possible gene x environment interaction with regards to adverse childhood environmental conditions. 184 adult male, caucasian volunteers referred for forensic examination were assigned to a violent and a nonviolent group. The participants were rated regarding childhood environment using a standardized instrument. In each individual, DNA was analysed by PCR for the 5HTTLPR and the MAO-uVNTR promoter polymorphisms. In univariate analysis violent behavior was associated with more adverse childhood environment (mean score 0.44 ± 0.57 vs. 0.69 ± 0.59; $p = 0.002$). 45 % of violent, but only 30 % of nonviolent probands carried the short MAO-A allele ($Chi^2 = 4.22$; $p = 0.040$). In the violent group, 5HTTLPR ss/ls genotypes were found in 77 %, compared to 59 % in the non-violent group ($Chi^2 = 5.87$; $p = 0.015$). Multivariate analysis revealed an independent effect of childhood environment and MAO-A genotype. In addition, a significant influence of an interaction between childhood environment and 5HTTPLR on violent behavior was found. No independent effect for the 5HTTLPR genotype and no gene x gene interactions were found. These findings provide evidence for gene x environmental interactions in the development of disruptive behavior.

V-01-05

Polysomnographic longterm assessment of patients with Alzheimer and frontotemporal dementia

A. Thum, R. Rocamora, M. Giesler, A. Haag, A. Becker, T. Penzel, J.-C. Krieg, U.-M. Hemmeter (Marburg, Reus)

Beside the cognitive impairment patients with dementia present with a sleep-wake rhythm disturbance. To date very few studies evaluated sleep disturbance in different classes of dementia. In 22 patients with Alzheimer's dementia (DAT) and 8 with frontotemporal dementia (FTD) who were free of psychotropic medication a polysomnography was performed. A subgroup of this sample 5 men, 2 women (age 68.1 ± 8.0, MMSE 23.0 ± 4.2) with DAT and 4 men, 2 women, age (56.8 ± 10.6, MMSE 23.4 ± 3.7) with FTD who were on monotherapy with a cholinesterase inhibitor (Che-I) could be re-examined after several months. In all patients a marked sleep continuity disruption was observed. Patients with DAT presented with a REM sleep reduction in comparison to FTD. Treatment with Che-I did not improve sleep continuity. REM-sleep increased in patients with DAT, but not in patients with FTD. The prevalence of sleep disorders in patients with primary dementias is clearly higher as previously suspected. The observed REM-sleep reduction in patients with DAT compared to FTD may suggest that cholinergic neurotransmission is more impaired in DAT than in FTD. However, it remains unclear whether the increase of REM-sleep after long-term treatment with Che-I in DAT may reflect a mere pharmacological effect or whether this increase may be related to the efficacy of anti-dementia treatment.

V-01-06

Mapping effects of sleep deprivation on basic cognitive performance: A combined EEG/fMRI study

M. Czisch, R. Wehrle, P. Sämann, H. Harsay, T. C. Wetter, F. Holsboer, S. P. Drummond (Munich, San Diego)

Detrimental effects of sleep deprivation on cognitive performance are correlated to regional alterations of activity in various brain areas. Aim of the present study is to elucidate the effect of 36 hrs of total sleep deprivation (SD) on basic cognitive performance employing combined EEG/fMRI measurements to allow for vigilance monitoring and ERP extraction. 20 subjects have performed cognitive tasks including an active acoustic oddball task twice, once after a well-rested night (NN) and once after SD. Whole brain fMRI data were acquired from 19:30 onwards on a 1.5T GE scanner. The simultaneous EEG recordings revealed fluctuations in vigilance states which do not necessarily lead to notable alterations in response times but may strongly affect the BOLD signal by intrusion of sleepiness. Analysis focussing exclusively on oddball trials without signs of alterations in vigilance during the run showed increased activation after SD compared to NN in the bilateral cingulate and frontal cortex, and in the putamen. These activation may comprise increased recruiting of task specific activation centres, additional compensatory areas as well as the "default mode brain network", reflecting unspecific disengagement from the task.

V-01-07

MR-Morphometric changes and their association with neuropsychological performance in patients with mild cognitive impairment

V. Dos Santos Pedro, P. A. Thomann, U. Seidl, P. Schönknecht, F. I. Giesel, P. Toro, M. Essig, J. Schröder (Heidelberg)

Introduction: The objective of this study is to reveal the associations of structural cerebral alterations with neuropsychological deficits in patients with mild cognitive impairment (MCI).

Methods: 53 patients with MCI, 26 patients with mild AD and 30 healthy controls underwent structural magnetic resonance imaging (1.5 Tesla). We use optimized voxel-based morphometry (VBM) to investigate (a) differences in gray matter (GM) density between the three groups and (b) the putative relation of neuropsychological performance (CERAD) to specific structural alterations.

Results: In relation to healthy comparison subjects, loss of GM density in MCI subjects was accentuated in the temporal lobe (both neocortical fields and substructures of the medial temporal lobe) and in parietal regions. Congruent results were revealed when control subjects were compared to patients with AD, indicating that MCI indeed represents its preclinical stage. We are currently analyzing the associations between GM density and several scores in neuropsychological performance; results will be presented at the congress.

V-01-08
The role of dissociation in memory processes in PTSD – Evidence for a disturbed fronto-limbic network
C. Amrhein, D. Huber, R. Engel, M. Reiser, H.-J. Möller, K. Fast, T. Meindl (Muenchen, Munich)

Dissociation is an important characteristic of PTSD and seems to play a major role in the development and maintenance of the disorder. Dissociation may be one of different strategies to keep traumatic contents away from consciousness, but it might also hinder integration of traumatic experiences into autobiographical memory. Using a divided attention paradigm, we aimed to examine the role of frontal and limbic areas during encoding vs. suppressing trauma-relevant word stimuli when attention is distracted. 13 PTSD patients and 13 healthy controls performed the task while fMRI activity was registered on a 1.5T-MR scanner (Vision, Siemens) using BOLD-sensitive EPI-sequences. Results on recognition performance indicated that during divided attention, a standard "directed forgetting" effect was observed in healthy controls for both neutral and trauma stimuli, while in PTSD patients, this effect was absent for trauma stimuli. fMRI data for healthy controls revealed an activation of parahippocampal areas during "encoding" trauma words and an activation of the ACC during "suppressing" them. In PTSD patients, however, the medial PFC and the amygdala were activated during encoding, the insula during suppressing traumatic content. These findings are in accordance with a disturbance in the control of memory processes in PTSD, being related to a disturbance in fronto-limbic areas.

V-02 Neuropsychology and TMS

V-02-01
Assessing storage and retrieval deficits in patients with mild cognitive impairment (MCI) and healthy elderly: A multinomial model vs. neuropsychological assessment
K. Fast, A. Aigner, S. Teipel, H. Hampel, R. Engel, H.-J. Möller, A. Bröder (Munich)

In common assessment of memory parameters drawn from processes of encoding and retrieval are often confounded. Consequently, a process-related interpretation of memory impairments in neurodegenerative diseases is limited. Multinomial processing tree models can be used as a tool to determine memory deficits in clinical populations and normal aging beyond standardized measurement by seperating storage and retrieval processes. We focused on processes of encoding and retrieval of verbal information, using the validated multinominal measurement model of Batchelder and Riefer (1980; 1996) that allows to disentangle these processes. Patients with mild cognitive impairment (MCI) and a group of young and elderly participated in the study. A 40-item word list was presented six times with interposed free recall. Finally a recognition test were administered. An additional comprehensive neuropsychological test battery, including the California Verbal Learning Test (CVLT), was given. The comparison of neuropsychological and model based data supports the potential use of the multinomial model for early diagnosis of progredient memory decline in dementia.

V-02-02
Amisulpride doses and plasma levels in the treatment of different target syndromes of schizophrenia
M. J. Müller, B. Regenbogen, C. Hiemke (Nieder-Olm, Mainz)

In controlled trials amisulpride (AMI) was effective at higher doses for positive (POS) and negative symptoms (NEG) of acute schizophrenia, and at low doses for predominantly NEG. This naturalistic study investigated syndrome-specific effects of AMI in schizophrenia. 130 patients with a specified schizophrenic target syndrome (POS 78 %, NEG 22 %) treated with AMI (100–1550 mg) were included (42 % female, 19–69y). Plasma levels, clinical improvement (CGI), side-effects, and comedication were assessed. Daily AMI doses and plasma levels were lower ($P < 0.01$) for NEG (563 ± 225 mg; 226 ± 173ng/ml) than for POS (710 ± 286 mg; 352 ± 280ng/ml); responder rates were similar (POS 73 %; NEG 61 %). NEG-responders had lower ($P < 0.05$) AMI plasma levels (210 ± 190ng/ml) than non-responders (280 ± 148ng/ml); AMI doses were similar. AMI doses and plasma levels were not different between responders and non-responders with POS. No significant results were obtained regarding side-effects and comedication. Patients with clinically defined NEG received lower AMI doses than patients with POS. However, NEG-responders had significantly lower AMI plasma levels than non-responders, whereas AMI doses were comparable. This finding underlines the usefulness of TDM of AMI, particularly in patients with NEG, and supports the concept of a dose-dependent syndrome-specific effectiveness of AMI in schizophrenia.

V-02-03
The influence of reward-dependent mental effort increase on brain function and cognitive performance: A simultaneous 61-channel EEG/fMRI study comparing schizophrenic patients and healthy controls
G. Leicht, I. Giegling, V. Kirsch, K. Körner, M. Lang, F. Sokollu, D. Rujescu, C. Mulert, J. Lutz (Munich)

Functional neuroimaging and electrophysiological studies have focused on anterior cingulate cortex (ACC) dysfunction as a possible key-region for attention deficits in schizophrenia. In the present study, we addressed the influence of reward on brain activity and performance in schizophrenic patients during an attention-requiring auditory choice reaction task that is known to require ACC-activity. We investigated 50 patients with schizophrenia and 50 healthy subjects combining ERP and simultaneously acquired functional MRI data. After a first run (control condition) the subjects were told to repeat the task with increased mental effort in order to reduce reaction times and error rates. Subjects were informed to get a reward if they could improve their performance during the second run (effort/reward condition). In the fMRI analysis, we found a significant increase in the SMA and the ACC during the effort/reward condition in comparison to the control condition in healthy subjects. Differences in the fMRI activation between healthy controls and schizophrenic patients in the ACC were more distinct during the effort/reward condition. Our results are in line with earlier investigations describing a disturbed ACC-function in cognitive tasks with mental effort demands in patients with schizophrenia and suggest a lower capacity for reward-related performance increase.

V-02-04
Repetitive transcranial magnetic stimulation (rTMS) at two different high frequencies on depressed patients: A randomized, double blind controlled trial
F. Jakob, H. Danker-Hopfe, M. Bajbouj, N. Schommer (Berlin)

Context: High-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to have antidepressant effects. However, the relationship between the clinical efficacy of TMS and stimulation parameters remains obscure. In the present the authors compared the antidepressant effectiveness of two different high frequencies of rTMS (20HZ/50Hz) versus placebo.

Objective: To determine the antidepressant efficacy of different rTMS stimulation parameters in comparison to placebo stimulation.

Methods: Thirty-six depressed patients were randomly assigned to 10 sessions of 20Hz or 50Hz high rate rTMS or to sham TMS, applied over the left dorsolateral prefrontal cortex. Subsequently, all patients received another 10 sessions of 20Hz rTMS.

Main outcome measures: Hamilton Depression Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Beck depression inventory (BDI).

Results: After two weeks of treatment the real stimulated groups (n = 12/12) and the sham stimulated group (n = 12) had a measurable benefit. However, overall the placebo stimulation did not differ significantly from real stimulation, nor were differences observed between the two different frequencies of rTMS.

Conclusions: Neither real TMS treatment at 50Hz nor at 20Hz were superior to the placebo rTMS condition.

V-02-05
Double pulse transcranial magnetic stimulation technique reveals increased motor cortex excitability in adults with Attention Deficit Hyperactivity Disorder (ADHD)
M. Schneider, P. Retz-Junginger, M. Rösler, W. Retz (Homburg/Saar, Homburg)

Double pulse transcranial magnetic stimulation technique (dpTMS) is a useful tool to analyze inhibition and facilitation of motor cortex excitability. As ADHD is clinically also characterized by motor phenomena, the ongoing study with adult ADHD patients investigates disinhibitory mechanisms by dpTMS. More than 30 adult ADHD patients according to ICD-10 criteria could until now be recruited and compared with age and sex matched healthy controls. Motor evoked potentials (MEP) are sollicited by suprathreshold testpulse following a subthreshold conditioning pulse with different interstimulus intervals at the motor cortex. They are recorded by surface electrodes at M. interosseus dorsalis I. At short insterstimulus intervals, MEP amplitudes are smaller in relation to the MEP evoked by testpulse alone (< 100 % relative amplitude), called inhibition. With increasing interstimulus intervals (> 5ms) the relative amplitude gets higher than the MEP evoked by testpulse alone (> 100 %) – called facilitation. It turns out that motor inhibition is significantly weaker (40 % of relative testpulse MEP vs. 15 % in controls; $p < 0.001$) and motor facilitation is markedly increased in ADHD (230 % of relative testpulse MEP vs. 130 % in controls). These results provide evidence for increased motor cortex excitability in ADHD. Stimulant medication effects on motor cortex excitability will be discussed.

V-02-06
Pattern of neural activity after episodic memory training
P. Schönknecht, F. I. Giesel, A. Hunt, M. Essig, J. Schröder (Heidelberg)

Introduction: Mnestic deficits occur long before the onset of dementia in patients with mild cognitive impairment (MCI). Memory decline proceeds in these patients whereas cognitively unimpaired older persons show a stable memory performance. In order to investigate the neural basis underlying cognitive training effects in patients at risk to develop Alzheimer's disease (AD) and in healthy controls we developed a fMRI paradigm of explicit memory function.

Methods: 11 patients with MCI and 11 controls were enrolled in the study. Before and after an one-week-training period all participants underwent fMRI scan during verbal memory encoding. Image analysis was done using SPM.

Results: In healthy controls, before training a temporal, parietal, cingulate, and left frontal cortex activation occurred which decreased after the one-week-cognitive training. In contrast, MCI patients showed at baseline a rather week temporal, cingulate and left frontal cortex activation which increased after training.

Conclusion: In conclusion, the results of this study demonstrate an economisation of cerebral activity in healthy persons after training whereas in the MCI patients after training a compensation for cerebral activation deficits occurs.

V-02-07
A neurocognitive study on memory performance in patients with a posttraumatic stress disorder
N. Gryschok, T. Meindl, R. Rosner, M. Reiser, R. R. Engel, K. Fast (Munich)

Individuals with a posttraumatic stress disorder (PTSD) often report problems with memory. This subjective cognitive symptom is included in the defining diagnostic criteria for PTSD. As a result, many attempts have been made to obtain objective quantifications of memory deficits associated with PTSD. Recent studies have reported memory deficits and a reduced hippocampal volume. However little is known about the functional role of the hippocampus in PTSD. Therefore it seems important to investigate the functional integrity of the hippocampus with the assistance of memory paradigms. In our study we compared patients with a PTSD and healthy control subjects to clarify whether hippocampal activation and cognitive functioning is related to PTSD. Each participant had to undergo a functional neuroimaging scanning session (fMRI) where we investigated the hippocampal activation during an associative learning paradigm. This paradigm consists of learning an association between different female faces and different professions. Additionally cognitive functioning, i. e. memory, attention, executive functions and estimated intellectual potential, was examined with an elaborated neuropsychological testbattery.

V-02-08
Neuropsychological profiles in mild cognitive impairment
E. Wiedemann, P. Schönknecht, P. Toro (Heidelberg)

In a recent consensus conference a differentiation of the diagnosis mild cognitive impairment (MCI) was suggested depending on whether an isolated impairment of memory or another cognitive domain exists (a-MCI single domain, na-MCI single domain) or whether other areas are also affected (a-MCI multiple domain, na-MCI multiple domain). In the present study we examined to what extent these concepts can be confirmed empirically. For this aim we compared the performance of 159 patients with MCI, 54 healthy controls and 25 patients with Major Depression (MD) in several subtests of the CERAD and the WMS. After the results of a factor analysis these subtests built three factors ("verbal episodic memory", "figural episodic memory" and "mental flexibility"), with which the MCI patients were divided into three clusters. While the clusters showed comparable impairment in verbal episodic memory, the values in the factors figural episodic memory and mental flexibility reached statistical significance with pronounced cluster-specific deficits. According to the concept above, only one cluster could be described as a-MCI single domain, the remaining two subgroups as a-MCI multiple domain. MCI patient groups without memory disorders couldn't be identified.

V-03 Schizophrenia

V-03-01
Relationship between brain dysfunctions and psychopathology in schizophrenia
S. Karch, O. Pogarell, G. Leicht, J. Lutz, H.-J. Möller, H. Hegerl, C. Mulert, L. Jäger (Munich)

Schizophrenia is associated with multiple cognitive deficits such as decreased performance in tasks comprising executive and memory processes. It is assumed that these deficits are the consequence of functional and anatomical abnormalities especially comprising frontal and temporo-parietal brain regions. We investigated the characteristics of P300 generators (oddball paradigm) and their association to the psychopathology of schizophrenics using simultaneous fMRI and EEG recordings. The comparison of 14 schizophrenic patients with healthy controls revealed as expected a reduced P300 component mainly in parietal brain regions in patients. Concerning fMRI the attention task led to BOLD activations in the supplementary-motor area, ACC, insula, thalamus, putamen, middle prefrontal gyrus, as well as temporo-parietal brain structures in healthy persons. In patients comparable brain regions were activated to a significantly lesser extent. Furthermore there was a significant negative correlation between the extent of paranoid-hallucinatory symptoms as well as apathy and activations in the SMA, precuneus and left parietal area. The ACC, right insula and left temporal area correlated negatively with paranoid symptoms but seem not to be influenced by apathy. This may indicate that frontal and temporal brain areas particularly contribute to paranoid symptoms of schizophrenic patients.

V-03-02
Neural correlates of disorganised symptoms in schizophrenia
A. Rapp, M. Erb, M. Bartels, W. Grodd, T. Kircher, D. Leube (Tübingen, Aachen)

Disorganised symptoms are a key symptom of schizophrenia. Knowledge about the pathophysiology of these symptoms is still sparse. However abnormalities of the language system in the brain may play a role in the pathophysiology of disorganisation.

Aim of the study: To investigate neural correlates of disorganised symptoms in schizophrenia Event-related functional magnetic resonance imaging was applied to 9 patients with DSM IV schizophrenia. Subjects read short German sentences with either metaphoric or literal meaning silently and decided by button press whether the sentences had a metaphoric or literal meaning. Psychopathology was rated with the PANSS. Severity of disorganised behaviour was defined as sum score of the PANSS items P2, N5, N7, G5, G11 and G13 (based on Klingberg et. al., Eur Arch Psych Clin Neurosci, in press). This score was correlated with brain activation for reading metaphoric language. A negative correlation was found between sum-score of disorganised symptoms in the PANSS and brain activation in the left superior temporal gyrus (BA 22, TAL XYZ: –59, –43,13). Dysfunction of the left superior temporal gyrus, a key region of language comprehension, could play a role in the pathophysiology of disorganised symptoms in schizophrenia. Results are discussed in the background of structural findings and language abnormalities in schizophrenia.

V-03-03
Antibrain antibodies in schizophrenia – A reevaluation
K. Schott, E. Stransky, A. Batra (Tübingen)

The occurrence of antibrain antibodies was regarded widely as a hallmark of an autoimmune process in this disorder. However, the results were not unequivocal and our own results were largely negative. Since ten years this issue has lost the attention of the scientific community. However, new results on autoantibodies against heat shock proteins, cholinoreceptors, and neuroblastoma proteins in schizophrenia have encouraged us to re-examine our investigations with a large series of Western blot analyses on the occurrence of serumantibodies against bovine brain proteins in schizophrenia.We performed a pattern analysis of the stained proteins as to their molecular weight and could indeed detect irregularities in comparison to control subjects.Serum from paranoid schizophrenics (PS) and other schizophrenias exhibit more bands (IgG) in the MW region from 47 to 54 kd. In the MW region from 55 to 63 kd patients with schizoaffective psychosis (SAP) and PS exhibit an increased number of bands (IgG).With respect to IgM antibodies patients with SAP and other schizophrenias exhibit more bands in the MW region from 85 to 99 kd. Of course we cannot estimate the impact of these results on the pathogenesis of schizophrenia. However, these results are new and demonstrate that the issue of antibrain antibodies in schizophrenia is not accomplished.

V-03-04
Balance of apoptosis and neural cell proliferation in an animal model of psychosis based on chronic NMDA-antagonism
J. Genius, H.-J. Möller, D. Rujescu (Munich)

The psychotomimetic effects of N-methyl-D-aspartate (NMDA) receptor antagonists in healthy humans have promoted the notion of altered glutamatergic neurotransmission and imbalances between proliferation and apoptosis as factors being implicated in the pathogenesis of schizophrenia. Inducing a state of impaired glutamatergic neurotransmission in rats by chronic application of MK-801 we were able to establish an a model of psychosis, which revealed marked parallels with genuine schizophrenia. In analogy to schizophrenia, MK-801 induced anomalies of the glutamate distribution in the hippocampus, along with enhanced stem cell proliferation. Our data suggest that apoptosis plays a minor role in this model. Moreover, the effect of haloperidol seems to be mediated through yet unidentified mechanisms, not directly related to D2 antagonism. To further substantiate our hypothesis of altered glutamatergic neurotransmission as a pathogenetic substrate of psychosis and to identify possible candidate molecules, we performed a microarray-based analysis of differentially expressed genes. Again, substantial alterations were detected in proliferation-related genes. These convergent lines of evidence indicate, that further research should be focused on the biology of neuronal stem cells and that our animal model may provide a suitable tool to explore the biology of schizophrenia.

V-03-05
The search for memory-related genes in humans
A. Papassotiropoulos, D. de Quervain (Zürich)

Background: Experimental work in animals has shown that memory formation depends on a cascade of molecular events. In humans, heritability estimates of ~50 % suggest that genetic factors have an important impact on this fundamental brain function.

Objective: To identify memory-related genes and gene-clusters in humans.

Methods: We used a combination of whole-genome association (500K SNP chip), candidate gene approach (gene clustering) and fMRI.

Conclusions: Variability of human memory performance is related to variability in genes encoding proteins of a signaling cascade, including NMDA receptor, metabotrobic glutamate receptor, adenylyl cyclase, CAMKII, PKA and PKC. Functional magnetic resonance imaging during memory formation reveals that this genetic profile correlates with activations in memory-related brain regions, including the hippocampus and parahippocampal gyrus. The whole-genome association study revealed the existence of novel genes significantly related to human memory performance and brain activation. Relevant literature: de Quervain and Papassotiropoulos, PNAS 2006; 103(11):4270–4274. de Quervain et al. Nature Neuroscience 2003; 6(11):1141–1142.

