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ABSTRACTS

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ORAL PRESENTATIONS

LECTURE 1

SCNP 2015 OPENING LECTURE

L1 Novel pharmacological approaches in the treatment of schizophrenia

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Four main topics have shaped research and clinical practice in the past decade. These have dealt with: 1) Early intervention in the prediagnostic stage, i.e. the attenuated psychosis syndrome; 2) Novel neurobiological treatment targets; 3) The introduction of alternative formulations; 4) Attempts to predict treatment response.

1) In a number of RCTs, researchers have investigated whether treating prodromal symptoms of schizophrenia helps to reduce the conversion risk to full-blown schizophrenia. Results are ambiguous and the discussion on whether or not an intervention at the stage is justified is ongoing.

2) Following the enhanced understanding of the pathophysiology of schizophrenia, also with respect to specific symptom domains, pharmacological targets beyond D2 receptor antagonism have been explored. Much work and enthusiasm has revolved around nicotinergic and glutamatergic compounds, so far with mostly discouraging results.

3) Several new generation antipsychotics have become available as long-acting depot formulations. All of them have demonstrated a significant positive impact on relapse rates in placebo controlled studies. Whether these compounds also have advantages over first generation depots and / or oral antipsychotics is still debated and investigated. The development of an inhalable antipsychotic has complemented the treatment options for the management of acutely agitated schizophrenia patients.

Lastly, attempts from various perspectives, including genetics and neuroimaging, have investigated whether it is possible to predict treatment response and drug safety. Although some look promising, they have not yet reached a stage in which they can be applied to everyday clinical practice. What has become clear though, is, that early non response predicts late non response, leading to the recommendation to switch antipsychotics much earlier than stated in most treatment guidelines.

SYMPOSIUM 1

UPDATE ON NEW DRUGS

S1.1 Vortioxetine, a novel antidepressant with multimodal activity: A review of its preclinical

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Background: Vortioxetine is a novel antidepressant that was approved for treatment of major depressive disorder (MDD) by the Food and Drug Administration and the European Medicines Agency (EMA) in 2013 and first launched in the US in January 2014. In 2015, vortioxetine received a positive opinion from the EMA regarding the inclusion of certain aspects of cognitive function in MDD in its label.

Objectives: An overview of vortioxetine's preclinical profile and the potential contribution of its combined action on serotonin (5-HT) receptors and the 5-HT transporter (SERT) to its clinical profile.

Methods: Preclinical in vitro and in vivo studies used cellular systems expressing vortioxetine's primary biological targets and rodent models assessing its antidepressant and pro-cognitive potential, impact on sexual behavior and sleep architecture. Clinical efficacy in reduction of depressive symptoms and improvement in cognitive function was assessed in adults with major depressive disorder (MDD). Tolerability was based on the incidence of adverse events (AEs) in short-term clinical trials.

Results: In preclinical studies vortioxetine led to changes in the function of several neurotransmitter systems including 5-HT, norepinephrine, dopamine, acetylcholine, histamine, gamma butyric acid (GABA) and glutamate in the rat brain. These effects likely derive from its interaction with serotonin receptor-mediated negative feedback mechanisms controlling neuronal activity of these brain areas, which is different from the mechanism of action of current antidepressants, such as SSRIs. Studies in rodents revealed a differentiated profile in models predictive of antidepressant activity, increased synaptic plasticity and improved cognitive function compared to SSRIs and SNRIs. Furthermore, vortioxetine showed reduced interference with sexual function and sleep architecture compared to SSRIs in rats.

In placebo-controlled clinical trials of adults with MDD, vortioxetine (VOR) was efficacious in reducing depressive symptoms vs placebo (and vs agomelatine in

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a trial of patients with an inadequate response to SSRI/SNRI treatment) and was significantly superior to placebo in pre-defined cognitive outcomes. In a pooled analysis of patients treated with placebo (n=1621) or VOR (5-20mg/day) (n=2616), the incidence of insomnia-related AEs was 2.0-5.1% for VOR vs placebo (4.4%) and sexual dysfunction-related AEs was 1.6-2.6% for VOR vs placebo (1.1%). In a sleep EEG study with healthy subjects, VOR at a given SERT occupancy seemed to affect REM sleep less than paroxetine. In a pooled analysis of 7 clinical trials, the risk of developing treatment-emergent sexual dysfunction was not significantly different between VOR (5-20 mg/day) and placebo using the Arizona Sexual Experience Scale (ASEX). MDD patients treated with VOR experienced a significantly greater improvement in the Changes in Sexual Functioning Questionnaire (CSFQ-14) total score compared to escitalopram in a head-to-head study.

Conclusion: The preclinical studies in rodents indicate a markedly different mechanism of action of vortioxetine compared to SSRIs and SNRIs. The unique pharmacological profile of vortioxetine suggests the potential for a differentiated clinical profile that differs from that of SSRIs and SNRIs, with a low incidence of sexual dysfunction and sleep disruption.

S1.2 Esketamine Clinical Development Program

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Esketamine is the S-enantiomer of racemic keta-mine. It has 3- to 4-fold greater affinity for the N-methyl-d-aspartate (NMDA) subtype of gluta-mate receptor compared to the R-enantiomer. The potency of the S-enantiomer allowed devel-opment of a formulation for intranasal admin-istration; the compound is rapidly absorbed via this route and is systemically bioavailable. In-tranasal doses of 28 to 84 mg produce serum lev-els comparable to 0.5 mg/kg intravenously. An increase in synaptic plasticity mediated by glu-tamatergic neurotransmission may underlie the antidepressant action of ketamine/esketamine. This results in an enhanced firing rate of glutama-tergic neurons, increasing the synaptic release of glutamate and preferential activation of post-synaptic α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA activation leads to downstream neurotrophic and intracellular signalling that increases synaptogen-esis in relevant brain regions. Based on its puta-tive mechanism of action and potential antide-pressant properties, low-dose intravenous keta-mine was administered to patients with treat-ment resistant depression and other mood dis-orders. Preliminary clinical data indicate that in-travenous ketamine at subanaesthetic doses produces a rapid and potent antidepressant re-sponse in patients who have failed oral antide-pressant therapy.

Three phase 2 studies have been conducted to date as part of the development program for in-tranasal esketamine in treatment resistant de-pression, evaluating intravenous ketamine, intra-venous esketamine or intranasal esketamine compared to placebo. In aggregate, these studies defined the dosing and frequency of esketamine treatment sessions to be utilized in phase 3 trials. The regimen for intranasal esketamine treatment to be evaluated in these studies consists of a four-week induction phase consisting of twice weekly treatments, followed by a maintenance phase during which treatment sessions will con-tinue at a reduced frequency. Efficacy and safety data collected to date and the further plans for clinical development of intranasal esketamine will be presented.

S1.3 Inhalable Loxapine – Real life experience

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Abstract not available at the time of printing.

SYMPOSIUM 2

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, on page 13, as they are also presented as posters.

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LECTURE 2

SCNP LECTURE

L2 How have recent advances changed the way we think about schizophrenia?

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Traditional psychiatric textbooks describe schizophrenia as a disease of unknown aetiology. However, this is wrong on two counts. First we now realise that schizophrenia itself is not a disease but rather a clinical syndrome. It is simply the severe manifestation of psychosis, and there exists a continuum of psychosis which stretches into the general population. Thus, psychosis is distributed like hypertension, and schizophrenia is the equivalent of malignant hypertension

Secondly, we now know a great deal about the risk factors, or contributory causes, of schizophrenia. These can be roughly divided into two main types; those which result in a) aberrant neurodevelopment and b) those which cause dopamine dysregulation; both characteristic abnormalities found in schizophrenia.

Genetic factors are, of course, pre-eminent. In 2014 a landmark GWAS study of 37,000 people with schizophrenia and 113,000 healthy controls identified 108 loci significantly associated with schizophrenia. Each of these polygenes has only a very small effect but cumulatively they account for about 30% of the variance in occurrence of schizophrenia. Some such as neurexin or TCF4 subtly impair neurodevelopment while others such as DRD2 or AKT3 impact on dopamine signalling. A small proportion of schizophrenia (perhaps 3%) results from copy number variants (CNVs) impacting on neurodevelopmental genes; these CNVs can have a much bigger effect size, increasing risk 3- to 20-fold.

Various environmental factors have been consistently associated with schizophrenia. Some such as adverse obstetric events (e.g. prenatal infection, perinatal hypoxia) impair neurodevelopment. Others such as abuse of drugs such as amphetamines, cocaine and cannabis which increase striatal dopamine, also increase risk. In recent years it has become clear that heavy use of high potency cannabis is responsible for a significant proportion of psychosis (>20% in South London). Psychotogenic "legal highs" such as synthetic cannabinoids and cathinones are becoming an increasing cause of acute psychosis sometimes termed "spiceophrenia".

A range of social adversities such as child abuse, adverse life events, migration/minority ethnicity appear also to facilitate dopamine dysregulation and consequent psychosis. Curiously, psychosis is more common in those born and brought up in large cities than in rural areas. The exact reason(s) for these differences are unclear but speculation centres on social fragmentation and social isolation.

LECTURE 3

SCNP LECTURE

L3 Preventive and intensive treatment of in the early phases of psychosis

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Background: Clinicians have increasingly accepted the need to initiate treatment as soon as possible after the onset of sustained positive psychotic symptoms. Long delays in treatment routinely occur and are associated with many damaging psychosocial consequences as well as risk of self-harm and aggression. It has also been recognized that for most patients a prolonged period of attenuated symptoms and impaired functioning precedes the first psychotic episode. Much of the disability associated with psychotic disorders, particularly schizophrenia, develops long before the onset of frank psychosis and is difficult to reverse even if the first psychotic episode is successfully treated.

