ABSTRACTS

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ORAL PRESENTATIONS

LECTURE 1

SCNP 2014 OPENING LECTURE

L1 Recent advancements of molecular imaging on monoaminergic neurotransmission systems

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The so-called 'monoamine neurotransmitters', which include dopamine, noradrenalin, serotonin and histamine, are released from neurons in both the brain and the peripheral nervous system. The central neurotransmission systems, defined by the different monoamines, share similarities in that they originate from the brain stem and projects widely to sub-cortical and cortical brain regions. Each monoamine binds to several G-protein coupled receptors or transport proteins. The history of neuropsychopharmacology shows that the binding pocket is suitable also for binding of synthetic molecules such as antipsychotic or antidepressive drugs. This biological condition of the drug targets has over decades prompted industry to generate extensive series of synthetic molecules for monoaminergic receptors and targets.

In the early 80's, Positron Emission Tomography (PET became available for molecular imaging of radioligand binding to receptors, enzymes, and transporters of the living human brain. The methodology benefited considerably from the above mentioned availability of synthetic molecules suitable for radiolabeling. As of today, molecular imaging of markers for the monoaminergic neurotransmission systems has dominated the field. The aim of the present introductory presentation is to review the state-of-the-art and highlight some recent advancement of particular relevance to neuropsychopharmacology.

SYMPOSIUM 1

TOBACCO SMOKING IN

PSYCHIATRIC PATIENTS - A HARMFUL SELF-MEDICATION WITH NICOTINE?

S1.1 Tobacco smoking in major psychiatric disorders: why do our patients smoke as much as they do?'

Leif Lindström

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Abstract published seperately.

S1.2 Future medication in schizophrenia and depression: Role of alpha 7 nicotinic receptor agonists, partial agonists and positive allosteric modulators.

Torgny H. Svensson

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Abstract published seperately.

S1.3 Nicotinic receptor agonists and antagonists in animal models of depression

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Abstract published seperately.

S1.4 Smoking cessation in psychiatric patients. Pharmacological treatment alternatives and outcomes. Pros and Cons of e-cigarrettes

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Abstract published seperately.

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, at page 14, as they also are presented as posters.

LECTURE 2

SCNP LECTURE

L2 Probiotics: a novel treatment avenue in psychiatric disorders?

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There is a growing appreciation of the relationship between gut microbiota, and the host in maintaining homeostasis in health and predisposing to disease. Bacterial colonisation of the gut plays a major role in postnatal development and maturation of key systems that have the capacity to influence central nervous system (CNS) programming and signaling, including the immune and endocrine systems. Individually, these systems have been implicated in the neuropathology of many CNS disorders and collectively they form an important bidirectional pathway of communication between the microbiota and the brain in health and disease. Over the past 5 years substantial advances have been made in linking alterations in microbiota to brain development and even behaviour and the concept of a microbiota-gut brain axis has emerged. Animal models have been essential in moving forward this frontier research area. In order to assess such a role we use studies involving, germ free mice and early-life microbiota manipulations and finally probiotic administration in adulthood. We assess neurochemical, molecular and behavioural effects following these manipulations. Our data show that the gut microbiota is essential for normal stress, antidepressant and anxiety responses. Moreover, microbiota is essential for both social cognition and visceral pain. Finally, there are critical time-windows early in life when the effects of microbiota on brain and behaviour appear to be more potent. Our data also demonstrates that these effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. Such data offer the enticing proposition that specific modulation of the enteric microbiota by dietary means may be a useful "psychobiotic"-based strategy for both stress-related and neurodevelopmental disorders ranging from depression to autism. Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Results from large scale placebo-controlled studies are awaited. However, evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Moreover, neuroimaging studies are showing the ability of psychobiotics to modulate key brain circuits.

SYMPOSIUM 3

DEBATE SYMPOSIUM

S3 Antidepressants. Is efficacy a myth?

S3.1 The questioning of antidepressants is unfounded and harmful

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Several authors have recently attracted attention by publishing meta-analyses concluding that the difference between antidepressants and placebo is too small to be clinically meaningful, and that this small difference can be explained by side effects augmenting a placebo effect (by breaking the blind) in patients receiving active substances. According to these workers, the previous assumption that antidepressants exert a specific, pharmacological antidepressant effect by interacting with certain brain neurotransmitters is hence nothing but a myth. Though not agreeing with this harsh stance, also official bodies, such as NICE, often convey the message that the specific efficacy of antidepressants is at best modest. However, a notorious problem in this field, that is often ignored by those conducting and interpreting meta-analyses, is that drug trials often reveal highly inconsistent result: while a certain antidepressant may outperform placebo in one trial, the same drug may appear equal to placebo in another. Clearly, one of these outcomes must be inaccurate, methodological shortcomings being the only reasonable explanation for the results being disparate. In such a situation, one should not expect meta-analyses to reveal the true efficacy of the substance in question – on the contrary, such analyses are doomed to be misleading. However, if one instead of conducting meta-analyses considers the possible reasons for the divergences in outcomes, one inevitable conclusion is that a number of – since long well-documented and thoroughly discussed – methodological shortcomings are unfortunately at hand in modern

antidepressant trials, almost all of which can be expected increase the risk for falsely negative results. In contrast, the outcome of those high-quality trials showing various antidepressants to be markedly superior to placebo, or showing one antidepressant to be clearly superior to another in studies without a placebo arm, can hardly be explained in terms of methodological problems, but provide conclusive evidence for the assumption that at least some of these drugs are indeed remarkably effective, and that this effect is specific rather than being caused by side-effects breaking the blind.

S3.2 Antidepressants have not been shown to be effective

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The legal requirement is that a medicine be proven effective before it is licensed. At present there is no evidence that Antidepressants are effective in the sense of saving lives or even getting people back to work. We have changes in surrogate outcomes that are at best a marker for possible effectiveness. In terms of clinical benefits it is close to impossible from trial data to make a convincing case for the merits of "antidepressants" developed since the tricyclics other than for their use in conditions such as obsessive-compulsive disorder.

This doesn't mean that antidepressants don't have an effect. They do but under the influence of controlled trials, clinicians have less understanding of how to deploy these effects to benefit either their patients or themselves than they once did.

If we are to benefit patients and if doctors are to survive as a profession, they need to insist that antidepressants are complex agents that need expert input if they are to be deployed safely – a position that the clinical trial evidence reflects rather well.

LECTURE 3

SCNP LECTURE

L3 DSM-5 – facts and fiction

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Background: Categorical diagnoses of psychiatric illnesses using logical operators were developed in the U.S. in the 1970's, gaining rapid world-wide use with DSM-III from 1978. The number of defined disorders covered grew from 265 (DSM-III) to 292 (DSM-III-R, 1987), 297 (DSM-IV, 1994), and stabilizing at around 300 (DSM-5, 2013). Necessary operators have included duration, a set of symptoms and signs, functional disability, and specific excluding situations. Emphatically, the system is etiologically acausal, with a small number of exceptions such as PTSD.

Objectives: DSM-5 was launched by the APA in May 2013 after more than 10 years of preparation. The debate pro and contra had been intense, following mainly four paths: (1) the proper use of psychological dimensional measures, (2) the risk of over-diagnosis and application of psychiatric treatment to essentially healthy individuals, (3) the assumed necessity of finding diagnostic biomarkers before a valid diagnosis can be made, and (4) the poor progress in refining descriptive phenomenology/psychopathology and in phenotyping.

Results: All these 4 areas will be criticized. The dimension debate has led to a postponement in developing the conceptually difficult personality disorders, and the proposed rating scales for depression, anxiety, and suicidality have been assigned to a Section 3 (in need of further work). The over-diagnosis and over-treatment issue led to a moratorium in developing criteria for risk syndromes, e.g. attenuated psychosis. Finding biological markers are a sine qua non to some critics; NIMH developed its own Research Domain Criteria, the RDoC (but clinicians are encouraged to use DSM-5!). And poor phenotyping, often resulting in multiple co-diagnoses, competes with poor genotyping, where an array of psychiatric diagnoses share a large number of genes without specificity in sight. Furthermore, the cultural formulation from earlier DSM work has been enlarged and made even more relevant. The abolition of the five-axes system was surprising, but not without merit.

Conclusion: DSM-5 is a useful development in operational diagnostics — not by being nearer to "truth", but by being more logical and by incorporating a larger body of research. It is an aid to those assigned to make psychiatric diagnoses. It is neither a law text nor a bible. The final formulation continues to rest with the educated clinician.

SYMPOSIUM 4

TREATMENT OF ALCOHOL DEPENDENCE: A CURRENT UPDATE

S4.1 Extending Treatment Options in Alcohols Use Disorders: the Nalmefene Data

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Background: Reduction of alcohol consumption is increasingly recognised as a valid and needed option. DSM 5 has collapsed the dependence and abuse categories. Therefore the reduction of alcohol consumption will have to be an integrated part of the management of patients with "alcohol use disorders". The European Medicines Agency (EMA) published guidelines in 2010 where the reduction of alcohol consumption can be a valid goal in the treatment of alcohol dependent patients.

Objectives: Sponsored by Lundbeck three phase III studies placebo controlled RCTs where performed to evaluate the efficacy and safety of as-needed use of nalmefene 18mg (base) in reducing the monthly number of heavy drinking days (HDDs) and the monthly total alcohol consumption (TAC; g/day) in alcohol-dependent patients. Drinking measures were derived from daily drinking estimates collected with the Timeline Follow-back method.

Results: A total of almost 2000 patients were randomised. All three studies showed a significant reduction of alcohol consumption in the placebo groups. This underlines the feasibility of alcohol reduction over at least one year even in alcohol dependent patients. There were significantly superior effects (mixed model repeated measures) of nalmefene compared to placebo in reducing the number of heavy drinking days (HDDs) and total alcohol consumption (TAC). Improvements in Clinical Global Impression - Global Improvement and Severity of Illness scores and reductions in liver enzymes gamma‑glutamyltransferase and alanine amino-trans¬ferase from baseline were significantly larger in the nalmefene group compared to placebo. Undesired effects (nausea, dizziness, headache…) were mild to moderate and transient. Post hoc analyses looked at subgroups of patients whose benefit from nalmefene might be bigger than for the total group. Results will be presented.

