# CINP 2018 Vienna World Congress

## Speaker Abstracts

*16th – 19th June*

*Austria Centre Vienna*

16TH – 19TH JUNE 2018 VIENNA WORLD CONGRESS

W: www.cinp.org E: cinp@cinp2018.org

# CINP 2018 – Speaker Abstracts

## Sunday 17th June 2018
## 08.45-09.30
## PL01: The environment and resilience against mental illness
Chair: John Krystal, USA

### Speaker: Andreas Meyer Lindenberg, Germany

**Abstract**
The size and burden of mental illness should ideally prompt a strategy of preemption and early intervention. On the neuroscientific side, this leads to the question of brain mechanisms of risk and resilience for these common and disabling disorder. In this presentation, we review emerging evidence that combines epidemiology, social psychology and neuroscience to bring neural mechanisms of social risk factors for mental illness into focus. In doing so, we discuss existing evidence on the effects of common genetic risk factors in social neural pathways and outline the need for integrative approaches to identify the converging mechanisms of social environmental and genetic risk in brain. On the environmental side, we focus on exposures that have a presumed social component such as urbanicity, migration/refugee status and social status. We propose a specific risk and resilience circuit mediating these effects that links perigenual cingulate cortex to subcortical structures such as ventral striatum and amygdala as well as dorsolateral and anterior medial prefrontal cortex.

*Ref.: Tost, H., Champagne, F. A., & Meyer-Lindenberg, A. (2015). Environmental influence in the brain, human welfare and mental health. Nat Neurosci, 18(10), 1421-1431. doi:10.1038/nn.4108*

## Sunday 17th June 2018
## 09.45-11.30
## S1: GABA regulation: from mechanisms to novel therapeutic targets
Chair: Oliver Howes, Germany
Co-Chair: Thomas Klausberger, Austria

### Speaker 1: John Cryan, Ireland
**Title:** *GABA and stress resilience- The role of GABA B*

**Abstract**
Stressful life events increase the susceptibility to developing psychiatric disorders such as depression; however, many individuals are resilient to such negative effects of stress. Determining the neurobiology underlying this resilience is instrumental to the development of novel and more effective treatments for stress-related psychiatric disorders. GABAB receptors are emerging therapeutic targets for the treatment of stress-related disorders such as depression. These receptors are predominantly expressed as heterodimers of a GABAB(2) subunit with either a GABAB(1a) or a GABAB(1b) subunit. Here we show that mice lacking the GABAB(1b) receptor isoform are more resilient to both early-life stress and chronic psychosocial stress in adulthood, whereas mice lacking GABAB(1a) receptors are more susceptible to stress-induced anhedonia and social avoidance compared with wild-type mice. Stress resilience in GABAB(1b)(-/-) mice is coupled with increased proliferation and survival of newly born cells in the adult ventral hippocampus and increased stress-induced c-Fos activation in the hippocampus following early-life stress. GABAB1a-/- mice also demonstrated profoundly blunted hypothermic and motoric responses to 8-OH-DPAT. Furthermore, 8-OH-DPAT-induced corticosterone and adrenocorticotropic hormone (ACTH) release were both attenuated in GABAB(1a)-/- mice. [35S]GTP-γ-S autoradiography suggested that altered 5-HT1AR G-protein coupling only partially contributes to the functional presynaptic 5-HT1AR desensitization, and not at all to the blunted postsynaptic 5-HT1AR-mediated responses, seen in GABAB(1a)-/- mice. Taken together, the data suggest that GABAB(1) receptor subunit isoforms differentially regulate the deleterious effects of stress and, thus, may be important therapeutic targets for the treatment of depression.

### Speaker 2: John Krystal, USA
**Title:** *Human cortical GABA systems in alcohol response and alcohol dependence.*

**Abstract**
Ethanol is a small molecule that has complex effects on the brain and that causes big problems when used in maladaptive ways. This presentation will review the state of the evidence that ethanol effects on GABA systems contribute to both intoxication, tolerance, dependence, and withdrawal. It will begin by reviewing data from animals and humans suggesting that ethanol potently facilitates the function of extrasynaptic GABA-A receptors and suppresses cortical GABA levels. This presentation will review data from preclinical studies suggesting that alterations in GABA-A receptor subunit composition, rather than alterations in GABA-A receptor number, account for tolerance by reducing the neural sensitivity to ethanol. This reduction reflects the shift from low-potency, high-conductance chloride channels to

high-potency, low-conductance channels. During ethanol withdrawal, the mechanisms that produce tolerance by reducing neural inhibition are inadequate to compensate for increased glutamatergic tone that contributes to withdrawal symptoms, including seizures. We provide evidence that suggests that during the first week of human withdrawal, we see evidence that the more effective receptors are recruited in association with the abatement of withdrawal symptoms. This presentation also highlights interactions between smoking and alcohol use that protect against GABAergic adaptations, perhaps promoting the comorbidity of smoking and drinking. Interestingly, this protective effect is mediated by a substance in tobacco smoke other than nicotine.

## Speaker 3: Oliver Howes, Germany

**Title:** Human cortical GABA systems in alcohol response and alcohol dependence.

**Abstract**

Background: Converging lines of preclinical, genetic, pharmacological and clinical evidence implicate dysregulation of GABAergic function in the pathoetiology of schizophrenia. In particular, hypofunction of parvalbumin positive GABAergic interneurons regulating the control of subcortical dopaminergic function has been proposed as a mechanism underlying the onset of the disorder. The current studies using translational imaging approaches to test this hypothesis in two complementary studies. Study 1 comprises a PET study in patients with schizophrenia; and study 2 comprises a PET study in mice treated with ketamine to block NMDA receptors on GABA interneurons and using chemogenetic manipulations.

Methods: Study 1 used PET imaging with [11C]-Ro15, a PET tracer selective for the GABA A receptors, in patients with schizophrenia and controls. Study 2 used [18F]-DOPA PET imaging in mice who had received sub-chronic ketamine treatment. Chemogenetic techniques were used to manipulate the circuit thought to be activated.

Results: Study 1: RO15 volume of distribution in brain was reduced in patients relative to matched controls. Study 2: ketamine increased dopamine synthesis capacity in the striatum, and this required activation of midbrain dopamine neurons. Moreover, parvalbumin levels were reduced in cortical projection regions.

Conclusions: These findings indicate that there is reduced GABA function in schizophrenia, and show that ketamine treatment increases striatal dopamine synthesis capacity, similar to levels seen in patients with schizophrenia, and show that this involves a cortico-midbrain circuit..

