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ABSTRACTS

SCANDINAVIAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

SCNP

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Copenhagen, Denmark

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ORAL PRESENTATIONS

LECTURE 1

SCNP 2013 OPENING LECTURE

L1 Converting biological psychiatry into clinical tests: Why has it taken so long and what to do about it?

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Patients with mental disorders show many biological abnormalities; however, few of these have converted into tests with clinical utility. Why is this the case? The talk will suggest that the lack of a biological 'gold standard' definition of psychiatric illnesses; a profusion of statistically significant, but minimally differentiating, biological findings; 'approximate replications' of these findings; and a focus on comparing prototypical patients to healthy controls has limited clinical applicability.

Overcoming these hurdles will require a new approach. Rather than seek biomedical tests that can 'diagnose' DSM-defined disorders, the field should focus on identifying biologically homogenous subtypes within the current psychiatric classifications (thereby side-stepping the issue of a gold standard). Rather than chasing p-values versus normal controls, we must focus on clinically meaningful effect sizes within a diagnosis and in particular identify biomarkers that lead to 'discordant predictions'. And validating these new biomarker-defined subtypes will require longitudinal studies, standardised measures at a scale not previously attempted by biological psychiatry. To achieve this scale will need to consortia that share individual patient-data across studies – thereby overcoming the problem of significance chasing and approximate replications.

Such biological psychiatry derived clinical tests, and the subtypes they define, will exist, at least for the foreseeable future, side-by-side of the DSM-like diagnosis. However, they will provide a natural basis for new therapeutics and if this venture is successful, it will give rise to a 'stratified psychiatry' that will improve clinical outcomes across conventional diagnostic boundaries.

The talk will make the case for these assertions by reviewing data from within psychiatry and from the rest of medicine – and will point out the early signs of success.

SYMPOSIUM 1

SIDE EFFECTS MANAGEMENT IN PSYCHIATRY

S1.1 Sexual side effects of antidepressant drugs

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Pleasurable sexual activity is an important component of many human relationships, providing a sense of physical, psychological and social well-being. Epidemiological and clinical studies show that depressive symptoms and depressive illness are associated with impairments in sexual function and satisfaction, in untreated and treated patients.

Randomized placebo-controlled trials demonstrate that most of the currently available antidepressants are associated with the development or worsening of sexual dysfunction, in a substantial proportion of patients. Sexual difficulties during antidepressant treatment often resolve as depressive symptoms lift; but can endure over long periods, and may reduce self-esteem and affect mood and relationships adversely. Sexual dysfunction during antidepressant treatment is typically associated with many possible causes, but the risk and type of dysfunction varies with differing compounds, and should be considered when making decisions about the relative merits and drawbacks of differing antidepressants.

A range of options can be considered when managing patients with sexual dysfunction associated with antidepressants, including the prescription of phosphodiesterase-5 inhibitors; but none of these approaches can be considered 'ideal'. As treatment-emergent sexual dysfunction is less frequent with certain drugs, presumably related to differences in their pharmacological properties, and because current management approaches are less than ideal, a reduced burden of treatment-emergent sexual dysfunction represents a tolerability target in the development of novel antidepressants.

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S1.2 Metabolic side effects of antipsychotic drugs

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Antipsychotic drugs play a very important role in the treatment of schizophrenia. Unfortunately, several commonly used atypical antipsychotics as well as some typical drugs impose a high risk of metabolic side effects in the patients, including weight gain, dyslipidemia and glucose dysregulation, with subsequent increased risk of cardiovascular disorders. Major research efforts have been launched to better understand, treat and prevent this problem, but the underlying mechanisms are still not fully known. The presentation will review the current knowledge in the field and also cover recent advances, ranging from molecular metabolic actions of antipsychotic drugs to various treatment options. The topics will also include pharmaco-epidemiological and clinical aspects of antipsychotic-related metabolic adverse effects, together with data from relevant pharmacogenetic and preclinical studies.

S1.3 Lithium: Side effect management today

Per Vestergaard

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Contemporary International guidelines recommend lithium as first-line long-term maintenance treatment for patients with bipolar disorder. Treatment with lithium, however, is complicated and far from always successful. Patient non-compliance due to the development of side effects is one important reason for the lack of treatment success. Other reasons are doctor lack of compliance with guidelines for proper clinical management of lithium treated patients and hospital management lack of continuous quality assessment. Renal side effects of lithium are the most serious threats to the patients and their importance seem at the present time to be underestimated.

SYMPOSIUM 2

POST TRAUMATIC STRESS DISORDER

S2.1 PTSD in military cohorts; what have we learned?

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In this presentation an overview will be provided of the progress in one centennial after the Great War. In 2014 it will be 100 years after the start of WWI. Wars have changed, but the impact on the soldier probably not. The clinical presentation of PTSD (formerly shell shock) changed from non-verbal to a verbal presentation. Today the diagnosis of combat stress disorder or PTSD is based on self-assessment in structured clinical interviews. The accuracy is based on perception of memory overrepresentation, stress sensitisation, anxiety, emotional dysregulation and sleep problems. The biology of the disorder has lagged behind in diagnosis since it is not driving our diagnostic assessment. Yet the symptom manifestations are biologically based and are know manifestations of chronic allostasis in which it appears as if the 'resilience' has disappeared out of biological systems. Important to note that the last two decades studies have changed and moved beyond cross-sectional designs to longitudinal designs that enable identification of more causal relationships in parameters of interest. This type of research has also been applied in Dutch military cohort studies. We are looking into candidate biomarkers of responses to traumatic stress that allow us to differentiate between combat stress effects. In treatment domain several evidence-based treatments are available and effective including trauma focused cognitive behavioral therapy (tfCBT), eye movement desensitisation and reprocessing (EMDR), and narrative exposure therapy (NET). New approaches in therapy are using new technology as well as a combination of exposure and medication to facilitate reconsolidation. The combat-related PTSD clinical profile will be discussed as well as insights from a research perspective.

S2.2 What is the stressor in PTSD? A memory based model

Dorthe Berntsen

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The memory based model of Posttraumatic Stress Disorder (PTSD; Rubin, Berntsen & Bohni,2008) proposes that the current memory of a negative, traumatic event, not the event itself, determines symptoms of PTSD. The memory based model is an alternative to the current event-based etiology of PTSD represented in the DSM-IV (American Psychiatric Association, 2000), according to which PTSD symptoms may follow particular classes of stressful events – events involving (A1) life danger and injury and (A2) fear, horror and

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helplessness. The memory based model uses insights from research on autobiographical memory to understand posttraumatic stress reactions in response to negative events. According to the model, the interaction between the characteristics of the event and the processes of remembering determines whether PTSD symptoms will follow; the symptoms derive from the memory, not from the event per se. Thus, our general theoretical understanding of remembering and emotion can be used to predict the nature of the traumatic memory andhow it generates PTSD symptoms. The model has the following key predictions: (1) negative events and emotions that do not satisfy the current diagnostic criteria for a trauma canbe followed by PTSD symptoms; (2) predisposing factors that affect the current memory--including the history of the person -- have large effects on PTSD symptoms after a negative event; (3) the current accessibility and centrality of the traumatic memory is an important predictor for current level of PTSD symptoms. I review multiple studies showingthat the accessibility and perceived self-relevance of the traumatic memory as measured by the Centrality of Event Scale (Berntsen & Rubin, 2006) is an important predictor of PTSD symptoms, consistent with predictions from the model. I present findings from a recent study of trajectories of PTSD symptoms in 746 Danish soldiers measured on five occasions related to a six month deployment to Afghanistan. Consistent with the memory based model, other factors than immediately preceding stressors were critical for new cases of PTSD with childhood adversities playing a central role. Also consistent with the model, the development of PTSD symptoms showed heterogeneity, indicating the need for multiple measurements and more complex analytic strategies in order to identify those in the need of treatment.

S2.3 Prevention of traumatic memory consolidation as a therapeutic tool in PTSD

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The core pathology in Post Traumatic Stress Disorder (PTSD) is the traumatic memory. For those who suffer from PTSD it is as if the time has stopped and they are constantly haunted by the memory of the traumatic event. In an animal model of PTSD prevention of the consolidations of the traumatic memory by an administration of Anisomycin - protein synthesis Inhibitor which blocks the transition of Label short term memory to fix long term memory - was associated with a significant decrease in PTSD like behavior.

Support for the potential benefit of prevention of memory consolation came from human study in which individuals with traumatic brain-injury with amnesia were found to have less PTSD as compared to their matched control who did not suffer from amnesia.

Along those lines it was found that individuals with repression copying style (psychological mechanism which to some extant mimic amnesia) has less PTSD as compared to individuals with other type of defense mechanism.

Another support for the potential utility of amnesia drives from a study looking at long term follow up of debriefing. Debriefing is a commonly practice intervention in which detailed active verbalization of the trauma is encouraged in the first few hours after the trauma exposure. Based on the hypothesis that amnesia is beneficial – this intervention might be actually harmful and indeed this was the finding in some of the studies.

In pilot study in administration of cortisol (100-140mg of hydrocortisone i.v) was associated with significant favorable change in the trajectory of PTSD. Individuals who got those injections no later than 6 hours after exposure to the trauma ("The Golden Hours") were less likely to develop PTSD in 2 weeks, 1 months and 3 months as compared to the individuals who got placebo. The molecular mechanism of this finding and its relation to prevention of consolidation of the traumatic memory will be presented.

LECTURE 2

SCNP 2013 EDUCATIONAL LECTURE

Neurotransmitter approaches to the treatment of depression

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The discovery of antidepressants was through serendipity, but subsequent neuro-chemistry studies revealed the target mechanisms to be amine catabolic enzymes [MAOIs] and reuptake site [tricyclics] respectively. Since these discoveries there has been significant advances in terms of the safety of antidepressant agents but not real breakthroughs in terms of mechanisms. My talk will explore these issues in relation to the nature of depression and suggest ways in which the field might be facilitated to develop new neurotransmitter-mediated treatments.

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SYMPOSIUM 3

SCNP YOUNG SCIENTIST SYMPOSIUM

The speakers in the SCNP Young Scientist Symposium are selected among the best abstracts submitted by young scietists.
The selection of the speakers was not finished at time of printing.
However, all abstracts can be found in the poster section, at page 15, as they also are presented as posters.

