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ABSTRACTS

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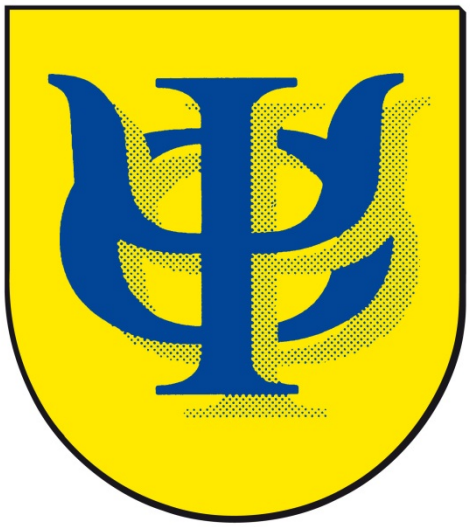

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ORAL PRESENTATIONS

LECTURE 1

SCNP 2017 OPENING LECTURE

L1 A perspective on ethical and practical aspects of forced treatment.

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Background: Forced treatment is an often overlooked reality in mental health provision. Given its ubiquity it must, for good or bad, be regarded as one of the treatment tools in psychiatry.

Objectives: In this lecture an overview is provided over the ethics of forced treatment. A practical review of aspects of forced treatment follows.

Methods: A reflection based on the literature on ethical and practical aspects of forced treatment.

Results: The two main ethical justifications for forced treatment are: a) a paternalistic view of the duty of the state (and doctors as its agents) to alleviate illness and control abnormal behaviour, b) the "harm principle", a duty to prevent risk to self and others. Forced treatment entails both involuntary admission and coercion while being admitted. Coercion under admission includes mechanical restraints, holds, rapid tranquillisation and other forced therapeutics as well as seclusion and other restrictions on liberty of movement. Data on different types of forced treatment is scarce but indicate widely varying practices. Recent changes in international circles indicate less tolerance towards forced treatment.

Conclusion: Highly variable practice exists within and between countries on the rates and types of forced treatment, indicating a field influenced more by culture and practice norms than science. Different forms of forced treatment hold different risks. A better therapeutic environment and adequate training of staff reduce the need for forced treatment, a purpose worth aiming towards.

SYMPOSIUM 1

UPDATE ON NEW DRUGS

S1.1 Guanfain - pharmacological profile and clinical use

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Abstract not available

S1.2 NMDA receptor modulators as possible treatments for CNS disorders

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Background: NMDA receptors are part of a family of glutmatate receptors expressed throughout the CNS. They serve as “co-incidence detectors” in the signaling between nerve cells, and are thus critically involved in fundamental neural processes, such as cognition and memory formation. Alterations in NMDA receptor function is associated with multiple psychiatric and neurological disorders, such as depression, schizophrenia, PTSD, pain, and stroke. While NMDA receptors have been a target of drug development for decades, due to the complexity of the receptor, and the multiple subtypes, there has been little success until recently. Currently, several NMDA receptor active drugs are in late phase development, and in clinical use. This presentation will discuss the profile of the currently tested drugs in the context of different indications.

S1.3 Recent advances in targeting α2-adrenergic receptors for new neuropsychiatric therapeutics

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Background: Alpha2-adrengeric receptors play a key role in modulating adrenergic neurotransmission both in the peripheral and central nervous system. Dysregulation of brain adrenergic function has been implicated in a variety of psychiatric disorders including major depression and schizophrenia. Indeed a number of neuropsychiatric drugs possess a significant adrenergic pharmacology (e.g. mirtazapine, asenapine, clozapine) thought to be involved in their mode of action. Whilst effective, these agents tend have limitations in terms of adverse effects due to broad pharmacology and alpha2

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adrenergic receptor subtype non-selectivity. Thus there is continued interest from a drug discovery perspective to identify molecules with better selectivity and in particular for the alpha2c adrenergic receptor.

Objectives: To determine if selective alpha2c antagonism is associated with potential for the treatment of a variety of neuropsychiatric symptoms.

Methods: Several animal models with predictive validity and translational approach were to used to investigate the neuropsychopharmacology of the alpha2C antagonist ORM-10921.

Results: ORM-10921 showed antidepressant-like and antipsychotic-like properties as well as improving memory related performance in several animal models. In addition evidence from combination treatment approach indicate it can bolster the effects of haloperidol in the social isolation reared rat model.

Conclusion: Selective alpha2C adrenergic receptor antagonism represents a promising approach for further clinical evaluation towards the treatment of symptoms associated with neuropsychiatric disorders.

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 14, as they are also presented as posters.

LECTURE 2

SCNP LECTURE

L2 Progressive neuroanatomical abnormalities in the psychoses and the impact of psychopharmacology

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There is evidence from cross sectional neuroimaging studies of psychotic disorders for an apparent differential effect of psychotropic medication, in that bipolar disorder patients taking lithium display grey matter increase compared to those not taking this medication, whereas cumulative antipsychotic medication is associated with greater grey matter deficit in patients with schizophrenia. There is a relative dearth of longitudinal neuroimaging studies to establish progression of brain abnormalities in schizophrenia or bipolar disorder, or indeed in patients with certain clinical characteristics, risk factors or medication exposure. This presentation will review progression of structural brain abnormalities in patients with psychotic disorders, discuss results of longitudinal sMRI studies and consider the impact that psychotropic medications usage plays in neuroanatomical deviations detected.

Longitudinal structural neuroimaging studies in Galway incorporating samples of first episode psychosis patients rescanned three years after initial presentation and patients with treatment resistant schizophrenia rescanned six months after commencing clozapine treatment support progression of neuroanatomical deviations. Patients with first episode psychosis demonstrated significantly reduced volume of white matter, increased right caudate and increased volume of the left lateral ventricle, which was associated with poorer quality of life scores. Patients with treatment resistant schizophrenia displayed significantly increased deficits of bilateral prefrontal cortex and the periventricular area over time, most prominent in younger patients.

As sample sizes have increased through collaborative efforts, evidence has accumulated for a grey matter thickening effect of lithium usage in bipolar disorder, in contrast to a cortical thinning with the use antipsychotic medication. However teasing apart potential confounders in observational studies, such as the impact of psychotic symptoms and illness severity is complex. Large scale longitudinal neuroimaging studies with repeated rich phenotyping will be required to clarify the dynamic nature of brain changes in psychosis and how differential psychotropic medication usage impacts upon brain structure and functioning.

LECTURE 3

SCNP LECTURE

L3 Erythropoietin to target cognitive impairment: key findings from studies in mood disorders and methodological implications

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Background: Cognitive dysfunction is an emerging treatment target in depression and bipolar disorder but

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there are no available cognition treatments with reliable, enduring effects. Impaired neuroplasticity is a putative neurobiological pathway underlying cognitive deficits and mood symptoms. Novel treatments with rapid and enduring effects on neuroplasticity such as erythropoietin (EPO) therefore hold great promise for targeting both cognition and mood symptoms in these patients.

Objectives: The present studies therefore aimed to assess the efficacy of EPO on cognitive impairment and mood symptoms in patients with treatment-resistant depression or bipolar disorder as well as the neurobiological underpinnings of potential beneficial effects.

Methods: We conducted two prospective randomized, double-blind, placebo-controlled clinical trials of the effects of eight weekly infusions of EPO (40,000 IU) (N=40) or saline (N=39) on cognitive deficits and mood symptoms in patients with treatment-resistant depression who were moderately depression or with bipolar disorder in remission. Cognition and mood symptoms were assessed at baseline (week 1), after treatment completion (week 9) and at follow-up (week 14). Functional and structural magnetic resonance imaging (MRI) assessments were conducted at weeks 1 and 14 to assess the underlying neuronal mechanisms of treatment-related improvements in cognition.