V-03-06
Influence of negative symptoms, apathy and depression on cognitive function in schizophrenic patients
M. Huber, M. Kunz, J.-C. Krieg, S. Gebhard, B. Kundermann, S. Lautenbacher (Marburg, Bamberg)

Negative symptoms are considered as an essential psychopathological correlate of the cognitive disturbances observed in schizophrenic patients. In addition, many patients suffer from depression which also comes along with cognitive deficits. A related but less often considered construct is apathy. In this study we tried to explain the cognitive symptoms on hand of the three different constructs. Attention (TAP) and Memory (VLMT) were investigated in 37 patients with schizophrenia and related to rating-scales for depression (HAMD), negative symptoms (PANSS-N) and apathy (AES). The Patients got noticeable results on all three scales. The relation between depression, negative symptoms and apathy was significant but it was small enough to consider them as largely independent constructs. However, the calculation of correlations did always extract the respective other impairments. Depression and apathy were only minor associated with measures of cognitive function. In contrast, negative symptoms proved to be predictive for cognitive impairments: increased negative symptoms were significantly combined with longer reaction times in the test "alertness". Therefore – with respect to the three constructs – it seems that negative symptoms are particular useful as a correlate of cognitive deficits.

V-03-07
Cerebral morphological correlates of neurological soft signs in first-episode schizophrenia
P. A. Thomann, V. Dos Santos Pedro, S. Bachmann, C. Bottmer, U. Seidl, P. Toro, P. Schönknecht, M. Essig, J. Schröder (Heidelberg, Halle/Saale)

Background: A subtle impairment of motor coordination functions is frequently found in patients with manifest schizophrenia. Clinically these deficits present as neurological soft signs (NSS).

Methods: Optimized voxel-based morphometry (VBM) was used to investigate gray matter (GM) density and its putative association with NSS in 42 patients with first-episode schizophrenia and 22 healthy controls. VBM analysis comprised (a) structural comparison of the two groups and (b) correlation between NSS-scores and GM density.

Results: NSS scores were significantly higher in patients. In relation to healthy comparison subjects, loss of GM density was pronounced in the temporal lobe (both neocortical fields and substructures of the medial temporal lobe). In patients with schizophrenia, higher rates of NSS were related to a reduced GM density in the pre- and postcentral gyrus, the cerebellum and in subcortical regions (caudate nucleus and thalamus).

Conclusion: This results might support the hypothesized model of a disrupted cortico-cerebellar-thalamic-cortical circuit in schizophrenia.

V-04 Depression

V-04-01

Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3alpha-hydroxysteroid dehydrogenase activity

C. Schüle, T. C. Baghai, S. Wenninger, K. Mainka, C. Nothdurfter, R. Rupprecht, D. Eser (Munich)

Concentrations of 3α-reduced neuroactive steroids are altered in depression and normalize after antidepressant pharmacotherapy with SSRIs. We investigated the impact of mirtazapine on the activity of a key neurosteroidogenic enzyme, the 3α-hydroxysteroid dehydrogenase (3α-HSD), and on the levels of neuroactive steroids in relation to clinical response. Twenty-three drug-free inpatients suffering from major depression (DSM-IV criteria) underwent 5-week treatment with mirtazapine (45 mg/day). Plasma samples were taken weekly at 8:00 AM and quantified for neuroactive steroids by means of combined gas chromatography/mass spectrometry analysis. Enzyme activity was determined by assessment of steroid conversion rates. Irrespectively of clinical outcome, there were significant increases in 3α-reduced neuroactive steroids after mirtazapine treatment, whereas 3β-reduced steroids were significantly decreased. In-vitro investigations demonstrated a dose-dependent inhibitory effect of mirtazapine on the activity of the microsomal 3α-HSD in the oxidative direction, which is compatible with an enhanced formation of 3α-reduced neuroactive steroids. However, the changes in neuroactive steroid concentrations more likely reflect direct pharmacological effects of this antidepressant rather than clinical improvement in general.

V-04-02

The first association study with G72 in depression in a large sample of patients and controls of German descent

T. G. Schulze, A. Georgi, S. Höfels, A. Karpushova, W. Maier, P. Propping, M. Nöthen, S. Cichon, M. Rietschel (Mannheim, Bonn)

G72/G30 is considered a strong susceptibility gene for both schizophrenia (SZ) and bipolar disorder (BD). We recently reported association between identical G72/G30-haplotypes and SZ, BD and panic disorder (PD). We studied a German sample of 500 MD patients and 1030 population-based controls. We were interested whether our previously identified risk haplotype of markers M22, M23, and M24 was also associated with MD. To further explore any relationship between G72/G30 and MD, we genotyped 9 additional SNPs highlighted in other studies. The haplotype C-C-T was significantly more frequent in MD patients than in controls (40.5 % vs. 36.1 %; $p = 0.027$; OR = 1.2). The exploratory analysis on 9 further G72/G30 SNPs of interests yielded significant associations for M12 ($p = 0.038$), M14 ($p = 0.046$), while M15 ($p = 0.090$) and rs1935062 ($p = 0.055$) did not reach significance. Permutation analysis adjusting for the 9 SNPs yielded a global $p = 0.176$. This is the first and largest case-control study on G72/G30 and MD. We found an association between MD and the same risk haplotype that we previously found associated with SZ, BD, or PD. We also found suggestive associations with other variants. Given that depressive symptoms are present across these diagnostic groups, G72/G30 might predispose to "core symptoms" prevalent in all four disorders, for the elucidation of which further studies are needed.

V-04-03

Hyperforin activates TRPC6 channels in PC12 cells

W. E. Müller, I. Henke, C. Harteneck, K. Leuner, A. Foik (Frankfurt, Frankfurt Berlin, Berlin)

The preclinical antidepressant profile of hyperforin is supported by a large body of evidence. Hyperforin is active in many relevant behavioral models, alters brain levels of serotonin, norepinephrine, dopamine and inhibits synaptosomal uptake of all three neurotransmitters in vivo. In contrast to classic antidepressants, Hyperforin inhibits neurotransmitter uptake via elevating intracellular sodium concentrations. We have previously shown that hyperforin elevates the intracellular sodium and calcium concentration in PC12 cells by activating TRPC channels (Treiber et al. 2005). Previous work by Tesfai (Tesfai et al. 2001) showed an expression of TRPC6 in PC12 cells. Therefore, we now adress the question if hyperforin activates TRPC6 channels in PC12 cells. With RT-PCR and western blotting we were able to confirm TRPC6 expression in PC12 cells. To directly investigate the effect of Hyperforin on TRPC6 channels, we transiently transfected TRPC6 channels in HEK293 cells and analyzed hyperforin induced cation influx with whole-cell patch-clamp technique and calcium imaging experiments. In both experiments, hyperforin activates TRPC6 channels. These results indicate that hyperforin acitvates TRPC6 channels in PC12 cells and probably mediates it's antidepressant activity via this non-selective cation channel.

V-04-04

Lithium effect on serotonin – A camouflaged Prozac?!

J. Benninghoff, H. Grunze, D. Rujescu (Munich)

The mechanism of lithium-serotonin interaction remains unclear – at least until reports on enhanced hippocampal neurogenesis (NG). Since NG is driven by neural stem cells,we generated hippocampal adult neural stem cells (ANSCs) under serum-free conditions.We treated undifferentiated ANSCs with 0.8 mM Li. After 3 weeks of Li treatment, TPH1 and TPH2 mRNA levels detected by real-time PCR were increased up to 5 fold.We also verified TPH protein expression by fluorescence-activated-cell-sorting (FACS), showing that 94 % of undifferentiated ANSCs expressed TPH. In order to prove TPH function in undifferentiated ANSCs, we assessed the effect on the cardinal functional features (proliferation, self-renewal and differentiation) by pharmacologically blocking TPH. Here, we saw a significant drop in the BrdU labeling index (44 % ± 18 vs. 17 % ± 10 ($p < 0.001$)) suggesting absence or reduction of 5-HT levels affects stem cell proliferation and suggests a link with the decreased NG observed in vivo. In conclusion, using a standardized in vitro system, we showed that Li strongly up-regulates TPH1/2 mRNA. Treatment antagonizing TPH decreases ANSC proliferation. Consistent with the concept that both lithium and SSRIs stabilize serotonergic neurotransmission and likely rendering neural tissue more resistant to further changes by balancing serotonin levels, we heretically consider lithium a camouflaged SSRI.

V-04-05

The effects of antidepressant, neuroleptic and anxiolytic drugs in chronic psychosocial stress in rats

R. Rygula, G. Flügge, C. Hiemke, U. Havemann-Reinecke, N. Abumaria (Göttingen, Mainz)

In a new model of chronic social stress induced by a resident-intruder paradigm, rats show behavioural changes like anhedonia and motivational deficits as depressive like symptoms. The present study was designed for pharmacological validation of this model. Animals were socially stressed for five weeks and, in parallel, treated with different

pharmacological compounds. The drugs were administered chronically via drinking water (citalopram 30 mg/kg, reboxetine 30 mg/kg, haloperidol 2 mg/kg,) or once injected (diazepam 2 mg/kg). The effects of social stress and drugs were assessed by behavioural tests: The gene and protein expression were assessed in parallel cooperational studies. After four weeks of treatment, plasma levels of each drug and their metabolites were found to be within the human therapeutic range. Chronically stressed rats showed reduced locomotor and exploratory activity, reduced sucrose preference and increased immobility time in the forced swimming test. Chronic oral administration of citalopram and reboxetine abolished those effects and normalised behaviours related to motivation and reward sensitivity. Neither haloperidol nor diazepam had beneficial effects on these chronic social stress induced changes. These observations provide evidence for the predictive validity of the chronic social stress paradigm as model of depressive like symptoms in rats.

V-04-06
FKBP51 – A genetic marker for depression and course of the disease?
M. Gawlik, K. Moeller-Ehrlich, M. Mende, M. Jovnerovski, S. Jung, M. Knapp, G. Stöber (Rottendorf)

Background: A dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been proposed as an important pathogenic factor in depression. Genetic variants of FKBP5, a protein of the HPA system modulating the glucocorticoid receptor, have been reported to be genetically associated with improved response to medical treatment and an increase of depressive episodes.

Methods: We examined three single nucleotide polymorphisms (SNPs) in FKBP5, rs4713916 in the proposed promoter region, rs1360780 in the second intron and rs3800373 in the 3'-untranslated region (3'-UTR), in a case-control study of Caucasian origin (affective psychosis: n = 248; controls: n = 188) for genetic association and association with disease related traits.

Results: Allele and genotype frequencies of rs4713916, rs1360780 and rs3800373 were not significantly different between cases and controls. Odds ratios were not increased between cases and controls, except the rare haplotype G-C-G (OR 6.81), representing 2.1 % of cases and 0.3 % of controls. The frequency of rs4713916AG in patients deviated from expected Hardy-Weinberg equilibrium, the genotype AA at rs4713916 in monopolar depression (P = 0.011), and the two-locus haplotype rs1360780T – rs3800373T in the total sample (overall P = 0.045) were associated with short duration of disease.

Conclusion: In summary, our data do not support a significant genetic contribution of FKBP5 to affective psychosis in the analysed markers, and the findings are inconclusive regarding putative risk haplotypes or association with disease-related traits.

V-04-07
The effect of smoking on nicotine deprived depressed and non-depressed smokers under conditions of cortisol suppression and stress
P. Netter, J. Hennig, N. Conrad, M. Rüger (Giessen)

Two studies were performed based on the close relationships between depression, smoking urge, stress, and cortisol release. Therefore it was investigated, if nicotine deprived depressives and non-depressives would differ with respect to 1. stress induced cortisol responses, arousal, alertness and cigarette craving; 2. the same responses when cortisol is suppressed; 3. effects of smoking on the same variables under conditions of stress and cortisol suppression. The first study compared depressed patients with matched controls under mental stress conditions, the second one high and low depressive healthy subjects with and without stress and cortisol suppression by metyrapone with respect to smoking effects on the above variables. Results confirmed the lower cortisol and higher craving, fatigue and arousal response to stress in depressives.Cortisol suppression reduced cigarette craving only in groups without stress. Interactions between drug, stress and depression revealed that smoking may counteract the stress induced drop in alertness only in the metyrapone treated depressive group. It may be concluded that 1. depressive healthy persons respond like depressed patients. 2. cortisol suppression may decrease craving, but not after stress; 3. depressives may benefit from reduced cortisol levels when they smoke, perhaps because adrenergic effects are less counteracted by cortisol.

V-04-08
Angiotensin converting enzyme gene polymorphisms influence the speed of response to electroconvulsive therapy
T. Baghai, C. Schüle, D. Eser, P. Zill, B. Bondy (Munich)

Variants of the ACE gene have impact on therapeutic efficacy of antidepressant pharmacotherapies. ECT is an effective treatment of MDD. Data are lacking as to whether the speed of clinical improvement is influenced by ACE gene variants. We investigated 35 SNPs in unipolar depressed patients and healthy controls. ACE serum activity, HPA axis activity and the treatment courses of 39 patients were analyzed to detect dependencies between the onset of response to ECT monotherapy and genetic variants. Unipolar MDD was associated with SNP rs4291 in the promoter area of the ACE gene, which also has influence on ACE serum activity and HPA axis activity. We could show a divergent clinical outcome in relation to different ACE genotypes depressed patients who undervent an ECT treatment course. Patients with a homozygote deletion in the ACE gene similar to patients homozygous for the SNP rs4291 T-allele and the rs4295 G-allele responded to ECT faster than other groups. Our investigation gives the first hint that the speed of onset during an ECT treatment course is dependent of variants of the ACE gene. A faster response could be seen in patients with higher probability of HPA-axis hyperactivity. Clinical consequences could possibly be an earlier recommendation of bilateral or high dose unilateral ECT in patients with a lower probability of a fast response.

V-04-09
St. John's wort extract in psychic stress: Effect and mechanisms of action in an animal model
V. Butterweck, O. Grundmann, K. Zeller, O. Kelber (Gainesville, Darmstadt)

Earlier results indicate an effect of St. John's wort extract not only in medium severe depression, but also in psychic stress. To elucidate mechanisms of action responsible for this effect, the St. John's wort extract STW 3-VI (Laif 900) and its components were tested in stress-induced hyperthermia (SIH) in comparison to standard drugs. SIH is observed in man, but also inducible experimentally in mice by exposing them to a new environment (open field, OF). Male C57/BL6 mice, 6–8 animals per group, were treated orally with test substance or control. 60 min later they were exposed to the OF for 10 min. Body temperature was measured rectally after 60 min. STW 3-VI in doses of 250 mg/kg and 500 mg/kg, as well as its main components, hypericin and flavonoids, significantly reduced OF-induced SIH ($p < 0.05$), while hyperforin had no effect. Imipramine (20 mg/kg) and fluoxetine (10 mg/kg) had no effect, while the anxiolytics diazepam (1 mg/kg) and buspiron (10 mg/kg) and the β-receptor antagonist propranolol (5 mg/kg) induced a significant reduction of SIH. The results show a direct effect of St. John's wort extract, STW 3-IV (Laif 900), in an in vivo model of psychic stress, and point to the involvement of GABAergic as well as β-adrenergic signalling in its mechanisms of action.

V-05 Miscellaneous

V-05-01
Partial seizures: "Limbic Psychotic Trigger Reaction" (24 cases). A primate model implicates kindling by memory revival of moderate stresses
A. Pontius (Frankfurt)

24 so far unexplainable cases of motiveless, unplanned, nonvoluntary, out-of-character acts were committed with flat affect by 17 murderers, 4 fire setters, one bank robber. Memory for the acts was retained, implicating atavistic regression to a limbic level of "paleo-consciousness". The brief symptoms emerged upon a chance encounter with a highly individualized trigger stimulus, suddenly reviving memories of mild to moderate stresses, a scenario reminiscent of experimental seizure kindling (a) Aura: autonomic arousal, onset of de novo psychosis; (b) ictus: bizarre behavior (not necessarily criminal, might be "merely" socially injurious): (c) post-ictus inefficient behavior, implicating prefrontal dysfunctioning. A brief fronto-limbic dysbalance is implicated, whereby a seizure-activated limbic system briefly overwhelms prefrontal modulation and controls. Note that seizure kindling requires no morphological brain damage and none has been detected afterwards, thus only 12 patients had some abnormal brain test at some time during their lives, and 14 had a closed head injury.

Conclusion: Seizure kindling needs to be ruled out in bizarre paroxysmal acts (potentially also in social misbehavior). (Ref. e. g. Pontius & Wieser, Epi Behav 2004; 5:575–583).

V-05-02
Treatment of aggression with Topiramate in male borderline patients: A double-blind, placebo-controlled study
M. Nickel, C. Nickel, P. Kaplan, M. Mühlbacher (Simbach am Inn, Salzburg)

Borderline personality disorder (BPD) is a complex mental disease associated with severe serious functional impairment, affective instability and impulsive aggression. The aim of this study was to compare the efficacy of topiramate versus placebo in the treatment of aggression in men with borderline personality disorder. We conducted an 8-week, double-blind, placebo-controlled study of topiramate in 42 male subjects (42 out of 44) meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for BPD. The Structured Clinical Interview (SCID I and II) was carried out. The subjects were randomly assigned to topiramate ($n = 22$) or placebo ($n = 20$). In comparison with the placebo group, significant changes on four STAXI scales (State-Anger, $p < 0.01$; Trait-Anger, $p < 0.05$; Anger-Out, $p < 0.01$; Anger-Control, $p < 0.01$) were observed in the subjects treated with topiramate. A non-significant difference was found on the Anger-In scale ($p = 0.86$). Additional significant weight loss was observed (difference in weight loss between the both groups was 5.0 kg, $p < 0.01$, 95 %-CI = [–6.5; –3.4]). All subjects tolerated topiramate relatively well. Topiramate appears to be an effective agent in the treatment of anger in men with BPD as defined by SCID for DSM-IV criteria. Mild weight loss can be expected.

V-05-03
Guidance of inhibitory rTMS treatment of auditory verbal hallucinations in schizophrenias by Near-Infrared Spectroscopy
A. Fallgatter, A.-C. Ehlis, M. M. Richter, M. M. Plichta (Würzburg)

Auditory verbal hallucinations (AVHs) are among the most frequent and disabeling symptoms of schizophrenic diseases. In approximately one quarter of patients, AVHs have to be considered as therapy-refractory with regard to pharmacological treatment options. This group of patients may benefit from a treatment protocol with repetitive Transcranial magnetic stimulation (rTMS) aiming on an inhibition of AVH-associated increased activity of auditory brain areas in the temporal cortex. However, optimal protocols for the guidance and control of such innovative treatment regimens are still lacking.We propose the application of a non-invasive optical imaging technique (functional Near-Infrared Spectroscopy; fNIRS) for the measurement of the AVH-related activity of the auditory cortex, for the guidance of the rTMS-treatment and for the control of a treatment success on the brain metabolic level. In the reported patient, NIRS measurement indicated AVH-related activity in the left auditory cortex which strongly decreased after a period of three weeks with daily inhibitory rTMS treatment, in parallel with drastically diminished AVHs. This is the first report of a NIRS-guided and -controlled inhibitory rTMS treatment of therapy-refractory AVHs in a schizophrenic patient. Given the excellent clinical applicability of the applied methods, the combination of fNIRS and rTMS might have the potential to establish new treatment options in psychiatry aiming on the modulation of pathological regional brain activity patterns.

V-05-04
Prevalence of Borna Disease Virus antibodies in clinical personnel
K. Bechter, B. Geitner, W. Behr, R. Kilian, C. Wolff, S. Herzog, H. Moser (Günzburg, Augsburg, Giessen)

Introduction: The prevalence of Borna Disease Virus antibodies in clinical personnel in 2 hospitals from Southern Germany was assessed to detect a possible risk of transmission from patients to clinical personnel.

Results: A total of 655 clinical personnel was investigated (mean age 31 years) in the Augsburg and Günzburg hospitals with different patient spectra (hosp. A: internal Med. + Surgery + Anaesthesiol., others; hosp. GZ: mainly Psychiatry). The prevalence of BDV serum antibodies was 5.95 % (6.08 % in hosp. GZ, 5.62 % in hosp. A). The BDV seroprevalence seemed to increase with older age. The risk of BDV seropositivity was not increased in clinical personnel in both hospitals. Nevertheless, in hospital A such personnel regularly working over many years with infectious patients BDV seroprevalence was increased with duration of employment. There was no increase of neuropsychiatric disorders reported in BDV seropositive personnel.

Conclusions: There is no detectable risk of acquiring BDV infection in psychiatric settings in this study. But because infectious patients generally may increase the risk of transmission of various infections to clinical personnel, the findings of these studies suggest to perform larger epidemiological studies on possible transmission of BDV infections in settings such as intense care units, were infectious patients are frequently treated.

V-05-05
Genetics of suicidal behavior and aggression-related genes
I. Giegling, B. Schneider, M. Dickmann, A. M. Hartmann, A. Schnabel, K. Maurer, H.-J. Möller, D. Rujescu, A. Thalmeier (Munich, Frankfurt)

Risk of suicide-related behavior is supposed to be determined by a complex interplay of sociocultural factors, psychiatric history, personality traits, and genetic vulnerability. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution that is independent of the heritability of Axis I and II psychopathology. Neurobiological studies have shown that serotonergic dysfunction is implicated in suicidal behaviors. We initiated a large genetic association study on over 1800 healthy controls, 250 suicide attempters and 100 suicide completers and investigated the role of a comprehensive set of serotonergic candidate genes. Since both, aggression related traits and serotonergic activity are partially heritable and correlate inversely, variations in genes of the serotonergic system might then account for variations in aggression-related behavior. Thus, we investigated the relationship between serotonergic genes and aggression-related behavior. Nevertheless, complex neural circuitry needs to be considered when delineating the genetics of these complex phenotypes. We conducted a genome-wide gene expression analysis to identify new candidate-genes and found genes to be differentially expressed in the orbitofrontal cortex of suicide completers. These genes were investigated in our genetic study and these results will be discussed.

V-05-06
Evaluation of the CCK-4 model as a challenge paradigmin a population of healthy volunteers
D. Eser, T. Bagahi, R. Engel, C. Schüle (Munich)

Experimental panic induction with cholecystokinin-tetrapeptide (CCK-4) has been established as a model to study the pathophysiology of panic disorder and might serve as a tool to asses the antipanicogenic potential of novel anxiolytic compounds. So far, assessment of CCK-4 induced panic does not follow consistent rules. To provide a basis for the use of the CCK-4 model in proof-of-concept studies we investigated CCK-4 induced panic according in healthy volunteers. 85 healthy male subjects underwent CCK-4 injection. Subjective panic responses were measured with the Acute Panic Inventory and the Panic Symptom Scale. Heart rate, blood pressure and neuroendocrine responses were assessed concomitantly. Compared to the PSS panic definition according to the API resulted in a 10.6 % higher panic rate. CCK-4 elicited a significant increase in heart rate, systolic blood pressure and a significant elevation of ACTH and Cortisol, which did not differ between panickers and nonpanickers. The panic criterion applied appears to be of major importance for the panic rate achieved, whereas CCK-4 induced cardiovascular and hormonal alterations are not valuable as an objective "read out". The CCK-4 challenge might serve as a useful model to study putative anxiolytic effects of novel compounds if the challenge procedure is carried out according to strictly standardized conditions.