SYMPOSIUM 4

TREATMENT TARGETS IN NEUROPSYCHIATRY

S4.1 When the serotonin transporter gene meets adversity: contribution of animal models to our understanding of epigenetic mechanisms in disorders of emotion regulation

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Adverse childhood experiences are associated with increased risk for psychiatric diseases later in life, especially anxiety disorders and depression. Several studies indicate that whether a individual develops disorders of emotion regulation following early-life stress is influenced by variation of the serotonin transporter gene (5-HTT). Multimodal fMRI in humans suggested that life stress interacts with the 5-HTT genotype to influence amygdala and hippocampal resting activation. There are also compelling data from nonhuman primates. In rhesus monkeys (Macaca mulatta), maternal separation during the first months of life results in deficient social adaptation and peer interaction. These deficiencies are related to brain serotonin system function, based on testing for interactions between early life stress and 5-HTT: in addition to main effects of 5-HTT genotype and early stress to variation in serotonergic function in later life, 5-HTT also interacts with deleterious early rearing experience to influence attentional and emotional resources, stress reactivity, and alcohol preference and dependence. However, the molecular mechanisms by which stress increases disease risk in adulthood is not known, but may include epigenetic programming of gene expression. Various gene-by-environment interaction (GxE) paradigms in the mouse allow investigations of the molecular mechanisms underlying epigenetic programming by early adverse environment in an animal model amenable to genetic manipulation. Using these GxE paradigms it was shown that prenatal stress or dominant/subordinate social interaction on anxiety-related behavior is modulated by inactivation of 5-HTT. These findings suggest that the molecular mechanisms involved in these GxE models are relevant to the etiology of disorders of emotion regulation in humans.

S4.2 Role of p11 in depression-like states

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Studies of the multifunctional protein, p11, are shedding light on the molecular and cellular mechanisms underlying depression. Studies demonstrating that the levels of p11 are regulated in depression and by antidepressant regimens and, conversely, that p11 regulates depression-like behaviors and/or responses to antidepressants will be presented. Data implicating p11 both in the amplification of serotonergic signaling and regulation of gene transcription will be presented. Future studies of p11 may provide a molecular and cellular framework for the development of biomarkers of affective disorders and novel antidepressant therapies.

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S4.3 Epigenetic Mechanisms and Targets in Depression

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Epigenetic refers to changes in DNA packing and chromatin structure that control gene expression without changing the original DNA sequence, thus leading to different cellular phenotypes without a change in genotype. Therefore, epigenetic modifications are important mechanisms by which environmental experience can modify gene function in the absence of DNA sequence changes and produce long-lasting changes in protein availability and brain function.

Amongst the epigenetic processes that modulate chromatin structure and gene expression, covalent changes to DNA (methylation) and post-translational modifications of histone N-terminal tails (such as acetylation and methylation) have been the most studied in relation to the neurobiology of depression. For example, histone acetylation of lysines, which is most often associated with transcription activation through its ability to relax condensed areas of chromatin, is induced by chronic antidepressant treatment. In addition, inhibition of histone deacetylase (HDAC) induces antidepressant-like effects in animals associated to increases in BDNF expression, as well as other genes involved in the neurobiology of depression.DNA methylation is a process accomplished by DNA methyltransferases (DNMTs), which results in condensed chromatin state and transcriptional repression. Recent evidence has shown that stress exposure increases the expression of DNMTs in different brain regions, what is accompanied by increased DNA methylation and decreased expression of genes that regulates synaptic plasticity and neurotransmission. Additionally, higher levels of DNA methylation have also been described in specific genomic loci in brain regions of suicide victims. Therefore, it has been suggested that stress-induced DNA methylation could contribute to the pathophysiology of depression. Corroborating this idea, our group has

SYMPOSIUM 5

SOMATIC COMORBIDITY IN PSYCHIATRY

S5.1 Overlapping genetic profiles of schizophrenia and cardiovascular risk factors

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Background: Several lines of evidence suggest that genome-wide association studies (GWAS) have the potential to explain more of the 'missing heritability' of common complex phenotypes. However, reliable methods to identify a larger proportion of single nucleotide polymorphisms (SNPs) are currently lacking. Here, we present a genetic pleiotropy-informed method to improve gene discovery using summary statistics data from GWAS. Epidemiological and clinical studies suggest co-morbidity between schizophrenia (SCZ) and cardiovascular disease (CVD) risk factors, including systolic blood pressure, triglycerides, low and high-density lipoprotein, body mass index, waist-hip-ratio, and type 2 diabetes.

Methods: We apply our new genetic pleiotropy-informed methods (based on False Discovery Rate - FDR) to identify additional loci associated with SCZ, a highly heritable disorder with significant missing heritability.

Results: Using stratified Q-Q plots we show enrichment of SNPs associated with SCZ as a function of association with several CVD risk factors, with a corresponding reduction in FDR. We validate this 'pleiotropic enrichment' by showing increased replication rate across independent SCZ sub-studies. Applying the stratified FDR method, we identify 25 loci associated with SCZ at a conditional FDR level of 0.01. Of these, 10 loci are associated with both SCZ and CVD risk factors, mainly triglycerides, low and high-density lipoproteins, but also waist hip ratio, systolic blood pressure, and body mass index.

Discussion: Together, these findings suggest the feasibility of using genetic pleiotropy-informed methods to improve gene discovery in SCZ and identify potential mechanistic relationships with various CVD risk factors.

S5.2 Pain and psychiatric disorders - Pain, anxiety and depression

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Pain, anxiety, and depression are often associated. Thus, patients with symptoms and diagnoses of depression and anxiety are often in pain, and patients with chronic pain often have symptoms and diagnoses of anxiety and depression. The association between diagnoses and symptoms of pain, anxiety, and depression are most likely seen because they share disturbances in the same neurotransmitter systems, especially the monoamines

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serotonin and noradrenaline in the brain and spinal cord. We determined the pain thresholds (mechanical, thermal, and cold pressor test) in 1) patients during and after treatment with electroconvulsive therapy of severe depression (ICD-10), 2) patients with an ICD-10 depressive episode (mild and moderate) and 3) ICD-10 panic disorder compared with age- and gender-matched healthy controls. Furthermore we investigated the correlation between pain and mental symptoms (self- and doctor-ratings) inpatients with fibromyalgia (FM) and neuropathic pain patients (NP) compared with age- and gender-matched healthy controls.

We found that patients with a diagnosis of depression or panic disorder have normal sensory thresholds, but have lower or tend to have lower tolerance thresholds to the cold pressor test than controls. Furthermore chronic pain patients, especially patients with fibromyalgia as opposed to patients with neuropathic pain, have more symptoms of depression, anxiety, and other psychopathology than controls.

S5.3 Is there a connection between heart disease and anxiety?

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Objective: Epidemiological studies have reported an association between panic-like anxiety and an increased risk for cardiac morbidity and sudden cardiac death. One hypothesis attributes the link between panic disorder (PD) and coronary artery disease (CAD) to an elevated incidence of risk factors for CAD in PD patients. Other hypotheses emphasize an association between anxiety and heart rate variability or hypercoagulation. Among patients referred to cardiology clinics and emergency departments because of chest pain, PD is experienced by 25-60 % of patients with non-cardiac chest pain and 10-50% of patients with chest pain and CAD. With this background we examined the long-term relationship between PD at baseline and mortality and cardiac morbidity at follow-up in a clinical sample of chest pain patients.

Method: Patients (n=199) consecutively referred to a cardiology outpatient clinic because of chest pain were reassessed after 9 years. At the initial examination 16% suffered from CAD (n=32) and 38% from PD (n=76). Seven patients suffered from both CAD and PD. At follow-up 82% of the original sample met to a bicycle exercise test and a psychiatric investigation including SCID I interview. Data were collected on mortality, cardiac events, cardiac risk factors, chest pain, current psychiatric disorder and health-related quality of life.

Results: No significant association was found between PD at baseline and mortality and cardiac morbidity at follow-up. There was no significant difference between patients with and without PD regarding cardiac risk factors (family history, obesity, dyslipidemia, smoking, diabetes and hypertension). Panic disorder at baseline was associated with chest pain persistence and low health related quality of life. One fourth of the patients with PD at baseline still fulfilled the diagnostic criteria for PD at follow-up.

Conclusions: The PD patients had a favorable outcome in terms of mortality and cardiac events, but the majority still suffered from chest pain after nine years and they reported their quality of life as poor. The results are discussed in the context of the current knowledge regarding the link between heart and anxiety disease at the SCNP meeting.

SYMPOSIUM 6

OPTIMISING TREATMENT IN PSYCHIATRY. WHERE ARE WE NOW?

S6.1 The biology of psychosis and treatment resistance: Clinical implications

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Schizophrenia remains one of the top ten causes of global disease burden in young adults despite our best current treatments. Fifty years on from the discovery of chlorpromazine, all licensed antipsychotic drugs still use essentially the same mechanism, dopamine D2 receptor blockade. These drugs have failed patients in a number of ways. First, about one in three patients does not respond - they are treatment refractory to multiple different antipsychotics. Second, they do not work effectively for many of the most troubling symptoms, particularly negative symptoms and cognitive impairments.The old models of drug discovery, whilst effective at producing more dopamine blocking drugs, failed to produce effective drugs with novel mechanisms. However recent imaging findings shed new light on the pathophysiology of treatment refractory schizophrenia to inform drug development.

To investigate this we studied dopaminergic and glutamatergic function in cohorts of patients who were stratified by their response to treatment. We compared patients meeting modified Kane criteria for treatment

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resistance with matched patients who met standardized remission criteria following standard treatment and matched controls. In a further study we investigated dopaminergic and glutamatergic function in a cohort of people with prodromal signs of psychosis to investigate the relationship between glutamatergic and dopaminergic function in the evolution of psychosis.

Subjects received [18F]-DOPA PET scans to measure dopamine synthesis capacity, and MR spectroscopy to index glutamatergic function.

Patients who had not responded to standard antipsychotic treatments showed significantly lower dopamine synthesis capacity than patients who had responded (mean (sd) Ki/min= 0.013(0.0013) versus 0.014 (0.0014) respectively; effect size (ES)=1.11, p=0.02). Moreover the patients who had not responded showed no significant difference in dopamine synthesis capacity from controls (controls mean (sd) Ki/min=0.0132 (0.0013); p>0.4), whilst dopamine synthesis capacity was significantly elevated in the treatment responders compared to controls (p=0.02, corrected; ES=1.12). However, the patients who had not responded instead showed significantly increased GLU/Cr ratios (Glu/Cr ratio (=1.11 (0.3) versus 0.76(0.23), p=0.05). People with prodromal signs of psychosis showed an altered relationship between dopaminergic and glutamatergic function compared to controls (r=-0.6, p=0.03versus r=0.04, p=0.9 respectively, interaction F=3.4, p<.05) which was most altered in those who subsequently went on to develop a psychotic disorder (F=4.0, p<0.05).

These data suggest there might be neurobiologically distinct sub-types of schizophrenia and point to the need for new glutamatergic and dopaminergic treatments to address this.

