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ABSTRACTS

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ORAL PRESENTATIONS

LECTURE 1

SCNP 2018 OPENING LECTURE

L1 Predicting treatment response in depression

Thomas Frodl

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Background: Major depressive disorder is one of the leading causes of disability in the world since depression is highly frequent and causes a strong burden. In order to reduce the duration of depressive episodes, clinicians would need to choose the most effective therapy for each individual right away.

Objectives: A prerequisite for this would be to have biomarkers at hand that would predict which individual would benefit from which kind of therapy (for example, pharmacotherapy or psychotherapy) or even from which kind of antidepressant class.

Methods: Literature overview and presentation of own research

Results: In the past, neuroimaging, electroencephalogram, genetic, proteomic, and inflammation markers have been under investigation for their utility to predict targeted therapies. The present overview demonstrates recent advances in all of these different methodological areas and concludes that these approaches are promising but also that the aim to have such a marker available has not yet been reached. For example, the integration of markers from different systems needs to be achieved.

Conclusion: With ongoing advances in the accuracy of sensing techniques and improvement of modelling approaches, this challenge might be achievable.

SYMPOSIUM 1

DRUGS IN THE PIPELINE

S1.1 Avenues for new antidepressants

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Abstract not available

S1.2

New Strategies in the Treatment of Psychosis and related disorders

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Background: Lurasidone is an atypical antipsychotic with a high affinity for 5-HT7, 5-HT2A and D2 receptors. It is licensed in Europe for the treatment of schizophrenia in adults and it is likely that its antipsychotic effects are mediated through a combination of D2 and 5-HT2A receptors, although the mechanism of action is unclear.

Objectives: Less is known about the role of the 5-HT7 receptor.

Methods: Preclinical data suggests that lurasidone improves cognition in a model of glutamate hypofunction in rodents, which is mediated through the 5-HT7 receptor. In a 6-week, acute-phase clinical study in schizophrenia patients, followed by 6 month flexible dose extension, secondary analyses suggested a significant effect of lurasidone on cognition. The 5-HT7 receptor is found in high levels in the suprachiasmatic nucleus, an area associated with circadian rhythms, and pharmacological manipulation of this receptor can modulate in vitro and in vivo diurnal activity in rodents. In preclinical models lurasidone demonstrated an 'antidepressant-like' profile which is mediated through the 5-HT7 receptor.

Results: In clinical trials, a pooled analysis of schizophrenia patients also showed a decrease in the symptoms of depression. In 2 short term trials in patients with bipolar depression, lurasidone, as monotherapy and adjunctive to mood stabilisers, also demonstrated a decrease in depressive symptoms.

Conclusion: More research is required to define the precise role of the 5-HT7 receptor in psychiatric disorders.

S1.3 Finding cognitive enhancers: A translational approach focusing on enhancing cyclic nucleotide signaling

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Background: Cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) have been suggested to play specific roles in processes of memory. These cyclic nucleotides are

hydrolyzed by specific enzymes, i.e. phosphodiesterases (PDEs). Thus, selective PDE inhibitors preventing the breakdown of cAMP and/or cGMP could improve memory. An alternative approach is to increase their synthesis via stimulation or activation of adenylate or guanylate cyclases, respectively.

Objectives: To present the latest results of specific PDE inhibitors and cyclase stimulators on cognitive processes and discuss its implications for finding and testing new cognition enhancers.

Methods: Behavioral and in vitro (long-term potentiation) studies with rodents and neuropsychological testing of human subjects.

Results: Studies with different timing of treatment with specific PDE inhibitors indicated that distinct underlying signaling pathways for early and late consolidation processes exist corresponding to specific time-windows for memory consolidation into long-term memory. Most likely the underlying mechanisms are a cGMP/PKG pathway for early consolidation processes and a cAMP/PKA pathway for late consolidation processes. In addition, the early-phase cGMP/PKG signaling actually requires late-phase cAMP/PKA-signaling in long-term memory formation. Further, it was shown that elevation of central cGMP levels or cAMP levels after treatment with a specific PDE inhibitor both improve acquisition processes/short-term memory. In vitro studying the effects of PDE inhibitors on long-term potentiation, the physiological substrate of memory, support the in vivo data and further show that AMPA receptor trafficking very likely mediates the memory enhancing effects. In a translational approach we also investigated the effects of cGMP elevation via PDE5 inhibition with vardenafil or sildenafil on cognition in humans. However, in contrast to studies with rodents and monkeys, PDE5 inhibition had no effect in humans on cognition including memory processes. Likewise, an alternative approach stimulating soluble guanylate cyclase to increase cGMP levels, improved memory in rodents, yet not in humans. Thus, it is clear that the transition of a drug from preclinical to clinical creates translational hurdles. Nevertheless, based on the expression patterns of its isoforms in the brain, PDE4, which is cAMP specific, appears more interesting for CNS targeting than PDE5. Indeed we found that a low dose of the PDE inhibitor roflumilast clearly improved cognition in humans. Interestingly, this pro-cognitive effect was not associated with emetic side effects (nausea, vomiting), which are commonly associated with PDE4 inhibition.

Conclusion: It can be concluded that inhibiting PDEs or stimulating cyclases can be considered as an interesting target to improve cognition, despite translational hurdles. In particular, we suggest that the future for disease-specific PDE4 enzyme inhibition lies in the development of PDE4 isoform-specific inhibitors without emetic effects.

S1.4 Nasal administration of Esketamine - a promising new antidepressant

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Major depressive disorder (MDD) is considered a large health concern, and one third have a treatment-resistant depression (TRD). This has consequences for the affected individual, and is associated with a significant economic burden on our society. Despite the large public health impact, the there are few new major breakthroughs in pharmacological agents since the introduction of selective serotonin reuptake inhibitors in the 1980's. The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has emerged as a promising therapeutic agent, with intravenous (IV) administration demonstrating rapid antidepressant effects and striking response rates.

Recently the results from the first clinical trial of intranasal esketamine, which is the more potent S-enantiomer of ketamine, as adjunctive to antidepressants in TRD was reported (Daly et al, 2017). The study was a randomized, double-blind trial including 67 participants with TRD, who continued their existing antidepressant treatment. The results show that twice weekly administration of esketamine has a significant effect on depressive symptoms (MADRS) as early as 1 week of treatment. Another interesting aspect of the study was the use of intranasal drug delivery, which is receiving increasing attention in psychiatry (Quintana et al. 2016). The previous findings of antidepressant effect are mainly based on IV administration . This limits the use of Esketamine in outpatient clinics and primary care. Intranasal administration also increases bioavailability compared to oral administration, due to the avoidance of first pass liver metabolism.

Ref:

Daly EJ, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: Results of a Double-Blind, Doubly-Randomized, Placebo-Controlled Study. JAMA Psychiatry. 2017.

Quintana DS, et al. The promise and pitfalls of intranasally administering psychopharmacological agents for the treatment of psychiatric disorders. Mol Psychiatry. 2016;21(1):29-38.

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.

LECTURE 2

SCNP LECTURE

L2 What - if anything - can we learn from pre-clinical trials without replication?

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Background: Few drugs are developed without some background in pre-clinical research.