Objectives: To evaluate the effectiveness of interventions in high risk populations (Ultra High Risk of psychosis, UHR), and the effectiveness of interventions in First Episode Psychosis

Methods: Systematic review of the literature was conducted.

Results: A number of studies examined risk factors for transition to psychosis in Ultra High Risk populations (UHR), and some randomized clinical trials have tested the effect on transition rates of different kind of interventions. Overall there is convincing evidence that interventions in UHR groups can reduce transition rate, and especially cognitive behavioural therapy seems effective, but also fish oil is promising. Results from the NEURAPRO-E trial, testing the effect of fish oil in a large multicentre study, will be available from April 2015.

Specialised early interventions services are also shown to be effective and have effects on psychotic and negative symptoms and risk of readmission. The long term outcome regarding course of psychotic symptoms and treatment with antipsychotic medication will be

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presented, and it will be discussed how long term treatment of psychotic disorders should be handled.

Conclusion: It is likely that interventions in UHR can reduce transition rate and improve long term prognosis. Specialized early intervention services are effective and should be widely implemented.

LECTURE 4

SCNP LECTURE

L4 Societal consequences of (long-term) psychopharmacological treatments

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RCTs are the golden standard for investigating effects of pharmacological treatments. This is because the randomization takes care of all confounders. However, sometimes RCTs are unfeasible or even unethical to do. An example is long-term effects (e.g. criminality).

One strategy that is particular useful in the Nordic countries is to use register data to evaluate effects. However, in psychiatric pharmacological studies without randomization "confounding by indication" is a major problem. That is, individuals who have most problems are the one who will get most medication.

One way to address "confounding by indication" in observational (register) studies of pharmacological treatment is to study the rate of the outcome (e.g., criminality) when individuals have been on treatment compared to when they were off treatment. Thus, each individual serves as his/her own control. Therefore, these analyses adjust for confounders that are constant within each individual during follow-up (e.g. genetic make-up and childhood environment).

We have done a series of such studies where we have investigated the long-term effects of psychopharmacological treatment on for example criminality, suicidal behavior, drug misuse, and accidents using Swedish population-based and nation-wide data from the Prescribed Drug Register, the Patient Register, the Crime Register, and the Cause of Death Register We have studied the long-term effects of among others ADHD-medication, anti-psychotics, mood stabilizers, anti-depressants and medications against addiction. In this presentation I will present some recent and forthcoming results and discuss their clinical implications.

SYMPOSIUM 3

CENTRAL EFFECTS OF GLUCAGONE LIKE PEPTIDE-1 (GLP-1) RECEPTOR STIMULATION

S3.1 GLP-1: Central and periferal effects of GLP-1 receptor stimulation

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Background: Glucagon-like peptide 1 (GLP-1) is a predominant post-translational product of preproglucagon. The processing of pre-proglucagon into GLP-1 is specific for enteroendocrine cells of the enteric lining and for a select population of CNS neurons situated in the caudal part of the nucleus of the solitary tract. The bioactive form of GLP-1 (GLP-1(7-37) is released by enteroendocrine cells of the enteric lining upon ingestion of a meal, whereas less is known about stimuli leading to release of GLP1(7-37) in the CNS. In the CNS, GLP1 receptors are predominantly expressed by neurons in the limbic system but binding sites of GLP1 seems more widespread suggesting that GLP1 signals through receptors situated at both axonal terminals and dendrites.

Solid evidence exists to propose a functional role of GLP1 in central behaviors associated with homeostatic regulation of energy and fluid balance. Thus, anorectic effects of GLP1 are dependent on hypothalamic expression of GLP1 receptors, but it is hitherto unsettled whether neuronally released or blood borne GLP1 comprise the endogenous signal to this energy hemostatic response. Endogenous GLP-1 has also been linked to appetitive behaviors involved in hedonic responses, but the physiological relevance of such mechanism is less well understood.

More recently, it has been suggested that endogenous GLP1 provides neuroprotection to a variety of neuoropathological conditions such as Alzheimer's and Parkinson's diseases.

Objectives: The aim of the presentation is to introduce the audience to the GLP-1 containing system of the CNS and review currently available evidence supporting a role of GLP-1 as a neurotransmitter.

Methods: A wide array of neuroanatomical and neuropharmacological techniques has been applied.

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Conclusion: The presented data confirms that the GLP-1 receptor may be a novel target for the pharmacological treatment of a variety of CNS mediated diseases.

S3.2 Cocaine addiction - role of Glucagon-like peptide 1 (GLP-1).

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Background: Drug use disorders are major health problems, and effective pharmacological interventions to treat them are lacking. To develop novel treatment strategies, a better understanding of the complex neurobiology involved is needed. Glucagon-like peptide 1 (GLP-1) analogues are used for the treatment of type 2 diabetes, but it is also well described that GLP-1 can decrease food intake. GLP-1 receptors are expressed in the brain, e.g. in areas that are involved in the rewarding effects of drugs of abuse.

Objectives: The aims of the reported studies were to investigate the possible effects of GLP-1 analogues on cocaine-mediated effects.

Methods: A large number of behavioral and biochemical techniques have been applied.

Results: A growing body of data reports on the ability of the GLP-1 system to modulate cocaine's effects on behavior and dopamine homeostasis.

Conclusion: The presented data indicates that the GLP-1 receptor may be a novel target for the pharmacological treatment of cocaine addiction.

S3.3 Glucagon-like peptide-1 receptor agonists decrease alcohol intake and alcohol reward in rodents

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Background: Development of alcohol use disorders largely depends on the effects of alcohol on the brain reward systems. Emerging evidence indicate that common mechanisms regulate food and alcohol intake and raise the possibility that endocrine signals from the gut, such as glucagon-like peptide 1 (GLP-1), may play an important role for alcohol consumption, alcohol-induced reward and the motivation to consume alcohol.

Objectives: To investigate the effects of GLP-1 receptor agonists, such as Exendin-4 (Ex4), on measures of alcohol-induced reward as well as on alcohol intake and alcohol seeking behaviour in rodents.

Methods: In rodents models of alcohol-conditioning, intermittent alcohol access model and alcohol-induced locomotor and accumbal dopamine release were used in vivo.

Results: We found that treatment with Ex4, at a dose with no effect per se, attenuated alcohol-induced locomotor stimulation and accumbal dopamine release in mice. Furthermore, conditioned place preference for alcohol was abolished by both acute and chronic treatment with Ex4 in mice. Finally, we found that Ex4 treatment in rats decreased alcohol intake in the intermittent access to 20% alcohol paradigm (two-bottle-choice model), as well as alcohol seeking behaviour in the progressive ratio test in the operant self-administration model.

Conclusion: These findings indicate that the role of GLP-1 signalling extends beyond glucose homeostasis and food intake regulation to include effects on alcohol reinforcement. Collectively these findings implicate that the GLP-1 receptor may be a potential target for the development of novel treatment strategies for alcohol use disorders.

SYMPOSIUM 4

RECENT UPDATES ON ADHD

S4.1 Medication for ADHD and criminality and other consequences

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Randomized controlled studies suggest that ADHD medication have beneficial short-term effects on symptoms of ADHD (impulsivity and attention problems) and related traits such as conduct problems. However, does medication work in real life situations where the ideal conditions from RCT are not present? Also, there have

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been concerns over the long-term effects on the development of substance abuse, where risk for substance abuse might be particularly pronounced for youths who use stimulant ADHD medication during a sensitive developmental period. Here I will present some recently published and ongoing work on the association between ADHD medication and criminality, substance use, suicidal behaviors and accidents using Swedish population based health registers.

S4.2 Mortality in Children, Adolescents and Adults with ADHD - a nationwide cohort study

Søren Dalsgaard [1,2,3,4], Søren Dinesen Østergaard[2,5], James F. Leckman[6], Preben Bo Mortensen[1,2,3], Marianne Giørtz Pedersen[1,2]

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Background: ADHD is a common mental disorder associated with factors that likely increase mortality, e.g., oppositional defiant disorder/conduct disorder (ODD/CD), criminality, accidents and substance abuse. However, it remains unknown whether ADHD itself is associated with increased mortality.
Objectives: Examine whether ADHD is associated with increased mortality
Methods: Using Danish national registers, we followed 1•92 million individuals including 32 061 with ADHD from their 1st birthday through 2011. Adjusted mortality rate ratios (MRRs) were estimated by Poisson regression, comparing individuals with and without ADHD.
Results: During follow-up (24•9 million person-years), 5580 cohort members died. Mortality rate per 10 000 person-years was 5•85 among individuals with ADHD compared to 2•21 in those without, yielding a fully adjusted MRR of 2•07 (95% confidence interval [CI] 1•70-2•50). Accidents were the most common cause of death. MRRs in individuals diagnosed with ADHD under age six, between 6 and 17, and after 18 were 2.23 (1•11-3•91), 1•83 (1•40-2•35) and 5•24 (3•73-7•12), respectively. After excluding individuals with ODD/CD and substance abuse, ADHD remained associated with increased mortality (fully adjusted MRR 1•50; 1•11-1•98), higher in females (MRR 2•85; 1•56-4•71) than in males (MRR 1•27; 0•89-1•76).
Conclusion: ADHD was associated with significantly increased mortality rates. Being diagnosed with ADHD in adulthood carried a higher MRR compared to being diagnosed earlier in childhood and adolescence. Both comorbid ODD/CD and substance abuse increased the MRR even further. However, when adjusted for these comorbidities, ADHD remained associated with excess mortality, with higher MRR in females with ADHD than in males with ADHD. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents.