S6.2 The use of pharmacogenetics to guide psychiatric treatment

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There is a tremendous development in genetic tools and techniques. Much hope has therefore been allocated into finding genes which influence response to antipsychotic or antidepressant treatment in psychiatry. Pharmacogenetics presents a major challenge, given that the biological mechanisms responsible for response to e.g. antipsychotics or antidepressants are far from being understood. In spite of these difficulties, first genetic predictors for response and side effects have been identified. Dan Rujescu will present new pharmacogenetic findings in schizophrenia treatment including results from a large-scale association study on response to haloperidol. Dan Rujescu will especially focus on a genome wide association study on the response to haloperidol and on side effects.

S6.3 Major cognitive disorders - drug development based on disease mechanisms: does it work?

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Dementia disorders, e.g. Alzheimer's disease, are highly prevalent and associated with major humane suffering and huge societal costs. Current transmitter-replacement therapies are rather inefficient and not aimed at modifying underlying degenerative processes. Genetic research of autosomal dominant forms of familial neurodegenerative disease has generated powerful tools to get insights into the pathogenesis of several neurodegenerative disorders. It is now apparent that accumulation of misfolded proteins often is pathogenic. There is a recurrent theme of disease-causing mutations leading to protein misfolding. The genetic knowledge has enabled development of protein-depositing transgenic models which has accelerated pathogenic understanding and the possibilities for new drug candidates to enter clinical trials. Importantly, a number of biomarkers are now available which leads to more accurate diagnosis and new putative measures of efficacy in clinical trials. New knowledge on the molecular pathogenesis of dementia is also changing existing disease classification, which traditionally has been largely based on clinical observations. These developments will likely result in better designed clinical trials with more homogenous patient groups in terms of disease and stage of disease, and also enable the inclusion of risk groups and patients in preclinical stages. Still there are many remaining challenges. There is a lack of detailed mechanisms whereby misfolded proteins damage neuronal structures and disrupt communication between neurons. Misfolded proteins can form aggregates of various size and shape, and perhaps only some aggregates are neurotoxic. Alternatively, they could instigate a cascade of rather unspecific destructive processes in neurons and surrounding tissue resulting in cellular dysfunction, neurodegeneration and functional impairment. Examples of such downstream effector-mechanisms are inflammation, oxidative stress, excitotoxicity, impaired axonal transport and mitochondrial dysfunction. Better understanding of neurodegenerative processes and dementia could lead to animal models with such phenotypes and thereby more successful drug development. A major challenge is also getting

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biological drugs, e.g. fusion proteins, antibodies or RNA-based drugs, to easily cross the blood-brain barrier such that an amount needed to affect a pathogenic process enters the brain and reaches the intended drug target.

SYMPOSIUM 7 (DSBP)

SLEEP DISTURBANCES - FROM BENCH TO BEDSIDE

S7.1 Chronic insomnia and hyperarousal - state of the art

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Chronic insomnia is characterized by problems to fall asleep, difficulties in mantaining sleep, the experience of non-refreshing sleep and associated daytime sequelae like decreased attention, fatigue, irritability, dysphoric mood etc. Chronic insomnia afflicts up to 10% of the population in western industrialized countries and is conceptualized in the upcoming version of DSM-V as "insomnia disorder". In recent years, the concept of hyperarousal on an emotional, behavioral and cognitive level has gained much attention as a pathophysiological concept for insomnia, especially its primary form. Own work focussed especially on neurobiological aspects of hyperarousal. Thus, we were able to demonstrate that the polysomnographically recorded sleep of patients with chronic primary insomnia is characterized by an increased frequency of micro-arosuals (especially during REM sleep) and increased amounts of fast frequencies dominantly in the beta-range, when spectralanalysis was applied to the sleep EEG. Work on heart rate and heart rate variabilityrevealed that inspite of being asleep, patients with insomnia showed higher autonomicactivation than good sleeper controls. For ocrtisol, other groups have demonstratedincreased levels of this stress hormone in the afternoon and directly prior to sleep.Neuroimaging studies have shown higher activation of the "sleeping insomniac brain"compared to unafflicted sleepers. Neuroanantomical studies initially indicated dereasedhippocampal volumes of patients with insomnia, though we were unable to replicate thesefindings in own larger studies. Summarizing,many evidences from different research avenuessupport the concept of hyperarousal as a relevant pathophysiological factor - it is,however, unclear what the direction of causality is: is insomnia caused by hyperarousal ordoes vice versa the insomnia lead to hyperarousal?.

S7.2 Co-morbid insomnia

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The objective of this review is to highlight the impact of insomnia in central neurological disorders by providing information on its prevalence and give recommendations for diagnosis and treatment. Insomnia in neurological disorders is a frequent, but underestimated symptom. Its occurrence may be a direct consequence of the disease itself or may be secondary to pain, depression/other psychiatric, medical or neurological diseases and/or co-treatment with medication. Insomnia can have a significant impact on the patient's cognitive and physical function and may be associated with psychological distress and depression. Diagnosis of insomnia is primarily based on medical history and validated questionnaires. Actigraphy is a helpful diagnostic tool for assessing the circadian sleep-wake rhythm. For differential diagnosis and to measure the duration of sleep full polysomnography may be recommended if primary sleep disordes are suspected. Prior to initiating treatment the cause of insomnia must be clearly identified. First line management aims to identify the underlying sleep, psychiatric or neurologic disease.

The few treatment studies available shows limited effect with traditional hypnotics. Recently alternative treatment options using sedating antidepressants or melatonin, Cognitive behavioral therapy (CBT) can be effective in treating insomnia symptoms associated with most of the central neurological diseases. The prevalence and treatment of insomnia in neurological diseases still need to be studied in larger patient groups with randomized clinical trials to a) better understand their impact and causal relationship and b) to develop and improve specific evidence-based treatment strategies.

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S7.3 Insomnia in psychotic disorders

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Sleep disturbances in schizophrenia are associated with reduced quality of life and social functioning. Several studies of schizophrenia patients demonstrate disturbances in sleep continuity (reduced sleep efficiency and total sleep time, increased sleep latency), disturbances in sleep architecture (alterations of stage 2 sleep, slow wave sleep, and rapid eye movement (REM) sleep variables), and disrupted circadian rhythmicity. Insomnia, defined as subjective complaints of difficulties falling or staying asleep or non-restorative sleep that is associated with marked distress or significant daytime impairment, constitutes an important part of the dysfunctional sleep pattern in schizophrenia.

Acute insomnia is associated with the inherent hyperarousal state in psychotic exacerbation, but insomnia often persists in a residual form after otherwise adequate treatment of the psychotic symptoms. These sleep disturbances are based on a complex interaction between the pathological disturbances of neurotransmitter function in schizophrenia and the influence on neurotransmitter systems by antipsychotic drugs. Sleep disturbances are associated with reduced quality of life in schizophrenia patients but current treatment guidelines do not include advice on the best treatment approach. Substituting an otherwise efficient antipsychotic drug-therapy with a more sedating drug carries the risk of psychotic relapse during the switch, and adding another drug carries the disadvantages of polypharmacy including increased rate of side-effects, drug-drug interactions, patient non-compliance and medication errors. The sparse literature on treatment of residual insomnia in schizophrenia is discussed and likewise whether insomnia can be interpreted as a clinical marker of possible psychotic relapse.

SYMPOSIUM 8

ADHD TREATMENT UPDATE

S8.1 Methylphenidate treatment of adult prison inmates with ADHD: A randomised double-blind placebo-controlled trial with open-label extension

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ADHD in the presence of early disruptive behaviours increase the risk for later delinquency. Approximately 25-45% of adult prison inmates are estimated to have ADHD.

Despite the high prevalence of ADHD within inmates and serious consequences of untreated ADHD for the individual and for society, stimulant treatment was not previously evaluated in prison inmates. We evaluated treatment with OROS-methylphenidate in a 5-week randomised, double-blind, placebo-controlled, fixed-dose trial in 30 adult male long-term prison inmates with ADHD and high rates of coexisting disorders.

In a subsequent 47-week open-label, flexible-dosing extension phase, we evaluated long-term effectiveness of OROS-methylphenidate when delivered alongside regularly provided psychosocial interventions within a high-security prison setting.

Treatment was highly effective and overall safe, both in the short-term relative to placebo (Cohen's d=2.17; NNT=1.1), and in the long-term when delivered together with psychosocial programs. No misuse of medication or side-abuse was detected. Treatment improved ADHD symptoms, global functioning, executive functioning, behaviour control and quality of life.

A majority of participants attended and completed crime preventing treatment programs, educational activities and vocational training. The results of our study suggest that stimulants provided under strictly controlled conditions could be a useful component of multimodal treatment for ADHD also within prison settings.

S8.2 Pharmacological treatment of ADHD with amphetamine dependence

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Background: Attention Deficit/Hyperactivity disorder (ADHD) is a neurodevelopmental disorder that frequently occurs with substance use disorders (SUD). Stimulant pharmacotherapy, such as methylphenidate is one of the most frequently used treatment of ADHD. So far, only a few randomized controlled trials have investigated efficacy of methylphenidate treatment for patients with ADHD and comorbid SUD. The results from these studies have been inconclusive and the evidence is still lacking. In a pilot study of 72 mg/day extended release methylphenidate in amphetamine dependent individuals with comorbid ADHD we found

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no difference between the groups on neither the ADHD symptoms nor drug use. The treatment was well tolerated with no severe side-effects. In a subsequent randomized placebo-controlled trial we tested the efficacy and safety of methylphenidate, in doses up to 180 mg, for treatment of ADHD with comorbid amphetamine dependence.

The trial was double-blind, placebo-controlled with parallel groups design. The trial included 54 males with amphetamine dependence and ADHD recruited while serving time in prison in Stockholm County, Sweden. The assessment of ADHD comprised of rating scales, psychiatric interview and a neuropsychological screening. The daily dose tested was up to 180 mg of extended release methylphenidate compared with placebo. The medication started 14 days before release from the prison and continued for 22 weeks at an outpatient clinic with twice weekly visits. The primary end point was relapse in drug use as measured by urine toxicology. Secondary outcomes were self-rated ADHD-symptoms, craving, other psychiatric symptoms and retention to treatment.All patients participated in weekly sessions of a cognitive behavioural therapy targeting relapse prevention

Results: MPH treated group had more drug negative urines and significantly better retention to treatment compared to the placebo group. In addition, the MPH group significantly reduced their self-rated ADHD symptoms during the 24-week treatment. There was no difference between the groups in psychiatric symptoms from baseline to week 24. No serious adverse events were reported in the methylphenidate group.

Conclusions: The results support the utility of diagnosing ADHD in amphetamine dependent individuals with criminal behaviour, and the efficacy of MPH pharmacotherapy to reduce ADHD symptoms and increase retention to treatment.

S8.3 The Potential Role of LDX (lisdexamfetamine) in the Treatment of ADHD Across the Life-span

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Attention-deficit hyperactivity disorder (ADHD) is among the most common psychiatric disorders in children and adolescents, and persists into adulthood in approximately two thirds of sufferers. It is associated with significant symptomatology and functional impairment throughout the lifespan, including difficulties in family, social, academic and occupational activities.