Objectives: Demonstration of a biological effect in a single study - even if that study is perfectly designed and adequately powered - gives no guarantee that the biological effect is sufficiently widespread to make it an attractive target for drug development.

Methods: Failures of attempts to replicate pivotal pre-clinical findings should not in my view be considered a "failure".

Results: Rather, they may be due to the influence of latent "nuisance" variables, and research to better understand the nature and influence of these may illuminate hitherto unrecognised biological phenomena.

Conclusion: The challenge then is to ensure, as best we can, that our work is perfectly designed and adequately powered; to seek to demonstrate the existence of biological effects under a range of circumstances; and where there are unexplained differences in the manifestations of these effects to conduct further research - which may involve multicentre studies - to understand reasons for this heterogeneity

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LECTURE 3

SCNP LECTURE

L3 Efficacy of SSRIs in depression revisited

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Abstract not available

LECTURE 4

SCNP LECTURE

L4 The mechanisms behind Glutamatergic antidepressants in depression

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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

PSYCHOSIS, IMPLICATIONS FOR DIAGNOSIS AND INTERVENTION

S3.1 PANSS-6: A new brief rating scale for both research and clinical care in schizophrenia

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The 30-item Positive and Negative Syndrome Scale (PANSS-30) is the most widely used measure of the severity of schizophrenia and related psychotic disorders in clinical studies. However, PANSS-30 is rarely used in routine clinical care because it is too time consuming to administer. Therefore, researchers and clinicians have called for the development of a shorter schizophrenia symptom rating scale. A shorter scale would allow for use of the same measure in research and clinical care, which would facilitate the translation of research results into clinical care and help pave the way for measurement-based care of schizophrenia. We recently demonstrated in acutely exacerbated schizophrenia that a six-item version of PANSS (PANSS-6: P1=Delusions, P2=Conceptual disorganization, P3=Hallucinations, N1=Blunted Affect, N4=Social withdrawal, N6=Lack of spontaneity/flow of conversation) was scalable (all items provide unique information regarding syndrome severity) and able to separate the effect of antipsychotics from placebo. PANSS-30 was not scalable. Since, this initial study was based on data from the randomized controlled sertindole trials by Zimbroff et al. and van Kammen et al. in acutely ill hospitalized patients with schizophrenia, we followed up with a study of the validity of PANSS-6 in patients with chronic schizophrenia based on Phase 1 data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. The results of this study suggested that PANSS-6 is also a valid measure of chronic schizophrenia (PANSS-6 was scalable and PANSS-30 was not). Most recently, we have tested the validity of PANSS-6 in treatment-'resistant' schizophrenia based on data from Phase 2E of CATIE (the clozapine phase). The results of this (still unpublished) study showed that PANSS-6 was also scalable in this clinically important patient population, whereas PANSS-30 was not. Furthermore, PANSS-6 was able to capture the beneficial effect of clozapine as demonstrated in the primary publication of these data (using treatment discontinuation for any reason as the primary outcome). During the talk, the results from the three studies mentioned above will be presented and discussed. Furthermore, the newly developed, 15-minute stand-alone Simplified Negative and Positive Symptoms Interview (SNAPSI) that can facilitate PANSS-6 rating will be introduced.

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3. Ostergaard SD, Foldager L, Mors O et al. The Validity and Sensitivity of PANSS-6 in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study. Schizophr Bull 2018;44:453-462.

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S3.2 Effectiveness of antipsychotic treatments in schizophrenia

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Background: Antipsychotic drugs remain the mainstay of the pharmacological treatment in schizophrenia. The effectiveness of the drug group is under debate.

Objectives: The primary aim of the presentation is to give an update on the current evidence base regarding antipsychotic treatment effectiveness of schizophrenia. A secondary aim is to assess treatment effectiveness in different sub-populations.

Methods: The PubMED, Cochrane library, and EMBASE were searched for systematic reviews and meta-analyses of antipsychotic drug treatment compared to placebo and head-to-head comparisons of different antipsychotics. Another search for single studies not included in the systematic reviews was also conducted.

Results: Antipsychotic drugs have moderate to large effect sizes compared to placebo for overall antipsychotic effectiveness. Differences among some of the agents exist but effect sizes are generally small. A subgroup of patients seems to be non-responders from the start and represents a particular challenge. Response rates are substantially larger in first-episode studies compared to in studies in chronic phase samples. Antipsychotic drugs show large effect sizes for relapse prevention compared to placebo.

Conclusion: Antipsychotic drug treatment has moderate to large effect size, but is not equally effective in all sub-groups of patients.

S3.3 Psychosis genetics in the clinical setting, from here on out

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Background: Genetics and personalized medicine is an emerging field in psychiatry. However, genetics (at least at a syndromal level) have been used in diagnosis of psychosis for quite some time. The genetic background of psychosis is unraveling at an increasing pace, but how and when will this help the clinician?

Objectives: This presentation aims to give a short introduction to how genetics are currently used in psychosis diagnostics, what the current research trends are at the moment and what we should expect in the future.

Methods: Literary search of, attending international congresses on and expert interviews about the listed topics.

Results: Genetic information is already used in the clinical setting of psychosis diagnostics, mainly by trying to spot and diagnose well defined syndromes with foreseeable courses (eg. DiGeorge or Klinfelter syndromes). Currently large population cohort studies are underway to elucidate the hereditary mechanisms and biological processes underlying psychoses. In the future, genetic information will likely be usable to estimate treatment effect and disease trajectories, and even to test them in laboratory settings before applying the treatments to patients (eg. Patient derived stem cells and brain organoids).

Conclusion: Genetic information of psychosis is already employed in the clinical setting, but we have only scratched the surface of it's potential. The future will likely bring many new ways to utilize genetic information in clinical decision making for the benefit of the patient.

SYMPOSIUM 4

PSYCHOPHARMACOLOGY IN CHILD AND ADOLESCENCE

S4.1 Optimal management of ADHD in older adults

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Background: The manifestation of attention-deficit hyperactivity disorder (ADHD) among older adults has become an interesting topic of interest due to an increasing number of adults aged 50 years and older seeking assessment for ADHD. Unfortunately, there is a lack of research on ADHD in older adults, and until recently only a few case reports existed.

Objectives: In 2016 the authors published the first review on ADHD in older adults. Today's presentation aims to summarize some of the initial findings and to present an update on recent research on ADHD in older adults.

Methods: A systematic search was conducted in the databases Medline/PubMed and PsycINFO in order to identify studies regarding ADHD in adults 50 years of age and older.

Results: ADHD persists into older ages in many patients, but the prevalence of patients fulfilling the criteria for the diagnosis at age 50 years and older is still unknown. It is reason to believe that the

prevalence is falling gradually with age, and that the ADHD symptom level is significantly lower in the age group 70–80 years than the group 50–60 years. There is a lack of controlled studies of ADHD medication in adults 50 years of age and older. The problem with side effects and somatic complications may rise to a level that makes pharmacotherapy for ADHD difficult after the age of 65 years. Physical assessment prior to initiation of ADHD medication in adults 50 years of age and older should include a thorough clinical examination,and medication should be titrated with low doses initially and with a slow increase.

Conclusion: It is essential when treating older adult patients with ADHD to provide good support based on knowledge and understanding of how ADHD symptoms have affected health, quality of life, and function through the life span.