## Speaker 4: Jackie Borg, Sweden

**Title***: The role of GABA in autism spectrum disorders*

**Abstract**

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterised by impairments in social communication and interaction alongside restricted and repetitive behaviours and interests. The prevalence of ASD prevalence is estimated at approximately 1% of children and adults world-wide, and each individual with of ASD is associated with an estimated cost for society of around $1.5 million. Currently, there is no pharmacological treatment for the core symptoms of ASD and drug discovery has been hampered by poor understanding of the pathophysiology of the condition. Findings from gene, post mortem and brain imaging studies have suggested that GABA neurotransmission, particularly the $GABA_A$ receptor, is deficient in ASD. However, human studies have hitherto been confounded by medication and co-morbidity of intellectual disability and epilepsy. Hence, we have measured $GABA_A$ and $GABA_A$ α5 receptor availability using Positron Emission Tomography (PET) with [$^{11}$C]flumazenil and [$^{11}$C]Ro15-4513 in a homogenous sample of medication-free adults with ASD and normal IQ and control subjects matched for age, gender and non-verbal IQ. We found no significant differences between ASD individuals and controls in $GABA_A$ receptor availability, or the $GABA_A$α5 subtype, in any brain region. Our results are thus not in line with the hypothesis of $GABA_A$ involvement in ASD, and suggest that other targets may be more promising in the search for ASD biomarkers and treatments.

## Sunday 17th June 2018
## 09.45-11.30
## S2: The use of technology in mental illness and mental wellbeing

Chair: Barbara Sahakian, UK
Co-Chair: Katharina Domschke, Germany

## Speaker 1: Barbara Sahakian, UK

**Title:** *Cognitive training using a game on an iPad in Schizophrenia and mild cognitive impairment*

**Abstract**

While many people monitor their physical health using mobile devices and wearable technology to preserve their physical health throughout their life course, they rarely consider improving and monitoring their brain health. If we are going to have good mental capital and wellbeing

throughout our lives, it is imperative that we consider mental health as being every bit as important as physical health and move to game-changing initiatives which include early detection and early effective treatment of neuropsychiatric disorders (Narayan and Manji 2016; Beddington et al 2008; Sahakian 2014). Major approaches will include biomarkers, including cognitive ones, for early detection, but also will utilise novel pharmacological and also technological approaches to treatment, including neuroprotective drugs for Alzheimer's disease, fast acting antidepressant drugs for depression, cognitive enhancing drugs and game apps for delivering cognitive training on mobile phones or tablets in schizophrenia and other neuropsychiatric disorders (Savulich et al 2017; Sahakian et al 2015; National Academies of Sciences Engineering and Medicine 2015; Insel et al 2013; Bruhl and Sahakian 2016). Cognitive training of memory using games can improve memory, motivation and psychosocial functioning in patients with schizophrenia or amnestic mild cognitive impairment (aMCI) (Savulich et al 2017; Sahakian et al 2015). Using game technology makes it possible to individualize cognitive training programmes by titrating the level of difficulty of play, so the game maintains motivation. In changing the framework by moving to early detection and early effective treatment, we can stop these mental health disorders becoming debilitating, chronic and relapsing. Using these novel pharmacological and non-pharmacological treatment approaches, we can ensure that patients with neuropsychiatric disorders have better quality of life, functionality and wellbeing. Not only can innovation and technology promote a flourishing society, but could also reduce the cost and burden of neuropsychiatric disorders for governments.

## Speaker 2: Andreas Meyer Lindenberg

**Title:** *New technologies: application to mental health and resilience*

## Speaker 3: John O'Brien, UK

**Title:** *Wrist-worn activity measurement as a potential biomarker for late life depression*

**Abstract**

Late-life depression (LLD) is associated with a decline in physical activity and social withdrawal. Typically these are assessed by self-reported questionnaires and, more recently, with actigraphy. We sought to explore the utility of a bespoke activity monitor to characterise activity profiles and social interaction (specifically for speech) in people with LLD.

A bespoke activity and speech monitor was developed, validated and then worn for seven days by 29 adults with LLD and 30 healthy controls. Subjects underwent neuropsychological assessment, quality of life and activities of daily living (ADL) and social questionnaires.

Physical activity was significantly reduced in subjects with LLD compared to controls, primarily in the morning. Those with LLD showed slower fine movements ($p<0.001$), and activity reductions were related to impairments in ADL and lower quality of life. The device proved a feasible mechanism to capture speech as well as physical activity, for which analysis is ongoing.

In conclusion, subject with LLD had a significant reduction in physical activity compared with controls as assessed by a wrist-worn device. Such devices can also capture other elements of daily activity, including assessments of sleep and social engagement, in an objective and convenient way. This would suggest that novel wearable technology has the potential to provide an objective way of monitoring real world function and has potential both for naturalistic clinical studies and as an outcome measure for therapeutic interventions.

## Speaker 4: Ellen Frank, USA

**Title:** *Real life monitoring for mental health*

**Abstract**

Ellen Frank, PhD[1,2], Mark Matthews, PhD[2], Michael Merrill, BS[2], M. Hane Aung, PhD[2], Noshirwan Petigara, MBA[2], Tanzeem Choudhury, PhD[2,3]

*[1]University of Pittsburgh School of Medicine, [2]HealthRhythms, Inc., [3]Cornell University*

In outpatient contexts, mental disorder symptoms and syndromes have typically been assessed using self-report or clinician-administered instruments at frequencies varying from weekly to every few months. The constraints associated with these methods, including repeat testing bias, patient burden, costs of clinician time and, perhaps most important, the fact that the arbitrary timing of such assessments may miss critical changes in levels of symptom severity have long been recognized, but few viable alternatives were available. In the last decade, however, a number of technologic advances have permitted truly revolutionary solutions to these constraints. Smartphones are ubiquitous and highly personal devices, equipped with sensors that offer an opportunity to measure and understand changes in key behaviors on a 24/7 basis, in real-world

contexts, and over long periods of time with essentially no effort on the part of patients. Furthermore, advanced computer technology makes it possible to summarize and interpret the data obtained from those sensors in a manner that permits nearly instantaneous understanding of the patient's status on the part of the clinician. In this presentation, we will first describe one program of such smartphone-based approaches to capitalizing on the sophistication of today's technology to better monitor and understand patients' mental health. Finally, we will present results from initial studies suggesting that such approaches lead to highly specific and personalized profiles of patients' clinical state and have the potential to lead to improved patient management and a clearer understanding of medication efficacy.

References
*Abdullah, S., Matthews, M., Frank, E., Doherty, G., Gay, G. and Choudury, T. Automatic detection of social rhythms in bipolar disorder. Journal of the American Medical Informatics Association, 2016.*
*Aung, H., Matthews, M., Frank, E., Forkish, C., Kupfer, D.J., Merrill, M and Choudhury, T. Continuous behavioral data as a potential depression biomarker. Poster presented at the Global Brain Health and Performance Summit. Columbus, OH, April, 2017*
*Frank, E., Merrill, M., Aung, H., Soares, C., Kennedy, S., Matthews, M., Kupfer, D.J., Lalovic, A., and Choudhury, T. Sensing depression: Using smartphone sensors to predict changes in depression severity. Poster presented at the Annual Meeting of the American College of Neuropsychopharmacology, Palm Springs, CA, December, 2017.*
*Murnane, E.L., Cosley, D, Chang, P., Guha, S., Frank, E., Gay, G. and Matthews, M. Self-monitoring practices, attitudes and needs of individuals with bipolar disorder: implications for the design of technologies to manage mental health. Journal of the American Medical Informatics Association, 2016*

