Acta Neuropsychiatrica, Volume 31, Supplement 1:1-32

ABSTRACTS

SCANDINAVIAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

SCNP

61st Annual Meeting, 7 – 9 June, 2021
Stockholm, Sweden

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ORAL PRESENTATIONS

PRESIDENT'S WELCOME

SCNP: 61 years of progress

LECTURE 1

SCNP 2023 OPENING LECTURE

L1 Immunotherapy for Alzheimer´s disease

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Abstract: Immunotherapy against amyloid-beta has emerged as a promising treatment for Alzheimer's disease (AD). Lecanemab is a humanized IgG1 monoclonal antibody, selectively targeting amyloid-beta protofibrils. In a Phase 3 clinical trial in early AD subjects, lecanemab demonstrated potential disease-modifying effects on both clinical endpoints and clearance of amyloid-beta plaques in the brain. We have characterized the main target for lecanemab, i.e. amyloid-beta protofibrils in AD brain, describing the levels, content and size of size of amyloid-beta protofibrils, in relation to the APOE genotype. The binding of lecanemab to amyloid-beta protofibrils and the mechanism of action in clearance of amyloid-beta has been studied. Amyloid-beta protofibril levels, extracted from post-mortem human brain tissue, were measured using the mAb158 antibody, the murine version of lecanemab. Size exclusion chromatography was used to characterize amyloid-beta protofibrils and to evaluate lecanemab's binding profile. Amyloid-beta protofibrils were shown to be predominantly composed of amyloid-beta 42, and were heterogenous in size, and lecanemab was shown to bind similarly to amyloid-beta protofibrils of all sizes. Lecanemab has a unique binding profile with a high selectivity for amyloid-beta protofibrils and effectively clears amyloid-beta protofibrils and amyloid plaques. Other antibodies targeting amyloid-beta will be discussed.

LECTURE 2

GENETICT AND IMMUNIOLOGICAL ASPECTS IN PSYCHIATRY

L2.1 Diagnosis and treatment of maladaptive immunological disorders

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Abstract: Since 2015, the Immunopsychiatry team at Uppsala University has strived toward a collaborative multidisciplinary approach to improve and integrate care for patients with moderate to severe psychiatric disorders. Neuroimmunological markers in CSF suggest an underlying biological groups that do not harmonize with the current clinical grouping. Multivariate patient classification and pattern detection as well as a single-subject research design has identifed sets of biomarkers that delineate clear endpoints with potential relevance for diagnosis and clinical prognosis in future studies. Our early results indicate that a spectra of immunological mechanisms, both alone and in combination, are associated with a broad range of psychiatric disorders. The underlying pathology incorporates autoimmune, autoinflammatory disorders but also genetic, metabolic, and other immunological disorders. Treatment of these cases must embrace integrated models of disease, as both maladaptive immunological responses and psychological processes influence mental health. Several challenges need to be overcome to efficiently merge psychiatric and somatic disease paradigms and medical care ranging from language and conceptual barriers to organizational barriers. Ahead lies a complex task to further develop and hone in these emerging concepts that encompass several medical disciplines while challenging previously well-established algorithms and healthcare structures

L2.2 The role of synaptic pruning in schizophrenia

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Abstract: Recent multi-disciplinary data have indicated complement-dependent synaptic pruning as a pathophysiological mechanism in schizophrenia. The rapid development of novel patient-derived cellular models has made it possible to model interactions between microglia and neuronal networks in a disease context and these tools have been instrumental for linking genetic risk variance to excessive synapse

pruning in schizophrenia. In the current talk, state-of-the-arts model systems for assessing the role of human microglia in a schizophrenia context will be presented. New data will be featured that cover genetic as well as environmental (early-life infection) risk factors for schizophrenia.

L2.3 Bridging the great divide: a systematic comparison of GWAS across neurological and psychiatric disorders

Olav B Smeland[1,2], Gleda Kutroli[1], Shahram Bahrami[1], Nadine Parker[1], Vera Fominykh[1], Guy Hindley[1], Oleksandr Frei[1], Alexey S Shadrin[1], Ole A Andreassen[1,2]

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Background:Accumulating evidence from neuroscience, epidemiology and clinical observations indicate that neurological and psychiatric disorders are not categorically distinct disease entities. However, the extent to which these groups of disorders share genetic influences remain unclear.

Objectives: Here, we aimed to provide a comprehensive comparison of the genetic risk architecture across major neurological and psychiatric and re-investigate whether the existing clinical division is apparent at the genetic level.

Methods. To this end, we systematically analyzed large-scale GWAS data using complimentary statistical tools to evaluate genetic overlap and provide biological insights. We included GWAS on 20 major neurological and psychiatric disorders, comprising close to 1 million cases. Additionally, we included GWAS data on eight somatic and brain-related comparators. The total sample size included more than 13 million individuals, including some sample overlap. We assessed shared genetic influences at both the local and genome-wide level and functionally characterized the results using a variety of biological resources.

Results. We demonstrate widespread genetic sharing with unique patterns of overlap across distinct disorders, as well as disorder-specific effects. Using a variety of tools, we find that there is no sharp distinction in the genetic risk underlying neurological and psychiatric disorders, despite evident differences in their genetic architectures. Further, GWAS on both psychiatric and neurologic disorders implicated human brain tissue, cell-types and neurobiological pathways indicating that psychiatric disorders, like neurological disorders, also have a neural basis.

Conclusion. Altogether, the study demonstrates that neurological and psychiatric disorders are not fundamentally disparate in their nature, but partly share a genetic and neural basis, which have important implications for disease classification, clinical practice and research.

L2.4 Understanding the genetics of psychiatric disorders in the era of GWAS

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Abstract: Although a genetic component to risk for psychiatric disorders has been widely acknowledged for many decades, specific genetic markers have only been confidently identified fairly recently. Genome-wide association studies (GWAS) have revolutionized our understanding of the genetic foundations of psychiatric disorders, with many significant loci now identified for all major disorders. I will start by summarizing the findings and etiological insights imparted by GWAS so far for several disorders: attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa, anxiety disorders, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), schizophrenia, and Tourette's syndrome. Next, I will describe the secondary analyses enabled through use of the GWAS results, such as polygenic risk scoring and pathway analyses, which deepen our understanding of the impact of this genetic risk on other phenotypes/disorders and the biological mechanisms that give rise to them. Finally, I plan to outline the challenges and opportunities for future avenues of investigation and clinical translation by which genetic findings can contribute to a meaningful impact for the lives of patients.

L2.5 Lithium- Pharmacokinetics, genetics and nanofluidics

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Background: Lithium is the most effective treatment available for bipolar disorder. Its therapeutic range, however, is very narrow and treatment initiation requires individual titration to address inter-individual variability to achieve correct serum levels. We aim at

improving lithium dose prediction and methods for measuring lithium using clinical and genomic data applying microfluidic technology. There is need for patient-centric methods for lithium monitoring. We therefore tested the feasibility of dried blood spots for determination of lithium concentration by introducing a volumetric technique developed for home-sampling.

Methods: Two Swedish cohorts, with a total of 2357 lithium treated patients and 5627 data points were used to model lithium clearance (LiCL) with respect to several clinical variables. The residual effects after accounting for age and sex, representing the individual-level effects in LiCL, were used as dependent variables in a genome-wide association study (GWAS). Capillary blood was sampled by finger-prick using a volumetric device that collects 10 µL volumes as a dried blood spot. Lithium was measured in the dried blood spots using a validated atomic absorption spectroscopy method.

Outcomes: Age, sex, glomerular filtration rate, serum lithium concentration, co-medication with diuretics and agents acting on the renin-aldosterone-angiotensin system were clinical predictors of LiCL. Interestingly, an association between LiCL and SL was observed. In a GWAS of LiCL, one locus was associated with LiCL (rs583503; b=-0·053 (95%-Confidence Interval:-0·071;-0·034), p=3·8.10-8). We also found enrichment of the associations with genes expressed in the medulla and the cortex of the kidney, as well as associations with polygenic risk scores for eGFR, body mass index, and blood urea nitrogen. The model based on clinical variables explained 61·4% and 49·8% of the variance in LiCL in the two cohorts. Adding genetic markers marginally increased the predictive ability of the model. Using the dried blod spot technology we observed a range of serum lithium concentrations of 0.41-1.22 mmol/L, and the dried blood spot/serum ratio was 0.78. A strong linear correlation between the two specimens was shown with Pearson's R = 0.95 (r2 = 0.90). Adding hematocrit as a variable only minimally improved prediction.

Interpretation: Our model predictors could be used clinically to better guide lithium dosage, shortening time to reach therapeutic levels, thus improving care. The first genomic locus and PRS to be associated with LiCL introduce the opportunity of individualized medicine in lithium treatment. Volumetric dried blood spots is a promising technique for measurement of lithium concentrations. This will enable home-sampling and could potentially save resources, improve compliance, and make treatment safer. This may facilitate the use of lithium treatment in regions where monitoring via venous blood sampling remains difficult.

SYMPOSIUM 1

SCNP YOUNG SCIENTIST SYMPOSIUM

The speakers in the SCNP Young Scientist Symposium are selected among the best abstracts submitted by young scietists.

S1.1 Risk factors for developing disorder and impulse-control disorders under dopaminergic medication

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Background: Dopaminergic therapy, commonly used to treat the neurological conditions Parkinson's disease (PD) and restless legs syndrome (RLS), is known to increase the risk for developing gambling disorder (GD) and impulse-control disorders (ICDs).

Objectives: Our goal is to identify risk factors associated with developing GD and ICDs under dopaminergic therapy. We consider demographic factors, neurological and psychiatric diagnoses and prescriptions.

Methods: On a large dataset from Swedish national registries including drug prescriptions and diagnoses of 250 000 patients with dopaminergic prescriptions, we investigate factors associated with GD or ICDs. Using chi-square tests and logistic regressions, we examine the role of age, sex, mortality and underlying neurological conditions, but also the impact of different dopaminergic substances. We are interested in psychiatric comorbidities and will examine both psychotropic drug prescriptions in general, and the effect of certain substances like aripiprazole or haloperidol, that have been described to increase the risk for GD and ICDs themselves.

Results: GD and ICD diagnoses are associated with a later birth year and younger age at death. Women are only slightly less affected than men, which is surprising with GD being much more prevalent in men in the general population. Interestingly, RLS patients seem to be a more vulnerable patient group than PD patients. In line with many other studies, we find dopamine agonists to have the strongest association with GD or ICDs, even confirming the D2-class agonists pramipexole and ropinirole as being especially disadvantageous. GD and ICD patients have a compromised mental health, measured by the frequencies of common psychiatric diagnoses, psychotropic prescriptions, and events of self-harm.

Conclusion: Our results could help to improve neurological care regarding psychiatric side effects and

also suggest, that large scale studies in RLS populations are needed, as they have been performed for PD patients within the last years.

S1.2 Initiation of antidepressant treatment and the risk of manic episodes in children and adolescents with unipolar depression

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Background: Pediatric patients may be particularly vulnerable to severe adverse reactions induced by antidepressants, such as treatment-induced mania, which is pressing considering the increasing rates of which these medications are prescribed.
Objective: To estimate whether patients treated with antidepressants have an elevated incidence of mania/hypomania compared with patients not treated with antidepressants, and to identify patient characteristics associated with mania among those receiving medication.
Methods: In this register-based study, we included individuals with a diagnosis of unipolar depression from inpatient or outpatient setting in 2006–2020, aged 4–17, with no prior diagnosis of mania, bipolar disorder, or schizoaffective disorder, and no prior lithium prescriptions. The treatment group consisted of patients who initiated any antidepressant medication within 90 days of diagnosis. The control group included patients who did not initiate antidepressants. Patients were followed-up until 12/52 weeks after treatment initiation.
Results: The cohort included 43,953 patients (66% girls). The cumulative incidence of new onset mania was 0.24% (95% CI: 0.17–0.30) in the treatment group, and 0.23% (0.16–0.29) in the control group at 12 weeks, with a risk difference of 0.01% (-0.09–0.11). At 52 weeks, the cumulative incidence was 0.73% (0.62–0.84) in the treatment group and 0.54% (0.43–0.65) in the control group, with a risk difference of 0.19% (0.03–0.35). Psychosis, developmental disorders, hospitalizations, parental bipolar disorder, and the use of antiepileptics and sedatives were the most important predictors of mania in the treatment group.
Conclusion: We did not find evidence of treatment-emergent mania by 12 weeks, which corresponds to the timeframe for antidepressants to exert their psychotropic effect. A small risk difference was found only in the longer follow-up, suggesting the risk increase is attributable to factors other than the medication. Certain patient characteristics were associated with mania after antidepressant initiation, which warrants clinical attention.

S1.3Quasi-tenacious depression (QTD) as an alternative framework to treatment-resistant depression (TRD)

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Treatment of major depressive disorder (MDD) is challenging, as almost one-third of patients are not adequately responsive to current treatments. This subgroup of patients is commonly referred to as treatment-resistant. Nonetheless, it may not be accurate to attribute the lack of response to the patients themselves. Non-response could stem from various reasons including but not limited to misdiagnosis, non-adherence, improper choice of pharmacotherapy, protracted presence of a stressor, accompanied possible comorbidities, etc. In this context, we argue that TRD may be semantically and clinically misleading, and we propose a new model, QTD, which is derived from the tenacity index (TI), a potentially measurable outcome. The current approach to diagnosing depression is solely based on descriptive data, rather than quantifiable measures, that specifically relate to the etiology and pathophysiology of the underlying disorder. TI can be used to quantify potential barriers and predict the degree to which a patient with depression seems tenacious to respond to a particular treatment strategy and differentiate between whether the tenacity observed is a result of the manifestation of the disorder or the other factors masking the response. The incessant search for new treatment options with varied profiles of activity, and identification of factors leading to such higher tenacity indices are what QTD demands. This model acknowledges that all patients with depression have some degree of tenacity that needs to be overcome with proper treatment modalities. Additionally, it provides a measurable concept that aids clinical decision-making while having a scientific foundation to present a positive and dynamic perspective of the disorder for both patients and healthcare providers.