S4.2 Identification of novel treatment targets in ADHD and its comorbid conditions

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Background: Most current pharmacological treatments against ADHD and other common neuropsychiatric disorders were discovered by serendipity 50-130 years ago. As these drugs have major limitations in terms of efficacy and safety, there is an urgent demand for new treatment options. Recent discoveries of susceptibility genes and biological pathways for neuropsychiatric disorders, the access to millions of chemical compounds and 3D-structures of macromolecular targets are now paving the way for new drug discoveries in this field. Moreover, insights into shared pathophysiological mechanisms and off-target effects may be used to repurpose existing drugs for new indications.

Objectives: In this talk, I will present our recent efforts to identify druggable targets in the human genome for ADHD and its major somatic and neuropsychiatric conditions and how we are using structure based drug discovery to identify new molecules that can interact with selected protein targets for these conditions.

Methods: To identify possible drugs targets, we first we performed genome-wide exploration of recent genome wide association data for ADHD and its co-morbid conditions. For structure based early stage drug discovery, we used a combination of x-ray crystallography and in silico and in vitro screening of chemical libraries and functional assays, mainly of enzyme targets.

Results: Many of the loci/genes that have been discovered for ADHD were considered less suitable for drug development, as they correspond to non-coding RNA, transcription factors, or apparent structural proteins with unknown functions. Among the genes that are known targets of current ADHD drugs, few revealed signs of association with this disorder and these genes mainly encode targets of atomoxetine. When testing for association between putative "druggable" genes associated with ADHD and ADHD co-morbidities, we noticed strong signals with neuropsychiatric and immunological disorders. In this talk I will also describe our efforts to identify new molecules that can interact with some signaling enzymes that could be involved in ADHD and its psychiatric or somatic comorbid conditions, such as depression, migraine, SUD and obesity.

Conclusions: Our study provides a proof of principle of how genetic data for ADHD and its comorbid conditions can be used for identification of candidate drugs and protein targets and how we can find novel molecules that interact with these proteins

LECTURE 5

SCNP LECTURE

L5 Inflammation and negative affective states: mechanisms and circuits

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Background: Signals from the activated immune system induce depressed mood and aversion during acute and chronic inflammatory diseases. In addition, converging lines of evidence suggest that inflammation contributes to the pathogenesis of major depression.

Objectives: The presentation will focus on how inflammatory mediators can influence the signaling in neural circuits signaling aversion and reward.

Methods: We used behavioral models in genetically modified mice. In particular we used conditioned place aversion to systemic inflammation and other aversive stimuli. For interventions, we primarily relied on cell-type specific gene deletions and chemogenetic approaches.

Results: Immune-to-brain signaling underpinning aversion and depressive symptoms is mediated by cytokine-mediated activation of the brain endothelium followed by microglial production of prostaglandins that inhibit dopaminergic transmission. Further, our findings show that the melanocortin system is central for aversive signaling.

Conclusion: Prostaglandins acting on monoaminergic circuits are critical for the impact of inflammation on affective function. Melanocortins have a broad role in aversion and represent an interesting therapeutic target.

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SYMPOSIUM 5

MICROBIOME: CLINICAL PHARMACOLOGY AND PHARMACOLOGICAL RELEVANCE

S5.1 The microbiome in health and disease

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Background: The human microbiota are thought to have a tremendous influence on human health and diseases. Although it was virtually impossible to study them until a few years ago, next generation sequencing technologies have enabled us to access and characterize the microbiota in a culture-free manner. Cross-sectional studies have shown associations between changes in human gut microbiota and several diseases. Among them, a new family of studies known as metagenome-wide association studies (MGWAS) have reported significant associations between the gut microbiota and diseases such as type 2 diabetes. For most of these associations though, whether the relationship is causality or reverse causality still remains to be elucidated. On a more promising note, studies in mouse models have provided glimpses of causality – microbiota were essential for triggering multiple sclerosis in a model, and metabolic phenotypes from human donors could be transferred to germ-free mice. This is only the beginning of a new trend to elucidate the role of host-associated microbiota in diseases, and bioinformatics is becoming increasingly important in this endeavor.

Objectives: To investigate the possibility of affordable biomarkers from fecal microbiome for colorectal cancer diagnosis.

Methods: Fecal shotgun metagenomics in a Chinese cohort of 127 individuals.

Results: We identified microbial gene biomarkers from fecal microbiome and validated them in multiple cohorts from Europe. Quantitative PCR measurements of some of these markers showed promising potential for affordable diagnosis of colorectal cancer using fecal microbiome.

Conclusion: In this talk, our published and ongoing research on understanding the role of the gut microbiome in diseases will be discussed.

S5.2 Probiotics – a novel antidepressant? Lessons from preclinical studies

Anders Abildgaard[1,2], Betina Elfving[1], Heidi Müller[1], Marianne Hokland[3], Sten Lund[4], Gregers Wegener[1]

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Background: The gut microbiota has recently emerged as an important regulator of brain physiology and behavior in animals, and ingestion of certain bacteria (probiotics) therefore appear to be a potential treatment for major depressive disorder (MDD). Also, we have previously shown that depressive-like behavior in rats may hold a dysmetabolic component. The gut bacteria are believed to affect the brain through interactions with the immune system and hypothalamic-pituitary-adrenal (HPA) axis and through their release of metabolites into the host circulation

Aims: In a series of pre-clinical studies we therefore aimed at evaluating the potential of probiotic treatment as a novel anti-depressant and further studied how probiotics could interfere with the plausibly involved mechanisms.

Methods: Outbred Sprague-Dawley (SD) rats were used in addition to selectively bred Flinders Sensitive Line (FSL) rats that inherently display an increased level of depressive-like behavior. A mix of eight bacterial species (Lactobacillus, Lactococcus and Bifidobacterium strains) was chosen as probiotic intervention, and a high-fat diet (HFD), consisting of 60 kJ-% animal-derived fat, was used as a metabolic stressor. Depression-related behaviour was evaluated, and HPA axis regulation and immunological markers were examined. Finally, the plasma metabolome was analysed to identify metabolites associated with probiotics.

Results: Probiotic treatment reduced depressive-like behaviour in SD rats independently of diet, while leaving FSL rats on control diet completely unaffected. In addition, probiotic treatment protected against a pro-depressant like effect of HFD in FSL rats. These behavioural findings were highly equivalent to changes in T lymphocyte CD4/8 ratios in the brains only. The metabolomics revealed an increased level of a potential neuroprotective microbial metabolite indole-3-propionic acid (IPA) associated with probiotic ingestion. Finally, probiotics and HFD had a major impact on hippocampal HPA axis regulation.

Conclusion: These findings clearly support the novel concept of "psychobiotics" and lend inspiration to further studies into probiotics as a potential antidepressant treatment. Furthermore, our results suggest that MDD may indeed hold a dysmetabolic component that potentially involves the gut microbiota. The underlying mechanisms may involve an altered regulation of the immune system and HPA axis as well as the plasma metabolome.