V-05-07
Transcranial magnetic stimulation (TMS) against tinnitus
C. Plewnia (Tübingen)

In this series of experiments, we applied high-frequency (hf) TMS to assess the functional relevance of cortical regions for tinnitus perception, used [15O]H2O-PET to navigate low-frequency (lf) TMS to the individual areas of tinnitus-related activity, and evaluated the efficacy of an experimental tinnitus treatment with repeated sessions of navigated lf-TMS. Comparing the effects of hf-rTMS applied to 12 cortical and non-cortical regions on tinnitus loudness, we found that stimulation of the left temporoparietal cortex induced distinctive transient tinnitus suppressing effects. Lf-TMS individually guided to areas of tinnitus-related cortical hyperactivation resulted in a reduction of tinnitus for up to 30 minutes. This reduction was dependent on the number of stimuli, differed from sham stimulation, and was negatively correlated with tinnitus duration. Unlike sham stimulation, two weeks of daily lf-TMS to the maximum of activity resulted in a moderate reduction of the tinnitus-questionnaire score. These studies emphasize the effectiveness of TMS as an interventional tool in tinnitus and support the pathophysiological concept of maladaptive plasticity reflected in focal cortical hyperactivity in tinnitus. However, therapeutic efficacy of navigated lf-TMS is only moderate, interindividual responsiveness varies and the attenuation seems to wear off with time.

V-05-08
Behavioral performance within an approach-avoidance paradigm and serotonergic funtion in patients with Anxiety Disorders and Borderline Personality Disorder
B. Nekwasil, A. Thum, T. Schneyer, M. Bender, T. Wübbena, M. Giesler, J. C. Krieg, U.-M. Hemmeter (Marburg, Herborn)

According to Gray (1973) impulsivity and anxiety are independent personality traits which are related to a different susceptibility for reward and punishment. Furthermore, these dimensions of personality differ in serotonergic reactivity. Patients with Borderline personality disorder (BPD) and anxiety disorders (AD) clearly contrast in both of these traits. Therefore, a study in patients with BPD and AD has been conducted, which includes the parallel assessment of personality, behavioral performance and endocrine responsiveness to a serotonergic stimulation. 15 patients with BPD and 15 with AD who have been characterized by a variety of personality questionnaires underwent an approach-avoidance paradigm in which reward and punishment were systematically varied. In addition, a serotonergic stimulation (citalopram 20 mg) with the assessment of cortisol and prolactin was performed. The results show that BPD patients were more responsive in citalopram stimulation of cortisol and prolactin than AD. In the approach-avoidance paradigm a significant better performance was found only in the condition, in which reward could be easily achieved for BPD patients compared to AD. No differences between groups were observed in the conditions of difficult reward and punishment. Furthermore, citalopram induced cortisol-secretion was closely related to performance in the reward condition.

V-05-09
Effects of haloperidol, clozapine and olanzapine on the survival of human neuronal and immune cells in vitro
P. Heiser, F. Enning, J.-C. Krieg, H. Vedder (Marburg)

Cytotoxic effects on neuronal as well as on immune cells have been reported for both, typical and atypical neuroleptic drugs. We here evaluated the effects of different concentrations of a typical (haloperidol) and two atypical (clozapine, olanzapine) neuroleptics on the survival of human neuronal (SH-SY5Y cells) and immune cells (U937 cells) by determining the metabolic activity after 24 hours of incubation. A lack of such activity indicates cell death. To further elucidate possible mechanisms of action we also determined the ATP content in the cultured cells. After experimental treatment, significant effects were detected by ANOVA for all treatment conditions. Post-hoc tests (Dunn's method) showed that haloperidol and clozapine at their two highest concentrations (25 and 50 µg/ml) caused a significant decrease of metabolic activity in both cell systems, which was also detectable after treatment with clozapine at a concentration of 12.5 µg/ml in U937 cells. In contrast, olanzapine induced a significant increase in metabolic activity of SH-SY5Y cells at all concentrations except for the concentration of 3.1 µg/ml, whereas the metabolic activity in U937 cells was increased at concentrations of 1.6 and 6.25 µg/ml. For the determination of ATP content, the LD50 values of the metabolic activity were used, except for olanzapine for which no distinct LD50 value was available. Significant changes were detected for all treatments and post-hoc tests revealed that haloperidol caused a significant decrease compared to the control condition in both cell systems. These findings suggest that neuroleptic substances of different classes exert differential metabolic effects in both, neuronal und immune cell systems.

Poster Session

P-01 Pharmacotherapy I

P-01-01
Aripiprazole in treatment of borderline patients: A double-blind, placebo-controlled study
M. Nickel, W. Buschmann, M. Mühlbacher (Simbach am Inn, Salzburg)

A few neuroleptics have been used in therapy for patients with borderline personality disorder (BPD), which is associated with severe psychopathological symptoms. Aripiprazole, however, has not yet been tested for this disorder, and the goal of this study was to determine whether aripiprazole is effective with the multifaceted borderline symptomology. Subjects meeting the DSM-IV Structured Clinical Interview II criteria for BPD (43 female and 9 male) were randomly assigned in a 1:1 ratio to 15 mg aripiprazole per day (n = 26) or placebo (n = 26) for eight weeks. Primary outcome measures were changes on the Symptom-Checklist (SCL-90-R), the Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS), and the State-Trait Anger Expression Inventory (STAXI) and were assessed weekly. Side effects and self-injury were assessed by a non-validated questionnaire. According to the indent-to-treat principle, significant changes on most scales of the SCL-90-R, HDRS, HARS and on the all scales of the STAXI, were observed in the aripiprazole-

treated subjects after eight weeks. Significantly but rarely, self-injury was observed in the aripiprazole-treated group. The reported side effects were headache, insomnia, nausea, numbness, constipation, and anxiety.

P-01-02
Influence of Topiramate on olanzapine-related adiposity in women: A random, double-blind, placebo-controlled study
M. Nickel, C. Egger (Simbach am Inn, Salzburg)

The aim of this study was to compare the efficacy of Topiramate versus a placebo in the treatment of adiposity in women undergoing Olanzapine therapy. We also assessed changes health-related quality of life, the patient's actual state of health, and psychological impairments. The ten week, random, double-blind, placebo-controlled study included 43 female subjects who had been treated with Olanzapine (mean dose 7.8 ± 3.6 in the topiramate-group and 7.2 ± 3.1 in the placebo-group) and had gained weight as a side effect. The subjects were randomly assigned to Topiramate (n = 25) or a placebo (n = 18). Weight loss was observed and was significantly more pronounced in the Topiramate-treated group (difference in weight loss between the two groups: 5.6 kg, 95 %-CI = [–8.5; –3.0], $p < 0.001$). In comparison with the placebo-group, significant changes on seven (7/8) scales of SF-36 Health Survey (all $p < 0.001$), on all six scales of the EWL-60-S and on the Bf-S were observed in the Topiramate-treated subjects after ten weeks. All patients tolerated Topiramate well. Topiramate appears to be a safe and effective agent in the treatment of weight gain that occurred during Olanzapine treatment. ignificantly positive changes in health-related quality of life, the patient's actual state of health, and psychological impairments were observed.

P-01-03
Typical versus atypical antipsychotics: Are there really differences in subjective outcome?
R. Schmid, C. Cording, H. Spießl, T. Neuner (Regensburg)

Aim: This study examined differences between typical and atypical antipsychotics regarding subjective outcome.

Methods: 117 schizophrenic inpatients were surveyed by the questionnaires ZUF-8, SWN-K, WHOQOL-BREF, KKG and FKV. 72.6 % received exclusively atypical agents, 12 % typical, and 11.1 % an atypical-typical combination. Beside parametric and non-parametric tests, regression analyses on subjective outcome (ZUF-8, SWN-K, WHOQOL-BREF) were carried out; total/subscale scores, sociodemographic and disease-related variables from the German Basic Documentation System (BADO) entered computation.

Results: There were no differences between typical and atypical antipsychotics regarding ZUF-8 ($p = 0.770$), SWN-K ($p = 0.447$) and WHOQOL-BREF global score ($p = 0.560$). Also no differences could be found between quetiapine (n = 15), risperidone (n = 15), olanzapine (n = 15) and typical monotherapy (n = 13) with respect to ZUF-8 ($p = 0.061$), SWN-K ($p = 0.407$) and WHOQOL-BREF global score ($p = 0.554$). Antipsychotics could not be revealed as significant predictors for subjective outcome in regression analyses, whereas subjective concepts were relevant.

Conclusion: Using different statistical analyses, no differences between typical and atypical antipsychotics could be found. If these preliminary results could be confirmed with a larger sample, superiority of atypical antipsychotics has to be discussed again.

P-01-04
A clinical investigation of the effects of mirtazapine and reboxetine on car driving skills and driving simulator performance in depressed patients
A. Brunnauer, E. Geiger, G. Laux (Wasserburg/Inn)

Introduction: Psychomotor and cognitive slowing can frequently be found in depressed patients and may have an important influence on the ability to drive. Additionally, effects of sedation, as seen in some antidepressants, probably impair driving performance. The aim of the present study was to examine the influence of mirtazapine and reboxetine on psychomotor function related to driving skills and on simulated driving scenes in depressed patients.

Methods: Depressive inpatients (ICD 10) were assigned to either a group treated with mirtazapine (n = 15) or reboxetine (n = 15). Patients were tested before medical treatment (day 0) and on days 7 and 14 with computerized tests related to driving skills and additionally on day 0 and day 14 with a driving simulator.

Results: In both treatment groups significant improvements in tasks related to driving skills and in driving simulator performance could bee seen. After the post-acute treatment phase about 80 % of patients reached the criteria according to regulations of the German road safety board.

Conclusions: Treatment with either mirtazapine or reboxetine did not negatively affect driving related psychomotor skills on day 7 and day 14 of treatment in depressed patients.

P-01-05
Prescription of antidepressants and antipsychotics at a psychiatric state hospital
W. König, G. Laux, S. Artmann (Wasserburg, Wasserburg/Inn)

Objective: Aim of the study was to investigate the present mode of psychopharmacological treatment of depressive and schizophrenic inpatients at a large state hospital.

Methods: By means of the basic documentation all depressive and schizophrenic inpatients hospitalised in 2004/05 were examined with respect to their medication during their stay.

Results: The sample consisted of 474 depressive and 774 schizophrenic inpatients. Analysing prescriptions from the day of admittance to the day of discharge we found that in numerous cases the first line drug did not lead to sufficient symptom reduction, and that a switch was needed (antidepressants 69 %,antipsychotics 49 %). At the time of discharge 78.9 % of the depressive patients were treated with "modern" antidepressants,whereas only 58.6 % of the schizophrenic patients were treated with "modern" antipsychotics.

Conclusions: Comparing the prescription of older and newer psychotropics in ordinary clinical practice at a state hospital we found that in the treatment of depressive disorders the new drugs were highly preferred whereas in the field of schizophrenia the second generation antipsychotics did not dominate.

P-01-06
Long term effects of aripiprazole on the lipid profiles of patients with schizophrenia or bipolar I disorder
M. Ebrecht, M. Kungel, T. Spevakne-Göröcs, S. Modell, C. Werner, F. Grossman, A. Pikalov (Munich, Frankfurt, Wallingford, CT, Princeton, NJ)

Serum lipid level changes in patients with stabilized chronic schizophrenia and in bipolar I disorder patients undergoing long term treatment with aripiprazole were assessed. Incidences of treatment-emergent abnormal lipid levels associated with aripiprazole 15 mg/d (n = 153) or placebo (n = 153) were assessed at Weeks 6, 18, and 26 for schizophrenic patients. The same incidences for aripiprazole 15–30 mg/d (n = 77) or placebo (n = 83) were assessed at Weeks 8, 16, 26, 38, 52, 76, and 100 in the bipolar patient group. Abnormal lipid values were defined as total cholesterol (TC) ≥ 240 mg/dL, low-density lipoprotein (LDL) ≥ 160 mg/dL, high-density lipoprotein (HDL) < 40 mg/dL, or triglycerides ≥ 200 mg/dL. Total pooled incidences of abnormal fasting and nonfasting lipid levels did not differ significantly between aripiprazole- and placebo-treated patients in both studies. Schizophrenia patients: TC = 14.1 % aripiprazole, 7.2 % placebo; LDL = 8.6 % aripiprazole, 7.3 % placebo; HDL = 33.1 % aripiprazole, 38.4 % placebo; triglycerides = 23.2 % aripiprazole, 23.2 % placebo. Bipolar patients: TC = 14.9 % aripiprazole, 15.1 % placebo; LDL = 13.5 % aripiprazole, 12.3 % placebo; HDL = 44.6 % aripiprazole, 32.9 % placebo; triglycerides = 35.1 % aripiprazole, 34.2 % placebo. Lipid profiles in long-term aripiprazole treatment of patients with schizophrenia and bipolar I disorder were comparable to placebo.

P-01-07
Metabolic syndrome rates and changes in non-HDL cholesterol levels in schizophrenic patients treated with olanzapine vs. aripiprazole
M. Ebrecht, T. Spevakne-Göröcs, S. Modell, C. Werner, R. Marcus, M. Kungel (Munich, Frankfurt, Wallingford, CT)

Patients with schizophrenia exhibit higher rates of metabolic syndrome (METs, defined according to ATP III criteria) compared with the general population. Further, non-HDL cholesterol is a significant and independent predictor of cardiovascular events. This study compares METs rates and changes in non-HDL-c among schizophrenia patients randomized to either aripiprazole or olanzapine. The study sample consisted of patients from 4 pooled clinical trials of aripiprazole versus placebo and olanzapine. Rates of METs were compared between treatment arms at 26 weeks by Mantel-Haenzel Chi Square (LOCF). Mean change from baseline in non-HDL-c was compared between treatments at 26 weeks (LOCF) by ANOVA in a post-hoc pooled analysis using data from 2 of the clinical trials. After 26 weeks of treatment in the placebo-controlled studies, METs rates were 41 % for aripiprazole (n = 141) versus 43 % for placebo (n = 73) (P = 0.843). METs rates were 35 % for aripiprazole (n = 158) and 67 % for olanzapine (n = 141) in the comparative trials at 26 weeks (P = 0.0002). The mean change from baseline in non-HDL-C was statistically significant (P < 0.001) with an increase of 6.4 (± 2.4) mg/dL for olanzapine (n = 155) and decrease of 12.7(± 2.6) mg/dL for aripiprazole (n = 135). Levels of non-HDL-c can be significantly improved among patients treated with aripiprazole, but not for olanzapine patients.

P-01-08
Transition from IR methylpenidate to OROS®-methylphenidate: A naturalistic study is indicating significant improvements of functionality of patients with ADHD as assessed by physicians and caregivers
L. Hargarter, J. Czekalla, F. Mattejat, M. Gerwe (Neuss)

Background: The investigation of the effectiveness and tolerability after transition from IR-methylphenidate to OROS-methylphenidate due to suboptimal pretreatment should also include functionality and QoL.

Methods: Interim analysis of an open label, prospective, multicenter, non-interventional study up to 12 weeks for children and adolescents (aged 6–18 years), who met DSM-IV criteria for ADHD. Data was obtained after switching to OROS®-methylphenidate.

Results: Data from 296 patients (aged 10.4 ± 2.5 years, 85 % male) was documented. Symptoms improved from 29 ± 11 to 19 ± 11points (p < 0.0001) on IOWA Connors' Parent Rating Scale. QoL significantly improved from 29 ± 6 to 25 ± 6 points on the ILK Parent Rating Scale (p < 0.0001) and from 21 ± 5 to 18 ± 5 points on the ILK Child Rating Scale (p < 0.0001). Global assessments of functioning also improved (C-Gas reduction of 12 ± 14 points, p < 0.0001). CGI rated "better" or "much better" in 76 % and tolerability was documented "good" or "very good" in 87 % of patients after transition.

Conclusions: This naturalistic study indicates significant improvements of functionality of patients with ADHD as assessed by physicians and caregivers. Transition to OROS®-methylphenidate seems effective and well tolerated.

P-01-09
Antidepressants in the practice: Decision criteria underlying treatment strategies exemplified by mirtazapine (Remeron 45)
A. Delini-Stula, B. Scherrer, M. Kokic (Basel)

Introduction: There are hardly studies which have systematically analyzed factors influencing or determining treatment strategy with an antidepressant in the practice. We have therefore found of interest to investigate in this sense the results of an observational study with mirtazapine, in which the dosing of the drug was decided by investigators. One of the objectives of this analysis was to find out which treatment strategy provided optimum benefit to the patient.

Methods: A sample for the analysis consisted of 489 depressed patients attending private psychiatric practices in Switzerland and treated with mirtazapine for at least 8 weeks. During this period the demographic and other variables related to treatment and treatment outcome, pre- and co-medication as well as adverse events were recorded at the start of the drug therapy and 4 and 8 weeks thereafter. The interactions and correlations between the dosing schedules and a number of possible interfering variables were analyzed, among others, by means of a multivariate factor analysis.

Results and Discussion: The results revealed 4 principal treatment strategies: a) start with low dose (15 mg/d, 21.2 % of patients) with subsequent, stepwise dose increase, b) start with 30 mg/d (28.2 %) with increase to 45 mg/d in 12.5 % of patient c) start with 45 mg/d (41 %) with subsequent dose reduction in rather small proportion (8.5 %) of patients and d) start with high (≥ 60 mg/d, 2.8 %) and maintenance of the dose throughout. The factors best explaining the selection of these treatment strategies (from low to high doses) were, surprisingly enough, not the features of depression (p = 0.99), but severity of anxiety (positive correlation with high starting doses, p = 0.0005), severity of somatic symptoms (negative correlation, p = 0.0001) and age (negative correlation, p = 0.0001). The results also showed that starting the treatment with high e. g. 45 mg/d of mirtazapine and maintaining this dose throughout is the most optimal treatment strategy with best efficacy/tolerability ratio.

P-02 Personality disorders/Anorexia

P-02-01
Pain sensitivity is reduced in borderline personality disorder, but not in PTSD and bulimia nervosa
C. Schmahl, A. Zeuch, M. Meinzer (Mannheim)

Background: Several studies revealed reduced pain sensitivity in patients suffering from Borderline Personality Disorder (BPD) under baseline and stress conditions. To establish whether these findings are specific for BPD, we compared pain thresholds in patients with BPD, PTSD and Bulimia nervosa and healthy controls.

Methods: The study included 18 patients with BPD, 16 patients with PTSD, 21 patients with Bulimia nervosa and 24 healthy controls. Heat and cold pain thresholds were assessed under baseline and stress conditions, using a contact thermode. Mental stress induction was induced by the paced auditory serial additional task (PASAT-C).

Results: Under baseline conditions, pain thresholds in the BPD were significantly higher compared to healthy controls. Patients with PTSD and Bulimia nervosa did not show significant differences in pain thresholds compared to healthy controls. Under stress conditions, the difference between BPD patients and healthy controls became even more prominent, whereas the results in the other patient groups remained insignificant.

Conclusions: Our results support the hypothesis that reduced pain sensitivity is a prominent feature of BPD, which differentiates this disorder from other stress-related psychiatric conditions. The increased alteration of pain sensitivity under stress conditions is consistent with earlier studies.

P-02-02
Arachnoid cysts may cause adult personality change
K. Bechter, K. Seitz, G. Antoniadis, R. Wittek (Günzburg)

Introduction: Arachnoid cysts (ACs) are relatively frequent neuroradiological findings (3/1000) usually considered harmless if not space occupying. Even in so-called symptomatic ACs with headaches and seizures, it is not definitely clear whether AC surgery may improve the symptoms. Case reports We observed by chance (friend of K. B.) our first case of a so-called non-symptomatic arachnoid cyst. The person suffered from adult personality change. Against established rules the arachnoid cyst underwent neurosurgery and personality change reversed to normal (catamnesis 8 years). In a 2nd clinical case with personality disorder because of therapy resistance against established rules neurosurgery of a frontal AC was performed. Catamnesis and

test performance over > 1 year showed complete recovery from the personality disorder in case 2 also.

Conclusion: We conclude that adult personality disorder can be causally related to fronto-temporal ACs. We suggest systematic studies and a rediscussion of neurosurgery criteria of so-called non-symptomatic ACs in the case of personality change in adulthood, because even minor personality disorder may lead to severe life consequences.

P-02-03
Emotion perception and modulation in patients with borderline personality disorder and its effect on memory performance: fMRI and behavioural data
A. Beraldi, T. Zetzsche, C. Born, M. Reiser, R. R. Engel, K. Fast, T. Meindl, R. R. Engel, M. Reiser, H.-J. Möller, K. Fast (Munich)

Available functional imaging in BPD suggest that the amygdala and the prefrontal cortex play an important role in the pathophysiology of BPD (Herpertz et al. 2001). In the present study affective and cognitive components of the implicit encoding instruction of a memory task were modified in order to detect changes in emotional processing in BPD compared to healthy controls. Therefore two sets of fourty affective pictures each, of four valences (positive, neutral, low and high negative), have been presented in fMRI. On the one side we examined the influence of valence on perception and memory. On the other side we intended to study the capacity to modulate ones affective response and its influence on memory. We found in patients with BPD an increased activation of the amygdala even for low negative stimuli and more activation in the frontal regions during passive perception of the negative stimuli. No difference in amygdala activation was found in the regulation condition. In BPD more false recognition were observed, especially in the regulation condition. Although modulation of the amygdala activation seems to be possible by deliberate suppression in BPD, it seems to have an effect on the capacity of differentiation in memory performance.

P-02-04
Neuropsychological results in patients with borderline personality disorder
A. Beraldi, T. Zetzsche, R. R. Engel, S. C. Herpertz, K. Fast, B. Ruppel, H.-J. Möller, K. Fast (Munich)

To advance a better understanding of the neuropathophysiology of the borderline personality disorder (BPD) several neuropsychological, neuroanatomical and neurofunctional studies have focused on BPD showing consistent but also heterogeneous results. Neuropsychological data suggest impairments in cognitive domains of attention, memory, visuospatial and executive functions (O'Leary, 1991; Swirsky-Sacchetti, 1993; Judd & Ruff, 1993; Sprock et al., 2000; Dinn et al., 2004; Monarch et al., 2004; Posner, 1999; Van Reekum, 1993, 1996; Bazanis et al., 2002). In our study patients with BPD and healthy controls have undergone a vast neuropsychological battery. In our initial sample (n = 20) we found impairments in cognitive flexibility, immediate visual and verbal memory as well as in working memory (Beraldi, Fast et al., GNP 2005). In a experimental "Directed-Forgetting"-Paradigm (Korfine and Hooley, 2000) we found in the patient group an inability to inhibit negative words. This result confirms those found by (Domes et al., 2006) showing a deficit in cancelling negative stimuli from working memory. We will present new results of a bigger sample.