S4.3 ADHD and substance use - the patient's perspective

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Background: Although ADHD and substance use disorders (SUD) commonly co-occur, the specific nature of the link between ADHD and SUD remains unclear. The link has not been studied from the patient´s perspective. There is a lack of studies focusing on experiences and thoughts of individuals with ADHD and SUD as expressed in their own words.
Objectives: The primary aim of this study was to investigate how adult individuals with ADHD perceive the role of alcohol and drugs in their lives. A secondary aim was to identify factors that those individuals consider useful in the treatment and prevention of co-occurring ADHD and substance use disorders.
Method: A qualitative interview study with ADHD outpatients (n=14) at a psychiatric clinic. Data were analyzed based on pre-defined areas of interest using a deductive content analysis method.
Results: The yearning for belongingness was identified as an important driving force underlying substance use. The participants felt that alcohol/drugs helped them being normal and thus respected and accepted. Early diagnosis of ADHD was perceived essential to avoid SUD. Caregivers were recommended to discuss reasons for alcohol/drug use and to include treatment of SUD as part of ADHD treatment.
Conclusion: Adults with ADHD may have strong rational and emotional reasons for the use of alcohol and drugs. When planning for the treatment of adult ADHD, investigation of personal reasons for alcohol/drug use deserves a place.

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LECTURE 5

SCNP LECTURE

L5 Metabolic consequences of chronic low grade inflammation in depression

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Abstract not available at the time of printing.

SYMPOSIUM 5

DEPRESSION: NEW OPTIONS IN TREATMENT RESISTANCE

S5.1 The Diagnostic Apathia Scale predicts a dose-remission relationship of home-care T-PEMF in treatment-resistant depression

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Background: The Diagnostic Apathia Scale was based on earlier work from 2010 by Per Bech et al who identified an 'apathia factor' in

patients resistant to antidepressant medication.

Objectives: The aim of this study was to evaluate the predictive validity of the apathy subsyndrome in patients with therapy-resistant depression in the dose–remission study with transcranial pulsating electromagnetic fields (T-PEMF).

Methods: The apathy subsyndrome consists of the symptoms of fatigue, concentration and memory problems, lack of interests, difficulties in making decisions, and sleep problems. We evaluated 65 patients with therapy-resistant depression. In total, 34 of these patients received placebo T-PEMF in the afternoon and active T-PEMF in the morning, that is, one daily dose. The remaining 31 patients received active T-PEMF twice daily. Duration of treatment was 8 weeks in both groups.

The Hamilton Depression Scale (HAM-D17) and the Bech-Rafaelsen Melancholia Scale (MES) were used to measure remission. We also focused on the Diagnostic Apathia Scale, which is based on a mixture of items from the MINI and the HAM-D17/MES.

Results: In patients without apathy receiving one active dose daily 94.4% remitted versus 50% for patients with apathy ($p \leq 0.05$). In patients without apathy who received two active doses 69.9% remitted versus 66.7% for patients with apathy ($p > 0.05$).

Conclusion: Taking the baseline diagnosis of the apathy syndrome into consideration, we found that in patients without apathy one daily dose of T-PEMF is sufficient, but in patients with apathy two daily doses are necessary. Including the apathy syndrome as predictor in future studies would seem to be clinically relevant.

S5.2 PEMF - a new treatment option

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Background: Despite different attempts to find new medications and new psychotherapeutic methods for depression during the last decades almost one third of depressed patients do not reach remission after several trials. Other methods are urgently needed. The ECT therapy has consistently been shown to be highly effective for the treatment of depression. But high relapse rates after ECT and its cognitive side effects are a major problem.

Objectives: The aim of the presented studies was to investigate the effect of a new physical treatment with transcranial pulsating electromagnetic field therapy (PEMF) for treatment resistant depression.

Methods: The PEMF is given by using a treatment helmet that incorporates 1 pair of coils in the anterior and 1 pair in the posterior temporal region on both sides, 1 pair in the upper parietal region and 1 coil in the centre of the lower occipital region. The helmet is connected to a power source (220 V), which leads to induction of a pulsating magnetic field. All patients were treated for 30 min in a session. Coil applicators introduced pulsating electrical fields (50 Hz) of a very low magnitude (0.1 – 4 mV/cm) into brain tissue. The pulses were constructed to mimic the pulsating electrical fields (E-fields) measured outside excitable tissue. The E-fields induced into neural tissue by the coils were five orders of magnitude (10-5) smaller than the E-field across a biological membrane with a Vm of -70 mV. Thus, this device distinguishes itself in this regard from rTMS and ECT.

Results: In our first randomized double blind controlled trials we achieved remission in 34% after 5 weeks (25 patients in each group) vs. 4% in the sham group. In our second randomized double blind controlled trial (34 vs 31 in each group) after 8 weeks remission rate was 70%

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and didn't change if treatment was given once or twice daily. The second study did not have a sham group.

Conclusion: The high remission rate found in the second study of T-PEMF as augmentation in patients with treatment resistant depression were not explained by a dose effect (once versus twice daily applications) but rather by the extension of the treatment time from 5 weeks to 8 weeks. During this trial the baseline side-effects of the antidepressant medication, which remained unchanged over the 8 weeks, were reduced by approximately 50%. This outcome of high remission rate and reduced side-effects was reflected by the patients' self-reported WHO-5 well-being scale scores which increased significantly during the trial.

S5.3 ECT in Treatment refractory Depression

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ECT has clear effect in a number of severe conditions. This is most notably in mood disorders with accompanying psychotic features. In less severe or treatment resistant depression the efficacy is less pronounced. The success rate from different studies varies and so does the predictors of success. An attempt is made to outline a description of treatment resistant patients where caution is especially warranted before ECT is suggested as treatment. Consistent with its broad spectrum of efficacy, ECT induces widespread neurophysiologic changes within the brain. Mechanisms of action has been postulated and researched on a physiological level through action on seizure threshold and pituitary axis, on a cellular level through neuroplasticity and neurogenesis and on a molecular level on ion channels, neurotransmitters, cytokines and their receptors. It is suggested that the morbid neuronal circuits involved in treatment resistant depression is "harder wired" than those of the acute condition. Therefore it takes more points of attack than that of a selective drug. ECT is perhaps the treatment with the richest pharmacology.

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POSTERS

Poster 1

Probiotic treatment has anti-depressant effect independent of diet

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Background: The literature suggests a bi-directional association between depressive disorder and diabetes mellitus type II as well as the metabolic syndrome. The gut microbiota may play an important role in metabolic disorders, and diet influences considerably on the microbiota composition. Interestingly, gut microbes have also recently been shown to affect behaviour in animals, and several studies have found them to be important regulators of the hypothalamic-pituitary-adrenal (HPA) axis.

Objectives: The study aimed at examining whether probiotic treatment would affect glucose metabolism or depressive-like behaviour in healthy rats. Furthermore, we wanted to study if probiotic treatment could protect against the adverse effects of a high-fat diet or, on the other hand, whether a high-fat diet could attenuate any effect of probiotic treatment.

Methods: 40 male Sprague-Dawley rats were fed a high-fat or control diet for 10 weeks. In addition, a probiotic mix (8 lactobacillus, bifidobacteria and lactococcus species, 5x10^9 CFU per rat) or placebo were administered daily during the last 5 weeks. Next, the animals were subjected to the Forced Swim Test, the Open Field Test as well as an oral glucose tolerance test. Furthermore, the expression of selected genes and proteins in the brain was assessed, and the cytokine production from anti-CD3/28 stimulated peripheral blood mononuclear cells was measured.

Results: Independent of diet, probiotic treatment was associated with a marked reduction in depressive-like behaviour without altering locomotor activity. Consumption of high-fat diet led to increased body weight as well as increased plasma glucose, insulin and endotoxin levels, but probiotic treatment did not affect these measures. High-fat diet and probiotics were associated with oppositely directed changes in the expression of neurotrophic and HPA axis regulating factors in hippocampus, but no changes were seen in frontal cortex. Changes in the cytokine profile were also observed with probiotic treatment. Most noticeably, probiotic treatment reduced the relative interleukin 6 production.

Conclusion: Our findings add perspective to the potentially important role of the gut-brain axis and clearly supports the novel concept of "psychobiotics". However, the probiotics used in this study should also be validated in a depression model. Nevertheless, our study lends inspiration to further studies into the involved pathophysiological mechanisms. Our findings suggest that the HPA axis and immune system could be involved.

Poster 2

Investigation of the Structural Alteration of Hippocampus One Week after Ketamine Administration

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Background: Based on current clinical trials, most of the patients who receive antidepressant treatment only partially respond to the treatment and in some patients there is no clinical response after the first period of treatment. Furthermore, recent studies indicate strong support for the etiologic role of ionotropic glutamate N-methyl-D-aspartate receptor (NMDA) in the psychopathology for major depression.

Objectives: The aim of this study is to utilize ketamine, a NMDA receptor antagonist, as entry-point to obtain insight into the structural basis sustained antidepressant effect.

Methods: Flinders Sensitive line rats (a highly validated genetic animal model of depression) and Flinders Resistant line rats as control group received a single injection of ketamine (15 mg/kg) or saline intraperitoneally one week before transcardial perfusion. Depressed behavior of animals was assessed by a forced swim test. Thereafter, hippocampus was sectioned on a vibratome perpendicular to its longest axis at a thickness of 65 µm. The sections were used for quantifying the number of neurons in granular cell layer (GCL) of dentate gyrus (DG) and the length of microvessels in the molecular layer of DG of rat hippocampus by using stereological methods.

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Results: Without any kind of treatment, FSL rats showed longer immobility time versus FRL rats ($p<0.05$). Interestingly, one week after ketamine treatment the duration of immobility significantly decreased in depressed animals ($p=0.02$), however there was no significant difference in the control group after treatment ($p>0.05$).

Investigation of the structural alteration of hippocampus showed significant sustained effect of ketamine on enhancement of the number of neurons in GCL area of FSL rats ($p=0.01$). However, the difference in the number of granule cells in GCL in FRL rats after treatment did not reach statistical difference ($p>0.05$). Regarding the vascularization of the molecular layer of DG, the results demonstrated that microvessels in depressed rats was significantly shorter than in the control group ($p<0.05$). Interestingly, the total length of the microvessels one week after ketamine treatment in FSL rats was significantly increased ($p<0.05$).