S5.3 The Gut Microbiome and Stress-related Psychiatric Disorders: From Prebiotics and Probiotics to Psychobiotics

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Background: The gut microbiome exerts a marked influence on brain function and behaviour via bidirectional signalling routes along the gut-brain axis. This includes behaviours relevant to stress-related psychiatric disorders such as depression and anxiety. Preclinical studies have indicated that there is an expanding range of therapeutic targets in the CNS that are influenced by this community of microorganisms in our gastrointestinal tract. Although a number of approaches may to taken to beneficially modulate the gut microbiome, prebiotics and probiotics have received most attention to date.

Objectives: The definition of a 'Psychobiotic' now includes both live bacteria (probiotics) and ingested substrates selectively utilized by host microorganisms (prebiotics) that might confer mental health benefits.

Methods: We outline here the promising data from preclinical screening platforms that have identified a range of candidate psychobiotics of potential therapeutic utility in psychiatric disorders.

Results: Many of these agents await further evaluation in human subjects and mixed results have been demonstrated depending on the strain evaluation.

Conclusion: Moving from probiotics and probiotics to verified psychobiotics is an appealing prospect but not one without translational challenges. Current discovery pipelines and platforms may need to be further refined to enable a more systematic identification of psychobiotics and to successful deliver new therapeutic options in the clinic.

POSTERS

Poster 1

All-cause mortality in patients with schizophrenia following an acute myocardial infarction

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Background: Patients with schizophrenia have an increased mortality compared to the general population. The increased mortality can partially be explained by the higher prevalence of cardiovascular diseases such as acute coronary syndrome (ACS). There is however a paucity of knowledge regarding the all-cause mortality, post ACS complications and length of in-hospital stay (LoS).

Objectives: This study aims to investigate the effect of schizophrenia on all-cause mortality, post ACS reinfarction and stroke rates following ACS. The length of in-hospital stay following admission for ACS and prevalence of cardiac risk factors were also investigated.

Methods: Data from three nationwide databases in Denmark were used in this study, including; The Danish Civil Registration System, the National Patient register and the Danish Psychiatric Central Register. Patients diagnosed with a first ACS (unstable angina ICD-10 I20.0, NSTEMI ICD-10 I21.4 and STEMI ICD-10 I21.0-I21.3) between 2000-2014 were identified and categorized for an additional diagnosis of schizophrenia ICD-10 F20. The patients were matched 1:2 to a psychiatric healthy control (PHC) population on gender, age and year of first ACS diagnosis.

Results: A total of 1,572 patients were analysed (schizophrenia: n = 524), 65.27% of the population were males and the mean age was 61.13 years. Having schizophrenia had a significant effect on all-cause mortality (HR 2.69, 95% CI: 2.25-3.20) and stroke rates (HR 1.47, 95% CI: 1.29-1.68). There was no difference in LoS ($p>0.05$) between the populations. Patients with schizophrenia had a higher prevalence of cardiac risk factors such as anaemia and diabetes mellitus.

Conclusion: Patients with schizophrenia had increased all-cause mortality and stroke rates following ACS, however, they did not have a longer LoS than their matched PHCs despite having a higher prevalence of cardiac risk factors.

Poster 2

Systematic Review & Meta-Analysis: Effects of Ketamine in Animal Models of Depression

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Background: Depression is the leading source of disability wordwide. The search for potential effective and novel therapeutic targets is a high research and healthcare priority with treatment resistance for existing pharmacological therapeutics among patients estimated at roughly 50% (Rush et al., 2006, Thomas et al., 2013). Ketamine is a selective NMDA receptor antagonist and has been shown to possess acute anti-depressant effects, in contrast with current antidepressants that have delayed onset of action on symptoms. Systematic review & meta-analysis are great tools to provide an unbiased overview of the literature and explore aspects of experimental design that contribute to treatment efficacy.

Objectives: We aimed to provide an unbiased overview of the published literature on the effects of ketamine in animal models of depression and to use meta-analysis to assess the impact of study characteristics on the behavioural and neurochemical effects of ketamine in depressive-like outcomes.

Methods: A pre-specified protocol was written and published on SyRF.org.uk. We searched the CAMARADES Animal Models of Depression database using regular expressions for ketamine or known enantiomers of ketamine. The database is built using a systematic search of PubMed and EMBASE, conducted in May 2016, for all primary animal experiments investigating depression. Primary controlled animal studies were included if they modelled some aspect of depression and assessed the impact of ketamine on behavioural and/or neurochemical outcomes. The primary outcome of interest in this review is behavioural outcomes reported in primary articles, including the forced swim test, sucrose preference test and measures to assess memory. The secondary outcomes are neurochemical outcomes, including BDNF levels, GSK-3 and mTOR expression. Risk of bias will be assessed using the CAMARADES checklist.

Results: 259 articles were identified as being potentially relevant to the research question. 142 articles were included at the title and abstract screening stage. Data is in the processing of being extracted from articles that meet full-text inclusion criteria. If feasible, a meta-analysis will be carried out to investigate the sources of heterogeneity. Normalised mean difference or standardised mean difference will be used to pool effect sizes. Meta-regression will be

used to investigate the impact of different study characteristics on the outcome. Factors that will be investigated are the strain, species, sex and age of the animals, method of model induction, the treatment dose, the route of administration of ketamine, and measures reported to reduce the risk of bias (i.e. allocation concealment, blinded assessment of outcome, randomisation, and a prior sample size calculation).

Conclusion: This systematic review will provide an overview of the literature and assess the quality of preclinical research investigating the effects of ketamine on depression. These findings may have implications for research improvement and provide directions for future research including identifying gaps in the literature.

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Poster 3

DOES GENETICS OF OBESITY OVERLAP WITH PHARMACOGENETICS OF ANTIPSYCHOTIC INDUCED WEIGHT GAIN? A MOLECULAR PATHWAY ANALYSIS.

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Background: Weight gain is a prime concern of antipsychotic drug treatment, as it is a major cause of treatment discontinuation. Reports in literature stress the role of the individual genetic background to drive weight gain during pharmacological tests. A number of genes have been implicated in obesity, including: ADIPOQ (Adiponectin, C1Q And Collagen Domain Containing), FTO (FTO, Alpha-Ketoglutarate Dependent Dioxygenase), LEP (Letpin), LEPR (Letpin receptor), INSIG2 (Insulin Induced Gene 2), MC4R (Melanocortin 4 Receptor), PCSK1 (Proprotein Convertase Subtilisin/Kexin Type 1) and PPARG (Peroxisome Proliferator Activated Receptor Gamma).

Objectives: .

Methods: Cytoskape was instrumental to define a molecular pathway from a list of genes previously reported to be consistently associated with obesity in literature. GeneMania further enriched the original pathway. That pathway was tested for enrichment in the CATIE trial through the interrogation of reactomePA and bioconductor. Outcome was the largest increase in weight throughout the different phases of the trial. Analysis of clinical covariates was conducted prior to the genetic tests and, when found significantly associated with the phenotype under analysis were included as covariates for genetic tests. Plink and R were instrumental for the analyses. As for the genetic genome-wide analysis, quality checking were set as standard for this kind of analysis (genotype call rate > 0.95; maf > 0.01; hwe < 0.0001), inflation factor was controlled by lambda values and imputation was run with the use of 1000 genomes in a Plink environment. Pathway analysis was conducted at the SuperCluster PC at Aarhus University.