Conclusion: Nalmefene seems to extend our treatment paradigms for alcohol dependent patients. In the hands of General Practitioners and specialists alike it may help to get more patients involved into treatment than at present.

S4.2 Recent RCTs in Alcohol Dependence – Mixed Effects of Varenicline (partial nicotine receptor agonist) and Org 25935 (glycine uptake inhibitor)

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Background: Alcohol dependence generates immense suffering and costs. New effective treatments are urgently needed. We have for several years studied mechanisms involved in ethanol´s activation of the mesolimbic dopaminergic reward system in rodents. Crucial roles for nicotinic acetylcholine receptors in the ventral tegmental area and glycine receptors in the nucleus accumbens have been revealed and pharmacological manipulations of these receptor populations reduce ethanol intake in rats.

Objectives: To explore whether varenicline, a partial nicotinic receptor agonist, and Org 25935, a glycine receptor uptake inhibitor, reduce alcohol consumption also in man.

Methods: RCTs according to standard procedures. In the varenicline study the effects of varenicline and placebo on ongoing alcohol consumption in alcohol dependent individuals (n=162) was explored, whereas in the Org 25935 study (n=144) the active treatment was compared to placebo with respect to relapse into heavy drinking after initial detoxification.

Results: The varenicline study was negative on primary and secondary outcomes, but both treatments reduced self-reported alcohol consumption by approx. 50 %. When excluding placebo-responders during the initial two-week placebo run-in, in order to make the study comparable to a recent positive American study on the same topic, there was a trend for a positive effect of varenicline, as compared to placebo, on participants with moderate consumption levels. Further, when using phosphatidylethanol (PEth) in plasma as outcome variable, this was significantly reduced compared to baseline by varenicline but not by placebo. The Org 25935 study was subjected to an interim analysis after 144 patients (powered for n=300) and was interrupted due to futility. The percentage heavy drinking days as compared to pre-detox was reduced by approx. 85% both in the placebo and the Org 25935 group.

Conclusion: Support for our concept of interfering with nicotinic receptors in order to reduce alcohol consumption in alcohol dependent individuals was obtained in our secondary analyses and in an independent American study with varenicline. Further, it may be of utmost importance to monitor alcohol intake with an objective measure of alcohol consumption in order not to miss a treatment effect. The study also suggests that subjects receiving placebo, as compared to active treatment, may overestimate their reduction of alcohol intake. The design of the Org 25935 study yielded a pronounced placebo effect that left little room for further improvement. Other possible reasons for failure of the glycine receptor concept will be discussed.

S4.3 The Gut-Brain Axis and Addiction: The Involvement of Gastrointestinal Hormones in the Brain Reward Orchestra

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The mechanisms involved in alcohol use disorders are complex and involve various signaling systems. In a series of experiments we have recently obtained results implicating ghrelin signaling as a novel candidate. We found that ghrelin, an orexigenic peptide, activated the mesocorticolimbic dopamine system an effect that could be antagonized by a nicotinic acetylcholine antagonist indicating that ghrelin, like ethanol, can activate the cholinergic-dopaminergic reward link. Support for our hypothesis of an important role for ghrelin as a player on the reward scene was given in experiments showing that ghrelin increased ethanol intake in a two bottle choice paradigm and that the dopamine-enhancing (in nucleus accumbens) effect, the locomotor stimulating effect as well as the rewarding effect in a conditioned place paradigm of ethanol was significantly reduced in animals with suppressed ghrelin signaling by means of ghrelin receptor (GHS-R1A) knockout mice or mice treated centrally or peripherally with GHS-R1A antagonists. Our findings that reduced ghrelin signaling also attenuated the rewarding and dopamine enhancing effect of amphetamine and cocaine suggest that ghrelin may be of general importance in increasing the incentive value of signals associated with motivated behaviors such as drug-seeking. Data will also be presented indicating that the ghrelin driven activation of the mesolimbic dopamine system may involve the nitric oxide signaling pathway. Translational validity of our results are implied by our findings of an association between a single nucleotide polymorphisms in the ghrelin receptor and individuals with alcohol use disorders.

Conclusively, this study provides further evidence for that the ghrelin signaling system is implicated in the rewarding and neurobiological effects of alcohol as well as for other drugs of abuse. Taken together, these data imply that the GHS-R1A may constitute a novel therapeutic target for the treatment of substance use diorders.

SYMPOSIUM 5

NEW TREATMENT OPTIONS IN ADHD

S5.1 Current evidence for pharmacological treatments in adult ADHD

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Objectives: To summarise the current literature and present expert consensus recommendations for the pharmacological treatment of ADHD

Methods: Literature review and expert consensus

Results: Psychostimulants are first-choice pharmacological treatment both in children and adults.

Conclusion: More pharmacological studies in humans are necessary to understand the full range of actions of ADHD medications in the brain and the individual variations that may limit efficacy or cause side effects

S5.2 Current evidence for psychological treatments of adult ADHD.

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Background: Historically, clinical guidelines have recommended medication treatment as the first line treatment for adults with ADHD. This is mostly because of the numerous studies that have shown that medication treatment is efficient but also because other treatment forms such as psychological treatments have not been investigated extensively. Recently however, a few clinical studies on the effectiveness on psychological treatments have been published, both for individual and group treatment.

Objectives: The aim of this presentation is to look at controlled studies on psychological treatments for adults with ADHD, especially cognitive behavioural treatments. In light of the high rates of comorbidity in ADHD, psychological treatments not only need to target ADHD core symptoms but also other problems such as anxiety and depression. It is therefore interesting to look at how psychological treatments target these different problems.

Methods: Selected studies that measure changes in ADHD core symptoms and comorbidity will be discussed.

Results: The findings from these studies suggest that the provision of psychological treatment in medicated patients – whether delivered in individual or group sessions – is effective in treating ADHD symptoms and has an additive effect over and above medication alone. Additionally, psychological treatments show positive long term effect.

Conclusion: A pattern of steadily increasing use of medication has been apparent for the last few years while psychological treatments have not paralleled this growth. However, the few clinical studies that have been conducted indicate that psychological treatments do work for adults with ADHD and have a long term effect. The findings for treating comorbid problems however are limited and need to be studied further. In light of limited treatment options and often high costs of treatment it is now important to emphasise clinical studies on other cost-effective interventions such as cognitive behavioural treatment.

S5.3 New treatment options in adult ADHD

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Background: Psycho-stimulants are the gold standard in the medical treatment of ADHD. Despite their well-documented efficacy, there are still many adult patients who do not respond satisfactorily to these drugs, and there is also a concern about their potential long-term adverse effects and risk of abuse (controlled substances). The few available non-stimulants drugs have so far shown to be less effective.

Objectives: The objective of the lecture is to present new drugs that are currently being tested for the treatment of ADHD in adults.

Methods: Different databases, including PubMed and ClinicalTrials.gov, were searched for clinical trials on treatment of ADHD in adults, and references were also obtained from articles and experts in the field.

Results: Some clinical trials with potential new treatment options for ADHD were identified and will be presented in more detail in the lecture. Most of these represent new formulations or variants of drugs that are already available for ADHD or other conditions (e.g. metadoxine), whereas some are novel drugs (e.g. the nicotinic receptor agonist AZD380). Interesting studies with "nutraceuticals" (micronutrients) will also be discussed. Some of these new drugs may have more specific effects on parts of the symptomatology in ADHD, i.e. cognition and symptoms of mood/emotional dysregulation.

Conclusion: The development of new drugs in the treatment of ADHD has been quite slow compared to other psychiatric disorders. However, the rapidly expanding knowledge of pathophysiological mechanisms of ADHD increases the possibilities of targeting this development and will hopefully result in a larger sortiment of effective and safe treatment options for adults with ADHD in the near future.

SYMPOSIUM 6

NOVEL APPROACHES IN SCHIZOPHRENIA

S6.1 Stratifying schizophrenia: Can we use neurochemical imaging and genetic data to target responders to novel glutamatergic drugs in schizophrenia?

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Background: A third of patients with schizophrenia fail to respond to standard dopamine-blocking antipsychotic drugs. This is a major clinical problem, causing immense personal and family suffering and costing billions in health, social care and lost productivity. We currently make prescribing recommendations in schizophrenia using an empirical approach, trying successive treatments almost at random until we find one that is effective. With the exception of clozapine, there is little evidence to guide us in our choice of treatments. Furthermore, all our treatments have the same assumed mechanism of action.

Objectives: Our goal is to use genetics and/or neurochemical imaging to stratify patients at first episode according to their likely drug response, thus avoiding failed treatment trials and reducing the duration of under-treated psychosis.

Methods: Two converging streams of findings suggest that abnormalities of the glutamate system may identify patients who are non-responsive to dopamine blockers (T-Non-Resp). Imaging studies have shown that T-Non-Resp patients have abnormal glutamate systems, but seemingly normal dopamine systems. Meanwhile, genetic research has demonstrated that T-Non-Resp patients have an excess of genetic abnormalities in glutamate system pathways, but fewer abnormalities in dopamine pathways, than typical patients with schizophrenia. This raises the possibility that novel drugs acting on the glutamate system may be indicated in these patients. Together with colleagues from around the UK we have developed a research program to refine and test a stratified medicine approach in schizophrenia, focusing on the glutamate system.

Conclusion: A stratified medicine approach is needed in the treatment of schizophrenia. We hope that the research strategy we have outlined will bring this closer to reality.

S6.2 Striatal and extrastriatal dopamine D2/3 receptor binding and reward abnormalities in antipsychotic-naïve first-episode patients with schizophrenia: Relation to treatment outcome?

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Background: Disturbances in striatal dopamine activity and reward processing are believed to be related to each other as well as to psychotic symptoms. Moreover, one of the best-validated findings in schizophrenia research is the association between the effect of antipsychotic compounds on positive psychotic symptoms and dampening of dopamine activity by blockade of dopamine D_2 receptors. We have recently demonstrated highly significant alterations of the reward system in antipsychotic-naïve first-episode schizophrenia patients – and an association between these disturbances and positive symptoms[1]. Treatment for 6 weeks with a D_2 blocker (amisulpride) partly normalized the disturbances in the patients responding to treatment[2]. In another, comparable, cohort of antipsychotic-naïve, first-episode schizophrenia patients, we have reported significant associations between frontal dopamine D_2 receptor binding potentials (BP) and positive symptoms[3].