Conclusion: Our results suggest that structural alteration of hippocampus may be one of the mechanisms underlying the alleviation of depression symptoms one week after a single injection of ketamine.

Poster 3

Searching for footprints of positive selection on schizophrenia associated genes in Danish and worldwide samples of human populations

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Background: Schizophrenia is considered an evolutionary paradox. Heritability is found to be up to 81%, but it shows strongly negative fitness since people suffering have a standardized mortality rate (SMR) of up to 3.6 compared to the general population and have ¼ - ½ as many children as the general population. Despite these disadvantages schizophrenia is relatively common, with a lifetime risk of 0.5 – 1% all around the world and onset of disease peaking in the early twenties.

Objectives: The aim of this study is to investigate whether genes associated with schizophrenia have been subject to positive selection in the evolution of humans, and thus indicating that the high prevalence of schizophrenia can at least partially be explained by previous positive selection of genes increasing the risk of schizophrenia in contemporary human populations.

Methods: The genetic data was drawn from a previous genome-wide association (GWA) analysis of all Danish residents with an ICD-10-DCR diagnosis of scizophrenia identified in the Danish Psychiatric Central Research Register since 1981 diagnosed with schizophrenia as well as matched controls from the same birth cohort. After quality control, the sample was comprised of 1770 individuals with 888 schizophrenia cases and 882 controls and a total of 541,148 single nucleotide polymorphisms (SNPs). Gene lists was derived from the GWAS catalogue and the most recent results from the Psychiatric Genomics Consortium, and will be compared to the webinterface Haplotter that display results of a scan for positive selection on HapMap data. To test wether schizophrenia associated genetic regions have been subject to positive selection, we used two tests based on extended haplotype homozygosity (EHH) tests. REHH measure EHH, integrated EHH (iHH), and the log-ratio of iHH (iHS). iHS is standardized using the average and standard deviation values over all SNPs with simialar frequency. The other method, nSL, is also based on the iHS-statistic, but measure the length distance by segregating sites and not recombination distance as REHH does. This makes the statistic less sensitive to recombination rate and increases the power to detect both soft and hard sweeps.

Results and conclusion: Identifying genomic regions associated to schizophrenia that are subject to positive selection is one step towards understanding why these regions are conserved in the human lineage despite the apparent negative fitness. This will help us understand whether schizophrenia is actually a part of a maladaptive function that we would expect to be selected against over time, or if it is linked to genomic regions that increase reproductive success. Is the latter the case, we would expect schizophrenia to continually occur and therefore the development of better targeted treatment will be of great value.

Poster 4

Demographics and medical treatment in patients with agitated episodes: A patient level perspective

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Background: Agitation (excessive motor or verbal activity) is a common symptom in patients with schizophrenia or bipolar disorder. Acute agitation can escalate unpredictably (in minutes, hours or days) into aggressive behavior and can, if poorly controlled, potentially lead to

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injury and distress in patients and staff. Consequently, rapid-acting treatment is needed. Current standard medical treatment of acute agitation includes per oral and intramuscular administration methods. Limited research describes the patient perspective and preference in the administration method of the medicine given to treat agitation episodes.

Objectives: The aim of this study was to assess patient preference and experience associated with agitation episodes and the impact of the medicine administration method on patient health-related quality of life, using a time trade-off utility approach. In this abstract, demographics and patients current experience of medical treatment of agitation episodes are described.

Methods: A survey was conducted November-December 2014 and carried out in Denmark and Sweden. Data were collected via an internet-based survey, using an existing panel of respondents (Userneed's email panel), which included patients with schizophrenia or bipolar disorder. Respondents needed to report a diagnosis of schizophrenia or bipolar disorder and were >18 years old and participated at their discretion, remaining anonymous throughout. There were no exclusion criteria to participation.

Results: In total, 237 respondents completed the survey and were included in the analysis, of which 176 (74%) reported diagnosis of bipolar disorder. Respondents were predominantly female (59%) and the average age was 40 years. The reported average age at diagnosis was 23 years for respondents with schizophrenia and 31 years for patients with bipolar disorder. In total, 84% of the patients with schizophrenia reported to have been hospitalized, of which 46% were hospitalized in the last year. Thirty-one percent of the patients with bipolar disorder reported to have been hospitalized in the last year. In total, 83% of the respondents in this study reported to receive treatment with tablets, and 31% of the patients with schizophrenia were currently treated with injections. Agitation episodes were experienced by 90% of the respondents. More agitation episodes were experienced in schizophrenic respondents in the last year as 73% of these patients had experienced 3 of more episodes compared to 57% of the bipolar respondents. In both groups, more than half of the respondents had requested medication to calm down (63%). More patients with schizophrenia reported to request medication; however more patients with schizophrenia than patients with bipolar disorder also reported to be given medication against their will. The most common reason for requesting medication was to calm down and reported by 78% of the respondents. Injection as administration method was reported by 14% of the patients with bipolar disorder and of 7% of the patients with schizophrenia requesting medication. Twenty percent reported to have been given medication against their will, and injection as administration method was most frequently reported by patients with bipolar disorder (62%). More patients with schizophrenia reported to receive both injection and tablets compared to the bipolar respondents (19%) when medication was given against their own will.

Conclusion: Agitation episodes are experienced by the vast majority of patients with schizophrenia or bipolar disorder in this survey. Notably, the patients reported predominantly to request medicine by themselves, and the most common reason for requesting medicine was to calm down. The most common administration method was tablets.

Poster 5

Patient reported preference for mode of medicine administration in agitation

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Background: Agitation (excessive motor or verbal activity) is a common symptom in patients with schizophrenia or bipolar disorder. Acute agitation can escalate unpredictably (in minutes, hours or days) into aggressive behavior and can, if poorly controlled, potentially lead to injury and distress in patients and staff. Consequently, rapid-acting treatment is needed. The route of administration is known to have a great impact on the onset and the duration of action. Current standard medical treatment of acute agitation includes per oral and intramuscular administration methods. A new treatment option administered by inhalation is now available. Limited research describes the patient perspective and preference in the administration method of the medicine given to treat agitation episodes.

Objectives: The aim of this study was to assess patient preference and experience associated with agitation episodes and the impact of the medicine administration method on patient health-related quality of life, using a time trade-off utility approach. In this abstract, the impact of the onset and duration of action on the patient's willingness of taking and avoiding medicine, and the patient's preference regarding onset and duration of action are described.

Methods: A survey was conducted November-December 2014 and carried out in Denmark and Sweden. Data were collected via an internet-based survey, using an existing panel of respondents (Userneed's email panel), which included patients with schizophrenia or bipolar

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disorder. Respondents needed to report a diagnosis of schizophrenia or bipolar disorder and were >18 years old and participated at their discretion, remaining anonymous throughout. There were no exclusion criteria to participation.

Results: In total, 237 respondents completed the survey and were included in the analysis, of which 176 (74%) reported to be diagnosed with bipolar disorder. When the respondents were asked about how they feel about receiving medical treatment for their schizophrenia or bipolar disorder, 43% responded that they would avoid take medication as a rule, of which sedation was the most common reason for avoiding medication (50%). In total, 78% of the respondents in this survey had experienced drowsiness, feeling like living in a bubble or grogginess, and 73% reported that they had refused medication in order to avoid these side effects. When asked about the ideal time from administration of medication to onset of efficacy, 68% of the patients preferred 2 minutes compared with 30 minutes or 1 hour. In total, 88% preferred that the duration of drowsiness, 'bubble feeling' or grogginess lasted for a shorter period of time. When asked about the preferred administration method, 66% of the patients preferred inhalation, compared to administration with tablets (24%) or injection (13%).

Conclusion: The onset and duration of action are important for patients with schizophrenia or bipolar disorder. Possible side effects of the medication such as sedation may be reasons for patients refusing taking medication. The patients in this survey preferred inhalation as administration method during an agitation episode.

Poster 6

Inactivation of the cholinergic M4 receptor results in a low anxiety-like phenotype predicting future alcohol preference

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Background: We have previously shown that the muscarinic acetylcholine M4 receptor is involved in the regulation of operant self-administration of alcohol in mice. However, the mechanism(s) by which this is established remains to be fully understood. Underlying traits such as anxiety, novelty seeking, and cognitive flexibility have previously been associated with drug taking behavior in a complex fashion.

Objectives: For a better understanding of how the M4 receptor is involved in mediating alcohol-drinking behavior we here investigate the role of the M4 receptor function for basal activity and anxiety performance and how these traits relate to alcohol consumption and relapse. We also investigate a general role of the M4 receptor in regulation of novelty seeking behavior and cognitive flexibility.

Methods: M4−/− and M4+/+ mice were screened for activity in locomotor activity boxes and anxiety on the elevated plus maze. The same mice were later exposed to a voluntary choice of drinking either alcohol or water before and after an alcohol deprivation period, in their home-cages. In a separate set of M4−/− and M4+/+ mice novelty-seeking and spatial learning was examined via novel environment and object exploration tests and the barns maze, respectively.

Results: The M4−/− mice displayed a high degree of disinhibited exploratory behavior on the elevated plus maze open arms. This behavior was later correlated to increase basal as well as relapse driven alcohol preference. In follow up studies the M4−/− genotype showed markedly reduced latency to explore both a novel arena and a novel object while spatial learning ability and basal activity was unaffected compared to controls.

Conclusion: The M4−/− genotype show both disinhibited approach behavior and increased alcohol consummatory behavior. The M4 receptor may therefore control voluntary alcohol consumption via on anxiety-like and novelty seeking related mechanisms, possibly in combination with other reward related mechanisms. The M4 receptor constitutes a novel target that should be further investigated as a future treatment option for alcohol use disorders.