Results: Erythropoietin improved verbal memory, speed of complex cognitive processing across attention, memory and executive function and the recognition of happy facial expressions in comparison with saline. These effects occurred in the absence of change in mood symptoms and prevailed at the six weeks follow-up assessment after treatment completion. Structural MRI revealed that the EPO-associated memory improvement was mediated by reversal of subfield volume loss in the left hippocampus. In addition, fMRI showed that improvements of spatial memory and working memory in EPO-treated patients were accompanied by increase in task-related dorsolateral prefrontal and temporo-parietal activity as well as suppression of default mode network activity. Secondary analyses of the trial results revealed that patients with objectively-assessed cognitive impairments at baseline showed substantially greater chances of achieving treatment efficacy on cognition.

Conclusion: The findings highlight EPO as a promising candidate treatment for cognitive dysfunction in mood disorders. Putative neuronal underpinnings were structural increase in the left hippocampus and neural activity increase in dorsolateral prefrontal and temporo-parietal regions. Together, the findings provide novel evidence for potential circuitry-based biomarkers for therapeutic effects of cognition treatments in mood disorders. Further, the impact of baseline objectively-assessed cognitive impairments highlights a need to implement neuropsychological screening in future cognition trials to ensure enriched populations with greatest scope for improvements.

LECTURE 4

SCNP LECTURE

L4 Rapid acting antidepressant intervention: from ketamine to future strategies

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Depression is the leading cause of ill health and disability worldwide. According to the latest estimates from WHO, more than 300 million people are now living with depression, an increase of more than 18% between 2005 and 2015. Unfortunately, all current established therapeutic options for Major depressive disorder (and bipolar disorder), which primarily affects monoaminergic signalling, are associated with a substantial lag of onset prolonging distress and impairment for patients. Furthermore, their antidepressant efficacy is often variable and unpredictable. Importantly, Glutamate (which is the major excitatory neurotransmitter in the central nervous system) ,and its cognate receptors are implicated in the pathophysiology of the disorders, and currently target of the development of novel pharmacotherapeutics for the conditions. Specifically, the rapid and robust antidepressant effects of the N-methyl-d-aspartate (NMDA) antagonist ketamine, first clinically described in 2000, have gained attention. Since then, other glutamatergic candidates have been studied in MDD, with variable results.This presentation highlights many of these findings, and points to future avenues.

SYMPOSIUM 3

TREATMENT RESPONSES AND PATHOPHYSIOLOGY IN MOOD DISORDERS

S3.1 Biomarkers of lithium response

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This presentation will give the audience an overview of current efforts to identify biomarkers of response to lithium treatment in bipolar disorder (BD). First, I

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will present the work of the Consortium on Lithium Genetics (www.conligen.org) bringing together more than 20 centers from all over the world. This consortium recently published the largest genome-wide association study (GWAS) of response to lithium treatment, comprising 2,563 BD patients. A single locus of four linked SNPs (rs79663003, rs78015114, rs74795342, and rs75222709; minimum p=3.31E-09) met corrected genome-wide significance criteria for association with lithium response. In an independent prospective validation study in 73 patients treated with lithium monotherapy for a period of up to two years, carriers of the response-associated alleles showed a significantly longer time to relapse than carriers of the alternate alleles (p=0.03; OR=3.8). The associated region contains a long, non-coding RNA (lncRNA). Second, I will underscore how our approach of "friendly data sharing", honoring the invaluable efforts by all researchers involved, clinicians and basic scientists alike., has been pivotal for this first success in ConLiGen and how it will shape the next steps. Third, I will present in-depth analyses on a potential link between lithium response and genes involved in circadian rhythms. Finally, I will give talk about latest transcriptomic approaches that might help shed light on lithium's mechanism of action.

S3.2 Quinolinic acid and suicide

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Background: New evidence implies immune activity as a causal factor in severe psychiatric disorders, including depression and suicidal behavior. Our research points to the kynurenine pathway as a putative pathogenic link between the immune system and aberrant brain neurotransmission and psychiatric illness. In this pathway several neuroactive metabolites are produced: kynurenic acid (KYNA) is neuroprotective, astrocyte-derived, and blocks the N-methyl-D-aspartate (NMDA)-receptor and quinolinic acid (QUIN) is an excitotoxic N-methyl-D-aspartate receptor (NMDA) agonist, mainly produced by microglia. In the cerebrospinal fluid (CSF) of suicidal patients, levels of inflammatory cytokines and QUIN, are increased. The enzyme amino-β-carboxymuconate-semialdehyde-decarboxylase (ACMSD) limits QUIN formation by competitive production of the neuroprotective metabolite picolinic acid (PIC). Therefore, decreased ACMSD activity can lead to excess QUIN.

Objectives: We tested the hypothesis that deficient ACMSD activity underlies suicidal behavior by measuring PIC and QUIN in CSF and plasma samples from patients exhibiting suicidal behavior and healthy controls.

Methods: We used DSM-IV and the Montgomery-Åsberg Depression Rating Scale and Suicide Assessment Scale to assess behavioral changes and analyzed PIC and QUIN with GC/MS.

Results: Suicide attempters had reduced PIC and a decreased PIC/QUIN ratio in both CSF and blood. The reduction of CSF PIC sustained over 2 years after the suicide attempt. The minor C allele of the ACMSD SNP rs2121337 was more prevalent in suicide attempters and associated with increased CSF QUIN.

Conclusion: Taken together, our data suggest that increased QUIN levels may result from reduced activity of ACMSD in suicidal subjects. We conclude that measures of kynurenine metabolites can be explored as biomarkers of suicide risk, and that ACMSD is a potential therapeutic target in suicidal behavior.

S3.3 CSF GABA is reduced in first-episode psychosis and associates to symptom severity

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Growing evidence from genetic and post-mortem studies implicates an altered transmission of gamma-aminobutyric acid (GABA) as a significant component of schizophrenia pathophysiology. However, robust evidence from CSF studies of an involvement of GABA is still lacking. We here analyze CSF GABA, and four other amino acids, i.e. glutamate, glycine, taurine and tyrosine, with a sensitive HPLC analytical assay, in healthy volunteers (n=21) and well-characterized patients with first-episode psychosis (FEP; n=41), most of them drug-naïve to antipsychotic medication. We found lower CSF GABA concentration in FEP patients compared to the healthy volunteers, a condition that was unrelated to antipsychotic and/or anxiolytic medication. Moreover, lower CSF GABA levels were associated with total and general score of positive and negative syndrome scale (PANSS), illness severity and with poor performance in a test of attention. No differences in CSF glutamate, glycine, taurine or tyrosine were found between controls and patients. This study offers clinical in vivo evidence for a potential role of GABA in early-stage schizophrenia.

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SYMPOSIUM 4

RECENT NEW UPDATES ON ADHD AND AUTISM SPECTRUM DISORDERS

S4.1 ADHD in criminal offenders: short and long term effects of treatment

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Background: Despite high rates of ADHD among criminal offenders, effects of pharmacological treatment for ADHD, particularly the long-term effects, remain unclear.

Objectives: To evaluate efficacy, effectiveness, safety, and long-term outcome of treatment with osmotic-release oral system methylphenidate (OROS-MPH) in adult male imprisoned offenders with ADHD.