Objectives: The objectives of the presentation is to discuss the potential predictive value of striatal as well as extrastriatal D_2 receptor BP in antipsychotic-naïve first-episode schizophrenia patients as markers for treatment outcome. An additional aim is to present new data linking disturbances in reward processing to striatal D_2 receptor BP in the antipsychotic-naïve patients at baseline and to D_2 receptor blockade following the patients' first antipsychotic treatment.

Methods: Two comparable cohorts of antipsychotic-naïve first-episode schizophrenia patients were examined before and after their first antipsychotic treatment. The first cohort was examined with single-photon emission computerized tomography (SPECT) using the $D_{2,3}$ receptor ligand $[^{1,2,3}\text{I}]$epidepride before and after 3 months of treatment with either the second generation compound, risperidone, or the first generation compound, zuclopenthixol. The second cohort was assessed before and after 6 weeks of treatment with the relatively selective $D_{2,3}$ blocker, amisulpride. The examination program included functional magnetic resonance imaging (fMRI) using a variant of the monetary incentive delay task and SPECT using $[^{123}\text{I}]$iodbenzamid (IBZM) as the radioligand. Epidepride and IBZM are suitable for examinations of extrastriatal respectively striatal dopamine $D_{2,2}$ receptors. Both cohorts were assessed with the Positive And Negative Syndrome Scale (PANSS).

Results: The analyses are still ongoing. The preliminary results suggests that treatment outcome with regard to positive symptoms is associated with low striatal, respectively high frontal dopamine $D_{2,3}$ BP in the antipsychotic-naïve patients. The preliminary analyses further suggest that reward processing in the patients is associated with

$D_{2,3}$ receptor BP at baseline and $D_{2,3}$ occupancy following treatment.

Conclusion: The preliminary data suggest an inverse relationship between striatal respectively frontal dopamine $D_{2,3}$ receptor BP in antipsychotic-naïve first-episode schizophrenia patients and treatment outcome, hereby supporting an inverse relationship between striatal and frontal dopamine activity. Our preliminary data additionally support an association between $D_{2,3}$ receptor availability and reward processing.

[1]Nielsen et al. Biol Psychiatry 2012;71:898-905
[2]Nielsen et al. Arch Gen Psychiatry 2012;69:1195-1204
[3]Glenthøj et al. Biol Psychiatry 2006;60:621-9

S6.3 Subgrouping of antipsychotic-naïve first-episode schizophrenia patients based on by the application of unsupervised machine learning approach on cognitive and psychophysiological data

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Background: Schizophrenia is a heterogeneous brain disease with insufficient treatment methods. Nevertheless, the diagnosis is still entirely based on clinical symptomatology rather than objective measures of key endophenotypic markers for the disease such as cognitive and electrophysiological disturbances. There is an urgent need for identification of biologically valid subgroups of schizophrenia that can be used for stratification of patients in future studies, and could hopefully help the psychiatrist in choice of antipsychotic compound for the individual patient. Machine-learning (ML) algorithms can be used to reveal patterns in complex data that cannot be identified with more classical methods. In the present study, we have used advanced unsupervised ML in order to identify subgroups purely based on cognitive and electrophysiological markers in first-episode antipsychotic naïve schizophrenia patients.

Objectives: To identify objectively measurable, biologically valid, and clinically meaningful subgroups of patients with schizophrenia

Methods: These initial analyses were performed on cognitive (32 measures) and electrophysiological (17 measures) data from a sample of a cohort of antipsychotic-naïve first episode schizophrenia patients and matched controls. The principal components (PCs) of the complete standardized dataset were determined. The

two first PCs of the patient data were used as input in the unsupervised machine learning model (a Gaussian Mixture Model) to identify group structures in schizophrenia. Leave one out (LOO) cross-validation was used to estimate the probability of the model.

Results: The first PC was found to be driven by the cognitive measures while the second PC was driven by the electrophysiological measures. The LOO cross-validation indicated that a two group model (mixture components) of schizophrenia patients was the most likely in our dataset. In one of these groups it seemed there is dependency between the PCA components, while they seem more independent in the other group. Post hoc analyses revealed no significant differences between groups in clinical measures such as PANSS or GAF scores, or cannabis use. The analyses are ongoing: the last subjects in the cohort are still being recruited, and methods for handling missing data are being developed.

Conclusion: We show that there is a statistically valid group structure in a sample of first episode, antipsychotic naïve schizophrenia patients with two subgroups based on cognitive and electrophysiological features. The structure of the cognitive and electrophysiological measurements in the two groups indicate that they can be important for stratification in future studies, thereby reducing sampling variance and may potentially lead increased sensitivity.

SYMPOSIUM 7

BIOMARKERS AND NEW DRUG DEVELOPMENT

S7.1 The Sensodetect® - method as biomarkers and diagnostic support for schizophrenia and adult ADHD in relation to healthy controls.

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Background: The SD-BERA (SensoDetect® - Brainstem Evoked Response Audiometry) method records auditory brainstem responses to 13 different click sound stimuli and utilizes digitalization of the analogue BERA responses and a newly developed moving minimum subtraction method for detailed analysis of the waveforms of the evoked responses. Application of the method in groups of patients has shown differences in ABR waveforms between patients with schizophrenia and patients with adult ADHD vs. healthy controls.

Methods: An investigator-initiated clinical study of patients with DSM-IV TR schizophrenia and adult ADHD vs. no psychiatric diagnosis controls with blind

evaluation of SD-BERA recordings was performed at the Uppsala University Hospital. Clinicians were in charge of recruiting test persons and of performing the SD-BERA test. A separate team at SensoDetect AB, Lund, evaluated the recordings blind to their clinical diagnoses. Blind-breaking was overseen by an independent third party. Patients with schizophrenia (n=28), adult ADHD (n=24) and healthy controls (n=59) were included in the analysis.

Results: The main finding was that SD-BERA identified patients with schizophrenia and adult ADHD vs. controls with high sensitivity and specificity. The sensitivity for schizophrenia vs. controls was 82.7%, for ADHD vs. controls 87.5%, and for both patient groups the specificity was ≥93.1%. The SD-BERA test indicated ADHD in 1/29 patients with clinical schizophrenia, and schizophrenia in 1/24 patients with clinical ADHD.

Conclusion: The present study confirms previous findings and suggests that the SD-BERA method might provide useful biomarkers and support for the clinical diagnoses of the two disorders.

S7.2 Can new psychiatric genetics findings facilitate drug targets

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Background: Genome-wide association studies (GWAS) have identified a large number of gene variants associated with schizophrenia, but these variants explain only a small portion of the heritability. It is becoming increasingly clear that schizophrenia is influenced by many genes, most of which have effects too small to be identified using traditional GWAS statistical methods.
Objectives Identify more of the polygenic contribution to psychiatric phenotypes to identify new potential targets.
Methods: Empirical Bayes statistical approaches to GWAS summary statistics data. Utilizing independent schizophrenia substudies, we investigate the replication rates in *de novo* samples, indicating that they likely represent true schizophrenia risk genes.
Results: By applying recently developed Empirical Bayes statistical approaches, we have demonstrated that functional genic elements show differential contribution to phenotypic variance, with some elements (regulatory regions and exons) showing strong enrichment for association with schizophrenia. Applying related methods, we also showed abundant genetic overlap (pleiotropy) between schizophrenia and other phenotypes, including bipolar disorder, cardiovascular disease risk factors, and multiple sclerosis. By applying our novel statistical framework, we dramatically improved gene discovery and detected a large number of new gene loci associated with schizophrenia that have not yet been identified with standard GWAS methods. A distinct pattern of gene vari-

ants are related to molecules involved in synaptic transmission – with potential new treatment targets.

Conclusion: The new statistical tools provide a powerful approach for uncovering more of the missing heritability of schizophrenia and other complex disorders. In conclusion, the highly polygenic architecture of schizophrenia strongly suggests the utility of research approaches that recognize schizophrenia neuropathology as a complex dynamic system, with many small gene effects integrated in functional networks.

S7.3 Obesity and Psychotic Disorders, Uncovering Common Mechanisms through Metabolomics

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Background: Primary obesity, and psychotic disorders and their treatments, are similar with respect to associated changes in energy balance and co-morbidities, including metabolic syndrome. These similarities do not necessarily demonstrate causal links, but instead suggest that specific causes of and metabolic disturbances associated with obesity also play a pathogenic role in these co-morbidities, potentially even before obesity develops.

Methods: Metabolomics – the global study of metabolites, which are small molecules generated by the process of metabolism – has been important in elucidating the pathways underlying obesity-associated co-morbidities.

Results: I will describe how recent and ongoing metabolomics studies have advanced biomarker discovery and the elucidation of mechanisms underlying obesity and its comorbidities, with a specific focus on psychotic disorders. The importance of identifying metabolic markers of disease-associated intermediate phenotypes – traits modulated but not encoded by the DNA sequence – will be emphasized.

Conclusion: The metabolic markers would be applicable as diagnostic tools in a personalized healthcare setting and might also open up novel therapeutic avenues.

POSTERS

Poster 1

Probiotic treatment alters behavior in rats on standard and high-fat diet

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Background: The literature suggests a bi-directional association between metabolic disorders (e.g. diabetes mellitus type II and metabolic syndrome) and depressive disorder. The gut microbiota may play an important role in metabolic disorders and has been shown to affect behavior in animals as well, and diet is known to alter the gut microbiota composition. The immune system is believed to play a major role in this interplay.

Objectives: To study the effects of probiotic treatment on glucose metabolism, behavior and immune system in rats on a standard or high-fat diet.

Methods: 40 male Sprague-Dawley rats were fed a high-fat or control diet for 10 weeks. Additionally, a probiotic mix (10 lactobacillus/bifidobacteria species) or placebo were administered daily during the last 5 weeks (n = 10). The animals were subjected to behavioral tests (Barnes Maze, Novel Object Recognition, Open Field, Forced Swim Test) as well as an oral glucose tolerance test. Cytokine production from anti-CD3/28 stimulated blood lymphocytes was measured, and a dexamethasone cytokine production suppression test was performed on these cells as well.