Poster 7

Differentiated antidepressant-like profiles of ketamine, fluoxetine and vortioxetine in Flinders Sensitive Line rats depleted of endogenous 5-HT

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Background: Current first-line treatments for clinical depression have a delayed therapeutic effect, sometimes up to several weeks, and provide unsatisfactory efficacy in a substantial proportion of patients. Therefore, identification of novel antidepressant mechanisms is pivotal.

Consistent with clinical results, single-dose ketamine exhibits acute and protracted antidepressant-like effects in

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Sprague-Dawley rats [1]. The mechanisms mediating these antidepressant effects are far from fully understood; however, one hypothesis ascribes ketamine's antidepressant effect to enhanced glutamate transmission via inhibition of NMDA receptors on gamma-aminobutyric acid (GABA) interneurons. Recent research showed that serotonin (5-HT) depletion abolishes ketamine's protracted antidepressant-like effect in Sprague-Dawley rats [2].

Vortioxetine is a multimodal-acting antidepressant that is hypothesized to exert its therapeutic activity through 5-HT3, 5-HT7 and 5-HT1D receptor antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism, and inhibition of the 5-HT transporter [3]. Preclinical studies indicate that this pharmacological profile results in enhanced monoamine and glutamate neurotransmission and inhibition of GABA interneurons expressing 5-HT3 receptors in key brain structures relevant for depression [3].

Objectives: Novel mechanistic insights may be gained by studying the antidepressant-like profile of ketamine, vortioxetine, and the prototypical SSRI fluoxetine in response to manipulation of serotonergic neurotransmission. Here we investigate the acute and protracted antidepressant-like effects of ketamine and the acute effects of vortioxetine and fluoxetine under normal and low 5-HT levels in a genetic model of depression, Flinders Sensitive Line (FSL) rats.

Methods: Tryptophan hydroxylase is the rate-limiting step in the synthesis of 5-HT, and therefore, the irreversible tryptophan hydroxylase inhibitor p-chlorophenylalanine (pCPA) was used to induce 5-HT depletion (>90% hippocampal reduction). FSL rats were pre-treated with pCPA (100 mg/kg/day) or saline once daily for three consecutive days. Three days after the last pCPA injection, antidepressant-like activity was assessed using the forced swim test. In this test, a reduction of immobility is considered to reflect an antidepressant-like activity.

48 hours prior to the forced swim test, FSL rats were single-dosed with ketamine (15 mg/kg) or saline. One hour prior to testing, rats were dosed with ketamine (15 mg/kg), vortioxetine (10 mg/kg), fluoxetine (10 mg/kg) or saline. Accordingly, pCPA and saline pre-treated FSL rats were randomly assigned to ketamine/saline, saline/ketamine, saline/vortioxetine, saline/fluoxetine, or saline/saline treatment regimens.

Results: FSL rats exhibited similar immobility under normal and low 5-HT levels. Single-dose ketamine at 1 or 48 hours prior to evaluation significantly decreased the immobility of FSL rats with normal 5-HT tone. There was no effect at low 5-HT levels.

Fluoxetine treatment at 1 hour prior to testing decreased immobility only at normal 5-HT levels. In contrast, single-dose vortioxetine reduced immobility under normal and low 5-HT tone.

Conclusions: 5-HT depletion prevented the acute and protracted antidepressant-like effects of ketamine without affecting the depressive-like phenotype of FSL rats. These observations indicate a critical role of endogenous 5-HT tone for ketamine's antidepressant-like effects. The 5-HT receptors involved remain to be identified.

Acute vortioxetine treatment, but not fluoxetine, exhibited an antidepressant-like effect in 5-HT depleted rats. This effect may potentially be ascribed to vortioxetine agonism at 5-HT1A and/or 5-HT1B receptors, since these receptors are engaged at the dose tested [3]. Results from studies testing this hypothesis will be presented.

In conclusion, these data support the notion that 5-HT1 receptor agonism may be important for an antidepressant-like effect in this model.

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Poster 8

Altered tryptophan metabolism in female FSL rats, a genetic model of depression.

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Background: Depression is a devastating and highly prevalent disease worldwide. The aetiology is largely unknown and the symptomatology varies among patients, which indicates that the pathophysiology underlying the disease is heterogeneous. Several studies suggest that subtypes of depression are linked to dysfunctions in the tryptophan metabolism, which involves the serotonin and the kynurenine pathways. Thus, stress and inflammation can lead to serotonergic- and glutamatergic-dysregulation, through the kynurenine pathway, which gives rise to potential neurotoxic intermediates: 3-Hydroxykynurenine and quinolinic acid, with possible serotonin depletion as a result. Interestingly, even though depression is twice as prevalent in women as in men most preclinical studies are performed in male animals.

Objectives: In order to understand the involvement of tryptophan metabolism in depression further, the aim of our study was to investigate the metabolism of tryptophan in female Flinders Sensitive Line (FSL) rats, a genetic model of depression, and female Flinders Resistant Line (FRL) rats, the control counterpart.

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Furthermore, we wanted to evaluate the impact of the oestrous cycle on the depressive-like behaviour.

Methods: FSL and FRL rats aged 12-20 weeks old were subjected to open field test and the modified forced swim test (FST), a standard model of depressive-like behaviour. Subsequently rats were euthanized to collect plasma and both left- and right-side brain hemispheres, including cerebellum. A total of 13 tryptophan metabolites (TRYMETs), encompassing both the serotonergic and kynurenine pathways were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Vaginal smears were obtained throughout the experiment to control for oestrous cycle.

Results: FSL rats showed increased activity in the open field and increased immobility behaviour in the FST. Brain level of the potential neurotoxin, 3-hydroxykynurenine, was increased and levels of anthranilic acid and the serotonin precursor, 5-hydroxytryptophan were decreased compared to FRL rats. In plasma, anthranilic acid, picolinic acid and quinolinic acid concentrations were lower compared to FRL rats. There was no impact of the oestrous cycle on either behavioural or TRYMETS and no hemisphere-differences with respect to TRYMETs.

Conclusion: The depressive-like phenotype of female FSL rats compared to FRL rats was associated with a different tryptophan metabolism through the serotonin and kynurenine pathways. This included a shift in the levels of brain quinolinic acid precursors, but not quinolinic acid, from anthranilic acid to 3-hydroxykynurenine. Interestingly, none of these measures were found to vary with the state of the oestrous cycle.

Poster 9

Effects of exercise on LPS-induced depression-like behaviour and central changes of the tryptophan-kynurenine pathway in rats

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Background: Exercise is a non-pharmacological and beneficial approach for a number of conditions, including psychiatric disorders such as depression [1]. The biological effects of exercise are partly attributed to the immune-modulating properties affecting both the body and the brain [2]. Depression may be associated with an activated immune system, and the tryptophan-kynurenine pathway has been proposed as the neurobiological link to the psychiatric symptoms [3]. Activation of this pathway by pro-inflammatory cytokines may result in down-stream activation of a "neurotoxic" arm, causing elevated levels of the harmful metabolites quinolinic acid and 3-hydroxykynurenine. However, it has yet to be explored whether exercise act centrally through this signalling pathway.

Aim: The aim of this study was to investigate the effects of long-term exercise in a model of chronic lipopolysaccharide (LPS) challenge, on behaviour and expression of brain cytokines and enzymes involved in tryptophan metabolism along the kynurenine pathway.

Methods: Rats were randomised to chronic LPS (600 µg/kg, i.p.) or saline injections, with or without free access to a running wheel for 8 weeks. Behavioural assessments included sickness and depression-like behaviour. Molecular assessments included brain and blood cytokine levels, and brain enzymes of the tryptophan-kynurenine pathway.

Results: Rats ran a similar total distance in the running wheel, regardless of treatment with LPS or saline. Chronic LPS treatment caused depression-like behaviour, indicated by an increase in immobility in the forced swim test (FST) and sickness behaviour, indicated by a lower body weight and food intake, and decreased locomotor activity in the open field. Exercise was able to reverse the depression-like behaviour, but had no effect on the LPS-induced sickness behaviour. Furthermore, LPS caused a region- and cytokine-specific response in the brain, but this was not reversed by exercise. Moreover, exercise decreased blood cytokine levels and the enzyme kynurenine-3-monooxygenase (KMO) in frontal cortex, regardless of treatment with LPS or saline.

Discussion and conclusion: Long-term exercise had antidepressant effects on the LPS-induced depression-like behaviour in rats. Exercise did not seem to induce this effect though down-regulation of central cytokine levels, but possibly acting trough the enzyme KMO, and thus lowering the level of the neurotoxic metabolites quinolinic acid and 3-hydroxykynurenine. Thus, these results could indicate that exercise has protective effects on brain health through targeting the tryptophan-kynurenine pathway. As this is an on-going study, further results will be presented at the conference.

Poster 10

Inflammatory markers are associated with general cognitive abilities in schizophrenia, bipolar disorder and healthy controls

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Background: The mechanisms underlying cognitive impairment in schizophrenia and bipolar disorders are largely unknown. Immune abnormalities have been found in both disorders, and inflammatory mediators may play roles in cognitive function.

Objectives: The aim of the study was to determine how markers of different proinflammatory pathways (sTNF-R1, IL-6, IL-1Ra, OPG, vWf, sCD40L and hsCRP) relate to general cognitive abilities in large well-characterized samples of SCZ, BD and healthy controls after adjusting for disease severity measures and somatic characteristics and other possible confounding factors.

We investigated if inflammatory markers are associated with general cognitive abilities.

Methods: Participants with schizophrenia spectrum (n=121), bipolar spectrum disorder (n=111) and healthy controls (n=241) were included. General intellectual abilities were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI). Serum concentrations of the following immune markers were measured: Soluble tumor necrosis factor receptor 1 (sTNF-R1), Interleukin 1 receptor antagonist (IL-1Ra), Osteoprotegerin, von Willebrand factor, C-reactive protein, Interleukin-6 and CD-40 ligand.