## Sunday 17th June 2018
## 09.45-11.30
## S3: PTSD Genetics in a military context

Chair: Joel Gelertner, USA
Co-Chair: Joseph Zohar, Israel

### Speaker 1: Jurjen Luykx, Netherland

**Title:** *Dissecting the genetics of PTSD-related phenotypes using an extensively phenotyped, longitudinal dataset of Dutch military personnel*

**Abstract**
Military personnel are at increased risk of mental health symptoms and psychiatric disease following deployment. Lifetime post-traumatic stress disorder (PTSD) prevalence is estimated to be 30% in military personnel. PTSD is a heterogeneous disorder with a moderate heritability, affecting multiple biological systems and psychological domains. Genome-wide association studies (GWAS) applying a case-control design have so far provided limited insight into the genetic variants associated with post-traumatic stress. We therefore set out to perform genetic association analyses in a cohort of approximately 1,000 Dutch military personnel deployed to a war zone. Questionnaire data on mental health, such as self-reported PTSD symptoms, and plasma levels of biochemical molecules were collected prior to deployment and one month after deployment. We also generated genome-wide data from these subjects. Using Software for Correlated Phenotype Analysis (SCOPA), we performed a regression analysis applying a multiple-phenotype model containing post-deployment data corrected for pre-deployment measurements. We identified one genome-wide significant locus (rs10100651, $p = 9.9 \times 10^{-9}$), which also survived multiple sensitivity analyses. In addition, this locus replicated in the UK Biobank case-control GWAS on self-reported PTSD
($p = 0.02$). Furthermore, we found this locus to be a significant expression quantitative trait locus (eQTL) for four surrounding genes (*INTS8*, *CCNE2, TP53INP1, NDUFAF6*) in multiple tissues. *In vitro* stimulation of fibroblasts with dexamethasone then confirmed a genotype-independent effect of dexamethasone stimulation on expression of *NDUFAF6* and *INTS8*. In conclusion, we identified a credible stress-responsive locus using a multiphenotype analysis on post-traumatic stress in a Dutch military cohort. This locus may be followed up in preclinical studies with the ultimate aim of detecting novel pharmacological targets. Our approach may aid the discovery of novel variants associated with this heterogeneous disease as sample sizes and phenotype density in PTSD cohorts increase in the future.

### Speaker 3: Murray Stein, USA

**Title:** *Results Informative for PTSD-related traits from the Army Study to Assess Risk and Resilience in Service members (STARRS)*

**Abstract**
**Background**: Posttraumatic stress disorder (PTSD) is a prevalent, serious public health concern, particularly in the military. The identification of genetic risk factors for PTSD (and PTSD symptom domains) may provide important insights into the biological basis of vulnerability and comorbidity.

**Methods**: We conducted genome-wide analysis in two cohorts of soldiers in the Army Study of Risk and Resilience in Servicemembers (STARRS). The first analysis compared lifetime DSM-IV PTSD cases to trauma-exposed controls without lifetime PTSD, and the second compared lifetime maximum severity of 3 PTSD symptom domains (re-experiencing, avoidance, and hyperarousal) assessed by an abbreviated 6-item version of the PTSD Checklist (PCL-6). SNP-based heritability and genetic correlation among symptoms was estimated in the European American samples.
**Results:** For the PTSD case-control analysis we observed a genomewide significant locus in *ANKRD55* on chromosome 5 (rs159572; odds ratio [OR] = 1.62, p-value =$2.43x10^{-8}$ in the African American samples from NSS. We identified one locus associated with re-experiencing severity in the European American sample (top SNP rs2311207, β=0.226, P=$2.5x10^{-8}$) in an intergenic region on chromosome 18 (nearest genes *DYNAP* and *RAB27B*). SNP-based heritability was non-significant for the disorder, but was nominally or nearly significant for its components: 0.060 for re-experiencing (p=0.070), 0.043 for avoidance (p=0.138) and 0.085 for hyperarousal (p=0.019). We observed strong pairwise genetic correlations between the three PTSD symptom severity scores ($r_g$ = 0.80 to 1.00).
**Discussion:** By examining key symptom domains of PTSD, we observed a novel association with re-experiencing severity in a European American sample, though this was not seen in African American and Latino American samples. Our analyses also suggest that PTSD symptom domains have a largely shared genetic basis. Replications of these results in independent samples are needed.

### Speaker 4: Joel Gelernter, USA
**Title:** *Results from the USVA MVP PTSD Cooperative Study GWAS.*

**Abstract**
Posttraumatic stress disorder (PTSD) is a major problem among the veteran population and presents treatment challenges. The US Veterans Affairs (VA) Million Veteran Program (MVP) biobank currently has >620,000 consented participants, with genotyping in progress. PTSD symptoms are categorized into 3 major symptom clusters by DSM-IV criteria: intrusive re-experiencing, avoidance of trauma-associated stimuli, and alterations in arousal or reactivity. We conducted a GWAS on the re-experiencing symptom cluster score based on a sum of 5 items from the PTSD Checklist. This is the symptom cluster most characteristic of PTSD. After cleaning, 146,660 European-Americans (EAs) and 19,983 African-Americans (AAs) were retained. In EAs, 8 distinct common-variant genomewide-significant (GWS) regions were identified—three with significance >5x10E-10. These latter regions map to chrom. 3 – lead SNP rs2777888, gene *CAMKV*; chrom. 17 – lead SNP rs2532252, closest to *KANSL1* but within a well-known long high-LD region (the site of an inversion common in EAs) that also includes *CRHR1* (corticotropin releasing hormone receptor 1); and chrom. 18 – lead SNP rs2123392, at *TCF4*. Other GWS associations were observed at *KCNIP4, HSD17B11, MAD1L1*, and *SRPK2*. *TCF4* and *MAD1L1* have both previously been GWS-associated to schizophrenia and other psychiatric traits. There were no GWS associations in the smaller AA sample, but with EA-AA meta-analysis, the lead SNP in the region on chrom. 17 shifted to rs1724409 (and increased significance to 3.6E-11). This new lead variant is intronic at *CRHR1,* a very strong functional candidate for PTSD. *CRHR1* was also identified as significant in gene-based analyses. LD score regression analysis showed polygenic association with numerous psychiatric and behavioral traits.
These results provide new insight into the biology of the most characteristic PTSD symptom cluster in what is the best-powered study undertaken to date.

## Sunday 17th June 2018
## 09.45-11.30
## S4: ADHD across the lifespan- biological mechanisms underlying disease onset and persistence, implications for treatment
Chair: Barbara Franke, Netherlands
Co-Chair: Thomas Vanicek, Germany

### Speaker 1: Andreas Reif, Germany
**Title***: How ADHD changes its presentation across the lifespan*

**Abstract**
While ADHD in childhood is characterized by the "classical" symptom domains hyperactivity and inattention, it significantly changes its appearance during the life span. On the syndromatic level, hyperactivity tends to disappear while inattention may dominate the clinical picture. Also, emotional problems including mood dysregulation become relevant and often overshadow the appearance of the disorder's childhood symptoms. While these three symptom domains comprise the core ADHD syndrome in the adult patient, ADHD in this age group is often cloaked by comorbid conditions. These include, amongst others, most prominently

mood and anxiety disorders, substance use, obesity, and antisocial behavior. Notably, even when mood disorders are corrected for, adult ADHD patients have a significantly higher risk for suicidal behavior. In addition, the risk for accidents is meaningfully higher as compared to non-ADHD controls. As a consequence, ADHD patients have a significantly elevated risk for premature death. On the other hand, if circumstances are good and the patient is resilient, ADHD patients can also live very successful lives as evidenced by a number of high achievers. Treatment with stimulant can decrease the risk for most of the negative outcomes, despite not fully normalizing it. The factors predisposing to a bad-outcome trajectory, dominated by comorbidity, or good outcome, are not yet fully described and include biological as well as environmental influences. As disease modification to increase the likelihood of good outcome might be an amenable goal, this should be a clear research priority.