Results: Probiotic treatment was associated with a significant and complex pattern of behavioral changes, but it did not affect body weight or caloric intake. However, animals on high-fat diet gained significantly more weight and suffered from impaired glucose tolerance. Final analyses are still ongoing.

Conclusion: Potentially, this interdisciplinary project could contribute to an understanding of the extensive significance of the newly discovered, intriguing world of the intestinal microbiota, including the "gut-brain-axis".

Poster 2

Efficacy outcomes in age and sex subgroups from two clinical trials of lisdexamfetamine dimesylate in the treatment of adults with attention-deficit/hyperactivity disorder

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Background: Attention-deficit/hyperactivity disorder (ADHD) is characterised by persistent symptoms of inattention and/or hyperactivity. While ADHD was historically believed to be limited to childhood, symptoms of ADHD are now recognised to continue into adulthood in many patients.

Objectives: Analyse post hoc the impact of sex and age on the efficacy of the prodrug stimulant lisdexamfetamine dimesylate (LDX) in the treatment of ADHD in adults.

Methods: Study NRP104.303 was a 4-week, double-blind, forced-dose study in adults (aged 18–55 years) with ADHD and a baseline ADHD Rating Scale IV with adult prompts (ADHD-RS-IV-Adult) total score of at least 28. Patients were randomized (2:2:2:1) to receive LDX 30, 50 or 70 mg/day, or placebo. Study NRP104.304 was a 12-month, open-label, dose-optimized, extension to NRP104.303. In both studies, the primary efficacy outcome was the change from baseline in ADHD-RS-IV-Adult total score and endpoint was defined as the last post-baseline treatment visit with a valid score. Post hoc analyses assessed improvements in ADHD-RS-IV-Adult total core in subgroups categorized according to sex and age.

Results: In NRP104.303, 420 patients were enrolled and randomized and 349 completed the study (LDX 30 mg, n=103; LDX 50 mg, n=96; LDX 70 mg, n=98; placebo, n=52). Least-squares mean changes from baseline to endpoint in ADHD-RS-IV-Adult total score (standard error) were significantly greater for all doses of LDX (range, –16.2 [1.06] to –18.6 [1.03]) than placebo (–8.2 [1.43]). Post hoc analyses revealed similar improvements with LDX in sex-related (male [n=224], LDX –16.7 [1.50] to –18.6 [1.53], placebo, –8.9 [2.12]; female [n=190], LDX –15.5 [1.56] to –19.3 [1.46], placebo –8.0 [2.02]) and age-related (18–39 years [n=262], LDX –15.3 [1.34] to –18.9 [1.31], placebo –5.6 [1.87]; 40–55 years [n=152], LDX –16.1 [1.81] to –17.1 [1.87], placebo –12.8 [2.52]) subgroups. In total, 349 patients were enrolled in NRP104.304 and 191 completed the study. In this 12-month extension study of open-label LDX treatment, improvements from baseline to endpoint in mean (standard deviation) ADHD-RS-IV-Adult total score were similar between the overall population (–24.8 [11.7]) and sex and age subgroups (male [n=188], –24.5 [11.5]; female [n=157], –25.2 [12.0]; 18–39 years [n=208], –25.3 [11.4]; 40–55 years [n=137], –24.1 [12.2]).

Conclusion: In short- and long-term adult studies, LDX was associated with similar improvements in ADHD symptoms in the overall study population and sex- and age-related subgroups.

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Poster 3

The economic impact of attention-deficit/hyperactivity disorder among children and adolescents in Sweden

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Background: Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity and impulsivity. The disorder causes functional impairment in various aspects of daily life and is estimated to affect approximately 4.0% of children/adolescents in Sweden. However, the economic burden of ADHD on patients and their families is poorly understood.

Objectives: To comprehensively identify and review published data on the costs of ADHD in Europe and apply the findings to quantify annual national costs relating to ADHD among children/adolescents in Sweden.

Methods: A systematic search (using MEDLINE, PsycINFO, EMBASE, HEED and ERIC databases) was conducted to identify original research articles published between 1 January 1990 and 23 April 2013 reporting costs associated with childhood/adolescent ADHD in Europe.1 Costs associated with healthcare (for the child/adolescent with ADHD and/or other family members), education, social services, and productivity and income losses (among family members) were evaluated. If more than one data source was available for each cost category, lowest and highest reported per-person cost estimates were used. Per-person costs (inflated to 2012 Euros and converted to krona [SEK]) for each category were used to estimate total annual ADHD-related costs for Sweden, using Swedish employment and ADHD prevalence rates, and 2012 national census and family composition data.

Results: Seven studies met the inclusion criteria and provided data on cost components: healthcare (n=7), education (n=2), social services (n=1) and productivity losses (n=2). No studies of the societal costs of childhood/adolescent ADHD relating to substance abuse, road traffic accidents or the justice system in Europe were identified. Estimated total annual costs associated with ADHD among children/adolescents in Sweden had a range of 4.31–6.28 billion SEK (95,211–138,749 SEK per patient). Up to three-fifths of the total cost was related to education for children/adolescents with ADHD (2.67 billion SEK; 43–62%). The remaining costs were related to: healthcare (for patients and other family members; 0.99–2.16 billion SEK), social services (0.018 billion SEK) and productivity losses (0.63–1.43 billion SEK). Up to one-third (30–33%) of the total annual cost of childhood/adolescent ADHD was related to (healthcare and productivity losses of) other family members.

Conclusion: This systematic review and data analysis illustrates the substantial economic burden of childhood/adolescent ADHD in Sweden and its financial impact on a wide range of public services. The few studies identified contribute to uncertainty in cost estimates and highlight the need for more research to assess the wider societal impact of ADHD in Europe.

Reference:

1. Le HH et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. Eur Child Adolesc Psychiatry 2013 Oct 29. Epub ahead of print.

Disclosure:

Poster 4

Genome-wide association study identifies common variants associated with metabolism of psychotropic drugs

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Background: Schizophrenia and bipolar disorder are severe psychiatric diseases collectively affecting about two percent of the world's population. Psychotropic drugs provide a cornerstone in the treatment of these psychotic disorders. However, there is a large unexplained inter-individual variation in the response to these drugs, and the metabolism of the drugs is a critical issue in the treatment. A large proportion of the variation in response is still not accounted for, but accumulating evidence suggests the involvement of genetic factors.

Objective: In the current study, we aimed to determine genetic variants associated with metabolic rate of psychotropic drugs based upon a homogenous Norwegian sample of 1334 individuals with psychotic disorders. The use of GWAS in psychopharmacology could lead to increased stratification of patients for better and more individualized treatment strategies.

Methods: For this purpose we undertook a genome-wide association study (GWAS) of the phenotype defined by standardized concentration/dose ratio (CDR), reflecting drug metabolisms as well as related pharmacokinetic properties.

Results: The GWAS revealed several polymorphisms associated with standardized CDR. One marker (rs16935279, P-value = 3.95×10^{-10}), located in an intronic region of the lincRNA LOC100505718, reached genome wide significance. Carriers of the minor allele have a lower metabolic rate of antiepileptic drugs compared to major allele carriers

Conclusion: In a clinical setting, we consider standardized CDR to be of the best measure of metabolic rate for a drug. The standardized CDR allows for direct comparison between subjects taking various drug dosages and minimizes the confounding effects in a clinical environment. The present findings indicate that common gene variants not related to the already well-investigated cytochrome P450 system can affect the metabolism of psychotropic drugs. In order to confirm these findings, replication in an independent sample is needed.

This warrants further investigation into the functional mechanisms involved as it could potentially lead to identification of predictive markers as well as novel drug targets.

Poster 5

Toxoplasma gondii seropositivity is positively associated with anxiety and burnout-syndrome

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Background: Toxoplasma gondii (TOX) is a common parasite affecting approximately one-third of the human population, primarily targeting neurons. An increasing number of studies are now providing evidence that the disease is associated with behavioural changes and psychiatric disease. It has for example been demonstrated that TOX seropositivity was higher in schizophrenia, depression, anxiety, and bipolar patients compared to healthy controls.

Objective: The aim of this study was to examine TOX seropositivity in a large human population in relation to psychiatric symptoms.

Methods: A population of 548 participants was initially included and the participants went through a semi-structured diagnostic interview (SCAN interview) followed by blood sampling. From this population, a control group (n=158) with no diagnosis of psychiatric disorders was extracted as well as a group consisting of subjects showing symptoms of anxiety (SCAN interview, n=106) and burnout syndrome (Copenhagen Burnout Inventory, n=51). Blood serum was examined for IgG antibodies to TOX using ELISA assays.

Results: Data were analysed using logistic regression models with gender, age and BMI as confounding factor and showed that seropositivity of TOX is positively associated with anxiety (adjusted odds ratio [OR]=2.05; 95% CI, 1.14-3.70; p=0.016). In addition, we find an association between seropositivity and burnout syndrome (OR=3.43; 95% CI, 1.67-7.05; p<0.001).

Conclusion: These data supports the notion that TOX is associated with psychiatric disorders. Our results are consistent with previous reports on an association between TOX and anxiety. Furthermore, we show a positive association between TOX seropositivity and the stress related syndrome, burnout syndrome.

Poster 6

Improving treatment of patients with schizophrenia – glutamatergic and GABAergic disturbances as possible markers of choice-of-treatment

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Background: Insufficient treatment response to dopaminergic antipsychotics constitutes a major challenge in the treatment of patients with schizophrenia and seems to be related to persistently high levels of the neurotransmitter glutamate. Excess glutamate is neurotoxic and highly likely causes the progressive loss of brain tissue and functions seen in many patients. The neurotransmitter gamma-amino-butyric-acid, (GABA), regulates levels of glutamate, and hypofunctional GABAergic interneurons may cause the high levels of glutamate in patients with schizophrenia.

Objectives: To test the hypothesis that a subgroup of initially antipsychotic naïve patients with schizophrenia with poor treatment response is characterized by persistently high levels of glutamate in two

interconnected brain areas termed the anterior cingulate cortex (ACC) and thalamus. Further, we wish to clarify the relationship between levels of glutamate and GABA and psychopathology as well as level of function.