Both medication and psychosocial interventions are recommended for the treatment of ADHD. However, ADHD treatment practices vary considerably, depending on medication availability, reimbursement and the evolution of clinical practice in different countries.

Lisdexamfetamine was the first stimulant treatment approved as a prodrug. The dose-dependant efficacy of lisdexamfetamine in the treatment of core symptoms of ADHD in children, adolescents and adults has been established by multiple clinical trials. The lisdexamfetamine molecule is inactive until it is enzymatically hydrolysed, primarily in the blood, cleaving off lysine to yield active dexamfetamine. Bioavaialability is unaffected by gastrointestinal pH and variations in normal transit times. Lisdexamfetamine has a unique pharmacokinetic profile characterized by low peak but sustained plasma dexamfetamine concentrations with long-lasting, predictable and reliable delivery of active medication. Studies have shown effectiveness that is consistent throughout the day and a post-dose duration of action for 13 hours in children and for 14 hours in adults. Based on trough plasma concentrations, dexamfetamine steady state is achieved after approximately five daily doses of lisdexamfetamine, and there is no unexpected accumulation of the parent compound or dexamfetamine.

Short-term and one year tolerability is similar to that of XR mixed amfetamine salts. Adverse events are generally mild to moderate in severity, attenuating within the first few weeks of treatment. Discontinuation rate due to adverse events over 12 months of treatment is low (9.2%). No clinically significant cardiovascular or other safety problems have been identified. Since lisdexamfetamine does not contain l-amfetamine, it is possible that lisdexamfetamine may offer less potential for adverse change in the motor and somatosensory cortices (e.g. nervousness, repetitive or compulsive behaviours).

Lisdexamfetamine is unlikely to be misused, since free dexamfetamine is not present in the capsules and mechanical manipulation (such as by crushing or extraction) will not yield the active ingredient. Drug abuse potential is obviated by its rate-limited enzymatic hydrolysis and the gradual release of dexamfetamine from the molecule. Studies of patients with a history of drug abuse showed decreased drug-liking effects with lisdexamfetamine in comparison with immediate-release dexamfetamine. The liking effect of a 50-mg i.v. dose of lisdexamfetamine did not differ significantly from placebo.

Also, since hydrolytic enzymes follow saturable kinetics and the hydrolysis of lisdexamfetamine is rate limiting, this decreases the potential for overdose toxicity. This is an important advantage, as emergency room visits due to the adverse events from stimulant overdose are not unusual. The prolonged release of dexamfetamine also minimizes rebound phenomena seen between doses of short-acting stimulants.

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POSTERS

Poster 1

Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders

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Objective: Previous studies of bipolar disorders indicate that childhood abuse and substance abuse are associated with the disorder. To what extent the association between substance abuse and clinical characteristics are moderated or mediated by childhood abuse is not clear, which is what we would like to investigate in this study.

Methods: 587 Patients with bipolar disorders were recruited from Norway and France (mean±age: 40.6±13.6; gender: 40% males). History of childhood abuse was obtained using the Childhood Trauma Questionnaire (CTQ). Diagnosis and clinical variables including substance abuse were based on structured clinical interviews (SCID-I or DIGS). All statistical analyses were performed with the packages PASW Statistics 18 (Release 18.0.1) and R (Version 2.12.0). Childhood trauma data was dichotomized into moderate - severe cutoff scores to classify subjects as having/not having a history of childhood trauma. Mann-Whitney and Chi-square tests were conducted to investigate the relationship between substance abuse and clinical variables. For the interaction and additive analyses, binary logistic regression and multiple linear regression analyses were performed. Age at onset, and mood episodes were transformed to ensure normality before entered into the regression analyses. Post hoc analyses were conducted controlling for possible confounders, such as gender, as well as duration of illness. Results were corrected for multiple testing.

Results: Significant associations were observed between cannabis abuse and childhood abuse, specifically for emotional and sexual abuse (X2=8.63, p=0.003 and X2=7.55, p=0.006, respectively). No association was observed between childhood trauma and lifetime alcohol dependence. Lifetime history of cannabis abuse was significantly associated with earlier age at onset (z=-4.17, p<0.001), suicide attempts (X2=11.16, p=0.001), as well as a trend for rapid cycling (X2=3.45, p=0.06). Alcohol dependence was associated with increased suicide attempts (X2=10.28, p=0.001), but not with age at onset or rapid cycling. After correcting for possible confounders and multiple testing, a trend was observed for an interaction between cannabis abuse and childhood trauma on increased number of suicide attempts (Nagelkerke r2=0.06, p=0.039). Significant additive associations were found between cannabis abuse and childhood trauma on earlier age at onset, increased rapid cycling, as well as more suicide attempts (p<0.001). No mediations effects were observed.

Conclusions: Our study is the first to demonstrate significant additive effects, but not mediation effects, between childhood abuse and cannabis abuse on clinical symptom severity in bipolar disorders.

Poster 2

Differential role of AMPA receptors in mouse models of depression and anxiety

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Depression and anxiety highly co-morbidity disorders, and they are responsive to common pharmacotherapeutic interventions; virtually all drug classes used to treat depression also reduce anxiety. Although dysfunctional monoamine (serotonin, noradrenaline and dopamine) systems have been associated with anxiety and depression, no monoamine-related findings are directly diagnostic for these disorders. Elucidating the link between the pharmacological effects of these drugs and their therapeutic action is an essential step in understanding the limitations of conventional antidepressants and in developing improved pharmacological treatments of depression and anxiety.

Preclinical evidence suggests that facilitation of signaling through alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPAR) produces antidepressant-like effects. For instance, treatment with positive allosteric modulators of AMPARs (AMPAR potentiators) show antidepressant-like effects and enhances the effects of conventional antidepressants in the mouse forced swim test (FST) of antidepressant efficacy, suggesting that monoamine-based antidepressants produce their antidepressant efficacy by increasing AMPAR-mediated glutamate signaling. The sparse studies addressing AMPARs in relation to anxiety have given ambiguous results, with both anxiolytic-like and anxiogenic-like effects observed after AMPAR blockade. Studies investigating the role of AMPARs in anxiety are therefore warranted.

Here, we compared the antidepressant-like and anxiolytic-like effects of the AMPAR potentiator

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LY451646 and the AMPAR antagonist GYKI53655, using the FST and three different mouse models of anxiety-related behaviour; the elevated zero maze (EZM), the marble burying test (MBT) and the novelty-induced hypophagia (NIH) test. LY451646 showed a pronounced increase in swimming activity in the FST (MED: 1 mg/kg), while it increased anxiety-like behaviour in the EZM as reflected by decreased number of entries (MED: 3 mg/kg). LY451646 was devoid of effects in the MBT or NIH test. This indicates that a potentiation of AMPAR function produces antidepressant-like while increasing anxiety-like behaviour in the EZM. By contrast, GYKI53655 was devoid of antidepressant-like effect in the FST, but showed marked anxiolytic-like effects in the EZM, as reflected by decreased latency to enter open areas (MED: 2.5 mg/kg), time spent in open areas (MED: 2.5 mg/kg), increased number of entries into open areas (MED: 5 mg/kg), decreased number of stretched-attended postures (risk-assessment behaviour) (MED: 5 mg/kg), and number of feacal boli (5 mg/kg). In the MBT, GYKI53655 significantly decreased digging behaviour (MED: 5 mg/kg). Finally, GYKI53655 deceased the latency to drink in the NIH test, indicating decreased anxiety.

Collectively, the present results suggest that AMPARs play different roles in depression and anxiety, with increased and decreased AMPAR activity promoting antidepressant-like and anxiolytic-like behaviour, respectively.

Poster 3

Nociceptin/Orphanin FQ receptor agonist SR 8993 as treatment in high alcohol intake- and anxiety- states

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Background: Alcoholism is a complex behavioral disorder in which interactions between stressful life events and heritable susceptibility factors contribute to the initiation and progression of the disease and affecting its onset, maintenance and therapy. Alcohol withdrawal refers to a cluster of symptoms that may occur from suddenly ceasing the use of alcohol after chronic or prolonged ingestion. These symptoms make alcohol abstinence difficult and increase the risk of relapse in recovering alcoholics.

The Nociceptin/Orphanin FQ (NOP) receptor plays a role in the regulation of reward and motivation pathways related to alcohol abuse. Previous studies have shown that NOP receptor activation by its endogenous ligand reduces alcohol intake in alcohol dependent rats. Also, it reduces home-cage alcohol consumption, alcohol-induced conditioned place preference and stress/cue induced reinstatement of alcohol seeking behavior.

Aim/Purpose: The present study aim to examine the efficacy of the novel and potent NOP receptor agonist SR 8993 in rodent behavioral models of anxiety and hangover-stress related behaviors, as well as in regulation of alcohol intake in continuous and intermittent alcohol drinking paradigm.

Methods: Male Wistar rats were used in all experiments. The NOP/OFQ receptor agonist, SR 8993, was given intraperitoneally at a dose of 1 mg/kg 45 minutes prior to behavioral testing. Anxiety-related behavior was measured using the elevated plus-maze model (naive as well as following alcohol withdrawal). Drinking was examined in two-bottle free-choice paradigms employing both continuous and intermittent access to alcohol.

Results: SR 8993 has mild anxiolytic effects when given to naive animals, reverses alcohol induced hangover anxiety-related behavior in the elevated plus-maze test and reduces alcohol-intake in both continuous/intermittent drinking paradigms.

Conclusion: These findings suggest and add further support to the idea that NOP agonist are effective in blocking the actions of ethanol important for its addictive potential in animal model and therefore may have therapeutic value in the treatment of alcoholism.

Poster 4

NMDA-receptor agonism and inflammation in suicide attempters - a long term study using repeated CSF sampling

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Purpose: Patients suffering from depression and suicidality show immune dysregulation and a centralactivation of the proinflammatory system. It has been suggested that proinflammatorycytokines induce depression though activation of the enzyme indoleamine 2,3-dioxygenase (IDO) which is the rate-limiting enzyme of tryptophan catabolism through the kynurenine pathway. Altering the kynurenine pathway affects NMDA receptor activation. We hypothetized that depressive and suicidal symptoms fluctuate over time, depending on the degree of inflammation, and the levels of potential glutamate agonism originating from kynurenine metabolites.

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Methods: Plasma and cerebrospinal fluid (CSF) from suicide attempters were collected at repeated time points after a suicide attempt. Expression of proinflammatory cytokines as well as the kynurenine metabolites kynurenic acid (KYNA) and quinolinic acid (QUIN) were examined using high-sensitivity electrochemi-luminescence-based multiplex immunoassay, High Performance Liquid Chromatography and Gas Chromatrography - Mass Spectrometry, respectively. Depressive-symptoms and suicidality were evaluated using the Montgomery Asberg Depression Rating Scale (MADRS) and the Suicide Assessment Scale (SUAS).