Methods: Within a Swedish high-security prison, a 52-week OROS-MPH trial was conducted in 30 adult male long-term prison inmates with ADHD and coexistent disorders (ClinicalTrials.gov: NCT0048231). Prospectively, the 25 trial completers were followed up clinically for three years post-trial. The OROS MPH trial consisted of an initial 5-week randomised, double-blind, placebo-controlled, fixed-dose (72 mg OROS-MPH daily) phase, followed by a 47-week open-label extension phase during which all 30 inmates received optimally titrated OROS-MPH (maximum of 1.3 mg/kg daily) alongside regularly provided offender treatment programs within prison. Primary outcome was change in ADHD symptoms after 5 weeks (observer-rated CAARS:O-SV). Secondary outcomes included self-reported ADHD symptoms, global severity, global functioning, cognition, motor activity, quality of life, and safety measures. Outcomes of the follow-up study included demographic data, ADHD symptoms, psychosocial functioning, substance misuse, and criminal reoffending.

Results: OROS-MPH was highly effective and safe overall in reducing ADHD symptoms, improving global and executive functioning and quality-of-life, both in the short-term (5 weeks) versus placebo (Cohen's d=2.17; NNT=1.1) and over 52 weeks when delivered as part of multimodal treatment. No misuse of ADHD medication or side abuse of other drugs was detected by repeated urine toxicology throughout the entire study period. The vast majority of participants attended and completed CBT-programs, educational activities and vocational training within the prison setting, aimed at reducing reoffending and increasing societal reintegration. Methylphenidate-related improvements in ADHD symptoms and psychosocial functioning obtained during the 52-week trial were maintained at 1- and 3-year-follow-ups. After 3 years, 75% of respondents had been released from prison, and two-thirds of these had employment, usually full time. In contrast, non-medicated respondents at 3-year follow-up (5/20), reported more ADHD symptoms, functional impairment and substance misuse compared with currently medicated (15/20). Further, 40% self-reported re-offending, indicating a substantially lower relapse rate than was expected (70-80%).

Conclusion: Although validation from new and larger samples is needed, these observations suggest that OROS-MPH could be useful as part of multimodal interventions for imprisoned offenders with ADHD, and that effects were maintained after four years of methylphenidate treatment. Overall, results imply that routines and collaboration to ensure continued motivation, support and treatment for ADHD are important and might reduce individual and societal injury from criminal (re)offending. Declaration of interests: This study was funded by the Swedish Ministry of Health and Social Affairs, and the Stockholm County Council, Sweden. Ylva Ginsberg has served as an investigator, consultant and/or speaker for Janssen, Novartis, Eli Lilly, HB Pharma and Shire; all outside the submitted work. Henrik Larsson has served as a speaker for Eli Lilly and Shire and has received research grants from Shire; all outside the submitted work. Niklas Långström has served as a speaker for Lundbeck; outside the submitted work. Nils Lindefors has no conflicts to declare.

S4.2 How to evaluate the treatment of ADHD in adults

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Background: During the last decade it has been an increasing rate of adults with ADHD referred for treatment in Norway similar to the other Nordic countries. The mainstay of therapy for ADHD in adults is medication, and it is a growing amount of evidence for efficacy of the centralstimulants including methylphenidate and amphetamine and the non-stimulant atomoxetine.

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Objectives: To clarify how to evaluate treatment, this session reviews the accumulating evidence, but also limitations such as how to generalize from short-time drug treatment for weeks in randomized placebo controlled trials into 'real-world' clinical practice.

Methods: Relevance of observational studies on effectiveness of long-term treatment is discussed, and exemplified by results from the lecturer's own longitudinal clinical study; adult ADHD patients (250) were treated with current ADHD-medication according to the national Norwegian guidelines. First line drug was methylphenidate, and second line was atomoxetine or dexamphetamine.

Results: At 12-months follow-up, results from repeated evaluations of the patients were analyzed. A majority (70%) continued on medication, and sustained improvement of symptoms and functioning were related to adherence to medication. Co-morbid mental disorders and side-effects were related to lower effectiveness and adherence, and 12% had interrupted their medication due to side-effects. Furthermore, this session discuss key points from the prevailing national and international guidelines for assessment and treatment of ADHD.

Conclusion: The question of how to evaluate medication includes relevant long-term outcomes, precautions, comorbidity, titration of dosage, and effects and side-effects of medication in a clinical setting.

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S4.3 Treatment and pathophysiology of Autism spectrum disorders

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Background: Autism spectrum disorders (ASDs) are characterized by impairments in social interaction and communication as well as by repetitive and restricted behaviors. Although ASD severely affects the life of approximately 1% of the population, no effective treatment is available. There is overwhelming evidence from twin and family studies for the importance of genetic factors in the development of autism. Recent genetic studies indicate that there are an extreme genetic heterogeneity among autism patients, including both highly penetrant mutations explaining about 20% of cases, and a polygenetic contribution explaining the majority of patients. About a hundred of specific genes have so far been proven to strongly contribute to the risk of autism. Initially, human genetic studies identified genes causing syndromes, like Fragile X (FMR1), Rett syndrome (MECP2) and Tuberous sclerosis (TSC1, TSC2), often co-occurring with autism, and more recently genes (e.g. NLGN3, SHANK3) strongly contributing to non-syndromic cases of autism. Although the discovered genes represent the underlying cause of autism only in a limited number of patients, they provide the first clues to the underlying neurobiology of autism and enable the possibility to develop animal models with constructive validity with potential to be used for drug screening. Hence, in the last decade a large number of mouse models for autism have been developed and a number of potential drugs and drug targets have been identified based on these models. In parallel and mainly independently of the genetic findings other promising treatment options, such as oxytocin and bumetanide, have emerged.

Objectives: The objectives are: 1) To give an update regarding genetic risk factors and recent potential pharmacological treatments for ASD, 2) To discuss the potential of using zebrafish as an animal model for autism and 3) To present our results from recent investigations of behavioral and neuronal effects of oxytocin in zebrafish and humans.

LECTURE 5

SCNP LECTURE

L5 Comparative efficacy and acceptability of anti-manic drugs in acute mania: a network meta-analysis

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Background: Conventional meta-analyses have shown inconsistent results for efficacy of pharmacological treatments for acute mania.

Objectives: We did a network meta-analysis, which accounted for both direct and indirect comparisons, to assess the effects of all anti-manic drugs.

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Methods: We systematically reviewed 68 randomised controlled trials (16,073 participants) from Jan 1, 1980, to Nov 25, 2010, which compared any of the following pharmacological drugs at therapeutic dose range for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. The main outcomes were the mean change on mania rating scales and the number of patients who dropped out of the allocated treatment at 3 weeks. Analysis was done by intention to treat.

Results: Haloperidol (standardised mean difference [SMD] -0·56 [95% CI -0·69 to -0·43]), risperidone (-0·50 [-0·63 to -0·38), olanzapine (-0·43 [-0·54 to -0·32], lithium (-0·37 [-0·63 to -0·11]), quetiapine (-0·37 [-0·51 to -0·23]), aripiprazole (-0·37 [-0·51 to -0·23]), carbamazepine (-0·36 [-0·60 to -0·11], asenapine (-0·30 [-0·53 to -0·07]), valproate (-0·20 [-0·37 to -0·04]), and ziprasidone (-0·20 [-0·37 to -0·03]) were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not. Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD -0·19 [95% CI -0·36 to -0·01]), quetiapine (-0·19 [-0·37 to 0·01]), aripiprazole (-0·19 [-0·36 to -0·02]), carbamazepine (-0·20 [-0·36 to -0·01]), asenapine (-0·26 [-0·52 to 0·01]), valproate (-0·36 [-0·56 to -0·15]), ziprasidone -0·36 [-0·56 to -0·15]), lamotrigine (-0·48 [-0·77 to -0·19]), topiramate (-0·63 [-0·84 to -0·43]), and gabapentin (-0·88 [-1·40 to -0·36]). Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Olanzapine, risperidone, and quetiapine led to significantly fewer discontinuations than did lithium, lamotrigine, placebo, topiramate, and gabapentin.

