Acta Neuropsychiatrica, Volume 28, Supplement 2:1-40

ABSTRACTS

SCANDINAVIAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

SCNP

57th Annual Meeting, April 27th – 29th, 2016
Aarhus, Denmark

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https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Acta Neuropsychiatrica, Volume 28, Supplement 2:1-40

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https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

ORAL PRESENTATIONS

LECTURE 1

SCNP 2016 OPENING LECTURE

L1 On the efficacy of the SSRIs

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In recent years, debaters arguing that selective serotonin reuptake inhibitors (SSRIs) exert no specific pharmacological antidepressant effect have gained marked attention in both scientific journals and lay media. In support for the questioning of these drugs, five different arguments have been put forward. First, it has been pointed out that 50% of the trials conducted by the drug companies in order to confirm the efficacy of the different SSRIs have failed to demonstrate a significant difference between active drug and placebo. Second, it has been claimed that the antidepressant effect is not characterized by a dose response relationship (which would have been expected if it were a true pharmacological effect). Third, it has been argued that the effect size for the antidepressant effect obtained when lumping both positive and negative trials together in meta-analyses is too low to be clinically meaningful. Fourth, it has been claimed that a possible beneficial effect, if there is one, is observed only in small subgroup of patients with very severe depression. Fifth, it has been suggested that a possible beneficial effect, if there is one, is not the result of a specific, pharmacological antidepressant effect, but caused by side-effects making the patient realize that he/she is not given placebo, hence augmenting a psychological placebo effect. By means of post hoc analyses of patient level data from all relevant drug-company-sponsored trials in which citalopram, paroxetine or sertraline have been compared to placebo, we have addressed all these claims, and also explored the possibility that SSRIs may elicit suicidal ideation in patients without this symptom at baseline. The results suggest that SSRIs do exert a dose-dependent antidepressant effect that is not restricted to those with severe depression, that is characterized by a respectable effect size and that cannot be explained by side effects breaking the blind. Moreover, the results suggest this effect to be more rapid in onset than previously assumed, a significant superiority of active drug over placebo in reducing both depressed mood and suicidal ideation being observed as early as after one week of treatment. It is concluded that the questioning of the SSRIs exerting a specific, pharmacological effect in depression is ill-founded.

SYMPOSIUM 1

UPDATE ON NEW DRUGS

S1.1 Brexpiprazole: a new treatment option in schizophrenia

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Background: Background: Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors, all at similar potencies. Brexpiprazole is approved in the US for the treatment of schizophrenia and for use as adjunctive therapy to antidepressants for the treatment of MDD.

Objectives: Objectives: To review efficacy, safety, and tolerability of brexpiprazole in patients with schizophrenia in short- and long-term phase 3 studies.

Methods: Methods: Patients experiencing a current exacerbation of schizophrenia received brexpiprazole in two fixed-dose (2 and 4 mg), 6-week, placebo-controlled studies1,2 (NCT01396421; NCT01393613; a low dose treatment group was included in each study [0.25 mg and 1.0 mg]; not presented here), one flexible-dose (2–4 mg), 6-week, placebo-control and active reference study3 (NCT01810380), and one 52-week, placebo-controlled maintenance study4 (NCT01668797).

Results: Results: The efficacy of brexpiprazole was demonstrated in the two short-term fixed-dose studies with consistent clinically meaningful 20 point improvements from baseline in Positive and Negative Syndrome Scale (PANSS) total score and greater improvements from baseline in PANSS total score compared with placebo (Study 1: $p<0.0001$ [2 mg] and $p=0.0006$ [4 mg]; Study 2: $p=0.1448$ [2 mg] and $p=0.0022$ [4 mg]). In the flexible-dose short-term study, treatment with brexpiprazole resulted in improvements in PANSS total score that approached significance versus placebo ($p=0.056$). A meta-analysis of these short-term studies showed a mean change in PANSS total score of -

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20.1 from baseline to week 6 for brexpiprazole, a 21.0% decrease, representative of a clinically meaningful improvement ($p<0.001$ versus placebo). In the maintenance study, brexpiprazole had a significant beneficial effect relative to placebo on time to exacerbation of psychotic symptoms/impending relapse ($p<0.0001$). For all studies, brexpiprazole demonstrated clinically meaningful treatment effects on social functioning. Brexpiprazole was well tolerated with a favorable safety profile, including a low incidence of activating and sedating side effects. Moderate weight gain was observed in the short-term studies. No additional safety concerns were observed with brexpiprazole in laboratory values, ECGs, or vital signs.

Conclusion: Conclusion: Overall the results indicate that brexpiprazole, used either short-term or as part of a long-term maintenance treatment program, is an efficacious therapy option in adults with schizophrenia and has a favorable safety/tolerability profile.

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4. Hobart M, Ouyang J, Forbes A, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. Presented at the American Society of Clinical Psychopharma

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

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The role of the NMDA receptors in a number of psychiatric and neurological disorders is well established, along with the important role played by the receptor in regulation of critical functions, such asLong term potentiation and synaptic plasticity.

Developing pharmaceutical agents that target the NMDA receptor have long been focused on blocking the NMDA receptor with compounds such as memantine and ketamine, or modulating a receptor co-agonist site, such as seen with d-cycloserine.

Aptinyx Inc. is a biopharmaceutical company discovering and developing innovative therapies for challenging disorders of the brain and nervous system. Aptinyx has a platform for discovering proprietary compounds that work through modulation of the NMDA receptor. This mechanism has applicability across a number of CNS disorders, and perspectives on this will be discussed at the presentation.

S1.3 Lurasidone – a new drug for the treatment of psychosis

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Lurasidone is an atypical antipsychotic that has been available to clinicians for prescription since 2011 in the USA, 2013 in Switzerland, and since then progressively in a growing number of European countries. As such it is in much of Europe the most recent antipsychotic to join the therapist's arsenal.

The tools allowing the practicing clinician to evaluate this new drug include clinical trials, results from meta-analyses and also predictions from pharmacological properties and preclinical studies. These can be then compared to direct clinical experience, with now over two years of use in Europe.

Overall the data and clinical use points to an effective antipsychotic, generally well tolerated, in particular concerning metabolic side effects, although comparatively prone to causing extrapyramidal side effects, and that seems to benefit from some unique clinical properties.

Recent clinical experience allows the proposal of some recommendations in clinical use that may improve patient selection and results.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

SYMPOSIUM 2

SCNP YOUNG SCIENTIST SYMPOSIUM

The speakers in the SCNP Young Scientist Symposium are selected among the best abstracts submitted by young scietists.
The selection of the speakers was not finished at time of printing.
However, all abstracts can be found in the poster section, on page 15, as they are also presented as posters.

LECTURE 2

SCNP LECTURE

L2 Magic mushrooms for depression

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To understand better the role of 5HT in human brain function in health and disease the Imperial College group has recently conducted a series of MRI and MEG studies comparing the psychedelic 5HT2A receptor agonist psilocybin (the active ingredient of magic mushrooms). The MRI studies of psilocybin (both ASL and fMRI) revealed unexpected reduction in brain blood flow and BOLD responses (Carhart-Harris et al 2013 PNAS) largely expressed in the default mode network (DMN) and thalamus. The cortical psilocybin MRI findings were confirmed by the MEG study that revealed a major loss of power in the alpha band after psilocybin, particularly in the posterior cingulate cortex, which correlated with ego-dissolution measures (Muthukumaraswamy et al 2013 J Neurosci). As a result of the BOLD reductions produced by psilocybin in the sub-genual cingulate cortex and other evidence for the role of overactivity of the default mode network in depression we are conducting the first study of psilocybin in resistant depression – defiend as failure to respond to at least two prior adequate courses of antidepressant treatments. So far 12 subjects have been treated with psilocybin po 25mg in a secure and psychotherapeutic out-patient environment. The study is nearing completion and the outcome data should be ready to present at the SNP meeting.

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LECTURE 3

SCNP LECTURE

L3 The translational potential of brain imaging in psychiatry: helping clinicians to predict clinical outcomes

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Background: A fundamental problem in the management of psychiatric disorders is that it is often difficult to predict outcomes on the basis of the patient's clinical features. However, data from recent neuroimaging research suggest that patients who have distinct clinical outcomes can be distinguished by differences in brain structure, function, and chemistry. This raises the possibility that neuroimaging could be used in a clinical setting to stratify patient samples according to future outcomes.

Objectives: To review the current literature on the use of neuroimaging measures in the prediction of clinical outcomes in psychiatry, and to highlight the main obstacles to translating these findings into clinical practice.

Methods: Two areas that are promising candidates for the development of predictive tools involve the prediction of illness onset in people at high risk for psychosis, and the prediction of therapeutic response in patients with psychosis.

Results: The findings from these areas of research will be reviewed, and the main challenges associated with translating them into clinical practice will be discussed.

Conclusion: Neuroimaging measures have the potential to facilitate the prediction of clinical outcomes in psychiatry. Key challenges to translating these findings into clinical practice are the need to make predictions on

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

the basis of data from an individual patient, and to have tools that are practicable and cost effective in a real world clinical setting.

References

McGuire et al (2015) Lancet Psychiatry 2: 1117-1122

LECTURE 4

SCNP LECTURE

L4 Rewiring Faulty Circuits – The Role of Deep Brain Stimulation

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The introduction of Deep Brain Stimulation for treatment resistant disorders might very well lead to the most significant development in clinical psychiatry of the last forty years – possibly offering a rise of hope for patients to whom medicine had hitherto little to offer. Furthermore, translational research on neuromodulation will allow us to glean something about the underlying cause of patient's illnesses before figuring out a treatment that addresses the source of the problem. Major depression offers perhaps the best example of the rapid progress being made in understanding the biology of mental illness. Studies on the underlying neurobiology of major depression have typically focused on the description of biological differences between patients and healthy subjects such as alterations of monoaminergic or endocrine systems. Psychotropic drugs work by altering neurochemistry to a large extent in widespread regions of the brain, many of which may be unrelated to depression. We believe that more focused, targeted treatment approaches that modulate specific networks in the brain will prove a more effective approach to help treatment-resistant patients. In other words, whereas existing depression treatments approach this disease as a general brain dysfunction, a more complete and appropriate treatment will arise from thinking of depression as a dysfunction of specific brain networks that mediate mood and reward signals. A better understanding of defined dysfunctions in these networks will invariably lead to a better understanding of patients afflicted with depression and perhaps contribute to a de-stigmatization of psychiatric patients and the medical specialty treating them.

SYMPOSIUM 3

CARDIOVASCULAR COMORBIDITY IN MENTAL ILLNESS AND TREATMENT, RELATIONSHIP TO PSYCHOPHARMACOLOGY

S3.1 Impairments in the kynurenine pathway as a shared vulnerability factor for schizophrenia and atherosclerosis

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Background: Life expectancy in schizophrenia is approx. 30% shorter than that of the general population1 and physical health problems, in particular cardiovascular disease, mainly account for the rise in standard mortality rates in schizophrenia2. These patients appears to be inherently vulnerable to metabolic dysregulation and cardiovascular disease, although, poor diet, high smoking rates, lack of physical exercise, psychological stress and high rates of depression among patients may contribute. Also the use of antipsychotics, by inducing weight gain, adds on to the emergence of cardiovascular disease. Clearly, a major shortcoming of studies investigating the comorbidity of cardiovascular disease in schizophrenia so far is the fact that all investigations have studied patients on antipsychotic treatment and hence underlying pathophysiological pathways remain unknown.

Objectives: To investigate frequency of early signs of atherosclerosis in first-episode psychosis patients and to study if dysfunctions in the kynurenine pathway are associated with both psychiatric symptoms as well as with signs of atherosclerosis.

Methods: In the present study (the Karolinska Schizophrenia Project; KaSP), we enroll first-episode, drug-naïve patients with psychosis as well as healthy controls. Follow-up investigations are performed after 1.5 years and then every 5th year. We collect cerebrospinal fluid, plasma and blood for whole genome sequencing. Additionally, all patients and controls are tested for early signs of atherosclerosis by means of the cardio-ankle vascular index (CAVI).