Results: After adjusting for age, sex and diagnostic group, significant negative associations with general cognitive function were found for sTNF-R1 ($p = 2x10^{-5}$), IL-1Ra ($p = 0.002$) and sCD40 ligand ($p= 0.003$). Among patients, the associations remained significant ($p=0.006$, $p=0.005$ and $p=0.02$) after adjusting for possible confounders including education, smoking, psychotic and affective symptoms, body mass index, cortisol, medication and time of blood sampling. Subgroup analysis, showed that general cognitive abilities were significantly associated with IL-1Ra and sTNF-R1 in schizophrenia, with sCD40L and IL-1Ra in bipolar disorder and with sTNF-R1 in healthy controls.

Conclusion: The study shows significant negative associations between three inflammatory markers and general cognitive abilities after adjusting for a broad set of possible confounders. The findings strongly support a role for inflammation in the neurophysiology of cognitive impairment.

Poster 11

Rat vocalizations: A new preclinical screening tool for depression?

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Background: The forced swim test (FST) is widely used in preclinical research as it offers a quick and reproducible way of assessing depressive-like behaviour in rats and mice. Interestingly, the FST was initially introduced as a model of depression and stresses the rats when carried out. This study explores rat vocalizations as an alternative non-stressful screening tool for depression.

Rats produce high-frequency sounds (USVs) inaudible to the human ear. These sounds are produced spontaneously e.g. during play and are hypothesized to reflect the affective state of the rat. The experimenter can imitate the rough-and-tumble play of juvenile rats through a tickling-like stimulation, which leads to an increase in sound production - said to reflect positive emotions.

The Flinders Sensitive Line (FSL) rat is a highly validated genetic rat model of depression.

Objectives: The current study investigates whether USVs produced during tickling stimulation can be utilized as an alternative non-stressful screening tool for depression. Furthermore, it examines the effect of ketamine, a NMDA-receptor antagonist with a rapid acting antidepressant effect, on the USV profile and the effect of tickling on the gene expression of kallikrein. Kallikrein is a supposedly stress-sensitive protein-family which is highly expressed in the submandibular glands.

Methods: We investigated the FSL rats' sound profile during six weeks of tickling. FRL rats, SD rats and light-touch groups were used as controls. Depressive-like behavior was evaluated with the FST. Ketamine or NaCl was administered acutely after five weeks of tickling and the rats were tickled/light-touched for an additional week after which the FST was repeated. The rats were euthanized by decapitation and the submandibular glands dissected and frozen on powdered dry ice. Kallikrein expression was analyzed with quantitative real-time polymerase chain reaction.

Results: The FSL rats produce significantly more calls than controls during tickling stimulation on all days in-

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vestigated. Tickling did not alter the expression of kallikrein in the submandibular glands as compared to the light-touch controls, however, there was a significant strain difference between FSLs and both of the control groups, with the FSL rats expressing significantly less kallikrein2 and Klk1c10 in the submandibular glands. The effect of ketamine on the USV profile is still being analyzed.

Conclusion: Our study is the first to investigate how the FSL rat responds to tickling. Interestingly, it displays an increased sound production compared to controls, indicating increased positive emotions. This calls into question whether it is born with a depressive-like phenotype or merely a predisposition. Further studies on other rat models of depression are needed to determine whether USVs during tickling stimulation may work as a new screening tool for depression. The altered kallikrein expression in the submandibular glands of the FSL rat as compared to controls is an interesting finding as a part of the ongoing exploration of the FSL rat as a model of depression.

Poster 12

Clinical experience of inhalable loxapine in the management of acute agitation at a specialized psychiatric treatment clinic in Sweden.

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Background: Agitation characterized by excessive motor and verbal activity is frequently seen in patients with schizophrenia, bipolar disorder and other psychiatric conditions. Pharmacological treatment is often needed to manage agitation and avoid physical damage to patients and health care professionals. Time to onset of effect of medication is thus of critical importance. Loxapine is an antipsychotic with D2 and 5HT2A blocking action (1). It is known for rapid calming effect in agitated patients (2). Inhalable loxapine (Adasuve®) is approved in the EU for acute treatment of mild to moderate agitation in patients with schizophrenia and bipolar disorder (1).

Objectives: The aim was to evaluate the usefulness of inhalable loxapine as a novel treatment option in the daily clinical management of patients with acute agitation at a specialized psychiatric in-patient treatment clinic in northern Sweden.

Methods: Agitated patients were prescribed inhalable loxapine which was administered by the patient in collaboration with the nurse. Pre-dose, the severity of agitation was assessed using the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) scale (3). The PANSS-EC scale measures five symptoms associated with agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each symptom is rated on a scale of 1 (absent) to 7 (extreme), and scores are summed. Therefore, total scores can range from 5 (all symptoms absent) to 35 (all symptoms extreme). Two hours post-dosing, the change from baseline agitation was measured using the Global Clinical Impressions-Improvement (GCI-I) scale. Scores range from 1 (very much improved) to 7 (very much worse). Safety was monitored for the first hour following inhalation.

Results: Ten patients (6M, 4F; average age 33 years) with acute agitation were prescribed inhalable loxapine, of whom 8 patients inhaled at more than one agitation episode. The average PANSS-EC score before dosing was 23 (range 15-30) indicating pronounced agitation in most cases. Following inhalation, de-escalation of the agitation symptoms was seen in 8 patients, with an average GCI-I score of 1.6 indicating much to very much improvement. Notably, an immediate effect was seen in 3 patients and within approximately 10 minutes the effect was seen for most of the other patients. Coercive measures were prevented on several occasions. Inhalable loxapine was well tolerated.

Conclusion: Inhalable loxapine is a new treatment of acute agitation. The rapid onset of action with marked reduction of agitation within minutes and the good tolerability, makes inhalable loxapine an attractive treatment option in the management of acute agitation. Further, with these attributes, inhalable loxapine prevents coercive measures such as injections and physical or mechanical restraints. Due to the non-invasive properties of inhalable loxapine and the ease of use, a trustful patient-caregiver alliance is developed which facilitates further long-term management.

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Poster 13

Endocannabinoid signaling in a genetic rat model of depression

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Background: Major depressive disorder (MDD) is an illness affecting one third of the world population and conventional antidepressant remain unsatisfactory in efficacy with a therapeutic delay of 4-6 weeks. In the process of developing more effective antidepressant a deeper understanding of the pathophysiology is needed. Both clinical and preclinical data suggest the involvement of the endocannabinoid (eCB) system in the pathophysiology of depression. Especially preclinical stress model paradigm has shown decreased eCB signaling.

Objectives: The aim of our study is to investigate how endocannabinoid (eCB) signaling affects depression like-behavior in an animal model of depression the Flinders Sensitive Line rats compared to Sprague Dawley rats.

Methods: Our aim will be investigated in the following two work packages: 1) How local enhancement of eCB signaling in medial prefrontal cortex (mPFC) of Flinders Sensitive Line rats alters their depression-like behavior compared to 'healthy' controls and an imipramine treated FSL group. 2) Differences in expression of central eCB components in mPFC, hippocampus and hypothalamus of Flinder Sensitive Line rats compared to controls.

Results: Preliminary results suggest significant changes in cannabinoid receptor expression in specific part of the brain of the FSL brain compared to control. To further investigate these findings behavioral studies is ongoing to evaluate how pharmacological enhancement of eCB in mPFC signaling affects depression like behavior in the forced swim test.

Conclusion: Our preliminary results suggest a significant change in endocannabinoid signaling in a rat model of depression. Further behavioral investigation and evaluation is ongoing to further explore the role of the endocannabinoid system in this genetic rodent model of depression.

Poster 14

Electroconvulsive shocks decrease α2-adrenoceptor binding in the Flinders rat model of depression

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Background: Despite years of drug development, electroconvulsive therapy (ECT) remains the most effective treatment for severe depression. However, the exact therapeutic mechanism of action of ECT is still unresolved.

Objectives: Here, we tested the hypothesis that the beneficial effect of ECT could in part be the result of increased noradrenergic neurotransmission leading to a decrease in α2- adrenoceptor binding.

Methods: We have previously shown that both the Flinders sensitive line (FSL) and Flinders resistant line (FRL) rats had altered α2-adrenoceptor binding compared to control Sprague–Dawley (SD) rats. In this study, we treated female FSL, FRL and SD rats with electroconvulsive shock (ECS), an animal model of ECT, or sham stimulation for 10 days before brains were removed and cut into 20 mm thick sections. Densities of α2-adrenoceptors were measured by quantitative autoradiography in the hippocampus, thalamic nucleus, hypothalamus, amygdala, frontal cortex, insular cortex, and perirhinal cortex using the α2-adrenoceptor antagonist, [3H]RX 821002.

Results: ECS decreased the binding of α2-adrenoceptors in cortical regions in the FSL and cortical and amygdaloid regions in the control FRL rats compared to their respective sham treated group. The normal SD controls showed no significant response to ECS treatment.

Conclusion: Our data suggest that the therapeutic effect of ECS may be mediated through a decrease of α2-adrenoceptors, probably due to a sustained increase in noradrenaline release. These data confirm the importance of the noradrenergic system and the α2-adrenoceptor in depression and in the mechanism of antidepressant treatments.

Poster 15

Cognitive Phenotyping of a Rodent Model of Depression Using Translational Touchscreen Tasks

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Background: Major depressive disorder (MDD) is one of the leading causes for disability worldwide. MDD affects approximately 350 million people and displays a burden for both the individuals as well as the society. Therefore, development and verification of antidepressant treatment strategies are vital to optimize therapy for patients and, hence, well established and validated MDD animal models are crucial. Chronic mild stress (CMS) has been shown to be a valid rodent model of depression as it induces anhedonia, one of the core symptoms of MDD. Anhedonia is defined as a loss of interest in activities that are usually perceived as pleasurable. Impaired cognition displays another symptom observed in depressed patients which was not fully investigated in the CMS model, yet.