Results: Firstly, we found a significant increase in central levels of QUIN and in the QUIN/KYNA ratio in patients compared to healthy controls. As QUIN is a NMDA receptor agonist and KYNA an NMDA receptor antagonist, these results point towards an increased NMDA receptor activation in the brains of the suicide attempters, possibly through microglial activation. Moreover, a negative correlation between CSF KYNA and MADRS scores was found, indicating that a decrease in NMDA receptor antagonism is associated with increased symptom severity. Positive correlations between symptom severity and CSF cytokines were also found confirming previous findings. Importantly, plasma and CSF KYNA levels did not correlate, stressing the value of CSF sampling as neither KYNA nor QUIN are actively transported across the blood-brain-barrier.

Conclusion: These results suggest that suicidal patients show central alterations in the kynurenine pathway. We suggest that the increase in central levels of proinflammatory cytokines leads to increased microglial activation, which in turn produce QUIN. These modifications lead to increased NMDA receptor activation, which correspond to increased symptom severity. This is in line with recent findings of rapid antidepressant effects of NMDA receptor antagonists such as ketamine. This compound model attempts to explain symptom fluctuation over time on a neuro inflammatory background, and needs further experiments to be confirmed.

Poster 5

The cell adhesion molecule nectin-1 as a therapeutic target in neurodegenerative diseases

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Background: Memory loss is a central symptom in neurodegenerative diseases, and represents asignificant social and economic burden. The available treatments can only relieve symptoms, and it is therefore of utmost importance to identify new therapeutic targets andneuroprotective drugs that can decelerate memory loss. Nectins are a family of celladhesion molecules comprising four members, nectin-1 through nectin-4. Nectin-1 is involved in formation of mechanical adhesion junctions in synapses in hippocampus, where it seems to play a role in synaptic plasticity, a mechanism essential for memory andlearning.

Objectives: The aim was to investigate if the third Ig module of nectin-1 (N1 Ig3) is a possibletherapeutic target in neurodegenerative diseases and if the peptide Nectide derived fromN1 Ig3 is a potential drug candidate to treat memory loss.

Methods: N1 Ig3 was produced as a recombinant protein in a P. pastoris expression system and a peptide termed Nectide corresponding to a putative receptor binding-site in N1 Ig3 was synthesized. Cerebellar granule neurons (CGNs) were isolated from 7 days postnatal Wistarrats. A neurite outgrowth assay with CGNs was used to determine if N1 Ig3 or Nectide could induce neuronal differentiation as reflected by neurite outgrowth, while a survival assay with CGNs treated to undergo apoptosis was used to estimate neuroprotective effects of N1Ig3 and Nectide.

Real-time biomolecular binding studies were performed to determine binding to fibroblast growth factor receptor (FGFR). Activation of FGFR by N1 Ig3 and Nectide was assessed in aFGFR1c phosphorylation assay and a neurite outgrowth assay with CGNs transfected with a dominant negative FGFR.

Results: N1 Ig3 induced neuronal differentiation and had a neuroprotective effect in CGNs treated to undergo apoptosis. N1 Ig3 mediates its neuritogenic effects through activation of FGFR that plays a critical role in the CNS during development, since N1 Ig3 bound FGFR, could induce phosphorylation of FGFR1c, and N1 Ig3-induced neurite outgrowth was abrogated inCGNs transfected with a non-functional dominant-negative FGFR. We identified an amino acid sequence motif in N1 Ig3 involved in FGFR binding and activation and showed that a corresponding peptide termed Nectide mimicked the neuritogenic effects of N1 Ig3.

Conclusion: Our findings demonstrate that N1 Ig3 is a potential therapeutic target in neurodegenerative diseases. The peptide Nectide mimics the effects of N1 Ig3 and is thus apotential drug candidate to treat memory loss.

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Poster 6

Long term treatment with gabapentin in an animal model of chronic neuropathic pain

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In preclinical animal pain research potential efficacy of a drug is often evaluate after a single exposure, which is in contrast to the long lasting treatment needed in chronic neuropathic pain (CNP) patients. Gabapentin remains one of the most efficacious drugs in the treatment of CNP.

The aims of the study were to evaluate the spinal cord contusion (SCC) model and 2 different measures of pain-like behaviour using a long term treatment schedule with gabapentin. Furthermore the effect on mobility and on anxiety, a pain-related behaviour, was included.

40 Female SD rats with a T13 SCC and sham animals.

Daily treatment with gabapentin 30 mg/kg sc. or saline for 6 consecutive weeks.

Mechanical sensitivity thresholds (MST) to von Frey stimulation of hindpaws and thorax measured by both reflex withdrawal and supra-spinal responses.

Anxiety-like behaviour using the openfield paradigm.

Drug effect was measured after initial dose, 1 and 6 weeks of treatment.

Preliminary results show that saline-treated SCC animals (N=10) have significantly lower MST with supra-spinal responses on the thorax compared to saline-treated shams (N=10), and gabapentin-treated SCC (N=10) and sham animals (N=10) throughout the study. The SCC animals had significantly decreased MST with reflex responses on the hindpaws in the two first time points compared with gabapentin-treated SCC animals (and both sham groups). There was no effect of injury on the MST with supra-spinal responses on the hindpaws and thus no effect of gabapentin. Furthermore, there was no significant decrease in the efficacy of gabapentin over the treatment period of 6 weeks.

There was no effect of injury or treatment on mobility and anxiety-like behaviour as a result of gabapentin treatment.

SCC result in persistent mechanical hypersensitivity on the thorax which is responsive to long term treatment with gabapentin, and that gabapentin continues to be effective in this model of CNP. Furthermore, SCC injury initially results in increased reflex responses in the hindpaws which are attenuated by acute and longterm gabapentin treatment.

Poster 7

Prevalence and treatment patterns of patients with newly diagnosed ADHD in Sweden

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Background: Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous behavioural disorder in children, adolescents and adults, characterised by symptoms of impulsivity, hyperactivity, and inattention. The National Board of Health and Welfare in Sweden estimates that around 3% to 5% of school-aged children suffer from ADHD. Few studies have been conducted with a focus of estimating the prevalence of ADHD diagnosis in Sweden and there are no studies assessing the current treatment patterns for this

population.

Purpose: The objective of this study was to use comprehensive national registry data sets to investigate the prevalence of diagnosis of ADHD during a 5-year period and to describe the pharmaceutical treatment patterns for this population in Sweden.

Methods: Data from the National Patient Register (NPR) and the Prescribed Drug Register (PDR) both held by the National Board of Health and Welfare, were used for this analysis. Newly diagnosed patients with ADHD were identified in the NPR by the ICD-10 codes for hyperkinetic disorders F90.0: Disturbance of activity and attention, F90.0A: DAMP, F90.0B: ADHD, F90.0C: ADD, F90.0X: Activity and attention disturbance, unspecified, F90.1: Hyperkinetic conduct disorder, F90.8: Other hyperkinetic disorders. The inclusion criteria included no ADHD medication (stimulants or atomoxetine) during 1 year prior to the first appearance in the NPR with the defined diagnosis. Data from 2006 to 2011 were used.

Results: The number of newly diagnosed patients has increased from 5148 patients (68% males, mean [SD] age 21.2 [12.7] years) in 2007 to 12 452 (60% males, mean [SD] age 22.3 [13.7] years) in 2011, with relatively larger increases in females (+200%) and in the adult population above 21 years (+168%). The proportion of newly diagnosed patients on ADHD medication has increased from 50% in 2007 to 78% in 2011. First-line drug treatment options for newly diagnosed patients for all years were: extended-release methylphenidate (MPH-ER) (64% year 2011), followed by modified-release methylphenidate (MPH-MR) (15% year 2011) and atomoxetine (10% year 2011). The most common second-line treatment option was MPH-MR followed by atomoxetine and MPH-ER. Hypnotics and anxiolytics

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were the most prevalent concomitant psychiatric medications.

Conclusions: The prevalence of newly diagnosed ADHD cases has increased almost threefold during the 5 years studied. The proportion of patients receiving pharmacological treatment has increased from 50% to 78%. The most prevalent first-line treatment option was MPH followed by atomoxetine during the period 2007 to 2011, with MPH accounting for approximately 80% of all first-line prescriptions for ADHD medication.

Poster 8

Mitochondrial dynamics in the hippocampus is influenced by antidepressant treatment in a genetic rat model of depression

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Post-mortem, genetic, brain imaging, and peripheral cell studies showed that mitochondria may play an important role in the pathophysiology of depression and effects of antidepressant therapy. Here we investigated whether chronic antidepressant treatment on rats induce changes of the mitochondrial number in hippocampus.

All rats were injected imipramine (a classic tricyclic antidepressant) or saline (i.p) once daily for 14 days on normal rats (10 mg/kg) and for 25 days on the Flinders Sensitive Lines (FSL) rats and their controls the Flinders Resistant Line (FRL) rats (15 mg/kg), a genetic rat model of depression. The unbiased stereoloy methods were used to estimate the mitochondria numerical density, the number of mitochondria and the mean size and volume of mitochondria in CA1 stratum radiatum (CA1SR) of hippocampus.

The results showed that the mitochondria numerical density and the number of mitochondria in CA1SR displayed significantly smaller in the FSL-saline group compared to FRL-saline group and SD-saline group. But the mean volume of mitochondria showed significantly bigger in the FSL-saline group compared to FRL-saline group and SD-saline group. Following treatment, the FSL-imipramine group showed a significant increase in the mitochondria numerical density and the number of mitochondria compared to the FSL-saline group.In conclusion, the mitochondria numerical density and the number of mitochondria in CA1SR were significantly smaller in the FSL-saline group compared to FRL-saline group and SD-saline group. Impramine treatment can significantly increase the mitochondria numerical density and the number of mitochondria in FSL-imipramine group.

Our results support the mitochondria plasticity hypothesis that depressive disorders may be related to impairments of mitochondria plasticity in hippocampus, and antidepressant treatment may counteract the structural impairments.

Poster 9

Childhood trauma is associated with antipsychotic medication, higher PANSS scores and lower GAF scores

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Background: The literature reports a higher prevalence of childhood trauma in patients with psychotic disorders compared to the general population. Also, studies report an association between childhood trauma and an earlier age at onset, as well as more mood episodes, and suicide attempts. In this study, we aimed to investigate whether childhood trauma is associated with increased symptom level and increased antipsychotic treatment in psychoses.