Results: Patients with schizophrenia and bipolar disorder patients with a history of psychosis display increased central levels of kynurenic acid (KYNA), an endogenous

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

blocker of the NMDA receptor. Recent data suggest that another metabolite in the kynurenine pathway, i.e. 3-hydroxyanthranilic acid (3-HAA) inhibits atherosclerosis by regulating lipid metabolism and inflammation.

Conclusion: Reduced activity in the kynurenine pathway enzyme kynurenine monooxygenase (KMO) is reported in schizophrenia and bipolar patients with psychosis, hereby leading to increased central levels of KYNA. Simultaneously, a polymorphism of the KMO would lead to decreased downstream activity of the kynurenine pathway including reduced levels of 3-HAA, making those patients more vulnerable for atherosclerosis. Presently, experiments are ongoing in our laboratory to evaluate plasma 3-HAA levels concomitant with an individual analysis of genetic variations. First data from CAVI will be presented.

References

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S3.2 Update on metabolic side effects of antipsychotics, and evidence-based management.

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Background: Metabolic side effects of antipsychotic drugs remain a major concern. Several pharmacological and non-pharmacological strategies to address the problem have been suggested in recent years.

Objectives: The aim of the presentation is to give an update on current evidence-based management of metabolic side effects of antipsychotics.

Methods: PubMED and recent guidelines for the treatment of psychosis and schizophrenia were searched for relevant reports.

Results: Strategies with the best evidence of effect include for pharmacological interventions switching to a different antipsychotic agent with a more benign metabolic profile, and the use of metformin. There is also accumulating evidence for the benefits of several other agents. Non-pharmacological evidence-based interventions include physical training and other lifestyle/ behavioral interventions.

Conclusion: Interventions for the management of antipsychotic-induced metabolic side effects exist, but well-designed studies with longer follow-up are needed.

S3.3 YKL-40 is a predictive marker for type 2 diabetes mellitus in patients with psychotic disorders

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Background: Background: Psychotic disorders are associated with decreased life expectancy with cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) as major causes for this excess mortality. Inflammation plays an important role in the initiation and progression of both CVD and D2M, and more recently, immune activation has been attributed a role in schizophrenia (SZ) and bipolar disorder.

Objectives: We evaluated if circulating YKL-40, a glycoprotein elevated in CVD and T2DM, with a role in inflammation and extracellular remodeling, were elevated in individuals with psychotic disorders, and could improve prediction of later development of T2DM.

Methods: Methods: We included a total number of 2182 cases, 1383 patients with a diagnosis of SZ or affective psychosis (Affective) and 799 healthy controls (HC). Plasma YKL-40 and metabolic risk factors were measured and medication was recorded. We retrieved data on incidence of T2DM for a 1-13 year follow up period from nationwide registries covering primary and specialist health care. Association between risk factors and later development of T2DM was assessed by survival analysis.

Results: Results: Plasma YKL-40 was elevated ($p=2.42x10-10$) in patients (mean 47.08, SD±35.50 ng/mL) vs. HC (mean 37.90, SD±23.94 ng/mL), also after adjusting for metabolic risk factors ($F=18.23$, $df=8$, $p=8.56x10-7$), with no difference between the diagnostic groups. Levels of YKL-40 were elevated also in the

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youngest age-group (<20 years) compared to their age-matched HC. Multivariate Cox regression analyses revealed that elevated YKL-40 (hazard ratio (HR) =5.62, p=0.001), elevated glucose (HR=3.56, p=0.001), and SZ-diagnosis (HR =2.97, p=0.014) at baseline predicted T2DM at a later stage (1-13 years follow up).

Conclusion: Conclusion: Patients with psychotic disorders have elevated levels of YKL-40, and elevated levels are associated with the development of T2DM at a later stage in life.

SYMPOSIUM 4

RECENT NEW UPDATES ON ADHD

S4.1 Scandinavian registerbased studies: What do they tell us about the course of ADHD, and the role of medication?

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ADHD affects approximately 3-7 % of the childhood and adolescent population. Numerous studies demonstrate the efficacy of pharmacological intervention for ADHD. However, most studies are describing the short term effect. Using registerbased studies offers the possibility to present long term course and consequences of ADHD and the possible effect of medication. Scandinavian registry studies show an increased risk of poor academic performance, criminality, drug abuse and adverse social outcome in diagnosed patients with ADHD. Some studies demonstrate that these negative outcomes can be moderated by medication.

S4.2 When ADHD and Substance Use Disorders Coexist - Etiology and Pharmacological Treatment

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Background: Individuals with attention-deficit hyperactivity disorder (ADHD) and comorbid substance use disorder (SUD) comprise a significant group of patients displaying various degrees of personal suffering, entailing a substantial economical burden on society and presenting with challenges in treatment. The overlap between the two disorders is well established, but the underlying genetic and environmental mechanisms of their coexistence, are poorly understood. Furthermore, little is known about the effectiveness and safety of stimulant medication when ADHD and SUD coexist.

Objectives: This thesis aimed to investigate the etiological relationship between ADHD and substance use problems (Studies I and II) and to explore doses of, and adherence to, pharmacological treatment for ADHD in the presence of SUD (Studies III and IV).

Methods: Quasi-experimental methods (Study I) were used to investigate whether smoking during pregnancy (SDP) is causally associated with ADHD in offspring. A family design (Study II) was applied to explore whether the overlap between ADHD and SUD arises from shared familial factors or is better explained by harmful effects of ADHD medication. Nationwide population-based cohort designs (Study III) were used to explore differences in and development of methylphenidate (MPH) doses in ADHD patients with and without SUD, and the impact of MPH doses on adherence to treatment in individuals with SUD (Study IV).

Results: The results show that the increased risk for ADHD in individuals exposed to SDP was attenuated when familial factors were accounted for, suggesting that genetically transmitted factors explain the association. Furthermore, genetic relatedness to an ADHD proband predicts SUD in ADHD-free relatives suggesting that the co-occurrence of ADHD and SUD may be due to common genetic factors shared between the two disorders. The studies focusing on stimulant treatment show that patients with comorbid SUD are prescribed higher MPH doses and have higher adherence to MPH treatment compared to patients with ADHD only. In both groups MPH doses stabilized within two years of treatment. Higher doses of MPH were associated with increased adherence to treatment. In conclusion, the collective findings from this thesis suggest that ADHD and SUD share common genetic underpinnings, that individuals with comorbid SUD receive higher stimulant doses than individuals with ADHD only, without signs of tolerance, and that stimulant doses predict adherence to

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

pharmacological treatment in individuals with comorbid SUD.

Conclusion: This thesis had two overall aims: a) to explore the etiological overlap between ADHD and SUD and b) to explore effectiveness and safety of stimulant medication when ADHD and SUD coexist. The results from the four studies included in this thesis expand current knowledge in several ways. Firstly, Studies I and II show that common genetic underpinnings largely explain the well-established overlap of ADHD and SUD. This will have several important implications for clinicians, researchers and policymakers. Familial history of ADHD needs to be taken into account when assessing risk for future SUD since it is not only the individuals themselves, but also their relatives who are at risk for SUD. Consequently, with further understanding of the etiological overlap between the two disorders, clinicians might be able to target individuals at high risk for SUD at an early stage. The findings of common genetic underpinnings for ADHD and SUD may help researchers to tailor molecular studies to increase the chances of identifying genetic risk variants shared across ADHD and SUD. This, in turn would generate a better understanding of the pathophysiological mechanisms that are common to ADHD and SUD. Even though there is mounting evidence that SDP is harmful in many ways, it is essential for policymakers to focus on true causal risk factors for ADHD. The results from the current thesis suggest that SDP is most probably not one of them. Secondly, Study III show that individuals with comorbid SUD were prescribed approximately 40% higher stimulant doses that those with ADHD only. Moreover, stimulant doses stabilized over time in both groups, with no signs of tolerance. Individuals with comorbid SUD rather surprisingly had higher adherence to pharmacological treatment than individuals with ADHD only. Furthermore, Study IV showed that higher MPH doses predict long-term treatment adherence in individuals with comorbid SUD. The studies, despite being of a naturalistic and descriptive nature, provide important information increasing knowledge of effectiveness and safety of stimulant treatment in individuals with ADHD who also have SUD. The lack of objective assessment procedures, biomarkers or clear treatment guidelines gives clinicians little guidance in managing ADHD in the presence of SUD. The concerns around the safety of stimulant treatment might make clinicians reluctant to increase doses to optimal levels for individuals with ADHD and SUD or result in the withholding of essential and effective pharmacological treatment in affected individuals. Finally, individuals with ADHD and SUD not only experience great personal suffering and functional impairment but are also exposed to a variety of misunderstandings, misinterpretations and misclassifications regarding their ADHD symptoms and SUD disorders. Hopefully the findings from this thesis can help to increase societal acceptance for ADHD and SUD as valid medical diagnoses, reduce the personal and psychosocial stigmatization associated with both disorders, and ensure that these individuals receive effective treatment.

S4.3 Long-term outcome in pharmacological treated versus non-treated adults with ADHD and substance use disorder: a naturalistic study

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Background: Patients in compulsory care with ADHD and severe SUD have complex and multiple treatment needs due to poor general cognitive ability, severe psychosocial problems, including antisocial behaviour, and other co-existing psychiatric conditions. Pharmacological treatment of this patient group is controversial and there are few studies on the long-term psychosocial outcome.

Objectives: To investigate whether pharmacological treatment was associated with improved long-term psychosocial outcomes.

Methods: The present naturalistic study was a long-term follow-up of 60 men with ADHD, all of which had been under compulsory care due to severe SUD. The average time interval for follow-up after discharge was 18.4 months. Patients who had received pharmacological treatment for ADHD (n=30) were compared to untreated patients (n=30) regarding mortality and psychosocial outcome, operationalized as substance abuse status, ongoing voluntary rehabilitation, current housing and employment status.

Results: Mortality was high in the total study group [5 out of 60 (8.3%) had deceased at follow-up, no significant between-group differences]. The group that had received pharmacological treatment for ADHD showed fewer relapses into substance abuse (p=0.02), more frequent voluntary treatments according to a

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rehabilitation plan and less frequent compulsory care (p=0.01), more frequent accommodation a according to the rehabilitation plan (p=0.028) and they were more often employed than individuals in the non-treated group.

Conclusion: Pharmacological treatment of ADHD may decrease the risk of relapses and increase ability to follow the non-pharmacological rehabilitation plan, thereby improving the long-term outcome. In high-risk populations, close monitoring is important not only for treatment compliance, but also for prevention of misuse or diversion of medicines.

LECTURE 5

SCNP LECTURE

L5 Some novel research tools in psychiatric neuroscience

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Understanding how neuronal signaling translates into behavior is a major challenge in neuroscience. Deciphering brain circuitry has historically relied upon experimental tools such as intracranial electrical stimulation/recording combined with post mortem neurochemical analyses. Newer non-invasive techniques such as functional resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic stimulation (TMS) has extended the methodological portfolio.

In recent years, advanced and extremely powerful methods such as optogenetic stimulation, the use of DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), and massively parallel optical recording of neuronal networks in vivo have revolutionized our understanding of brain circuitry. Researchers are now dissecting neuronal pathways involved in both neurological and psychiatric disorders at a level of detail that we a few decades ago could not even dream of.

This lecture will try to popularize some of these novel achievements, and look into some possible future developments.

SYMPOSIUM 5

NEW TREATMENT OPTIONS IN AFFECTIVE DISORDERS

S5.1 Using smartphones in the treatment and monitoring of Bipolar Disorder

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Background: E-mental health technologies are under great development and the use of these technologies is increasing rapidly.

Objectives: During this symposium, an overview of the use of smartphones in the treatment and monitoring of Bipolar Disorder will be presented.

Methods: Further, issues on the use of big data in psychiatry will be adressed.