Results: 765 individuals from the CATIE study, M=556, mean age=40.93±11.03 were included in the initial analysis. 28 genes were finally analysed as a consistent metabolic pathway. 2067 SNPs were available from the CATIE genetic dataset and harbored by genes belonging to the pathway under analysis. This selection of variations was tested against 105 permutated pathways randomly selected throughout the genome. Under a threshold of $p<0.01$ for significance, a permutated p of 0.005 for enrichment was retrieved from the pathway under analysis. No enrichment was detectable under a threshold of $p<0.05$.

Conclusion: Genes involved in obesity may compose a molecular pathway at risk of weight gain during antipsychotic treatment. A genetic test run before the drug treatment is initiated could grant the opportunity to prevent weight gain. Further independent analyses are warranted. A focus on the significant threshold to be used in enrichment analyses must be further investigated.

Poster 4

Can unilateral lesions of the nucleus accumbens and/or medial prefrontal cortex lesions induce depressive- and anxiety-like behavior in the rat?

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Background: Stroke survivors commonly experience post-stroke depression (PSD) and post-stroke anxiety (PSA). However, many cases are thought to remain undiagnosed and patients, which are diagnosed with PSD and/or PSA, are often undertreated, indicating a

need for a better understanding of the disease and the underlying mechanisms. To address this need, experimental research relies on appropriate animal models of this disease. In current rodent models of PSD/PSA, middle cerebral artery occlusion is used to induce a stroke and evaluate behavior. These models, however, are associated with severe motor impairment, which may confound commonly used behavioral tests of depression and anxiety. The vasoconstrictor endothelin-1 (ET-1) can be used to induce small lesions in specific brain areas associated with depression or anxiety, while at the same time avoiding areas linked to motor function.

Objectives: In an effort to avoid motor deficits, we investigated how unilateral ET-1 injections in the nucleus accumbens (NAc) and/or medial prefrontal cortex (mPFC) alter depressive- and anxiety-like behavior in rats.

Methods: Using stereotaxic surgery, vehicle control or ET-1 (400 pmol) was injected into the left NAc and/or mPFC of adult male Sprague Dawley rats (n = 10 per group). At 2 and 6 weeks post surgery, behavior was assessed using standard tests for locomotion (Open Field), cognition (Y-Maze Spontaneous Alternation Test), anxiety (Elevated Plus Maze), and depression (Forced Swim Test).

Results: Data analysis is still ongoing. Preliminary data will be available in April 2018.

Conclusion: In a pilot study, ET-1 injections into the left mPFC alone caused increased anxiety, without affecting motor function or depressive-like behavior. Thus, we expect that lesions of the NAc and mPFC cause increases in both anxiety- and depressive-like behavior, with no effect on motor function.

Poster 5

Circadian Rhythm disturbances in Treatment Resistant ACTH-Treated Rats

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Background: Circadian rhythm (CR) disturbances among the most prominent symptoms present in major depressive disorder. CR disturbances appear in several forms, including endocrine imbalance, sleep disturbances and changes in clock gene expression. It has been shown that clock gene (CG) expression rhythms are affected in both brain-tissue and blood from patients and in the chronic mild stress animal model of depression. This indicate that changes in CG is an essential part of the etiology and is translational between clinical and pre-clinical studies. Furthermore, antidepressants has been shown to be unable to normalize CG completely in both animal models and humans.

Objectives: In this study we aim to investigate the circadian rhythm disturbances in the treatment resistant ACTH-treated rats, to investigate the relationship between antidepressants and CG.

Methods: In this study, we used the treatment Resistant ACTH-rats. Animals were treated with either imipramine or vehicle before being tested in the forced swim test (FST). Brain regions were dissected and liver tissue was collected, along with trunk blood, at three time points. CG in the brain and liver will be analysed using real-time qPCR and melatonin and corticosterone will be measured in the blood using Luminex multiplex assay.

Results: FST revealed that ACTH-treatment indeed did suppress the effects of imipramine. Based on earlier studies on animal models, we expect that CG rhythm will be greatly affected ACTH-treatment paradigm and that treatment with imipramine will yield interesting insights into how antidepressants interact with CG.

Conclusion: In conclusion, animal models are useful tools in the studies of depression and CR.

Poster 6

Psilocybin modulated expression of plasticity-related genes and proteins in rat prefrontal cortex and hippocampus

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Background: Psilocybin has recently shown antidepressant efficacy in human studies (1). However, the underlying molecular mechanisms are still largely unknown.

Objectives: Our studies will examine whether psilocybin-administration induces changes in gene and protein expression related to synaptic plasticity, as this may be related to its antidepressant effect (2).

Methods: Rats will receive a single, intraperitoneal injection of psilocybin. Focusing on prefrontal cortex and hippocampus, we will examine changes in immediate early gene expression and protein expression, using qPCR and Western blotting, respectively. We will isolate synaptosomal fractions and measure the expression and complex-formation of pre- and postsynaptic proteins using two-color fluorescence immunoblotting and dual immunoprecipitation, to study the acute effects of psilocybin on receptor trafficking and synaptic regulation.

Results: The studies are ongoing and will be the first to investigate psilocybin-induced changes in gene expression together with proteins expression in rats.

Conclusion: Psilocybin has previously shown a great therapeutic potential for treating depression and has sparked a revival of the field of psychedelic research (3). The results from our studies will likely motivate further investigations into the signaling pathways induced by psilocybin and, in the future, help identify novel pharmacological targets for efficient treatment for depression.

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Poster 7

Socio-economic status, healthcare resource utilization and costs among patients with schizophrenia in Denmark

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Background: Schizophrenia is a chronic, debilitating psychiatric disease causing a burden on patients, families, caregivers, health systems and society, but the evidence and societal costs vary greatly between countries.

Objectives: To describe the current socio-economic status of patients with schizophrenia in Denmark, their healthcare resource utilization and associated costs.

Methods: This nationwide register-based study from Denmark used data on public welfare benefits and healthcare contacts to describe patients with schizophrenia in the years 2013 through 2016. Patients were required to have at least one hospital record of a schizophrenia diagnosis since 1996, and were included in the study on January 1st 2013 or the date of their first schizophrenia diagnosis, whichever came latest. Patients with at least 40% of their income from paid work or student grants were defined as a 'socio-economic self-supporting' subgroup in stratified analyses of healthcare resource utilization and costs.

Results: An average of 30,550 patients with schizophrenia were analyzed per year. The mean age was 45 years, and 42% were female. The majority of patients (87%) had their primary source of income from public welfare benefits (71% from retirement benefits, and 16% from cash benefits). A minority of patients (9%) had their primary income from employment (6%) or student grants (3%). The mean annual personal income for all patients was 28,728 EUR of which a mean of 24,559 EUR (85%) came from public benefits. On average, each patient had a mean of 16.3 contacts with GPs and specialists, and 2.3 hospitalizations with 12.6 hospitalization days per year. The mean annual costs per patient were 16,548 EUR for healthcare resource utilization and 1,402 EUR for prescription drugs, respectively. Compared to the total schizophrenia patient population included in the study, the 'socio-economic self-supporting' subgroup, consisting of 3,819 (12.5%) patients, were younger (mean age 38 years, 46% female), had fewer contacts with healthcare professionals per patient per year (12.7 contacts with GPs and specialists, and 1.6 hospitalizations with a mean of 5.7 hospitalization days), and had lower mean annual healthcare costs per patient (11,265 EUR for healthcare resource utilization and 775 EUR for prescription drugs, respectively).