P-02-05
[I-123] ADAM and SPECT in patients with borderline personality disorder and healthy control subjects
N. Schaaff, G. Pöpperl, C. Mulert, M. Reicherzer, C. Ehmer-von Geiso, U. Hegerl, K. Tatsch, O. Pogarell, W. Koch (Munich)

Background: An impairment of central serotonergic system is considered to be involved in the pathophysiology of borderline personality disorder (BPD). Aim of this study was to investigate serotonin transporter (SERT) availability in patients with BPD as compared to healthy volunteers taking account of the subjects' individual scores of impulsiveness.

Methods: We performed single photon emission computed tomography (SPECT) with the serotonin specific radioligand [I-123] ADAM in eight unmedicated female patients with BPD and nine healthy control subjects. Impulsiveness was assessed with the Barratt Impulsiveness Scale (BIS-11).

Results: Mean specific-to-nonspecific ratios showed a 27 % higher brainstem and a 29 % higher hypothalamus [I-123] ADAM binding in the patients as compared to healthy controls. Significant correlations of ADAM brainstem binding with both age and impulsiveness were found for the whole sample.

Conclusion: Our findings are in line with previous data suggesting a serotonergic dysfunction in the pathophysiology of BPD. Scores of impulsiveness, seem to be associated with serotonin transporter availability in both patients and healthy controls. SERT availibility might be an indicator of impulsiveness or impulsive behavior independent from diagnosis.

P-02-06
The Loudness Dependence of Auditory Evoked Potentials in patients with borderline personality disorder and healthy control subjects
N. Schaaff, M. Reicherzer, C. Ehmer von Geiso, W. Koch, G. Juckel, U. Hegerl, H.-J. Möller, O. Pogarell, C. Mulert (Munich, Bochum)

Background: A central serotonergic dysfunction is considered to be involved in the pathophysiology of borderline personality disorder (BPD). The loudness dependence of the N1/P2 component of auditory evoked potentials (LD) has been shown to indirectly reflect central serotonergic activity. The aim of this study was to investigate LD in patients with BPD and healthy controls and support earlier findings of an increased loudness dependence in BPD patients.

Methods: Nine unmedicated and drug-naive female patients with BPD were compared with nine healthy female control subjects. We assesed the stimulus intensity dependence of auditory evoked potentials after presenting acoustic stimuli in pseudorandomized form. The LD of the relevant subcomponents (tangential dipoles) reflecting the serotonergic activity of the primary auditory cortex was investigated using dipole source analysis.

Results: The LD of the tangential dipole was significantly higher in BPD patients as compared to healthy controls. The differences remained significant after controlling for the effects of age.

Conclusion: Our data are in line with earlier findings of a pronounced loudness dependence of auditory evoked potentials in patients with BPD and support the hypothesis of a serotonergic dysregulation which might play an important role in the underlying pathophysiology of BPD.

P-02-07
International study of discrimination and stigma outcomes in mental health (INDIGO)
P. Decker (Munich)

About a tenth of the adult population suffer from mental disorders at any one time. These disorders now account for about 12 % of the global impact of disability, and this will rise to 15 % by the year 2020. People living with schizophrenia, for example, experience reduced social participation, whilst public images of mental illness and social reactions add a dimension of disability, which have been described as a 'second illness'. Low levels of knowledge about mental illness, stigmatising attitudes and discriminatory behaviour among the general population against people with severe mental illness are common in all countries. Globally, little is known of effective interventions against stigma. It is clear that the negative effects of stigma can act as formidable barriers to active recovery. In this context the INDIGO project will establish detailed international data on how stigma and discrimination affect the lives of people with a diagnosis of schizophrenia, from the point of view of service users themselves. Aims of

the INDIGO Study are to conduct qualitative and quantitative interviews with a diagnosis of schizophrenia at each participating site, to elicit information about how the condition affects their everyday lives. First results of the interviews with in-patients and day care patients and future perspectives will be discussed.

P-02-08
Association between the personality dimension "Novelty Seeking"and variants at the G72/G30 locus in a large population-based sample from Germany
J. Strohmaier, S. Höfels, J. Schumacher, M. M. Nöthen, S. Cichon, T. G. Schulze, M. Rietschel (Mannheim, Bonn)

G72 has previously found to be associated with schizophrenia, bipolar disorder and panic disorder. Genotype-phenotype correlation studies in the general population of disease-associated personality traits could assist in unraveling the mechanisms which lead to disturbed functioning in the mentioned disorders. We assessed a population-based sample of 1105 German individuals using the Tridimensional Personality Questionnaire (TPQ). Individuals were genotyped for the G72-markers M23 and M24. Logistic regression analyses were performed, with genotypes as dependent variables and "harm avoidance" (HA), "novelty seeking" (NS), "reward dependence" (RD) and the respective subscales as independent variables. Individuals with genotypes carrying the previously identified risk alleles, i. e. "C" (M23) and "T" (M24) had significantly higher scores on NS ($p = 0.031$ and $p = 0.013$) and its subscale "exploratory excitability vs. stoic rigidity" ($p = 0.048$ and $p = 0.046$) than non-carriers. There were no associations with HA, RD or other subscales. Exploratory excitability characterizes individuals who respond extremely to environmental stimuli. Due to the observation that G72 activates DAAO which acts on the NMDA receptors it may be hypothesized that G72 disease alleles contribute to increased stimuli response, a feature which is common to the mentioned disorders.

P-03 Molecular mechanisms

P-03-01
Species-related differences in the modulation of ligand-gated ion channels by psychopharmacological drugs
K. Mainka, P. R. Rainer, G. Rammes, W. Ziegelgänsberger, C. Nothdurfter, R. Rupprecht (Munich)

The 5-HT3A receptor is a ligand-gated ion channel. In case of ligand-binding to this receptor the chanel opens and it comes to an influx of cations. We wanted to investigate which part of the 5-HT3A receptor is important for the increase of the affinity of the ligand. Therefore we expressed a construct of two different chimera of murine and human 5-HT3A receptors in HEK 293 cells and measured the electric current which was triggerd by the agonist serotonin and the competitive antagonist clozapin by means of patch-clamp technique. We could show that the murine sequence of the receptor has a stronger affinity to serotonin as the human sequence, especially if the murine part is at the c-terminal position. Both chimera receptors were inhibited by clozapine, but not to the same extent as the wild type receptors. The inhibition of the murine chimera was more explicit than the inhibition of the human chimera. If the human sequence was at the n-terminus, the chimera current was similar to the human wild type. In conclusion the murine part of the receptor seems to play an important role for the affinity to serotonin, especially if its position is c-terminal. In contrary, the human sequence is apperantly more important for the affinity to the antagonist clozapin, in particular if its position is n-terminal.

P-03-02
Numerical alterations of hippocampal and prefrontal GABAergic interneurons in an animal model of psychosis, induced by NMDA-receptor antagonism with MK-801
J. Genius, H.-J. Möller, D. Rujescu, I. Braun (Munich)

Post mortem studies reported alterations in distinct subgroups of inhibitory GABAergic interneurons (IN) in the prefrontal cortex (PFC) and hippocampal formation (HC) in schizophrenic patients. These IN exert control over the excitatory output of pyramidal cells. As IR express distinct types of calcium binding proteins (CBP), like parvalbumin (PV), calretinin (CR) and calbindin (CB), we were able to differentiate these cells in a rat model based on chronic NMDA-antagonism with MK-801 at subanesthetic doses. We hypothesized that a reduction of PV+ IN may lead to abnormal cognitive function. To this aim, adolescent rats received MK-801 (0.02 mg/kg), haloperidol (1 mg/kg), a combination of both drugs or saline for 21 days. The animals underwent extensive behavior tests. One hippocampus was processed for gene expression analysis (Affymetrix rat genome 230 2.0 microarray), the other hemisphere was immunostained for PV, CR and CB. MK-801 exposure led to an alteration of the HC and PFC cytoarchitecture and regional distribution of CBPs as well as to changes of cognitive function. In good agreement with previous data we could demonstrate distinct alterations of CBP-containing IN, especially PV+ IN in the HC and PFC. These findings may account for some of the behavorial abnormalities exhibited by MK-801 treated rats and supply further support for the validity of our animal model.

P-03-03
Influences of the Arg16Gly polymorphism of the beta-2-adrenergic receptor gene in the psychopharmacological treatment of schizophrenia
I. Spellmann, R. Musil, S. Dehning, P. Zill, N. Müller, H.-J. Möller, B. Bondy, M. Riedel (Munich)

Introduction: Adrenergic effects are involved in thermogenesis, glucose and lipid metabolism but little is known about the influence of different polymorphisms of adrenergic receptors on metabolic side effects of atypical antipsychotic treatment.

Methods: We have genotyped schizophrenic patients being treated with atypical antipsychotics and healthy controls for the Arg16Gly polymorphism of the β2 adrenergic receptor. In the patients group weight, glucose and serum lipids have been monitored over a period of five weeks.

Results: 188 patients (103 males and 85 females, mean age 33.9 ± 12.4 years) and 395 healthy controls (196 males and 199 females, mean age 44.4 ± 16.1 years) have been genotyped. There was a significant relation between the β2 receptor Arg16Gly polymorphism and weight, as in Arg/Arg homozygote patients weight gain was more pronounced during the first four weeks than in Gly allele carriers ($p = 0.023$). We further found higher basal cholesterol ($p < 0.001$) and triglyceride levels ($p = 0.028$) in patients which are homozygote for the Arg allele than in carriers of the Gly allele.

Conclusions: There is a possible influence of a polymorphism of the β2 adrenergic receptor gene (Arg16Gly) on the cholesterol and triglyceride metabolism and on weight gain during a treatment of schizophrenic patients with atypical antipsychotics.

P-03-04
Influences of the Ghrelin Leu72Met polymorphism on weight gain and obesity in schizophrenic patients with antipsychotic treatment
I. Spellmann, R. Musil, S. Dehning, P. Zill, N. Müller, H.-J. Möller, B. Bondy, M. Riedel (Munich)

Introduction: Ghrelin is a recently discovered peptide with somatotrophic properties predominantly produced in the stomach. The Leu72Met substitution is an amino-acid-change in the protein sequence of the prepro-ghrelin found to be associated with an earlier onset of obesity. The objective of the present study was to investigate whether the Leu72Met polymorphism of the ghrelin gene could be

correlated with a more pronounced weight gain in schizophrenic patients being treated with antipsychotics.

Methods: We have genotyped schizophrenic patients being treated with different antipsychotics for the Leu72Met polymorphism of the ghrelin gene. Weight has been monitored weekly over a period of six weeks.

Results: 210 patients (118 males, 92 females) have been genotyped. We observed a significant increase in weight ($p < 0.001$) within six weeks of treatment with different antipsychotics. Furthermore there was a significant relation between the Leu72Met polymorphism of the ghrelin gene and weight, as carriers of the Met allele ($n = 34$) gained significantly more weight within the first ($p = 0.008$) and second week ($p = 0.044$) of antipsychotic treatment than patients being homozygote for the Leu allele ($n = 176$).

Conclusions: There is a possible influence of a polymorphism of the ghrelin gene (Leu72Met) and weight gain during an antipsychotic treatment of schizophrenic patients.

P-03-05

The modulation of the mineralo-corticoid receptor function by spironolacton and fludrocortisone has effects on basal cortisol secretion and learning performance under a stressful learning task

A. Thum, M. Giesler, B. Flux, P. Klee, A. Haag, J.-C. Krieg, B. Kundermann, U.-M. Hemmeter (Marburg)

Hippocampal mineralo (MR) and glucocorticoid (GR) receptors control basal and stress induced cortisol secretion. Furthermore, MR and GR are involved in learning and memory processes. We examined the effects of a modulation of the MR-system on basal and stress induced cortisol secretion and on learning and memory function. In a placebo (PL) controlled completely balanced repeated measurement design 24 healthy male subjects received a single oral dosage of either 200 mg spironolacton (SP), 0.1 mg fludrocortisone (FLU) or PL 3 hours before a stressful learning task. Number of trials, correct and false answers during learning and the number of correctly recalled associations were assessed. Cortisol samples were obtained from saliva. The application of 200 mg SP significantly increased basal cortisol compared to PL and FLU. After the application of FLU there was a trend for a faster learning performance than under SP. No differences between conditions for memory retrieval could be observed. SP is able to increase the basal tone of the HPA-axis reflected by an increased cortisol secretion. Stress induced cortisol secretion was not substantially modified by either FLU or SP application. The observation of a faster learning performance under FLU compared to SP suggests that the MR-function is related to cognitive processing during learning but not to memory retrieval.

P-03-06

Functional consequences of the accumulation of psychopharmacological drugs in "lipid rafts" on ligand-gated ion channels

C. Nothdurfter, M. Uhr, G. Rammes, W. Zieglgänsberger, K. Mainka, F. Holsboer, R. Rupprecht, B. Eisensamer (Munich)

"Lipid rafts" are specific microdomains within the cell membrane that are enriched with cholesterol and glycosphingolopids. Biochemically, they are characterized as detergent-resistant membranes that float at a light buoyant density an sucrose gradient density centrifugation. "Lipid rafts" are thought to participate in a variety of cellular functions, such as membrane trafficking and signal transduction. We could show an enrichment of different antidepressants and antipsychotics in "lipid rafts". This seems to play an important role in the allosteric modulation of the 5HT3-receptor which also accumulates in these membrane microdomains. On the other hand, psychopharmacological drugs that did not accumulate in "lipid rafts" were devoid of antagonistic properties at the 5HT3-receptor. Futher work will have to be done to show if the accumulation of psychopharmacological drugs in "lipid rafts" is of general significance for the modulation of ligand-gated ion channels which will be exemplary shown for GABAA-receptors.

P-03-07

The varying gene expression of proencephalin in human orbitofrontal-cortex of suicide victims

M. Dickmann, A. Thalmeier, I. Giegling, B. Schneider, A. M. Hartmann, K. Maurer, A. Schnabel, H.-J. Möller, D. Rujescu (Munich, Frankfurt)

Suicide is an old known phenomena in mankind. The biochemistry and physiology of suicidal behaviour is widely unknown. It seems to be a complex interplay of social-cultural factors, live events, personal traits and genetic vulnerability. Further more family and twin studies showed an incidence of heritability of suicidal behaviour and aggression related traits. Therefore our group designed a large scale case control genetic association study which included over 250 suicide attempters and 1600 healthy volunteers and investigated the role of a comprehensive set of candidate genes in this behavior. Additionally we performed a large scale micro array study in order to identify even new candidate genes for suicide using RNA derived from post mortem orbitofrontal cortex of suicide victims and matched controls. Data was validated by semi quantitative real-time-PCR (qPCR). On interesting gene we identified is proencephalin, a pentapeptide which competes with and mimics the effects of opioid drugs. It is involved in the physiological cell functions of pain perception and analgesia, the response of stress, aggression and dominance at the mammalian opioid system. It is expressed in most regions of the brain. We will discuss our results regarding proencephalin and its role in suicide-related behaviour. Additionally we did associations of this gene and aggression- and anger-related traits.

P-03-08

Clozapine enhances differentiation of preadipocytes

K. Fehsel, C. Gummersbach, K. Hemmrich, N. Pallua, C. Luckhaus (Düsseldorf)

Psychoactive drugs and especially clozapine cause massive weight gain in patients. Recent studies focussing on the activation of neuropeptides which are involved in the appetite regulating network presented controversal results. We postulated a direct effect of clozapine on fat cells. Therefore we studied the influence of clozapine on progenitor fat cells. Preadipocytes were isolated from human subcutaneous adipose tissue samples and cultured in Dulbecco's modified Eagle medium (DMEM)/F12 (1:1) with 10 % fetal calf serum (FCS). Differentiation was induced by insulin, isobuthylmethylxanthine, pioglita-zone, dexamethasone and transferrin after 7–14 days of culture expansion and in absence of FCS. Clozapine, haloperidol or LiCl were added every second day for the first 5 days of differentiation. Differentiation was assayed after 8–15 days by cell counting, Oil red staining and determination of glycerophosphate dehydrogenase (GPDH) activity, an enzyme only expressed in mature adipocytes. Treatment of preadipocytes with clozapine induced rapide triglyceride accumulation in the cells without effect on cell proliferation. In differentiation medium clozapine induced a significant rise in GPDH activity (126 ± 10 % in cells treated with 5 µM clozapine versus 100 % in untreated preadipocytes) and an elevated number of differentiated cells (57 % versus 46 % of control cells). Differentiation induction did not involve nitrite oxide/cGMP signalling, but might be caused by mitochondrial stress. Lithium chloride and haloperidol did not affect standard differentiation. In conclusion, our results suggest a new explanation for weight gain in patients treated at least with clozapine: increased fat mass due to enhanced differentiation from progenitor fat cells to mature adipocytes. Green tea extract which effectively inhibited preadipocyte differentiation in vitro, might also help preventing this weight gain in vivo.

P-03-09

A 5'UTR variant in the estrogen sulfotransferase (STE) gene is a candidate risk modifier for Alzheimer's disease in women

C. Luckhaus, B. Ibach, P. Fischer, I. Wichart, G. Gatterer, K. H. Tragl, E. Grünblatt, P. Riederer, P. Sand (Düsseldorf)

Sex steroids play an important role in the developmental organization of the brain and in activation across the life span. Estrogen, in partic-

ular, has been proposed to increase cholinergic transmission, to possess neurotrophic and antiamyloidogenic properties, and to improve cognitive performance. The estrogen-preferring sulfotransferase (STE) catalyzes the sulfate conjugation, and inactivation, of estrogens in the brain. This suggests a potential role of STE in modifying the susceptibility to cognitive decline, as in Alzheimer's disease (AD). To address this issue, we investigated an exonic STE gene variant in 118 subjects suffering from AD, and in 109 healthy controls matched for sex and age. When viewed in isolation, STE alleles did not associate with disease status. However, when the APOEμ4 genotype was taken into account, an association of STE and AD was noted in female μ4 carriers (OR = 3.47, p = 0.04). We conclude that genetic variation in the STE gene may act as a modifier of the risk for Alzheimer's disease in women and may relate to cholesterol transport.

P-04 Imaging

P-04-01
Proton MRS at 3 tesla in brain of schizophrenic patients: Elevated glutamate and reduced NAA in hippocampus
K. Leopold, F. Schubert, J. Gallinat, M. Schaefer, M. Krebs (Berlin)

We performed proton MRS in hippocampus and different cingulate regions of schizophrenic patients and healthy controls, focusing on quantitation of both glutamate and NAA in order to test the hypothesis of disturbed neurotransmission/energy metabolism and a possible parallel axonal loss. Eighteen patients (age 18 to 40 years) having schizophrenia according to DSM-IV criteria were examined and compared with 30 healthy age matched volunteers. MR examinations were performed on a 3T-scanner. Following T1-weighted imaging of the whole brain 1H-MR spectra were acquired using PRESS optimized for glutamate detection from 3 voxels including the left hippocampus (HC), the anterior cingulate gyrus (AC) and the posterior cingulate gyrus (PC). Apart from regional level differences, the Glu concentration in the HC voxel was significantly higher (11.8 mmol/l vs 10.4 mmol/l, p = 0.001) and the NAA concentration significantly lower (10.5 mmol/l vs 11.2 mmol/l, p = 0.016) in patients than in controls whereas there were no significant differences for the AC and PC voxels. Our finding suggests dysfunctional glutamatergic neurotransmission with concomitant disturbed neuronal integrity in a region playing a key role in the pathophysiology of schizophrenia.

P-04-02
Attention and behavioral control in alcohol use disorder: Simultaneously recorded ERP and fMRI
S. Karch, L. Jäger, A. Stammel, E. Karamatskos, C. Graz, O. Pogarell, U. Hegerl, M. Soyka, C. Mulert (Munich)

Chronic alcoholism is accompanied by neuropsychological deficits. However there is little consistency on whether there are circumscribed impairments or rather relatively general declines in cognitive functioning. In order to get further insight into the neurobiological correlates of alcoholism, we examined attention (oddball paradigm) and response inhibition (go/nogo task) in detoxified patients and healthy controls. A positive going ERP fronto-central during response inhibition was observed in patients. Also, a P300 was found mainly in parietal areas during the attention task. Both ERPs were slightly less pronounced compared to the control group. Concerning fMRI, we found attention-related activity in the ACC, insula, right middle frontal gyrus and temporo-parietal areas in both groups. In controls neuronal responses were more pronounced in the medial and right frontal areas and the ncl. caudatus. Patients showed enhanced activations in the thalamus, the left orbito- and middle-frontal gyrus. In the go/nogo task the contribution of right frontal and temporo-parietal areas was less distinct in patients than in controls. These results may indicate a right hemispheric dysfunction in subjects with alcohol use disorder. Taking into account the unimpaired behavioral results, one could speculate that the increase of left frontal activity may serve as compensation.

P-04-03
Simultaneous acquisition of EEG/fMRI during a working memory task in schizophrenic patients
S. Karch, I. Giegling, J. Lutz, A. Spörl, P. Hey, M. Buselmeier, D. Rujescu, C. Mulert, G. Leicht (Munich)

Working memory is a construct that describes the ability to transiently store and manipulate information on-line to be used for cognition or for behavioral guidance. Numerous functional imaging studies examined the neuronal correlates of working memory and revealed a distributed network that is activated during task execution. Deficits of various aspects of information processing including working memory are frequently found in schizophrenia. The study comprises 40 schizophrenic patients and 40 healthy controls. We used a parametric n-back task to incrementally increase working memory load during the same experiment. Spatial and temporal characteristics were investigated using fMRI and simultaneously recorded EEG. MR imaging was performed at 1.5 T Siemens Sonata scanner (EPI sequence; 16 slices; TR/TE: 4000/53 ms). EEG signals were recorded with an amplifier that can not be saturated by MR activity (61 channels according to the international 10/10 system; Cz reference). Regarding brain imaging data preliminary results showed the expected activations of the dorsolateral prefrontal cortex, ACC, premotor cortex, SMA, parietal cortex, thalamus and Ncl. caudatus in the control group. We expect abnormalities especially in the dorsolateral prefrontal cortex in schizophrenic patients. Further analysis will concern the temporal characteristics of functional abnormalities.

P-04-04
The transient gamma response and its sources in the auditory and the anterior cingulate cortex: Influence of task difficulty and mental effort
G. Leicht, R. Mergl, S. Karch, G. Juckel, U. Hegerl, O. Pogarell, C. Mulert (Munich, Bochum)

Investigating high frequency EEG oscillations in the 40Hz (gamma)-range can give answers to questions about interaction of brain regions and temporal dynamics of brain activity. In the present study, we were interested in the relationship between the transient gamma response (TGR) and task difficulty and mental effort. The TGR is known to be affected by attention. It has been suggested that besides auditory cortex activity, a frontal or anterior cingulate cortex (ACC) generator exists for the TGR. Since the TGR occurs quite early and the auditory association cortex (BA 22) is a major efferent target of the dorsal ACC, the ACC generator could be relevant for further auditory processing. 30 healthy subjects were investigated with six auditory reaction tasks with increasing difficulty and mental effort demands. Using a MANOVA with repeated measurements we found a significant main effect of task difficulty on both the TGR-amplitude and the auditory evoked N1-potential with higher amplitudes in the more difficult tasks. In a LORETA-region of interest analysis, this effect was only due to increased dorsal ACC-activity during the TGR-timeframe. For the later N1-timeframe, besides a strong effect in the dorsal ACC a similar main effect was found in the auditory association area 22. This might suggest an early feedback loop between dorsal ACC and auditory association area 22.