Results: Results from studies on the effect of smartphone-based interventions in Bipolar Disoder will be presented. Further., the use of subjective self-monitored smartphone data and objective behavioral smartphone data collected using smartphones will be presented.

Conclusion: Future perspectives and implications on the use of smartphones in Bipolar Disorder treatment and research will be adressed.

S5.2 Targeting the endocannabinoid system in depression – a new option for intervention

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A growing body of evidence has supported an important involvement of non-monoaminergic mechanisms in the neurobiology of stress and depression. Amongst those, the endocannabinoid system has received considerable attention. Endocannabinoids, such as anandamide (AEA), are synthesized and released on demand by the post-synaptic neuron, being able to act in the presynaptic terminal at cannabinoid type 1 receptor (CB1) to negatively modulate neurotransmitter release. AEA effects are terminated by hydrolysis mediated by fatty acid amide hidrolase (FAAH). Evidence has suggested that at lower doses, AEA would preferentially activate CB1 receptors while, at higher doses, AEA would activate the transient receptor potential vanilloid type-1

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

(TRPV1) channel and trigger opposite effects. This has been proposed to be a fine-tuning mechanism by which the endocannabinoid system would modulate behavioral responses to stress. In fact, CB1 and TRPV1 are able to modulate the main neurotransmitters systems that are relevant for stress adaptation and mood regulation, including monoaminergic, glutamatergic and gabaergic ones. Thus, the study of the endocannabinoid system can reveal different targets to be explored for the identification of new antidepressant drugs. In agreement with that, preclinical data shows that systemic administration of FAAH inhibitors, CB1 receptor agonists or TRPV1 antagonists induce antidepressant-like effects. At the neuroanatomical levels, these effects seem to involve the prefrontal cortex and the hippocampus. Further studies are still necessary for a better comprehension of the neural mechanism involved in the endocannabinoid signaling in stress and depression. Ultimately, this could provide important information for the future development of new non-monoamine based antidepressants.

S5.3 Bio-behavioral characterisation of a selective α2C-receptor antagonist in animal models of schizophrenia and depression

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Background: Despite significant research efforts aimed at understanding the neurobiological underpinnings of major depressive disorder (MDD) and schizophrenia (SCZ), effective treatment remains problematic. With symptom presentation of psychosis and mood on a continuum, it is not unreasonable to consider these illnesses as presenting with common biological determinants. Cognitive dysfunction is one such symptom evident in both illnesses and is especially difficult to treat. Deficits in monoaminergic neurotransmission with altered hippocampal brain derived neurotrophic factor (BDNF)-signalling has been described in both illnesses. However, different biological roles for α2A,B&C subtypes of the α2-adrenoceptor (AR) are evident. In fact, selective α2C-AR-antagonists are purported to have antidepressant, pro-cognitive and anti-psychotic-like properties while α2A-AR-antagonists have variable, often opposing effects. Further, the atypical antipsychotic, clozapine, is effective in refractory schizophrenia and improves associated cognitive deficits while its α2C-AR modulating activity suggests a therapeutic role for this receptor in schizophrenia.

Objectives: The above actions have not been demonstrated in validated animal models of MDD and/or schizophrenia, while any benefits for α2C-AR-antagonism remain unclear. Here we report investigations into the ability of selective α2C-AR antagonism to reverse the bio-

Methods: The effects of the selective α2C-AR antagonist, ORM-10921, and non-selective α2A-AR-antagonist, idazoxan, were studied in the Flinders Sensitive Line (FSL) rat model of depression with respect to behavioural despair and novel object recognition (NOR). ORM-10921, clozapine and haloperidol, were also studied with respect to modulation of prepulse inhibition (PPI) and NOR in the social isolation rearing (SIR) model of SCZ. Frontal-striatal and hippocampal BDNF levels, respectively, were analysed in the SIR and FSL models. Drugs were administered subcutaneously for 14 days.

Results: In the FSL study, ORM-10921 (0.03; 0.3mg/kg) but not idazoxan (3mg/kg) reversed cognitive deficits and behavioural despair in FSL rats, although failed to reverse reduced BDNF levels in these animals. In the SIR study, clozapine (5mg/kg), ORM-10921 (0.01mg/kg) and haloperidol (0.2mg/kg)+ORM-10921, but not haloperidol alone, significantly improved SIR-associated deficits in PPI and NOR, with ORM-10921 significantly improving PPI vs. haloperidol-treated SIR animals. Although cortical BDNF was unaffected by rearing condition or treatment, haloperidol+ORM-10921, but neither drug alone, reversed reduced striatal BDNF levels vs. SIR controls and vs. SIR-haloperidol treated animals.

Conclusion: These studies confirm the potential of selective α2C-antagonism as a novel therapeutic strategy in the treatment of MDD and cognitive dysfunction, while it also shows similar potential to treat SCZ. Particularly noteworthy is its ability to bolster the effects of a typical antipsychotic in the SIR model.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

POSTERS

Poster 1

Investigation of changes in microRNA expression during antidepressant treatment.

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Background: The treatment of depression is not always successful with 50% of treated patients not responding to the first line of treatment and 30-40% being treatment resistant. It is therefore of great interest to find specific diagnostic and prognostic biomarkers for this disorder. MicroRNAs, a class of small non-coding RNAs involved in gene silencing, are potential biomarkers because of their stability in blood and their involvement in depression.

Objectives: In this study, microRNAs targeting BDNF and VEGF, two neurotrophic factors shown to be involved in the pathology of depression, were investigated for their potential as biomarkers for treatment response. The clinical sample consisted of 41 depressed indiv

Methods: MicroRNAs were extracted from serum samples collected at baseline (T0) and following 12 weeks of antidepressant treatment (T1). 11 microRNAs (hsa-miR-103a-3p, hsa-miR-107, hsa-miR-122-5p, hsa-miR-125b-5p, hsa-miR-126-3p, hsa-miR-16-5p, hsa-miR-185-5p, hsa-miR-191-5p, hsa-miR-20a-5p, hsa-miR-328-3p and hsa-miR-93-5p) were investigated with quantitative real time polymerase chain reaction.

Results: The following analyses are ongoing. The potential differential expression of microRNAs between the two treatment arms, as well as between T0 and T1 will be investigated. Additionally, target gene identification and functional pathway analyses will be performed for differentially regulated miRNAs.

Conclusion: As the results are ongoing, conclusions are not drawn. Results and conclusions will be presented at the congress.

Poster 2

Morphological Alteration of Hippocampal Astrocytes One Day after a Single Dose of Ketamine

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Background: Dysfunction of glial cells is one of contributor mechanisms in the pathophysiology of major depression. Moreover, it has been indicated that astrocytes are likely to have remarkable role in modulating the synaptic plasticity.

Objectives: The present study investigated the rapid effect of single dose of ketamine on morphological alteration of hippocampal astrocytes in genetic rat model of depression.

Methods: Flinders Sensitive Line (a highly validated genetic animal model of depression) and Flinders Resistant Line rats as control group received a single injection of ketamine (15 mg/kg) or saline intraperitoneally one day before transcardial perfusion. Depressed behavior of animals was assessed by forced swim test. GFAP positive astrocytes were investigated in the hippocampal subregions by applying quantitative stereological techniques.

Results: Results: In this study, FSL rats with ketamine treatment exhibited a significant reduction in immobility time in comparison with FSL-vehicle group ($p=0.01$). Investigation of the morphological alteration of hippocampal astrocytes showed significant rapid enhancement in the size of the astrocytes in hippocampal subregions (CA1.stratum radiatum and molecular layer of DG) ($p<0.05$). Moreover, sholl analysis revealed that astrocytic arborization significantly altered in both FSL and FRL rats one day after a single injection of ketamine. Interestingly, the total length of astrocytic processes had negative correlation with the duration of immobility time ($r=-0.64$, $p=0.001$).

Conclusion: The remarkable morphological modification of hippocampal astrocytes 24 hours after a single dose of ketamine, suggested the hypothesis of an important role of astrocytes in rapid action of ketamine at the cellular level.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Poster 3

The effect of voluntary exercise on the kynurenic pathway in the muscles from a genetic rat model of depression

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Background: Depression affects up to 17 % of the population during their lifetime, and is the second leading cause of years lived with disability (YLD). Traditional pharmacological treatment helps only about 50 % and has several adverse effects; therefore alternative treatment strategies are needed. Exercise has attracted increasing interest as a non-drug treatment for depression. Both animal and human studies have shown promising results, but despite substantial progress in defining the mechanisms underlying the action of exercise on the central and peripheral systems, the physiological effects still remain to be elucidated. Recently, the metabolism of kynurenine in skeletal muscles was suggested to play a beneficial role in the effects of physical exercise. In this study the effect of voluntary exercise was investigated in our genetic rat model of depression, the Flinders Sensitive Line (FSL) rats and their control rats, the Flinders Resistant Line (FRL) rats.

Methods: At the beginning of the experiment the rats were 7-9 weeks old. 20 FSL rats and 20 FRL rats were used, with half of each group housed under reversed day/night cycle. 10 FSL rats and 10 FRL rats, half with reversed cycle, were exposed to exercise by voluntary treadmill for 12 hour per day for 7 weeks during their night cycle. The control groups consisted of 10 FSL rats and 10 FRL rats, half with reversed cycle, which did not have access to exercise. The running data was collected each day and the rats were weighted every week. Six days before euthanization the rats were subjected to two behavioral tests; the FST (forced swim test) and the OFT (open field test) to assess depression-like behavior of the rats. After 7 weeks the rats were euthanized by decapitation and selected brain areas, musculus gastroc meniscus, liver, plasma, and serum were collected. Changes in the expression of enzymes involved in the metabolism of kynurenine will be assessed using quantitative real-time polymerase chain reaction and Western blotting in the muscles.

Results: There was a huge difference in the daily running distance; ranging from 20-100 meter/night and up to 18 km/night. Data from the behavioral tests (FST and OFT) are currently being analyzed. In parallel, examination of mRNA transcript and protein levels of 10-15 enzymes of the kynurenic pathway is ongoing.

Conclusion: Currently it is not possible to conclude anything.

Poster 4

The role of Toxoplasma gondii in depression and anxiety - gene-environment interactions in the FSL rat model

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Background: Toxoplasma gondii (TOX) is a common parasite affecting approximately one-third of the human population. An increasing number of studies are providing evidence that the disease is associated with behavioural changes and psychiatric disease.

Objectives: Using the Flinders Sensitive-Line (FSL) rat model, the objective of the current study was to characterize TOX-induced behavioural changes and whether the behavioural outcome is affected by genetic vulnerability.

Methods: Rats were infected p.o. with 20 TOX-cysts. Twelve weeks post-infection, the animals were subjected to a behavioural test-battery including tests for depression (sucrose-preference test (SPT) and forced-swim test (FST)) and anxiety (elevated plus-maze (EPM) and light-dark box (LDB)).

Results: In the LDB TOX-infected animals, independent of phenotype, spent less time in the light area ($p<0.05$). In the EPM a strain effect was found, with FSL animals spending less time in the open arms compared to their FRL controls ($p=0.01$). Furthermore, a strain X treatment interaction was found; when treated with TOX, FRL animals spent as little time in the open arms as the FSL animals ($p=0.01$). In the SPT an interaction between strain and treatment was also found; vehicle treated FSL animals did not show anhedonia when compared to FRL animals, whereas TOX treated FSL, but not FRL, animals displayed a marked decrease in sucrose consumption ($p=0.010$). A similar interaction is found in the FST where FSL, but not FRL, animals displayed increased despair following TOX treatment ($P<0.05$).

Conclusion: These data show that TOX can induce anxiety-like behaviour in rats independent of phenotype. Furthermore, we find that genetically vulnerable FSL animals display more severe depressive-like symptoms following TOX infection. Such results are in line with clinical studies showing a marked increase of toxoplasmosis in anxiety patients compared to healthy controls and moreover suggest an interplay between gene

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

and environment leaving genetically vulnerable subjects susceptible to depression induced by chronic toxoplasmosis.