Methods: 449 patients with a broad DSM-IV schizophrenia spectrum or bipolar disorder (mean±age: 30.21±10.55; gender: 54.1% males; diagnosis: 58.3% schizophrenia spectrum), were consecutively recruited to the Thematically Organized Psychosis (TOP) Study. Antipsychotic medication was divided into: no antipsychotic medication, one type of antipsychotic medication, or two and more types of antipsychotic medication. Histories of childhood adverse events were obtained using the Childhood Trauma Questionnaire (CTQ). Diagnosis was based on the Structured Clinical Interview for DSM- IV Axis I disorders (SCID-I). Current positive and negative symptoms were rated using the Positive and Negative Syndrome Scale (PANSS); Functional level was assessed with the Global Assessment of Functioning Scale, split version-function score; Global Assessment of Functioning (GAF-F), and Symptoms (GAF-S). As the childhood trauma data was not normally distributed, Spearman's correlation was conducted investigating the association between childhood trauma and symptom levels.

Results: No significant difference in prevalence of total childhood trauma score was observed between the schizophrenia spectrum and the bipolar group (X2=52.48, p=0.87). Childhood trauma total score was significantly associated with higher scores on PANSS positive scale (r=0.16, p=0.001). When dividing into

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subtypes of childhood trauma, physical abuse, emotional abuse, and emotional neglect were significantly associated with increased scores on PANSS positive scale ($p<0.007$), as well as physical neglect ($p=0.019$). Childhood trauma total score was also significantly associated with higher scores on PANSS general psychopathology scale ($r=0.18$, $p<0.001$); with p value ranging from <0.001 to 0.04 depending of childhood trauma subtype. Childhood trauma total score was significantly negatively associated with GAF-F and GAF-S ($r=-0.14$, $p=0.001$; $r=-0.16$, $p=0.001$, respectively). When dividing into different subtypes of childhood trauma the association varied between $p=0.001$-$p=0.04$). Only sexual abuse did not show an association to PANSS positive scale and GAF scores. Lastly, childhood physical abuse was positively associated with antipsychotic medication ($r=0.11$, $p=0.02$), as well as a trend for physical neglect ($r=0.08$, $p=0.069$).

Conclusion: Childhood trauma is associated with a more severe expression of psychiatric disorders, demonstrated by higher PANSS scores, lower GAF scores as well as links to antipsychotic medication.

Poster 10

Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: evidence for direct serotonin receptor modulation

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Rationale: Cognitive dysfunction (e.g., executive function and memory) is common in depression. Recent clinical findings indicate that the investigational antidepressant vortioxetine has a positive effect on cognitive dysfunction related to depression. Vortioxetine has a multimodal mechanism of action, modulating two protein classes; 5-hydroxytryptamine (5-HT; serotonin) receptors and the 5-HT transporter (SERT). In cell studies, vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and SERT inhibitor. It was hypothesized that vortioxetin's activity at 5-HT receptors plays a role in memory function. Furthermore, acute 5-HT depletion impairs memory and mood in vulnerable patients.

Objectives: To establish a preclinical model of 5-HT depletion-induced memory deficits in rats; to assess the effects of the antidepressants escitalopram, duloxetine, and vortioxetine on these deficits; and explore vortioxetine's mechanism of action.

Methods: Recognition and spatial working memory were assessed in the novel object recognition (NOR) and Y-maze spontaneous alternations (SA) test, respectively. Rats were administered 4 daily doses (85.5 mg/kg) of an irreversible tryptophan hydroxylase inhibitor, 4-chloro-DL-phenylalanine methyl ester hydrochloride (PCPA). PCPA effects on NOR and SA performance were assessed along with the effects of acute treatment with escitalopram, duloxetine, vortioxetine, the 5-HT3 receptor antagonist ondansetron, or the 5-HT1A receptor agonist flesinoxan, in PCPA-treated animals. Additionally, the effect of chronic vortioxetine administration was investigated in these models. Extracellular 5-HT levels in the dorsal hippocampus of PCPA-treated rats were assessed using microdialysis following acute treatment with the 5-HT releaser fenfluramine, or vortioxetine.

Results: PCPA-treatment consistently impaired memory performance in both the NOR and SA test. Acute vortioxetine reversed these deficits, whereas escitalopram and duloxetine were inactive at equivalent SERT occupancies. Acute ondansetron and flesinoxan treatment reversed NOR performance, whereas only flesinoxan was effective in the SA test. Chronic vortioxetine treatment prevented PCPA-induced deficits in NOR, but not SA performance. Microdialysis studies showed a 70% reduction in extracellular 5-HT by PCPA. Unlike fenfluramine, vortioxetine did not increase hippocampal extracellular 5-HT after PCPA, indicating that it is not a 5-HT releaser.

Conclusion: 5-HT depletion impaired memory performance in rats. Unlike escitalopram and duloxetine, acute treatment with vortioxetine reversed these memory impairments. The facilitating effect of vortioxetine on spatial working memory involved 5-HT1A receptor agonism, whereas the effect on recognition memory implicated both 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The finding that 30% of extracellular 5-HT remained in PCPA-treated rats indicates that a neutral 5-HT3 receptor antagonist may be effective.

Poster 11

Interferon-alpha induced depressive-like behavior in rats

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Background: A subpopulation of individuals with major depressive disorder (MDD) show increased levels of

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peripheral inflammatory biomarkers, indicating an association of MDD with a chronically activated immune system. Administration of the immune stimulating cytokine, interferon-alpha (IFN-α), also used in the treatment of cancer and hepatitis, commonly leads to neuropsychiatric side effects with approximately 16–45% of patients developing depressive-like symptoms during the course of therapy. Given that treatment-resistant depression has been associated with increased levels of inflammatory markers, the development of an inflammation-induced model of depression is highly relevant.

Aim: The objective of this study was to investigate whether IFN-α can induce a chronic low-grade inflammatory state in rats, and whether this may lead to a depressive phenotype.

Methods: Male Sprague-Dawley rats (n=40, mean weight 328.3 ± 1.55 g) received daily subcutaneous injections with human recombinant IFN-α (1×106 U/kg/day) or vehicle (saline) for one week. After six days, animals were tested either 1h or 24 hours after injection for depressive-like behavior using the saccharin preference test (SPT) and Forced Swim test (FST), which respectively measure anhedonia and behavioral despair in rodents.

Results: IFN-a did not induce sickness behavior, indicated by similar body weight, food and water intake, temperature measurement and locomotor activity between the groups. However, daily injections with IFN-α for one week induced a depressive-like phenotype as measured both after 1h and 24h in the FST and SPT.

Discussion and perspective: Peripherally injected IFN-α crosses the blood-brain-barrier and reaches the central nervous system where psychological side-effects including depression can be induced. The finding in this study that IFN-α-treated rats show depressive-like behavior supports this notion, and indicates that IFN-α treatment in rats could represent a viable inflammation-induced animal model of depression. Several theories have been suggested to link inflammation and depression, such as increased levels of the neurotoxic tryptophan metabolite, quinolinic acid (QUIN), and decreased brain-derived neurotrophic factor (BDNF), a protein that plays an important role in survival, differentiation and growth of neurons. The successful development of an inflammation-induced model of depression will be pivotal for our understanding of the underlying pathophysiological immune mechanisms in MDD and may lead to the design of better and more effective treatment options in the near future.

Poster 12

Acute effects of 17ß-estradiol on anxiety-like behavior and on cholecystokinin-like immunoreactivity in the female rat limbic system

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Background: The neuropeptide cholecystokinin (CCK) has been implicated in the neurobiology of anxiety and panic disorders, as well as in dopamine-related behaviors. Anxiety and panic-disorders are twice as common in females compared to males, and sex-differences in the dopamine system have been reported. However, studies of the involvement of CCK in these diseases are very sparse in females. Limited studies have found that CCK fluctuates in some limbic regions during the estrous cycle and that CCK and its receptors are sensitive to estrogen.

Aim/Purpose: The aim of the present work was to study acute effects of 17ß-estradiol on anxiety-like behavior and CCK-like immunoreactivity (LI) in the female rat brain (amygdala, hippocampus, nucleus accumbens and cingulate cortex). Methods: Four groups of female Sprague-Dawley rats were used: ovariectomized, ovariectomized+17ß-estradiol -replacement, sham, and sham+17ß-estradiol -replacement. Anxiety-related behavior was measured on the elevated plus maze (EPM). CCK-LI concentration was measured in punch biopsies by means of radioimmunoassay.

Results: Both in ovariectomized and sham-operated animals, 17ß-estradiol decreased anxiety-like behavior two hours after administration as demonstrated by increased exploration of the EPM open arms compared to respective sesame oil-treated controls. This effect was not present when testing occurred at 24hrs post-treatment. The rapid behavioral effect of 17ß-estradiol was accompanied by changes in CCK-LI concentrations. In amygdala, ovariectomy and sesame oil decreased CCK-LI compared to sham-animals administered with 17ß-estradiol. In cingulate cortex on the other hand, ovariectomy and sesame oil increased CCK-LI compared to both sham-animals receiving 17ß-estradiol and with those who did not.

Conclusion: These data suggests that estrogen rapidly influences both anxiety-like behavior as well as the CCK system in related brain- regions. A deeper understanding of how sex-hormones can affect the CCK system in the brain may open new possibilities in our understanding of neuropsychiatric disorders in females.

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Poster 13

Comparative Effectiveness and Safety of Concomitant Use of SSRIs in Combination with NSAIDs or Paracetamol.

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Objective: An increased risk of gastrointestinal bleeding due to concomitant use of selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs) is known, however, results regarding their synergistic antidepressant effect are inconsistent. Nevertheless, these drugs are frequently used concomitantly. Therefore, we performed a register-based follow-up study among SSRI users with and without concomitant NSAID or paracetamol use.

Methods: Within a 25% random sample of the Danish population, we identified all incident SSRI users between 1997 and 2006. We compared rates of all-cause and cause-specificmortality, any psychiatric hospitalization, hospitalization with depression or somatic events during periods of SSRI use only with rates during periods of combined SSRI and NSAID or paracetamol use. We applied COX regression and competing risk analyses with adjustment for confounders and report adjusted hazard rate ratios (HRR) with 95% confidence intervals (CI).

Results: We identified 124,465 incident SSRI users, 24,284 (19.5%) using NSAIDs and 13,286(10.7%) paracetamol concomitantly. Comparing SSRI in combination with NSAIDs to SSRI monotherapy was associated with a decreased risk for any psychiatric hospitalization [HRR(95%-CI): 0.75 (0.67; 0.85)] and hospitalization with depression [0.80 (0.67; 0.94)] andno increased mortality [1.10 (0.98; 1.24)]. Paracetamol in combination with SSRIs revealed an increased mortality-risk [2.72 (2.46; 3.00)], especially cardiovascular [2.98 (2.40;3.70)]. No associations with gastrointestinal adverse events were observed. Concomitant use of low-dose acetylsalicylic acid (ASA) reduced the risk for psychiatric hospitalizations [0.44 (0.33; 0.58] and due to depression [0.38 (0.27; 0.52)] and death[0.86 (0.73; 0.99)]. Ibuprofen showed synergistic and safe treatment effects, whereas diclofenac [1.88 (1.39; 2.54)] and the group of selective COX-2 inhibitors [1.79 (1.35;2.36)] showed an increased mortality.