P-04-05
Suppression of verbal hallucinations and correlative changes in regional cerebral blood flow after intravenous lidocaine
C. Plewnia, M. Reimold (Tübingen)

Simple and complex auditory phantom-perceptions such as tinnitus and musical hallucinations occur predominantly in elderly subjects and are often associated with hearing impairment. Isolated phantom perception of voices without other psychotic features are rare and the underlying pathophysiology is unclear. It has been shown that an intravenous injection (i. v.) of lidocaine can transiently suppress tinnitus. Here we present the case of a 74 year old, left handed women with severely distressing, continuous phantom-perception of voices with-

out other psychotic features. I. v. injections of 100 mg lidocaine but not saline resulted in substantial transient suppressions of the hallucinations for several hours. Using [15O]H2O positron-emission tomography (PET) increased regional cerebral blood flow associated with the perception of voices was found in the right angular and supramarginal gyrus, right inferior frontal gyrus, orbitofronal cortex and in major parts of the cingulate cortex. These data suggest to further investigate the clinical relevance of i. v. lidocaine in patients with therapy-resistant verbal hallucinations, support the notion of common pathophysiological mechanisms in different forms of auditory phantom-perception and demonstrate the feasibility of a new strategy for imaging studies on auditory hallucinations.

P-04-07
Sensitivity and specificity of hippocampus volumetry and Diffusion-Tensor-Imaging (DTI) in amnestic MCI
M. J. Müller, D. Greverus, P. R. Dellani, C. Weibrich, A. Scheurich, P. Stoeter, A. Fellgiebel (Nieder-Olm, Mainz)

Hippocampus atrophy is frequently considered as a sensitive biological marker of mild cognitive impairment (MCI). Recently, Diffusion-Tensor-Imaging (DTI) has been successfully used to detect subtle brain tissue changes in neuropsychiatric diseases including MCI. The present study compared the diagnostic sensitivity and specificity of both methods. High resolution MRI-scans for hippocampus volumetry and co-registered DTI-scans for ROI-based mean diffusivity (MD) and fractional anisotropy (FA) were assessed in 18 patients with amnestic MCI (7 females, age 67 ± 9 years, MMSE 25 ± 2 points) and 18 controls (age 67 ± 9 years, MMSE 29 ± 1 points). Sensitivity and specificity of normalized hippocampus volume (HV) and DTI measures with regard to MCI status were estimated by receiver operating characteristics (ROC) curves; logistic regression was performed to analyze diagnostic accuracy (correct classifications). Parameters of the left hippocampus showed superior predictive power when compared to the right. At a specificity set to 80 %, left HV had low sensitivity (50 %); left hippocampal MD values revealed superior sensitivity (89 %), similar to left hippocampal FA (78 %). The results demonstrate higher sensitivity of DTI-derived left hippocampal parameters than volume measures in detecting subtle hippocampal abnormalities related to amnestic MCI.

P-04-08
Neuroimaging findings for associative learning in trauma
N. Gryschok, R. Lermer, T. Meindl, K. Latscha, M. Reiser, R. R. Engel, K. Fast (Munich)

Studies in animals suggest that prolonged exposure to stressful events is associated with an increase of the stress-hormone cortisol. Because of its glucocorticoid (GC) receptor sites the hippocampus is the primary spot to regulate cortisol levels. Direct GC exposure however results in a loss of neurons in the hippocampus and reduces the ability to form new memory traces. Studies showing the hippocampal toxity and memory dysfunction with stress led to the hypothesis that severe stress, such as the experience of trauma, may result in similar deficits in human subjects. Since policemen have a great chance to experience a traumatic event, we compared 10 trauma-exposed and 15 trauma-nonexposed policemen to clarify whether hippocampal activation is related to trauma and whether we find differences in cognitive functioning. We used functional neuroimaging (fMRI) to investigate the hippocampal activation during an associative learning paradigm. Additionally we examined cognitive functioning with an elaborated neuropsychological testbattery. The neuropsychological results show significant differences between the groups with worse results for the trauma-exposed policemen in explicit and implicit memory and in reaction times. The imaging data suggest a greater activation for the parahippocampal and the fusiform gyrus in trauma-nonexposed than in trauma-exposed policemen.

P-05 Neuropsychology

P-05-01
A neurofunctional study on associative learning in policemen with and without trauma
N. Gryschok, R. Lerner, T. Meindl, K. Latscha, M. Reiser, R. R. Engel, K. Fast (Munich, Munich)

Recent studies have reported memory deficits in patients with a Posttraumatic Stress Disorder (PTSD) which were associated with a reduced hippocampal volume. However very little is known about the functional role of the hippocampus in PTSD. Therefore it seems necessary to investigate the functional integrity of the hippocampus with the assistance of memory paradigms. The goal of the current research is to use functional neuroimaging (fMRI) to investigate the hippocampal activation during an associative learning paradigm. This paradigm consists of learning an association between different female faces and a profession. Additionally we examined cognitive functioning (memory, attention, executive functions and intellectual potential). Since policemen have a great chance to experience a trauma because of their profession, we compared 10 trauma-exposed policemen and 15 trauma-nonexposed policemen to clarify whether hippocampal activation is related to trauma and whether we find differences in cognitive functioning. The neuropsychological results show significant differences between the groups with worse results for the trauma-exposed policemen in explicit and implicit memory and in reaction times. The imaging data suggest a greater activation for the parahippocampal and the fusiform gyrus in trauma-nonexposed than in trauma-exposed policemen.

P-05-02
Interactions between affect and cognition in paranoid schizophrenia: The role of psychosis
K. Fast, A. Beraldi, S. Haralanov, E. Haralanova (Munich)

Although both emotional dysregulation and cognitive dysfunction in schizophrenia are well documented, the interactions between them remain unclear. The aim of the study was a comparison between schizophrenic patients and healthy controls, based on their cognitive evaluation of emotional arousal (EA) and the effect of EA on recognition memory performance. 30 patients with paranoid schizophrenia (15 psychotic and 15 post-psychotic) and 30 matched healthy controls performed two tasks: 1) Picture-viewing task: 40 affect-laden pictures of different social situations were presented randomly and the subjects had to rate each picture, according to the EA level it provoked. 2) Immediate recognition task: the 40 target pictures were intermixed with 40 new ones. The main finding was that cognitive dysfunctions interact with emotional dysregulation and vice-versa, especially during psychosis. The study provided measures for abnormal interactions between affect and cognition, discriminating psychotic from post-psychotic patients, as well as both schizophrenic subgroups from healthy controls.

P-05-03
Neurofunctional underlyings of a stable selective loss of autobiographical memory and self-awareness following a state of dissociative fugue
K. Fast, T. Meindl, A. Beraldi, C. Born, F. Padberg, R. Engel, M. Reiser, H.-J. Möller, F. Meister (Munich)

Neural correlates underlying the ability to richly re-experience autobiographical memory are known to primarily comprise areas of prefrontal cortex, medial and lateral temporal cortex, as well as posterior cingulate and retrosplenial cortex. Moreover, it was found that this form of memory more strongly engages parts of the frontal lobes involved in self-awareness as well as areas involved in visual memory apart from the limbic system. Our follow-up fMRI-study is based upon the case of NJ who suffered from a complete loss of autobiographical memory and of identity after a dissociative fugue. During scanning autobiographical and parallelised fictitious autobiographi-

cal cue words were presented. Directly after the fugue state NJ's neural activation was increased in left medial and inferior frontal regions, right precentral gyrus and posterior cingulate, whereas one year later a neurofunctional improvement of the network underlying autobiographical retrieval was given. This advancement indicates a recovery of neuronal dysfunctions and an efficiency of lasting psychogenic defense mechanisms in terms of a stable loss of autobiographical memories.

P-05-04
Episodic memory and active suppression: The effects of aging on the neuropsychological functioning of control processes
F. Meister, T. Meindl, C. Born, R. Engel, M. Reiser, H.-J. Möller, K. Fast (Munich)

Active suppression is a part of self-regulative functioning. Within a so-called think/no-think paradigm (subjects have either to remember or to suppress former studied words) a network model of memory control (Anderson et al. 2004) has been developed: the dorsolateral prefrontal cortex seems to play a crucial role in controlling the hippocampus while retrieving neutral material. On behavioural level was found that words of the think condition are better stored in memory than words of the no-think condition. In an own pilot-study we adapted this paradigm and compared the behavioural data of 15 younger (mean age 26.2 years) and 15 older healthy adults (mean age 65.9 years). We found a significant suppression effect in both groups and a general age-related memory decrease with an outstanding significant age-related effect of suppression. The ability to suppress seems to increase in aging. To further investigate this suppression effect we measured the brain activation of young (19–30 years) and older (> 55 years) healthy subjects with functional magnetic resonance imaging (fMRI) during the think/no-think paradigm. The activation pattern found in this paradigm is presented and discussed with regard to the behavioural and neuropsychological data as well as the underlying networks in suppression as proposed by Anderson et al. (2004) and the general neural substructures of aging.

P-05-05
X-Cog(R) – Evaluation of cognitive training effects in patients with alcohol dependence
H.-D. Hartung, N. Mamistvalov, T. Bchor, T. Schneider (Berlin)

Objective: To examine if the cognitive capacities of patients with alcohol dependence can be improved by a systematic training with the computer based X-Cog(R) program.

Method: Patients suffering from alcohol dependence who underwent alcohol withdrawal treatment in the Jüdische Krankenhaus Berlin were recruited for the experimental group (EG, 7 men, 3 women) and on a matched case basis for the control group (CG). EG patients trained the cognitive areas attention and working memory for approx. 2 weeks with X-Cog(R) (in mean 5 sessions of each 45 min. per patient). CG patients did not receive cognitive training.

Results: In a one-factor analysis of variance with repeated measures sign. post-training differences could be found concerning attention: All 3 relevant values (performance, quality and continuity) of the FAIR test (a German test measuring attention) were sign. higher for EG compared to CG. To measure the working memory, the test KAI-N was used: Post-training, the EG was able to memorize significantly more numbers and letters than the CG. However, with regard to the capacity of the working memory in general, no significant differences could be found, although tendencies have been uncovered.

Conclusion: The computer based cognitive training program X-Cog(R) seems to be effective for short-term training of cognitive functions in patients with alcohol dependence.

P-05-06
Sex-related effects of beta-adrenergic blockade on memory for traumatic events from the perioperative period of cardiac surgery
T. Krauseneck, G. Nollert, F. Padberg, G. Schelling (Munich)

Background: Women remember emotional events better than men. Encoding emotional stimuli depend on beta-adrenergic activation in both genders but they use different neural circuits. Beta-Blockers (BB) showed gender-related effects on emotional memory. Therefore we predicted different effects of BBs on traumatic memories.

Methods: A traumatic memory in this study is the patient's recollection of: 1. respiratory distress/dyspnea, 2. anxiety/panic, 3. pain and 4. nightmares/hallucinations. Baseline was evaluated 1 day before CS and then 1 week and 6 months after CS. BB could be administered any time postoperatively.

Results: Baseline showed no significant difference in NTR between male ($n = 95$) and female patients ($n = 33$). One week after CS, NTR in male patients was significantly higher ($p = 0.04$). BB had no significant effect in either sex. At six months, females with BB ($n = 18$) showed significantly lower NTR than females without BB ($n = 15$) ($p = 0.018$) and there was a significant 2-way interaction between gender and beta-adrenergic blockade. NTR correlated with totally administered epinephrine in males ($p = 0.004$) but not in females.

Conclusions: These findings support that beta-adrenergic stimulation with epinephrine en-hances memory for adverse experiences in males but not females and BB reduces memory for postoperative adverse events in females but not in males.

P-05-07
Cortisol increase during pair associate learning under stressful conditions in volunteers: Relationship to learning and memory performance
M. Giesler, A. Thum, B. Flux, P. Klee, B. Kundermann, J.-C. Krieg, A. Haag, U.-M. Hemmeter (Marburg)

Cortisol secretion is closely related to stress stimulation and learning and memory processes. In order to evaluate the effects of a stress induced cortisol secretion on learning and memory function we applied a computer based learning task in 24 healthy male subjects (age 20–30 years). This task had to be performed with (stress condition) and without (baseline) a time limitation. Both conditions were randomly assigned and completely balanced. The number of trials, correct and false answers during the learning task and the number of correctly recalled associations were assessed. Cortisol samples were obtained from saliva. The stressful learning condition induced a significant increase of cortisol compared to baseline learning without stress. In addition, stress related items of subjective mood (BSKE-scale) and vegetative symptoms (MSKL-scale) increased significantly. Cortisol increase during the stressful learning was not related to learning performance. However, subjects with a stronger increase of cortisol during learning performed worse in free recall after the experiment. In contrast, increase in subjectively experienced vegetative symptoms was closely related to a worse learning performance. The stressful learning task applied in this study is able to provoke a stress response on the endocrine and subjective level, which both affect learning and memory functions.

P-05-08
Prevalence and natural course of aging-associated cognitive decline (AACD) in a longitudinal population-based study (ILSE) in Germany: Preliminary results of the third wave
P. Toro, P. Schoenknecht, J. Pantel, A. Kruse, J. Schröder (Heidelberg, Frankfurt)

Objective: Little is known about prevalence and conversion from mild cognitive impairment (MCI) to dementia of subjects at risk in the general population.

Method: Within the population-based Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE), neuropsychological functioning was assessed in 500 community-dwelling subjects who were born during 1930–1932 in Heidelberg and Leipzig. The par-

ticipants were carefully screened for physical and mental health in 1994 (t1), 1998 (t2) and are being re-examined since July 2005 (t3). MCI was diagnosed according to the "aging-associated cognitive decline (AACD)" criteria. All diagnoses including conversion to AD were result of a consensus conference under supervision of senior consultant in old age psychiatry.

Results: Onto now, 130 participants have been re-examined in the third wave (t3). At t1, 13.4 % of the subjects were diagnosed as AACD. (t2) prevalence rates rose to 23.6 %, and at t3 37.7 % of the participants fulfilled the AACD criteria. At t3, 5.4 % of the participants investigated had developed AD.

Conclusions: As indicated by the longitudinal population-based study (ILSE), AACD is a frequent condition in the general population. While AACD prevalence increased in the longitudinal course, a subgroup of the AACD patients developed AD.

P-06 Pharmacotherapy II

P-06-01
Polymorphisms in the metabotropic Glutamate-Receptor 5 are possibly associated with response to treatment in schizophrenic patients
R. Musil, I. Spellmann, M. Riedel, B. Bondy, A. Douhet, S. Dehning, N. Müller, P. Zill (Munich)

Besides the dopamine-hypothesis a hypofunction of glutamatergic NMDA-currents is discussed as pathophysiologic correlative of symptoms in schizophrenia. NMDA-receptor-antagonists, such as PCP, can generate the positive, negative and cognitive symptoms of schizophrenia. Polymorphisms within metabotropic glutamate receptors (mGluRs) were found to be associated with schizophrenia in several studies and antagonists at the mGlu5 receptor can evoke negative symptoms in animal studies. In previous post-mortem studies we found an association between metabotropic glutamate receptors and schizophrenia. In the presented study we investigated several SNPs in the mGlu3 and mGlu5 receptors and tried to find an association to response in therapy. We genotyped 202 schizophrenic patients, who were treated monotherapeutically with different atypical antipsychotics within randomized controlled trials. Psychopathology was measured weekly using the PANSS. We found an association between the rs1993842 SNP of the mGlu5 receptor and therapeutic response. The G/T-allele carriers showed a statistically significant reduction in the PANSS-negative and -global subscales in comparison to the T/T-allele carriers ($p = 0.003$). This is the first study which shows, despite a low number of the G/T-allele carriers, an association between therapy response of negative symptoms in schizophrenia and the mGlu5 receptor. For the future we will try to find an association to cognitive symptoms.

P-06-02
Treatment of neuropathic pain with pregabalin under clinical practice conditions: impact on comorbidities
M. Brasser, C. Tilke, R. Mallison (Karlsruhe)

Patients who suffer from chronic pain often experience concomitant sleep disorders and depression/anxiety ("triad of pain"). These interrelating factors must be addressed for satisfactory treatment. Pregabalin, which modulates Ca-ion influx at presynaptic nerve terminals, is licensed for the treatment of peripheral neuropathic pain since 2004. In an open prospective observational phase IV trial, a total of 15,301 patients with peripheral neuropathic pain of various etiologies were treated with pregabalin under clinical practice conditions. Besides the Patient Health Questionnaire (PHQ), numerical scales (10 = worst, 0 = best rating) were used to measure presence and severity of pain, sleep disorders, depression/anxiety and wellbeing, respectively. At week 6 of pregabalin treatment, the mean pain score was reduced from 6.7 ± 1.6 at baseline to 2.6 ± 1.9. Pain-associated sleep disorders were reduced from 5.8 ± 2.5 to 2.0 ± 2.0. General wellbeing improved from 6.5 ± 2.1 to 2.4 ± 2.0. According to the PHQ, the rate of subjects with a major depression syndrome decreased from 64.3 % to 45.5 %. The rate of subjects with other anxiety syndromes decreased from 25 % to 4.7 %. A total of 87 % of subjects were satisfied with drug efficacy. Under clinical conditions, pregabalin significantly improved neuropathic pain and comorbidities, confirming findings from previous controlled studies.

P-06-03
A retrospective cohort survey – Switching to aripiprazole
M. Kungel, T. Spevakne-Göröcs, S. Modell, C. Werner, M. Ebrecht (Munich)

We present a cohort survey that was initiated in order to gain experience with switching treatment from other antipsychotics to aripiprazole. In the survey, a total of 86 patients with schizophrenia were evaluated retrospectively according to descriptions provided by physicians. In more than 80 % of the patients, previous medication was tapered off in 19.2 ± 14.3 (olanzapine) to 36.8 ± 24.3 (amisulpride) days, while aripiprazole was up-titrated in 83 % of the cases over 19.8 ± 22.0 days. Having completed the switch to aripiprazole, in 95.3 % of the patients an improvement of drive and in 76.7 % an improvement of cognitive function was observed. Sexual activity improved in 44.8 %, a reduction of previous drug abuse was observed in 7 % of the patients. Occurring side effects and interactions after switching such as agitation and sleeplessness were mainly transient. 88 % of the patients sought for continued treatment with aripiprazole, however, in 12 % of the cases therapy was discontinued due to lack of efficacy or increasing agitation. Although statistical significance is limited because of the small number and heterogeneity of the patients included, these results are in agreement with previous clinical findings, which have shown a good efficacy and safety profile of aripiprazole in patients with schizophrenia.

P-06-04
Schizophrenia Trial of Aripiprazole (STAR): Effectiveness of aripiprazole versus standard of care
M. Kungel, T. Spevakne-Göröcs, S. Modell, C. Werner, G. L'Italien, R. McQuade, M. Ebrecht (Munich, Frankfurt, Wallingford, CT, Princeton, NJ)

This naturalistic open-label study aimed to compare the effectiveness of aripiprazole and standard-of-care (SOC) in community-treated schizophrenic patients. 555 schizophrenic patients were equally randomised and treated with either aripiprazole (10–30 mg/day) or SOC (olanzapine 5–20 mg/day, quetiapine 100–800 mg/day or risperidone 2–8 mg/day) for 26 weeks. Overall effectiveness was evaluated using the Investigator Assessment Questionnaire (IAQ), the Clinical Global Impressions-improvement (CGI-I), the Preference of Medication (POM) and the Quality of Life (QoL) scales. At Week 26, the mean IAQ Total score was significant superior (LOCF, $P < 0.001$) for aripiprazole (25.7 ± 0.5) compared with SOC (27.7 ± 0.5). A significantly higher CGI-Improvement response rate was observed in the aripiprazole group (44 %) compared with the SOC group (34 %) (LOCF, $P = 0.009$). Significantly more patients in the aripiprazole group (47 %) compared with the SOC group (29 %) rated their study medication as being "much better" than their prior medication (LOCF, $P < 0.001$) on the POM scale. The mean change from baseline in the QLS total score was 8.17 ± 1.24 in the aripiprazole group and 3.22 ± 1.31 in the SOC group at Week 26 (LOCF, $P < 0.001$). In this naturalistic controlled trial aripiprazole showed a significantly superior effectiveness compared to SOC as measured by the IAQ, CGI-I, POM and the QoL score.

P-06-05
Schizophrenia trial of Aripiprazole (STAR): Safety and metabolic effects of Aripiprazole versus standard of care
M. Kungel, T. Spevakne-Göröcs, S. Modell, C. Werner, G. L'Italien, R. McQuade, M. Ebrecht (Munich, Frankfurt, Wallingford, CT, Princeton, NJ)

Certain antipsychotics are associated with metabolic adverse events such as weight gain. The STAR naturalistic open-label trial provides

the opportunity for a comparison of these events among patients treated with several major atypical antipsychotics. A total of 555 patients with schizophrenia were randomised to either aripiprazole (10–30 mg/day) or standard of care (SOC: Olanzapine 5–20 mg/day, quetiapine 100–800 mg/day or risperidone 2–8 mg/day) for 26 weeks. Mean changes from baseline in levels of total, HDL, LDL cholesterol, triglycerides, glucose, prolactin and weight were measured after 26 weeks. At Week 26, there was a statistically significant larger mean decrease of total cholesterol and triglycerides in the aripiprazole group vs the SOC group. Body weight decreased by 1.3 kg among aripiprazole patients and increased by 2.1 kg among SOC patients ($P < 0.001$). Glucose changes were not significantly different between aripiprazole and SOC. The proportion of patients with potentially clinically significant abnormal serum prolactin levels was 16.8 % in the aripiprazole group vs 54.4 % in the SOC group. The mean change from baseline in serum prolactin was -32.1 ± 1.8 in the aripiprazole group and -12.3 ± 1.9 in the SOC group (26 weeks LOCF $P < 0.001$). Patients treated with aripiprazole showed a greater improvement in metabolic parameters, in prolactin levels and in body weight.

P-06-06
Type and frequency of exclusion criteria in clinical phase III and IV trials in a psychiatric inpatient clinic
K. Meyer zur Capellen, M. Schmauss, T. Messer, C. Minov (Augsburg)

Clinical trials have essential importance for launching new and testing approved psychotropic drugs. The generalizability of treatment outcome research depends among other things on the recruited subjects restricted by inclusion and exclusion criteria in clinical trials. Particularly the use of exclusion criteria can optimize internal validity and feasibility, reduce cost and serve ethical functions. At the same time, these criteria can have negative implications for the generalizability of results to all patients because the included and excluded patients differ therefore. Type and frequency of exclusion criteria in clinical phase III and IV trials are presented for a psychiatric inpatient clinic and discussed with appropriate possible implications for forthcoming clinical trials and recruitment strategies.