Conclusion: Schizophrenia was found to be associated with substantial costs mainly due to healthcare costs of hospitalizations and contacts with healthcare professionals, and non-healthcare related welfare benefits. Still, some patients managed to remain socio-economic self-supporting with reduced healthcare resource utilization and less associated costs. Future efforts should aim to understand better how to help patients with schizophrenia to continue their studies, stay in employment and thereby remain socio-economic self-supported.

Poster 8

Antidepressant treatment effects and side effects of anti-inflammatory agents: A systematic review and meta-analysis of randomized clinical trials

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Background: Specific anti-inflammatory agents may yield antidepressant effects; however, no study has gathered the evidence on all anti-inflammatory drugs including a detailed assessment of side effects and risk of bias.

Objectives: To systematically review all randomized clinical trials (RCTs) that studied antidepressive treatment and side effects of pharmacological anti-inflammatory intervention.

Methods: We searched CENTRAL, PubMed, EMBASE, Psychinfo, Clinicaltrials.gov, and review articles for trials published prior to January 1, 2018. We included RCTs investigating anti-inflammatory intervention in adults with depressive symptoms or major depressive disorder (MDD). Two independent reviewers extracted data. Pooled standard mean differences (SMD) including 95%-confidence intervals (95%-CI) were calculated. Outcomes included depression scores after treatment including remission and response and side effects.

Results: A total of 41 RCTs (N=10,344) were included, whereof 13 investigated NSAIDs (N=4,362), 11 cytokine-inhibitors (N=3,533), 9 statins (N=2,118), 3 minocycline (N=158), 3 pioglitazone (N=114), and 2 glucocorticoids (N=59). Overall, anti-inflammatory agents improved antidepressant treatment effects compared to placebo by a SMD of -0.46 (95%-CI=-0.62 to -0.30; I2=89%; N=9,459), which was present as add-on in patients with MDD (SMD=-0.56; 95%-CI=-0.84 to -0.27; I2=66%; N=634) and as monotherapy against depressive symptoms (SMD=-0.41; 95%-CI=-0.60 to -0.22; I2=93%, N=8,825). Better antidepressant effects were observed for NSAIDs as add-on (SMD=-0.82; 95%-CI=-1.17 to -0.46; I2=0%; N=132) and monotherapy (SMD=-0.29; 95%-CI=-0.51 to -0.06; I2=84%; N=4,082), cytokine-inhibitors as monotherapy (SMD=-0.65; 95%-CI=-1.04 to -0.26; I2=95%; N=3,285), statins as add-on (SMD=-0.73; 95%-CI=-1.05 to -0.42; I2=0%; N=164), minocycline as monotherapy (SMD=-1.06; 95%-CI=-1.68 to -0.44; N=46), and glucocorticoids as add-on (SMD=-0.90; 95%-CI=-1.44 to -0.36; I2=0%; N=59). All studies were associated with high risk of bias. Only 19 trials reported on adverse events, and we found no increased risks for pain/muscle aching, gastrointestinal or cardiovascular events but a trend towards an increased risk for infections.

Conclusion: The majority of anti-inflammatory agents improved antidepressant treatment effects. Future large, high-quality RCTs need to include longer follow-up, identify optimal doses and subgroups of patients that can benefit from anti-inflammatory intervention, possibly guided by neurovegetative symptoms, somatic comorbidity and pro-inflammatory markers.

Poster 9

Biomarkers of depression in the skin – a novel approach

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Background: The mechanism of major depressive disorder (MDD) is not fully understood. Consequently, it is currently only possible to diagnose depression at a subjective level and it would thus be of great clinical importance to identify biomarkers of MDD to aid the diagnosis. Recently, it has been shown that the combined miRNA-mRNA profile in human dermal fibroblasts might lead to the discovery of promising peripheral biomarkers in MDD.

Objectives: In selected rat models of depression (stress and genetic), miRNA/mRNA extracted directly from rat-skin and rat dermal fibroblasts will be compared and investigated as peripheral biomarkers of MDD. A list of miRNA/mRNA targets have been compiled from the published human study.

Methods: The methods of this project aim to collect skin tissue and purify RNA from skin/fibroblasts for subsequent real-time qPCR analysis. This includes establishment of fibroblast cultures, high quantity and quality RNA extraction from skin and fibroblast cultures, cDNA synthesis, target selection/primer design, real-time qPCR and statistical analysis.

Results: Several miRNAs from the human study are significantly different in the animal models of depression compared to a control, both in skin and fibroblasts. In addition, some miRNAs were not normalized in treatment resistant rats after treatment.

Conclusion: Animal studies are performed under increasingly controlled conditions compared to human studies. Fewer significant miRNAs were found in the animal models which could indicate increased specificity. The loss of normalization in treatment resistant rats further validates these miRNAs' relationship with depression.

Poster 10

Early effects on depressed mood, suicidality and anxiety of duloxetine in depression

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Background: Recent patient-level post-hoc analyses show that SSRIs, already after one week of treatment, cause i) a reduction in depressed mood(1), ii) a reduction in suicidality(2) and iii) a reduction in psychic anxiety, but also that they iv) elicit a transient increase in somatic anxiety during the first week(3).

Objectives: The aim of the present study was to explore if these findings could be extended to a serotonin and noradrenaline reuptake inhibitor, duloxetine.

Methods: We had access to patient-level data for 11 company-sponsored, acute-phase, placebo-controlled trials of duloxetine in adult depression using the Hamilton Depression Rating Scale (HDRS-17). A pooled analysis comprising in total 2521 subjects was undertaken using MRMM (Mixed-Effect Model Repeated Measures, SAS 9.4). All patients with ≥15 points on the HDRS-17 at baseline were included. Doses ranged between 40-120 mg. Total HDRS-17-sum, as well as the individual items depressed mood, suicidality, psychic anxiety and somatic anxiety were analyzed.

Results: The duloxetine-induced reduction in depressed mood, suicidality and psychic anxiety, but not that in HDRS17-sum, was significant already at week 1. In contrast, somatic anxiety was rated higher in patients on duloxetine at week 1.

Conclusion: In line with our previous observations regarding the SSRIs, duloxetine also displayed a significant superiority over placebo already after one week of treatment with respect to depressed mood, suicidality and psychic anxiety, but not with respect to the conventional effect parameter, i.e. total HDRS-17-sum. Also in line with previous data regarding the SSRIs, psychic anxiety was rated lower but somatic anxiety rated higher at week 1 in patients given active drug. The results support the notion that a small but significant antidepressant effect, that cannot be detected using HDRS17, is at hand earlier than previously assumed, and also that reuptake inhibitors may cause an initial aggravation of somatic anxiety but not psychic anxiety.