Objectives: Our overall goal is to develop and optimize an animal model of depression which also enables the assessment of changes in cognitive functions.

In the current study, our objectives are: 1) to investigate the eligibility of Long Evans (LE) rats exposed to CMS as a model of depression, 2) to identify if the CMS paradigm impairs cognitive performance in LE rats, and 3) to determine if Wistar or LE rat strains are more suitable for cognitive assessment with the touchscreen operant platform.

Methods: Sixteen LE rats were exposed to the CMS paradigm testing susceptibility of this strain towards stress exposure. The sucrose consumption test was used as readout on the anhedonic-like state in rats exposed to CMS. A decrease of over 30% of the baseline sucrose water intake after stress onset reflects an anhedonic- and therefore depressive-like state in rats. Additionally, social interaction, y-maze, elevated plus-maze and open field were used for behavioral phenotyping of stressed vs. LE controls.

Subsequently, stress exposed LE rats (N=16) and controls (N=12) as well as Wistar controls (N=12) were tested in the Bussey-Saskida touchscreen operant platform.

To investigate cognitive abilities between strains and between stressed and non-stressed animals, LE control and stressed groups as well as a Wistar control group were tested with the Bussey-Saksida touchscreen operant platform. Pairwise discrimination reversal task and retention were used to assess visual discrimination, stimulus-reward association learning, perseveration and memory consolidation.

Results: Preliminary data revealed a significant difference of cognitive performance in the touchscreen tasks between LE and Wistar control rats. In the CMS paradigm, LE rats proved to be equally susceptible to stress exposure as Wistar rats shown with the SCT

Conclusion: LE rats are more suitable for testing in the touchscreen operant platform by demonstrating a better performance level. Furthermore, rats of the LE strain react similar to the CMS paradigm as the well investigated Wistar rats and seem therefore suitable for this stress model. Since no differences were found between LE stress and control groups, we cannot conclude that CMS affects cognitive function, such as cognitive flexibility, in this rather simple and non-hippocampus dependent task. This could be due to the fact that the LE CMS group was heterogeneous by consisting of anhedonic-like but also resilient and non-assignable rats. A comparison of a pure anhedonic-like with a control group may lead to a clear difference in regard to cognitive performance.

In summary, Long Evans rats are susceptible to the CMS paradigm and perform well in simple cognitive tasks and thus appear to be a good model for investigating cognitive function in depression.

Poster 16

Role of Noradrenergic Innervation of Thalamus in Generation of EEG Background Rhythm Frequency in Patients With Parkinson's Disease.

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Background: The electroencephalographic (EEG) background rhythm frequency (BRF) is modulated by specific thalamic nuclei. It is reduced in patients with Parkinson´s disease (PD) at risk of developing PD---related dementia. Similarly, damage to cortical and thalamic noradrenergic innervations that originate in the locus coeruleus may play an important role in the pathophysiology of cognitive dysfunction in patients with PD.

Objectives: We tested the hypothesis that loss of noradrenergic innervation of the thalamus would be more pronounced in patients with PD compared to healthy controls, as measured with [11C]MeNER, a labelled noradrenaline transporter antagonist, by positron---emission

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tomography (PET). We also tested whether the putative loss of noradrenergic innervation would be proportional to the decline of BRF.

Methods: Patients with PD (N=11, mean age 66.0±2.6 years, Hoehn&Yahr 2.4±0.5) and 7 healthy age---matched controls (mean age 66.7±3.1 years) underwent PET with ligand [11C]MeNER with arterial blood sampling to calculate volumes of distribution and binding potentials using one---tissue compartment modeling. We used corpus callosum as reference region to calculate [11C]MeNER binding potential (BPND), and we recorded routine EEG to determine BRF.

Results: As expected, BPND of [11C]MeNER in the thalamus was lower in patients 0.8±0.2 than in healthy controls 1.2±0.1 (one---tailed t---test $P<0.05$). Similarly, the BRF was reduced in PD patients at 7.5 Hz (±0.3) compared to healthy controls at 9.6 Hz (±0.3) (one---tailed t---test $P<0.05$). However, multiple linear regression analyses showed no significant correlations between BRF and [11C]MeNER BPND in thalamus in patients or in healthy controls ($P>0.05$).

Conclusion: Background rhythm frequency, as measured with EEG, and noradrenaline transporter density in thalamus, as measured with [11C]MeNER PET, are significantly reduced in PD compared to healthy controls. We tested the hypothesis that reduction in BRF could be related to loss of noradrenergic tone in specific thalamic nuclei, but found no significant correlation between the two measures. This may be due to the relatively advanced stage of PD in this cohort of patients, as noradrenergic neurons undergo degeneration in the early stages of PD.

Poster 17

Vitamin D status in psychotic disorder patients and healthy controls – the influence of ethnic background

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Background: Vitamin D deficiency has been suggested as a contributing risk factor for psychotic disorders especially in dark skinned immigrants in the Northern hemisphere (here called visible ethnic minorities).

Objectives: We hypothesized that the serum concentrations of 25- hydroxy vitamin D (S-25 OH D) would be lower in psychotic disorder than in healthy controls both in first episode patients as well as in a comparable multi episode sample, and that visible ethnic minorities would have lower serum concentrations than the corresponding reference population

Methods: A total of 284 participants were included in this cross-sectional study. Seventy-one first episode patients with a DSM-IV psychotic disorder were matched on age, gender and visible ethnic minority status with participants from a multi episode patient sample (1:1) and healthy controls (1:2). S- 25 OH D (D2 and D3) levels were determined.

Results: First episode patients' adjusted S- 25 OH D (mean 40.6 nmol/L) did not differ significantly from multi episode patients (mean 39.9 nmol/L) or healthy matched controls (mean 40.2 nmol/L). In a general linear model, visible ethnic minority background ($F = 47.20$, $p<0.001$) and winter season ($F= 6.63$, $p= 0.01$) influenced the S- 25 OH D negatively while diagnostic group had no effect ($F = 0.02$, $p= 0.98$).

Conclusion: Our study did not support the hypothesis that patients with psychotic disorders have lower S- 25 OH D compared to healthy controls. Visible ethnic minority status was however a strong predictor of vitamin D deficiency in all groups

Poster 18

Investigation of Shape, Orientation and Volume of Neurons from Flinders Rats and Neuronal Nuclei from Human Cerebral Cortex

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Background: Exploring the shape and orientation of neurons in tissue sections is interesting in terms of translational approaches in neuroscience. Derangement in the shape, orientation and volume of neurons in cortical layers of rat and human brain has been shown in several neuropsychiatric disorders.

Objective: We applied Volume Tensors, a stereological method for investigating shape, orientation and volume of neurons in histological sections. We investigated neurons from prelimbic (PL) cortex of the Flinders

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Sensitive Line (FSL) rat (genetic animal model of depression) and Flinders Resistant Line as well as maternal separated (MS) rats which is an example of early-life adversity that leads to alteration in corticogenesis and depressive like behaviors. BA4 from two normal human autopsy brains were also investigated.

Methods: Using 140-µm-thick, Nissl-stained sections, layer-III of the prelimbic region of rat mPFC and layer-III of the BA4 cortical region of human brains were delineated using a 4× objective (Olympus, Plan Apochromat, N.A. 0.20) at a magnification of 220. Rat neurons and human neuronal nucleoli were sampled systematically by the optical disector and analysed by the optical rotator in relation to the cortical surface. The nucleolus of a neuron was marked as reference point for local sampling. The thickness of each field of view (FOV) was measured using a 100× oil immersion objective (NA: 1.25, WD: 160 µm) to check for shrinkage, which was negligible. All samplings were performed in relation to a vertical axis (NewCast Ver 4.1) which was set perpendicular to the cortical surface. Recently developed mathematical tools for spatial sampling and estimation of line segments intersecting with cellular or nucleolar boundaries were used to provide information about the shape, orientation and volume of neurons.

Results: Our preliminary results on the prelimbic region from rat cortex showed that there was a substantial alteration in the mean shape of neurons from FSL-MS rats compared to the two other groups ($p<0.05$). In the human brains, the orientation of nuclei of neurons was aligned perpendicular to the brain surface.

Poster 19

Neonatal domoic acid increases receptor density of α2 adrenoceptors and GABAA α5 receptors in limbic brain regions of adult rats

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Background: The presymptomatic events involved in neurological disorders such as epilepsy remain elusive but represent an opportunity to understand disease development and stop the pathogenic processes leading to chronic epilepsy. Previous studies using Western blot and immunohistochemistry have found increased levels of α2 adrenoceptors in the hippocampal membrane of adult rats treated neonatally with low-dose domoic acid (DOM) along with decreased levels of both isoforms of glutamic acid decarboxylase (GAD), a catalyst of the decarboxylation of glutamate to GABA, indicating a reduction in GABAergic interneurons.

Objectives: The aim of the present study was to investigate the expression of GABAA α5 and α2 adrenoceptors in limbic brain regions in a DOM rat model of epilepsy using autoradiography.

Methods: Male Sprague-Dawley rats (N=3) were injected (s.c.) daily from postnatal day 8-14 with saline or low sub-convulsive doses of the glutamate agonist DOM (20µg/kg), weaned on day 22 and left undisturbed except for routine husbandry. At ~120 days of age the rats were euthanized by decapitation. The brains were removed, frozen in isopentane/dry ice and cut into 20 µM thick slices. Receptor autoradiography was performed using tracers of the α5 subtype of the GABAA receptor ([11C]Ro15-4513) and the α2 adrenoceptors ([3H]RX821002) to determine the total binding of these receptors in the hippocampus, amygdala and hypothalamus. High concentrations of unlabeled Ro15-4513 and phentolamine were used to assess non-specific binding in the GABAA and α2 adrenoceptor studies, respectively, and these values were subtracted from the total binding values to yield the specific binding.