Poster 5

Stereological analysis of volume and cell number in the postmortem hippocampus in depression, schizophrenia, and suicide

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Background: Background: The hippocampus has long been associated with the pathophysiology of psychiatric disorders, especially major depressive disorder (MDD) and schizophrenia. Also, in vivo imaging studies indicate that the volume of hippocampus may be reduced in both disorders. Moreover, suicide may have a unique neurobiology.

Objectives: Objectives: The aim of the present study is to investigate if severe depression, schizophrenia or suicide is associated with reduced volume of the hippocampal formation and/or changes in the numbers of neurons and/or glial cells in the different subregion

Methods: Methods: The postmortem brain samples were composed of 10 subjects with schizophrenia, 8 subjects with major depression, 11 suicide victims with a history of depressive disorder, and 10 control subjects with no history of psychiatric or neurological diseases. The microscopic analysis is based on state of the art design-unbiased stereological techniques: the Cavalieri estimator is used to estimate the volume of hippocampus and its subregions, and the optical fractionator method is used to estimate the total number of neurons and glial cells in the individual cell layers in four main regions of hippocampus: the granular cell layer, hilus, CA2/3, and CA1.

Results: Results: We found the volume and the number of neurons and glial cells reduced in a similar way by approximately 20% to 35% in depressed and schizophrenia subjects relative to control subjects across all hippocampal regions.

Conclusion: Conclusion: In conclusion, the volume and number of cells are reduced in depressed and schizophrenia subjects relative to control subjects across all hippocampal regions. Our findings imply that the hippocampus may be a common site of pathophysiology in depression and schizophrenia.

Poster 6

THE CLOCKWORK BEHIND DEPRESSION - disturbances of diurnal rhythms in a rat model of depression

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Background: A dysregulation of diurnal rhythmicity of the biological clock that affects sleep, mood, body temperature, hormone secretion, etc. is reported in a subgroup of MDD patients. The suprachiasmatic nucleus (SCN) is well known for its function as the master clock and regulates several circadian systems at the level of clock gene expression. In addition to central expression, peripheral clock genes have also been found.

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

Methods: The study is based on the validated animal model of depression, the chronic mild stress model (CMS). Depression-like rats and control rats were killed by decapitation every 4th h during 24 h. Trunk blood, brain, and liver tissue were collected. The quantitative amount of plasma corticosterone and melatonin were measured using an ELISA and RIA kit, respectively. Identification of specific clock genes in the liver was done by using the q-PCR method. Quantification and visualization of clock genes in the brain were established by the in situ hybridization method.

Results: We studied three of the most essential clock genes, Per1, Per2 and Bmal1. Per1 expressed a robust circadian rhythm in the master clock and in two other brain structures related to depression. However, Per2 and Bmal1 expression were more susceptible to the stress paradigm indicated by an abnormal expression of clock genes. Further, we measured an increased nocturnal melatonin secretion, an additional peak in daytime corticosterone level, and hypothermia in the nocturnal phase.

Conclusion: The results suggest that depression-like state is associated with abnormalities of the circadian system. Therefore, it is tempting to speculate that

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

normalization of this pattern is essential for the recovery from the pathological state.

Poster 7

The role of mTOR in the inflammatory alterations and antidepressant response following ketamine in a rat model of depression

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

Objectives: The main objective of this study is to elucidate the role of mTOR in the antidepressant response of ketamine and in the reversal of neuroinflammation induced depression.

Methods: The study will be performed on Sprague Dawley rats injected with LPS to create a depressive-like state similar to a clinical depression. The antidepressant response of ketamine will be measured through the forced swim test (FST) and Sucrose Preference Test. To elucidate the role of mTOR several proteins associated to synapto- and neurogenesis will be quantified. Furthermore, activated mTOR is measured. These procedures will be carried out through Western Blotting on hippocampal and prefrontal cortex tissue. To confirm an inflammatory state we will measure pro-inflammatory cytokine levels with ELISA-based assays.

Conclusion: Perspectives Understanding the pharmacodynamics of fast-acting antidepressants is necessary to develop novel antidepressants with an improved response and fewer adverse effects. Besides treating depression, elucidating the mechanism underlying rapid antidepressants is essential to understand the pathogenesis of depression.

Poster 8

Structural aspects of subiculum and the effect of SorCS2

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Background: Subiculum (SC) is a unique component of hippocampal formation and constitutes the anatomical transition zone between the hippocampus and the entorhinal cortex. It is important to understand SC and its relation to neurodegenerative disorders. SorCS2 belongs to the category of leucine rich repeat transmembrane proteins, members of which many are involved in the regulation of neuronal growth and survival, and it has been shown to have a high expression in SC.

Objectives: To compare SC volume, number of neurons and glial cells in wild-type (wt) and SorCS2 ko mice. Investigate ratio of SorCS2 positive neurons between dorsal and ventral SC in wt mice. Compare pyramidal dendritic length, spine number as well as spine classes

Methods: Design-unbiased stereological techniques including Cavalieris estimator and optical fractionator were used to quantify total volume and number of neurons [pyramidal cells (PCs) and fusiform cells (FCs)] and glial cells (GCs) in wt and SorCS2 ko mice in SC. Immunohistochemistry (IHC) was used to study the expression of SorCS2 in the SC. Z-stacks of whole PC dendritic trees were 3D reconstructed and spine subtypes were identified and quantified using Imaris XT spine classification module.

Results: PCs in the pyramidal layer and FCs in the polymorphic layer were significantly reduced in the SorCS2 ko mice. We observed 68% SorCS2 positive PCs in the dorsal SC and 32% positive PCs in the ventral SC. Total length of dendrites and total number of dendritic spines were unchanged. SorCS2 ko PC neurons showed increases in volume, spine neck and terminal point diameter (head) of filopodia and mushroom spines.

Conclusion: Our results demonstrate that lack of SorCS2 results in a loss of neuronal cells and alteration of spine morphology which could lead to a changed synaptic input to PCs in the SC.

Poster 9

Biological aspects of the dopamine transporter

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https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

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Background: Parkinson's disease (PD), mood disorders, psychotic disorders, addiction, attention deficit hyperactivity disorder (ADHD) and Tourette syndrome have been associated with pathological changes of the dopamine (DA) activity. This association relates to the ability of DA to influence movement control, reward, motivation and emotion. The dopamine transporter (DAT) is a key factor for the physiological control over the DA tone.

Objectives: In the present contribution the current knowledge about the DAT gene and protein, and the molecular cascades associated with its activity are reviewed and discussed.

Methods: A systematic research of published evidence on DAT as a gene, as a protein and as a protein involved in specific molecular cascades is conducted on PubMed.

Results: The gene that encode for the DAT is described along with the most relevant regulatory areas and the genetic variations associated with human diseases. The DAT protein is described and its interaction with current pharmacological treatments and drugs of abuse is detailed and discussed.

Conclusion: DAT genetic source, protein activity and its molecular interactions are associated with a number of human mental disorders, and with the pharmacodynamics of a number of relevant drugs used in everyday clinic. A better understanding of the functions of DAT will be instrumental for the better comprehension of a number of mental disorders and the synthesis of new drugs.

Poster 10

Videoconferencing in psychiatry, a meta-analysis of assessment and treatment

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Background: Videoconferencing in psychiatry allows some aspects of psychiatric assessment and treatment to be dealt remotely. RCTs on psychiatric assessment and treatment in remote settings were not systematically analysed.

Objectives: A meta-analysis is performed to investigate whether assessment and treatment in remote can replace face-to-face settings. Focus of research was the general psychiatric approach, which includes pharmacotherapy, counselling and some not specific psychothera

Methods: Human randomised clinical trials (RCTs) with a sample size per arm >= 10 were identified through a systematic review conducted in Medline, the Cochrane Library, Embase and the reference list of single papers. A random-effect model or a mixed-effect model served to estimate the reliability of psychiatric assessment in remote, together with the non inferiority of remote treatment.

Results: 26 RCTs were selected, involving 765 (assessment) and 1585 patients (efficacy). Assessment in remote and in vivo had high consistency (COR=0.73 [0.63 - 0.83]), but heterogeneity could not be excluded under the best fitting model (p-val = 0.003). A non superiority for in vivo treatment results from the analysis (SDM=-0.11 [-0.38 - 0.16]), while excluding heterogeneity (p-val = 0.06). A mixed-model analysis (meta-regression) best fitted the available data.

Conclusion: Current evidence shows high levels of consistency between remote and in vivo psychiatric assessment of a number of psychiatric conditions. Efficacy of remote treatment was shown to be not inferior to in-vivo settings in a number of psychiatric conditions. Heterogeneity could not be excluded for assessment, and further analyses are mandatory. The presence of multiple diagnoses was controlled during the meta-regression, but it still represents a limit of the present investigation as a potential stratification factor.

Poster 11

Endogenous 5-HT receptor stimulation is critical for the antidepressant-like of ketamine but not vortioxetine

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

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

of ketamine exhibits acute and sustained antidepressant-like effects in rats. The mechanisms mediating the ketamine's antidepressant effect have only been partly resolved. Recent preclinical reports implicate serotonin (5-hydroxytryptamine; 5-HT) in the antidepressant-like action of ketamine. In support of this notion, it has been hypothesized that modulation of 5-HT1B receptors is involved in mediating ketamine's antidepressant effects. Vortioxetine is a multimodal-acting antidepressant that is hypothesized to exert its therapeutic activity through 5-HT3, 5-HT7 and 5-HT1D receptor antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism, and inhibition of the 5-HT transporter. Preclinical studies indicate that this pharmacological profile results in enhanced monoamine and glutamate neurotransmission and inhibition of GABA interneurons expressing 5-HT3 receptors in key brain structures relevant for depression.

Objectives: To evaluate the role of endogenous stimulation of 5-HT receptors in the therapeutic-like effects of ketamine, vortioxetine, and the serotonin reuptake inhibitor fluoxetine.

Methods: Flinders Sensitive Line (FSL), a genetic model of depression, were depleted of 5-HT by repeated administration of 4-chloro-DL-phenylalanine methyl ester HCl (pCPA). Using pCPA-pretreated and control FSL rats, we investigated the acute and sustained effects of ketamine (15 mg/kg), fluoxetine (10 mg/kg), or vortioxetine (10 mg/kg) on recognition memory and depression-like behavior in the object recognition task (ORT) and forced swim test (FST), respectively. In the FST, the combination of ketamine and the selective 5-HT1B receptor agonist CP94253 was additionally investigated in pCPA-pretreated FSL rats.

Results: The behavioral phenotype of FSL rats was unaffected by 5-HT depletion. Vortioxetine, but not fluoxetine or ketamine, acutely ameliorated the memory deficits of FSL rats in the ORT irrespective of 5-HT tone. No sustained effects were observed in the ORT. In the FST, all three drugs demonstrated acute antidepressant-like activity but only ketamine had sustained effects. Unlike vortioxetine, the antidepressant-like responses of fluoxetine and ketamine were abolished by 5-HT depletion. Combining ketamine with a sub-effective dose of CP94253 rescued ketamine's acute and sustained antidepressant-like effects.

Conclusion: These observations are consistent with a role for endogenous 5-HT in the acute and sustained antidepressant-like actions of ketamine in FSL rats. Moreover, some degree of 5-HT1B receptor activation appears to be critical for ketamine's antidepressant-like potentials. On the other hand, the acute beneficial effects of vortioxetine on memory and depression-like behavior appear to be unaffected by 5-HT depletion. Thus, these effects may be ascribed to vortioxetine's direct actions at 5-HT receptors, which may result in modulation of multiple neurotransmitter systems, including glutamate.