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Poster 11

Environmental Enrichment as Potential Breakthrough in Moderating Autistic Like Behaviors Following Maternal Separation

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Background: Adverse environmental experiences during early life have been identified as potential concerns for neurodevelopmental disorders including Autism spectrum disorder (ASD) with 1% prevalence among populations. Maternal separation is an animal model that is widely used to study long-term behavioral abnormality. To date, a great deal of studies is focused on the potential therapeutic role of environmental enrichment for the early life stress-inducing anxiety, depression and learning deficits. However, the effect of environmental enrichment on the autistic like behaviors induced by maternal separation has not been studied extensively.

Objectives: The main focus of current study is to investigate the therapeutic effect of environmental enrichment on the behavioral deficits related to ASD in connection with neuroglial plasticity of hippocampus in maternal separated rat model.

Methods: Rats will be separated from the mother for 3 hours daily from PND1 to PND14. After weaning time, the rats will be subjected to environmental enrichment for 2 weeks. In the next step, autism-related behaviors such as social interaction, social communication and stereotype behaviors will be tested. In parallel, neuroglial plasticity of hippocampus will be investigated doing the 3-D quantification by applying stereological methods (NewCAST software) and

measuring the volume, number of neurons and astrocytes of the hippocampal sub-regions.

Results: It is assumed that enrichment of the environment will lead to the improved performance in behavioral tests and structural neuroglial plasticity of hippocampus.

Conclusion: By implementing this project, we will have a broader knowledge of environmental effects, including early life stressors on developing autism and mechanisms of the therapeutic effect of environmental enrichment in modulating the symptoms of the disorder at the structural level.

Poster 12

How common is early exacerbation of anxiety in depressed patients participating in placebo-controlled trials?

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Background: Selective serotonin reuptake inhibitors (SSRIs) are often claimed to provoke anxiety or agitation, especially when treating anxiety disorders such as panic disorder, and such an effect is held to be especially pronounced during the first few days of treatment. How prevalent such reactions are when these drugs are used for the treatment of major depressive disorder however remains largely unknown and the estimates that do exist vary considerably[1].

Objectives: In this post hoc analysis, patient-level data from 8262 adult subjects with depression that had participated in drug company-sponsored placebo-controlled trials regarding sertraline, paroxetine or citalopram were analyzed to explore the prevalence of an increase in Hamilton Depression Rating Scale (HDRS)-assessed anxiety or agitation during the first weeks of treatment with SSRI or placebo. In addition, the prevalence of early anxiety-related adverse events was assessed in those trials where this information was available (i.e. those regarding paroxetine and citalopram; 5712 subjects).

Methods: A generalized linear mixed model was employed to test for treatment differences in likelihood of worsening of anxiety-related items while changes in mean scores were analysed using a linear mixed model. Prevalence of early anxiety- or agitation-related adverse events was assessed using the Maentel-Haenszel random-effects method.

Results: After one week of drug administration, SSRI-treated subjects displayed moderately but significantly higher rating of somatic anxiety (Effect size (ES) -0.09; $p<0.00.1$) than those given placebo, and the likelihood of subjects reporting an increase in this symptom was also higher in the actively treated group (placebo 6.7%, SSRI 9.3%; $p<0.001$). In contrast, mean ratings of psychic anxiety (ES 0.09; $p<0.001$) and agitation (ES 0.08; $p=0.003$), as well as the risk of displaying an increase in the rating of psychic anxiety (placebo 8.5%, SSRI 7.0%; $p=0.03$), were moderately but significantly lower in patients given an SSRI. The higher rating of somatic anxiety, but not the lower rating of psychic anxiety, in SSRI-treated subjects had vanished at the week 2 visit. Displaying an anxiety- or agitation-related adverse event during the first 2 weeks of treatment was more common in patients given an SSRI than in those given placebo (5.2% vs. 10.2%; odds ratio 1.68 (1.31-2.15)). The overlap between worsening as measured by HDRS changes and AE reporting was limited, 51.4%. Neither an aggravation in HDRS-assessed anxiety nor an early anxiety-related AE in SSRI-treated subjects precluded a subsequent beneficial effect of the treatment: at endpoint SSRI thus outperformed placebo with respect to reduction in the sum of all HDRS items, as well as with respect to reduction in depressed mood, also in subjects displaying indices of early enhancement of anxiety.

Conclusion: The results confirm that SSRIs may exert an anxiety-reducing effect already during the first week of treatment, but also that they, in a minority of susceptible subjects, may elicit or aggravate anxiety.

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Poster 13

Immune activation is related to reduced GABAergic and enhanced dopaminergic transmission in first episode psychosis patients

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Background: Accumulating evidence implicates innate immune activation, hyperactivity of dopamine transmission and reduced γ-Aminobutyric acid (GABA)-ergic activity in the development of schizophrenia.

Objectives: The aim of the present study was to investigate the relationship between immune activation and central neurotransmission, by studying immune

cells, cytokines (interleukin (IL)-18), chemokines (monocyte chemoattractant protein-1 (MCP-1) and chitinase-3-like protein 1 (YKL-40)) in relation to cerebrospinal fluid (CSF) levels of GABA and dopamine in first-episode psychosis (FEP) patients and healthy controls.

Methods: CSF and blood markers were analyzed in 42 FEP patients and 22 age- and sex-matched healthy controls, enrolled within the Karolinska Schizophrenia Project (KaSP), a multidisciplinary research consortium that investigates the pathophysiology of schizophrenia. The number of white blood cells was counted using an XN-9000-Hematology-Analyzer. Plasma and CSF levels of cytokines and chemokines were measured by electrochemiluminescence assays. CSF GABA, dopamine and its metabolites DOPAC and HVA were analyzed by high-performance liquid chromatography.

Results: We recently reported increased levels of plasma IL-18 and decreased levels of CSF GABA in FEP patients. In the present study, we found higher plasma levels of MCP-1 (115.9 ± 6.97 pg/mL, n= 41 vs. 87.5 ± 4.87 pg/mL, n= 17, p=0.0015) and YKL-40 (228.7 ± 15.56 ng/mL, n= 42 vs. 175.7 ± 10.08 ng/mL, n= 19, p=0.0059) in FEP patients compared to healthy controls, a condition that was unrelated to antipsychotic and/or anxiolytic medication. This was combined with an increased number of blood monocytes (0.49 ± 0.021 x109/L, n= 39, vs. 0.42 ± 0.024 x109/L, n=21, p=0.025) and increased levels of CSF dopamine (0.57 ± 0.12 □M, n=41 vs. 0.19 ± 0.063 □M, n=21 vs. p=0.0061). Significant correlations among FEP patients were found between CSF dopamine and plasma MCP-1 (r=0.55, p=0.004) and between CSF dopamine and plasma IL-18 (r=0.55, p=0.005). CSF GABA was found to correlate with the dopamine metabolites DOPAC (r=0.50, p=0.001) and HVA (r=0.37, p=0.017) in FEP patients.

Conclusion: We conclude that these data strengthen the notion that innate immune activation and abnormalities in GABAergic and dopaminergic neurotransmission is associated with early onset psychosis. Future studies may elucidate whether associations between these markers are explicitly involved in the development of schizophrenia.

Poster 14

An inward-facing conformation is a critical step in the folding trajectory of the human serotonin transporter

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Background: The serotonin transporter (SERT) is a membrane protein that is responsible for the reuptake of serotonin (5-HT) from the synaptic cleft and is targeted by antidepressant medicine. Point mutations within the coding sequence of human membrane proteins can result in their retention in the endoplasmatic reticulum (ER), and give rise to clinically relevant phenotypes.