Results: The specific binding of postsynaptic GABA receptors was significantly increased in the hippocampus, medial amygdala and hypothalamus of the DOM treated rats. A trend towards an increase in the density of α2 adrenoceptors was also found throughout the limbic system of the DOM treated rats compared to saline-treated controls in our small sample.

Conclusion: Although preliminary, the observed increase in postsynaptic GABA receptor concentrations in DOM-treated rats may represent a compensatory up-regulation in response to reduced GABAergic input. Further, the preliminary data supports earlier findings of increased levels of α2 adrenoceptors in DOM treated rats. Because noradrenaline reduces neuronal excitability, elevated receptor expression could be a protective mechanism that attempts to compensate for the lowered seizure threshold caused by DOM. These results indicate that low-dose neonatal DOM induces seemingly permanent changes in receptor expression that may be important in delayed-onset epilepsy.

Poster 20

Time-dependent functional changes induced my ketamine in the glutamate system: focus on glutamate release, glutamate receptors and dendritic morphology

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Background: Recent compelling evidence has shown that the glutamate (Glu) system is a target for rapid acting AD, suggesting that direct pharmacological intervention on Glu may exert rapid AD action. Recent studies reported that a single infusion of sub-anesthetic dose of the non-competitive NMDA receptor antagonist ketamine (KET; a dissociative anesthetic) induces rapid (within hours) and sustained (up to 1 week) AD effect in treatment-resistant patients. KET seems to directly target core depressive symptoms, rather than inducing a nonspecific mood-elevating effect. The drug has also shown AD properties in rat models of depression. It has been proposed that the rapid AD effect of KET is due to a burst of glutamate release and transmission, which activates glutamate receptors and downstream signaling, in turn inducing synaptogenesis.

Objectives: It is difficult at present to understand how the effect of KET can be related to a burst of Glu, and the following questions are open: 1. What are the short- and long-term effects of acute KET on Glu release/transmission in PFC/FC and HPC of a rat model of depression (Flinders sensitive line (FSL))? 2. What are the time-dependent effects of KET on the expression levels of Glu receptor subunits (AMPA and NMDA) in FSL rats?

Methods: FSL rats, a genetic animal model of depression, was used to study the effects of KET on neurotransmitter release in the prefrontal cortex. [3H] D-Asp release was measured in PFC synaptosomes from FRL, FRL treated with KET ((i.p. 15 mg/kg, 2h), FSL and FSL treated with KET rats with the superfusion technique. Triton insoluble fraction (TIF), corresponding to the postsynaptic density, were purified with an ultracentrifuge (Beckman TL100) and the expression level or the phosphorylation level of NMDAR2A, NMDAR2B, GluR1, pGluR1S831, pGluR1S8345, GluR1 and GluR3 were measured by Westerner blotting in the PFC of FRL, FSL and FSL + KET rats.

Results: Our preliminary data show a robust increase in stimulated [3H]-D-aspartate release in FSL rats compared to the control FRL rats, while a single injection of KET 2 h prior to the experiment markedly reduced this increase in evoked [3H]-D-aspartate release. This data suggest that KET may reduce excessive glutamate transmission in the prefrontal cortex of FSL rats.

In parallel we investigated if the changes observed in glutamate release are correlated with changes in the phosphorylation level and total expression of AMPA and NMDA receptor subunits. Firstly, we set up the purification of (TIF) that represents the postsynaptic spine membranes. This subcellular fraction is particularly enriched in AMPA and NMDA receptors. We have obtained preliminary results in the PFC where after 2 h of treatment, KET appears to reverse an increase in the expression levels of NMDAR2A and NMDAR2B (2 subunits of NMDA receptor)in the FSL rats. Moreover, in FLS rats KET seems to decrease the phosphorylation levels of GluR1 in two phosphorylation sites and the expression of the GluR3 subunit

Conclusion: We expect that this project will shed light on to the mechanism by which KET works as a fast acting antidepressant. The understanding of the effect of KET on glutamate transmission will be important to clarify how antidepressant drugs modulate the glutamatergic system and it will open up new avenues for drug development acting on the glutamatergic system without the side effects of KET.

Poster 21

The role of Brain-derived neurotrophic factor (BDNF), early adverse events and physical exercise in severe mental disorders

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Background: The majority of patients with schizophrenia function at a cognitive level of at least one standard deviation below that of healthy comparison groups. Brain-derived neurotrophic factor (BDNF) is important for brain development and plasticity. Patients with psychosis have lower levels of BDNF in the brain, plasma, and serum, compared to the general population. The BDNF gene has at least one functional variant with a single nucleotide polymorphism (SNP; rs6265) resulting in a valine to methionine substitution at codon 66 of the proBDNF. The low activity methionine (met) variant is related to reduced BDNF release, at least in patients with schizophrenia. On the cellular level, both acute- and chronic high levels of stress exposure are linked to atrophy of dendrites and suppression of neurogenesis, possibly mediated by stress-based reductions in neurotrophic factors, including BDNF. Long-term chronic stress, such as a history of childhood trauma, could be related to lower BDNF levels in psychosis. Our data will contribute to new knowledge on the field of a combined genetic and environmental risk, on cognitive and brain abnormalities in severe mental disorders.

Physical exercise could potentially be a protective factor against reduced BDNF levels, and cognitive impairment in psychosis. Recent animal studies show that regular

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physical exercise improves cognitive function and increases Brain-derived neurotrophic factor (BDNF) levels in the brain. Thus, the role of physical exercise on cognitive function and BDNF levels in psychosis will be explored.

Objectives: Study aims; investigate in a group of patients with severe mental disorders: 1) The role of BDNF and childhood trauma on cognitive function and hippocampal subfields important for neurogenesis (the the CA2/3 and the CA4 DG); 2) investigate if regular physical exercise will be associated with better cognitive functioning and increased BDNF mRNA levels.

Methods: A total of 323 patients with a broad DSM-IV schizophrenia spectrum disorder or bipolar disorder (mean±age: 30.40±10.76; gender: 54% males; diagnosis: 56% schizophrenia spectrum) were recruited to the NORMENT, TOP research study. A history of childhood trauma was obtained using the Childhood Trauma Questionnaire. BDNF val66met and BDNF mRNA were analyzed using standardized procedures. A subsample of n=108 underwent MRI scanning, and the FreeSurfer was used to obtain measures of hippocampal subfield. Cognitive function was assessed through a comprehensive, standardized neuropsychological test battery. Physical exercise was measured as hours spent on any type of regular physical exercise per week.

Results: Additive effects were observed between a history of childhood trauma and BDNF val66met, in the direction of met carriers with high levels of childhood trauma having the lowest BDNF mRNA levels. Moreover, met carriers reporting high levels of childhood trauma had significantly reduced hippocampal subfield volumes of CA2/3 and CA4 dentate gyrus, as well as reduced cognitive function. Lastly, physical exercise was significantly associated with an increase of BDNF mRNA levels and improved cognitive function.

Conclusion: Our results need replication but underline the role of a BDNF – chronic stress pathway behind brain and cognitive abnormalities in psychosis. Our data also demonstrate that increased BDNF mRNA levels as a result of regular physical exercise are associated with improved cognitive function in patients with severe mental disorders. Thus, regular physical exercise could be a protective factor in psychosis.

Poster 22

Elevated levels of YKL-40 in patients with psychotic disorders

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Background: Psychotic disorders are associated with substantially decreased life expectancy (10-20 years) compared to the general population, with cardiovascular disease being one of the major causes for all these years of lost life. Cardiovascular research has shown that immune-mediated activity plays a central role in the pathophysiological mechanisms underlying atherosclerosis. Recent emerging evidence from genetic, epidemiological and clinical studies implicates the immune system in the pathophysiology of schizophrenia and bipolar disorder.

Objectives: The current study investigated whether plasma levels of YKL40, a glycoprotein involved in both neuroinflammation and cardiovascular disease, were elevated in individuals with psychotic disorders compared to age-matched healthy controls.

Methods: We included a total number of 1550 cases - 937 patients with a diagnosis of schizophrenia (SZ), bipolar disorder (BP) or psychosis not otherwise specified (PNOS) and 613 healthy controls. Plasma levels of YKL-40 and several cardiovascular risk factors (glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, CRP) were measured. In addition, smoking status current medication and BMI were recorded.

Results: There was a highly significant (p=2.42x10-10) increase in plasma levels of YKL-40 in patients (mean 47.32, SD±35.43) compared to healthy controls (mean 37.88, SD±23.90). There was no significant difference between the diagnostic sub-groups (mean SZ= 47.45, mean BP=48.55, mean PNOS=45.17). YKL-40 was positively correlated with glucose (p=0.005), total cholesterol (p=7.72 x10-11), LDL-cholesterol (p=1.00 x10-5), triglycerides (p=1.50 x10-11), hsCRP (p=2.06 x10-19), BMI (p= 3.00 x 10-5), age (p=2.97x10-10) and negatively correlated with HDL-cholesterol (p=0.042). We found no effect of gender, smoking status or antipsychotic medication. Even after adjusting for these significant confounders, the difference in plasma levels of YKL-40 remained significantly increased in patients with psychotic disorders (p=1.93x10-7).

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Conclusion: Our results show that patients with psychotic disorders have elevated levels of YKL-40, a marker of cardiovascular disease and endothelial dysfunction. This might imply that they face an additional risk for cardiovascular disease beyond the risk accounted for by overweight, dyslipidemia and environmental factors such as medication and smoking. YKL-40 could potentially be a valuable bio-marker in monitoring and assessing cardiovascular risk in patients with psychotic disorders.

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