S1.4 Cardiovascular proteins are elevated in first-episode psychosis patiens compared to healty controls

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Background: The leading cause of death among patients with schizophrenia is cardiovascular disease. Inflammation is involved in the development of atherosclerosis and is also proposed to be part of the pathophysiology of schizophrenia. It has therefore been suggested that the same inflammatory changes could contribute to both the psychotic symptoms and the increased mortality in cardiovascular disease for patients with schizophrenia.

Objectives: Our aim was to study a large number of cardiovascular biomarkers in first episode psychosis (FEP) patients that are drug-naïve or under short time anti-psychotic medication and healthy controls (HC). We also wanted to perform correlations of these biomarkers with clinical and cognitive ratings as well as known cardiovascular risk factors.

Methods: Ninety-two cardiovascular markers in plasma of 73 FEP patients (of which 42 were later diagnosed with schizophrenia) and 55 healthy controls were analyzed using the OLINK Proximity Extension Assay, Cardiovascular II Panel. The study was a part the Karolinska Schizophrenia Project (KaSP).

Results 16 out of 92 cardiovascular biomarkers were elevated in FEP patients compared to HC and 19 out of 92 biomarkers were elevated in patients later diagnosed with schizophrenia compared to HC. One biomarker was decreased in FEP patients compared to HC and in patients later diagnosed with schizophrenia compared to HC. In FEP patients, levels of these biomarkers correlated with symptoms severity, cognitive measures and known cardiovascular risk factors, but correlations were not significant after correcting for multiple analysis.

Conclusion: Several cardiovascular biomarkers are elevated in FEP patients and patients later diagnosed with schizophrenia compared to HC. This could contribute to both the psychiatric symptoms of schizophrenia and the development of atherosclerosis and increased mortality in cardiovascular disease.

S1. 5 Accumbal Cholinergic signaling regulates ethanol intake in the rat

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Alcohol use disorder is associated with serious medical consequences leading to preterm death. Although few in numbers, cholinergic interneurons (CIN) have arisen as an important cell population within the nucleus accumbens (nAc) that may exert a regulatory impact on local dopamine (DA) neurotransmission. In fact, a defect in CIN have been implied in psychiatric diseases such as alcohol addiction. The exact mechanisms through which endogenous cholinergic activity modulates DA release in response to ethanol administration and its role in development of addiction is not known. However, we have recently shown that the ethanol-induced increase in extracellular levels of accumbal DA is blocked by a combination of a muscarinic and a nicotinic antagonist given locally, implicating cholinergic signaling. Moreover, ablation of accumbal CIN attenuate the ethanol-induced increase of extracellular DA. Together these data suggest that activation of CIN, probably resulting in increased acetylcholine level, is involved in ethanol's DA releasing effect. The objective of this project was to investigate the functional role of accumbal CIN to confirm the importance of the recent molecular findings. To this end, an intermittent ethanol consumption paradigm, know to induce high ethanol intake in outbreed rats, was used together with a toxin-based method to selectively ablate accumbal CIN. A selection of rats presenting a high ethanol intake during an initial screening period, underwent stereotactic surgery to receive anti-choline acetyltransferase-saporin or a sham solution bilaterally into the nAc. Rats treated with anti-choline acetyltransferase-saporin consumed significantly less ethanol than sham-treated animals, whilst consuming the same amount of water and gaining weight in the same extent. Further, the alcohol deprivation effect was abolished in toxin-treated animals whilst being present in sham-treated rats. In conclusion, these data support a functional role of accumbal CIN in ethanol´s rewarding effect, opening up for new potential pharmacological targets for treatments of alcohol use disorder.

S1. 6 Effects of different doses of indole-3-propionic acid on regulating the brain and peripheral kynurenine pathway metabolism in male Sprague-Dawley rats

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Background:
The metabolism of dietary tryptophan generates various biologically active molecules in both the host and gut microbiota. However, the relationship between microbiota-produced and endogenously-produced tryptophan metabolites is under-investigated. Indole-3-propionic acid (IPrA) is a microbiota-derived tryptophan metabolite that exhibits multiple biological activities in the brain and peripheral. Our previous research revealed that IPrA treatment increases kynurenic acid (KYNA) levels in the brain and plasma, linking microbial tryptophan metabolites with the host's kynurenine pathway, the primary route of tryptophan catabolism. Increased KYNA has been implicated in regulating behavior and cognition.
Objectives:
The present study investigated how IPrA affects the kynurenine pathway metabolism and behavior in male Sprague-Dawley rats.
Methods:
Two batches of 4-6 weeks rats were used. In the first batch, each rat received a single intraperitoneal injection of 2, 20, 100, or 200 mg/kg IPrA or vehicle and was terminated 90 minutes later. Targeted metabolomics analysis of tryptophan, kynurenine, KYNA, 3-hydroxykynurenine (3-HK), quinolinic acid (QUIN), and picolinic acid (PIC) was carried out in the brain hippocampus and plasma. In the second batch, rats were evaluated for recognition memory and locomotor activity in the novel object recognition (NOR) test with IPrA (200 mg/kg, i.p.) or vehicle treatment.
Results
IPrA dose-dependent increases the levels of tryptophan, kynurenine, KYNA, 3-HK, and PIC in the brain, without changing QUIN's levels. In plasma, IPrA administration dose-dependently increases KYNA and 3-HK concentrations and reduces tryptophan concentration without changing QUIN and PIC concentrations. The impact on plasma kynurenine levels varied among doses. In the NOR test, IPrA-treated rats showed signs of impaired recognition memory accompanied by reduced locomotor activity.
Conclusion
IPrA treatment induces both the neuroprotective and the neurotoxic branches of the kynurenine pathway, tentatively leading to impaired recognition memory. In future experiments, we will in more detail investigate the impact on behavior following the administration of IPrA.

LECTURE 3

TREATMENT OF DEPRESSIVE DESORDERS

L3.1 Management of treatment-resistant depression:old ideas(& new)

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Abstract: This presentation will provide a brief survey of possible per oral pharmacological strategies in cases of therapy-resistant depression (here defined as patients failing to respond adequately to the usual first line of treatment, i.e., an SSRI). The issues to be addressed are: i) when are dose escalations justified?, ii) are some per oral antidepressants more effective than others (prompting a swich preferentially to certain drugs after an initial treatment failure)?, and iii) what is the current evidence with respect to adding another antidepressant (e.g., mirtazapine) or an atypical antipsychotic to the ongoing SSRI administration (and what mechanisms could underlie the possible benefit of such strategies)? Finally, the rational underlying an ongoing 4-centre trial in Sweden exploring the possible benefit of adding the dopamine stabiliser OSU6162 to an SSRI in patients not responding the latter drug *per se* will be revealed.

L3.2Real-World effectiveness of pharmacotherapies in psychotic depression

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Background: Psychotic depression is a severe mental disorder associated with a high risk of suicide. Although the main burden of the illness is caused by the long-term relapsing nature of the disorder, there is limited knowledge about the comparative effectiveness of pharmacological maintenance treatment.

Objectives: The aim of this study was to investigate comparative effectiveness of specific antipsychotics and antidepressants on risk of relapse among persons diagnosed with psychotic depression.

Methods: Individuals with psychotic depression (PD) were identified from Finnish nationwide registers of inpatient care, specialized outpatient care, sickness absence and disability pension during 2000-2018 as those with a first-time diagnosis of PD at age of 16-65 years. Specific antipsychotics and antidepressants were the main exposures, and relapse defined as psychiatric hos-

pitalization was the main outcome measure. Replication was conducted in a similarly defined Swedish cohort covering years 2006-2021. The Finnish cohort included 19,330 individuals (mean age 39.8, SD 14.7, 57.9% women). The Swedish cohort included 13,684 individuals (mean age 41.3, SD 14.0, 53.5% women). We used a within-individual design, where each person acted as his or her own control, and was analyzed with stratified Cox models. The cohorts were analyzed separately, and the results were pooled using fixed effects meta-analysis.

Results: Any antidepressant use was not associated with the risk of outcome, meta-analysis HR 1.01 (95%CI 0.97-1.05 vs. antidepressant non-use), nor did any antipsychotic use (0.99, 0.96-1.03, vs. antipsychotic non-use). However, specific drugs were associated with decreased risk of relapse, namely antidepressants bupropion 0.74 (0.63-0.85) and venlafaxine 0.92 (0.86-0.98), and any long-acting injectable antipsychotics (LAI) 0.60 (0.45-0.80).

Conclusion: In long-term treatment of PD, bupropion and LAIs were associated with the lowest risk of relapse. In real-world circumstances, beneficial results on LAIs may imply that adherence to medications should be carefully monitored and enhanced among patients with PD.

LECTURE 4

KEYNOTE LECTURE

L4.1 Cannabis- The Good, The Bad and the Ugly in Relation to Psychiatric Risk

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Abstract: Cannabis and its cannabinoid products have increased in use across the globe in recent years due to sociopolitical shifts that have led to their decriminalization and legalization, particularly in western countries. Many questions have continued to mount regarding the potential impact of cannabis on mental health. One of the most critical issues relate to developmental exposure to cannabis given the sensitivity of the developing brain—fetal, childhood and adolescence—to certain environmental conditions that can place individuals at risk for addiction and other psychiatric disorders later in life. This talk will provide insights from translational studies—basic molecular and behavioral animal studies as well as human longitudinal investigations—regarding the neurobiological consequences of developmental cannabis exposure and the long-term impact on brain and behavior relevant to psychiatric risk. It is clear that numerous factors, including THC potency and sex, can impact negative outcomes. It is also evident that the complexity of the cannabis plant may conversely hold opportunities to alleviate psychiatric disorders. For instance, while THC has been linked to many of the negative outcomes associated with the drug, recent attention has also focused on other cannabinoids such as cannabidiol (CBD) with potential pharmacological beneficial properties. The presentation will discuss translational studies regarding the medicinal potential of CBD for treating substance use disorders and related psychiatric illnesses. It is hoped that insights gained from a growing number of studies can be leveraged to provide science-based evidence to guide future clinical and treatment approaches to better address the question of cannabis and mental health.

SYMPOSIUM 2

IN MEMORIAN OF TORGNY H. SVENSSON

S2.1 Professor Torgny H.Svensson 1945-2020

Göran Engberg

Abstract is missing.

S2.2 Rethinking the mechanism of antidepressants

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Antidepressant drugs can open a 'window-of-opportunity' of brain plasticity associated with increased levels of brain-derived neurotrophic factor (BDNF) and the activation of its receptor (tropomyosin-related kinase B - TRKB). However, the molecular mechanisms of this process are not fully comprehended and were assumed to be indirect. Recently, we discovered that TRKB carries a transmembrane cholesterol recognition and alignment consensus motif (CRAC) that, upon dimerization, can form a transitory binding pocket for antidepressant drugs. Our findings indicate that antidepressant drugs stabilize a signaling-competent conformation of TRKB dimers, providing a molecular mechanism for the TRKB-mediated window-of-opportunity. Using point mutations of TRKB CRAC motif, we observed a loss of response to drug-induced brain plasticity without affecting BDNF binding or TRKB basal function. Moreover, the membrane environment plays a central role in the whole process. Taken together, our findings provide a new framework, incorporating the membrane composition and receptor dimerization, as crucial factors to understand drug-induced plasticity, as well as in the pipeline for development of new compounds.

SYMPOSIUM 3

Honorary member lecture

S3.1 Psychedelics in depression- opportunities and challenges

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The current treatment of depression is still suboptimal, with a large degree of non-response. Unfortunately, few new traditiional antidepressant treatments have been developed the last years. However, there has been a large interest in psychedelics, which has received a lot of attention as new treatment alternatives, both from clinicians as well as lay peoople and the media.

Recently, several high impact papers have been published from recent clinical trials, and there is a lot of hope for these new treatment alternatives in depression. Still, there are several challenges related to duration of effect and potential side effects. However, these seems to be minor, but more studies are needed.

The talk will include a state of the art of current evidence, provide a short historical setting, and discuss the large opportunities, while emphasizing the need for solid, scientific, well-conducted trials to ensure that we can take advantage of the new treatment alternatives in a safe way to the best for our patients.

SYMPOSIUM 4

UPDATE ON NEW DRUG

S4.1 Targeting Brain Kynurenic Acid for Cognitive Improvement

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Abstract: The kynurenine pathway, the major route of degradation of the essential amino acid tryptophan, contains several neuroactive metabolites, including kynurenic acid (KYNA). Because of its ability to inhibit the function of both NMDA and α7 nicotinic receptors at endogenous concentrations, and its related ability to bi-directionally regulate the fate and function of glutamate, dopamine, acetylcholine and GABA, KYNA is increasingly viewed as a unique neuromodulator. Thus, fluctuations in brain KYNA levels are involved in physiological processes including synapse formation, neuronal plasticity and a number of cognitive functions. Notably, abnormal KYNA elevations in the prenatal brain, as well as acute increases in brain KYNA levels later in life result in cognitive dysfunctions in adulthood. Moreover, unrelated to antipsychotic medication, the levels of KYNA are elevated in brain and cerebrospinal fluid of persons with schizophrenia, and genetically modified mice with increased brain KYNA levels exhibit several of the cognitive deficits seen in schizophrenia and other psychiatric diseases. Pharmacological agents capable of selectively reducing KYNA production are therefore expected to yield pro-cognitive effects under both physiological and pathological conditions. The neosynthesis of KYNA in the mammalian brain is controlled primarily by the astrocytic enzyme kynurenine aminotransferase II (KAT II), and attenuation of KAT II activity by selective genetic and pharmacological interventions indeed shows remarkable beneficial effects in a variety of well-established, translationally informative animal models of cognitive dysfunction. This bodes well for upcoming first clinical trials in humans, which are designed to test the pro-cognitive efficacy of brain-penetrant KAT II inhibitors in persons with schizophrenia.