Poster 12

Safety, tolerability, and efficacy of zicronapine in adults with schizophrenia: results from a randomised, double-blind, risperidone-controlled study

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Background: Zicronapine (ZIC) is a serotonin-dopamine activity modulator, acting as an antagonist at dopamine D1 and D2 receptors and serotonin 5-HT2A and 5-HT6 receptors. Three previous studies (NCT00768326; NCT00770744; NCT01377233) have indicated that ZIC is efficacious and well tolerated in adults with schizophrenia. Here, we report on a study comparing the safety, tolerability, and efficacy of ZIC with that of risperidone (RIS) in adult patients with schizophrenia treated for 6 months. RIS is a dopamine D2 and serotonin 5-HT2A receptor antagonist approved in Europe and the United States for the treatment of schizophrenia.

Objectives: Primarily to assess the effect of ZIC versus RIS on metabolic parameters and secondarily to assess the overall safety, tolerability and efficacy of ZIC versus RIS.

Methods: This was a multi-national, randomised, double-blind, parallel-group, RIS-controlled, fixed-dose study (NCT01295372). Adult, stable outpatients with a primary diagnosis of schizophrenia and in need of change of their antipsychotic medication due to poor efficacy or tolerability were randomised to treatment with ZIC (7.5 mg/day; 78 patients) or RIS (5 mg/day; 82 patients) for 6 months. The primary endpoints were change from baseline to Week 24 in bodyweight, body mass index (BMI), waist circumference, and levels of fasting blood lipids and glucose. Secondary endpoints included adverse events (AEs), serum prolactin levels, and changes from baseline in PANSS total and subscale scores and CGI-S scores. Data were summarised using descriptive statistics and analysed using mixed models for repeated measurements (MMRM).

Results: Mean bodyweight and BMI increased more in the ZIC group (2.2 kg; 0.7 kg/m2) than in the RIS group (0.7 kg; 0.2 kg/m2); mean waist circumference (MWC) increased in the ZIC group (1.2 cm) and decreased in the RIS group (-0.2 cm). The mean differences between the

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

treatment groups at Week 24, however, were not statistically significant (p=0.11, 0.08, and 0.12 for weight, BMI, and MWC, respectively). The proportion of patients with a potentially clinically significant (PCS) increase in weight and BMI was statistically significantly higher for ZIC than for RIS (21% versus 8% at last visit, p=0.020; 22% versus 10% at any visit, p=0.049). Mean changes in metabolic parameters (fasting blood lipids and glucose) were minimal, and the proportion of patients with PCS values was similar in both groups for all metabolic parameters. Approximately 77% of patients in both groups had treatment-emergent AEs; 15 patients had serious AEs (RIS: 5/82 [6.1%]; ZIC: 10/78 [12.8%]). The pattern of AEs differed: the most common AEs in the ZIC group were weight increased (18%), anxiety (14%), and insomnia (13%); the most common AEs in the RIS group were insomnia (17%), somnolence (16%), and akathisia (12%). Serum prolactin levels decreased in the ZIC group (mean decrease: 30%) and increased in the RIS group (mean increase: 300%). Both treatments improved PANSS total and subscale scores, CGI-S score, and measures of general functioning; ZIC induced a larger change in PANSS total score at Week 1 and PANSS Negative Symptoms subscale score at Weeks 1 and 2.

Conclusion: ZIC was generally well tolerated. Compared with patients receiving RIS, patients receiving ZIC had a PCS weight gain; however, their metabolic profile was not significantly affected. Contrary to RIS, ZIC did not induce hyperprolactinemia and was associated with a lower rate of extrapyramidal symptom-related AEs (including akathisia), indicating low levels of D2 receptor occupancy consistent with the pharmacological profile of ZIC. In terms of overall antipsychotic efficacy and health outcome improvements, ZIC was comparable to RIS. Notably, ZIC displayed early onset of action and distinct effects on negative symptoms.

Poster 13

Acute and chronic probiotic treatment of rats: molecular changes in the adrenal glands

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Background: Recently, the gut microbiota has been shown to modulate brain function and behavior through several pathways, including the hypothalamic-pituitary-adrenal (HPA) axis. This physiologic crosstalk is known as the microbiota-gut-brain (MGB) axis. In our laboratory, chronic (8 weeks) probiotic treatment has been demonstrated to reduce depressive-like behavior in rats. In addition, altered mRNA levels of HPA axis regulating factors in hippocampus have been reported. However, not much is known about molecular changes in the adrenal glands.

Objectives: The aim of this study was to investigate molecular changes in the adrenal glands following probiotic treatment for 2 days, 3 weeks, and 7 weeks in rats. The molecular studies include mRNA, microRNA (miRNA), and protein studies.

Methods: Male Sprague Dawley rats were randomly assigned to one of the treatment periods as well as to treatment with placebo or probiotics (Winclove Ecologic® BARRIER multispecies formula). The experimenter was blinded to treatment groups. The rats were euthanized by decapitation and adrenal glands were collected from the rats. mRNA and protein were isolated with the PARISTM RNA and protein isolation kit.

Results: Protein and RNA were extracted from the left adrenal glands. Initially, quantitative real-time polymerase chain reaction (real-time qPCR) and Western blotting studies will be conducted within pathways related to depression.

Conclusion: The study is on-going and a conclusion will be presented.

Poster 14

The regulation of orexins and their cognate receptors in two distinct rat models of depression and effects of treatments

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Background: Sleep disturbances is a key symptom of depression and recently sleep disturbances have been suggested as a new area to optimize treatment in depression. This study aims to investigate possible implications for abnormalities in orexin, a neuropeptide important in controlling sleep and arousal, in depression. Orexin is produced in the hypothalamus and projected throughout the brain innervating a number of structures important in depression. Orexin also controls a number of other physiological processes including cognitive processes, stress response and feeding, all of which are affected during depression in humans and disturbed in a number of depressive-like animal models.

Objectives: The aim of the study is to provide molecular and behavioral insights into the relationship between depression and sleep disturbances with perspectives for

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

novel treatment strategies. To this effect we are investigating orexin which are linked to a numbe

Methods: Using real-time qPCR and Western blotting optimal sampling time is determined by an initial assessment of the diurnal variation of orexin expression. Differences in the expression of orexin and its cognate receptors are investigated in the hypothalamus, the hippocampus, and the prefrontal cortex of two rat models of depression: the Flinders Sensitive Line (FSL) and the Chronic Mild Stress (CMS) model. Behavioural and molecular response to treatment with a conventional antidepressant, an orexin receptor antagonist, and of orexin-A itself will be addressed in the FSL rats. In addition we will include exercise as a non-invasive treatment, which has shown positive effects on both sleep and depression in human subjects. In parallel studies, we are investigating possible effects of the sleep inducing agent isoflurane on the orexinergic system.

Results: Real-time qPCR analysis showed increased expression of the orexin-1 receptor (40%) and the orexin-2 receptor (39%) in the prefrontal cortex of FSL rats compared to its control strain, the Flinders Resistant Line (FRL) rat. The diurnal variation study showed the predicted variation across the day corresponding to rats being night active and the hormone promoting arousal and wakefulness.

Conclusion: The preliminary results support the hypothesis that orexinergic dysregulation is present in the Flinders Sensitive Line rat model of depression. Based on this the study may provide a platform for screening of drugs with positive effects on both sleep and depressive symptoms; thus the project provides perspectives for the development of novel strategies for improving treatment of depression.

Poster 15

The regulation of miRNA in a genetic animal model of depression

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Background: MicroRNAs (miRNAs) are a prominent class of gene expression regulators with important roles in both normal function and disease states. Recent studies have demonstrated that miRNA expression profiles are altered in brain of rodent models of depression, in human postmortem brain of depressed subjects, and in blood from depressed patients during antidepressant treatment. MiRNAs offer a great potential as useful biomarkers due to their stability and ease of detection in many biological samples, especially blood.

Objectives: To further investigate the role of miRNAs in relation to the neurotrophic hypothesis of depression. Furthermore the possibility of miRNAs as diagnostic markers is explored.

Methods: In the present study the expression of 50 selected miRNAs were investigated in the brain (hippocampus and frontal cortex) in a genetic model of depression, the Flinders Sensitive Line (FSL) rats. Sprague Dawley (SD) and Flinders Resistant Line (FRL) rats were included as control. Based on the literature and target prediction algorithms miRNAs were selected for their function of targeting neurotrophic factors and their cognate receptors, which are known to be implicated in depression. The relative concentrations of the miRNAs were measured using quantitative real-time polymerase chain reaction (real-time qPCR) and locked nucleotide acid primers.

Results: In the hippocampus two miRNAs were up-regulated; miR-103 (65%) which is predicted to target BDNF and miR-92a targeting TrkA (130%), and three were down-regulated; miR-126 predicted to target VEGF (25%), miR-206 targeting BDNF (40%) and miR-485 targeting TrkC (35%), in the FRL and FSL rats compared to the SD rats. In the frontal cortex 20 miRNAs were found upregulated compared to SD rats and some also to the FRL rat. Three miRNAs (miR-92a, miR-126 and miR-485) were altered in both hippocampus and frontal cortex.

Conclusion: These findings support a role for microRNA in dysregulation of neurotrophic factors in depression.

Poster 16

Side-effects breaking the blind does not explain the antidepressant effects of the selective serotonin reuptake inhibitors

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Background: According to a theory that has recently been widely disseminated in both scientific journals and lay media, antidepressant drugs do not exert any genuine pharmacological antidepressant effect, but outperform placebo in controlled trials only by causing side-effects which are assumed to enhance a psychological placebo effect by making the patient realize that he/she has not been randomized to placebo.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Objectives: To challenge this hypothesis by investigating if the presence of side effects may indeed explain the differences between SSRIs and placebo in drug company-sponsored trials.

Methods: Pooled post-hoc analyses of all company-sponsored, acute-phase, placebo-controlled trials using the Hamilton Depression Rating Scale (HDRS) to evaluate the effect of citalopram, paroxetine or sertraline in adult major depression. The single item depressed mood, which has proven a more sensitive measure to detect an antidepressant signal than the conventional one, i.e. the sum score of all HDRS items (HDRS-17-sum), was designated primary effect parameter. The HDRS-17-sum was used as secondary effect parameter.

Results: With respect to the reduction in depressed mood, the effect size for the difference between active drug and placebo after 4 weeks of treatment in patients not experiencing any adverse events was 0.29 (95% C.I. 0.16 – 0.43; $p < .001$). In patients reporting adverse events the corresponding effect size was 0.28 (95% C.I. 0.22 – 0.38; $p < .001$). The results of the analysis using HDRS-17-sum as effect parameter were similar to those of the primary analysis. Likewise, analyses comparing patients reporting an early side effect (during the first week of treatment) with those not reporting an early side effect yielded a similar outcome.

Conclusion: Effect sizes for the difference between SSRI and placebo being similar regardless of the presence of side-effects argues against the hypothesis that side-effects breaking the blind is a major contributor to the antidepressant efficacy of the SSRIs.

Poster 17

A pattern of TNF-pathway activation in schizophrenia and bipolar disorder across brain tissue and plasma

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Background: Previous studies indicate a shift towards a pro-inflammatory imbalance in the tumor necrosis factor (TNF) system with elevated plasma levels of TNF markers in schizophrenia (SCZ) and bipolar disorders (BD).

Objectives: The aim of the current study was to investigate the functional relationship between TNF levels and mRNA expression in blood, and how this relates to changes in the TNF system in brain

Methods: In a large sample of SCZ and BD spectrum patients (n= 816) and healthy controls (HC, n= 624) we measured plasma levels of soluble TNF (sTNF), TNF receptor 1 (sTNFR1) and TNF receptor 2 (sTNFR2) and A Disintegrin And Metalloprotease-17 (ADAM17) protein using enzyme immunoassays, and calculated the TNF-ratio (sTNF/sTNFR1+sTNFR2). TNF, TNFR1, TNFR2 and ADAM17 mRNA levels were determined in whole blood, and postmortem prefrontal cortex mRNA levels were obtained from an independent sample (113 patients and 88 controls).