Conclusions: Analyses of the different NSAID-groups highlighted the heterogeneity of this therapeutic class with very different safety and treatment outcomes in combination with SSRIs. Specific NSAIDs, especially low-dose ASA, may represent a beneficial adjunctive antidepressant treatment option. The finding concerning paracetamol should be investigated further, although it may be caused by confounding by indication.

Poster 14

PET imaging sugar addiction in minipigs

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Background: 1.6 billion people worldwide are overweight of which 400 million are clinically obese, resulting in increases in type 2 diabetes, cardiovascular diseases, respiratory problems and clinical depression. Our working hypothesis is that obesity, in addition to being a metabolic disorder, also consists of critical disturbances in thebalance of the reward systems in the brain, which may override the physiological controls of appetite.

Objective: Here we investigate the effects of subchronic sugar addiction on the dopamine reward system in healthy Göttingen minipigs of average weight.

Methods: Six female minipigs were anesthetized and scanned at baseline with C-11 labeled raclopride (an antagonist to dopamine D2/3 receptors) in a Siemens PET/CT scanner. Pigs were then given access to sugar water for one hour each morning for 12 consecutive days and were PET scanned again on the 12th day. Two of the minipigs were scanned again 2 weeks later, after cessation of the sugar treatment. PET data were registered to an average minipig MRI atlas and processed using Montreal Neurological Institute software. The binding potential (BPND) of raclopride was obtained using the Logan graphical analysis and cerebellum activity as input function.

Results: On average in the six pigs, raclopride BPND was significantly reduced by 19% in the caudate, 13% in the total striatum and 28% in the thalamus after 12 days of sugar access. Two weeks after the cessation of sugar treatment, the BPND returned toward baseline values.

Conclusions: After 12 days of sugar access, raclopride binding to dopamine D2/3 receptors decreased in striatal and thalamic brain regions in minipig. These observations may indicate increased dopamine release in response to the incentive salience associated with the sugar intake since dopamine is released as part of the wanting of drugs of abuse and other pleasurable activities. Alternatively, the decreased D2/3 BPND may reflect are duction in the number of receptors. The observed reduction in binding is consistent with human

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studies demonstrating decreased D2/3 BPND in the brains of obese individuals.

Poster 15

Neuropeptide S (NPS) rescues behavior in a rodent model of posttraumatic stress disorder by increasing expression of brain derived neurotrophic factor (BDNF) and neuropeptide YY1 receptor (NPYY1R)

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Background: Neuropeptide S, mainly localized in clusters of cells around Locus coeruleus and with a wide receptor (NPSR1) distribution in the limbic areas, is an anxiolytic and arousal peptide in rodents while in humans it is associated with panic disorders (Xu et al 2004; Reinscheid et al 2005; Domschke et al 2011). We have shown that NPS given centrally has potent anxiolytic effects in rat and mouse models of high anxiety-like behavior as well as in the Flinders Sensitive Line rat, a genetic model of depression, where it affects anxiety-like but not depression-like behavior (Slattery et al, in review; Wegener et al 2011). In the previous study (Cohen et al 2012) we demonstrated a strong association between the magnitude of behavioral responses to predator scent stress (PSS) and patterns of decreased neuropeptide Y (NPY) expression in brain. Animals whose behavior was extremely disrupted (EBR) selectively displayed significant down-regulation of NPY in the hippocampus, periaqueductal gray, and amygdala compared with animals whose behavior was minimally (MBR) or partially (PBR) disrupted, and with unexposed controls. NPY infused bilaterally into dorsal hippocampus significantly reduced prevalence rates of EBR and reduced trauma-cue freezing responses. In an ongoing series of experiments to further elucidate neurobiological correlates of behavior in PTSD and dissect anxiolytic versus antidepressant actions of NPY (conceivably involving amygdala, respectively hippocampus and frontal cortex) instead of injecting NPY into the dorsal hippocampus, we injected the anxiolytic peptide NPS into amygdala.

Methods: Anesthetized rats were restrained in a stereotactic apparatus and a 26-gauge stainless steel guide cannula implanted bilaterally into amygdala. A needle was placed in the guide cannula to prevent clogging. Following one week recovery the rats were exposed to PSS or fresh unused litter for 15 min and NPS or vehicle infused 60 min later. After additional 7 days the behaviors were assessed by the elevated plus-maze (EPM) and acoustic startle response (ASR) tests, performed consecutively. After 24h the brains were perfused with paraformaldehyde. Frozen coronal sections were obtained and stained for immunohistochemistry. A computer-assisted image analysis system was used for quantitative analysis of the number of immunoreactive (IR) NPY, NPYY1R, and BDNF positive cells in the hippocampus that was divided into three separately counted areas: CA1, CA3 and dentate gyrus (DG). Corticosterone in serum was measured by ELISA.

Results: PSS exposure increased all indices of anxiety behavior, e.g. open arms entries and time spent in open arms ($p's < 0.02$). Immediate post-exposure treatment with NPS had marked protective effect; no animal treated with NPS displayed EBR. Interestingly, NPS decreased ASR in both exposed and unexposed animals. Consistently with previous experiments, exposure significantly reduced NPY ($p's<0.02$) as well as NPYY1R and BDNF expression ($p's< 0.001$) in CA1, CA3 and DG. NPS microinfusion into amygdala increased NPYY1R and BDNF ($p<0.001$) but had no effect on NPY in CA1, CA3 and DG. Serum corticosterone was increased following scent stress ($p<0.05$). Moreover, in line with its arousal properties, NPS further elevated corticosterone levels 40 min after the injection.

Discussion: Present experiments demonstrate the high reproducibility of PSS as an animal model of PTSD. In similarity to the previous experiment (Cohen et al 2012) PSS reduced expression of BDNF, NPY and NPYY1 receptor in hippocampus. The most salient new finding was that the anxiolytic peptide NPS completely abolished the extreme behavioral response to PSS. Moreover, it restored the decreased expression of BDNF and, unexpectedly, NPYY1 receptor. Since NPS did not affect the decreased expression of NPY, it is conceivable that NPS acts, directly or indirectly, on NPYY1 receptor. In order to dissect underpinning biology of anxiety versus depression we are exploring effects of NPS and NPY injected into hippocampus and/or amygdala on behavior and biochemistry of frontal cortex, PAG, hippocampus and amygdala.

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Poster 16

Stress-induced impairment of glutamatergic terminals ultrastructure: high vulnerability of medial prefrontal cortex and preventing action of desipramine

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Background: Limbic structures where glutamatergic transmission is considered to be prevalent such as amygdala, hippocampus and prefrontal cortex, have shown a deep impairment in stress-related disorders [1].

A number of studies have highlighted the cumulative effects of stress and its major mediators, glucocorticoids, on brain volume and dendritic remodeling, in both humans and rodents. Nevertheless, few is still known on the structural changes exerted by behavioral stress on the features of glutamatergic synapses as sites of neuronal communication. Indeed, in excitatory synapses synaptic communication is driven by neurotransmitter which is stored, within the presynaptic terminal, in morphologically distinct pools of vesicles, namely the readily-releasable pool of vesicles (RRP), docked to the active zone and ready for release, and the reserve pool of vesicles. When neurotransmitter is released, exchange of informations takes place through interaction of glutamate with receptors sitting on the post-synaptic density.

Alterations of such synaptic ultrastructure might underlie following impairment of glutamatergic release and transmission.

Aim: Main goal of the present study was therefore to shade light on the consequences of an acute and short-termed stressor on medial prefrontal cortex (mPFC) ultrastructure. Effects of antidepressant desipramine administered chronically previous to stress was also assessed.

Methods: Rats were treated chronically with either desipramine (DMI) or vehicle (2 weeks); at the end of the treatment animals were subjected to acute Foot-Shock (FS) stress and soon after they were deeply anesthetized and perfused. mPFC subareas (prelimbic area, dorsal anterior cingulate and medial precentral area) were identified, based on their noticeable citoarchitectural features, and overall volume quantified [2]. Distribution of glutamatergic synaptic terminals was evaluated with immunohistochemistry. Asymmetric-glutamatergic synapses were identified and the size of readily-releasable pool and reserve-pool of vesicles estimated, through serial section electron microscopy. Extension of post-synaptic density as well as of active zone area was measured; presynaptic terminal volume was also assessed.

Results: Glutamatergic synapses were found to be the majority within mPFC. Acute behavioral stress selectively induced a strong increase in the number of vesicles docked to the membrane and ready for release: only a specific population of glutamatergic synapse-subtypes was affected. The stress-induced increase in the number of docked vesicles was partially prevented by chronic treatment with DMI. Moreover, following acute stress volume of presynaptic glutamatergic terminals was also reduced. No effects was observed on the volume of medial prefrontal cortex.

Conclusions: In the present study we proved ultrastructural evidence that acute stress was able to deeply challenge the structure of glutamatergic terminals' in a matter of one hour. Previous treatment with chronic DMI seemed to only partially prevent such stress-induced changes. Identifying the effects of stress on excitatory transmission will provide further knowledge in developing drugs directly targeting the glutamatergic system.

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Poster 17

Pituitary volume, cortisol and stress in healthy controls, ultra high-risk subjects and first episode psychosis subjects.

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Background: Previous studies have shown that the HPA-axis might allready be affected prior to the patients transitioning to psychosis. During a psychotic episode it appears that the heightened stress response dereases. The HPA-axis is one of the many biolgical systems involved in the developement of psychosis and mediates the association between stress and onset of psychosis.

Method: All the FEP (first episode of psychosis) subjects had to meet criteria for schizophrenia,the UHR (ultra high-risk) subjects had to meet the UHR criteria of Comprehensive Assesment of At-risk Mental States. The pituitary gland was traced on structural MRI. Cortisol was measured upon awakening and +15, 30, 60 minutes

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after awakening, at 12 am and 8pm. The stress scales were the Perceived Stress Scale.

Results: Perceived stress score: healthy (N=18) 10.6 (CI 8.2-12.9), UHR (N=29) 24.4 (CI 21.8-27.0) and FEP (N=17) 25.7 (CI 18.7-23.2); p<0.01 (ANOVA). Cortisol area under the curve (AUCg), morning, cortisol nmol/liter*minutes: healthy controls (N=15) 406.3 (CI 322.3-490.2), UHR(N=15) 697.2 (CI 483.7-910.8), FEP (N=20) 480.7 (379.9-581.6); p=0.01. The adjusted mean,pituitary gland volumes, cm3: healthy controls (n=27) 0.72 (CI 0.66 to 0.79), UHR (n=30)0.72 (CI 0.66 to 0.78) and FEP (n=28) 0.79 (CI 0.71 to 0.83); p=0.45 (ANCOVA). We adjusted for age, gender and brain volume.