S.4.2. Ulotarint: A Novel TAAR1 Agonist in Development for the Treatment of Schizophrenia

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Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) and 5-HT_{1A} receptor agonist in Phase 3 clinical development for the treatment of schizophrenia. Ulotaront was discovered through a target-agnostic approach optimized to identify drug candidates lacking D2 and 5-HT_{2A} receptor antagonism, while demonstrating an antipsychotic-like phenotypic profile *in vivo.*
Objectives: To provide a summary of preclinical evidence, pharmacology, and emerging clinical efficacy and safety profile of ulotaront.
Method: Results of preclinical and clinical studies reported in more than two dozen peer-reviewed articles and posters will be summarized.
Results: The antipsychotic potential of ulotaront was confirmed in pre-clinical psychosis models, including reduction of phencyclidine (PCP)-induced hyperactivity; reversal of sub-chronic PCP-induced social interaction deficits; increase in prepulse inhibition (PPI); and reduction in MK-801-induced deficits in PPI and hyperactivity. Ulotaront has completed two Phase 2 trials (4-week study; 26-week extension study). Ulotaront has been granted Breakthrough Therapy Designation for the FDA for the treatment of schizophrenia. In the double-blind, placebo-controlled study, ulota-

ront was associated with significant (p<0.001) improvement in Positive and Negative Syndrome Scale (PANSS) total score (effect size [ES]: 0.45), Clinical Improvement Severity score (ES: 0.52), and the Brief Negative Symptom Scale total score (ES: 0.48). Initial studies suggest that ulotaront is ell-tolerated and lacking in clinically significant D2 antipsychotic class-related adverse events (e.g., extrapyramidal symptoms, hyperprolactinemia, sedation, and adverse weight and metabolic effects). The open-label extension demonstrated further improvement across schizophrenia symptoms and confirmed the tolerability of ulotaront, with a 6-month completion rate of 67%. At Week 26, 93.3% of patients met stringent responder criteria (≥30% reduction in PANSS total score), and fully 72.1% achieved ≥50% reduction.
Conclusion: Based on current data, ulotaront shows potential to be a first-in-class TAAR1 agonist for the treatment of schizophrenia, with a mechanism of action distinct from the current D2-blocking class of antipsychotics.

S4.3 Rituximab as adjunctive treatment for schizophrenia spectrum disorder or obsessive-compulsive disorder

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Background: Immunological mechanisms may contribute to mental illness. For psychotic disorders and OCD, accumulated research implicates neuro-inflammation in at least subgroups of patients, e.g. anti-NMDAR-encephalitis and Pediatric Acute-Onset Neuropsych-iatric Syndrome (PANS). However, treatment results with anti-inflammatory or immunomodulating drugs have hitherto been unconvincing for schizophrenia and OCD *per se*.
Aim: Repurposing Rituximab, a B-lymphocyte depleter, targeting CD20, is highly effective in autoimmune disorders, such as rheumatoid arthritis and multiple sclerosis.
Patients: Severely ill, treatment-resistant patients, 9 with schizophrenia and 10 with OCD.
Mean age: 27 years (19 – 39), *Age at onset:* 14 years (6 – 27).
Intervention: One infusion of 1000 mg Rituximab (Mabthera®) at baseline.
Maintenance drug treatment was unchanged during the first 5 months.
Clinical results: In schizophrenia: marked improvements of all PANSS subscales, depressed mood and anxiety after 3 months, when 7 of 9 patients had decreased > 40% on PANSS. Then gradual return to the pre-treatment state. Psychosocial functioning (PSP scale) improved by 64% after 3 months.
In OCD: 2 of 10 patients were improved on Y-BOCS after 5 months, the others, however, were unchanged. 3 schizo-obsessive patients improved both on PANSS and Y-BOCS
Preliminary biochemical and fMRI results: Among cytokines measured, for instance, changes of Transforming growth factor (TGF)-β1 correlated with clinical improvement in schizophrenia but not in OCD. Connectivity changes between baseline and 5 months post-treatment correlated with symptom improvement; seed in the left anterior insula, cluster in right lingual gyrus and right intracalcarine cortex.
Conclusion: Despite the open-label treatment of a small number of subjects, our findings may represent the end of the beginning of the search for effective schizophrenia treatments based on inflammatory mechanisms.

LECTURE 5

KEYNOTE LECTURE

L5.1Treatment of ADHD and Substance Use Disorders

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Abstract: ADHD is a widely prevalent disorder in children, adolescents, and adults. Over the past three decades, it has become increasingly clear that most individuals diagnosed with childhood ADHD continue to have impairing symptoms into adulthood. The presence of a comorbid substance use disorder (SUD) makes it more difficult to treat the ADHD symptoms. Similarly, untreated ADHD may make it less likely that standard treatments for SUD will be as effective. Several ADHD instruments may have utility for screening individuals with an SUD with ADHD, though a comprehensive diagnosis is required to accurately diagnose adolescents and adults with an SUD with ADHD. Recent trials have suggested that treatment of ADHD by stimulants may lead to reduction in both ADHD symptoms and drug use across the lifespan. Fewer data exist to support the use of non-stimulants or nonpharmacologic treatment alone for adults with ADHD and a SUD. The use of robust doses of long-acting stimulants has shown the best efficacy to date in adults with ADHD and stimulant use disorders. Strategies to mitigate the risk of nonmedical use of prescription stimulants in substance using populations with ADHD will be discussed. Given the substantial subpopulation of persons with SUD and adult ADHD, further research is warranted.

LECTURE 6

ADDICTION, SIUCIDE AND ADHD

L6.1 Suicide prevention- how to turn the tide

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Abstract: Suicide is still a huge public health problem with 800,000 deaths per year. Some countries have experienced declining trends, especially in Asia, partly due to restrictions in access to highly lethal pesticides. USA are facing increasing trends and in many western European countries there has been declining tendencies, but most recently rates have been rather stable.
Suicide preventive strategies have focused on universal prevention, thus intervention targeting the who population, selective prevention aiming to reduce risk in different high risk groups, and indicated prevention targeting people who are already having suicidal behavior. However, the distinction between universal, selective and indicated prevention needs to be specified into situation-specific prevention, since suicidal behaviour and intention fluctuate. Even for a person with a very high risk of suicide, survival is by far the most likely outcome each day. In most cases, suicidal acts are carried out within a short period of time, and in many cases without a long period of warning signals. In a way, suicidal acts resemble heart attacks or epileptic episodes more than other complications that often develop slowly and gradually. This makes the task of creating awareness programmes even more difficult.
However, a thorough mapping of risk groups and risk situations will enable us to plan a more targeted intervention. Thus, epidemiology and clinical research can play together. The suicide rates in different risk groups will be presented and linked to considerations about which interventions are needed.
The most important task is to identify those of immediate risk of suicide and provide treatment and support. There are four distinct risk groups with a very high suicide rate. These are 1) people sent home from psychiatric emergency room visits, 2) people recently discharged from psychiatric hospitalization 3) people who were hospitalized due to attempted suicide 4) people who have called life-line or other NGO-driven helplines because of suicidal thoughts. All these four groups have a very high risk of suicide and the help they are offered are in most countries fragmented and not well organized
It can be helpful to evaluate the population attributable risk associated with different risk factors. The population attributable risk is an estimate of the proportion of the problem that could be avoided if the increased risk in a specific risk group could be reduced to the level of the general population. This approach will be demonstrated.
Interventions involve persons who will never commit a suicidal act, and they also involve monitoring persons in high-risk groups for long periods with no suicidal acts.

L6.2 Neuromodulation of subjective experience

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Abstract: Many psychoactive substances are used with the aim of altering experience, e.g. as analgesics, antidepressants or antipsychotics. These drugs act on specific receptor systems in the brain, including the opioid, serotonergic and dopaminergic systems.
In this talk, I will summarise human drug studies targeting opioid receptors and their role for human experience, with focus on the experience of pain, stress, mood, and social connection. Opioids are only indicated for analgesia, due to their potential to cause addiction. When these regulations occurred, other known effects were relegated to side effects. This may be the cause of the prevalent myth that opioids are the most potent painkillers, despite evidence from head-to-head trials, Cochrane reviews and network meta-analyses that opioids are not superior to non-opioid analgesics in the treatment of acute or chronic non-cancer pain. Understanding the effects of these commonly used medications on other aspects of the human experience is important to ensure correct use and to prevent unnecessary pain and addiction risk.

L6.6 Role of Cognition in Alcohol Use Disorders

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Missing Abstract

L6.7 Gut-brain axis and addictive disorders

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Abstract: Alcohol use disorder (AUD) is a neuropsychiatric disorder with high mortality and morbidity rates. As the treatment outcome of existing pharmacotherapies is insufficient, novel treatment options are needed. Intriguingly, gut-brain peptides like amylin and glucagon-like peptide-1 (GLP-1) have been suggested as such candidates as activation of their recep-

tors (AMYR or GLP-1R) independently reduces alcohol intake in rodents. This is further evident as polymorphisms of the GLP-1R is associated with AUD and an agonist reduces alcohol consumption in overweight AUD patients. Our most recent preclinical studies reveal that semaglutide, a clinically available GLP-1R agonist used for diabetes and obesity, reduces alcohol drinking, prevents relapse drinking and suppresses alcohol reward via acccumbal mechanisms. The mechanistic complexity of AUD raises the possibility of a beneficial reduction after the combination of the GLP-1R and AMYR agonist on alcohol drinking. Supportively, a combination of AMYR and GLP-1R agonists decreases the body weight gain in obese rats. Recently, we demonstrated that acute or repeated combination treatment decreases alcohol intake and relapse drinking in male and female rats. Intriguingly, the treatment outcome depends on the treatment regime. Besides, the tested combination treatment paradigms profoundly decrease the body weight in male and female rats. In summary, the outcome of these preclinical studies raises the urge to test the efficacy of these gut-brain peptides in AUD patients with obesity.

L6.6 Intravenous misuse of Methylphenidate in Iceland

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Background: Methylphenidate (MPH) is a prescription psychostimulant used to treat attention-deficit hyperactivity disorder (ADHD). MPH prescriptions have increased significantly in the past two decades in Western countries. MPH has known abuse potential but MPH is considered to have less abuse liability than amphetamine (AMP) and cocaine. Intravenous (i.v.) use of MPH has sporadically been reported in the past but comprehensive systemic studies of i.v. MPH use have not been conducted. Clinical observations in Iceland have shown that MPH has been growing in popularity among people who inject drugs (PWID)

Method: The study was cross-sectional using a semi-structured interview. All substance users who were admitted during a 12 month period to any of the addiction treatment centers in Iceland and reported any i.v. use in the past 30 days were offered to participate. A total of 108 patients were recruited over one year from all inpatient addiction centers in Iceland.

Results: A vast majority of participants (88%) had used i.v. MPH during the past 30 days. MPH was both the most commonly used and preferred i.v. substance among participants. Of the different MPH formulations, a majority used and preferred i.v. MPH sustained released (SR) whereas only 3% preferred MPH osmotic released (OROS). Nonetheless, a third of the participants had used MPH OROS at least once in the past month. The subjective effects and pattern of use for MPH SR and cocaine were rated similar in terms of injection rate per day and length and intensity of the "euphoria" and "high".

Conclusions: I.v. misuse of MPH is very common among PWID in Iceland and it is currently the most commonly used and preferred i.v. substance in among PWID seeking detoxification treatment. One of the sustained MPH formulations (MPH SR) was preferred by PWID and subjective effects and consumption pattern was reported similar to cocaine. This indicates that i.v. MPH may have no less abuse potential than cocaine. These findings are of relevance for countries where MPH prescriptions have been increasing in recent years because of growing demand for pharmaceutical treatment of ADHD. Vigilance and surveillance of possible misuse are recommended, especially when treating patients with history of substance use.

POSTERS

Poster 1

Proteomic Plasma Profiling of Patients with First-Episode Psychosis Identifies Inflammatory Markers Associated with Illness Severity.

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Background: Numerous studies from the past 20 years suggest that the immune system and inflammatory responses may be crucial in psychiatric illnesses. Thus, enhanced secretion of inflammatory cytokines and chemokines have been found in patients with depression, schizophrenia and bipolar disorder. Increased levels of immune markers have also been found to correlate with impaired cognitive ability.

In the present study, Olink Proximitiy Extension Assay (PEA) technology was used to investigate immune activation in first-episode psychosis (FEP) patients and healthy controls (HC) and to further analyze if the immune profile differs between FEP patients later diagnosed with schizophrenia and those not receiving such diagnosis. Furthermore, since correlations of

disease severity and neurocognitive decline has been shown previously, we aim to explore patterns of correlations with altered inflammation markers and psychopathology and cognitive scores.

Methods: Somatically HC (n=55) with no prior drug addiction and FEP patients (n=73) were recruited in the Karolinska Schizophrenia Project (KaSP) in Stockholm, Sweden. The existence of neurologic illnesses or severe somatic illness, a history of illegal substance addiction, and the presence of co-existing neurodevelopmental abnormalities were exclusion criteria. Global Assessment of Functioning (GAF, the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) were performed to assess clinical characteristics of the patients. 46.6% of the patients (n=34 of 73) were treated with antipsychotics at the time of serum sampling. Maximum number of days of antipsychotic treatment was 26 days, mean number of days was 9.6. Thirty-eight patients have not used any kind of antipsychotics prior, or at the time of serum sampling. Venous blood samples were collected using standard venipuncture techniques. 92 inflammatory proteins in the serum were analyzed by Olink Bioscience, Uppsala, Sweden using the multiplex proximity extension assay technology (PEA) inflammation panel.