Conclusion: Overall, antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes. These results should be considered in the development of clinical practice guidelines.

SYMPOSIUM 5

EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR STIMULATION – A MOLECULAR TARGET RELEVANT FOR PSYCHIATRY

S5.1 Effects of glucagon-like peptide-1 (GLP-1) receptor stimulation on alcohol consumption in mice and non-human primates

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Background: Glucagon-like peptide-1 (GLP-1) is both an incretin gut hormone and a neurotransmitter, and GLP-1 analogues are used in treating type 2 diabetes. GLP-1 receptor agonists can also decrease alcohol drinking in rodents.

Objectives: One aim was to ascertain that GLP-1 analogues modulate the direct reinforcing effects of alcohol, rather than ingestive behaviors generally. A second aim was to test whether GLP-1 analogues can also decrease alcohol intake in primates.

Methods: We trained mice to self-administer alcohol intravenously, then tested the effect of acute pretreatment with the GLP-1 receptor agonist exenatide (Exendin-4, Bydureon©). Effect of exenatide on behavior reinforced by a palatable food was similarly evaluated. We also studied the effects of exenatide on alcohol drinking in 24 naturally alcohol-preferring vervet monkeys. Exenatide was administered once weekly for 6.5 weeks to obtain steady state levels, first in the absence of alcohol, then after monkeys resumed access to alcohol. We measured water and alcohol consumption, and plasma levels of exenatide.

Results: Intravenous alcohol functioned as a positive reinforcer in most mice, producing high alcohol intake. 3.2 µg/kg exenatide decreased intravenous alcohol intake by at least 70%, with no effect on food-maintained operant responding. In monkeys, exenatide significantly reduced alcohol consumption in the first half of the testing period, without signs of emesis.

Conclusion: GLP-1 receptor agonists can decrease voluntary alcohol intake by directly modulating the reinforcing effects of alcohol, in rodents and in primates. These findings support the potential usefulness of GLP-1 receptor agonists in the treatment of alcohol use disorder.

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S5.2 GLP-1 receptor agonists have a sustained stimulatory effect on corticosterone release after chronic treatment

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Background: Glucagon-like peptide-1 (GLP-1) receptor agonists are popular antidiabetic drugs with potent glucose-lowering effects and low risk of hypoglycemia. Interestingly, GLP-1 does not only serve as a glucose regulatory endocrine signal in the intestinal-pancreatic axis, but may have many additional physiological functions in the cardiovascular system and brain. GLP-1 is implicated in the regulation of multiple processes including food intake, memory formation, stress, anxiety, and depression.

Objectives: The aim of the current study was to examine behavioural and neuroendocrine changes in mice following acute and chronic treatment with exenatide and liraglutide.

Methods: We have studied the behavioural and neuro-endocrine effects of two GLP-1 R agonists, exenatide and liraglutide in mice.

Results: Both exenatide (1-20 µg/kg) and liraglutide (200-1200 µg/kg) decreased the glucose levels up to 30 % in freely fed animals. In glucaemically equipotent doses the drugs induced very similar acute behavioural and hormonal effects: there was no change on anxiety level or immobility time, however, both drugs suppressed motor activity and increased corticosterone levels. Two weeks of treatment with exenatide or liraglutide did not affect the anxiety level in a light-dark compartment test nor induce an antidepressant-like effect in the forced swim test in mice. Interestingly, hypolocomotion induced by the drugs in mice disappeared after chronic dosing. Both of the GLP-1 receptor agonists induced robust increases in corticosterone levels in mice under basal conditions as well as in the case of combination with swimming stress. Remarkably, exenatide was as potent a stimulator of corticosterone release after 2 weeks as after acute administration, demonstrating that tolerance does not develop towards this particular effect of GLP-1 agonists.

Conclusion: These findings raise questions in a clinical context, as increased HPA axis activity may potentially imply an increased risk for developing psychiatric disease and may offset the positive effect of these drugs on glucose homeostasis.

S5.3 The GLP-1 Analog Liraglutide Improves Glucose Tolerance and Reduces Body Weight in Schizophrenia Spectrum Disorder Patients Treated with Clozapine or Olanzapine

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Background: Compared to the background population, patients with schizophrenia have two-to-three-fold higher mortality rates, primarily caused by cardiovascular disease. So far, interventions designed to counteract antipsychotic-induced weight gain and cardiometabolic disturbances have had limited success.

Objectives: We investigated the effects of the GLP-1 analog liraglutide, 1.8 mg/day, in 103 overweight/obese patients with prediabetes and schizophrenia-spectrum disorders on stable treatment with clozapine or olanzapine. Primary endpoint was change in glucose tolerance.

Methods: A 16-week, randomized, placebo-controlled, double-blinded trial.

Results: The randomization (1:1) resulted in comparable groups. Drop-out rate was low and 97 participants were included in the effect analyses (age: 43±11 years; BMI: 34±6 kg/m2). Glucose tolerance improved with liraglutide (P<0.001) compared to no change with placebo (P=0.95) (between group P<0.001). Altogether, 63.8% of the liraglutide-treated participants developed normal glucose tolerance compared to 16.0% of the placebo-treated participants (P<0.001, number-needed-to-treat=2). Body weight

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decreased with liraglutide (-4.7±0.5 kg) and increased with placebo (+0.5±0.7 kg) (P<0.001). Reductions in waist circumference (-4.0±0.6 vs. +0.5±0.7 cm, P<0.001), systolic blood pressure (-1.4±2.0 vs. +1.1±1.8 mmHg, P=0.04), visceral fat (-315.8±75.3 vs. -24.0±41.7 g, P=0.02), and LDL-cholesterol (-0.4±0.08 vs. -0.06±0.05 mmol/l, P<0.001) were significantly greater with liraglutide compared to placebo. Adverse events with liraglutide were mainly gastrointestinal and serious adverse events were significantly lower in the liraglutide group (12 vs. 26%, P=0.04).

Conclusion: Liraglutide was well tolerated and significantly improved glucose tolerance, body weight and other cardiometabolic disturbances in clozapine- or olanzapine-treated patients with schizophrenia-spectrum disorders.

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POSTERS

Poster 1

Stroke severity in an animal model of depression and its potential treatment

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Background: When assessing stroke and depression in combination, it is primarily the functional stroke outcome related to depression status that has been investigated and not if pre-stroke depression, in addition to increasing the risk of stroke, also increases the infarct volume. Several studies indicated that antidepressants improve infarct volume and neurological outcome in animal stroke models. However, the effect of antidepressants on stroke outcome is mainly investigated in "pure" animal stroke models, instead of looking at the effect of antidepressant on rats subjected to both depression and stroke.

Objectives: This project aims to elucidate if depression symptoms can affect stroke infarct volume in rats and if antidepressants can reverse this effect.