## Speaker 2: Martine Hoogman, Netherlands

**Title:** *Brain imaging of ADHD across the lifespan – results of the largest study worldwide from the ENIGMA ADHD Working Group.*

**Abstract**

Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD. However, these studies are often underpowered and heterogeneous in their methods. In this talk I will present data from the largest worldwide collaboration for research of the neural substrates of ADHD, the ENIGMA-ADHD Working Group. This collaborative consist of 37 cohorts, and more than 4000 subjects of all ages. I will show where in the brain (subcortical and cortical) there are structural differences between cases and controls in three different age groups; children, adolescents and adults. In addition, effects of clinical features such as presence of comorbid disorders, medication use and severity scores are shown. Knowing that ADHD is the extreme of a continuum, I also studied the association between cortical measures and ADHD symptoms scores of the Child Behaviour CheckList in the general population of children aged 9 and 10 years old (Generation R study, n=2900). The results of the clinical samples and the population sample show an interesting overlap. Finally, to learn more about brain differences being cause or consequence, I'll present brain data of unaffected siblings in relation to cases and healthy controls, in a subsample of ENIGMA-ADHD. These familiality analysis will shed light on the etiology of brain differences in ADHD.

## Speaker 3: Marta Ribases, Spain

**Title:** *Genome-wide association studies of ADHD across the lifespan - differences between the genetics of disease onset and persistence?*

**Abstract**

Attention-Deficit and Hyperactivity Disorder (ADHD) is among the most heritable psychiatric disorders. Given that around 65% of children diagnosed in childhood continue to suffer from ADHD during adulthood, we aim to identify the genetic influence on the stability of ADHD symptoms that may contribute to discern between ADHD subjects with and without symptomatic persistence using the genomic data from the International Multi-centre persistent ADHD CollaboraTion (IMpACT) and iPSYCH. In an attempt to unravel novel genes underlying persistent ADHD, we conducted a meta-analysis of GWAS for adult ADHD in a total sample of 6,619 cases and 15,976 controls. None of the findings exceeded the genome-wide threshold for significance (P<5e-08). Top hits included genes previously associated with cell adhesion, neurite formation or neuronal migration and differentiation. The SNP heritability for adult ADHD was estimated as h2=0.21 (S.E.=0.025), which is in line with previous estimates in children. The partition of SNP heritability by functional category showed nominal significant enrichment in the ADHD heritability by SNPs located in conserved regions and on specific histone marks. We also found evidence for a strong overlap in genetic risk variants between adult and children ADHD (rg=0.81 (SE=0.08); P-value=5.1e-21), supporting a shared genetic background. These data suggest that common genetic variation is involved in the etiology of the persistent form of the disorder and that many risk loci exert shared effects on ADHD through lifespan. We also identified genetic correlation between adult ADHD and other psychiatric disorders and related traits including major depressive disorder, neuroticism, risk taking, smoking, years of schooling, intelligence or childhood IQ. Prospective studies of children with ADHD may discern between individuals with and without symptomatic remission and will provide more insights into the genetic influence on the stability of ADHD symptoms.

### Speaker 4: Barbara Franke, Netherlands

**Title:** *Epigenetic DNA-methylation in humans with ADHD: biomarker or more?*

**Abstract**

**Background:** Epigenetics describes the modification of DNA and chromatin that regulates the expression of genes and in that way contributes to the maturation and function of cells. Epigenetic modifications are partly determined by genetic factors, but also represent a way by which gene expression can be modified in response to environmental influences. DNA-methylation is the most stable form of epigenetic modification and is increasingly studied for its potential involvement in psychiatric disorders, including ADHD. However, with DNA-methylation being highly celltype-specific, investigating the role of epigenetics in brain disorders is challenging in humans.

**Methods:** In this presentation, I will introduce the basic principles of epigenetic modifications and the role of genetics and environmental factors in determining epigenetic profiles of cells. I will then present a review the existing research on DNA-methylation in ADHD and related psychiatric disorders.

**Results:** Recent studies of candidate genes suggest that the methylation of some of these genes may be altered in ADHD. However, most of these studies have very limited sample sizes. In addition, first epigenome-wide studies suggest new candidate genes for ADHD as well as for longitudinal symptom profiles of ADHD symptoms in the population. In schizophrenia, where the study of DNA-methylation is further advanced, replicated studies indeed confirm a role for altered DNA-methylation in disease risk.

**Conclusion:** Epigenetics is an interesting new area of research in psychiatric disorders. With those disorders being influenced by both genetics and environmental factors, the study of epigenetic modifications can provide insight into mechanisms underlying gene-environment interactions and may explain, how (early) environmental insults can have lasting effects on the brain.

## Sunday 17th June 2018
## 09.45-11.30
## S5: CINP initiative for public private partnerships (PPPs) for innovative CNS drug development

Chair: Shigeto Yamawaki, Japan
Co-Chair: Peter Falkai, Germany

---

### Speaker 1: Shigeto Yamawaki, Japan

**Title:** *CINP initiative for public private partnerships (PPPs) for innovative CNS drug development*

**Abstract**

In 2014 CINP published “Innovative Public Private Partnerships (PPPs) to accelerate CNS drug discovery for improved patient care” in Nature Review Drug Discovery 13:871-872 (2014) and “10 action-points” in the White Paper in International Journal of Neuropsychopharmacology 18:1-16 (2015) as a result of extensive discussion and collaboration with Academia, Industry and Regulators to address the sluggish CNS drug development. Similar initiatives have been also developed such as NEWMEDS project of Innovative Medicines Initiative in Europe and Biomarker Consortium in the US. To promote a PPPs initiative in Asia, CINP CNS Drug Innovation Summit was held in Tokyo in 2015, which led an establishment of a PPPs taskforce by Japanese Society of Neuropsychopharmacology (JSNP). More than 20 Japanese pharma companies joined the taskforce activity where development of imaging biomarker, neuroscience-based stratification, and database and its sharing system have been discussed. At the same time Brain and Mind Sub-Committee of Japan Science Council also recognized the importance of such initiative and compiled “Proposal of the model of private public partnerships to develop treatment of neuropsychiatric disorders” in July 2017. In this symposium, the outcome of the JSNP PPPs Taskforce activities will be reported and also the future perspective of PPPs toward CNS drug development using AI technology to analyze big data will be presented.