Methods: The study is a prospective follow-up study of 60 antipsychotic naïve patients with schizophrenia and 60 matched healthy controls. Levels of glutamate and GABA are measured with proton magnetic resonance imaging (1H-MRS) before and after 6 weeks' treatment with a partial dopamine agonist (aripiprazol) and treatment response by clinical rating scales measuring psychopathology and level of function. Patients are retested after 6 months and 2 years.

Results: Inclusion started on 1 January 2014. To date, 5 of the planned 60 patients have been included. Preliminary analyses based on the first included patients will be presented at the meeting.

Conclusion: Elucidation of glutamatergic and GABAergic disturbances in a presumed subgroup of patients is clinically crucial. The results can pave the way for development of new antipsychotic medication modulating glutamatergic and GABAergic disturbances and lead to better prevention strategies for the progressive loss of brain tissue and functions. Lastly, it is the hope that glutamatergic disturbances in the future can be used as a clinical marker for best choice of treatment in the clinical practice.

Poster 7

Ultrastructural (Synaptic and mitochondrial) plasticity of the hippocampus in a genetic rat model of depression after repeated electroconvulsive seizures

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Background: In addition to neurogenesis, synaptic and mitochondrial plasticity are important form of neuronal plasticity in the pathophysiology of depression and the effects of antidepressant treatment. The underlying mechanism of the therapeutic effect of Electroconvulsive Therapy (ECT) is still unclear.

Objectives: Here we investigated whether repeated electroconvulsive seizures (ECS), an animal model of ECT, induce changes in synapse and mitochondria number in a rat strain that displays a genetic susceptibility to depressive behavior, the Flinders Sensitive and Resistant Lines (FSL/FRL).

Methods: Design-based stereological methods were used to estimate the number of synapses and mitochondria and volume of mitochondria in CA1 of the hippocampus in two different strains of rats; the Sprague–Dawley (SD) and Flinders rats.

Results: Results showed, under untreated conditions, the number of synapses and mitochondria were significantly smaller in the FSL-sham group (untreated "depressed" rats) compared to the FRL-sham group (normal rats), showing correlation to the observed decreased immobility in the forced swim test. Moreover, mitochondrial number between axons and dendrites was firstly revealed differences in "depressed" rats. However, the mean volume of mitochondria was significantly larger in the FSL-sham group compared to the FRL-sham group. ECS treatment significantly increased the number of synapses and mitochondria in the FSL-ECS group (treated "depressed" rats) compared to the FSL-sham group. The changes of mitochondrial number only happened in axons without dendrites. But there were no significant differences in the number of mitochondria after ECS treatment in SD rats.

Conclusion: Our results indicate that depression may be related to impairments of synaptic and mitochondrial plasticity in the hippocampus and antidepressant treatment may counteract with the structural impairments. Moreover, the changes in mitochondrial morphology and number are a consistent feature of neuroplasticity.

Poster 8

Disturbances of Circadian Rhytm in a Rat Chronic Mild Stress Model of Depression

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Background: It has been suggested that abnormalities in circadian rhythm (CR) may be a causal factor in the development of major depressive disorder (MDD). Blunted or abnormal CR has been found in depressed individuals in a variety of body functions including sleep/wake pattern, body temperature and hormone secretion. The suprachiasmatic nucleus (SCN) is well known for its function as the master clock and regulates several circadian systems according to clock genes (CG) expression. In addition to central expression, peripheral CGs have also been found.

Objectives: The aim of this project is to provide new insights into the pathology and etiology of (MDD) and to find new molecular targets focusing on the CR.

Methods:The study is based on a highly validated animal model of depression, the chronic mild stress model (CMS). Depression-like and control rats were terminated

by decapitation in a 24 h timespan and the brain removed from skull. Quantification and visualization of CGs in the brain were established by the in situ hybridization method.

Results: We studied three of the most essential clock genes, Per1, Per2 and Bmal1, and found that depression-like animals showed an abnormal CR in subregions of rat brains related to depression; Expression of Per1 showed a significantly robust CR in the SCN, the hippocampus and the pineal gland. In the SCN a significantly robust CR of Per1, Per2 and Bmal1 is shown. As for Per2 and Bmal1, a shift in phase has been observed in the SCN. Furthermore, a significantly different expression of Per1 and Per2 is measured between CMS susceptible rats and control rats in the hippocampus. Expression of clock genes in the Pineal gland are not affected by stress induced depression.

Conclusion: We conclude that abnormalities in CRs are related to depression-like state in the CMS model. However, the effect of chronic stress is selective; Per1 expresses a robust CR in the master clock and in two other brain structures related to depression. However, Per2 and Bmal1 expression might be more susceptible and responsive to chronic stress induced depression.

Poster 9

Neuropeptide S: new anxiolytic therapeutic avenues explored using viral vectors

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Background: Though anxiety disorders are among the most common psychiatric illnesses, novel-acting compounds are still lacking. Recently, the receptor for Neuropeptide S (NPS), a highly conserved peptide, was found to be implicated in the regulation of anxiety in both humans and rodents.

Objective: The aim of this study was to overexpress NPS in amygdala, using Adeno-associated viral (AAV) vectors and to investigate the potential anxiolytic effects hereof.

Methods: NPS- or Empty AAVvector was injected bilateral into amygdala of male Wistar rats. After three weeks, the animals were subjected to anxiety-, locomotion- and depression related behavioural tests; Elevated Plus Maze (EPM), Light/Dark box (LDB), Open Field (OF) and Forced Swim Test (FST). The overexpression of NPS protein was verified by immunofluorescence staining of brain sections.

Results: The immunohistochemical staining showed a clear, but discrete overexpression of the NPS protein in basomedial/basolateral amygdala in all NPS-AAV treated animal.

In the behavioural tests, the NPS-AAV treated animals were found to spent significantly more time at the open arms (p<0.05, Student´s t-test) of the EPM, though no differences in the number of open arm entries was found between the groups. Likewise, the latency to fully enter the open arms was markedly decreased (p<0.05, Student´s t-test) for the animals treated with the NPS-AAV vector. This anxiolytic behaviour observed in the NPS-AAV treated animals was also seen in the LDB test, were these animals had a clear tendency to enter the light compartment more frequently than the Empty-AAA treated animals. This tendency could not be ascribed an increase in locomotor activity, since no difference in the OF test was observed between the two groups. Finally, we found no effect of NPS overexpression in the FST of depression like behaviour.

Conclusion: We conclude that long-term overexpression of NPS protein in amygdala using AAV vectors, have a clear anxiolytic effect in normal wistar rats. These findings could open doors to new strategies in the treatment of panic disorders.

Poster 10

A serotonin-dependent mechanism is essential for the sustained antidepressant-like effect of ketamine in a rat model of depression

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Background: An intravenous infusion of ketamine, a non-competitive NMDA receptor antagonist, produces an antidepressant effect within two hours that persists for more than one week in treatment-resistant patients (Zarate et al., 2006). Likewise, ketamine exhibits a rapid and sustained antidepressant-like effect in a genetic model of depression, Flinders Sensitive Line (FSL) rats. The mechanisms mediating the antidepressant effects of ketamine are currently not well understood, however, studies in the FSL rat model may offer an opportunity to gain new mechanistic insights. Since cognitive dysfunction is common in depression, and FSL rats perform worse than their control strain, Flinders Resistant Line (FRL), in a memory test of object recognition, FSL rats may constitute a valid platform to study cognitive aspects of depression and impact of drug treatment. The preclinical literature indicates that ketamine at higher doses may affect

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cognitive function negatively. However, any sustained effect of ketamine at antidepressant doses on memory function has practically not been studied.

Objectives: A large body of literature supports that serotonin (5-HT) is implicated in antidepressant responsiveness and regulation of memory function. Hence, the objective was to assess the impact of endogenous 5-HT tone on ketamine's sustained antidepressant-like effect and any sustained effect on memory function by comparing its effects in rats with normal 5-HT tone to 5-HT depleted rats.

Methods: The enzyme tryptophan hydroxylase is the rate-limiting enzyme for the synthesis of 5-HT, and therefore, the irreversible tryptophan hydroxylase inhibitor, p-chlorophenylalanine, (pCPA) was used to induce 5-HT depletion. FSL rats were pre-treated with pCPA (150 mg/kg/day, IP), or saline once daily for three consecutive days. On the day following the last pCPA injection, the FSL rats were acutely treated with ketamine (15 mg/kg, IP) or saline. Saline/saline-treated FRL rats were included as controls. Ketamine's effects on recognition memory and its antidepressant-like activity were assessed in the novel object recognition test (24 hours following ketamine treatment) and the forced swim test (48 hours following ketamine treatment), respectively. In the forced swim test, a reduction of immobility is considered to reflect an antidepressant-like activity.

Results: In the novel object recognition test, control FSL rats exhibited a significantly lower memory performance than control FRL rats. Neither, pre-treatment with pCPA nor treatment with ketamine affected the memory performance of the FSL rats. In the forced swim test, control FSL rats displayed a significantly higher immobility than control FRL rats, supporting the depressive-like phenotype of FSL rats. Vehicle pre-treatment in combination with ketamine treatment significantly decreased the immobility of the FSL rats, whereas pCPA pre-treatment alone did not affect immobility. However, pCPA pre-treatment significantly prevented the antidepressant-like effect of ketamine treatment.

Conclusion: 5-HT depletion prevented the antidepressant-like effect of ketamine treatment without affecting the depressive-like phenotype of FSL rats. These observations suggest that ketamine elicits its antidepressant-like effect via a 5-HT-dependent mechanism. Neither ketamine nor 5-HT depletion affected the memory performance of FSL rats in the object recognition test.

Poster 11

Chronic LPS administration induces prolonged sickness behavior in rats

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Background: Acute inflammation produces an adaptive motivational state termed sickness behavior, to cope with inflammatory mediators and the subsequent negative energy balance. This response is short acting, whereas prolonged sickness behavior manifest with a different survival response. Objective: Our aim of this study was to investigate the behavioral, metabolic and brain cytokine changes following chronic administration of a low dose LPS in rats.

Methods: Sprague-Dawley rats were injected with lipopolysaccharide (LPS from Escherichia coli, 055:B5, dose 600 microgram/kg) or saline, once or for eight weeks. Sickness behavior was evaluated, including body weight, food intake, locomotor activity, depressive-like behavior, together with cytokine and chemokine levels in frontal cortex and hypothalamus. Energy related parameters including fasting glucose, fat mass and liver weight was also measured.