Methods: Flinders Sensitive Line (FSL) rats will be used to model depression and Sprague Dawley rats will be used as controls. In the first study, stroke will be induced as a transient filament middle cerebral artery occlusion (MCAO) model with a 45-min occlusion and 48 h of reperfusion. The animals' locomotor asymmetry will be tested in a cylinder test and with a forelimb placing reaction. Following euthanasia, the brains will be cut in 2 mm slices, TTC-stained and immersed-fixed for infarct volume estimation. In a second study, we will evaluate if antidepressant treatment prior to stroke induction can reverse the potential increase in infarct volume in FSL rats.

Results: We hypothesize that infarct volumes will be increased in depressive-like rats compared to controls, and that antidepressant treatment prior to the stroke procedure can abolish this infarct volume increase.

Conclusion: Establishing a depression-stroke model in FSL rats enables further studies on the biological mechanisms underlying depression's effect on stroke risk. Additionally, the study may show if non-treated depressed patients with a high-risk of stroke should be given antidepressant treatment as a precaution, since it could potentially decrease the infarct volume during a stroke.

Poster 2

Vascular and mitochondrial support of synaptic plasticity in the hippocampus in a genetic rat model of depression after repeated electroconvulsive seizures

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Background: Electroconvulsive therapy (ECT) is the fastest acting and most efficient treatment of depression used in the clinic. However, the underlying mechanism of its therapeutic effect is still unclear.

Objectives: Here we investigated whether repeated electroconvulsive seizures (ECS), an animal model of ECT, induce synaptic plasticity and non-neuronal plasticity (vessels and mitochondria) accompanying by BDNF level changes.

Methods: ECS or sham treatment was given daily for 10 days to two rat strains: the Sprague–Dawley (SD) rats and the Flinders Sensitive and Resistant Line (FSL/FRL) rats (a genetic rat model of depression). Stereological principle was employed to quantify number of synapse and mitochondria, and density and length of microvessels. BDNF protein levels were evaluated with immunohistochemistry.

Results: Results showed lower number of synapses and mitochondria and concomitant smaller density and length of microvessels in the FSL-sham rats. After ECS treatment, the number of synapses and mitochondria, and density and length of microvessels significantly increased in the FSL-ECS rats. Nevertheless, the optical density of BDNF labeling used to estimate expression of BDNF protein showed significant increase in both FSL and FRL rats after ECS.

Conclusion: Our results indicate that the rapid and efficient therapeutic effect of ECS may be related to synaptic plasticity, accompanying by BDNF level elevation, mitochondrial and vascular support.

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Poster 3

Stress-resilient Rats and the Circadian System in the Chronic Mild Stress Model of Depression

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Background: It is frequently reported that disturbances of the circadian rhythm are observed in individuals suffering from depression. In contrast, the circadian rhythm of stress-resilient individuals is poorly investigated. This paper focuses on core components of the circadian system using a subgroup of stress-resilient rats from the chronic mild stress (CMS) model of depression.

Objectives: The primary objective of the study is to investigate the circadian system in stress-resilient rats of the CMS model and thereby gain insight into the etiology of depression.

Methods: After 3.5 weeks of CMS, groups of 8 stress-resilient rats and groups of 8 naïve control rats were decapitated at 3 different time points/zeitgeber time (ZT) (ZT2, ZT6, and ZT18, respectively). Prior to decapitation, the resilient phenotype was furthermore characterized by two behavioral tests, the open field (OF) test and the spontaneous alternation behavior (SAB) test. The levels of plasma melatonin and corticosterone were measured using immunoassays. Expression of core clock genes (Per1, Per2, and Bmal1) in liver and in brain tissue was quantified using quantitative real-time polymerase chain reaction (real-time qPCR) and in situ hybridization histochemistry, respectively.

Results: No significant differences were shown between groups neither in hormone levels nor in behavioral parameters scored in the OF test and in the SAB test. However, Per2 clock gene expression was affected by CMS, both in liver and in nucleus accumbens. Interestingly, Per2 alterations in resilient rats, in nucleus accumbens, associate with increased reward consumption.

Conclusion: Our study points to potentially promising candidate clock genes to be investigated in future studies aiming to clarify the role of clock genes in stress susceptibility and in major depression.

Poster 4

Intracellular and behavioral alterations following ketamine in a rat model of depression

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Background: Major Depressive Disorder is a severe and life-threatening disease with life a time prevalence of 17%. Only approximately 50% of the patients suffering from Major Depressive Disorder respond to conventional pharmacological treatment. In addition, traditional pharmacological treatment has a therapeutic delay of several weeks to months. Ketamine is a novel fast-acting antidepressant with potential to overcome several clinical challenges in the treatment of depression. Ketamine acts on numerous intracellular pathways of which activation of Mammalian Target of Rapamycin (mTOR), Akt and Erk may be of importance. Furthermore, a link between ketamine's mechanism of action and reversal of the pathological alterations of neuroinflammation induced depression is emerging.

Objectives: We wish to elucidate time-dependent signal transduction in the induction and maintenance underlying ketamines rapid antidepressant response and in the reversal of neuroinflammatory induced depression.

Methods: Sprague-Dawley rats were injected with sup-septic doses of LPS to induce depressive-like behavior, then treated with ketamine to reverse the neuroinflammatory induced behavioral alterations. Thirty minutes prior to ketamine, randomly selected animals were pretreated with inhibitors of several pathways associated with ketamines antidepressant response including mechanistic target of rapamycin (mTOR), Akt and Erk. To elucidate time-dependent signal transduction, behavioral assessment, including Open Field (OF) and Forced Swim Test (FST), was carried out at two different time points from ketamine injection: With a 1 hour delay and a 24 hour delay. Animals were then decapitated and hippocampus and PFC were harvested for Western Blotting. We quantified several proteins associated with synaptic plasticity and signal transduction.

Results: LPS increases immobility time in the FST. Ketamine reversed the behavioral alterations following LPS. Several inhibitors of signal transduction blocked ketamines antidepressant response: Rapamycin inhibited the reduction in immobility time 1 hour post ketmaine treatment, but not after 24 hours. In contrast, Akt inhibition did not inhibit ketamines antidepressant response after 1 hour, but completely blocked ketamine 24 hours post treatment. Similarly, we observed an increase of several synaptic proteins following ketamine treatment and a decrease following LPS.

Conclusion: We observed an increase in immobilyt time following LPS administration, suggesting neuroinflammatory induced depressive-like behavior. Furthermore, ketamine rapidly reversed the behavioral alterations. This effect was blocked by rapamycin,

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indicating mTOR activation as a requirement in the induction of ketamines antidepressant response, while Akt inhibition is required in the maintenance. Several synaptic proteins are associated with ketamines antidepressant response, but our findings suggest regional differences between hippocampus and PFC.

Poster 5

Effects of olanzapine long-acting formulation in mice

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Background: Schizophrenia is a debilitating mental disorder associated with great personal suffering and economic burden. The use of antipsychotics is essential in relieving symptoms, and today so-called atypical antipsychotics are in widespread use. Unfortunately, many of these drugs have a tendency to induce severe metabolic side effects, such as weight gain, dyslipidemia and deranged glucose metabolism. The molecular mechanisms underlying these adverse effects are to a large extent unknown. In order to investigate the biological basis further, the development of animal models is important. Antipsychotic agents have very short half-lives in rodents when administered orally or through injections of standard drug. We recently showed that intramuscular administration of the long-acting formulation of olanzapine in female rats resulted in clinically meaningful and stable plasma concentrations, accompanied by hyperphagia and weight gain. Since genetic models of schizophrenia may be more easily established in mice than in rats, it should be examined whether injection of long-acting olanzapine produces relevant dysmetabolic effects also in this species.

Objectives: To investigate the effects of olanzapine long-acting formulation in mice, mapping the metabolic phenotype at different drug doses.