### Speaker 2: Tetsuya Suhara, Japan

**Title:** *The role of imaging biomarker in the drug development process*

**Abstract**

Neuroimaging biomarkers have played important roles in aiding CNS drug development. We proposed a new paradigm containing 5 distinct tiers to further clarify the use of biomarkers and establish new strategies for decision-making in

the context of CNS drug development (Int J Neuropsychopharmacol 2017: 285–294). The imaging biomarker can provide translational information between animal models and patients and sometimes essential to determine optimal dosing and patient stratification. Within several imaging methods, PET can provide direct molecular information using specific radioligands. However, available ralioligands for various drug targets are limited and the development of ideal radioligands for target molecule or biological effect is not easy for single drug company. Recently National institutes for Quantum and Science and Technology (QST) in Japan developed alliance based on the concept of public-private-partnerships. This is a unique system in the collaboration, since the initial discussion is open among 14 drug companies. Usually each drug company has different interest and collaboration is made between single academia and single drug company. In this relation, the style of confidential agreement and handling intellectual property has been established. However, the collaboration style among several different companies has not been established yet. This presentation will review the role of imaging biomarker in the drug development process and several critical points in the collaboration among different drug companies whether this kind of alliance can work or not.

## Speaker 3: Christer Halldin, Sweden

**Title:** *Translational PET Neuroimaging for Drug Development*

**Abstract**

PET provides a new way to image the function of a target in a translational way from mouse to man, and by elevating the mass, to pharmacologically modify the function of the target. The main applications of PET radioligands in brain research concern human neuropsychopharmacology and the discovery and development of novel drugs to be used in the therapy of psychiatric and neurological disorders. A basic problem in PET brain receptor studies is the lack of useful radioligands with ideal binding characteristics. Prerequisite criteria need to be satisfied for a radioligand to reveal target binding sites in vivo. Molecular biological techniques have now revealed the existence of hundreds of novel targets for which little or no prior pharmacological or functional data existed. Most of the currently used drugs for the treatment of psychiatric and neurological disorders interact with central neurotransmission. Several receptor subtypes, transmitter carriers, and enzymes have proven to be useful targets for drug treatment. Due to the lack of data on the functional significance of these sites, pharmacologists are now challenged to find the physiological roles of these receptors and identify selective agents and possible therapeutic indications. This presentation will review recent examples in translational PET neuroimaging for drug development with focus on the collaboration between academia and pharma. In Europe, public-private-partnerships (PPPs) is exemplified by Innovative Medicines Initiative (IMI) in which academics are collaborating with European Federation of Pharmaceutical Industries and Associations (EFPIA) with support from EU. One successful example of IMI was “Novel Methods leading to New Medications in Depression and Schizophrenia”. Drug research now benefits from the fast development of functional imaging techniques such as PET.

## Speaker 4: Johannes Tauscher, USA

**Title:** *Role of Public-Private Partnerships for Imaging biomarker development and sharing from the Pharmaceutical Industry perspective*

**Abstract**

Imaging biomarkers are used in R&D of Pharmaceutical Companies for critical decision-making in both, preclinical drug discovery, as well as in translational and clinical drug development. In the context of drug discovery and development for CNS disorders, mainly MR-based (structural and functional MRI, as well as MRS), and Positron Emission Tomography (PET) with appropriate and specific ligands, labelled mostly with either [$^{11}$C] or [$^{18}$F] have traditionally been used. Most pharmaceutical companies use these imaging biomarkers as tools for drug discovery and development, and do not pursue commercialization of those probes. Therefore, Imaging biomarkers lend themselves to sharing between Academia and Pharmaceutical companies, as their commercial value is limited. Furthermore, usually Imaging biomarkers are co-developed for a therapeutic target, and require resource intensive commitment to assay discovery, development and validation. If as part of a public-private partnership (PPP), that biomarker is in turn more widely used to better understand the target, both the originator and the public will profit from advancing science and general understanding of the underlying pathophysiology of CNS disorders, thereby offsetting potential concerns around “giving away” a conceived competitive advantage by not aggressively protecting confidentiality of a novel Imaging biomarker. Historically, the American College of Neuropsychopharmacology (ACNP) with an effort to serve as a Radiotracer Clearinghouse, the National Institutes of Mental Health (NIMH) as well as the FNIH biomarkers initiative, and various public private partnerships, such as e.g. the Alzheimer’s Disease

Neuroimaging Initiative (ADNI) or MIND MAPs sought to increase awareness for sharing and disseminating knowledge around the use of Imaging biomarkers for CNS drug development.

## Sunday 17th June 2018
## 09.45-11.30
## CP01: Addiction

Chair: Helena Calil, Brazil
Co-Chair: Konstantinos Papageorgiou, Austria

### Speaker 1: Toshikazu Saito, Japan

**Title:** *Definition, Diagnosis and Treatment of Alcohol Addiction*

**Abstract**

The lecture composed of concept/definitions, biomarkers, screening, treatment and biological basis of alcohol dependence. Concept and definitions: The concept and classification of alcoholism has undergone a series of changes over the decades. In 1977, WHO organized an expert conference and presented the concept of alcohol dependence and alcohol related disabilities. This concept of alcohol dependence influenced ICD-10 and DSM-3 and-4 diagnostic criteria. There are similarities between DSM-4 and ICD-10 diagnostic criteria of alcohol dependence, however, the recently published DSM-5 has abandoned the concept of dependence. Diagnostic criteria of DSM-5 consist of all diagnostic items from alcohol dependence, three diagnostic items from alcohol abuse and craving. Threshold level of DSM-5 criteria of alcohol use disorder lower than the those of alcohol dependence of DSM-4 and ICD-10. Biomarkers: State and trait (including Endophenotypes) markers and its clinical significance will be discussed. Screening test: It'll be introduced several tests and their significance. Treatment: Psychotherapies, pharmacotherapies and self-help groups will be discussed. We will discuss a goal of treatment, brief intervention, group therapy and occupational therapy as psychotherapies for alcohol dependence (alcohol use disorder). Pharmacotherapies for management of alcohol withdrawal syndrome and consumption reduction and relapse prevention will be also discussed. Biological basis: Inhibition on neuro-stem cell differentiation by ethanol will be discussed as a biological basis of alcohol dependence.

### Speaker 2: Hisatsugu Miyata, Japan

**Title:** *The structure of craving for substance and behavioral addiction*

**Abstract**

In this session, the clinical features and treatment of substance addiction (addiction to methamphetamine, heroin, nicotine, etc.) and behavioral addiction (addiction to gambling, internet gaming, etc.) are reviewed, and the similarities and differences of the two types of addiction are discussed from the perspective of the structure of craving. The structure of craving is considered to be composed of three determinants: the primary reinforcing property, the secondary reinforcing property, and the negative affective motivational property during withdrawal. Firstly, the primary reinforcing property of a substance of abuse was investigated by a self-administration experiment, and the magnitude of the primary reinforcing property was reported to be in order of heroin, cocaine, amphetamines, alcohol, and nicotine. However, it is difficult to define or determine the primary reinforcing property in behavioral addiction. Secondly, the second determinant of the structure of craving is the secondary reinforcing property of a substance or behavior (i.e. conditioned aspects of the environment, such as contextual or specific cues associated with either substance taking or experience of the behavior). Both substance and behavioral addiction show a robust conditioning property. Thirdly, regarding the third determinant in eliciting craving, the negative affective motivational property during withdrawal, behavioral addiction produces negative affective symptoms with a lesser degree of somatic withdrawal signs than substance addiction. As for the nature of secondary conditioning processes and the negative motivational aspects of withdrawal, both substance and behavioral addiction have similar characteristics. Treatment strategies are discussed using the putative structure of craving.