Results: No significant differences were observed between HC and FEP patients regarding age, gender, or body mass index. Total PANSS score for patients was 71.9 ± 2.4. DUP was 8.5 ± 1.6 (mean ± s.e.m.) months for FEP patients. Differential expression analysis showed 12 proteins upregulated in FEP patients. AXIN1 was identified to be the most differentially abundant (logFC = 1.48, adj.p.val = 0.00002). The second most differentially abundant protein, with highest log fold change, was STAMBP (logFC =1.01, adj.p.val = 0.00002). CASP-8 and SIRT2 are other top differentially abundant inflammation markers with high log fold changes found in patients. The chemokines CXCL1, CXCL5, CXCL6, IL7 and TNFSF14, playing important roles in ERK signaling pathways and neutrophil activation, were also found to be elevated. The levels of the anti-inflammatory cytokine, IL-10RA, was found to be decreased in patients. Differential expression analysis between HC and disease groups (SCZ and Non-SCZ) showed that 15 proteins are upregulated in patients diagnosed with schizophrenia compared to HC. Here, AXIN1 was identified to be the most differentially expressed with an elevated log fold change. (logFC = 1.87, adj.p.val = 4.54E-07). Ten out of 12 of the inflammation proteins (namely AXIN1, STAMBP, CASP-8, 4E-BP1, CXCL1, CXCL5, IL7, TNFSF14, CXCL6 and IL-10RA) showed a significant correlation with PANSS positive scores. The NPX values for AXIN1 (rs= 0.36), STAMBP (rs= 0.38), IL-7 (rs= 0.50) and IL-10RA (rs= -0.7) showed a high correlation with PANSS positive score. Correlations between differentially expressed proteins and symptom ratings were also performed in the subgroup of patients diagnosed with SCZ. The NPX values for AXIN1 (rs= 0.45), STAMBP (rs= 0.4), CASP-8 (rs= 0.67), SIRT2 (rs= 0.53), CXCL5 (rs= 0.35), IL-7 (rs= 0.56), TNFSF14 (rs= 0.33), CXCL6 (rs= 0.43), CD40 (rs= 0.34) and MCP-2 (rs= 0.50) showed a high correlation with PANSS positive score. PANSS Negative was found to correlate to the NPX values for CXCL6 (rs= 0.33), CCL11 (rs= 0.36), CXCL11 (rs= 0.32), PANSS General was found to correlate to the NPX values for AXIN1 (rs= 0.35) and PANSS total scores was found to correlate to the NPX values for AXIN1 (rs= 0.34), STAMBP (rs= 0.32), CASP-8 (rs= 0.5), IL-7 (rs= 0.35), CXCL6 (rs= 0.39) and MCP-2 (rs= 0.34). Correlations were not significant after correction for multiple testing.

Conclusions: The current study's findings demonstrate that peripheral immunological markers are significantly elevated in FEP patients. Interestingly, several of the markers had previously been proposed to be implicated in psychosis. We also discovered that the markers significantly associated to illness severity and cognition. This is consistent with our discovery that immunological activation was even stronger in a subset of patients eventually diagnosed with schizophrenia.

Poster 2

Cardiovascular proteins are elevated in first-episode psychosis patients compared to healthy controls

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Background: The leading cause of death among patients with schizophrenia is cardiovascular disease. Inflammation is involved in the development of atherosclerosis and is also proposed to be part of the pathophysiology of schizophrenia. It has therefore been suggested that the same inflammatory changes could contribute to both the psychotic symptoms and the increased mortality in cardiovascular disease for patients with schizophrenia.

Objectives: Our aim was to study a large number of cardiovascular biomarkers in first episode psychosis (FEP) patients that are drug-naïve or under short time anti-psychotic medication and healthy controls (HC). We also wanted to perform correlations of these biomarkers with clinical and cognitive ratings as well as known cardiovascular risk factors.

Methods: Ninety-two cardiovascular markers in plasma of 73 FEP patients (of which 42 were later

diagnosed with schizophrenia) and 55 healthy controls were analyzed using the OLINK Proximity Extension Assay, Cardiovascular II Panel. The study was a part the Karolinska Schizophrenia Project (KaSP).

Results 16 out of 92 cardiovascular biomarkers were elevated in FEP patients compared to HC and 19 out of 92 biomarkers were elevated in patients later diagnosed with schizophrenia compared to HC. One biomarker was decreased in FEP patients compared to HC and in patients later diagnosed with schizophrenia compared to HC. In FEP patients, levels of these biomarkers correlated with symptoms severity, cognitive measures and known cardiovascular risk factors, but correlations were not significant after correcting for multiple analysis.

Conclusion: Several cardiovascular biomarkers are elevated in FEP patients and patients later diagnosed with schizophrenia compared to HC. This could contribute to both the psychiatric symptoms of schizophrenia and the development of atherosclerosis and increased mortality in cardiovascular disease.

Poster 3

Dysregulation of the kynurenine pathway is related to persistent cognitive impairments after tick-borne encephalitis

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Background: Tick-borne encephalitis (TBE) patients frequently suffer cognitive and neuropsychiatric sequelae, which may be both severe and long-lasting. Underlying mechanisms for post-encephalitic symptoms remain poorly understood, and informative biomarkers and targeted treatments are currently unavailable. Tryptophan metabolism via the "kynurenine pathway" (KP) is elevated in viral infections and may contribute significantly to related neuropathology through generation of the neuroactive metabolites quinolinic (QUIN) and kynurenic acid (KYNA).
Objective: To relate long-term cognitive performance in TBE patients to concentrations of KP metabolites in cerebrospinal fluid (CSF) and serum.
Methods: Tryptophan metabolites were measured with UPLC-MS/MS in paired samples from TBE patients (n = 87; acute phase, and at 6 and 18-months), and healthy controls (n = 12). Cognitive performance was evaluated by the Matrics Consensus Cognitive Battery at 6 and and 18-months.
Results: TBE patients displayed robust induction of the KP during acute disease, with elevated QUIN (TBE: median 544.2 nM, control: median 10.3 nM, $p < 0.001$) and KYNA (TBE: median 8 nM, control: median 2.7 nM, $p < 0.001$) in CSF. The kynurenine/tryptophan ratio (rKT), a proxy for KP activity, remained significantly elevated in serum of patients at 6 and 18-months. Negative associations were observed between patient cognitive performance and measures of KP activity both in CSF (Spearman's ρ -0.39, -0.32 for overall composite T-scores at 18 months with acute CSF kynurenine and QUIN, respectively) and serum (Spearman's ρ -0.55, -0.37 for attention and vigilance, and working memory T-scores at 18 months, respectively, with concurrent serum rKT).
Conclusions: KP activity is elevated in TBE patients and is associated with cognitive impairment. Our results suggest a particular role for dysregulated peripheral KP activity, likely through increasing availability of precursor for brain synthesis of neuroactive kynurenines. The KP may offer new avenues for treating post-encephalitic cognitive impairment.

Poster 4

Quasi-tenacious depression (QTD) as an alternative framework to treatment-resistant depression (TRD)

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Treatment of major depressive disorder (MDD) is challenging, as almost one-third of patients are not adequately responsive to current treatments. This subgroup of patients is commonly referred to as treatment-resistant. Nonetheless, it may not be accurate to attribute the lack of response to the patients themselves. Non-response could stem from various reasons including but not limited to misdiagnosis, non-adherence, improper choice of pharmacotherapy, protracted presence of a stressor, accompanied possible comorbidities, etc. In this context, we argue that TRD may be semantically and clinically misleading, and we propose a new model, QTD, which is derived from the tenacity index (TI), a potentially measurable outcome. The current approach to diagnosing depression is solely based on descriptive data, rather than quantifiable measures, that specifically relate to the etiology and pathophysiology of the underlying disorder. TI can be used to quantify potential barriers and predict the degree to which a patient with depression seems tenacious to respond to a particular treatment strategy and differentiate between whether the tenacity observed is a result of the manifestation of the disorder or the other factors masking the response. The incessant search for new treatment options with varied profiles of activity, and identification of factors leading to such higher tenacity indices are what QTD demands. This model acknowledges that all patients with depression have some degree of tenacity that

needs to be overcome with proper treatment modalities. Additionally, it provides a measurable concept that aids clinical decision-making while having a scientific foundation to present a positive and dynamic perspective of the disorder for both patients and healthcare providers.

Poster 5

Preclinical support for antidepressant and anxiolytic effects of the dopamine stabiliser (-)-OSU6162S

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Background: (-)-OSU6162 is a dopamine stabiliser with unique properties of stabilising dopamine transmission and dopamine-driven behaviour depending on prevailing tone. The substance thus exerts psychomotor activation in rodents habituated to their environment and psychomotor inhibition in active and hence exploring, or amphetamine-treated rodents. Although (-)-OSU6162 does not exhibit any intrinsic activity at the D_2 receptor *in vivo*, its stimulating properties mimic those of D_2 receptor agonists while its inhibiting properties resemble those of D_2 antagonists, though without any evidence of catalepsy even at high doses. The substance binds to D_2, 5-HT_{2A} and sigma-1 receptors with high affinity and thus shares pharmacological similarities with atypical antipsychotics displaying antidepressant effects as add-on to SSRIs in treatment-refractory depression. Clinical studies for other indications have however shown (-)-OSU6162 to be considerably better tolerated than the atypical antipsychotic agents.

Purpose: To investigate possible antidepressant- and anxiolytic-like effects of the dopamine stabiliser (-)-OSU6162 in rodents.

Methods: To assess antidepressant-like effects, rats were exposed to a chronic mild stress paradigm and then treated with active doses of (-)-OSU6162 or saline prior to being subjected to the forced swim test. Registration of locomotor activity was performed to control for possible stimulatory effects. To assess anxiolytic-like effects, the context-conditioned fear test was used in which rats were administered (-)-OSU6162 in ascending doses following foot shock exposure in a fear conditioning chamber. With respect to the latter model, mechanism of action was investigated by systemic delivery of a D_2, 5-HT_{2A}, or sigma-1 antagonist prior to the administration of (-)-OSU6162.

Findings: (-)-OSU6162 in doses of 10 and 30 mg/kg significantly reduced immobility in the forced swim test as well as conditioned fear-induced freezing without increasing general locomotion. The reduction of fear behaviour was completely reversed by pre-treatment with the D_2 antagonist raclopride but unaffected by pre-treatment with the 5-HT_{2A} antagonist MDL 100907 or the sigma-1 antagonist BD 1063.

Conclusions: The dopamine stabiliser (-)-OSU6162 showed behavioural effects in preclinical rat models of antidepressant and anxiolytic response. The effects are likely due to preferential blockade of the D_2 auto receptor leading to enhanced dopamine release and hence enhanced activation of postsynaptic D_2 receptors not antagonized by (-)-OSU6162 (but by raclopride). As (-)-OSU6162 is exceptionally well tolerated, the results justify clinical studies exploring the possible antidepressant and anxiety-reducing effects of the drug.

Poster 6

Project Plan: Exploring a signature of synaptic pruning during adolescent brain development

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Postnatal cortical maturation is characterized by re-wiring of inter- and intracortical connections and goes along with pronounced changes in synaptic density. During childhood there is an extensive synapse production resulting in a density twice as high as in the adult brain. This is followed by a period of synaptic pruning which, in the prefrontal cortex, occurs during adolescence and predominantly affects layer 2/3 excitatory synapses. The reduction in synaptic density is believed to be the result of refined neuronal circuits and increased network efficiency, facilitating essential functions of the adult prefrontal cortex. A disruption in synaptic pruning is observed in a number of psychiatric disorders, including autism spectrum disorder and schizophrenia, where it coincides with symptom manifestation during adolescence.
Synaptic pruning is likely regulated by a complex interplay of genetic and environmental factors but the exact cues that determine which synapses will be pruned are still largely unknown. The aim of this project will be to explore whether a specific cell population defined by its projecting region, input source, transcriptome, or proteome is especially affected by synaptic pruning. We will quantify synapses of selected subpopulations of layer 2/3 pyramidal neurons in mouse prefrontal cortex in pre- vs post-adolescent stages. We will fluorescently label subpopulations by injection of retrograde or trans-synaptic anterograde virus into selected projection regions or input regions

of layer 2/3 neurons, respectively. This cell population-based labeling approach will be combined with endogenous tagging of selected synaptic proteins via intra-bodies to visualize their expression pattern in single synapses and assess whether one or a combination of synaptic proteins serve as a pruning signature. Once we have determined a pruning-susceptible subpopulation, we will isolate synaptosomes and compare the proteomic and transcriptomic signatures of pruned versus spared synapses.
With this study, we hope to provide a deeper understanding of the extensive synaptic remodeling occurring during adolescence in the prefrontal cortex. Knowledge of the molecular and cellular processes underlying adolescent synaptic pruning will be the basis for studying aberrant synaptic remodeling in Schizophrenia and other psychiatric disorders.

Poster 7

Identification of a novel pharmacological target for the treatment of cognitive dysfunction

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Background: Cognitive impairment is commonly observed in patients with psychiatric disorders and infectious diseases, andthere is a lack of pharmacological treatment for this condition. Growing evidence suggests immune activation to be important for cognitive dysfunction. Specifically, immune activation increases the levels of brain kynurenic acid (KYNA), a neuroactive metabolite interfering with neurotransmission and impairing cognitive functioning. Kynurenine aminotransferases (KAT I-IV) convert kynurenine to KYNA. Under normal conditions, KAT II is responsible for 70% of the production of KYNA. However, the role of KATs in KYNA production during immune activation is not clear.