P-06-07
Factors affecting the pharmacokinetics of escitalopram studied in a naturalistic design
U. Havemann-Reinecke, D. Wedekind, C. Genee, C. Hiemke, A. Brückner (Gottingen, Mainz)

The aim of this study was to analyse the relevance of epigenetic factors on the pharmacokinetics of escitalopram (S-CIT). In patients treated with S-CIT under naturalistic conditions steady state plasma concentrations of S-CIT and it major metabolite S-demethylcitalopram (S-D-CIT) were measured. Drug concentrations were related to dose, age, gender, comedication and comorbidity. Primary diagnoses of included patients ($n = 201$) were affective disorders (53 %, f>m), anxiety and somatoform disorders (14 %, m>f) and addiction diseases (14 %, m>f). The most frequent daily dose of S-CIT was 10 mg/day (49 %). Most patients were under polypharmacotherapy (84.4 %). The mean dose corrected plasma concentrations (C/D ratio) of S-CIT under monotherapy ($n = 31$) was 2.0 ± 1.4 ng/ml/mg. Under 20 mg, plasma levels were significantly higher in ♀♀ than in ♂♂. Correlation studies showed a significant positive relation of age and C/D ratio of S-CIT. Alcohol dependence associated with pathological liver changes did not influence blood levels of S-CIT. Only severe cirrhosis increased the level of S-CIT. Polypharmacotherapy lead to lower C/D of S-CIT. In benzodiazepine dependent patients the ratios of the metabolite S-D-CIT was significantly higher than under monotherapy with S-CIT. Data of this naturalistic study revealed that age and gender affect the pharmacokinetics of S-CIT.

P-06-08
QTc-changes in inpatients – A comparison of the atypical antipsychotics Ziprasidon and Olanzapin in a naturalistic study design
M. Opgen-Rhein, M. Riedel, N. Müller (Munich)

Abstract: Atypic antipsychotic medication may due to prolongation of the QTc-interval in the ECG. A abrupt rise in the QTc-interval, as well as a critically prolonged QTc-interval is associated ventricular arrhythmia, torsade de pointes and sudden death. In monotherapy trials Ziprasidon extend the QTc-intervall stronger than olanzapin, which has shown to have only a slight effect on the QTc-interval. We invastigated the influence of ziprasidon and olanzapin in clinical practice. ECG measurments of 71 inpatients were analysed in retrospect. As we used a naturalistic study design, there were no restriction in terms of comedication. 61 inpatients received at least one more medication. Patients treated with ziprasidon showed a significant larger QTc-intervall, than patients treated with olanzapin. There were no differences in the potential of ziprasidon or olanzapin to cause critical QTc-prolongation (QTc-interval >440ms). The different effects of the two medicaments were greatest in women and in higher aged persons. A direct connection between medication with ziprasidon or olanzapin and the appearance of fatal ventricular arrhythmia could not be proven until today. In each indivual case a risk profile of the patient to develop abnorm prolonged QTc-intervals should be acquired and the suitable antipsychotic should be chosen in dependence on side effects of the medicament.

P-07 Immunology

P-07-01
Defective immune response in Alzheimer's disease
E. Richartz-Salzburger, A. Batra, K.-J. Schott (Tübingen)

Introduction: Systemic immunological alterations may contribute to the pathogenesis of AD.

Methods: Patients and controls were >65 years and free of any other disease as well as of relevant drug intake. We measured antibodies against a series of autoantigens in serum and CSF using IFL and ELISA. Cytokines were examined in stimulated whole blood cell cultures by ELISA. Distribution of T-, B- and NK-cells was determined by FACS analysis.

Results: 1. AD patients show significantly lower CSF-concentrations of antibodies against Gm1-gangliosides than aged controls. 2. Levels of pro- and anti-inflammatory cytokines and of IL-2 after stimulation are significantly lower in AD patients. 3. AD-patients show a significant decrease of CD3+(T)-cells and of CD19+(B)-cells.

Discussion: We assume a generally diminished immune reactivity in AD, which may contribute to insufficient removal of amyloid-β. This hypothesis is supported by immunization trials enhancing both the humoral and cellular immune response. Lymphocyte dysfunction could be due to exaggerated telomere shortening or replicative senescence. Our observations resemble alterations seen in advanced immunaging, as is the case in Down's syndrome, where clinical and immunological progerie is associated with a high risk for AD. Hence, we hypothesize a premature immunosenescence as a pathogenetic factor in spontaneous forms of AD.

P-07-02
Elevated CSF and serum levels of S100B in first onset schizophrenia are not related to a degenerative release of GFAP, MBP and NSE from glia or neurons
J. Steiner, H.-G. Bernstein, B. Bogerts, M. T. Wunderlich, H. Bielau (Magdeburg)

Increased levels of S100B in serum and CSF have been observed in association with acute psychotic episodes in schizophrenia. This finding has been interpreted as a consequence of astrocytic damage or dysfunction. However, this assumption has not been proven yet. We

investigated CSF and serum samples from 12 patients with first onset schizophrenia and 17 control subjects by ELISA (GFAP/Glial fibrillary acidic protein, MBP/Myelin basic protein) or immunoluminometric sandwich assays (NSE/Neuron specific enolase, S100B). Patients with schizophrenia had significantly higher levels of S100B in CSF ($p = 0.004$; 2.73 ± 0.80 vs. 1.92 ± 0.58 microg/L) and serum ($p = 0.032$; 0.09 ± 0.03 vs. 0.08 ± 0.02 microg/L) in comparison to the matched control group. No diagnosis-dependent differences of protein concentration were seen for GFAP, MBP and NSE. A positive correlation was found between age and protein levels in CSF (MBP: $p = 0.000$; NSE: $p = 0.044$; S100B: $p = 0.003$) and serum (GFAP: $p = 0.000$; S100B: $p = 0.001$). Our finding of increased levels of S100B in schizophrenia without an indication for significant glial (GFAP, MBP) or neuronal (NSE) damage could be interpreted as indirect evidence for an increased active secretion of S100B in the brain during an acute psychotic episode in first onset schizophrenia.

P-07-03
Cellular immunity in patients with current posttraumatic embitterment disorder
C. Bruenahl, M. Linden (Berlin)

Chronic stress can lead to endocrinological and immunological changes. The assumption is that patients with prolonged stress should therefore show more signs of related illnesses. Yet, the clinical significance of these theoretical and to some part empirical findings is still unclear. Included were 50 inpatients who were suffering from posttraumatic embitterment disorder (PTED). They were compared with 50 matched control patients with unselected psychosomatic disorders but no immediate stress. PTED is a psychological reaction to negative life events which causes prolonged mental stress resulting in embitterment, withdrawal, phobic reactions, aggressive impulses towards oneself and others. Gender distribution and age were the same in both samples (60 % women; Mean Age: 49). PTED patients showed in the SCL-90 an average GSI-score of 1.13 (SD: 0.55) as compared to 0.74 (SD: 0.50) in the controls. We compared between both groups results from screening laboratory tests. We observed a significant decrease of polymorphphonuclears in patients with PTED and noticed a tendency to lower blood sedimentation rate and lower concentrations of GGT and higher concentrations of triglycerides compared to the control group.The study suggests that PTED, as a subtype of adjustment disorder, is associated with alterations in physiological systems. Additional research is needed.

P-07-04
Microglial density in schizophrenia and depression is independent from diagnosis but associated with suicide
J. Steiner, H. Bielau, G. Meyer-Lotz, R. Stauch, H.-G. Bernstein, B. Bogerts (Magdeburg)

We observed no significant microgliosis in schizophrenia in a previous postmortem study [Acta Neuropathol, online 06/2006]. However, single case analysis revealed increased microglial densities in two schizophrenics who had committed suicide. This led us to the hypothesis of microglial activation during acute psychosis. Alternatively, "suicide" would be a diagnosis-independent factor leading to microgliosis. To clarify this question, microglial HLA-DR expression was analyzed in 16 schizophrenics, 14 patients with depressive affective disorder and 10 matched controls, including a subgroup of 6 schizophrenics and 7 patients with affective disorder who died from suicide. Dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MD) and hippocampus (Hi) were investigated. ANOVA revealed no influence of diagnosis on microglial density (DLPFC: $p = 0.469$; ACC: $p = 0.349$; MD: $p = 0.569$; Hi: $p = 0.497$). Significant microgliosis was detected in the DLPFC ($p = 0.004$), ACC ($p = 0.012$) and MD ($p = 0.004$) of suicide patients, but not in the hippocampus ($p = 0.057$). In conclusion, immune aspects may play a hitherto underestimated role in suicide. One might speculate on a role of IL-1β, IL-2 or NO which are released from microglia and were shown to modulate noradrenergic and serotonergic neurotransmission. These transmitters are known to be associated with suicide.

P-07-05
Active immune processes in schizophrenia (SCH) – New evidence by elevated levels of serum Macrophage-migration-Inhibitor-Factor (sMIF)
L. de la Fontaine, P. Zill, R. Gruber, N. Müller, M. J. Schwarz (Munich)

Objective: Involvement of immune processes in the pathogenesis of SCH is discussed controversial but immunological alterations, partly similar to that of autoimmune diseases, have been constantly reported. Because of these cytokine alterations, the negative correlation of SCH and rheumatoid arthritis (RA) and MIF's important role as inductor of proinflammatory mediators, we investigated sMIF levels in both diseases and additionally the promoter polymorphisms: G173C and CATT-(5–8), reported to be associated with sMIF.

Patients and Methods: 95 SCH, 98 RA patients and 72 healthy individuals were included. Polymorphisms were determined by PCR, sMIF (ng/ml) by ELISA. Comparison of genotype frequencies: chi-2 test, sMIF levels between groups and genotypes: Kruskal-Wallis-test.

Result: Polymorphisms were equally distributed and showed no association with sMIF levels, but mean sMIF concentrations (SCH: 32.8, RA: 48.1, CON: 22.0) differed extremely between groups ($p < 0.0001$).

Conclusion: The profile of activities suggests an important role of MIF in the pathogenesis of inflammatory diseases. Independent from genotype, we found an extremely significant elevation of sMIF in SCH compared to healthy people, resembling results in RA. This again underlines the hypothesis of an activated immune system being involved in the pathogenesis of SCH as proved for other immune mediated diseases like RA.

P-07-06
Tourette-Syndrome – A sub clinical course of neuroacanthocytosis?
S. Dehning, R. Gruber, M. Riedel, N. Müller (Munich)

Tourette-Syndrome (TS) is characterized by vocal and motor tics frequently accompanied by self-injurious behaviour and compulsions. Etiologically a complex mode of inheritance with the involvement of several genes is assumed, at the same time immunological factors are postulated. Blood from 48 patients suffering from TS and 43 healthy controls were studied according to hemogram, inflammation parameters and clinical chemistry. Surprisingly, patients with TS showed a highly significant elevated mean corpuscular hemoglobin concentration (MCHC) and a lower hematocrit (HK), as well as a significantly elevated CRP, moreover they expressed elevated values for LDH, transaminases and CK. Such variances have not yet been described in psychiatric diseases. Phenomenological similarities arise clinically and chemically from the hereditary neuroacanthocytoses (NA). In NA, tics as well as self-injurious behaviour and compulsions are found. However, in contrast to TS, NA is associated with a degenerative course and the development of epilepsy, parkinsonism and dementia. In part, acanthocytes are detected in NA, in line with elevated MCHC and lower HK in TS. Elevated values for LDH, transaminases and CK are shown as well. For the NA-subtypes chorea-acanthocytosis and McLeod-syndrome, locations of genes are known. Gene typing of VPS13A and the XK-gene is now being carried out in TS.

P-07-07
Metabolic alterations in patients with narcolepsy
P.-A. Beitinger, R. Wehrle, S. Fulda, H. Himmerich, T. Pollmächer, T.-C. Wetter (Munich)

Sleep regulation and metabolism interact. Narcolepsy might be a particular interesting clinical model to investigate this interaction, as the disorder involves central deficiency of orexins, known to be involved in sleep regulation and in the regulation of food intake and body weight. Moreover, obesity is a well-known feature of narcolepsy, and some reports suggest that the incidence of type II diabetes is in-

creased. We examined 57 patients of the German Narcolepsy Society. Venous blood glucose, HbA1c, plasma-cholesterol, -LDL- and HDL-cholesterol, -triglyceride, -uric acid, -fibrinogen, -lipoprotein A and -homocysteine levels were assessed after overnight fasting together with anthropometric measurements. The International Diabetes Federation definition for the metabolic syndrome was applied. To date, the diagnosis of narcolepsy was confirmed in 28 patients (19 F/9 M). Nine patients showed abnormally high levels of fibrinogen, 7 patients of each with homocysteine or glucose or uric acid, 6 patients of HDL, 5 patients of LpA and trigylcerides, 2 patients of LDL and total-cholesterol and one patient of HbA1c. Nine patients met the criteria for the metabolic syndrome. These preliminary results suggest an elevated rate of individual metabolic abnormalities and of metabolic syndrome in narcoleptic patients.

P-07-08
Plasma levels of TNF-alpha and soluble TNF receptors in narcoleptic patients
P.-A. Beitinger, H. Himmerich, S. Fulda, R. Wehrle, J. Linseisen, S. Himmerich, T.-C. Wetter, T. Pollmächer (Munich, Freising-Weihenstephan, Ingolstadt)

Narcolepsy is a disabling sleep disorder characterized by excessive daytime sleepiness and cataplexy, hypnagogic hallucinations, and sleep paralysis. Recent studies suggest that the immune system might play a pathogenic role pointing to a possible involvement of inflammatory cytokines. We investigated a sample of 30 narcoleptic patients in comparison to 120 gender- and age-matched and 101 gender-, body mass index-, and age-matched randomly selected normal controls. In these groups, plasma concentrations of tumor necrosis factor-alpha and its soluble receptors p55 and p75 were measured using ELISAs. Narcoleptic patients showed a significantly higher BMI compared to controls of the same age. sTNF-R p75 levels were consistently elevated in the narcoleptic patients compared to their gender- and age-matched ($p = 0.001$) as well as gender-, BMI- and age-matched counterparts ($p = 0.003$). Female narcoleptics exhibited higher sTNF-R p55 levels than their gender- and age-matched controls ($p = 0.01$), but this difference disappeared when comparing patients to gender-, BMI- and age-matched normal controls. TNF-α levels did not differ significantly between groups. Narcoleptic patients show increased plasma levels of sTNF-R p75 suggesting a functional alteration of the TNF-α cytokine system further corroborating a possible pathogenetic role of the immune system in this sleep disorder.

P-07-09
Immunemodulatoric therapy in Tourette's disorder – A comparison
A. Cerovecki, A. Michler, M. Riedel, N. Müller (Munich)

The quest for the aetiology of Tourette's disorder (TS) pursuits, among others, infectious, alternatively allergic genesis as a cause, increasingly leading to immunemodulatoric therapy efforts. A retrospective study with 34 patients suffering from Tourette's disorder, who had received antibiotic and/or immunglobulin therapy compared the effectiveness of the different treatments, using a retrospective clinical staging (CGI, TSGS) and considering factors as microbiological results prior to the first immunmodularising therapy. Comparing different therapeutic outcomes pointed at an improved efficacy of the antibiotic therapy, if patients displayed an increased Streptokokkentiter (especially with enhanced Anti-DNAse-Titern) before first treatment. The Immunglobulintherapie proved to be more effective for TS-patients with increased Chlamydientitern. Given the fact, that patients with conspicuous levels of Mykoplasmen- und Streptokokken responded well more effectively to an immunemodulatoric therapy, undergirds a potential infectuously triggered genesis of tics in a subgroup of TS-patients. Furthermore the study showed an increased responsiveness to immunemodulatoric therapy for patients with multiple infections, compared to patients with only a single conspicuous microbiological diagnostic finding. The effect of multiple infections on the genesis or alternatively exacerbation of tics, as well as the prognostic importance of increased Anti-DNAse-Titers for the efficacy of immunemodulatoric therapy will have to be analysed in future studies.

P-08 Genetics

P-08-01
5,10-methylenetetrahydrofolate reductase (MTHFR) C677T Polymorphism and its influence on Plasma Homovanillic Acid among alcohol dependent patients
U. Lutz, G. Wiatr, W. Kolb, F. Machicao, S. Maurer, M. D. Köhnke, A. Batra (Tübingen, Oppenweiler)

Elevated plasma homocysteine levels are found in alcoholics. MTHFR plays a crucial role in homocysteine metabolism. Among alcoholics MTHFR C677T polymorphism has a high impact on plasma homocysteine levels. Recent studies indicate that homocysteine has toxic effects on dopaminergic neurons and lowers levels of homovanillic acid (HVA) in the rat striatal region. The mesolimbic dopamine system is important for the rewarding effects of alcohol. It was shown that plasma HVA is significantly lower in alcoholics compared to healthy controls. This is the first study investigating the impact of MTHFR C677T polymorphism on HVA plasma levels. 142 alcohol dependent patients and 101 healthy controls have been recruited. Alcoholics were examined after a minimum of 22 days of abstinence. Among alcohol dependent patients carriers of MTHFR C677T T-allele had significantly lower HVA plasma levels compared to non-carriers of T-allele: 11.9 vs. 14.4 ng/ml (chi-square: 5.39; $p = 0.02$). Analyzing only healthy controls revealed no difference between T-allele carriers and T-allele non-carriers concerning HVA plasma levels: 15.1 vs. 15.3 ng/ml (chi-square: 0.04; $p = 0.82$). The data suggest a MTHFR C677T polymorphism-dependent, probably homocysteine-mediated decrease of plasma HVA among alcohol dependent patients. This might be due to neurotoxic effects of homocysteine on the dopaminergic system.

P-08-02
Gene expression profiling of post mortemorbitofrontal cortex in suicide victims
A. Thalmeier, I. Giegling, B. Schneider, A. M. Hartmann, K. Maurer, A. Schnabel, H.-J. Möller, D. Rujescu, M. Dickmann (Munich, Frankfurt)

Suicide is a great public health problem, causing more than 10,000 deaths in Germany each year. Twin, adoption and family studies have shown that suicidal behavior has a heritability of about 40–50 %, but only few is yet known about the responsible genes. We have conducted a large scale microarray study in order to identify new candidate genes for suicide using RNA derived from post mortem orbitofrontal cortex of suicide victims and matched controls. 124 transcripts out of the more than 24,000 assessed showed significant expression changes with fold changes greater than 1.3 and $p <= 0.01$. 60 of these mRNAs were under-expressed in the suicide-group and 66 were over-expressed. The validation of particulary interesting transcripts with semiquantitative Real-Time-PCR yielded significant expression changes for 9 genes. The classification of the identified genes further demonstrated that the Gene Ontology categories 'transmission of nerve impulse', 'central nervous system development', 'homophilic cell adhesion', 'regulation of cell proliferation' and 'transmission of nerve impulse' were significantly enriched. In summary, the present study yielded interesting new candidate genes and identified Gene Ontology categories, that migth be involved in the etiology of suicidal behavior.

P-08-03
Neuropsychological endophenotypes in schizophrenia as tools for genetic studies
H. Konnerth, A. M. Hartmann, P. Muglia, A. Ruppert, H.-J. Möller, D. Rujescu, I. Giegling (Munich, London)

Clinical classification systems may describe heterogeneous disorders implying that the current psychiatric classification might not be op-

timal for genetic studies. In contrast, endophenotypes describe quantifiable measures of neuropsychiatric functioning which might not be restricted to one clinical entity but are more easily attributable to genetic variations. Our ongoing project includes a broad range of schizophrenia-related endophenotypes. These comprise, among others, neuropsychological endophenotypes (working memory, attention/vigilance, verbal/visual learning and memory, speed of processing and problem solving). The aim was to analyse a broad range of neuropsychological endophenotypes in patients with schizophrenia, first degree relatives and healthy controls and to search for associated genes. Over 200 patients with schizophrenia according to DSM-IV, siblings and over 400 healthy volunteers were included. Facets of memory, learning and attention were assessed by the Wechsler Memory Scale-Revised. As expected, schizophrenic patients as well as their healthy siblings had clear deficits in these tasks comparing with healthy controls. Additionally, we will present data on the influence of common genetic variations (from the glutamatergic and dopaminergic system) on individual differences in these endophenotypes and discuss the findings in the context of schizophrenia.

P-08-04
Association of short-term response to haloperidol treatment with polymorphisms in the dopamine D(2) receptor gene
A. M. Hartmann, P. Kraemer, M. Schäfer, B. Bondy, H.-J. Möller, D. Rujescu, I. Giegling (Munich, Essen)

Objective: Pharmacogenetic influences on therapeutic response to neuroleptic treatment are poorly understood. This study investigates the association of response to short-term haloperidol treatment with 24 polymorphisms in the DRD2 and the adjacent ANKK1 genes.

Method: 118 patients with acute psychosis were treated with haloperidol for up to 28 days. Improvement and response were measured using the Positive and Negative Syndrome Scale. Genotyping of 24 SNPs was performed.

Results: Two haplotype blocks were identified, with block one beginning at the 5'end of ANKK1 and stretching to exon 8, and block two starting with the DRD2-TaqA1/A2 polymorphism in the 3'end of the ANKK1 gene and reaching into intron 1 of DRD2, thereby spanning most of the coding region of DRD2. Four SNPs localised in haplotype block two were associated with improvement of negative symptoms, and additional two SNPs showed a trend. Differences in improvement of positive symptoms reached statistical significance for 2 SNPs. Regarding the general subscale, a subset of 3 SNPs remained significant.

Conclusions: These results support the hypothesis that genetic variations in the DRD2 gene may influence the individual response to antipsychotics. The recently identified ANKK1 gene is probably not involved but can not be completely ruled out as a candidate gene.

P-08-05
Working memory deficits as endophenotypes for genetic studies in schizophrenia
S. Schertl, A. M. Hartmann, P. Muglia, A. Ruppert, H.-J. Möller, D. Rujescu, I. Giegling (Munich, London)

Family, twin and adoption studies demonstrate a strong genetic influence in schizophrenia. To clarify parts of the pathobiology and genetics of schizophrenia it is preferable to use complementary strategies including genetic association studies as well as endophenotypes which have the potential to facilitate the identification of genes associated with schizophrenia. We analyzed facets of working memory, executive function and attention. Over 200 patients and 400 controls performed a neuropsychological test battery containing Wisconsin Card Sorting Test and n-back. WCST is a common instrument used for the assessment of working memory and executive functions. The n-back task engages the working memory system in maintaining and updating information over short delays. SNP selection was performed using the NCBI SNP database. A pool of SNPs was designed by the MassARRAY Assay Design software using the iPLEX assay. Tests for associations using multi-marker haplotypes were performed using the statistics software "R". To compare quantitative traits between the haplotypes the package "haplo.score" was used adding the covariates sex, age, education and diagnosis as appropriate. As expected, siblings and patients showed a reduced performance in all of these tests. Findings in the context of schizophrenia, cognitive performance and genetic variations will be discussed.