Objectives: Here we investigated the conformational pharmacological chaperone effect of ibogaine on different conformational hSERT mutants; with a more inward- or outward-facing conformation.

Methods: This was done to address the importance of the conformation of hSERT as part of the folding trajectory and if ER stalled proteins can be rescued with ibogaine.

Results: he results showed that an outward-facing (T519AAPGAA) mutant that is sensitive towards ibogaine and is stalled in the ER can be rescued by ibogaine. However, an inward-facing F341Y and an outward-facing A169I mutants that are insensitive towards ibogaine and with no ER retention are not affected by ibogaine.

Conclusion: These observations show that ibogaine could only remedy SERT mutants that have a more outward-facing conformation by forcing the hSERT mutant in an inward-facing conformation and thereby overcome the folding deficiency.

Poster 15

Probing conformational changes of the GABA transporter by site-specific incorporation of a fluorescent unnatural amino acid

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Background: The ϒ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain, and GABA transporter 1 (GAT-1) belongs to the solute carrier 6 (SLC6) gene family together with the other neurotransmitter transporters such as the serotonin, dopamine, norepinephrine and glycine transporters (SERT, DAT, NET and GLYT respectively). The neurotransmitter transporters from this family are located in the plasma membrane of neurons and glia cells, and they are present at high density in areas facing synapses. The specialized members of this family transport different neurotransmitters across the cell membrane, thereby regulating signaling between neurons. Most of these transporters are important drug

targets in treating i.e. affective disorders such as depression and epilepsy.

Objectives: The role of the GABAergic system in mental disorders in general and in depression in particular is gaining momentum, thus studies of GAT-1 at the molecular level is highly attractive for understanding how it fulfills its biological role, how it could possibly be targeted better pharmacologically and how disease-related mutations may manifest themselves in both epilepsy and depression.

Methods: To get a fundamental understanding of the pharmacological, functional, conformational and structural aspects of GAT-1 we combine electrophysiological, fluorescence-based methods and unnatural amino acid mutagenesis to provide detailed knowledge of how ligand and ion binding control conformational change, and thus can provide the basis for developing drugs that target it.

Results: We have successfully established the groundwork for unnatural amino acid mutagenesis method for studies of GAT-1 and employ amber codon suppression technology to incorporate ANAP at specific sites in GAT-1 and determine the effect of mutations on functional activity of GAT-1.

Conclusion: Our data suggest that ANAP is well tolerated at the selected sites in GAT-1 gene. With this method in hand we will be able to answer some of the mechanistic questions regarding GAT-1 function that so far have been impossible to adress with other methods.

Poster 16

The role of opioid system in depression focusing on cognitive affective biases

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Background: Major depressive disorder (MDD) is one of the major psychiatric problems that may lead to other mental and physical disabilities. As a key characteristic of the disease, depressed patients show altering to negative biases in cognitive processes, like attention, perception, memory and learning. This phenomenon is referred to cognitive affective bias (CAB). For instance, facial expression in depressed patients are interpreted more negatively in comparison with healthy volunteers.

Objectives: The aim of the current research is to investigate a proper CAB rat model that mimic characteristics of depression and how CAB may be modulated by the opioid system.

Methods: Female Sprague Dawley rats become habituated in an arena box contains two bowls, which may include reward(s) hidden by a medium. For about one week, animals are trained to distinguish bowls and find out a connection between each medium with reward or blank inside the bowls. In the following week, one medium is paired with a drug injected 30-60 min prior the experiment or with high rewards every other day. On the day 5, both mediums with the same rewards are presented to animals without any drug injection. CAB are calculated based on the percentage of the correct medium choices, which were paired with drug injection or high rewards in the previous days. Corticosterone, as a known depressant and U50488, as a kappa opioid receptor (KOR) agonist were performed in affective bias test (ABT).

Results: We observed that animals show significantly positive biases to choose the medium paired with high rewards (two chocolate cornflake chips) instead of the medium paired with low reward in preference test. Animal shows -10.46 ±1.62 choice bias corticosterone 10 mg.kg-1 paired substrate, and -22.90 ±1.72 choice bias U50488 5 mg.kg-1 paired substrate. Moreover, we hypothesize that the biomarkers as brain-derived neurotrophic factor (BDNF) will increase in animals that are administrated with U50488 as a depressant KOR agonist.

Conclusion: Establishing a depression-cognitive bias model in a proper rat strain enable further studies on the mechanism behinds depression. With validating this model, it could be possible to use a translational approach in rodents and MDD patients. In this study, we emphasize on the involvement of the opioid system in altering CAB in depression and biomarkers.

Poster 17

Effect of Maternal Exercise on Developmental Programming of Hippocampal Neuroglial Plasticity and Associated Behavioural Deficits Induced by High-Fat Diet

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Background: Anxiety and major depressive disorder (MDD) is common in subjects exposed to adverse childhood events. Recently, maternal obesity and/or consumption of high-fat diets (HFD), have been proposed to have a negative impact on offspring mental health. Contrary, maternal exercise may prevent such disease progression. However, manifestations of a disease trait might depend on postnatal environmental triggers. The hypothalamic-pituitary-adrenal (HPA) axis represents a shared pathway underlying obesity, MDD and exercise. Further studies investigating the involvement of the HPA axis are crucial for elaborating the gene-environment interactions in the shared biology of depression and obesity.

Objectives: The aim of the present study was to examine the effect of maternal HFD on behaviour and hippocampal plasticity in adult offspring exposed to biological stress (e.g. administration of adrenocorticotropin hormone (ACTH)). Additionally, we investigated whether maternal voluntary wheel running during pregnancy would attenuate abnormalities in offspring.

Methods: Sprague-Dawley rats (dams) received control/HFD for 10 weeks before gestation. Both groups had access to either a sedentary or active running wheel 6 weeks including gestation. Adult offspring received ACTH (100µg/kg/day s.c.) or vehicle for 14 days. Anxiety- and depression-like behaviours were assessed. Hippocampal gene expression and protein levels were examined by real time qPCR and Western Blotting. Morphological quantification of hippocampal fibrillary glial acid protein (GFAP) positive astrocytes was performed in combination with 3-D image analysis. Hippocampal volume was estimated after magnetic resonance imaging (MRI) of the perfused brains.

Results: Our results showed that maternal HFD induced anxiogenic effects in male offspring. In males, both maternal HFD and adult stress increased immobility in the forced swim test. In the hippocampus, adult stress led to changes in mRNA expression of glucocorticoid receptor, mineralocorticoid receptor, corticotropin-releasing hormone receptor 1 and GFAP. Surprisingly, perinatal exercise counteracted the molecular impairments induced by adult stress. Furthermore, maternal exercise increased astrocytic number and length of astrocytic processes in non-stressed male offspring. Oppositely, in male rats exposed to ACTH, number and length of astrocytic processes and hippocampal volume, measured in the MRI, were reduced.

Conclusion: Overall, our results provide key insights into potential effects of gene-environment interactions on neurodevelopment. In the presence of a genetic predisposition to MDD, maternal diet and lifestyle may induce or protect offspring disease development, facing stress in adulthood.

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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.