Methods: In an initial experiment, female C57BL/6J mice (n=10 per group) received intramuscular injection(s) of 100 mg/kg olanzapine long-acting formulation or vehicle

Poster 6

Does stimulation of α7 nicotinic receptors alter NMDA receptor-mediated neurotoxicity in hippocampal cultures?

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Background: Cognitive deficits are seen in many neurological and neuropsychiatric diseases, including schizophrenia and Alzheimer's disease, and treating these deficits constitutes a major therapeutic goal. Many recent papers have described a role for α7 nicotinic acetylcholine receptors (α7 nAChRs) in hippocampal and cortical processes underlying cognition and cognitive enhancement; often involving glutamate receptors. The potential role of nAChRs in mediating glutamate excitotoxicity, however, is somewhat more controversial with reports of nAChRs being both neuroprotective and neurotoxic in certain systems.

Objectives: The aim of this study was to investigate the possible interaction between NMDA receptors and nicotinergic signaling systems via α7 nAChRs in vitro using organotypic hippocampal slice cultures (OHSCs).

Methods: OHSCs were prepared from P5/6 day old Sprague-Dawley rats and maintained for 13 days on semi-porous membrane inserts at 37°C. After confirming viability, slices were exposed for 4 hours to varying concentrations of NMDA and re-evaluated by propidium iodide exclusion after 24 hours in fresh media to construct toxicity-response curves. Two concentrations of NMDA in the low to medium range of the DRC (10 µM and 50 µM) were then co-administered with one of two concentrations of the α7 nAChR-selective agonist choline (or saline) alone or in combination with selective antagonists.

Results: Our results show that NMDA induces cellular injury in a concentration-dependent manner with the CA1 subfield being the region most sensitive to NMDA-mediated cell death. Co-administration of choline did not significantly alter NMDA toxicity. However, activation of α7 nAChRs by choline alone significantly increased cell damage as measured by PI uptake. This neurotoxic effect was inhibited by the administration of either the NMDA receptor antagonist CPP or the α7 nAChR antagonist methyllycaconitine.

Conclusion: Our results suggest that α7 nAChR activation does not alter NMDA receptor-mediated excitotoxicity in OHSCs, but that the neurotoxic effects of choline alone may be due to α7 nAChR-mediated glutamate release from either neurons or astrocytes, resulting in activation of NMDA receptors and neurotoxicity. If confirmed in vivo this would

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suggest that agonists of α7 nAChRs could enhance NMDAR-mediated processes (including cognition) at low concentrations but become neurotoxic at higher doses. With the α7 nAChR becoming an increasingly popular target for cognitive enhancement, further investigation of the contribution of α7 nAChRs to excitotoxicity and neuropathology is warranted.

Poster 7

A naturalistic study of antipsychotic-associated side effects

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Background: Antipsychotic-associated side effects represent a significant treatment challenge. RCTs are important for knowledge of these effects, but complementary descriptions of their extent in naturalistic settings are necessary.

Objectives: We aimed to investigate the occurrence of various side effects of antipsychotics in a large naturalistic sample, taking polypharmacy and patient characteristics into account.

Methods: We included 1087 patients with psychotic disorders with assessment of clinical and pharmacological data. Side effects were assessed using the UKU side effect rating scale, and statistical analyses were performed controlling for confounding factors.

Results: Side effects were present in 77.8% of the patients. Use of antipsychotics showed significant associations with both total and specific side effects, including neurologic and sexual symptoms, sedation and weight gain. More side effects were observed in patients using several antipsychotics, with increasing total dose and with antipsychotics in combinations with other psychotropic drugs. Female patients were more likely to report side effects than males, and age influenced occurrence for several symptoms.

Conclusion: Our study shows that patients with psychotic disorders on stable medication have a high occurrence of antipsychotic-associated side effects. Considering polypharmacy and patients characteristics for medical treatment evaluation is important.

Poster 8

Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after critical illness

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Background: Critical illness is associated with higher risk of depression and anxiety. Critical and mental illness may be linked by systemic inflammation.

Objectives: To examine the impact of pre-admission use of statins, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or a combination of these on risk of depression and anxiety after intensive care requiring mechanical ventilation.

Methods: Propensity score matched registry-based cohort study including mechanically ventilated patients in Danish intensive care units during 2005-2013. We excluded patients with a diagnosis of depression or anxiety or a prescription for an antidepressant or anxiolytic a year prior to admission. Use of statins, NSAIDs, glucocorticoids, or combinations was identified from prescriptions. We computed cumulative incidence and risk ratio of depression and anxiety.

Results: We included 48,207 intensive care unit patients, which after propensity score matching yielded 6,088 statin user pairs, 2,886 NSAID user pairs, 1,440 glucocorticoid user pairs and 1,743 combination drug user pairs. The cumulative incidence of anxiety and depression three years after intensive care was between 17.4% and 21.3% and similar in non-users compared with users within each drug group. The risk ratio of depression and anxiety three years after admission was 1.04 (95% CI 0.96-1.13) for statin users, 1.00 (95% CI 0.90-1.11) for NSAID users, 0.97 (95% CI 0.82-1.14) for glucocorticoid users and 1.05 (95% CI 0.90-1.21) for combination users, compared with non-users.

Conclusion: Approximately a fifth of mechanically ventilated patients in an intensive care unit had a depression or anxiety disorder within three years following admission. Preadmission use of statins,

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NSAIDs, glucocorticoids or combinations of these drugs did not alter the risk.

Poster 9

Inflammatory markers are altered in severe mental disorders independent of comorbid cardiometabolic disease risk factors

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Background: Inflammation has been implicated in the pathogenesis of severe mental disorders and cardiovascular disease (CVD). Despite the high level of comorbidity, many studies of inflammation in severe mental disorders have not systematically taken cardiometabolic risk factors into account.

Aim. We aimed to disentangle inflammation related to cardiometabolic risk factors from severe mental disorders in a large, well-characterized cohort with robust and novel inflammatory markers reflecting different aspects of the immune system.

Methods. We measured levels of the CVD-related inflammatory markers CXCL16, soluble interleukin-2 receptor (sIL-2R), soluble CD14 (sCD14), macrophage inhibitory factor (MIF) and activated leukocyte cell adhesion molecule (ALCAM) in 992 patients with severe mental disorders including schizophrenia (SCZ) and affective (AFF) disorders, and in 675 healthy controls (HC), in addition to cardiometabolic risk factors (blood lipids, body mass index and glucose). We investigated inflammatory markers in patients compared to HC, before and after controlling for comorbid cardiometabolic risk factors.

Results. Levels of CXCL16 (p=0.03) and sIL-2R (p=7.8x10-5) were higher, while sCD14 (p=0.05) were lower in patients compared to HC after controlling for confounders, with biggest effects in the SCZ group for CXCL16 (p=0.04) and sIL-2R (p=1.1x10-5). After additional adjustment for cardiometabolic risk factors, higher levels of sIL-2R (p=0.001) and lower sCD14 (p=0.002) persisted, also in the SCZ group (sIL-2R, p=3.0x10-4 and sCD14, p=0.01). This adjustment also revealed lower ALCAM levels (p=0.03) in patients.

Conclusion. The results indicate that inflammation and in particular enhanced T-cell activation and possible impaired monocyte activation may have a role in severe mental disorders independent of comorbid cardiometabolic risk factors. Experimental studies are needed to identify the underlying inflammatory disease mechanisms.