**Sunday 17th June 2018**
**14.45-16.30**
**S6: New approaches in transcranial magnetic stimulation for depression**
Chair: Siegfried Kasper, Austria
Co-Chair: George Kranz, Austria

## Speaker 1: Linda Carpenter, USA

**Title:** *Clinical insights to TMS therapy in depression*

**Abstract**
In 2008, the US FDA approved the first device for delivery of Transcranial Magnetic Stimulation (TMS) for treatment of medication-resistant major depressive disorder (MDD). Today, there are multiple TMS devices approved for depression and numerous other devices and stimulation protocols in various stages of development and clinical trial testing. TMS therapy involves application of pulsed MRI-strength magnetic energy fields in awake patients, to stimulate specific regions and circuits in the cortex. Data from industry- and government-sponsored multicenter trials show efficacy and safety of TMS for patients with pharmacoresistant MDD. In this presentation, we will review data from TMS clinical trials that have shaped the emergence of this novel therapy as a standard of care in modern psychiatry practice. Outcome data from TMS depression studies will be described, along with research examining ways to optimize TMS treatment for depression. Published consensus recommendations and guidelines will be highlighted to describe the steps involved in routine TMS clinical care.

## Speaker 2: Katharine Dunlop, Canada

**Title:** *Optimizing rTMS for accelerated antidepressant response*

**Abstract**
Repetitive transcranial magnetic stimulation (rTMS) is a form of non-invasive brain stimulation that uses focused magnetic field pulses to alter brain activity. Over 20 years of clinical trials have demonstrated the antidepressant effects of rTMS, specifically when targeting the dorsolateral prefrontal cortex (DLPFC) or dorsomedial prefrontal cortex (DMPFC). Conventional rTMS protocols to treat psychiatric disorders typical involve DLPFC or DMPFC stimulation lasting at least 30 minutes, once daily, for 4-6 weeks. However, recent studies have sought to improve costs, capacities, and outcomes by applying briefer rTMS protocols like theta burst stimulation, or by shortening a single course of rTMS by offering multiple rTMS sessions each day. The aim of this symposium talk will be to discuss trials in which accelerate rTMS protocols have been employed and highlight the advantages and limitations of accelerated rTMS in comparison to conventional rTMS protocols.

## Speaker 3: George Kranz, Austria

**Title:** *rTMS, monoaminergic neurotransmission and neuroplasticity*

**Abstract**
In this talk I will give an overview of present and past research focused on rTMS and other forms of TMS and their effects on monoaminergic neurotransmission in animals and humans. Several early studies in rodents indicate profound changes in dopamine release in the basal ganglia in response to acute rTMS. A handful of studies also investigated other monoamine transmitter systems such as serotonin and noradrenaline with mixed results. So far only few studies have been conducted to test such effects in humans. While it may be no surprise that rTMS affects most neurotransmitters and their receptors, which can be measured with PET in humans *in vivo*, the role for therapeutic efficacy of such effects still remain to be clarified. Hypotheses on the neuropastic effects of common pharmacological antidepressant strategies have yielded accumulating evidence indicating that neuroplasticity is, at least in part, controlled by monoaminergic neurotransmission, especially by serotonin. The standard model of the mechanism of action of rTMS endorses neuroplasticity as its essential component. By comparing physiological effects of antidepressant treatments including pharmacotherapy, electroconvulsive therapy and rTMS, I attempt to broaden our understanding of their shared mechanisms of action as a common ground for antidepressant treatment efficacy.

## Speaker 4: Mark George, USA

**Title:** *Refining the region stimulated and coordinating treatment with the brain state*

**Abstract**
This talk will cover new advances in determining the best location for treating depression, as well as coordinating stimulation with brain state. In terms of location, there has been progressive refinement of the best way to determine the left prefrontal cortex. These include anatomical or group EEG based approaches, as well as using individual resting state correlational maps with other subcortical regions. Additionally, evidence is growing that other prefrontal regions, including medial prefrontal, may also produce antidepressant effects. Turning to brain state, researchers are now combining TMS with either exposure (OCD, PTSD, Addictions) or cognitive behavioral therapy or exercise (depression). More

recent work attempts to match the exact TMS pulse to the person's EEG, either through matching their overall intrinsic alpha frequency (IAF), or timing the first pulse of each TMS train to the person's rising or falling EEG state. All of these approaches hold promise for improving acute efficacy or durability of this remarkable new approach to treating depression.

## Sunday 17th June 2018
## 14.45-16.30
## S7: New insights into the role of orbitofrontal cortex in compulsive behaviour psychopathology and its treatment

Chair: David Morilak, USA
Co-Chair: Andreas Reif, Germany

### Speaker 1: Catherine Winstanley, Canada

**Title:** *Deciphering decision making: when to bet on the orbitofrontal cortex*

**Abstract**

A unitary hypothesis regarding the role of the orbitofrontal cortex (OFC) in higher-order functions such as decision making has proved elusive. Increasingly sophisticated behavioural paradigms have been developed for use in laboratory rodents, and offer the opportunity to potentially isolate the factors which determine whether the OFC has a critical role to play in the decision-making process. Using a rodent analogue of the Iowa Gambling Task, in which rats have to avoid tempting "high-risk high reward" options to maximise their sugar pellet profits, we have found that lesions to the OFC, and also limiting connectivity between the OFC and basolateral amygdala (BLA), slow acquisition of the task, but do not prevent animals from ultimately acquiring a preference for the best options. As such, the OFC is not required to consistently maintain an optimal decision making strategy in a stable environment. In contrast, lesions to the BLA increase maladaptive, risky choice even after animals have learned the task. A dissociable patter of effects can be observed when silencing these brain regions on the rat betting task, which measures the simple preference for uncertain outcomes. Animals choose between the safe lever, which provides a guaranteed reward ("bet size"), and the uncertain lever which yields double the bet size, or zero reward, with 50:50 odds. As the bet size grows, a subset of animals shift their preference from the uncertain to safe outcomes even though such wager-sensitive behaviour is mathematically irrational, mimicking the escalation of commitment bias seen in humans. Inactivation of the OFC selectively reduces this decision making bias once it has been acquired. Silencing the basolateral amygdala, however, has no effect. As such, the OFC may be uniquely involved in mediating this kind of decision making phenomenon, which requires updating the value of outcomes according to subjective, rather than objective, criteria.