P-08-06
Genetic association study in schizophrenia and cognitive performance
M. Boxleitner, A. M. Hartmann, P. Muglia, A. Ruppert, H.-J. Möller, D. Rujescu, I. Giegling (Munich, London)

We first aim to identify schizophrenia genes in a large case-control and family-based study. 500 patients with schizophrenia according to DSM-IV and 200 first degree relatives were included. Furthermore, 1600 community-based healthy volunteers without relevant somatic, and with no history of psychiatric disorders in themselves and in first-degree relatives entered the study. All subjects are screened by SCID and characterized by other specific instruments. High-throughput genotyping of candidate genes has been performed using MALDI-TOF. Single nucleotide polymorphisms (SNPs) were selected (tag SNPs in addition to common functional variants and published candidate SNPs localized in selected genes). Furthermore, we use endophenotypes as a complementary approach. Our ongoing endophenotype project includes a broad range of schizophrenia endophenotypes. These comprise, among others, neuropsychological (e. g. working memory, attention/vigilance, verbal/visual learning and memory, speed of processing, and problem solving) measurements. We performed full scale IQ measurements in over 1600 healthy subjects, schizophrenic patients and their first degree relatives. Furthermore, we assessed the other above-mentioned endophenotypes in over 500 subjects. We present here data on the influence of common genetic variations on individual differences on cognitive performance and schizophrenia.

P-08-07
Estrogen Receptor (ESR) β gene haplotypes and Alzheimer's Disease (AD)
C. Luckhaus, B. Ibach, P. Fischer, I. Wichart, G. Gatterer, E. Grünblatt, P. Riederer, P. Sand (Düsseldorf)

In the CNS, estrogen receptors (ESR) α and β mediate beneficial effects of estrogen on neuronal survival and connectivity, and may modulate the risk for AD. We conducted a case-control association study in 126 subjects with AD and 111 healthy controls of German or Austrian descent. AD diagnosis was based on NINCDS-ADRDA criteria and was supported by results from an extensive screening protocol including laboratory blood screen, psychometric testing, and cerebral imaging. Subjects were genotyped for three biallelic ESRβ gene variants with PCR-based RFLPs. No significant group differences were noted when allelic distributions were compared for the three individual markers. However, two three-locus haplotypes differing by one allele jointly predicted disease status ($LR = 11.21$, $p = 0.003$) as did a core ESRβ diplotype ($LR = 5.31$, $p = 0.021$). This is the second study to describe an association of ESRβ variants and AD. The mechanism underlying the effects of the present risk diplotype from the gene's 3-UTR may involve post-transcriptional modifications and warrants further study.

P-08-08
Relative expression of tryptophan hydroxylase 1 and 2 in the brain: A spatial analysis
C. Kriegebaum, A. Schmitt, G. Ortega, K.-P. Lesch, L. Gutknecht (Würzburg)

The central serotonergic system is implicated in affective psychiatric disorders and neurodevelopment. The rate-limiting step in the serotonin biosynthesis is catalysed by two known enzymes: Tryptophan Hydroxylase 1 (TpH1) and 2 (TpH2) encoded by different genes. The

two isoforms are highly homologous and in spite of some sequence and biochemical variations, the main difference between TpH1 and TpH2 probably lies in their tissue-specific expressions. Several partial expression studies in different species, of one or both isoforms, performed in different tissues gave divergent results. Since this discrepancy needs to be clarified, we started to study in a more systematic manner, the relative expression of the two TpH isoforms in brain and some peripheral tissues, taking advantage of three different methods: quantitative real time-PCR, in situ hybridization and immunohistochemistry with specific antibodies we developed. Our results show that TpH2 expression is highly predominant in raphe nuclei-containing brainstem compared to TpH1 expression, while the relationship is inverted in the pineal gland. In all other tested brain regions, TpH2 is expressed at a lower level and TpH1 at a non-physiological relevant level. However, TpH1 is the main expressed TpH isoform in the periphery but we detected also TpH2 in some peripheral tissues. In conclusion, our preliminary results show that TpH2 is the most relevant isoform of the central nervous system, but the role of TpH2 in the periphery remains unclear.

P-08-09
SNAP-25 gene polymorphisms and weight gain in schizophrenic patients
R. Musil, M. Riedel, S. Dehning, A. Douhet, P. Zill, N. Müller, H.-J. Möller, B. Bondy, I. Spellmann (Munich)

Drug induced weight gain is a serious side effect of many atypical antipsychotics. As genetic factors play an important role in the homeostasis of hunger/satiety we tried to replicate a previous finding about an impact of three polymorphisms (MnlI, TaiI, DdelI) in the synaptosomal-associated protein of 25 kDa (SNAP-25) on clinical response and antipsychotic induced weight gain in a sample of schizophrenic patients.

Methods: Pharmacogenetic analyses were performed with 162 schizophrenic patients treated in monotherapy with atypical antipsychotics. PANSS scores and weight were measured weekly for five weeks. Patients and 312 control subjects were genotyped for the three polymorphisms in the SNAP-25 gene.

Results: Genotypes and allelic distribution did not differ between patients and controls. Significant associations were found between the TaiI and MnlI polymorphisms and basal serum triglyceride levels and for the DdelI polymorphism and weight gain during 5 weeks treatment. Homozygote TT-allele carriers gained less weight and BMI than those with TC and CC genotypes.

Conclusions: Our study can at least partly replicate previous findings concerning the impact of SNAP-25 gene polymorphisms on weight gain during antipsychotic treatment. The data give valuable hints that not only weight but also disturbances in the lipid profile might be influenced by variants in this gene.

P-09 Depression/Anxiety

P-09-01
The description of depression through an autonomic control structure
H.-U. Noffke (Stuttgart)

In 1970 W. R. Hess showed the similar topographic anchoring of opposing feelings, moods and autonomic regulation and emphasized the basic meaning of the principle of antagonistic control also for these psychological qualities. The ergotropic-trophotropic zones of the hypothalamus correspond to the division of the autonomic nervous system into sympathetic and parasympathetic and demonstrate in combination with the mesencephalic-limbic coupled ergotropic-trophotropic circuits the importance of the autonomic regulatory structure for central regulation. If one assumes in an ideal model, that the effector "mood", which shows itself characteristics of a vegetative effector, in similar "vegetative ways" receives input from the ergotropic and trophotropic system, a describability of normal and polar mood states becomes evident. The organization of polar mood states speaks for an increase in the degree of regulatory freedom upon transition from anger to fear and/or high to low mood.

P-09-02
Ginkgo Biloba Extract EGb 761 Inhibits MAO A and Synaptosomal uptake of Norepinephrine, Serotonin, and Dopamine
W. E. Müller, C. Fehske, K. Leuner (Frankfurt)

Current use of Ginkgo-biloba extract EGb 761® for the treatment of different types of mild-to-moderate dementia is supported by many preclinical and clinic studies. The latter ones also indicated certain antidepressant properties of EGb 761®, as within the behavioural and psychological symptoms of dementia, mainly the affective spectrum of the symptoms is alleviated by the ginkgo extract. In earlier investigations employing animal models for depression EGb 761® also exhibited weak antidepressant properties, yet these differed from classical antidepressants. On this background we investigated a possible mechanism of action for the proposed antidepressant efficacy of the ginkgo extract, using a MAO-acitivity assay and a synaptosomal neurotransmitter uptake assay in NMRI mice and Wistar rats. MAO-A was found to be inhibited by EGb 761® (IC50: 169 µg/ml), whereas MAO-B activity was almost unaffected. The uptake of three 3H-labelled neurotransmitters was inhibited in a concentration-dependant manner: For ^{3}H-serotonin and ^{3}H-dopamine uptakes, similar IC50 values were found, (130µg/ml and 143 µg/ml), while even lower concentrations inhibited the uptake of ^{3}H-norepinephrine (IC50: 40 µg/ml). These data suggest that a possible antidepressant activity of EGb 761® might be mediated through similar mechanisms already known to be relevant for the action of many antidepressant drugs.

P-09-03
Fatty acids and blood pressure in depressive inpatients
G. Irmisch, S. Herpertz, J. Richter, D. Schläfke (Rostock, Oslo)

Autonomic dysfunctions play an important role in depressive disorders. Depression is described either to be associated with elevated as well as with lowered blood pressure. The lowering effect of n-3fatty acids onto blood pressure is already well known. However, the particular pattern of relationships between fatty acids in blood, blood pressure and the severity of depression, is still unknown. Concentrations of various fatty acid in blood serum of 89 depressive inpatients, the severity of depression (assessed by means of Beck Depression Inventory [BDI] and Hamilton-Depression Rating Scale [HDRS]) and diastolic (DBP) and systolic (SBP) blood pressures were measured. Among the most frequent fatty acids in blood consisting of 12 to 22 carbons, myristic and oleic acids were significantly correlated with SBP (14:0 $r = 0.23$ $p = 0.028$; 18:1 $r = 0.23$ $p = 0.028$). DBP did not correlate significantly with fatty acid concentrations.The severity of depression was negatively correlated with the concentrations of lauric and eicosapentaenoic acids (BDI X 20:5 $r = -0.49$ $p = 0.022$; HDRS X 12:0 $r = -0.29$ $p = 0.040$). Regarding the relationship between blood pressure and the degree of depression, we found a significant negative correlation between BDI and SBP (BDI X SBP $r = -0.19$ $p = 0.056$).

P-09-04
Effects of a phytotherapeutic triple combination (St. John's wort, valerian, passion flower) on sleep EEG, cognitive performance and mood: A double-blind cross-over study in healthy volunteers
M. Giesler, A. Thum, A. Haag, A. Wartenberg-Demand, G. McGregor, B. Kundermann, J.-C. Krieg, U.-M. Hemmeter (Marburg, Giessen)

Almost all drugs for treating insomnia in depression improve sleep, but worsen cognitive performance (CP). Phytotherapeutics may improve depression, anxiety (St. John's wort, passion flower) and sleep (valerian) without affecting CP. Neurapas® balance (NB) is a combination of these extracts, which is widely used for treating minor depression in Germany. In this study, we tested the effect of NB on sleep-EEG, mood and CP in order to evaluate central nervous effects of NB. 20 healthy subjects were examined twice in a double-blind, randomized cross-over design and received either placebo or NB. De-

pendent variables were sleep-EEG parameters, mood (BSKE), vegetative symptoms (MSKL) and CP-tests. The results revealed that NB reduced wakefulness, REM-latency and NonREM-sleep in the first sleep cycle, which was compensated by an increase of NonREM-sleep in the second cycle. Positive trend effects of NB were found for the items, mental agitation and melancholy (BSKE), hand-trembling and hand-moisture (MSKL). No differences between NB and placebo were observed in CP-tests. The results show that NB has central nervous effects as reflected by changes in sleep EEG. Furthermore, sleep continuity and subjective mood were improved without negative effects on CP. These findings indicate that NB has neurophysiological effects on the brain and improves mood even in healthy subjects.

P-09-05
Anticipatoric anxiety as prediction for CCK-4 induced panic?
S. Wenninger, R. Rupprecht, C. Schüle, D. Eser (Munich)

Introduction: Since many years CCK-4 (Cholecystokinin-Tetrapeptide) is successful used in clinic studies to induce panic in healthy volunteers (e. g. Montigny 1989). Though many studies show the positive effects of CCK-4 in such panic-paradigmas, the most of them do not consider the individual state and trait anxiety-level of the subjects. This proof-of-concept-study was performed to evaluate the subjects' individual disposition of anxiety to CCK-4-response.

Methods: 40 healthy male subjects with an age of 31.4 (± 4.3) received 50µg of CCK-4 in a standarized panic-paradigma. The panic-outcome was measured by PSS-, API-Score and VAS-Scale (Visual-analog-Scale) for anxiety and tension, which divided the subjects into the groups of CCK-4-responders and nonrespnders. At baseline the PSS and API-Scores were measured and additional the subjects' anxiety disposition and trait for anxiety by STAI and ASI (State-Trait-Anxiety-Inventory and Anxiety Sensitivity Index).

Results: As expected the subjects of responders showed a significant increase of PSS- and API-Score after CCK-4-treatment, but the groups of responders and nonresponders showed no significance in ASI- and STAI-Scores.

Conclusion: The individual disposition of anxiety has no influence on the outcome of CCK-4-induced panic.

P-09-06
Possible association between genetic variants at the GRIN1 gene and schizophrenia with lifetime history of depressive symptoms in a German sample
A. Georgi, R. Abou Jamra, J. Schumacher, W. Maier, S. Cichon, M. M. Nöthen, T. G. Schulze, M. Rietschel (Mannheim, Bonn)

Disturbed glutamatergic neurotransmission has been implicated in the pathogenesis of schizophrenia (SCZ). The NR1 subunit of N-methy-D-aspartate receptors (NMDARs) is encoded by the gene GRIN1 on chromosome 9q34.3, a linkage region for SCZ. Controversy surrounds a potential association between SCZ and GRIN1. We present a case-control study on GRIN1 in a German sample. In 354 SCZ patients (44 % female, 56 % male) and 323 population-based controls (58 % female, 42 % male), we genotyped a microsatellite (position 137303343, build Nov 2002) and the SNPs rs4880213, rs11146020, rs6293 and rs10747050 (called Marker 1 to 5). Previous genetic studies in SCZ suggested that cases with a history of major depressive episodes (MDE) delineate a genetically distinct subgroup. Therefore, we analysed the subgroup of patients with MDE. There was no differential distribution of alleles or haplotypes between the cases and controls. The comparison between the subgroup of SCZ patients with MDE and controls showed several significant associations, e. g. a global p of 0.0113 for the four-marker-haplotype 1-2-3-4. After Bonferroni-correction for multiple testing owed to the sliding-window approach, our results were shy of significance. Although our exploratory study revealed no associations holding up to correction, our results suggest that GRIN1 be considered a candidate for future investigations.

P-09-07
Prevalence of affective disorders in a population-based sample of German adults: Preliminary results
P. Toro, J. Pantel, P. Schönknecht, U. Seidl, A. Kruse, J. Schröder (Heidelberg, Frankfurt)

Objective: Affective disorders are among the most frequent conditions in the elderly, but only a few epidemiological studies are available for the German population. We therefore established the prevalence and clinical course of affective disorders within the Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE).

Methods: Incidence and prevalence of affective disorders were investigated in 500 community-dwelling subjects from the birth cohort 1930/32 of two German urban regions. Participants were carefully screened for physical and mental health. In all subjects, the structured clinical interview according to DSM-III-R (SCID) was applied. The first examination wave (t1) was performed in 1994, t2 in 1998. Currently we are completing the t3 which was initiated in July 2005.

Results: Lifetime prevalence rates rose from 9.2 % at t1 to 12.5 % at t2. Preliminary analyses of the current examination wave led to lifetime prevalence rates of 12.3 % with a point prevalence of 5.4 %.

Conclusions: The results of the study are in accordance with previous studies in other countries and emphasize the high prevalence of affective disorders in city-communities. Since the respective conditions also affect general health and may also contribute to an increased risk of developing dementia, these results emphasize the clinical importance of affective disorders in the elderly.

P-09-08
Impaired neuregulin-1a localization in the cortex in schizophrenia and affective disorders
I. Bertram, H. G. Bernstein, U. Lendeckel, H. Dobrowolny, P. Falkai, B. Bogerts, H. G. Bernstein, U. Lendeckel, H. Dobrowolny, P. Falkai, B. Bogerts (Magdeburg, Göttingen)

Neuregulin-1 proteins function in migration, differentiation and survival of neurons and oligodendrocytes. The NRG-1 gene codes for different isoforms. At least four haplotypes of the NRG-1 gene may be associated with schizophrenia. Abnormal expression of NRG-1 mRNA was found in the prefrontal cortex of schizophrenics in comparison to controls. Less is known about NRG-1 proteins in psychiatric disorders. Hence we looked for NRG-1 protein expression in schizophrenia and mood disorders. We studied brains of 22 schizophrenics, 12 patients with affective disorders and 22 matched controls. Using antibodies directed against an epitope which is common to all NRG-1 isoforms we found a widespread neuronal distribution of immunoreaction. No significant differences were found in the number of NRG-1 expressing neurons between the three groups. However, when using an antiserum which selectively detects the NRG-1a isoform, much less neurons were seen. Stereologic analysis revealed a statistically significant reduction of NRG-1 ± cells in the white and in the gray cortical matter in schizophrenia and in depression. The diminished expression of NRG-1a in interstitial white matter neurons supports a neurodevelopmental component to schizophrenia. Supported by NBL-3 and Stanley Foundation.

P-09-09
Comparing the efficacy of a depression-specific group cognitive behaviour therapy and disorder-unspecific group therapy for inpatients with major depressive disorder
S. Zeugmann, F. Schindler, F. Bernard, I. Anghelescu (Berlin)

Objective: Even though disorder-specific psychiatric units have been common in Germany since the 1970s, evidence is lacking whether they are superiorly beneficial for inpatients. In particular, it is not known whether group cognitive behaviour therapy (CBT) for depression based on Beck and Hautzinger's work is advantageous for inpatients in comparison to unspecialised therapy programmes.

Method: Treatment outcomes (Hamilton-Depression-Scale-17

(HAMD-17) scores, days of hospitalisation) for 91 inpatients with a primary diagnosis of major depressive disorder were examined retrospectively following either a depression-specific group CBT (n = 48) or a disorder-unspecific group therapy (n = 43) on a specialised vs. unspecialised unit, respectively, within one psychiatric department.

Results: Overall, patients receiving specialised CBT had a significantly higher decrease in symptom number and severity during their hospitalisation ($t = -2.18$, $df = 89$; $p = 0.032$). There were also significantly more full responders in this patient group ($\chi^2 = 8.47$, $df = 1$, $p = 0.004$). However, there were no significant between-group differences regarding the days of hospitalisation ($t = -1.07$, $df = 89$, $p = 0.287$).

Conclusion: Depression-specific group CBT appears to be particularly efficacious for patients with major depressive disorder. Threats to the validity of this study are discussed.

P-09-10
Differential regulation of synaptic vesicle proteins in serotonin transporter deficient mice – A mouse model for anxiety disorders
A. Schmitt, S. Nietzer, M. Maier, G. Ortega, C. Kriegebaum, L. Gutknecht, L. Bogusch, P. Riederer, J. Deckert, K. P. Lesch (Würzburg)

5-HTT deficient mice represent an artificially hyperserotonergic environment, since released 5-HT is not taken back into the presynaptic neuron. The knockout (KO) of 5-HTT in these mice is accompanied by numerous pre- and postsynaptic adaptive changes including adaptive expression changes of different 5HT receptors. Furthermore, 5-HTT knockout mice show an increase in anxiety-like behavior and are less aggressive. These behavioral abnormalities support the notion that 5-HTT KO mice may act as a model for anxiety disorders. To achieve a better understanding of processes involved in altered serotonergic neurotransmission, we analyzed expression levels of synaptic proteins including synaptotagmin (Syt) 1 and 4, syntaxin 1A, and complexin (Cplx) 2 in 5-HTT deficient mice and wild-type littermates. The use of quantitative real-time PCR revealed significantly altered Syt 1, Syt 4 an Cplx 2 expression mainly in hippocampus, cortical regions and brainstem of 5-HTT deficient mice compared to wild-type controls, whereas we detected no differences in other brain regions. To investigate mRNA expression levels of these synaptic proteins at the regional and cellular level we used non-radioactive in situ hybridization (DIG-ISH). We showed a specific regional expression pattern of all investigated synaptic proteins in neurons of different murine brain regions. Additionally, by the use of immunohistochemistry with DIG-ISH slices and using two differently labelled ISH-probes (DIG- and 35S-cRNA) we started to characterize the phenotypic organization of cortical, hippocampal and raphe neurons depending on their synaptic protein mRNA content. Thus, our data further support the critical role of different synaptic proteins in the adaptive plasticity of serotonergic circuits.

P-10 Neurophysiology

P-10-01
Differences in brain activity by suppressing autobiographical memories respectively remembering them
F. Meister, C. Born, R. Engel, M. Reiser, H.-J. Möller, K. Fast, T. Meindl (Munich)

This study is based upon the single-case of the patient NJ who seemed to have lost his complete autobiographical memory. To investigate his loss, we collected individual autobiographical cues as well as semantic cues of public events and parallelised fictitious autobiographical and public cues (4 conditions). These events were presented to him during an fMRT session. He was advised to remember these events as vividly as possible. Eight control persons were undergone the same paradigm: Four subjects should remember their cued vivid memories like NJ, whereas the other four should suppress their memories. Six events of each condition were presented to the participants in succession (each for 5 sec) followed by a break of 3 sec. Stimuli were presented using Presentation software viewed via a mirror assembly attached to the headcoil. MR-Images were acquired using BOLD contrast T2*-weighted echoplanar MRI on a Magnetom Siemens Vision (1.5T). As anatomical reference T1 weighted images were collected. By comparing the both groups concerning the autobiographical condition following differences in activation were found: Increased activations in inferior frontal, cingulate and fusiform gyri as well as in parahippocampal areas were shown by the non-suppressors compared to the suppressors. In contrast we found increased activation in the insula and the temporal lobe in suppressors.

P-10-02
Reduced transient gamma response in schizophrenic patients during auditory stimulus processing
G. Leicht, C. Mulert, I. Giegling, S. Karch, F. Sokollu, O. Pogarell, U. Hegerl, D. Rujescu (Munich)

Previous electrophysiological investigations in animals and humans suggested that EEG gamma activity (oscillations at around 40Hz) is involved in the integration of distributed brain activities e. g. in cognitive functions like selective attention. Studies in schizophrenic patients provide evidence for a reduced gamma activity in the context of auditory stimulus processing. In a recent study, we could show that besides auditory cortex sources, a frontal or anterior cingulate cortex (ACC) generator exists for the evoked transient gamma response (TGR) which is known to be affected by attention, and could be relevant for further auditory processing. In the present study, we investigated 70 patients with schizophrenia and 70 healthy control subjects with an attention-requiring auditory choice reaction task. As expected, we found significantly increased reaction times and error rates in patients in comparison to healthy controls. The N1 amplitude and the TGR both were significantly higher in controls as compared to patients. EEG source localization of the TGR (using low-resolution electromagnetic tomography LORETA) showed lower activations of regions of interest in the dorsal ACC and in the auditory cortex in patients. These findings are in line with the idea of reduced gamma activity as a substitute of disturbances in integrative processing in patients with Schizophrenia.

P-10-03
Saccadic eye movements (SEMs) in schizophrenia and genetic variants
B. Schloesser, T. Eggert, I. Giegling, A. M. Hartmann, P. Muglia, A. Straube, A. Ruppert, H.-J. Möller, D. Rujescu (Munich, London)

Saccadic eye movements (SEM) are rapid eye movements which redirect gaze between different objects of interest. They consist of a large primary saccade which covers most of the target distance in one movement, usually followed by smaller corrective saccades. The consistently reported SEM abnormalities in schizophrenia occur in the non visually guided paradigms and are expected to be more useful in the identification of schizophrenia related genes than current clinical classifications. For that reasons we included over 150 patients, first degree relatives and over 300 controls. The saccadic eye movements were recorded with electrooculography and videooculography in complete darkness including the following paradigms: step paradigm (reflective saccades in a no gap, no overlap condition), gap paradigm (reflective saccades in a gap condition), antigap paradigm (suppression of a reflective saccade in a gap condition, memory paradigm (suppression of a reflective saccade in an overlap condition in a no gap/no overlap condition). Our results indicate that schizophrenic patients and their relatives have a higher rate of fixation suppression errors in the antigap paradigm and the memory paradigm. We are using these endophenotypes in our molecular genetics study which aims to find schizophrenia genes and will discuss these results.