Methods: Quantitative reverse transcription was used to analyze the mRNA expression levels and western blot toanalyze the protein expression levels of KAT isoforms (I-IV). To obtain single-cell transcriptomic profiles, we used publicly available human postmortem data sources. KYNA levels were quantified using an ultra-performance liquid chromatography–tandem mass spectrometry system.

Results: Our study provides evidence that KAT II is not the primary enzyme responsible for KYNA production under conditions of immune activation. Instead, we found that KAT III is the most prominent enzyme. We observed an upregulation of KAT III expression in the brains of mice, human fibroblasts, epidermal cells, and monocytes, following immune stimulation. Furthermore, we detected increased expression of KAT III in post-mortem brain samples fromCOVID-19 patients. In addition, we found that pro-inflammatory cytokines induced the expression of KAT III in a human cell model, and that a selective KAT III inhibitor effectively reversed the immune-induced KYNA.

Conclusions: Our study highlights the critical role of KAT III in the production of KYNA under conditions of immune activation. These findings have significant implications for the development of therapeutic strategies aimed at addressing the cognitive impairments commonly observed in patients with psychiatric disorders and infectious diseases.

Poster 8

Accumbal cholinergic signaling regulates ethanol intake in the rat

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Alcohol use disorder is associated with serious medical consequences leading to preterm death. Although few in numbers, cholinergic interneurons (CIN) have arisen as an important cell population within the nucleus accumbens (nAc) that may exert a regulatory impact on local dopamine (DA) neurotransmission. In fact, a defect in CIN have been implied in psychiatric diseases such as alcohol addiction. The exact mechanisms through which endogenous cholinergic activity modulates DA release in response to ethanol administration and its role in development of addiction is not known. However, we have recently shown that the ethanol-induced increase in extracellular levels of accumbal DA is blocked by a combination of a muscarinic and a nicotinic antagonist given locally, implicating cholinergic signaling. Moreover, ablation of accumbal CIN attenuate the ethanol-induced increase of extracellular DA. Together these data suggest that activation of CIN, probably resulting in increased acetylcholine level, is involved in ethanol's DA releasing effect. The objective of this project was to investigate the functional role of accumbal CIN to confirm the importance of the recent molecular findings. To this end, an intermittent ethanol consumption paradigm, know to induce high ethanol intake in outbreed rats, was used together with a toxin-based method to selectively ablate accumbal CIN. A selection of rats presenting a high ethanol intake during

an initial screening period, underwent stereotactic surgery to receive anti-choline acetyltransferase-saporin or a sham solution bilaterally into the nAc. Rats treated with anti-choline acetyltransferase-saporin consumed significantly less ethanol than sham-treated animals, whilst consuming the same amount of water and gaining weight in the same extent. Further, the alcohol deprivation effect was abolished in toxin-treated animals whilst being present in sham-treated rats. In conclusion, these data support a functional role of accumbal CIN in ethanol´s rewarding effect, opening up for new potential pharmacological targets for treatments of alcohol use disorder.

Poster 9

Prolonged fasting results in temporarily elevated levels of kynurenine pathway metabolites in healthy individuals

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Background: Different fasting protocols are increasingly used by the general population in everyday life, additionally as nutritional strategies for metabolic disorders. In this study, we investigate how fasting affects the kynurenine pathway (KP).

Objectives: The metabolism of the KP is affected in disease and KP metabolites may constitute potential future biomarkers. Therefore, it is important to investigate and understand how these may fluctuate following physiological stressors, e.g., fasting.

Methods: The current study comprised of a healthy cohort of young males that either fasted (zero-calorie restriction) for 6 days (FAST trial, n=14) or acted as controls (CON trial, n=10). Venous blood samples were collected on day 0, 2, 4, 6 of fasting and 1 week after recovery. Plasma samples were analyzed for KP metabolites using ultra-performance liquid chromatography-tandem mass spectrometry. Saliva, sampled for measuring stress markers, was collected every-day from 3 days before the baseline measurements until the experimental endpoint.

Results: Statistical analysis revealed an induction of the KP in FAST trial individuals. In plasma, picolinic acid, kynurenic acid and 3-hydroxykynurenine concentrations were significantly elevated, reaching peak levels on day 6. While tryptophan and quinolinic acid concentrations decreased, kynurenine and nicotinamide concentrations remained stable. Interestingly, salivary cortisol measurements were not significantly altered while noradrenaline and adrenaline levels showed significant increase on day 4 in both groups. All alterations in KP metabolites returned to baseline 1 week after recovery from the 6-day fasting regimen.

Conclusion: Several KP metabolites were found to be affected in plasma by fasting in healthy individuals. Recovery of metabolite concentrations to baseline levels upon refeeding suggests a rapid adaptation of KP synthetic enzymes to homeostatic perturbations. Further studies are needed to interpret the wider relevance of the observed fasting metabolic profile to diseases where the KP pathway is implicated.

Poster 10

Measuring lithium at home? A novel patient-centric method

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Background and method: Li is a first line treatment for bipolar disorder and concentration needs to be determined every 1-6 months; after dose changes and at the event of various health states (e.g. dehydration). DBS sampling could be done at home and sent by mail. Following method validation, we compared DBS (dried blood spots) from fingerprick against the serum standard method. (n = 39) at Karolinska University Hospital Huddinge. Inclusion criterium: Current Li treatment.
Results A strong correlation between serum and DBS lithium measurement (r = 0.949) was found. Concentration is lower in capillary blood with a ratio of 0.78 on average. No meaningful effect of hematocrit could be found.
Conclusion: We show that the concentration of lithium (Li) can be measured with volumetric dried blood spots (DBS). We compared DBS to the standard serum analysis (n = 39). A strong correlation with Pearson's r = 0.949 indicates that this method could be used clinically. The main limitation is that we have only one sample per person. Therefore, a follow-up study is planned to determine within-person stability.
Continuation: Our next step will be a study to analyze intra-individual stability, drawing multiple samples

from individuals over time. After this we aim to start trying out the method in clinical practice.

Poster 11

Physical Training for Patients with Depression and Anxiety – a Randomized Controlled Study

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Background: Pharmaceutical treatment and psychotherapy are major alternatives in treatment of depression and anxiety. Physical training has been shown to have comparable effect to cognitive behavioral therapy for treating mild to moderate depression and anxiety. Physically active individuals also have lower risks to develop depression and physical activity can also reduce relapse in depression.

Objectives: To evaluate if and how high-intensive interval training (HIIT) as an add-on group treatment to standard outpatient care, compared to relaxation therapy, affects treatment response, biomarkers in the blood and the gut and cognitive functions of patients with depression and anxiety.

Methods: 102 patients are randomized to two groups and undergo 12 weeks intervention in addition to standard outpatient care. Patients are recruited from the Department of Psychiatry and primary care units in Örebro. The first group will participate in HIIT three times per week and the other group will have relaxation therapy once a week. Daily physical activity will be measured before and at the last week of intervention with an accelerometer. Blood and faeces sample collection, symptom grading by clinician and with self-rating scales and cognitive screening will be performed at baseline, at week 12 and at one year of follow-up. The cognitive screenings are performed digitally in cooperation with Mindmore.

Results: We have so far included 79 patients.

Conclusion: The RCT is currently recruiting patients within Region Örebro and the Department of Psychiatry.

Poster 12

Effects of indole-3-propionic acid on regulating brain and peripheral kynurenine pathway metabolism in male Sprague-Dawley rats

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Background:
The metabolism of dietary tryptophan generates various biologically active molecules in both the host and gut microbiota. However, the relationship between microbiota-produced and endogenously produced tryptophan metabolites is under-investigated. Indole-3-propionic acid (IPrA) is a microbiota-derived tryptophan metabolite that exhibits multiple biological activities in the brain and in the periphery. Our previous research revealed that IPrA treatment increases kynurenic acid (KYNA) levels in brain and plasma, linking microbial tryptophan metabolites with the host's kynurenine pathway, the primary route of tryptophan catabolism. Increased KYNA has been implicated in regulating behavior and cognition.
Objectives:
The present study investigated how IPrA affects kynurenine pathway metabolism and behaviors in rats.
Methods:
Two groups of 4-6 week-old male Sprague-Dawley rats were used. In the first group, each rat received a single intraperitoneal injection of 2, 20, 100 or 200 mg/kg IPrA or vehicle and was euthanized 90 minutes later. Targeted metabolomic analysis of tryptophan, kynurenine, KYNA, 3-hydroxykynurenine (3-HK), quinolinic acid (QUIN), and picolinic acid (PIC) was carried out in hippocampus and plasma. In the second group, animals were evaluated for recognition memory and locomotor activity in the novel object recognition (NOR) test following i.p IPrA (200 mg/kg) or vehicle administration.
Results: IPrA dose-dependently increased the levels of tryptophan, kynurenine, KYNA, 3-HK, and PIC in the brain, without changing QUIN levels. In plasma, IPrA administration dose-dependently increased KYNA and 3-HK concentrations and reduced tryptophan concentration without affecting QUIN and PIC concentrations. The impact on plasma kynurenine levels varied among doses. In the NOR test, IPrA-treated rats showed signs of impaired recognition memory accompanied by reduced locomotor activity.
Conclusion: IPrA treatment stimulates both the neuroprotective and the neurotoxic branches of the kynurenine pathway, and may be causally related to cognitive impairments. Future experiments will be de-

signed to investigate the impact of IPrA in greater detail, using several behavioral and electrophysiological outcome measures.

Poster 13

Risk factors for developing disorder and impulse-control disorders under dopaminergic medication

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Background: Dopaminergic therapy, commonly used to treat the neurological conditions Parkinson's disease (PD) and restless legs syndrome (RLS), is known to increase the risk for developing gambling disorder (GD) and impulse-control disorders (ICDs).
Objectives: Our goal is to identify risk factors associated with developing GD and ICDs under dopaminergic therapy. We consider demographic factors, neurological and psychiatric diagnoses and prescriptions.
Methods: On a large dataset from Swedish national registries including drug prescriptions and diagnoses of 250 000 patients with dopaminergic prescriptions, we investigate factors associated with GD or ICDs. Using chi-square tests and logistic regressions, we examine the role of age, sex, mortality and underlying neurological conditions, but also the impact of different dopaminergic substances. We are interested in psychiatric comorbidities and will examine both psychotropic drug prescriptions in general, and the effect of certain substances like aripiprazole or haloperidol, that have been described to increase the risk for GD and ICDs themselves.
Results: GD and ICD diagnoses are associated with a later birth year and younger age at death. Women are only slightly less affected than men, which is surprising with GD being much more prevalent in men in the general population. Interestingly, RLS patients seem to be a more vulnerable patient group than PD patients. In line with many other studies, we find dopamine agonists to have the strongest association with GD or ICDs, even confirming the D2-class agonists pramipexole and ropinirole as being especially disadvantageous. GD and ICD patients have a compromised mental health, measured by the frequencies of common psychiatric diagnoses, psychotropic prescriptions, and events of self-harm.
Conclusion: Our results could help to improve neurological care regarding psychiatric side effects and also suggest, that large scale studies in RLS populations are needed, as they have been performed for PD patients within the last years.

Poster 14

Kynurenine negatively exaceberates the THC effects on tetrad and sensorimotor responses in adult mice

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Introduction: The main psychoactive component of marijuana (Δ9-tetrahydrocannabinol, THC) and synthetic cannabinoids intake, is correlated with untoward physiological effects in vulnerable individuals (D'Souza et al., 2016). Thus, cannabinoids misuse could be considered as a relevant factor in precipitating and/or perpetuating psychosis in these subjects. It has been reported, in rats and monkey, that the reinforcing effects of THC can be reduced by increasing endogenous kynurenic acid (KYNA) levels (Justinova et al., 2013). KYNA, a neuroactive metabolite deriving from tryptophan degradation (Schwarcz et al., 2012). Several studies suggest a pathophysiologically relevant association between increased brain KYNA levels and cognitive dysfunctions in individuals with schizophrenia (Wonodi and Schwarcz, 2010; Sathyasaikumar et al., 2011).
Methods: Male ICR (CD-1®) mice (25-30 g body weight) were treated with THC (30 mg/kg; i.p.) and kynurenine (20 mg/kg, i.p.), alone or in combination. Following the drug administration, body temperature, acute mechanical and thermal analgesia, motor activity sensorimotor responses (to visual, acoustic and tactile stimulation) were evaluated. Furthermore, brain levels of KYNA were measured 1 and 4 hours after kynurenine injection.
Results: Brain KYNA levels were significantly increased 1 hour, but not 4 hours, after kynurenine administration. The administration of kynurenine, amplified the THC-induced impairment of sensorimotor responses. In particular, kynurenine increased the THC-induced reduction in the visual placing response, acoustic response and tactile response (vibrissae, corneal and pinna reflexes). Furthermore, by using the "tetrad paradigm for screening cannabinoid-like effects" it has been observed that kynurenine significantly increased THC-induced motor activity reduction (as evaluated by the bar test, drag test and rotarod test) and hypothermia (core and surface body temperature), but not THC-induced analgesia.
Conclusions: Overall, the present data indicate that increased brain KYNA levels exacerbate "tetrad" and sensorimotor responses induced by the acute administration of THC. This confirm the existence of a cross-talk between the KP and endocannabinoid system which could be involved either in the

psychotropic properties of THC or in the ethiopatogenesis of schizophrenia.