Poster 10

Dose-dependent Social-cognitive Effects of Intranasal Oxytocin Delivered with Novel Breath Powered Device in Adults with Autism Spectrum Disorder: A Randomized Placebo-controlled Double-blind Crossover Trial

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Background: The neuropeptide oxytocin has shown promise as a treatment for symptoms of autism spectrum disorders (ASD). However, research progress has been hampered by a poor understanding of oxytocin's dose-response and sub-optimal intranasal delivery methods.

Objectives: The aim of this trial was to investigate the oxytocin dose-response to social-cognition task performance in ASD using a novel Breath Powered

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intranasal delivery device designed to improve direct nose-to-brain activity.

Methods: We examined two doses of oxytocin delivered using the Breath Powered device designed in a pre-registered, double-blind, crossover, randomized, placebo controlled trial. In a randomized sequence of single-administration sessions, 17 male adults with ASD received 8 international units (IU) of oxytocin, 24 IU oxytocin, or placebo followed by social-cognitive tasks.

Results: We observed a main effect of treatment on the primary outcome measure of emotion salience as measured by emotional ratings of faces (F=3.49, p=0.04), which was associated with a large effect size (eta squared=0.18). Posthoc tests (adjusted for multiple comparisons) revealed that compared to placebo, 8IU treatment increased emotion salience (p=0.02, d=0.63). There was no significant increase after 24IU treatment (p=0.12, d=0.4). Effects after 8IU oxytocin were observed despite no significant increase in peripheral blood plasma oxytocin concentrations (p=0.45).

Conclusion: This is the first trial to assess the dose-dependent effects of a single oxytocin administration in ASD, with results indicating that a low dose of oxytocin can significantly modulate emotion salience despite minimal systemic exposure. The data provide further support that oxytocin treatment may help ameliorate a core ASD feature.

Poster 11

Bromodomain containing 1 (BRD1) in psychiatric disorders: From genetic association to disease biology using brain transcriptomic profiling in genetically modified (Brd1+/-) mice

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Background: Post-translational modifications of histones are important in the pathophysiology of psychiatric disorders. Whereas histone acetyltransferases and deacetylases have been extensively explored as drug targets, less research has looked into readers of the histone code. Bromodomain-containing proteins serve as scaffolds in histone-, and chromatin modifying complexes and evidence supports their implication in neurodevelopmental disorders. Particularly, Bromodomain containing 1 (BRD1) has repeatedly shown genetic association with both schizophrenia and bipolar disorder and its interactome is significantly enriched with components implicated in neurodevelopment and mental illness.

Objectives: Through application of functional genomics and bioinformatics, we attempt to bridge the gap between genetic association and pathogenic effects.

Methods: We used a reporter assay to measure the transcriptional drive of a BRD1 risk variant in vitro. Accordingly, we generated a genetically modified Brd1+/- mouse to examine the effects of reduced Brd1 expression in an extensive behavioral screening followed by functional and integrative genomic analyses.

Results: Underlining the importance of BRD1 in mental health, hampered Brd1 expression manifest as general and sex-specific behavioural-, elecrophysiological-, brain morphometric-, and neurochemical deficits with broad translational relevance to psychiatric disorders. Supported by extensive transcriptomic profiling of multiple brain tissues in Brd1+/- mice, we provide novel evidence that links BRD1's function to nuclear receptor mediated signalling.

Conclusion: Our data support a model in which BRD1 acts as a regulatory hub protein in the developing-, and mature brain by facilitating the genomic actions of nuclear receptors. In light of the established link between i.e. vitamin D defieciency, hypothyroidism and mental illnesses, our findings may have implications in the treatment of psychiatric disorders and their gender-biased symptom profiles.

Poster 12

The effect of probiotics on mania-like behavior: a behavioral study in a mouse model of mania

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Background: According to the World Health Organization Bipolar Disorder (BD) is the 8th leading cause to Years Lost due to Disability with a lifetime prevalence of 1-2 %. The development of an endophenotypical mouse model of mania, the CLOCKΔ19-mouse, has made it possible to elucidate the neurobiology behind the disease. Several lines of evidence associate a dysregulated immune response and a low-grade inflammation with BD, especially in episodes of mania. Combined with recent work, which has proposed a bi-directional communication between the gut and the brain, the idea of probiotics working on BD has emerged.

Objectives: The aim of the current study is to investigate the effect of probiotics on the mania-like behavior seen in the CLOCKΔ19 model of mania.

Methods: The knockout CLOCK mice (KO) and their wildtype littermates (WT) will be randomly distributed into four groups. Two of the groups, one WT group and one KO group will be administered probiotics in their drinking water from the 5th to the 8th week of their life. The other two groups will be used as controls. Afterward they will be subjected to behavioral testing.

Results: Data collection is still ongoing. Preliminary data available in autumn 2017.

Conclusion: The results provided by this study are expected to help elucidate the role of the gut-brain axis in psychiatric diseases, especially BD. It will provide a better understanding of the neurobiological foundation for BD and give insight into how probiotics can influence health and behavior in BD patients.

Poster 13

The novel atypical antipsychotic drug brexpiprazole, alone and in combination with escitalopram, facilitates prefrontal glutamatergic transmission via a dopamine D1 receptor-dependent mechanism

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Background: Brexpiprazole (Rexulti®), an atypical antipsychotic drug (APD), has been approved for treatment of adult schizophrenia and as adjunct therapy for adults with major depressive disorder (MDD). Brexpiprazole is a partial agonist at both D2/3 and 5-HT1A-receptors (R), and a potent antagonist at the 5-HT2AR [1]. Given the significance of NMDARs and D1Rs for optimal cognitive functioning [2], facilitation of NMDAR-mediated synaptic transmission in the prefrontal cortex (PFC) may significantly contribute to ameliorate cognitive impairments in both schizophrenia and in depression. Furthermore, clinical studies show that low doses of APDs may augment the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) and reduce the time of onset. Preclinical studies indicate that the rapid and potent antidepressant effect of e.g. ketamine is critically dependent on AMPAR activation in the rat medial PFC (mPFC) with a subsequent facilitation of glutamatergic synaptic transmission [3].

Methods: Intracellular single-cell recording techniques were used in pyramidal cells in layer V/VI of the mPFC in slice preparations from rat brain.

Results: Clinically relevant concentrations of brexpiprazole facilitated NMDA-induced currents (maximal effect at 10 nM). The combination of low, by themselves ineffective concentrations of brexpiprazole and escitalopram, significantly enhanced the NMDA-induced current, an effect that was at least partly mediated via D1Rs, since the effect was blocked by the D1R antagonist SCH23390. Brexpiprazole alone (3-100 nM) had no effect on AMPA-induced currents. However, in combination with a low, subeffective concentration of escitalopram, a significantly enhanced AMPA-induced current was seen. This enhancement was also D1R dependent. Brexpiprazole (10 and 30 nM) facilitated the electrically evoked EPSP, an effect blocked by the selective NMDAR antagonist APV. Whereas neither brexpiprazole 3 nM nor escitalopram 3 nM given alone had any effect, the combination enhanced electrically evoked EPSPs.