P-10-04
[123I] ADAM brainstem binding correlates with the loudness dependence of auditory evoked potentials
O. Pogarell, C. Mulert, W. Koch, G. Pöpperl, H.-J. Möller, U. Hegerl, K. Tatsch, N. Schaaff (Munich)

Both neurophysiological and neuroimaging techniques are under investigation for the assessment of brain serotonergic activity. The loudness dependence of auditory evoked potentials (LD) is related to the serotonergic innervation of the auditory cortex and has been proposed as an indicator of central serotonergic function. SPECT and ADAM can be used to visualize serotonin transporters (SERT) which are located in highest density in the brainstem. Aim of the study was to investigate LD and ADAM-SPECT in 15 healthy volunteers and to correlate these parameters reflecting different aspects of the serotonin system. Evoked potentials were recorded following the application of acoustic stimuli, LD was assessed using dipole source analysis. SPECT was performed 4h after injection of 185 MBq [123I] ADAM. As a measure of SERT availability a ratio of specific to nonspecific ADAM binding for the brainstem region was used. The LD correlated significantly with SERT availability ($r = -0.57$, $p < 0.05$). The correlations remained significant after controlling for age or gender ($r = -0.60$, $p < 0.05$). The data provide evidence of an association between both variables of brain neurochemical function, are in line with a serotonergic modulation of auditory signal processing and further validate the use of neurophysiological approaches as non invasive measures of central serotonergic activity.

P-10-05
Deep brain stimulation in obsessive compulsive disorder – A case report
C. Plewnia (Tübingen)

Recently, deep brain stimulation (DBS) has been put forward as a new treatment for psychiatric diseases, e. g. obsessive compulsive disorder (OCD). We report a case of a 51 year old women with therapy-resistant OCD who underwent an unilateral implantation of electrodes targeted towards the right nucleus accumbens (NAC). Stimulation was started with the most distal electrode (130Hz, 60µs, 4.5V). After one week, the patient reported a marked reduction of obsessional thoughts without a significant effect on compulsions. A FDG-PET before and 3 months postsurgery indicated a reduced activity in the right dorsolateral-prefrontal and the orbitofrontal cortex. Registration of intracerebral EEG demonstrated differential patterns of oscillatory activity in the electrodes. Four months postsurgery the second distal electrode was activated. The severity of symptoms was judged with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). During the course of treatment, Y-BOCS score was reduced from '31' before to '24' five months after surgery. Depressive symptoms, quantified by the Beck-Depression Inventory (BDI), were reduced from '32' to '15'. Since improvement of symptoms continues in the patient, these results are preliminary. However, this case adds to evidence that DBS of the NAC could become a new option for patients with treatment-refractory OCD and symptoms of depression.

P-10-06
Schizophrenia and the recognition of facial affects: Topographical phenomena in an ERP-study
G. Heinz, A. Schneider, M. Rubly, S. Meilinger, P. Falkai (Homburg)

Recognition of faces is disturbed in schizophrenics, generating smaller N170 in the event-related potentials (ERP). The aim of this study was to examine this effect with different facial affects. We examined 17 patients and 21 matched controls. All patients were on a constant neuroleptic medication for months. We showed computer-generated faces with three different affects: neutral, happy, sad. ERP were recorded from Fz,Cz,Pz, C3/C4, and P3/P4. As results, we did not found significant group differences in the N170, but in the range 400–500 ms with more positive ERP in schizophrenics, possibly due to a lack of a N400 component. But topographical distributions of the ERP were significantly different between groups: central leads were more negative in controls and more positive in schizophrenics. Thus the areas between Fz/Cz were significantly larger in schizophrenics. Furthermore, we found significant hemispherical differences in controls (AUC C4 > C3), but not in schizophrenics. All differences were independent from the facial affects. These results reveal basic differences in the processing of faces in schizophrenics compared to controls. These differences are localized around central leads: central ERP are less lateralized and less negative in schizophrenics. The neuronal generators of these effects are unknown and should be revealed by fMRI-studies.

P-10-07
Cortical signal to noise ratio in healthy volunteers and postacute schizophrenic patients
V. Eichert (Bonn)

In 24 healthy volunteers (mean age: 28.9 ± 5.3 years, male) and 21 postacute schizophrenic patients (30.6 ± 6.5 years, male, neuroleptic steady state medication) the signal to noise ratio (SNR) during a selective reaction time task was analyzed (P300 paradigm, 7 min., eyes closed, 7 electrode positions, sampling rate 512 Hz, digital EOG correction, time window 0–400 ms).

Results: Both groups showed a significant higher SNR during the target sweeps compared to the nontarget condition. In both conditions the cortical SNR was lower in the patients' group. Analysis of variance revealed significant effects for group and condition, the interaction effect was insignificant. The highest SNR was found at the electrode positions Cz and Pz (0.7 vs. 0.43, $p = 0.003$; 0.83 vs. 0.57, $p = 0.018$). The SNR values at the electrode position Fz were lower (0.39 vs. 0.30, $p = 0.069$)

Discussion: The SNR ratio, as calculated in this study, is a measure for ERP variability. The lower level of cortical SNR in the schizophrenic group is in accordance with the assumption, that the basic regulation and task-induced modulation of cortical activity are more variable in schizophrenia, even in the postacute stage.

Satellite Symposium

SA-01 The use of cyclo-oxygenase-2 inhibitors in psychiatric disorders

sponsored by an educational grant of Affectis Pharmaceuticals AG

SA-01-01
Therapeutic targets and mechanisms of COX-2 inhibitors in psychiatric disorders
M. J. Schwarz, M. Riedel, N. Müller (Munich)

The involvement of an immune process in the aetiology of both, Major Depression (MD) and schizophrenia is intensely discussed. Accumulated data point to a pro-inflammatory reaction contributing to the pathophysiology of MD, while schizophrenia appears to be accompanied by a functional preponderance of the anti-inflammatory (Th2) arm of the immune system. Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, showed therapeutic efficacy in both psychiatric conditions. However, the mechanism of action may not only be related to a reduced production of the inflammatory mediator prostaglandin E2 (PGE2). The kynurenine pathway of tryptophan degradation may be involved in both psychiatric conditions. Kynurenine (KYN) is further metabolised either to the NMDA receptor antagonist kynurenic acid (KYNA), or to neurotoxic intermediates including quinolinic acid (QA). In MD, an enhanced activation of the key enzymes of the KYN/QA pathway, the indoleamine 2,3-dioxygenase (IDO) and the kynurenine 3-monooxygenase (KMO), is proposed to cause reduced tryptophan availability, which in turn effects down-regulation of the central nervous serotonin production. This mechanisms could explain the serotonergic deficiency observed in MD. Most remarkably, pro-inflammatory cytokines are potent IDO and KMO inducers. COX-2 inhibition may indirectly decrease the cy-

tokine-induced activation of IDO and KMO by reducing the production of the pro-inflammatory mediator PGE2. The target of COX-2 inhibitors in schizophrenia is suggested to be distinct from that proposed in MD. Due to the preponderance of Th2-like cytokines in schizophrenia, IDO and KMO may be inhibited, while the alternative key enzyme of kynurenine production, the tryptophan 2,3-dioxygenase (TDO), was shown to be over-expressed in certain brain regions. Accordingly, elevated levels of KYNA have been found in brain and CSF of schizophrenic patients. This is of particular interest, since NMDA receptor antagonists were shown to induce schizophrenia-like symptoms and KYNA is the only so far known endogenous NMDA receptor antagonist. The effect of COX-2 inhibitors may be directly related to KYNA formation, since they inhibit the corresponding enzyme. Moreover, COX-2 inhibitors are known to re-balance the preponderance of anti-inflammatory cytokines, probably resulting in a restoration of IDO and KMO activity.

COX-2 inhibitors may therefore act on the pathophysiology of MD and schizophrenia through different mechanisms.

SA-01-02
A double-blind, placebo-controlled trial of celecoxib addes to risperidone in first-episode and drug-naive patients with schizophrenia
Y. Zhang, D. Chun Chen, Y. Long Tan, D. F. Zhou (Beijing)

Background: There are number of indications that schizophrenia is associated with changes in the immune system. A recent study showed that additional treatment with celecoxib had significant positive effects on the therapeutic action of risperidone with regard to total schizophrenia psychopathology. The aim of the present study was to determine the effectiveness and to evaluate the side effects of celecoxib plus risperidone in first-episode, drug-naive inpatients with schizophrenia among a Chinese population.

Method: Forty patients meeting DSM-IV criteria for schizophrenia completed a double-blind, placebo-controlled, parallet-group study of celecoxib plus risperidone. Twenty of the patients were randomly assigned to receive a fixed dose of 400 mg/day of celecoxib plus 2–6 mg/day risperidone, and 20 were assigned to receive placebo plus the same dose of risperidone for 12 weeks. Efficacy and tolerability were assessed using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale, and Simpson Angus Scale at baseline, week 6 and week 12.

Results: There was a significant reduction in both groups in PANSS total score after 12 weeks of treatment (both $p < 0.01$). However, there was a lower PANSS total score in the celecoxib group than in the placebo group at the end of 12 weeks of treatment ($p < 0.05$). Moreover, a significantly greater proportion of patients treated with celecoxib achieved ≥ 20 % reduction from baseline PANSS total score at weeks 6, and at end point (last observation carried forward: $P < 0.05$). Tolerability assessments did not differ between groups.

Conclusion: These results suggest that celecoxib may enhance the efficacy of the atypical antipsychotic risperidone in first-episode and drug naïve patients with schizophrenia among Chinese population. Moreover, celecoxib may be well tolerated, with no significant side effect.

SA-01-03
A double-blind, placebo controlled study of a cox-2 inhibitor (celecoxib) as an adjunct in the treatment of depressive or mixed episodes in bipolar disorder
F. Nery, J. Hatch, S. Monkul, M. Fonseca, G. Zunta, B. Frey, C. Bowden, J. C. Soares (San Antonio)

Background: Lithium and valproate inhibit ciclooxygenase-2 (cox-2), an enzyme present in cell membranes, including neurons, and involved in the immune inflammatory response. Cox-2 inhibitors also may protect against the neurotoxicity promoted by glutamate. We investigated the effects of a cox-2 inhibitor (celecoxib) as an adjunctive treatment for bipolar disorders patients who did not show satisfactory response to treatment with mood stabilizers. We hypothesized that the celecoxib treatment would cause greater amelioration of depressive symptoms than a matched placebo.

Methods: Twenty seven bipolar disorder patients, in a depressive or mixed episode according to DSM-IV criteria, and on a sTable dose of a mood stabilizer or atypical antipsychotic medication, were randomized to receive 6 weeks of double-blind placebo or celecoxib (400 mg/d) treatment. Current mood stabilizer or antipsychotic medication was kept at the same doses during the trial. Depressive and manic symptoms were measured by the Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS), respectively, and side-effects by the UKU Side Effects Rating Scale.

Results: The patients receiving celecoxib showed significantly lower HAM-D scores after one week of treatment compared to the patients receiving placebo (intent-to-treat analysis, $F_{(1.25)} = 4.7$, $p = 0.039$). However, the two groups did not differ significantly on depressive or manic symptoms from the 2nd week until the end of the trial (Fig.). The rapid onset of improvement in the first week of treatment also was present when the analysis included only the subjects who completed the full 6 week-trial (11 in each group). Two patients receiving celecoxib dropped out of the study due to side-effects (rash). Reduced salivation, nausea/vomiting and dizziness were statistically more frequent in the celecoxib group.

Conclusion: Adjunctive treatment with celecoxib may produce a rapid-onset antidepressant effect in depressive or mixed episodes in bipolar disorder patients. Further research investigating the involvement of the cox-2 pathway in the pathophysiology of bipolar depression and the potential antidepressant and mood stabilizing effects of cox-2 inhibitors are needed.

Acknowledgments: This research was partly supported by the Stanley Medical Research Institute, RR-20571, UTHSCSA GCRC (M01-RR-01346), the Krus Endowed Chair in Psychiatry (UTHSCSA), and the Veterans Administration (VA Merit Review).

SA-01-04
The use of COX-2 inhibitors in schizophrenia and major depression
N. Müller (Munich)

COX-2 inhibition seems to balance the type-1/type-2 immune response, possibly via inhibition of prostaglandin E2 inhibition and COX-2 inhibition reduces proinflammatory cytokines. Moreover, COX-2 inhibition has an impact to the glutamatergic neurotransmission and influences the tryptophan/kynurenine metabolism: all three components seem to be involved in the pathophysiology of psychiatric disorders, particularly in schizophrenia and major depression. Therefore, we performed at first a prospective, randomized, double-blind study of therapy with the COX-2 inhibitor celecoxib add-on to risperidone in acute exacerbation of schizophrenia A therapeutic effect of celecoxib was observed. Immunologically, an increase of the type-1 immune response was found in the celecoxib treatment group. The clinical effect of COX-2 inhibition was especially pronounced regarding cognition in schizophrenia. The finding of a clinical advantage of COX-2 inhibition, however, could not be replicated in a second study. Further analysis of the data revealed that the outcome depends on the duration of the disease. The efficacy of therapy with a COX-2 inhibitor seems most pronounced in the first years of the schizophrenic disease process. This observation is in accordance with results from animal studies. Due to the increase of proinflammatory cytokines and PGE2 in depressed patients, antiinflammatory treatment would be expected to show antidepressant effects also in depressed patients. Accordingly, a clinical antidepressant effect of rofecoxib was found in patients with osteoarthritis. An own randomized double blind pilot add-on study using the selective COX-2 inhibitor celecoxib in MD showed a significant therapeutic effect of the COX-2 inhibitor on depressive symptoms. Although those preliminary data have to be interpreted cautiously and intense research has to be provided in order to evaluate further the therapeutic effects of COX-2 inhibitors in MD, those results are encouraging for further studies dealing with the inflammatory hypothesis of depression with regard to pathogenesis, course and therapy. It has to be considered, however, that therapy with COX-2 inhibitors is currently under discussion – as therapy with other non-steroidal antiphlogistics – due to cardiovascular side-ef-

fects. Regarding the possible role of inflammation in schizophrenia, depression and possibly other psychiatric disorders, anti-inflammatory therapy should be taken into the focus of further research.

Abstracts Addendum

WS-08–02

Spontaneous sleep and microsleep episodes and mood in depressed patients during 40 hours of sleep deprivation therapy

M. H. Wiegand, T. Jahn, M. M. Schröder, C. Pohl, B. Veselý, Z. Veselý, T. Brückner, J. Bäuml (München, Regensburg)

Aims: The mechanisms underlying the antidepressant effect of sleep deprivation continue to be unclear. The question as to whether the strict avoidance of sleep is crucial for this effect has been insufficiently investigated so far, since the vast majority of studies in this field did not control objectively (i. e., by sleep EEG) for the maintenance of wakefulness during the intended sleep deprivation period. To our knowledge, only Hemmeter et al. (1998) performed partial therapeutic sleep deprivations with continuous sleep EEG recordings and found a positive relationship between mood improvement and absence of objective sleep (including microsleep). The present study is the first to study this crucial relationship under total sleep deprivation conditions, i. e. forty hours of intended wakefulness. Do spontaneously occurring sleep episodes (even brief ones) lead to a nonresponse to sleep deprivation or a worsening of mood following an initial response to the treatment?

Methods: Thirty-three inpatients suffering from a major depression and being under a constant antidepressant medication were sleep deprived for a period of forty hours ("total sleep deprivation"). During this period, a continuos recording of EEG, EOG and EMG was performed using a portable device. The recordings were analyzed with respect to the occurrence of "sleep" (stage 1 to 4 or REM according to Rechtschaffen & Kales, based on 30 second epochs) and "microsleep" (occurrence of periods of dominating theta activity in the absence of alpha activity, lasting 5 to 15 seconds). Mood and sleepiness were self-rated by the patients in 2-hour intervals using visual analogue scales; in addition, patients rated their mood on the Adjective Mood Scale (AMS) twice daily. Depressive symptomatology was observer-rated at 09:00 a. m. in the mornings before and after the sleep deprivation nights using the Hamilton Depression Scale (6-item version, HAMD-6). Response was defined as a 30 % reduction in this score.

Results: In responders to sleep deprivation, the cumulative amount of sleep and microsleep during the 40 hours therapy period was lower than in nonresponders. During the course of the sleep deprivation period, a relationship between the occurrence of sleep (including microsleep) and fluctuations of mood was observed.

Conclusions: **T**he results confirm the hypothesis that the occurrence of sleep (and microsleep) episodes counteracts the antidepressant effect of therapeutic sleep deprivation. The data are in accordance with those reported by Hemmeter et al. (1998) in a partial sleep deprivation study, as well as the results from former studies on the effect of scheduled naps on mood during sleep deprivation therapy (Wiegand et al. 1993).

References

Hemmeter U, Bischof R, Hatzinger M, Seifritz E, Holsboer-Trachsler E (1998): Microsleep during partial sleep deprivation in depression. Biol Psychiatry 43:829–839;

Wiegand MH, Riemann D, Schreiber W, Lauer CJ, Berger M (1993): Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. Biol Psychiatry 33: 467–476

P-04–06

Specific functional neuroimaging of distinct neural processes using trial-by-trial integration of simultaneous EEG and fMRI

C. Mulert, L. Jäger, C. Seifert, S. Karch, G. Leicht, M. Moosmann, U. Hegerl, O. Pogarell (Munich)

The BOLD-effect is widely used for the investigation of brain function. However, it does not differentiate between different aspects of the underlying "real" neuronal activity. Simultaneous EEG and fMRI can be used to differentiate between different aspects of neuronal activity using trial-by-trial EEG-BOLD coupling. In the present study it was our aim to differentiate between N1-attentional effects and P300-related activations.

We investigated ten healthy subjects. The task was a choice reaction paradigm. FMRI-data: 1.5 T scanner; gradient echo EPI sequence; 12 slices. Trial by trial coupling of EEG and fMRI was done after decomposition of the ERP-signal using Schmidt-Gram orthogonalisation.

In the fMRI analysis we found a significant increase in the SMA and the anterior cingulate cortex (ACC) activation during the effort condition in comparison to the relaxed condition. Interestingly, there was a strong relationship between the N1 amplitude and the number of activated voxels in the ACC ($r = 0.76$), but not with any other region. Using trial-by-trial coupling of EEG and fMRI we could differentiate between N1-specific activations (including the ACC) and P300-specific activations (including the SMA). Our data show that trial-by-trial coupling of simultaneous EEG and fMRI allows a separation of distinct neural processes underlying the BOLD-effect.

P-05–09

Bipolar disorder in a patient suffering from cerebral cysticercosis – a case report

F. Abu-Tair, R. Schmitt, M. Blatow, N. Bergemann (Heidelberg)

Introduction: Cerebral cysticercosis is worldwide the most common parasitic disease of the human central nervous system. It is endemic in Mexico, Central- and South America, India, Eastern Europe and Africa. In Germany its occurrence is rare. Besides neurological manifestations it can cause psychiatric symptoms [1]. Forlenza et al. [2] reviewed 38 cases of neurocysticercosis; psychiatric disorders and cognitive decline were seen in 65.8 % and 87.5 % of the cases respectively. With 52.6 % of the cases depressive disorders were the most frequent noncognitive psychiatric disease, psychotic disorders were observed in 14.2 % of the cases. This is the first case report on bipolar disorder in a patient with cerebral cysticercosis.

Case report: A 65-year-old women was admitted to the hospital due to acute depression with psychotic symptoms. Her medical history revealed an earlier episode of depression seven years before and manic episodes in the past. The patient received antidepressant and antipsychotic medication, however, the treatment did not show good response. During her stay in hospital she made known that in 1974 after a vacation trip to India she had suffered from small bladder-like larvae of pork tapeworm taenia solium, which had been treated successfully. The neurological examination showed no abnormality. Morphological MRI showed a cystic lesion in the left cingulate gyrus with an eccentric "dot", corresponding to the scolex, compatible with the finding of cerebral cysticercosis. The CSF examination indicated a slight elevation of eosinophilic cell count. Likewise, there was evidence of cysticercosis in the serological examination. The patient was treated with albendazol 1200 mg and fortecortin for more than 8 days without any complications. Under this combined therapy, the neurological results remained unchanged and unobtrusive but the lesion in the left cingulate gyrus was suppressed distinctively. The patient was discharged in good mental condition.

Discussion and conclusion: As cerebral cysticercosis is rare in Germany, the disease is usually not considered in the differential diagnosis of bipolar disorders. With this case report we want to emphasize the necessity of neuroradiologic diagnosis in patients suffering from affective symptoms, especially when there are psychopatholgical signs of organic causes or when the symptoms are refractory to treatment.

References: [1] Mahajan SK, MachhanPC, Sood BR, Kumar S, Sharma DD, Mokta J, Pal LS (2004) Neurocysticercosis presenting with psychosis. J Assoc Physicians India. 52:663–665. [2] Forlenza OV, Filho AH, Nobrega JP, dos Ramos Machado L, de Barros NG, de Camargo CH, da Silva MF (1997) Psychiatric manifestations of neurocysticercosis: a study of 38 patients from a neurology clinic in Brazil. J Neurol Neurosurg Psychiatry 62: 612–616.

P-06–09

Risperidone plasma concentrations in patients suffering from various psychiatric disorders

N. Bergemann, F. Abu-Tair, P. Parzer, R. Aderjan, J. Kopitz (Heidelberg)

Introduction: Risperidone, a benzioxazole derivative, one of the older second-generation antipsychotics, that has favorable effects on both the positive and the negative symptoms of schizophrenia. It is extensively metabolized in the liver, primarily by the cytochrome P450 (CYP)2D6, and to a minor extent by CYP3A4, to its main metabolite 9-OH-risperidone. The elimination half-life of risperidone amounts to about 3 hours, that of 9-OH-risperidone to about 24 hours. The aim of the present investigation was to elucidate the clinical relevance of therapeutic drug monitoring of risperidone and to clarify the factors that affect risperidone plasma levels in a naturalistic setting.

Methods: 1,008 plasma risperidone levels of 202 patients suffering from various mental disorders were assessed by high performance liquid chromatography (HPLC) with UV-detection. Of the patients 118 were women and 84 were men; the mean age was 44.8 years (SD 20.11; range 16–90). Eighteen patients received risperidone as a monotherapy, the other patients received various co-medications. Drug therapy was strictly monitored under steady-state conditions (trough level).

Results and Conclusions: The average daily dose of risperidone was 3.8 mg/d (SD = 2.3 mg/d). The mean risperidone plasma concentration was 18.0 ng/ml (SD = 25.6 ng/ml), and the mean 9-OH-risperidone concentration was 30.1 ng/ml (SD = 32.2 ng/ml). A moderate correlation ($r = 0.29$; $p < 0.001$) between the daily drug dose and the sum of risperidone plus 9-OH-risperidone plasma concentrations could be observed. In addition, the effects of age, sex, weight, smoking behavior, and various concomitant medications were demonstrated. Further studies should include systematic ratings of the patients' psychopathology.

Authors Index