Results: We show a consistent and significant increase in TNF-related measures in the blood of patients compared to HC, with an increased TNF-ratio ($p = 6x10-5$) but decreased TNF mRNA expression ($p=1x10-4$). We found no significant differences between BD and SCZ ($p>0.12$), except for ADAM17 mRNA expression which was increased in BD compared to SCZ and HC in blood ($p=1.40x10-14$). We found similar nominally significant alterations in the prefrontal cortex.

Conclusion: Both patients with SCZ and BD have increased TNF pathway activity in the blood without corresponding increase in gene expression, while ADAM17 expression seems to differentiate BD and SCZ patients in blood. This suggests that the increase in TNF may come from the cortex, while other organs may be involved. The current findings highlight the role of TNF pathway in the pathophysiology of severe mental disorders.

Poster 18

Serotonin Transporter Binding in a Rat Model of Depression: Effects of Electroconvulsive Shocks

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

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Background: Depression is a debilitating mental illness and two thirds of patients respond insufficiently to conventional antidepressants. Electroconvulsive therapy (ECT) remains the most effective treatment to alleviate depression in drug-refractory patients, however the neurobiological mechanisms behind the therapeutic effect are mostly unknown. Dysfunction of the serotonergic system is thought to play an important role in depression and alterations in the serotonin transporter (SERT) are seen in depression and in response to antidepressant treatments.

Objectives: The first aim of this study was to investigate baseline levels of SERT densities in a genetic rat model of depression, Flinders Sensitive Line (FSL) rats, compared to control Flinders Resistant Line (FRL) and Sprague-Dawley (SD) rats. The second aim was t

Methods: Female rats of each strain were treated with ECS or sham (ear-clip placement with no current) for 10 days before brains were removed, frozen and cut into 20 µm thick sections. SERT density was measured in limbic and cortical regions by quantitative in vitro autoradiography using the SERT-radioligand, [3H]DASB.

Results: At baseline, higher SERT binding was observed in FSL rats (36-48% increase in motor cortex and striatum) compared to SD rats in several brain regions. In response to ECS, control SD rats had a tendency towards increased SERT binding (15-25% increase in motor cortex and striatal regions), whereas no changes were observed in FRL and FSL rats.

Conclusion: Increased SERT binding in FSL rats supports a dysfunction of the serotonergic system in depression. The trend towards increased SERT density after ECS, seen in SD rats but not FSL rats, suggests a different mechanism of action between normal and depressive-like rats. More studies on ECS response in animal models of depression are needed to clarify this.

Poster 19

A cannabinoid receptor antagonist attenuates ghrelin-induced activation of the mesolimbic dopamine system in mice.

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Background: Background: The orexigenic peptide ghrelin increases appetite as well as activates the mesolimbic dopamine system, i.e. the dopamine projection from the ventral tegmental area (VTA) to nucleus accumbens (NAc). Preclinical studies report that ghrelin receptor (GHS-R1A) antagonism decreases drug reinforcement, suggesting that this gut-brain peptide increases the incentive salience of motivated behaviours. Elevated plasma levels of ghrelin are associated with craving in patients with alcohol dependence, suggesting the hormone's involvement in alcohol use disorders (AUD).

Objectives: Objectives: The present experiments were designed to explore the involvement of cannabinoid receptors type 1 (CB1), specifically in the VTA, for the ability of ghrelin to stimulate the mesolimbic dopamine system.

Methods: Methods: Mice were administered ghrelin and a CB1 antagonist (Rimonabant) and subsequently locomotor activity, accumbal dopamine release and chow intake were attested.

Results: Results: We showed that peripheral (intraperitoneal, ip) administration of Rimonabant attenuates ghrelin (intracerebroventricular, icv) induced locomotor stimulation and accumbal dopamine release in mice. Ghrelin (icv) induced food intake was not altered by the CB1 antagonist. Finally, we showed that bilateral ventral tegmental administration of Rimonabant blocks the ability of intra-VTA ghrelin administration to increase locomotor activity in mice.

Conclusion: Conclusion: We conclude that antagonism of CB1 attenuates the activation of the mesolimbic dopamine system in mice following ghrelin administration. Moreover, the data suggest that ventral tegmental CB1 regulates this ghrelin-induced reward. Given the association of ghrelin levels with AUD, there is an emerging clinical relevance of the present study, exposing the possible link of cannabinoid receptors with alcohol disorders.

Poster 20

A dual inhibitor of FAAH and TRPV1 channels has a biphasic dose-response pattern on depression-like behaviour in rats

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https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

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Background: It has been proposed that the cannabinoid-receptor 1 (CB1) and transient potential vanilloid receptor 1 (TRPV1)-channel mediates opposite behavioural responses. Their common denominator is the endocannabinoid ligand anandamide (AEA) which is believed to mediate an-tidepressant-like effect via CB1-R stimulation and depressive-like effect via TRPV1-channel activation.

Objectives: In this study we investigated this assumption by administering the dual inhibitor of AEA hydrolysis and TRPV1-channel activation N-arachidonoyl-serotonin (AA-5HT) into the medial prefrontal cortex of Sprague Dawley rats.

Methods: Rats underwent stereotactic surgery and were bilaterally implanted with cannulaes into the mPFC and injected with AA-5HT at three different doses (0.125, 0.250, 0.500 nmol). Rat behaviour was assessed in open field (OF) and the forced swim test (FST).

Results: Our results show significant antidepressant-like effect of AA-5HT (0.250 nmol) which is believed to be mediated by CB1-R activation since blockade of the receptor attenuated the re-sponse. Interestingly low and high doses were ineffective on FST-induced behavioural changes.

Conclusion: In conclusion, AA-5HT induced a significant antidepressant-like effect mediated via CB1-R activation. The involvement of TRPV1-channel blockade seems to be less crucial in the FST paradigm.

Poster 21

Casein glycomacropeptide as a novel dietary treatment for mania

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Background: Clinical studies have found that amino acid mixtures that cause an acute depletion of tyrosine (Tyr) and phenylalanine (Phe) in the brain produce a significant improvement in mania symptoms within 6 hours of ingestion. This is likely mediated by a reduction in dopamine (DA) synthesis due to a depletion of its precursor amino acids. Casein glycomacropeptide (CGMP) is a peptide that is a byproduct of the cheese-making process. It lacks Phe, Tyr and tryptophan (Trp) and is rich in the branched-chain amino acids (BCAAs), isoleucine and valine. This unique amino acid profile should enable CGMP to cause a depletion of brain levels of Phe, Tyr and Trp by competing with other large neutral amino acids at the blood-brain barrier and hereby limit the synthesis of DA and serotonin (5-HT) in the brain. CGMP could therefore represent a more palatable dietary treatment option to alleviate manic symptoms compared to free amino acid mixtures.

Objectives: We investigated the depleting effects of CGMP (with or without supplementation with Leu and Trp) on the precursor amino acids of DA and 5-HT, as well as the levels of these neurotransmitters themselves and the time-dependency of any such effects. In addit

Methods: Sprague Dawley rats were treated with mixtures of CGMP and amino acids via oral gavage at a low (1500 mg/kg) or high (3000 mg/kg) dose and at different time points, i.e. 2, 4 and 8 hours before the collection of plasma and brain samples. The levels of DA and 5-HT in the hippocampus, frontal cortex and striatum and an array of amino acids in brain and plasma were measured using high-pressure liquid chromatography (HPLC) with electrochemical or fluorescent detection. To investigate the behavioural anti-manic effects of CGMP, we used the amphetamine-induced hyperlocomotion (AIH) test for rats after an acute (2 or 8 hours before the test) or chronic (1 week daily) treatment.

Results: Similar to the effects seen with the BCAA mixture, GMP induced a marked reduction in Tyr, Trp and Phe in brain and plasma and these effects were augmented by the addition of Leu. CGMP plus Leu reduced DA in the frontal cortex and 5-HT in the hippocampus, frontal cortex and striatum after 2 and 4 hours following treatment. CGMP plus Leu also had a significant anti-manic effect in the AIH test 2 hours after a single acute treatment as well as after 1 week of chronic treatment.

Conclusion: This study is the first to show that CGMP depletes central levels of Tyr, Phe and Trp in plasma and brain and reduces DA and 5-HT levels in the brain. These physiological effects, together with the behavioural anti-manic-like response observed in the AIH test, suggest that CGMP could be a useful dietary treatment for mania that is at least as efficient but more palatable than mixtures of free amino acids.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Poster 22

Decreased serotonin transporter levels in a minipig model of Parkinson's disease

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Background: Parkinson's disease (PD) is characterized by progressive decrease in activity of the ubiquitin proteasome system (UPS). This is thought to contribute to widespread cell death and protein aggregation (Lewy bodies) causing different motor and non-motor symptoms. Several non-motor aspects of PD are thought to be related to impairments in the serotonin system.

Objectives: In order to investigate the serotonin system in a minipig model of PD, we inhibited the UPS with injections of lactacystin. For characterization of the model, we measured the in vivo binding of [11C]DASB to the serotonin transporter (SERT) using Positron

Methods: Four adult female Göttingen minipigs were implanted in the cisterna magna with a catheter connected to a subcutaneous titanium injection port. After recovery, pigs were scanned at baseline with [11C]DASB. Minipigs then received weekly injections of lactacystin or sterile saline (control) directly through the port into the subarachnoid space. After 3 and 6 months of injections, minipigs were PET scanned again with [11C]DASB. Using PMOD software, the binding potential of DASB was obtained with the Logan graphical analysis and cerebellum as a reference region. The animals were longitudinally monitored for motor deficits.

Results: Lactacystin administration induced decreased SERT binding potential by 20-30% in striatal brain regions compared to the baseline scans. Moreover, impairments in motor performance were observed.

Conclusion: Our imaging data propose a loss of brain serotonergic innervation in response to proteasome inhibition. This decreased striatal binding of DASB is consistent with decreases found in PD patients. These data, together with previous PET studies in the same pig model demonstrating dopaminergic and noradrenergic deficits, show that this model mimics the multi-neurotransmitter deficits found in human PD. Importantly, our proteasome inhibition model may be useful in the investigation of non-motor deficits in PD and LDOPA-induced dyskinesia.

Poster 23

Molecular Pharmacology of Harmaline and Analogs on Monoamine Transporters

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Background: Anomalies in the serotonergic system are linked to several psychiatric disorders, such as depression. Tricyclic antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs) increase the extracellular concentration of serotonin in the synaptic cleft by blocking the reuptake facilitated by the serotonin transporter. Ayahuasca, a South American psychotropic beverage used by shamans for tribal rituals, has gathered attention as a new experimental treatment for depression. N,N-Dimethyltryptamine (DMT), harmine, harmaline and tetrahydroharmine are the distinctive psychotropic alkaloids found in Ayahuasca and these alkaloids are capable of elevating the concentration of the mood-regulating neurotransmitter serotonin in the brain by inhibiting the monoamine oxidase, thereby preventing the degradation of the neurotransmitter.

Objectives: These alkaloids also exhibit considerable structural similarity to serotonin and other ligands for the serotonin transporter. We hypothesized that an important effect of these alkaloids could also be by inhibition of the serotonin transporter and the othe

Methods: We here describe the molecular pharmacology of harmaline and analogs by determining their inhibitory potency against the monoamine transporters, thus obstructing the reuptake and clearance of monoamine neurotransmitters. Moreover, Substituted Cysteine Accessibility Method (SCAM) was applied to determine the conformational effects of the compounds and investigate whether the compounds will act as monoamine transporter substrates.

Results: Uptake-assays confirmed that harmaline and the analogs indeed exhibited inhibitory effect on the monoamine transporters in the micromolar range. Moreover, we found that several of the compounds induced a conformational shift from an outward-open conformation towards a more inward-facing conformation similar to serotonin, thus indicating that the inhibitors undergo transport through the serotonin transporter.

Conclusion: We conclude that harmaline and the analogs exhibit inhibitory effects on the action of the monoamine

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

transporters. Furthermore, it has been confirmed that certain harmala alkaloids will act as a substrate for the serotonin transporter.