Results: Chronic LPS administration resulted in lower body weight and food intake, decreased activity level and depressive-like behavior, similar to a single LPS injection. However, contrasting acute inflammation, chronic LPS administration induced hyperglycemia, decreased fat mass and increased liver weight. Chronic LPS induced a specific elevation of proinflammatory cytokines (IL-1beta and IFN-gamma) and chemokines (MIP-1alpha and MCP-1) in frontal cortex.

Conclusion: Chronic administration of LPS produced prolonged sickness behavior, distinct from the syndrome following a single LPS injection, which could partly be caused by the specific energy demand during chronic inflammation.

Poster 12

Acute treatment with the selective serotonin reuptake inhibitor escitalopram increases freezing behaviour in rats during presentation of brief acoustic stimuli

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Background: While long-term administration of selective serotonin reuptake inhibitors (SSRIs) is effective for the treatment of anxiety disorders, acute administration may exert the opposite effect, that is, eliciting or exacerbating anxiety.

Objectives: The aim of the current study was to explore if freezing behaviour during the presentation of brief acoustic stimuli is a feasible paradigm for investigating agents with anxiogenic effects. Freezing behaviour after acute administration of an SSRI has been assessed in previous studies. However, in these studies most commonly the rats undergo fear conditioning prior to testing, meaning that they are subjected to electric footshock which by itself is a very potent anxiety enhancer.

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Methods: 48 male Sprague Dawley rats were tested during a session consisting of 20 acoustic stimuli (0.2 s, 95 dB white noise bursts) with an interstimulus interval of 30 seconds. Half of the rats received a single injection of escitalopram (escitalopram oxalate, 10 mg/kg) one hour before testing. The remaining rats received 1 ml of 0.9% saline.

Results: We found an increase in freezing behaviour (p=0.002) in animals injected with escitalopram versus control.

Conclusion: Freezing behaviour measured during presentation of brief acoustic stimuli in rats that have not undergone fear conditioning (i.e. been subjected to electric footshock) is a promising tool for assessing agents with anxiogenic effects.

Poster 13

Oxytocin receptor SNPs and aggressive antisocial behavior

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Background: Antisocial behavior is a common reason for referral of adolescents to mental health clinics, and incurs significant public expenditures. The etiology of antisocial behavior is unclear, but there is growing evidence that genetic variation is a contributing factor. In light of indications that oxytocin may amplify prosocial behavior, dysregulation of oxytocin may consequently play a part in antisocial behavior.

Objectives: The aim of the current study was to investigate whether single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (OXTR) are associated with the expression of antisocial behavior.

Methods: A population of 2356 adolescent twins aged 18 years old and participating the Child and Adolescent Twin Study of Sweden (CATSS), were asked to fill out a self-assessment of antisocial and aggressive behavior. The instruments used were the Life History of Aggression scale (LHA), and the Self-Reported Delinquency scale (SRD). We genotyped eight SNPs in OXTR, and used mixed model statistics to investigate associations between genotype and phenotype. We performed analyses on all included individuals, as well as on boys and girls separately. As a replication sample, we used 2458 twins, aged 16-20 years old and drawn from the Twin Study of Child and Adolescent Development (TCHAD)

study. In this study, only SRD was available for attempted replication.

Results: We found associations between rs7632287 and both LHA and SRD in boys, where the association with SRD remained significant after correction for multiple testing. We also found associations between rs4564970 and LHA and SRD in boys, where the association with the LHA Antisocial subscale remained significant after correction for multiple testing. We then proceeded to attempt replication in TCHAD, where an association was again found between rs7632287 and SRD. In summary, after correction for multiple testing and replication, the AA genotype of rs7632287 seems to be significantly associated with higher SRD scores in boys.

Conclusion: We conclude that the rs7632287 SNP in OXTR may influence antisocial behavior in adolescent boys. Further replication of our results, as well as investigations into the underlying mechanisms, could be crucial to understanding how aberrant social behavior arises.

Poster 14

SensoDetect® Brainstem Evoked Response Audiometry (SD-BERA) biomarkers in patients with schizophrenia and adult ADHD.

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Background: Brainstem auditory evoked response (BAER) recordings (peaks I – VII) are usually characterized by measuring latencies in milliseconds (ms) and amplitudes in microvolt. The peaks correspond to brainstem anatomical structures of the auditory pathways. The waveforms of the AERs over 10 ms have previously been shown to be abnormal in patients with schizophrenia and other mental disorders. The changes of the analogue waveforms have, however, been difficult to characterize and quantify by just using these measures.

Objectives: In the present investigations was to apply novel techniques of analyzing the BAER waveforms with the aim to identify characteristics for neuropsychiatric disorders that might be utilized as biomarkers.

Methods: A set of 13 different sound stimuli (square wave click sounds with different frequencies and amplitudes including forward and backward masking) was presented binaurally to healthy volunteers and patients with DSM-IV diagnoses of schizophrenia and adult ADHD. The analogue BAER waveforms were digitalized in order to permit quantification of aberrancies and a novel method ("the moving minimum subtraction method") for baseline alignment of the troughs of the curves was applied. Approximately half the study participants were used as a training set in order to find differences between groups; the other half was used as

test set in order to secure stable characteristics for the respective groups. Female and male subjects were separated in these analyses due to previously known gender differences in BAER waveforms.

Results: Sets of 12 –16 traits were found to characterize the two diagnostic groups vs. no-diagnosis controls. Based on these traits an index was calculated for each individual indicating percentage similarity with either diagnostic group. The SD-BERA method was subsequently applied to separate groups of patients with schizophrenia and adult ADHD vs. no diagnosis controls and compared with their DSM-IV diagnoses (SCID-I). A sensitivity and specificity vs. controls of >80% was observed (see Abstract by Baghdassarian et al.).

Conclusion: The present methods of analyzing Brainstem Auditory Evoked Responses in patients with schizophrenia and adult ADHD vs. no diagnosis controls suggest that SD-BERA can be used as biomarkers and support for clinical diagnoses of the two disorders.

Poster 15

Longitudinal and cross-sectional studies of hippocampal subfield volumes and oxidative Stress in bipolar II disorder

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Background: The dentate gyrus (DG), a hippocampal subfield with lifelong neurogenesis, might play important roles in the etiology and treatment of mood disorders. Consistent with this notion, recent studies from our group and others found evidence for reduced DG volume in subjects with bipolar II disorder (BD-II) and major depressive disorder. Although the underlying mechanisms remain to be clarified, elevated oxidative stress might contibute to decreased DG volume in mood disorders.

Objectives: The aims of this study were 1) to longitudinally examine DG volume in subjects with BD-II, 2) to examine whether BD-II is associated with increased oxidative stress, and 3) to examine the relationship between DG volume and oxidative stress.

Methods: Twenty-nine subjects with BD-II and 33 healthy controls (HCs) underwent MRI at timepoint 1 (TP1) and on average 2.3 years later, at TP2. The volume of the DG-Cornu Ammonis (CA)4 complex was measured using the hippocampal segmentation tool in Freesurfer (http://surfer.nmr.mgh.harvard.edu). Blood samples were collected at TP2 for analyses of 4-hydroxy-2-nonenal (4-HNE) and lipid hydroperoxides (LPH), i.e., two indices of oxidative stress. All analyses were adjusted for age, gender, and total subcortical gray matter volume.

Results: At TP1, left dentate gyrus–CA4 was significantly smaller in subjects with BD-II than in controls, whereas no significant group difference was found for right dentate gyrus–CA4 volume. Likewise, left, but not right dentate gyrus–CA4 volume was significantly reduced at TP2 in subjects with BD-II. Larger number of depressive episodes between TP1 and TP2 was associated with greater loss of left dentate gyrus–CA4 volume. 4-HNE was significantly increased in patients with BD-II relative to controls, whereas no group difference in LPH was found. Significant negative associations between 4-HNE and left dentate gyrus–CA4 volume and right dentate gyrus–CA4 volume were found in subjects with BD-II.

Conclusions: This study indicates that larger number of depressive episodes is associated with greater DG–CA4 volume loss in subjects with BD-II. In addition, our findings suggest that BD-II is associated with increased oxidative stress and that elevated oxidative stress might contribute to reduced DG-CA4 volume in BD-II. These findings may have implications for psychopharmacology.

Poster 16

Temperament differences in male Wistar rats are accentuated by acute SSRI treatment but attenuated by serotonin depletion and chronic SSRI treatment

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Background: Behavioural responses to serotonin reuptake inhibitors (SRIs) in man depend on baseline anxiety; the anxiety-reducing effect of long-term administration of SRIs is hence not a non-specific sedative effect, but unique for subjects with enhanced anxiety, who are also more inclined than others to experience anxiety-enhancing effects of acute SRI administration.

Objectives In this study, we explored if inter-individual variation within a batch of male Wistar rats with respect to 'anxiety' as assessed using the elevated plus maze (EPM) influences the response to SRIs (experiment I), and also to what extent these inter-individual differences are influenced by a drug arresting serotonergic transmission (experiment II).

Methods: In experiment I, 120 animals were pre-tested in the EPM. Animals were then subjected to treatment with

the SRI escitalopram admixed to food pellets. After five weeks of treatment, animals were given one injection of another SRI, paroxetine, and then re-tested in the EPM. In experiment II, 65 animals were pre-tested in the EPM and re-tested three weeks later after three days of treatment with the TPH2 inhibitor p-chloro-phenyl-alanine (p-CPA). In both experiments the 1/3 of the animals displaying the highest level of baseline 'anxiety' were defined as high 'anxiety' (HA) rats and the remaining 2/3 as low 'anxiety' (LA) rats.

Results: Acute administration of paroxetine, exerted an 'anxiety'-enhancing effect in HA but not LA rats, which was eliminated by long-term pretreatment with escitalopram. Serotonin depletion obtained by administration of p-CPA eliminated the behavioural difference between the groups by reducing 'anxiety' in HA but not LA rats.

It is suggested that differences with respect to an "anxiogenic" impact of serotonin partly explains differences in anxiety-like behaviour amongst Wistar rats, and that this influence is enhanced by acute and dampened by subchronic SRI administration, as well as serotonin depletion.