Conclusions: Our results show that brexpiprazole facilitates glutamatergic, NMDAR-mediated transmission in the rat mPFC. Moreover, brexpiprazole added to an SSRI potentiated both AMPAR- and NMDAR-mediated transmission, and also electrically evoked EPSPs in the rat mPFC. These mechanisms may significantly contribute to the potent antidepressant effect of brexpiprazole when added to SSRIs in poorly responding patients. The enhanced effect on AMPA-induced currents is similar to that of ketamine and other drugs or drug

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combinations generating a rapid and potent antidepressant effect [4,5] and may thus contribute to the analogous effect of brexpiprazole in combination with SSRIs. Given the complex pharmacological profile of brexpiprazole, the specific mechanisms mediating the facilitation of glutamatergic transmission remain to be completely understood. However, D1R activation alone may not be sufficient to generate the facilitated AMPAR-mediated transmission, as previous studies indicate that also enhanced serotonergic activity and activation of 5-HT1A receptors may be needed. These novel data strongly support a cognitive-enhancing effect of brexpiprazole in both schizophrenia and depression as well as its utility as adjunctive treatment in MDD patients poorly responding to SSRIs.

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Poster 14

Afferent projections of GPR151-expressing neurons

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Background: The habenula is a phylogenetically well-preserved brain structure, which links several frontolimbic brain structures with monoaminergic brainstem nuclei. Thus from an anatomical standpoint, habenula seems to be ideally positioned for regulating emotional behavior. Postmortem and fMRI studies have shown habenular alterations in patients with major depressive disorder. GPR151 is a newly discovered G protein-coupled receptor (with a yet unknown ligand) that is highly expressed in the habenula. Specific ablation of GPR151-expressing neurons was recently shown to affect several behaviors associated with depression. To further elucidate the role of GPR151 in habenular function, we have characterized the afferent projections to GPR151-expressing neurons. Using pseudotyped rabies virus in a transgenic GPR151-Cre mouse line, monosynaptic afferents of GPR151-expressing habenular neurons were primarily detected in basal forebrain structures such as the entopeduncular nucleus, the lateral preoptic area and the lateral hypothalamic area. Interestingly, we found that GPR151 neurons in the neighboring paraventricular nucleus of thalamus receive input from other, primarily medial hypothalamic, areas. The novel in situ hybridization technique RNAscope was used to verify that Cre expression in the transgenic mice was indeed limited to GPR151-expressing cells. In conclusion, we have characterized the afferent connectivity of a diencephalic neuronal population defined by GPR151 expression. Future studies will include optogenetic modulation of GPR151 neurons and behavioral studies of GPR151 knock out mice. Potentially, this "orphan" receptor may play a role in the modulation of affective behavior, and thereby serve as an interesting target for future antidepressant drug development.

Poster 15

Rapid augmentation of antipsychotic drugs by sodium nitroprusside (SNP). Behavioral assessment and effect on brain dopaminergic transmission in rats.

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Background: Recently, a single injection of the nitric oxide donor sodium nitroprusside (SNP) was found to induce a rapid (within 4 hours) and sustained (several weeks) antipsychotic effect in treatment-resistant schizophrenic patients (Hallak et al. 2013). Moreover, a single injection of SNP was found produce a prolonged block of the psychotomimetic effects of phencyclidine or ketamine in rats that lasts for at least a week (Maia-de-Oliveira et al. 2015), as well as to generate both rapid and persisting changes in brain synaptic plasticity, including enhanced excitatory postsynaptic current (EPSC) responses and spine morphology in layer V pyramidal cells in rat medial prefrontal cortex (mPFC) brain slices (Liu et al. 2015).

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Objectives: The aim of this study was to find out if SNP could enhance the antipscyhotic effect of a sub-effective dose of risperidone in rats. Furthermore, we wanted to find out if SNP enahnced the risperidone-induced dopamine output in the mPFC and nucleus accumben

Methods: We used the conditioned avoidance response (CAR) test to investigate the antipsychotic-like efficacy, since this behavioral assay has shown a very high predictive validity to identify drugs with clinical antipsychotic activity, and in vivo microdialysis in freely moving animals to measure neurotransmitter efflux in the mPFC and the NAc, respectively.

Results: RISP 0.25 mg/kg i.p. caused when given alone only 20% suppression of CAR, which is far below the degree of CAR suppression required to indicate a significant clinical antipsychotic effect, which is 70-80%. Addition of SNP 1, 1.5 and 2 mg/kg i.p. to RISP dramatically enhanced the antipsychotic-like effect to 67, 86 and 100% CAR suppression, respectively, albeit addition of the highest dose of SNP, i.e. 2 mg/kg, resulted in escape failures indicating risk of non-specific side effects. SNP 2 mg/kg given alone generated only a small (11%) and clinically irrelevant CAR suppression. In the NAc, addition of SNP 1 mg/kg did not enhance the risperidone-induced dopamine output. In the mPFC on the other hand, addition of SNP 1 mg/kg significantly enhanced the risperidone-induced dopamine output.

Conclusion: The present preclinical results support the clinical observation that a single injection of SNP can rapidly and dramatically augment the clinical efficacy of antipsychotic drugs in schizophrenia, albeit within a relatively narrow dose-range. That a single injection of SNP alone was not found to exert any clinically relevant suppression of CAR makes it similar to other drugs that both clinically and preclinically have been shown to augment the antipsychotic effect of various neuroleptics, thus a major advantage of SNP over these compounds is the long-lasting augmentation generated by single exposure to the NO-donor. The antipsychotic effect of SNP seems to be achieved by enhanced prefrontal dopamine output and, via D1-R activation, facilitation of NMDA receptor-mediated transmission in the same brain region (Marcus et al. 2012). This mechanism of action may also be applicable for SNP, as we found that SNP selectively increased risperidone-induced prefrontal dopamine release, while not increasing risperidone-induced dopamine release in the NAc. Our results might imply that the very rapid and potent augmentation of the antipsychotic-like effect of risperidone by a single, low dose of SNP may be related to acute changes in brain synaptic function and morphology in pyramidal cells in the mPFC as previously described after a single high dose of SNP (Liu et al. 2015), and that the corresponding effects of the low dose may be potentiated by the concomitant administration of an antipsychotic drug. In this manner, both drugs could be administered in a low dose to patients, reducing the risk of side effects.

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ABOUT SCNP

At the XII meeting of the Nordic Psychiatric Congress in Copenhagen in 1958, the subcommittee on psychopharmacology had discussed the perspective of a Scandinavian Society of Psychopharmacology. Parallel with this initiative, the executive of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) contacted the Scandinavian colleagues about establishing a Scandinavian section of the CINP. It was the marked rise in psychotropic drugs in the 1950s (chlorpromazine and imipramine in Europe and the monoamine oxidase inhibitors in United States of America) that resulted in the birth of CINP in 1958.

On 5 February 1960, the SCNP was established with Arvid Carlsson (Sweden) as the Founding President and Jørgen Ravn (Denmark) as the Founding Secretary. Other board members were Erik Jacobsen (Denmark) and David H. Ingvar (Sweden). Present at this meeting were also (among others) Odd Lingjærde (Norway), Gunnar Lundqvist (Sweden), Carl-Gerhard Gottfries (Sweden), Asser Stenbäck (Finland), and Mogens Schou (Denmark) while Paul Kielholz from Switzerland was one of the guests from the Continent.

One of the major goals for establishing the SCNP was the standardisation of clinical trials with psychotropic drugs in Scandinavia.

The 1961 meeting was the first ordinary congress of the College. The board was elected at this meeting by the general assembly with Gunnar Lundqvist (Sweden) as the President and Jørgen Ravn (Denmark) as the Secretary. The other members of the board were Arvid Carlsson (Sweden), Erik Jacobsen (Denmark), and Tollak Sirnes (Norway). Since then, the SCNP has held annual congresses. Until 2009, the scientific contributions were all published in the Nordic Journal of Psychiatry. Starting in 2013, the abstracts from the SCNP congresses were published in Acta Neuropsychiatrica, the official journal of the SCNP.

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