Conclusion: We found increased cortisol AUCg in UHR and FEP subjects compared to healthy controls. Both UHR and FEP subjects experienced more subjective stress than healthy controls. We did not find any difference in pituitary gland volume. A higher level of stress in UHR subjects could be due to an early stage of psychotic illness.

Poster 18

Adolescents hypomania spectrum: A 15-year follow-up of non-mood (co)morbidity in adults

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Purpose: In a recent study we observed that adolescents with hypomania spectrum episodes and adolescents with only major depressive episodes had a similar risk of (hypo)manic and depressive episodes in adulthood. In the present study, we investigated if hypomania spectrum in adolescence indicates other health related problems in adulthood.

Method: A community sample of adolescents (N=2 300) was screened for the presence of depressive symptoms. Participants with positive screening and matched controls were diagnostically interviewed. Hypomania spectrum episodes were reported by 90, major depressive disorder (MDD) by 197, and no mood disorder by 229 participants. A follow up after 15 years included a blinded diagnostic assessment, self-assessments of personality, and national register data on prescription drugs and health service consumption.

Results: The overall health outcome of the adolescents with hypomania spectrum and MDD did not differ substantially. Any non-mood (co)morbidity in axis I diagnose was reported in adulthood by 53% with adolescent hypomania spectrum and 57% with adolescent MDD. Compared to the adolescent without mood disorders, both groups had a higher subsequent risk ofmental comorbidity and higher mental health care consumption. They had significantly moreoutpatient (11.7; 8.6/14.8 95% CI vs. 12.3; 9.7/15.0 95% CI vs. 6.8; 5.2/8.4 95% CI;p<0.001) and inpatient visits (2.3; 1.7/3.0 95% CI vs. 2.8; 2.1/3.6 95% CI vs. 1.8;1.4/2.2 95% CI; p<0.05) due to mental diagnoses (24% vs. 21% vs. 7%; p<0.001) than physical diagnoses (83% vs. 86% vs. 80%; n.s.) compared to without adolescents mood disorders as controls.The participants with history of adolescence hypomania spectrum andMDD had increased use of antidepressants (31% vs. 28% vs. 13%; p<0.01), anxiolytics (19%vs. 12% vs. 4%; p<0.001), antipsychotics (7% vs. 2% vs. 0%; p<0.01) and drugs for addictive disorders (3% vs. 5% vs. 0%; p<0.05) compared to controls. Remarkably, there were no significant differences between all hypomania spectrum and depression group concerning clinical consumption and drug prescription. No sex differences were found. As concerns of frequency somatic disorders during a follow up of subjects, there were no statistical differences between adolescent hypomania spectrum, MDD and controls (Table 4),except diseases of the digestive system (26% vs. 18% vs. 12%; p<0.05) and injury,poisoning and certain other consequences of external causes (38% vs. 32% vs. 21%; p<0.05). There were any gender differences found.

Limitations: 29% of the adolescents with hypomania spectrum were lost to follow-up. Due to the relatively small sample, the risk of type II errors must be considered.

Conclusions: The health outcome of adolescents with hypomania spectrum seems to be similar to that ofadolescents with MDD. However, adolescents with mood disorders in general are at increased risk of subsequent mental health problems and might benefit from better treatment and follow-up.

Poster 19

NMDA antagonist, but not nNOS inhibitor, requires AMPA receptors in the ventromedial prefrontal cortex (vmPFC) to induce antidepressant-like effects

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Depressed individuals and stressed animals show enhanced levels of glutamate and neuronal nitric oxide synthase (nNOS) activity in limbic structures, including the vmPFC. Systemic administration of glutamatergic

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NMDA receptor antagonists or inhibitors of nitric oxide (NO) synthesis induces antidepressant-like effects. Evidence has suggested that blockade of NMDA receptors would disinhibit glutamate release, which would then activate AMPA receptors. However, the precise involvement of NO in these events has not been investigated. The aim of the present study was to evaluate the participation of the glutamatergic and nitrergic systems of the vmPFC on the behavioral consequences induced by forced swimming (FS), an animal model of depression. Male Wistar rats (230-260g) with guide cannulas aimed at the prelimbic (PL) region of vmPFC were submitted to a 15min session of FS and, 24h later, they were submitted to a 5min session of the FS test when the immobility time (IT) was measured. Injection of LY235959 (LY; NMDA antagonist at 1, 3 and 10nmol/0.2µL), NPA (nNOS inhibitor at 0.01nmol/0.2µL), c-PTIO (NO scavenger at 1.0nmol/0.2µL), ODQ (soluble guanylyl cyclase-sGC-inhibitor at 1.0nmol/0.2µL) or vehicle was realized 5 min before the test session. An independent group of animals was submitted to the same treatments, received a local injection of NBQX 5 min before the other treatments (AMPA antagonist at 4nmol/0.2µL). All data were analyzed by ANOVA followed by Dunnet post-hoc test. LY administration into vmPFC-PL reduced the IT (Mean±SEM: vehicle: 116.3±21.17; LY 1nmol: 164.4±18.92; LY 3nmol: 28.71±10.21*; LY 10nmol: 39.43±7.99*; *p<0.05 from control group). NPA, c-PTIO and ODQ induced similar effects (Mean ± SEM: vehicle: 140.1±15.23; NPA: 47.57±10.42*; c-PTIO: 56.86±10.62*; ODQ: 81.20±15.99*; *p<0.05 from control group). NBQX did not reduce the IT per se but it abolished the effects of LY in the FST. On the other hand, the effect of NPA was not blocked by NBQX pre-treatment. (Mean±SEM: vehicle+ vehicle: 138.3±14,16; vehicle+LY: 35.00±7.629*; vehicle+NPA: 28.33±13,86*; NBQX+ vehicle: 137.6±15,36*; NBQX+LY: 103.00±20.48*; NBQX+NPA: 46.40± 3,84*; F(5,28)= 11.32; *p<0.05; Dunnett). These results show that the blockade of NMDA receptors, NO synthesis or sGC activity in the vmPFC-PL induces antidepressant-like effects. In addition, the results indicate that AMPA activation is required for the antidepressant-like effect induced by NMDA blockade, but not by nNOS inhibition. Therefore, our data suggest that the activation of NMDA receptors and NO pathway in the vmPFC might be dissociated in the development of behavioral/emotional outcomes of stress exposition.

Poster 20

PET Neuroimaging of Noradrenergic Transmission Using [11C]-yohimbine

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BACKGROUND Central alpha2 adrenoceptors have gained more attention in relation to major depression since post mortem studies have shown an increased receptor density in depressed subjects. In order to establish more knowledge of impaired noradrenergic transmission, in vivo investigation is required, as this enables longitudinal data collection and detection of early changes. Positron emission tomography (PET) using [11C]-yohimbine is a promising tool for in vivo studies as recent porcine studies with [11C]-yohimbine have shown that the tracer binding is selective and can be displaced by endogenous noradrenaline released in response to amphetamine challenge and also by exogenous alpha2 antagonist. However, the direct quantification of receptor density (Bmax) is still unsolved, as this requires the assessment of the binding potential.

OBJECTIVE The objective of this study is to demonstrate a mathematical approach using the Inhibition Plots to obtain the binding potential of [11C]-yohimbine, which can further be utilized to assess the receptor density.

METHODS Theory Alpha2 adrenoceptors are vastly distributed throughout the brain, which entails an absence of a reference region, where non-displaceable binding (V_ND) can be measured. To circumvent this, we implemented the Inhibition Plots, versions of the Lassen plot to assess a virtual V_ND to obtain the binding potential, 1) V_T(i)=(1-s)·V_T(b) +s·V_ND 2) V_T(i) = (1-s)·V_ND(i) /V_ND(b) ·V_T(b) +s·V_ND(i) V_T(b) and V_(T(i)) are the volumes of distributions at baseline and at inhibition with drug challenge, respectively, and 1-s is the fraction of receptors available for binding. Then, the binding potential (BP_ND) is assessed from, 3) BP_ND=V_T/V_ND -1 Dynamic PET Eleven Sprague Dawley rats were included, where each animal underwent a dual PET session at baseline and after pharmacological challenge (amphetamine 3mg/kg or cold yohimbine 0.3mg/kg). Arterial blood samples were drawn during the scanning to obtain the plasma activity input function.

RESULTS The binding potentials at baseline were highest in the striatum (8.9±0.56), followed in descending order by thalamus (8.6±0.52) frontal cortex (8.1±0.52), pons (6.9±0.47), and cerebellum (5.4±0.38). The binding was significantly decreased both in response

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to amphetamine (-36.0±1.3%) and cold challenge (-50.8±0.8%), where the displacement effect occurred with the same magnitude in all regions of interest.
CONCLUSION This study is the first to assess the binding potentials of [11C]-yohimbine. We demonstrated that the binding to alpha2 adrenoceptors was significantly reduced in response to amphetamine and cold challenge. Taken together, we suggest that the Inhibition Plots can be applied in future [11C]-yohimbine studies for in vivo investigation of alterations in alpha2 adrenoceptor density.

Poster 21

A single shot is enough: improving administration of antipsychotics to rats

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Treatment with antipsychotic agents is associated with serious metabolic adverse effects such as weight gain, dyslipidemia and diabetes through unknown molecular mechanisms, and the ability to study such mechanisms in animals is essential to make progress in this field. Due to the short half-life of antipsychotics in rodents, however, reproducing metabolic adverse effects through daily oral administration or injections has been challenging. We therefore administered commercially available depot injections of antipsychotics intramuscularly to female rats, followed by characterization of their metabolic phenotype. Depot injection of olanzapine yielded plasma drug levels approx. 160 times higher than those achieved through oral administration, in addition to increased plasma triglycerides, and activation of lipogenic gene transcription. Furthermore, we found pronounced hyperphagia with resultant weight gain, wearing off around 2 weeks after injection. A new injection two weeks after the initial one resulted in a second surge in weight gain, demonstrating that problems with drug tolerance experienced during daily oral treatment can be circumvented by means of depot injections. We made use of the reliable plasma olanzapine levels to clarify the role of the key hypothalamic molecular energy gauge AMP-activated protein kinase (AMPK) in olanzapine-induced hyperphagia, which has been subject to debate. Using hypothalamic nucleus-specific, adenovirus-mediated AMPK knockdown, we showed that the hyperphagic effect of olanzapine is associated with activation of AMPK in the arcuate (ARC), but not the ventromedial (VMH) hypothalamic nucleus. Depot administration of olanzapine provides an improved drug administration mode, relieves workload and minimizes animal stress, paving the way for sophisticated mechanistic investigations into undisclosed molecular mechanisms underlying antipsychotic-induced adverse effects.

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