Poster 15

Initiation of antidepressant treatment and the risk of manic episodes in children and adolescents with unipolar depression

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Background: Pediatric patients may be particularly vulnerable to severe adverse reactions induced by antidepressants, such as treatment-induced mania, which is pressing considering the increasing rates of which these medications are prescribed.
Objective: To estimate whether patients treated with antidepressants have an elevated incidence of mania/hypomania compared with patients not treated with antidepressants, and to identify patient characteristics associated with mania among those receiving medication.
Methods: In this register-based study, we included individuals with a diagnosis of unipolar depression from inpatient or outpatient setting in 2006–2020, aged 4–17, with no prior diagnosis of mania, bipolar disorder, or schizoaffective disorder, and no prior lithium prescriptions. The treatment group consisted of patients who initiated any antidepressant medication within 90 days of diagnosis. The control group included patients who did not initiate antidepressants. Patients were followed-up until 12/52 weeks after treatment initiation.
Results: The cohort included 43,953 patients (66% girls). The cumulative incidence of new onset mania was 0.24% (95% CI: 0.17–0.30) in the treatment group, and 0.23% (0.16–0.29) in the control group at 12 weeks, with a risk difference of 0.01% (-0.09–0.11). At 52 weeks, the cumulative incidence was 0.73% (0.62–0.84) in the treatment group and 0.54% (0.43–0.65) in the control group, with a risk difference of 0.19% (0.03–0.35). Psychosis, developmental disorders, hospitalizations, parental bipolar disorder, and the use of antiepileptics and sedatives were the most important predictors of mania in the treatment group.
Conclusion: We did not find evidence of treatment-emergent mania by 12 weeks, which corresponds to the timeframe for antidepressants to exert their psychotropic effect. A small risk difference was found only in the longer follow-up, suggesting the risk increase is attributable to factors other than the medication. Certain patient characteristics were associated with mania after antidepressant initiation, which warrants clinical attention.

Poster 16

Nicotinic modulation of striatal neurotransmission in female rats- electrophysiological and behavioral measurements

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Nicotine is a highly addictive substance, and cigarette smoking is a risk factor for cardiovascular and lung disease as well as cancer. Although it is known that tobacco use is the leading preventable cause of death worldwide, most who try to quit relapse and available intervention approaches are limited. Great effort has been made to understand the nicotinic mechanisms, but primarily in male animals. However, tobacco use amongst women has increased for several years, and epidemiological studies have shown sex-differences in nicotine sensitivity, that may influence the vulnerability to tobacco addiction in a sex specific manner. It is suggested that nicotine activates the reward system in ventral striatum (n. accumbens) in male animals, while nicotine mainly activates dorsal striatal areas in females. Amongst smokers, men are suggested to be more reinforced by nicotine itself, whereas women report more negative effects, more cue-induced craving and more difficulties quitting. Progressive nicotine-induced adaptations in striatal circuits are suggested to reflect an increasing risk of relapse. To this end, 45 adult female rats were injected with nicotine (0.36mg/kg, subcutaneous), or saline, with a total of 15 injections, followed by a three-month abstinence period. Behavioral effects of nicotine were assesed using locomotor activity measurements and elevated plusmaze, while neurophysiological changes were defined using ex vivo electrophysiological field potential recordings in striatal subregions.

Behavioral assessments demonstrated a robust sensitization to the locomotor stimulatory properties of nicotine, while anxiogenic behavior was not affected in the elevated plusmaze. Electrophysiological recordings revealed a selective increase in excitatory transmission in the dorsomedial striatum and nucleus accumbens during the acute abstinence phase. Following protracted abstinence, however, these regions demonstrated a depression of neurotransmission. Together, these findings suggest

that nicotine-induced modulation of neurotransmission partly separate from previous findings in male animals, in brain regions associated with drug addiction. Understanding how nicotine transforms the brain in female animals allows us to more fully grasp the complexity of nicotine dependence and, in extension, provides new means to challenge nicotine addiction.

Poster 17

Association between socioeconomic status and healthcare utilisation among individuals with a first depression diagnosis in primary care in the Stockholm region

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Background: Research on socioeconomic status (SES) and healthcare utilisation including the area of depression has produced inconsistent findings, which may reflect different healthcare structures and methodologies. Population-based surveys show that low SES is associated with higher rates of depressive symptoms and use of antidepressants (AD) while studies that utilise patient records for outcomes are more contradictory.

Objective: Investigate the association between SES and healthcare utilisation among individuals diagnosed with their first depression in primary care.

Method: This was a longitudinal study during 2010-2018 where SES was defined by the household using Mosaic classification. Outcomes were AD (N06A) dispensation and recording of psychiatric outpatient visit following their first depression diagnosis. Cox regression analysis was used to assess the association between SES and healthcare utilisation.

Results: A total of 117,193 individuals were included, 87,499 (75%) were dispensed an AD and 35,989 (31%) recorded a psychiatric outpatient visit during the follow-up period. Low SES was associated with lower rate of AD dispensation in the first year post-diagnosis (HR: 0.95 95% CI: 0.93-0.96, p<0.001) and higher rate of psychiatric visit (HR: 1.10, 95% CI: 1.07-1.12, p<0.001). Females had lower rate of AD (HR: 0.93, 95% CI: 0.92-0.94, p<0.001) and lower rate of psychiatric visit (HR: 0.82, 95% CI: 0.80-0.83, p<0.001) compared with males. Older age was associated with higher rate of AD (HR: 1.54, 95% CI: 1.52-1.57, p<0.001) and lower rate of psychiatric visit (HR: 0.40, 95% CI: 0.38-0.41, p<0.001).

Conclusion: This study suggests that the socioeconomic status of individuals diagnosed with depression could have an impact on the subsequent healthcare utilisation also in a healthcare system with virtually free access.

Poster 18

Effects of clozapine, risperidone, nd sodium nitroprusside on glutamatergic transmission in the hippocampus

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Evidence indicates that schizophrenia is a neurodevelopmental disorder, including an interplay between genetics and the environment, leading to different stages of the illness, i.e. the premorbid, prodromal, progressive, and residual phases. Whereas the premorbid and prodromal phases of the disease involve genetic and early developmental factors with mild motor, social and cognitive impairments, the phenotype of the disease is not manifested until after puberty. Then, the core symptoms develop, and the disease emanates into the progressive phase. The progressive phase of schizophrenia is characterized by different clusters of symptoms, i.e. positive and negative symptoms, as well as cognitive dysfunction, typically leading to significant functional impairment of the patients.

In the prodromal phase, or in early stages of schizophrenia, an increased intrinsic activity in the hippocampus has been shown, indicating that hippocampal hyperactivity is associated with positive symptomatology of the disease. During the prodromal stage, this hypermetabolism in the hippocampus CA1 region, with increased extracellular glutamate, will lead to atrophy of this brain region, which may contribute to the development of psychosis and hippocampal-related cognitive dysfunction.

Thus, it is important with an early pharmacology-based treatment of the patients, optimally in the prodromal phase, or in the early phases, since longer duration of psychotic periods has been shown to be associated to lower rates of symptom remission of the disease

Here we have examined, experimentally, the ability of co-administration of sodium nitroprusside to modulate the effects of clozapine or risperidone on hippocampal glutamate receptor-mediated transmission, by using an extracellular electrophysiological recording technique *in vitro*. Our results indicate that sodium nitroprusside has the capability of inhibit the glutamatergic transmission in the CA1 region of the hippocampus. Sodium nitroprusside also inhibited facilitating effects of both clozapine and risperidone on the glutmatatergic transmission in this brain region. These results indicate that sodium nitroprusside may be used as pharmacological treatment in the prodromal phase of schizophrenia, in order to downregulated the glutamate-induced atrophy of hippocampus, and that

the combination of nitroprusside and clozapine or risperidone would be useful for treatment of the early stages of the disease.

Poster 19

Developmental regulatory programs in the adult brain and their connection to schizophrenia

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Background: The biological processes pointed out as relevant in schizophrenia are to some extent contradictory. Transcriptional studies point to neurodevelopmental processes while the results from genetic studies largely converge on synaptic biology. A plausible explanation for this discrepancy is that regulatory programs controlling important aspects of brain development, later are repurposed to control synaptic function in the adult brain.

Objectives: We hypothesize that developmentally important transcription factors later control synaptic function. To test this hypothesis and attempt to reconcile divergent data, we take a molecular approach to investigate the role of developmental transcription factors in the adult mouse brain.

Methods: We will set up a CRISPR interference assay to silence the expression of selected transcription factors. The transcription factors have been selected based on single cell RNA sequencing data from the developing mouse brain and from neurons in the adolescent mouse brain (P40). We will use single cell RNA sequencing to read out the downstream effects on gene expression to identify the genes regulated by the selected transcription factors. Then, a possible enrichment of synaptic genes among the affected genes will be investigated but also whether any of the gene-regulatory programs downstream of the transcription factors are enriched for schizophrenia GWAS signal.

Results: The results have the potential to advance the knowledge about gene regulation in the adult brain. Even if the stated hypothesis is falsified, important insights into adult gene regulation will still be gained. These insights can also aid the interpretation of genetic and transcriptional data from psychiatric studies.

Conclusion:

A molecular approach to understanding schizophrenia and other psychiatric disorders, could potentially reveal the molecular mechanisms that are perturbed. Even if the cause of a disorder remains unknown, better understanding of the perturbed biological processes could result in therapeutic opportunities to balance a perturbed system.

Poster 20

Kynurenic acid promotes activity-dependent synaptic pruning and associates with genetic risk variance for schizophrenia

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Background: Several studies confirm that kynurenic acid (KYNA), an endogenous antagonist of NMDA and a7nACh receptors, is elevated in the cerebrospinal fluid and postmortem brain of individuals with schizophrenia (SCZ). So far, the mechanisms causing an elevation of KYNA and its pathophysiological consequences remain largely elusive.

Objectives: The aim of the study was to investigate the relationship between brain KYNA levels and 1) genetic risk variance for SCZ; 2) synaptic pruning implicated in SCZ.

Methods: We first integrated large-scale developmental postmortem brain tissue and genetic datasets to study co-expression networks for the KYNA producing kynurenine aminotransferases (KATs) regarding enrichment for common SCZ genetic risk variants, and functional annotations. Second, we used human induced pluripotent stem cell (iPSC) based 2D and 3D (organoid) models to study how KYNA influence microglial uptake of synaptic structures.

Results: We found that KAT networks enrich for genes governing synaptic processes as well as common genetic SCZ risk variance. In iPSC-derived co-cultures (2D) we first discovered that KYNA induces microglia-mediated synaptic pruning. In organoid models, we then observed decreased microglia-mediated synaptic pruning after inhibiting the production of KYNA.

Conclusion: These results provide a genetic background to the increased KYNA levels in SCZ and link KYNA to synapse pathophysiology while suggesting that the endogenous production of KYNA is a targetable mechanism that can reverse pathophysiological events in SCZ.

Poster 21

Low dose lithium, inflammation adjustment and applications across medicine

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At the beginning of the pandemic, we observed that lithium carbonate had a positive effect on the recovery of severely ill patients with COVID-19. Lithium is able to inhibit the replication of several types of viruses, some of which are similar to the SARS-CoV-2 virus, increase the immune response and reduce inflammation by preventing or reducing the cytokine storm. Previously, we published an article with data from six patients with severe COVID-19 infection, where we proposed that lithium carbonate could be used as a potential treatment for COVID-19. Now, we set out to conduct a randomized clinical trial number EudraCT 2020–002008–37 to evaluate the efficacy and safety of lithium treatment in patients infected with severe SARS-CoV-2. We showed that lithium was able to reduce the number of days of hospital and intensive care unit admission as well as the risk of death, reduces inflammatory cytokine levels by preventing cytokine storms, and also reduced the long COVID syndromes. We propose that lithium carbonate can be used to reduce the severity of COVID-19.

Poster 22

Esketamine nasal spray improves short- and long-term outcomes compared with quetiapine extended release in patients with treatment resistant depression: First results from ESCApE-TRD, a randomised, multi-centre phase IIIb clinical trial

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BACKGROUND: Treatment resistant depression (TRD) can be defined as non-response with ≥2 consecutive treatments in the current episode. Esketamine nasal spray (NS) improves depression symptoms in patients (pts) with TRD vs placebo, when both are given with a newly initiated selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI).[1] Previously, esketamine NS had not been directly compared to an active augmentation treatment.
OBJECTIVE: To report first results of ESCAPE-TRD (NCT04338321), the first study comparing esketamine NS with quetiapine extended release (Q-XR) in acute and maintenance treatment phases in pts with TRD.

METHODS: ESCAPE-TRD was a phase IIIb trial comparing the efficacy and safety of esketamine NS with Q-XR. Pts were randomised 1:1 to esketamine NS (56/84 mg; twice a week [wk], weekly or every 2 wks) or Q-XR (150–300 mg daily), both in combination with an ongoing SSRI/SNRI that had elicited non-response (<25% symptom improvement). Rates of remission at Wk8 (MADRS score ≤10; primary endpoint) and remaining relapse free to Wk32 after remission at Wk8 (key secondary endpoint) were compared between study arms, adjusting for age and number of prior treatment failures. All pts were analysed; treatment discontinuation was considered a negative outcome.
RESULTS: Most baseline characteristics were comparable between study arms. Of 676 randomised pts, a significantly greater proportion achieved remission at Wk8 with esketamine NS vs Q-XR (27.1% vs 17.6%; p=0.003). Furthermore, significantly more pts achieved remission at Wk8 with no relapse in to Wk32 on esketamine NS vs Q-XR (21.7% vs 14.1%; p=0.008). Treatment discontinuation occurred in 23.2% of esketamine NS vs 40.3% of Q-XR pts. No unexpected safety findings were observed with esketamine NS.
CONCLUSIONS: Significantly more esketamine NS-treated pts reached remission at Wk8 without subsequent relapse compared with Q-XR, meeting study primary and key secondary endpoints.