Poster 24

The effect of chronic mild stress on cognition using the paired-associates learning touchscreen task in rodents

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Background: Depression is the leading cause of disability worldwide. Given the obvious mood symptoms depressed patients suffer from, depression-associated cognitive impairments are often neglected. However, these impairments need to be treated likewise to restore daily functioning and therefore the quality of life of depressed patients.

Objectives: The aim of the current study was to test if cognitive impairments can be observed in the well-validated chronic mild stress (CMS) paradigm, a rodent model of depression, using a highly translational readout method, known as the touchscreen (TS) operant pl

Methods: Assigned by their hedonic state with the sucrose consumption test, CMS exposed resilient (N = 9) and susceptible (N = 10) rats, along with non-stressed controls (N = 10) were tested in TS operant boxes applying the different paired-associates learning (dPAL) task. This task is based on the human PAL task of the Cambridge Neuropsychological Test Automated Battery (CANTAB) testing object-in-place memory.

Results: Preliminary results show that rats of the control group are the first to learn the dPAL task, followed by CMS resilient and susceptible rats. Further detailed data analysis is required to verify these preliminary observations.

Conclusion: Confirmation of the preliminary results would indicate the dPAL TS task as suitable for detecting alterations in cognition of CMS susceptible rats. Hence, the CMS paradigm could represent an appropriate model for testing the efficacy of antidepressant drugs on cognitive impairments in depressed individuals.

Poster 25

Inflammatory Evidence for the Psychosis Continuum Model

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Background: Inflammation and immune activation have been implicated in the pathophysiology of severe mental disorders. Previous studies of inflammatory markers, however, have been limited with somewhat inconsistent results.

Objectives: We aimed to determine the effect sizes of inflammatory marker alterations across diagnostic groups of the psychosis continuum and investigate association to antipsychotic medications.

Methods: Plasma levels of soluble tumor necrosis factor receptor 1 (sTNF-R1), interleukin 1 receptor antagonist (IL-1Ra), osteoprotegerin (OPG), and von Willebrand factor (vWf) were measured in patients (n=992) with schizophrenia spectrum (SCZ, n=584), schizoaffective disorder (SA, n=93), affective spectrum disorders (AFF, n=315), and healthy controls (HC, n=638).

Results: Levels of sTNF-R1 (p=1.8x10-8, d=0.23) and IL-1Ra (p=0.002, d=0.16) were increased in patients compared to HC. The SCZ group had higher levels of sTNF-R1 (p=8.5x10-8, d= 0.27) and IL-1Ra (p=5.9x10-5, d=0.25) compared to HC, and for sTNF-R1 this was also seen in the SA group (p=0.01, d=0.3) and in the AFF group (p= 0.002, d= 0.12). Further, IL-1Ra (p=0.004, d= 0.25) and vWf (p=0.02, d=0.21) were increased in the SCZ compared to the AFF group. There was no significant association between inflammatory markers and use of antipsychotic medication.

Conclusion: We demonstrate a small increase in sTNF-R1 and IL-1Ra in patients with severe mental disorders

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

supporting a role of inflammatory mechanisms in disease pathophysiology. The increase was more pronounced in SCZ compared to AFF supporting a continuum psychosis model related to immune factors.

Poster 26

Antidepressant-like effects of Cannabidiol on a genetic animal model of depression

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Background: Cannabinoids have been extensively studied as new pharmacological agents for the treatment of neuropsychiatric disorders[1]. One of these agents is Cannabidiol (CBD), a phytocannabinoid without psychomimetic effects[1,2]. The anxiolytic and anti-psychotic effects of CBD have been widely studied, but only fewer studies have investigated the antidepressant-like effects of this compound[1,2].

Objectives: This project aimed to assess whether intraperitoneal injection of CBD could improve the behavioural response of rats exposed to the forced swim test.

Methods: Male Sprague-Dawley rats (SD) were exposed to the pre-test session (15 min, water at 24±1ºC) of forced swim (FST), and after 24h they were exposed to the open-field test (OFT, 5 min) and to the test session (5 min, water at 24±1ºC) of FST. Male Flinders Sensitive Line (FSL) and Flinders Resistant Line (FRL) rats were exposed to the OFT and to the test session of FST. All the animals received an intraperitoneal injection of CBD (10 or 30mg/kg), ketamine (15 mg/kg) or vehicle 1h before the test session.

Results: On the SD rats, CBD at 30 mg/kg significantly reduced the immobility time (IT) in FST ($F(3,23) = 3.348$, $*p< 0.05$; Dunnett). Ketamine also significantly reduced the IT in FST ($T(11) = 2.732$, $\#p< 0.05$; T test). On the FSL/FRL rats, CBD (10 and 30 mg/kg) and ketamine (15 mg/kg) significantly reduced the IT in FST ($F(3,25) = 8.441$, $*p< 0.05$; Dunnett). In both of rat strains neither ketamine nor CBD modify the locomotor activity of the animals in the OFT.

Conclusion: Our data show for the first time the antidepressant-like effects of CBD on SD rats and in a genetic animal model of depression, the FSL/FRL rats. The results reinforce the antidepressant potential of CBD, as previously shown in the literature. Similarly to ketamine, the antidepressant-like effects of CBD were observed with only one single i.p. injection, thus it might be interesting to investigate if CBD can induce long-lasting effects as it was previously observed with ketamine. More studies are necessary to investigate the mechanisms which cannabidiol induces its behavioural effects.

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Poster 27

Bioluminescence Resonance Energy Transfer (BRET) in the identification and characterization of protein-protein interactions regulating antidepressant targets

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Background: Neurotransmission is a tightly controlled and balanced process relying on the surface expression and activity of several proteins. Protein-protein interactions are major determinants of membrane protein expression. Therefore trafficking and regulation presents a potential intervention point for novel therapeutics.

Objectives: The study of protein-protein interactions with most conventional biochemical methods relies on solubilized protein. These methods conflict with the ubiquitous presence of a surrounding membrane for the correct function of the membrane-protein or the dele

Methods: BRET can be performed in both living cells and crude membrane preparations with superior sensitivity and versatility compared to other methods and can be highly valuable in the characterization of protein-protein interactions. BRET is a fluorescence-based proximity method that can be used to identify and give a quantitative measure of the affinity of protein-protein interactions. Furthermore, it is easily scalable to high-throughput screening of potential drugs interfering with the protein-protein interaction in question.

Results: We here describe how BRET can be generally used to characterize protein-protein interactions with the antidepressant-sensitive serotonin transporter and norepinephrine transporter as well as with the amphetamine- and cocaine-sensitive dopamine transporter.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Conclusion: By establishing BRET and identifying new protein-protein interactions, this may lead to new pharmacological targets in depression and addiction.

Poster 28

Intracellular loop 5 is important for the transport mechanism and molecular pharmacology of the human serotonin transporter

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Background: Serotonin transporter (SERT) is a member of the neurotransmitter: sodium symporter family and is responsible for the reuptake of 5-hydroxytryptamine (5-HT) from the synaptic cleft. SERT is an important drug target for therapeutic compounds such as antidepressant, 5-HT uptake inhibitors and drugs of abuse such as cocaine and ecstasy. The normal function of the SERT relies on large conformational changes and its inhibition by antidepressants represents a conformational lock.

Objectives: Understanding the molecular mechanism of inhibition and which structural elements are involved in inhibitor binding and conformational changes of the SERT will provide clues for the development of improved drugs for the treatment of depression.

Methods: Guided by our previous studies, we combined different biochemical methods to characterize the interplay between TM10-IL5-TM11 region and the rest of the SERT protein in response to inhibitor and substrate binding and as well as the conformational changes in SERT. We examined the importance of the length of IL5 for the function of SERT by increasing the length of IL5 by insertion of a tetracysteine (CCPGCC) or a tetraalanine (AAPGAA) motif.

Results: Using [3H]5-HT uptake, cell surface biotinylation and [125I]RTI-55 binding experiments we show that lengthening IL5 results in reduced cell surface expression of SERT, increased apparent 5-HT affinity, KM, and increased inhibitor potency. Furthermore, conformational analysis of IL5-insertion mutants indicate that CCPGCC and in particular AAPGAA insertion mutants induce a more outward-facing conformation in the apo-form compared to hSERT wt. Interestingly, 5-HT induced conformational changes are opposite to hSERT wt in AAPGAA and CCPGCC mutants.

Conclusion: Our data suggest that IL5 plays an important role in the conformational changes occurring during translocation and ligand binding.

Poster 29

Genetic overlap between schizophrenia and brain structural volumes indicates shared molecular genetic mechanisms with potential relevance for antipsychotics

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Background: The mechanisms of antipsychotic drugs point to the importance of subcortical structures such as putamen and hippocampus. Moreover, patients with both first-episode and chronic schizophrenia (SCZ) display differences in subcortical brain volumes. However, little is known about potential shared etiology between these brain phenotypes and SCZ.

Objectives: Here we aimed to investigate whether SCZ and volumes of subcortical structures and intracranial volume (ICV) share common genetic variants by analyzing summary data from genome-wide association studies (GWAS).

Methods: Applying conditional false discovery rate (FDR) methods, we compared GWAS of SCZ from the Psychiatric Genomics Consortium (PGC) (n=82 315) with GWAS of brain phenotype volumes from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium (n= 12 591). By combining GWAS data of associated phenotypes, the conditional FDR approach increases power to detect genetic loci and allows for evaluating overlap in risk loci regardless of their direction of effects.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Results: First, we constructed conditional Q-Q plots that demonstrate polygenetic overlap between SCZ and several brain phenotypes. We then used the conjunction FDR to identify one locus shared between SCZ and ICV, one locus shared between SCZ and hippocampus, one locus shared between SCZ and pallidum and three loci shared between SCZ and putamen. Next, we will test whether the implicated genetic variants are associated with differences in antipsychotic medication among SCZ patients.

Conclusion: Altogether, our preliminary findings indicate shared molecular genetic mechanisms between SCZ and brain structural volumes and ICV. We highlight six genomic loci that are potentially relevant for SCZ pathogenesis and antipsychotic mechanisms.

Poster 30

Serum concentrations of antipsychotics, mood stabilizers and antidepressants in relation to cognitive function in psychosis spectrum disorders

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Background: Cognitive dysfunction is a core feature of psychosis spectrum disorders. Typical domains affected include verbal memory, attention and executive function, and the deficits are a major cause of social and occupational disability. Knowledge of the cognitive effects of standard medication treatment in these disorders is sparse.

Objectives: To increase the knowledge of the relationship between use of psychopharmacological agents and cognitive function in psychosis spectrum disorders. We used serum concentrations as a new approach in the analyses of the relationship between cognitive function

Methods: Participants were recruited on the basis of a bipolar or schizophrenia spectrum disorder diagnosis. They underwent blood sampling with measurement of serum concentrations of second generation antipsychotics (N = 495), mood stabilizers (N = 217) and antidepressants (N = 187) the same morning as neuropsychological testing. The relationship between serum concentrations and neuropsychological test scores from six cognitive domains were analyzed with linear regression, adjusting for a range of potential confounders.

Results: Serum levels of olanzapine and venlafaxine plus O-desmethylvenlafaxine were positively associated with attention and verbal memory respectively ($p = 0.006 – 0.015$). Serum levels of quetiapine and risperidone were negatively associated with short term verbal memory and verbal fluency respectively ($p = 0.004 – 0.007$). Serum levels of lamotrigine, valproate, and lithium were not significantly associated with any of the neuropsychological test scores.

Conclusion: The findings indicate that serum levels of several psychopharmacological agents are associated with cognitive performance. Despite a positive effect on attention, antipsychotics should be used with caution as high doses are associated with poorer cognitive function in several domains. High dosage is not a major concern for the cognitive functioning during treatment with mood stabilizers or antidepressants, and may improve verbal memory during antidepressant drug treatment. The findings might give clues to the pathophysiological process of cognitive dysfunction in psychosis spectrum patients.