Poster 17

Is serotonin a mediator of sex differences in anxiety-like behavior?

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Background: Many serotonin-related psychiatric disorders display sex differences in prevalence, sex steroids influence serotonin transmission, and sex differences in sexual behavior are eliminated by a treatment arresting brain serotonergic neurotransmission (Liu et al, Nature, 2011, 472, 95-99). The possibility that serotonin is an important mediator of behavioural sex differences in general is hence worth considering. Supporting this notion, we recently found that administration of an inhibitor of serotonin synthesis, p-chlorophenyl-alanine (pCPA), eliminates sex differences in an animal model of anxiety, the elevated plus maze (EPM). Thus, while female Wistar rats normally display less anxiety-like behavior in the EPM than males, pCPA reduced "anxiety" in males but not females, hence eliminating this difference (Näslund et al, Psychopharmacology, 2013, 230, 29-35).

Objective: To explore how possible sex differences with respect to two other tentative aspects of "anxiety" in rat, i.e. fear-potentiated startle and freezing, are influenced by pCPA-induced serotonin depletion.

Methods: On the first day, rats were presented to a series of 10 inescapable foot shocks. On the three following days, they were given daily injections of pCPA (300 mg/kg) or saline. One day after the final injection, freezing and noise burst-induced startle were reassessed in the

same box where the animals had previously received the foot shocks (=contextual conditioning).

Results: While male rats displayed more fear-potentiated freezing than females, pCPA reduced freezing in males only, hence eliminating this sex difference. With respect to fear-potentiated startle, there was no sex difference in untreated animals; pCPA however enhanced startle in males but not in females, hence making pCPA-treated males differ from pCPA-treated females. Tentatively, this influence of pCPA on startle in male rats may however partly be secondary to the reduction in freezing observed in the same animals.

Conclusion: Our results illuminate an important difference in the regulation of fear-potentiated startle and freezing in the sense that pCPA reduced freezing but enhanced startle in males. The main finding of the study however is that a marked sex difference with respect to fear-potentiated freezing was abolished by serotonin depletion; in this regard, our observation is perfectly in line with our previous finding of a similar effect of pCPA on sex differences with respect to EPM behavior. We suggest that sex differences in anxiety-like behavior may be partly explained by an "anxiogenic" influence of serotonin being more important in males.

Poster 18

Investigator-rated symptomatological outcomes in a phase 4 study of Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder and impaired executive function

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Background: Attention-deficit/hyperactivity disorder (ADHD) is a childhood neurodevelopmental condition, but symptoms and functional impairment often persist into adulthood. Impairments in day-to-day functioning associated with ADHD in adults include deficiency in executive function (e.g. goal-directed behaviour, self-regulation, planning and problem-solving). Lisdexamfetamine dimesylate (LDX) is the first stimulant prodrug and the only long-acting amfetamine approved for treatment of ADHD in Europe (in selected countries).

Objectives: To evaluate the effect of LDX on ADHD symptoms as a secondary efficacy outcome in a phase 4 US study in adults with ADHD and impaired executive function.

Methods: This randomized, double-blind study enrolled adults (aged 18–55 years) with baseline ADHD Rating Scale IV with adult prompts (ADHD-RS-IV-Adult) total score ≥ 28 and baseline T-score ≥ 65 on the Behaviour Rating Inventory of Executive Function–Adult Version: Global Executive Composite (BRIEF-A:GEC). Patients

were randomized 1:1 to receive optimized doses of LDX (30, 50 or 70 mg/day) or placebo for up to 10 weeks. ADHD-RS-IV-Adult total score was a secondary efficacy outcome and was assessed by investigators at baseline, weeks 1, 2, 3, 4 and 10, and/or at early termination.

Results: Of 161 patients enrolled and randomized (LDX, n = 80; placebo, n = 81), 115 completed the study (LDX, n = 62; placebo, n = 53). The full analysis set comprised 154 patients (LDX, n = 79; placebo, n = 75). At baseline, mean ADHD-RS-IV-Adult total score was 39.9 in both groups (standard deviation [SD]: LDX, 7.37; placebo, 6.83) and mean changes from baseline to week 10 or early termination were −21.4 (SD, 11.27) and −10.3 (12.70) in the LDX and placebo groups, respectively. Statistical analysis showed a significant difference (LDX minus placebo) in least-squares mean changes of −11.1 (95% confidence interval: −14.9, −7.3), with an effect size of 0.94 in favour of LDX ($p < 0.0001$). In the previously reported primary efficacy outcome, LDX was also associated with significant improvements in self-reported BRIEF-A:GEC executive function ratings (Adler LA *et al. J Clin Psychiatry* 2013;74:694–702). The five most frequent treatment-emergent adverse events in the LDX group were decreased appetite, dry mouth, headache, feeling jittery and insomnia; mean changes in vital signs were not of clinical concern.

Conclusion: LDX was significantly more effective than placebo in relieving the symptoms of ADHD in adults with ADHD and clinically significant impairment of executive function. Safety outcomes were consistent the known effects of stimulant treatment.

Poster 19

A serotonergic deficit in the subchronic valproate model of autism in rat

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Background: Alterations in the serotonin (5-HT) system are often detected in patients with Autism Spectrum Disorders (ASD). Prenatal exposure to Valproate (VPA) is associated with ASD in the offspring. We have recently developed a novel animal model of autism in which pregnant rats were exposed to subchronic doses of VPA and we have detected increased neuronal cell number and behavioural deficits in the offspring of VPA- compared with saline-treated rats. Previous data from our group demonstrated decreased striatal 5-HT levels in rats prenatally exposed to VPA compared to controls.

Objectives: The aim of the current study is to further investigate the serotonin system with a focus on the 5-HT_{2A} receptor and the serotonin transporter (SERT).

Methods: Pregnant Wistar rats were treated with VPA (20 or 100 mg/kg) or saline from day 12 until the end of pregnancy. Brains from the male offspring (n=7/group) were removed and fresh frozen at 50 days of age and then sliced into 20 μm thick sections. We performed in vitro autoradiography of striatal $5HT_{2A}$ receptors using [^{3}H]Ketanserin as the radioligand and mianserin to assess non-specific binding. We assessed striatal SERT levels using [^{3}H]DASB as the tracer and citalopram to detect non-specific binding. Statistics were done on the specific binding values using a one-way analysis of variance (ANOVA) followed by a Bonferroni post hoc test.

Results: The 5-HT_{2A} receptor binding was significantly decreased in dorsolateral and ventrolateral striatum in rats prenatally exposed to VPA compared to saline controls ($p<0.05$ and $p<0.01$ respectively). The post hoc test revealed that the decrease in dorsolateral striatum was only significant for the rats exposed to 20 mg/kg/day whereas the decrease in ventrolateral striatum was significant in both VPA-groups. However, VPA did not induce changes in striatal [^{3}H]DASB binding.

Conclusion: The lower 5-HT_{2A} receptor binding combined with reduced levels of 5-HT in striatum indicate a down-regulation of the serotonin system in the VPA-exposed rats consistent with imaging studies in human in which 5-HT_{2A} receptor levels are altered. The lack of difference in SERT-binding is in contrast to human imaging studies which have detected reduced SERT availability, however methodological and species differences may account for the differences in data. The changes at the receptor and not the transporter level in our study may suggest changes in serotonin metabolism and release coupled to 5-HT_{2A} receptor regulations.

Poster 20

Associations between polymorphisms in NFKB and NFKBIL1 and autistic-like traits in a Swedish population of twins

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Background: Autism spectrum disorders are a complex group of neurodevelopmental disorders which are characterized by impairments in social interactions and both verbal and nonverbal communication as well as by unusual repetitive behaviour. The immune system has been suggested to be of importance for the development of

neuropsychiatric symptoms; for example, elevated levels of cytokines and the inflammation-related transcription factor nuclear factor kappa-B (NFKB) have been reported in both blood and brain tissue of autistic individuals.

Objectives: The aim of this study was to investigate possible associations between single nucleotide polymorphisms (SNPs) in NFKB and NFKB inhibitor-like protein 1 (NFKBIL1) and autistic-like traits in a Swedish population of twins.

Methods: The subjects in this study (n=12426, 9-12 years old) are from "The Child and Adolescent Twin Study in Sweden" (CATSS). Their parents participated in a telephone interview where the children were assessed by the Autism-Tics, ADHD, and Other Comorbidities Inventory (A-TAC) where autistic-like traits are measured using a continuous scale. DNA was extracted from saliva samples and polymorphisms were genotyped. Statistical analyses were performed in the SAS 9.3 (SAS Institute, Inc., Cary, NC) softwear.

Results: Four out of the five investigated SNPs (NFKB: rs4648022; NFKBIL1: rs2230365, 2239797 and rs2857605) showed significant associations with the A-TAC total autistic-like traits score.

Conclusions: To our best knowledge, polymorphisms in the genes encoding NFKB and NFKBIL1 have not previously shown to be associated with autism. These proteins may be involved in neuronal development and our findings support the hypothesis of the immune system being important in the aetiology of neuropsychiatric symptoms.

Poster 21

The Dopamine Stabilizer (-)-OSU6162 Specifically Reduces Aggressive Behaviour Without Affecting Neither Social Interaction Nor Locomotion in Mice

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Background: (-)-OSU6162 belongs to a new class of compounds named "dopaminergic stabilizers" and has been shown to be effective in several preclinical tests of schizophrenia as well as models of alcohol dependence. While its exact mechanism of action is still uncertain, it is assumed to maintain dopamine homeostasis mainly by exerting an atypical interaction with extrasynaptic and/or synaptic D2 receptors. Interestingly, it reduces stimulant-induced hyperlocomotion without inducing catalepsy even at high doses.

Objectives: To evaluate effects of (-)-OSU6162 on aggressive behavior in male mice.

Methods: Male mice of the outbred CD-1 strain were given (-)-OSU6162 (75 and 150 µmol/kg) and tested in the resident intruder paradigm. In addition, possible effects on spontaneous locomotion were evaluated in a separate experiment.

Results: (-)-OSU6162 dose-dependently reduced aggressive behaviour while not affecting other social behaviours and importantly, not by reducing spontaneous locomotion.