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ABSTRACT:

1.Ole Andreassen

Psychedelics in depression- opportunities and challenges

The current treatment of depression is still suboptimal, with a large degree of non-response. Unfortunately, few new traditiional antidepressant treatments have been developed the last years. However, there has been a large interest in psychedelics, which has received a lot of attention as new treatment alternatives, both from clinicians as well as lay peoople and the media.
Recently, several high impact papers have been published from recent clinical trials, and there is a lot of hope for these new treatment alternatives in depression. Still, there are several challenges related to duration of effect and potential side effects. HOwever, these seems to be minor, but more studies are needed.
The talk will include a state of the art of current evidence, provide a short historical setting, and discuss the large opportunities, while emphasizing the need for solid, scientific, well-conducted trials to ensure that we can take advantage of the new treatment alternatives in a safe way to the best for our patients.

2. Bejerot, Susanne

Rituximab as adjunctive treatment for schizophrenia spectrum disorder or obsessive-compulsive disorder

Background: Immunological mechanisms may contribute to mental illness. For psychotic disorders and OCD, accumulated research implicates neuro-inflammation in at least subgroups of patients, e.g. anti-NMDAR-encephalitis and Pediatric Acute-Onset Neuropsych-iatric Syndrome (PANS). However,

treatment results with anti-inflammatory or immunomodulating drugs have hitherto been unconvincing for schizophrenia and OCD *per se*.
Aim: Repurposing Rituximab, a B-lymphocyte depleter, targeting CD20, is highly effective in autoimmune disorders, such as rheumatoid arthritis and multiple sclerosis.
Patients: Severely ill, treatment-resistant patients, 9 with schizophrenia and 10 with OCD.
Mean age: 27 years (19 – 39), *Age at onset:* 14 years (6 – 27).
Intervention: One infusion of 1000 mg Rituximab (Mabthera®) at baseline.
Maintenance drug treatment was unchanged during the first 5 months.
Clinical results: In schizophrenia: marked improvements of all PANSS subscales, depressed mood and anxiety after 3 months, when 7 of 9 patients had decreased > 40% on PANSS. Then gradual return to the pre-treatment state. Psychosocial functioning (PSP scale) improved by 64% after 3 months.
In OCD: 2 of 10 patients were improved on Y-BOCS after 5 months, the others, however, were unchanged. 3 schizo-obsessive patients improved both on PANSS and Y-BOCS
Preliminary biochemical and fMRI results: Among cytokines measured, for instance, changes of Transforming growth factor (TGF)-β1 correlated with clinical improvement in schizophrenia but not in OCD. Connectivity changes between baseline and 5 months post-treatment correlated with symptom improvement; seed in the left anterior insula, cluster in right lingual gyrus and right intracalcarine cortex.
Conclusion: Despite the open-label treatment of a small number of subjects, our findings may represent the end of the beginning of the search for effective schizophrenia treatments based on inflammatory mechanisms.

3. Bergen Sarah

Understanding the genetics of psychiatric disorders in the era of GWAS

Abstract: Although a genetic component to risk for psychiatric disorders has been widely acknowledged for many decades, specific genetic markers have only been confidently identified fairly recently. Genome-wide association studies (GWAS) have revolutionized our understanding of the genetic foundations of psychiatric disorders, with many significant loci now identified for all major disorders. I will start by summarizing the findings and etiological insights imparted by GWAS so far for several disorders: attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa, anxiety disorders, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), schizophrenia, and Tourette's syndrome. Next, I will describe the secondary analyses enabled through use of the GWAS results, such as polygenic risk scoring and pathway analyses, which deepen our understanding of the impact of this genetic risk on other phenotypes/disorders and the biological mechanisms that give rise to them. Finally, I plan to outline the challenges and opportunities for future avenues of investigation and clinical translation by which genetic findings can contribute to a meaningful impact for the lives of patients.

4. Bjarnadottir, Gudrun Dora

Intravenous misuse of Methylphenidate in Iceland

Background: Methylphenidate (MPH) is a prescription psychostimulant used to treat attention-deficit hyperactivity disorder (ADHD). MPH prescriptions have increased significantly in the past two decades in Western countries. MPH has known abuse potential but MPH is considered to have less abuse liability than amphetamine (AMP) and cocaine. Intravenous (i.v.) use of MPH has sporadically been reported in the past but comprehensive systemic studies of i.v. MPH use have not been conducted. Clinical observations in Iceland have shown that MPH has been growing in popularity among people who inject drugs (PWID)

Method: The study was cross-sectional using a semi-structured interview. All substance users who were admitted during a 12 month period to any of the addiction treatment centers in Iceland and reported any i.v. use in the past 30 days were offered to participate. A total of 108 patients were recruited over one year from all inpatient addiction centers in Iceland.

Results: A vast majority of participants (88%) had used i.v. MPH during the past 30 days. MPH was both the most commonly used and preferred i.v. substance among participants. Of the different MPH formulations, a majority used and preferred i.v. MPH sustained released (SR) whereas only 3% preferred MPH osmotic released (OROS). Nonetheless, a third of the participants had used MPH OROS at least once in the past month. The subjective effects and pattern of use for MPH SR and cocaine were rated similar in terms of injection rate per day and length and intensity of the "euphoria" and "high".

Conclusions: I.v. misuse of MPH is very common among PWID in Iceland and it is currently the most commonly used and preferred i.v. substance in among PWID seeking detoxification treatment. One of the sustained MPH formulations (MPH SR) was preferred by PWID and subjective effects and consumption pattern was reported similar to cocaine. This indicates that i.v. MPH may have no less abuse potential than cocaine. These findings are of relevance for countries

where MPH prescriptions have been increasing in recent years because of growing demand for pharmaceutical treatment of ADHD. Vigilance and surveillance of possible misuse are recommended, especially when treating patients with history of substance use.

5. Casarotto. Plinio Cabrera

S2.2 Rethinking the mechanism of antidepressants

Antidepressant drugs can open a 'window-of-opportunity' of brain plasticity associated with increased levels of brain-derived neurotrophic factor (BDNF) and the activation of its receptor (tropomyosin-related kinase B - TRKB). However, the molecular mechanisms of this process are not fully comprehended and were assumed to be indirect. Recently, we discovered that TRKB carries a transmembrane cholesterol recognition and alignment consensus motif (CRAC) that, upon dimerization, can form a transitory binding pocket for antidepressant drugs. Our findings indicate that antidepressant drugs stabilize a signaling-competent conformation of TRKB dimers, providing a molecular mechanism for the TRKB-mediated window-of-opportunity. Using point mutations of TRKB CRAC motif, we observed a loss of response to drug-induced brain plasticity without affecting BDNF binding or TRKB basal function. Moreover, the membrane environment plays a central role in the whole process. Taken together, our findings provide a new framework, incorporating the membrane composition and receptor dimerization, as crucial factors to understand drug-induced plasticity, as well as in the pipeline for development of new compounds.

6. Cunningham, Janet

Diagnosis and treatment of maladaptive immunological disorders

Abstract: Since 2015, the Immunopsychiatry team at Uppsala University has strived toward a collaborative multidisciplinary approach to improve and integrate care for patients with moderate to severe psychiatric disorders. Neuroimmunological markers in CSF suggest an underlying biological groups that do not harmonize with the current clinical grouping. Multivariate patient classification and pattern detection as well as a single-subject research design has identifed sets of biomarkers that delineate clear endpoints with potential relevance for diagnosis and clinical prognosis in future studies. Our early results indicate that a spectra of immunological mechanisms, both alone and in combination, are associated with a broad range of psychiatric disorders. The underlying pathology incorporates autoimmune, autoinflammatory disorders but also genetic, metabolic, and other immunological disorders. Treatment of these cases must embrace integrated models of disease, as both maladaptive immunological responses and psychological processes influence mental health. Several challenges need to be overcome to efficiently merge psychiatric and somatic disease paradigms and medical care ranging from language and conceptual barriers to organizational barriers. Ahead lies a complex task to further develop and hone in these emerging concepts that encompass several medical disciplines while challenging previously well-established algorithms and healthcare structures

7.DeMartinis, Nicolas

Ulotarint: A Novel TAAR1 Agonist in Development for the Treatment of Schizophrenia

Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) and 5-HT_{1A} receptor agonist in Phase 3 clinical development for the treatment of schizophrenia. Ulotaront was discovered through a target-agnostic approach optimized to identify drug candidates lacking D2 and 5-HT_{2A} receptor antagonism, while demonstrating an antipsychotic-like phenotypic profile *in vivo.*
Objectives: To provide a summary of preclinical evidence, pharmacology, and emerging clinical efficacy and safety profile of ulotaront.
Method: Results of preclinical and clinical studies reported in more than two dozen peer-reviewed articles and posters will be summarized.
Results: The antipsychotic potential of ulotaront was confirmed in pre-clinical psychosis models, including reduction of phencyclidine (PCP)-induced hyperactivity; reversal of sub-chronic PCP-induced social interaction deficits; increase in prepulse inhibition (PPI); and reduction in MK-801-induced deficits in PPI and hyperactivity. Ulotaront has completed two Phase 2 trials (4-week study; 26-week extension study). Ulotaront has been granted Breakthrough Therapy Designation for the FDA for the treatment of schizophrenia. In the double-blind, placebo-controlled study, ulotaront was associated with significant (p<0.001) improvement in Positive and Negative Syndrome Scale (PANSS) total score (effect size [ES]: 0.45), Clinical Improvement Severity score (ES: 0.52), and the Brief Negative Symptom Scale total score (ES: 0.48). Initial studies suggest that ulotaront is ell-tolerated and lacking in clinically significant D2 antipsychotic class-related adverse events (e.g., extrapyramidal symptoms, hyperprolactinemia, sedation, and adverse weight and metabolic effects). The open-label extension demonstrated further improvement across schizophrenia symptoms and confirmed the tolerability of ulotaront,

with a 6-month completion rate of 67%. At Week 26, 93.3% of patients met stringent responder criteria (≥30% reduction in PANSS total score), and fully 72.1% achieved ≥50% reduction.

Conclusion: Based on current data, ulotaront shows potential to be a first-in-class TAAR1 agonist for the treatment of schizophrenia, with a mechanism of action distinct from the current D2-blocking class of antipsychotics.

8. Engberg, Göran

Missing abstract

9.Eriksson, Elias

Management of treatment-resistant depression:old ideas(& new)

Abstract: This presentation will provide a brief survey of possible per oral pharmacological strategies in cases of therapy-resistant depression (here defined as patients failing to respond adequately to the usual first line of treatment, i.e., an SSRI). The issues to be addressed are: i) when are dose escalations justified?, ii) are some per oral antidepressants more effective than others (prompting a swich preferentially to certain drugs after an initial treatment failure)?, and iii) what is the current evidence with respect to adding another antidepressant (e.g., mirtazapine) or an atypical antipsychotic to the ongoing SSRI administration (and what mechanisms could underlie the possible benefit of such strategies)? Finally, the rational underlying an ongoing 4-centre trial in Sweden exploring the possible benefit of adding the dopamine stabiliser OSU6162 to an SSRI in patients not responding the latter drug *per se* will be revealed.

9. Hurd, Yasmin

Relation to Psychiatric Risk

Abstract: Cannabis and its cannabinoid products have increased in use across the globe in recent years due to sociopolitical shifts that have led to their decriminalization and legalization, particularly in western countries. Many questions have continued to mount regarding the potential impact of cannabis on mental health. One of the most critical issues relate to developmental exposure to cannabis given the sensitivity of the developing brain—fetal, childhood and adolescence—to certain environmental conditions that can place individuals at risk for addiction and other psychiatric disorders later in life. This talk will provide insights from translational studies—basic molecular and behavioral animal studies as well as human longitudinal investigations—regarding the neurobiological consequences of developmental cannabis exposure and the long-term impact on brain and behavior relevant to psychiatric risk. It is clear that numerous factors, including THC potency and sex, can impact negative outcomes. It is also evident that the complexity of the cannabis plant may conversely hold opportunities to alleviate psychiatric disorders. For instance, while THC has been linked to many of the negative outcomes associated with the drug, recent attention has also focused on other cannabinoids such as cannabidiol (CBD) with potential pharmacological beneficial properties. The presentation will discuss translational studies regarding the medicinal potential of CBD for treating substance use disorders and related psychiatric illnesses. It is hoped that insights gained from a growing number of studies can be leveraged to provide science-based evidence to guide future clinical and treatment approaches to better address the question of cannabis and mental health.

11. Jayaram- Lindström, Nitya

Missing Abstract

12. Jerlhag, Elisabet

Gut-brain axis and addictive disorders

Abstract: Alcohol use disorder (AUD) is a neuropsychiatric disorder with high mortality and morbidity rates. As the treatment outcome of existing pharmacotherapies is insufficient, novel treatment options are needed. Intriguingly, gut-brain peptides like amylin and glucagon-like peptide-1 (GLP-1) have been suggested as such candidates as activation of their receptors (AMYR or GLP-1R) independently reduces alcohol intake in rodents. This is further evident as polymorphisms of the GLP-1R is associated with AUD and an agonist reduces alcohol consumption in overweight AUD patients. Our most recent preclinical studies reveal that semaglutide, a clinically available GLP-1R agonist used for diabetes and obesity, reduces alcohol drinking, prevents relapse drinking and suppresses alcohol reward via acccumbal mechanisms. The mechanistic complexity of AUD raises the possibility of a beneficial reduction after the combination of the GLP-1R and AMYR agonist on alcohol drinking. Supportively, a combination of AMYR and

GLP-1R agonists decreases the body weight gain in obese rats. Recently, we demonstrated that acute or repeated combination treatment decreases alcohol intake and relapse drinking in male and female rats. Intriguingly, the treatment outcome depends on the treatment regime. Besides, the tested combination treatment paradigms profoundly decrease the body weight in male and female rats. In summary, the outcome of these preclinical studies raises the urge to test the efficacy of these gut-brain peptides in AUD patients with obesity.