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Poster 31

Pre- and post-synaptic dopaminergic alterations in an alpha synuclein rat model of Parkinson's disease

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Background: Parkinson's disease (PD) is characterised by progressive degeneration of dopaminergic neurons in the substantia nigra (SN) and loss of striatal dopaminergic terminals. The protein alpha-synuclein

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

(asyn) is implicated in PD pathogenesis, but its role in the early disease stages remains to be elucidated

Objectives: The aim of this study was to characterize changes in the dopamine system in a rat model of PD induced by asyn overexpression, shown previously to exhibit synaptic deficits in the absence of cell death.

Methods: Rats were injected with recombinant adeno-associated virus pseudotype 2/6 encoding human wild-type asyn or enhanced green fluorescent protein (eGFP) in the right SN. Motor performance was assessed with cylinder test ten weeks after the injections. At twelve weeks, rats were decapitated and autoradiography was performed on the brain tissue with the following tracers: [3H]-DTBZ, a tracer of the vesicular monoamine transporter 2 (VMAT2); [3H]-GBR12935, a tracer of the dopamine transporter (DAT); and [3H]-Raclopride, a tracer of dopamine 2/3 (D2/3) receptors.

Results: The asyn rats exhibited motor defects absent in the GFP group. Tracer binding in the asyn animals significantly declined with DTBZ and GBR12935, and increased with raclopride in the ipsilateral vs. contrlateral striatum compared to the GFP group.

Conclusion: Reduced VMAT2 and DAT and increased D2 receptor expression together with asyn deposition and motor impairments replicates the pathology observed in PD patients. These changes in the absence of cell death makes this asyn model relevant to study treatments in early PD, when there is a greater chance to modify the disease course.

Poster 32

Altered in vivo binding of [11C]yohimbine to α2-adrenoceptors in a rat model of epilepsy

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Background: Noradrenaline reduces neuronal excitability, has anticonvulsant effects and is protective against seizure onset.

Objectives: The aim of the study was to investigated the role of α2-adrenoceptors in vivo in a neonatal domoic acid (DOM) rat model of epilepsy.

Methods: We injected male Sprague-Dawley rats daily from postnatal day 8-14 with saline or one of two sub-convulsive doses, 20µg/kg (DOM20) or 60µg/kg (DOM60) DOM, an AMPA/kainate receptor agonist. Rats were observed in open field, social interaction and forced swim tests at day 50, 75 and 98, respectively. At ~120 days of age, 4 rats per group were injected and scanned with [11C]yohimbine, an α2-adrenoceptor antagonist, and scanned in a Mediso micro positron emission tomography (PET) scanner to measure α2-adrenoceptor binding.

Results: DOM60-treated rats spent more time in the periphery during the open field test and had a significant 26-33% reduction in [11C]yohimbine binding in the hypothalamus, hippocampus and orbital prefrontal cortex compared to saline-treated rats. On the other hand, DOM20 rats had a significant 34-40% increase in [11C]yohimbine binding in the hypothalamus, amygdala and entorhinal cortex compared to saline-treated rats, with no obvious behavioural differences.

Conclusion: In conclusion, the current data clearly indicate that low concentrations of DOM given to rats in their second week of life induces long-term changes in α2-adrenoceptor binding in rat brain that may have relevance to the progression of an epilepsy phenotype.

Poster 33

A translational study of probiotics as antidepressiant treatment

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Background: The gut microbiome and its impact on human health and disease have received increasing attention over the past few years. Recent studies reported a favorable effect of probiotics (beneficial gut bacteria) on brain function and emotional states in both preclinical and clinical studies. Healthy subjects receiving probiotics showed reduced stress-induced gastrointestinal symptoms, decreased depression-and anxiety ratings, reduced cognitive reactivity to sad mood, lower brain activity in networks controlling central processing of emotion and sensation, and lowered urinary free cortisol. Overall, those studies yielded promising results regarding psychiatric symptom reduction with probiotic treatment.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Objectives: We propose that probiotics can reduce depressive-like behavior in both animal models of depression as well as a clinical sample of depressed patients given add-on probiotic treatment.

Methods: Aiming at creating a potential biomarker profile, this study will collect physiological measurements during probiotic vs. placebo treatment, including in-depth analysis of metabolomics, blood samples, pyrosequencing of fecal samples and brain wave activity using EEG.

Results: Results of the preclinical study are expected to be available in late 2016, while the clinical study will be conducted from 2017.

Conclusion: In a "from bench to bedside and back again" manner, we will use a unique translational approach where preclinical and clinical study complement one another to improve clinical efficacy. Overall, we hope to establish probiotics as a cost-effective, healthy add-on treatment for patients suffering from depression and aim to identify biomarkers that can reliably predict treatment response.

Poster 34

Anxiolytic-like effects after vector-mediated overexpression of Neuropeptide S in the amygdala

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Background: Anxiety disorders have a lifetime prevalence of almost 30% and pose a huge burden on both patient and society. Available treatment options commonly induce adverse effects, urging the need for novel compounds. Neuropeptide S (NPS) is highly distributed in key areas mediating anxiety and has attracted attention due to its anxiolytic properties demonstrated in rodents.

Objectives: The present study investigated the impact of NPS overexpression on anxiety-related behavior by infusing a recombinant adeno-associated virus (rAAV) into the medial amygdala.

Methods: Using stereotaxic surgery, viral vectors (rAAV-NPS vs. rAAV-Empty) were bilaterally injected into the medial amygdala of male adult Wistar rats using a thin glass micropipette. Behavior was characterized using standard anxiety, locomotion and depression tests. Immunohistochemical stainings were performed to verify overexpression of NPS. Statistical significance of differences between treatment groups was assessed using an independent samples t-test.

Results: Results showed that the experimental group (rAAV-NPS) spent significantly more time on the open arm in the Elevated Plus Maze (EPM) compared to the control group (rAAV-Empty), indicating an anxiolytic effect of NPS ($p=.018$). Importantly, this anxiolytic effect could be delineated from locomotion, since no treatment differences across conditions were observed in the Open Field test. Similarly, no confounding effects could be found when measuring body weight or depression-related behavior. Histology revealed NPS-positive cells in the medial amygdala in the experimental but not control group, suggesting successful transduction.

Conclusion: This is the first study successfully demonstrating anxiolytic properties of NPS via transgenic overexpression. Our results are largely consistent with studies elucidating the role of NPS in acute treatments, therefore providing evidence for the validity of both our viral vector and distinct long-lasting mechanisms of NPS. In sum, NPS remains an attractive candidate for novel compounds targeting anxiety pathophysiology.

Poster 35

Functional and morphological changes induced by ketamine in the rat hippocampus

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Background: Depressive disorders constitute a major burden for society in terms of productivity and years lost to disability. However, despite decades of research, the neurobiology of depressive disorders is largely unknown.

https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Recently it was shown that ketamine (KET), a non-competitive NMDA receptor antagonist, originally introduced as a dissociative anesthetic, induces a rapid (within hours) and sustained (up to 1 week) antidepressant effect in patients with treatment-resistant depression. The mechanism by which KET ameliorates depressive symptoms is still unclear. Therefore, the aim of the current study is to provide a morphological and functional characterization of the effect of ketamine in the hippocampus (HPC) of naïve rats.

Objectives: To measure changes in basal and depolarization-evoked endogenous glutamate (Glu) release in parallel with assessment of alterations in synaptic morphology induced by acute KET in the HPC of naïve rats.

Methods: Glu release experiments were assessed using purified synaptosomes in superfusion. Purified HPC synaptosomes were layered on microporous filters in parallel superfusion chambers and superfused with standard medium. A 90-sec period of stimulation with KCl was applied. Fractions collected were analyzed for endogenous Glu content by HPLC. For morphological analysis, one hemisphere per animal was processed for Golgi staining. The areas of interest were delineated using a light microscope (Olympus BX50). Collapsed Z-stacks were analyzed with IMARIS 7.6.

Results: Our preliminary results show that a single injection of KET modulates evoked Glu release. We are currently investigating morphological correlates in terms of dendritic morphology, spine types and spine density.

Conclusion: With this study we aim at dissecting the role of a single injection of KET on Glu system. This study will help to understand the mechanisms beyond the action of this drug.

Poster 36

Neuromedin U regulate alcohol intake and alcohol-induced reward in rodents via the mesolimbic dopamine system

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Background: Background: Alcohol use disorder (AUD) is characterized by compulsive drug seeking, loss of control and craving. The social-economic burden for this relapsing psychiatric disorder is substantial and the clinical efficacy of available medications is limited. By investigating the neurochemical mechanisms through which alcohol activates the cholinergic dopaminergic reward link (cholinergic projection from the laterodorsal tegmental area (LDTg) to the ventral tegmental area (VTA) together with dopaminergic neurons of the VTA projecting to the nucleus accumbens (NAc)) novel targets for treatment of AUD may be identified. In contrast to the common view of the function of gut-brain peptides, such as neuromedin U (NMU), to regulate food intake and appetite a novel role in reinforcement mediation has been implied.

Objectives: Objectives: Given that the anorexigenic effects of NMU are mediated via NMU2 receptors, which are expressed in several reward related areas in the brain, we hypothesize that these receptors in the reward related area might regulate alcohol reinforcement.

Methods: Methods: The present series of experiments were designed to evaluate the effect of local administration of NMU, into the NAc, VTA or LDTg on alcohol-induced locomotor stimulation, expression of conditioned place preference (CPP) as well on food intake in mice. In addition, the effect of NMU into NAc on alcohol consumption was evaluated in rats.

Results: Results: Local administration of NMU into the NAc significantly attenuated alcohol-induced locomotor stimulation, expression of CPP and reduced intake of palatable food in mice as well as reduced alcohol intake in rats. Intra-VTA or intra-LDTg NMU administration had no effect on alcohol-induced locomotor stimulation, expression of CPP or intake of palatable food. However, Intra-VTA or intra-LDTg NMU administration reduced the intake of normal chow in mice.

Conclusion: Conclusions: Collectively, these data suggest that intra-NAc NMU administration, rather than intra-VTA and intra-LDTg, had an effect on alcohol reinforcements and palatable food. It could be suggested that accumbal NMU2 receptors are involved in the development of AUD.

Poster 37

The 22q11.2 deletion syndrome: genetic subtyping and implications for decision on psychopharmacological treatment strategy

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https://doi.org/10.1017/neu.2016.18 Published online by Cambridge University Press

Background: The 22q11.2 deletion syndrome (22qDS), mostly caused by the *common* deletion (LCR-A-D) and including *TBX* and *COMT* genes, is highly associated with congenital anomalies and endocrine dysfunctions. The *distal* deletion (LCR-D-H) comprises the *MAPK1* gene and is associated with specific heart defects. The relatively rare *central* deletion (LCR-B-D), encompassing the *CRKL* gene, shows predominantly renal and urogenital anomalies. The 22q11.2DS subtypes differ also in their neuropsychiatric profile, in that the common is accompanied by schizophrenia-like psychoses and autism spectrum disorders, the distal by anxiety disorders, and the central by autistic-like behaviours.

Objectives: Investigating genetic subtypes of 22q11DS in order to ascertain the most appropriate psychopharmacological strategy.

Methods: Thirty patients with genetically proven 22q11DS were referred for detailed neuropsychiatric analysis.

Results: Apart from one distal and one central deletion, common deletion was found in 28 patients. The patients presented with a variable level of intellectual disability. Patients with common deletion had a history of relapsing schizophrenia-like psychoses, partial or non-responsive to conventional antipsychotics, and often accompanied by anxieties and mood instability. The patient with distal deletion displayed anxiety symptoms, whereas in the one with central deletion, autistic-like behaviour was present. Most patients with common deletion could effectively be treated with clozapine or quetiapine, often combined with valproic acid. The patient with distal deletion showed full remission upon treatment with citalopram whereas in the patient with central deletion, behaviour improved with contextual measures only.

Conclusion: Psychopharmacological treatment of psychopathology in patients with 22q11DS should be guided primarily by its genetic subtype.

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