Conclusion: This study is the first to suggest that (-)-OSU6162 has potential as an anti-aggressive agent. Given the well-established influence of dopamine on aggression, we suggest the effect to be exerted by the dopamine-stabilizing properties previously attributed this compound.

Poster 22

Genetic variation at the glucagon-like peptide-1 receptor gene locus is associated with alcohol use disorder

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Background: The glucagon-like peptide-1 (GLP-1) is a hormone involved in the regulation of metabolism and food intake. Preclinical studies show that this anorexigenic hormone and its receptor (GLP-1R) are involved in reward processing mechanisms; however, its role in individuals with alcohol use disorder (AUD) is largely unexplored. AUD is partially heritable, with contributions from numerous loci, most of which remain unknown.

Objectives: The aim of this study was to investigate whether genetic variation in GLP1R is associated with AUD.

Methods: Case-control analyses were conducted on a cohort consisting of participants enrolled in studies at the Laboratory of Clinical and Translational Studies (LCTS; n=908) of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Significant associations were further investigated for confirmatory purposes in the Study of Addiction: Genetics and Environment (SAGE; n=3803) genome-wide association study (GWAS) sample. To obtain functional validation of identified risk al-

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leles, secondary analyses were carried out on data from a human laboratory study of intravenous alcohol self-administration (IV-ASA; n=68).

Results: Five GLP1R SNPs were significantly associated with AUD in the case-control analysis. A trend-level association between a previously reported functional SNP (rs6923761; Ser168Gly) and AUD (p=0.004; Nyholt correction threshold p<0.0032) was also observed. Splitting the sample according to self-reported ancestry revealed internal replications (rs7766663, rs7341356, rs2235868 and rs7769547) and a trend-level replication (rs10305512) between all five SNPs and AUD. In the SAGE samples, the association between 168Ser allele and AUD was further confirmed in males (p=0.033), but not in females. In the human laboratory experiment, the 168Ser-allele was associated with peak breath alcohol concentrations (p=0.045) achieved during the IV-ASA.

Conclusion: These novel and convergent findings suggest that GLP-1 signaling may be of importance for the pathophysiology of AUD, making the GLP-1R an attractive target for personalized pharmacotherapy.

Poster 23

Acute stress rapidly increases the readily releasable pool of glutamate vesicles in prefrontal and frontal cortex through non-genomic action of corticosterone via mineralocorticoid and glucocorticoid receptors

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Background: Dysfunction of the glutamate (Glu) system is increasingly considered a core feature of neuropsychiatric disorders, including mood and anxiety disorders. It has been hypothesized that maladaptive changes in the structure and function of excitatory/inhibitory circuitry (representing the vast majority of neurons and synapses in brain) have a primary role in pathophysiology. Interestingly, preclinical studies have shown that stress enhances

Glu release/transmission in cortical/limbic areas, in turn inducing structural/functional changes. We have shown that acute stress induces in prefrontal and frontal cortex (PFC/FC) a rapid enhancement of depolarization-evoked Glu release from synaptic terminals (synaptosomes), dependent on corticosterone elevation and SNARE complexes accumulation. In addition, we have shown that chronic antidepressants (AD) prevent the enhancement of depolarization-evoked Glu release induced by acute stressors in PFC/FC.

Objectives: We compared the effects of acute behavioural stress with that of in vitro application of corticosterone (CORT) to prefrontal/frontal cortex (PFC/FC) synaptosomes, to verify if stress effects on glutamate neurotransmission were mediated by a synaptic action of CORT.

Methods: Rats were subjected to acute Footshock (FS)-stress. Synaptosomes were purified from PFC/FC; glutamate release was measured by superfusion. Electrophysiological experiments were performed on acute PFC slices. Changes in vesicle mobilization were measured by Total Internal Reflection Fluorescence Microscopy (TIRFM). Synapsin I phosphorylation was measured by Western blot.

Results: We found that both acute stress and CORT in vitro increase the size of the readily releasable pool (RRP) of vesicles in PFC/FC synaptosomes. This effect was abolished by selective mineralocorticoid or glucocorticoid receptor (MR/GR) antagonists. However, CORT did not affect glutamate release evoked by depolarization and did not alter excitatory transmission in medial PFC slices. We then confirmed, by using TIRFM, that CORT increases vesicle mobilization toward the RRP acting on synaptic GR/MR. Finally, we found that both stress and CORT increase the phosphorylation of synapsin I at site 1 in presynaptic membrane. This increase of synapsin I phosphorylation was also found to be dependent on GR/MR and necessary for the increase of RRP.

Conclusion: These results suggest that, despite the rapid increase of RRP size whereby CORT primes synaptic terminals in PFC/FC, the synaptic non-genomic action of CORT is necessary but not sufficient to enhance glutamate release.

Poster 24

Oxytocin enhances eye gazing irrespective of social relationship

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Background: Although it is well-known that oxytocin affects social behaviors the underlying mechanisms are not fully understood. Emerging evidence from

experimental studies on humans and other animals indicate that one major mechanism of oxytocin is to increase the salience of social cues. This would explain the well-established effects of oxytocin on social recognition in many species as well as on emotion recognition in humans. Probably the strongest evidence supporting the hypothesis that oxytocin selectively increase attention to social stimuli is data showing that intranasal oxytocin elevates gaze to the eyes, which probably is the most socially communicative aspect of the face. Although this effect is quite consistent between studies most studies so far have been conducted in men watching faces of strangers.

Objectives: The aims of this study were to investigate if the effect of oxytocin on face gazing is dependent on the sex of the observers and/or on their relationship to the observed subject. In addition, we investigated to what extent the effect of oxytocin is specific to human faces or also extends to non-human faces.

Methods: A double-blind, placebo-controlled eye-tracking study, assessing the effects of oxytocin on gaze to the eyes of a range of face stimuli in 84 (50% women) healthy volunteers was hence conducted. The participants´ eye gaze patterns were recorded during viewing of photos of strangers and familiar faces in different poses (frontal, ¾ view and profile images), and also of photos showing the faces of cats and horses.

Results: Analysis of gaze patterns revealed a significant increase of gaze to the eyes for both men and women treated with oxytocin. This effect was found for all frontal-view faces, including photos of strangers, celebrities, new acquaintances, even for the participants' own faces as well as for cats and horses. Importantly, our data also reveal a diminishing effect of oxytocin on gaze to stimuli of reduced social relevance, i.e. people looking and facing away from the observer. Specifically, oxytocin significantly enhanced gaze towards the eye region of faces facing and looking straight at the observer.

Conclusions: Our data support previous findings that oxytocin increases attention to social stimuli, and suggest that this effect might generalize across genders, species and different levels of social relationships. These findings have implications for the design of future studies of oxytocin's clinical effects on social deficits in patients.

Poster 25

Maternal perinatal high-fat diet induces anxiety-like behavior in male offspring

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Background: Maternal obesity during gestation has a significant health risk for the offspring becoming evident later in life and includes metabolic syndrome, cardiovascular disease and affective disorders. Inflammation has recently been shown to play an important role in the pathophysiology of affective disorders. Systemic inflammation is a hallmark consequence of a high-fat diet and maternal obesity may lead to fetal inflammatory responses. Therefore, we hypothesize that an altered immune response could be responsible for the altered metabolism and psychiatry related behavior in the offspring.

Objectives: The aim of this study was to investigate the influence of maternal high-fat diet (HFD) in offspring behavior and metabolism.

Methods: Age matched female rats (Sprague Dawley) (n=20) were fed a high-fat diet or a control diet 8 weeks before breeding, and continued on this diet throughout gestation and lactation. Bodyweight was monitored weekly. Male and female offspring were tested at the age of PND56 in different behavioral settings. Anxiety-like behavior was evaluated using the elevated plus maze (EPM), depression-like behavior in the forced swim test (FST) and cognition in the Barnes Maze. Insulin sensitivity was evaluated using the oral glucose tolerance test (OGTT).

Results: After 8 weeks on the obesogenic diet, female rats had a significantly higher intake (Kcal) than control dams. Offspring from high-fat fed rats were significantly heavier than control offspring at weaning. Male offspring exposed to perinatal high-fat showed decreased time spent in the open arms in the EPM, indicating anxiety-like behavior.

Conclusion: We conclude that maternal HFD administration produces an altered behavioral phenotype in male offspring when compared to control offspring at the age of PND56. The data suggests that dietary environment prior to pregnancy can have long term effects, which seems to be specific for anxiety-like behavior.

Poster 26

Development and clinical validation of the Psychotic Depression Assessment Scale (PDAS)

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Background: Unipolar psychotic depression (UPD) is a severe and debilitating condition, which needs intensive treatment and monitoring. Unfortunately, there is currently no established rating scale dedicated to the measurement of severity in UPD. This compromises the monitoring of the illness in clinical practice and the assessment of outcome in research studies. Recent analyses have indicated that the 11-item Psychotic Depression Assessment Scale (PDAS), consisting of the 6-item melancholia subscale (HAM-D6) of the Hamilton Depression Rating Scale and 5 psychosis items from the Brief Psychiatric Rating Scale (BPRS), is a clinically valid, unidimensional, and responsive measure for the severity of UPD.

Objectives: The aim of this study was to subject the PDAS, and its depression (HAM-D6) and psychosis (BPRS5) subscales to further clinical and psychometric validation based on an independent sample.

Methods: Patients with clinical diagnoses of UPD recruited at Danish psychiatric hospitals participated in semi-structured interviews. Video recordings of the interviews were assessed by two highly experienced clinical psychiatrists (global severity ratings of psychotic depression, depressive symptoms and psychotic symptoms) and by two psychiatry residents (rating on 27 symptom items, including the 11 PDAS items). The clinical validity of the PDAS and its subscales was investigated by means of Spearman correlation analysis of the global severity ratings versus the PDAS, HAM-D6, and BPRS5 total scores. The unidimensionality of the scales was tested by Mokken analysis.

Results: Forty patients with UPD were included in the analysis. The results of the Spearman correlation analysis indicated that the PDAS, and its HAM-D6 and BPRS5 subscales, were clinically valid measures in UPD. Furthermore, according to the Mokken analysis, the scales demonstrated acceptable unidimensionality.

Conclusion: The clinical validity and unidimensionality of the PDAS and its depression and psychosis subscales was confirmed in an independent sample of patients with UPD.

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