13. Lannfelt, Lars

L1 Immunotherapy for Alzheimer´s disease

Abstract: Immunotherapy against amyloid-beta has emerged as a promising treatment for Alzheimer's disease (AD). Lecanemab is a humanized IgG1 monoclonal antibody, selectively targeting amyloid-beta protofibrils. In a Phase 3 clinical trial in early AD subjects, lecanemab demonstrated potential disease-modifying effects on both clinical endpoints and clearance of amyloid-beta plaques in the brain. We have characterized the main target for lecanemab, i.e. amyloid-beta protofibrils in AD brain, describing the levels, content and size of size of amyloid-beta protofibrils, in relation to the APOE genotype. The binding of lecanemab to amyloid-beta protofibrils and the mechanism of action in clearance of amyloid-beta has been studied. Amyloid-beta protofibril levels, extracted from post-mortem human brain tissue, were measured using the mAb158 antibody, the murine version of lecanemab. Size exclusion chromatography was used to characterize amyloid-beta protofibrils and to evaluate lecanemab's binding profile. Amyloid-beta protofibrils were shown to be predominantly composed of amyloid-beta 42, and were heterogenous in size, and lecanemab was shown to bind similarly to amyloid-beta protofibrils of all sizes. Lecanemab has a unique binding profile with a high selectivity for amyloid-beta protofibrils and effectively clears amyloid-beta protofibrils and amyloid plaques. Other antibodies targeting amyloid-beta will be discussed.

14 . Leknes, Siri

Neuromodulation of subjective experience

Abstract: Many psychoactive substances are used with the aim of altering experience, e.g. as analgesics, antidepressants or antipsychotics. These drugs act on specific receptor systems in the brain, including the opioid, serotonergic and dopaminergic systems.
In this talk, I will summarise human drug studies targeting opioid receptors and their role for human experience, with focus on the experience of pain, stress, mood, and social connection. Opioids are only indicated for analgesia, due to their potential to cause addiction. When these regulations occurred, other known effects were relegated to side effects. This may be the cause of the prevalent myth that opioids are the most potent painkillers, despite evidence from head-to-head trials, Cochrane reviews and network meta-analyses that opioids are not superior to non-opioid analgesics in the treatment of acute or chronic non-cancer pain. Understanding the effects of these commonly used medications on other aspects of the human experience is important to ensure correct use and to prevent unnecessary pain and addiction risk.

15. Rudnick Levin, Frances

Treatment of ADHD and Substance Use Disorders

Abstract: ADHD is a widely prevalent disorder in children, adolescents, and adults. Over the past three decades, it has become increasingly clear that most individuals diagnosed with childhood ADHD continue to have impairing symptoms into adulthood. The presence of a comorbid substance use disorder (SUD) makes it more difficult to treat the ADHD symptoms. Similarly, untreated ADHD may make it less likely that standard treatments for SUD will be as effective. Several ADHD instruments may have utility for screening individuals with an SUD with ADHD, though a comprehensive diagnosis is required to accurately diagnose adolescents and adults with an SUD with ADHD. Recent trials have suggested that treatment of ADHD by stimulants may lead to reduction in both ADHD symptoms and drug use across the lifespan. Fewer data exist to support the use of non-stimulants or nonpharmacologic treatment alone for adults with ADHD and a SUD. The use of robust doses of long-acting stimulants has shown the best efficacy to date in adults with ADHD and stimulant use disorders. Strategies to mitigate the risk of nonmedical use of prescription stimulants in substance using populations with ADHD will be discussed. Given the substantial subpopulation of persons with SUD and adult ADHD, further research is warranted.

16. Nordentoft, Merete

Suicide prevention- how to turn the tide

Abstract: Suicide is still a huge public health problem with 800,000 deaths per year. Some countries have experienced declining trends, especially in Asia,

partly due to restrictions in access to highly lethal pesticides. USA are facing increasing trends and in many western European countries there has been declining tendencies, but most recently rates have been rather stable.
Suicide preventive strategies have focused on universal prevention, thus intervention targeting the who population, selective prevention aiming to reduce risk in different high risk groups, and indicated prevention targeting people who are already having suicidal behavior. However, the distinction between universal, selective and indicated prevention needs to be specified into situation-specific prevention, since suicidal behaviour and intention fluctuate. Even for a person with a very high risk of suicide, survival is by far the most likely outcome each day. In most cases, suicidal acts are carried out within a short period of time, and in many cases without a long period of warning signals. In a way, suicidal acts resemble heart attacks or epileptic episodes more than other complications that often develop slowly and gradually. This makes the task of creating awareness programmes even more difficult.
However, a thorough mapping of risk groups and risk situations will enable us to plan a more targeted intervention. Thus, epidemiology and clinical research can play together. The suicide rates in different risk groups will be presented and linked to considerations about which interventions are needed.
The most important task is to identify those of immediate risk of suicide and provide treatment and support. There are four distinct risk groups with a very high suicide rate. These are 1) people sent home from psychiatric emergency room visits, 2) people recently discharged from psychiatric hospitalization 3) people who were hospitalized due to attempted suicide 4) people who have called life-line or other NGO-driven helplines because of suicidal thoughts. All these four groups have a very high risk of suicide and the help they are offered are in most countries fragmented and not well organized
It can be helpful to evaluate the population attributable risk associated with different risk factors. The population attributable risk is an estimate of the proportion of the problem that could be avoided if the increased risk in a specific risk group could be reduced to the level of the general population. This approach will be demonstrated.
Interventions involve persons who will never commit a suicidal act, and they also involve monitoring persons in high-risk groups for long periods with no suicidal acts.

17. Schalling, Martin

Lithium- Pharmacokinetics, genetics and nanofluidics

Background: Lithium is the most effective treatment available for bipolar disorder. Its therapeutic range, however, is very narrow and treatment initiation requires individual titration to address inter-individual variability to achieve correct serum levels. We aim at improving lithium dose prediction and methods for measuring lithium using clinical and genomic data applying microfluidic technology. There is need for patient-centric methods for lithium monitoring. We therefore tested the feasibility of dried blood spots for determination of lithium concentration by introducing a volumetric technique developed for home-sampling.

Methods: Two Swedish cohorts, with a total of 2357 lithium treated patients and 5627 data points were used to model lithium clearance (LiCL) with respect to several clinical variables. The residual effects after accounting for age and sex, representing the individual-level effects in LiCL, were used as dependent variables in a genome-wide association study (GWAS). Capillary blood was sampled by finger-prick using a volumetric device that collects 10 µL volumes as a dried blood spot. Lithium was measured in the dried blood spots using a validated atomic absorption spectroscopy method.

Outcomes: Age, sex, glomerular filtration rate, serum lithium concentration, co-medication with diuretics and agents acting on the renin-aldosterone-angiotensin system were clinical predictors of LiCL. Interestingly, an association between LiCL and SL was observed. In a GWAS of LiCL, one locus was associated with LiCL (rs583503; b=-0·053 (95%-Confidence Interval:-0·071;-0·034), p=3·8.10-8). We also found enrichment of the associations with genes expressed in the medulla and the cortex of the kidney, as well as associations with polygenic risk scores for eGFR, body mass index, and blood urea nitrogen. The model based on clinical variables explained 61·4% and 49·8% of the variance in LiCL in the two cohorts. Adding genetic markers marginally increased the predictive ability of the model. Using the dried blod spot technology we observed a range of serum lithium concentrations of 0.41-1.22 mmol/L, and the dried blood spot/serum ratio was 0.78. A strong linear correlation between the two specimens was shown with Pearson's R = 0.95 (r2 = 0.90). Adding hematocrit as a variable only minimally improved prediction.

Interpretation: Our model predictors could be used clinically to better guide lithium dosage, shortening time to reach therapeutic levels, thus improving care. The first genomic locus and PRS to be associated with LiCL introduce the opportunity of individualized medicine in lithium treatment. Volumetric dried blood spots is a promising technique for measurement of lithium concentrations. This will enable home-sampling and could potentially save resources, improve compliance, and make treatment safer. This may facilitate the use of lithium treatment in regions where monitoring via venous blood sampling remains difficult.

18. Schearcz, Robert

Targeting Brain Kynurenic Acid for Cognitive Improvement

Abstract: The kynurenine pathway, the major route of degradation of the essential amino acid tryptophan, contains several neuroactive metabolites, including kynurenic acid (KYNA). Because of its ability to inhibit the function of both NMDA and α7 nicotinic receptors at endogenous concentrations, and its related ability to bi-directionally regulate the fate and function of glutamate, dopamine, acetylcholine and GABA, KYNA is increasingly viewed as a unique neuromodulator. Thus, fluctuations in brain KYNA levels are involved in physiological processes including synapse formation, neuronal plasticity and a number of cognitive functions. Notably, abnormal KYNA elevations in the prenatal brain, as well as acute increases in brain KYNA levels later in life result in cognitive dysfunctions in adulthood. Moreover, unrelated to antipsychotic medication, the levels of KYNA are elevated in brain and cerebrospinal fluid of persons with schizophrenia, and genetically modified mice with increased brain KYNA levels exhibit several of the cognitive deficits seen in schizophrenia and other psychiatric diseases. Pharmacological agents capable of selectively reducing KYNA production are therefore expected to yield pro-cognitive effects under both physiological and pathological conditions. The neosynthesis of KYNA in the mammalian brain is controlled primarily by the astrocytic enzyme kynurenine aminotransferase II (KAT II), and attenuation of KAT II activity by selective genetic and pharmacological interventions indeed shows remarkable beneficial effects in a variety of well-established, translationally informative animal models of cognitive dysfunction. This bodes well for upcoming first clinical trials in humans, which are designed to test the pro-cognitive efficacy of brain-penetrant KAT II inhibitors in persons with schizophrenia.

19.Sellgren, Carl

The role of synaptic pruning in schizophrenia

Abstract: Recent multi-disciplinary data have indicated complement-dependent synaptic pruning as a pathophysiological mechanism in schizophrenia. The rapid development of novel patient-derived cellular models has made it possible to model interactions between microglia and neuronal networks in a disease context and these tools have been instrumental for linking genetic risk variance to excessive synapse pruning in schizophrenia. In the current talk, state-of-the-arts model systems for assessing the role of human microglia in a schizophrenia context will be presented. New data will be featured that cover genetic as well as environmental (early-life infection) risk factors for schizophrenia.

20. Smeland, Olav B

Bridging the great divide: a systematic comparison of GWAS across neurological and psychiatric disorders

Background:Accumulating evidence from neuroscience, epidemiology and clinical observations indicate that neurological and psychiatric disorders are not categorically distinct disease entities. However, the extent to which these groups of disorders share genetic influences remain unclear.

Objectives: Here, we aimed to provide a comprehensive comparison of the genetic risk architecture across major neurological and psychiatric and re-investigate whether the existing clinical division is apparent at the genetic level.

Methods. To this end, we systematically analyzed large-scale GWAS data using complimentary statistical tools to evaluate genetic overlap and provide biological insights. We included GWAS on 20 major neurological and psychiatric disorders, comprising close to 1 million cases. Additionally, we included GWAS data on eight somatic and brain-related comparators. The total sample size included more than 13 million individuals, including some sample overlap. We assessed shared genetic influences at both the local and genome-wide level and functionally characterized the results using a variety of biological resources.

Results. We demonstrate widespread genetic sharing with unique patterns of overlap across distinct disorders, as well as disorder-specific effects. Using a variety of tools, we find that there is no sharp distinction in the genetic risk underlying neurological and psychiatric disorders, despite evident differences in their genetic architectures. Further, GWAS on both psychiatric and neurologic disorders implicated human brain tissue, cell-types and neurobiological pathways indicating that psychiatric disorders, like neurological disorders, also have a neural basis.

Conclusion. Altogether, the study demonstrates that neurological and psychiatric disorders are not fundamentally disparate in their nature, but partly share a genetic and neural basis, which have important implications for disease classification, clinical practice and research.¨

21. Taipale, Heidi

Real- World effevtiveness of pharmacotherapies in psychotic depression

Background: Psychotic depression is a severe mental disorder associated with a high risk of suicide. Although the main burden of the illness is caused by the long-term relapsing nature of the disorder, there is limited knowledge about the comparative effectiveness of pharmacological maintenance treatment.

Objectives: The aim of this study was to investigate comparative effectiveness of specific antipsychotics and antidepressants on risk of relapse among persons diagnosed with psychotic depression.

Methods: Individuals with psychotic depression (PD) were identified from Finnish nationwide registers of inpatient care, specialized outpatient care, sickness absence and disability pension during 2000-2018 as those with a first-time diagnosis of PD at age of 16-65 years. Specific antipsychotics and antidepressants were the main exposures, and relapse defined as psychiatric hospitalization was the main outcome measure. Replication was conducted in a similarly defined Swedish cohort covering years 2006-2021. The Finnish cohort included 19,330 individuals (mean age 39.8, SD 14.7, 57.9% women). The Swedish cohort included 13,684 individuals (mean age 41.3, SD 14.0, 53.5% women). We used a within-individual design, where each person acted as his or her own control, and was analyzed with stratified Cox models. The cohorts were analyzed separately, and the results were pooled using fixed effects meta-analysis.

Results: Any antidepressant use was not associated with the risk of outcome, meta-analysis HR 1.01 (95%CI 0.97-1.05 vs. antidepressant non-use), nor did any antipsychotic use (0.99, 0.96-1.03, vs. antipsychotic non-use). However, specific drugs were associated with decreased risk of relapse, namely antidepressants bupropion 0.74 (0.63-0.85) and venlafaxine 0.92 (0.86-0.98), and any long-acting injectable antipsychotics (LAI) 0.60 (0.45-0.80).

Conclusion: In long-term treatment of PD, bupropion and LAIs were associated with the lowest risk of relapse. In real-world circumstances, beneficial results on LAIs may imply that adherence to medications should be carefully monitored and enhanced among patients with PD.

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ABOUT SCNP

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

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

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

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