### Speaker 2: Francisco Sotres-Bayon, Mexico

**Title:** *Orbitofrontal cortex mediates choice behavior guided by taste memory*

**Abstract**

Survival and mental health depend on being able to choose stimuli not associated with danger. This is particularly important when danger is associated with stimuli that we ingest. Although much is known about the brain mechanisms that underlie associations with dangerous taste stimuli, very little is known about how these stored emotional associations guide behavior when it involves choice. By combining pharmacological and immunohistochemistry tools with taste-guided tasks, we found evidence for the key role of orbitofrontal cortex activity in choice behavior and show that this is dissociable from the adjacent insular cortex-dependent taste aversion memory. Understanding the brain mechanisms that underlie the impact that emotional associations have on survival choice behaviors may lead to better treatments for mental disorders characterized by emotional decision making deficits.

### Speaker 3: David Morilak, USA

**Title:** *A novel role for JAK-STAT signaling in reversal learning in the orbitofrontal cortex: Implications for new therapeutic mechanisms*

**Abstract**

Reversal learning is a form of cognitive flexibility mediated in the orbitofrontal cortex (OFC) that is impaired in depression and other stress-related psychiatric disorders. We have shown in rats that chronic stress induces a reversal learning deficit that models a cognitive dimension of depression. We have also shown that JAK-STAT signaling induced by low-level basal activity of the cytokine IL-6 is necessary for optimal reversal learning in the OFC, and stress-induced deficits in reversal learning were reversed by activating JAK-STAT in the OFC. Downstream mechanisms induced by JAK-STAT that are responsible for the beneficial cognitive effect in the OFC, and the potential

therapeutic significance of this effect are both unknown. Further, at higher levels of activity, IL-6 can be pro-inflammatory, so it would be advantageous to identify other endogenous processes by which JAK-STAT signaling can be modulated in the OFC. We will present data showing that acute low-dose administration of ketamine, an NMDA receptor antagonist and rapidly-acting antidepressant, induces JAK-STAT signaling in the OFC, and that JAK-STAT is necessary for both the beneficial effects of ketamine on reversal learning in stress-compromised rats, and for the functional plasticity induced in the OFC by ketamine that is associated with improved reversal learning after stress. We will show that JAK-STAT is involved in regulating Arc expression, which is important for synaptic plasticity in glutamatergic neurons in the OFC. And we have found that ciliary neurotrophic factor (CNTF), an endogenous neuroprotective growth factor in the OFC that also activates JAK-STAT signaling, can mimic many of these effects, thus representing a potentially novel therapeutic target in the management of cognitive dysfunction in stress and stress-related psychiatric disorders.

### Speaker 4: Trevor Robbins, UK

**Title:** *The role of the orbitofrontal cortex in compulsive behaviour*

**Abstract**

The orbitofrontal cortex has been implicated in many neuropsychiatric diagnoses, including notably substance use disorders, obsessive-compulsive disorder (OCD), depression and behavioral-variant fronto-temporal dementia (bv-FTD). The OFC has historically been associated with a major role in decision-making processes and with flexible stimulus-outcome learning; hence deficits in these processes are likely to contribute to various forms of neuropsychiatric psychopathology. This lecture examines current experimental evidence relating to the functioning of the orbitofrontal cortex (OFC), including regions associated with the ventromedial prefrontal cortex (vm-PFC). An important distinction across species is the division between the lateral and medial OFC. In the rat and marmoset, the OFC has been linked to efficient reversal learning, which is impaired in such disorders as cocaine dependence, bv-FTD and OCD. Reversal learning is a basic paradigm for examining flexible decisional processing across species, including both new learning and putative executive components. Recent evidence from experimental animals confirms an important role for serotonin (5-hydroxytryptamine, 5-HT) in the modulation of reversal learning, 5-HT depletion resulting in impairments in rats and marmosets, with links also to changes in 5-HT2A receptor binding. In rats, such impairments are reversed by appropriate treatment with sub-chronic citalopram, consistent with the therapeutic use of selective serotonin reuptake inhibitors in OCD. However, new evidence suggests that behavioral impairments in reversal and other paradigms produced by lateral OFC manipulations may contrast with the similar manipulations of the medial OFC in rats and may indicate the need for additional therapeutic approaches.

*Research supported by the Wellcome Trust Senior Investigator Grant 104631/Z/14/Z*

## Sunday 17th June 2018
## 14.45-16.30
## S8: Strategies to prevent neurobehavioral progression and suicide in bipolar disorder

Chair: Hilary Blumberg, USA
Co-Chair: Andreas Erfurth, Austria

---

### Speaker 1: Hilary Blumberg, USA

**Title:** *Neurobehavioral Progression in Adolescents and Young Adults with Bipolar: Implications for Treatment and Suicide Prevention*

**Abstract**

In this talk, multimodality magnetic resonance imaging (structural magnetic resonance imaging, diffusion weighted imaging and functional magnetic resonance imaging) data will be presented which support involvement of emotional regulation brain circuitry in bipolar disorder (BD). This includes differences in the structure and function of the ventral prefrontal cortex, its major connection sites such as the amygdala, and the connections between them. A neurodevelopmental model for BD will be presented that implicates differences in emotional regulation brain developmental trajectories during adolescence and young adulthood, a period when fully syndromic BD often emerges. BD is associated with a high risk of suicide; it is estimated that about 50% of individuals with BD will make a suicide attempt and 10-20% will die by suicide. Suicide ideation and behavior also often emerge during adolescence and young adulthood. In adults, converging research supports differences in brain circuitry that subserves regulation of emotions and impulses in suicide ideation and behavior. Neuroimaging research supporting involvement of emotional regulation brain systems in suicide ideation and behavior during adolescence and young adulthood will be presented. This will include preliminary longitudinal data which suggest the circuitry

differences are associated with risk of future suicide attempts. Influences of risk factors on the circuitry will be discussed, including those related to genetic and environmental mechanisms. Implications of the neuroimaging findings for identification of individuals at high risk for BD and for suicide, and for prevention of disorder progression in BD including risk for suicide, will be discussed.

### Speaker 2: Allan Young, UK

**Title:** *Cognitive Dysfunction in Bipolar Disorder*

**Abstract**

Cognitive dysfunction is an important aspect of bipolar disorder (BD) that encompasses problems with thinking, concentration and memory. Research suggests that this cognitive aspect of BD is highly prevalent and has a significant impact on patient functioning. Most research to date has focussed on Bipolar Disorder Type 1 but such evidence as is available suggests that Type 2 and subsyndromal states may be similarly impaired. The natural history of cognitive dysfunction in BD remains uncertain although some findings relate it to episodes of illness whereas other data suggests the contrary. Currently, cognitive dysfunction in BD is largely unrecognised, unmonitored and untreated however recently published consensus-based recommendations for cognition trials in bipolar disorder will, if adhered to, likely improve the sensitivity in detecting treatment efficacy in future trials and increase comparability between studies (1). In this presentation I aim to define cognitive dysfunction in bipolar disorder and explore its detection and management, highlighting priority areas to be addressed. Potential treatment approaches (including pharmacological and cognitive remediation) will be discussed.

### Speaker 3: Eduard Vieta, Spain

**Title:** *Enhancing Resilience and Preventing Allostatic Overload in Bipolar Disorder*

**Abstract**

Bipolar disorder is a neuroprogressive illness with huge phenotypic variability. Repeated manic episodes, especially those with psychosis, substance use and other comorbidities, may cause allostatic overload. The presentation will discuss the pharmacological and psychosocial strategies intended to prevent illness progression and improve resilience in patients with bipolar disorder.

Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016 Apr 9;387(10027):1561-72.

### Speaker 4: Frank Bellivier, France

**Title:** *Biomarkers of Lithium Response in Bipolar Disorder*

**Abstract**

1- INSERM UMR-S 1144, Paris Diderot University, Paris Descartes University, Paris, France
2- APHP, GH Lariboisière – Saint-Louis, Paris, France
3- FondaMental Foundation, Créteil, France

In Europe and USA, Lithium (Li) is the leading treatment for relapse prevention in bipolar disorders with many patients who remain asymptomatic for several years (even decades). In addition, it is the only psychoactive drug that has demonstrated efficacy in suicide prevention. However a large proportion of patients experience very high relapse rates (overall between 70 and 80% relapse, 2 years after an episode). Therapeutic response is quite variable, and it remains difficult for clinicians to accurately predict which patients will respond prior to a lengthy Li trial. Overall biomarkers predicting Li response are lacking and mechanisms of Li action remain poorly understood. The objective of this talk is to present preliminary results obtained in different research programs to contribute to the identification of biomarkers of Li response, including clinical, pharmacokinetic, gene expression and Li-7 MRS brain imaging studies in Humans and pre-clinical models.

## Sunday 17th June 2018
## 14.45-16.30
## S9: Cannabis shapes the morphological and epigenetic trajectory of mesocorticolimbic brain development relevant to psychiatric vulnerability

Chair: Yasmin Hurd, USA
Co-Chair: Tibor Harkany, Austria

### Speaker 1: Steven Laviolette, Canada

**Title:** *Neuronal and Molecular Effects of Adolescent Cannabinoid Exposure on Prefrontal Cortical Function: Implications for Schizophrenia*

**Abstract**

Clinical and pre-clinical evidence demonstrates a link between adolescent, neurodevelopmental exposure to the primary psychoactive compound

in marijuana, delta-9-tetrahydrocannabinol (THC) and an increased likelihood of developing schizophrenia-related symptoms in early adulthood. Translational research in our laboratory is examining the underlying molecular, neuronal and behavioural effects of adolescent THC exposure on the PFC and its regulation of sub-cortical dopamine (DA) systems. We find that adolescent THC induces molecular and neuronal abnormalities in the mammalian PFC that closely resemble those observed in schizophrenia. These effects include decreased intrinsic GABAergic inhibitory control in the PFC, sub-cortical hyperactivity in mesolimbic DA neurons and dysregulation of schizophrenia-related molecular pathways including the GSK-3, Akt and mTOR systems. This presentation will highlight the underlying molecular, neuronal and behavioural phenotypes resulting from adolescent THC exposure and how these pathological adaptations may serve as critical biomarkers for cannabinoid-related neuropsychiatric disorders.

## Speaker 2: Olivier Manzoni, France

**Title:** *Cannabinoids shape prefrontal development: Multiple scale visualization*

**Abstract**

Andrew F. Scheyer[1,2,3,#], Anissa Bara[1,2,3],Antonia Manduca[1,2,3,#], Axel benrabeu[1,2,3], Jim Wager-Miller[3,4], Olivier Lassalle[1,2,3], Anne-Laure Pelissier-Alicot[1,2,3,5,6], Ken Mackie[3,4], Olivier J.J. Manzoni[1,2,3].

[1] INMED, INSERM U901, Marseille, France.
[2] Aix-Marseille University, France.
[3]Cannalab Cannabinoids Neuroscience Research International Associated Laboratory. INSERM-Indiana University.
[4]Gill Center and Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, United States.
[5]APHM, CHU Conception, Service de Psychiatrie, 13005 Marseille, France
[6]APHM, CHU Timone Adultes, Service de Médecine Légale, 13005 Marseille, France
[#]Equally contributing authors.

Cannabis is the most widely used illicit drug in the world, and its usage is increasing with its widespread legalization. Use of the drug by mothers during pregnancy or lactation may transfer active cannabinoids to the developing offspring, altering postnatal neurodevelopment during earlier life critical periods and thereafter. During early life, GABA undergoes a functional switch from an excitatory to an inhibitory neurotransmitter due to changes in expression of the $K^+/Cl^-$ co-transporters KCC2 and NKCC1. We characterized the functional GABA switch in the prefrontal cortex of both male and female rats and described the molecular, synaptic and behavioral consequences of treating rat dams with ∆9-THC or a synthetic cannabinoid during early lactation in pups of both sexes. Our results indicate that the developmental trajectory of GABA in PFC neurons is significantly altered by perinatal exposure to cannabinoids through lactation during the early perinatal period.
We also discovered sex-specific differences in behavioral, molecular and neuronal deficits in the adult progeny of rat dams exposed to low doses of cannabinoids during gestation. In males, prenatal cannabinoid exposure (PCE) reduced social interaction, ablated endocannabinoid long-term depression (LTD) and heightened excitability of prefrontal cortex pyramidal neurons, while females were spared. Group 1 mGluR and endocannabinoid signaling regulate emotional behavior and synaptic plasticity. Notably, sex-differences following PCE included levels of mGluR1/5 and TRPV1R mRNA. Remarkably, positive allosteric modulation of mGlu5 and enhancement of anandamide levels restored LTD and social interaction in PCE adult males.
Together, these results highlight marked sexual differences in the effects of prenatal and early life cannabis and introduce innovative strategies for reversing its detrimental effects.

## Speaker 3: Yasmin Hurd, USA

**Title:** *The epigenetic trajectory of developmental cannabis exposure*

**Abstract**

The use of cannabis continues to grow worldwide with an increasing number of countries legalizing its use for recreational and medicinal purposes. One area of concern regarding the increased availability of cannabis is the reduced perception of its risk particularly in teens and young adults. This pattern is disconcerting especially in light of the increasing potency of delta-9-tetrahydrocannabinol (THC; the major psychoactive component of cannabis) being consumed today and that multiple studies have demonstrated that cannabis exposure during brain development has significant implications for mental health in adulthood. This presentation will focus on detailing specific perturbations of the adult epigenome and transcriptome within the prefrontal cortex and nucleus accumbens as a consequence of developmental THC exposure. Results will be discussed demonstrating the potential of THC to alter the morphological and epigenetic developmental trajectory of mesocorticolimbic neurons. Innovative state-of-the-art strategies such as laser capture microdissection combined with high-throughput sequencing used to profile the molecular

phenotype of individual cell populations emphasize the profound and persistent impairment of epigenetic modifications and synaptic plasticity-related networks in adults with adolescent THC exposure. The genes identified provide important insights linking developmental cannabis with mesocorticolimbic circuits and genes implicated in psychiatric vulnerability.

### Speaker 4: Francesca Telese, USA

**Title:** *Epigenetic signatures of cannabinoids in the developing brain*

**Abstract**

Adolescence represents a critical neurodevelopmental period of during which the brainundergoes critical changes at the behavioral, cellular and molecular levels. This plasticity might lend to this period of development a greater vulnerability to external insults, such as drugs of abuse. Chronic exposure to cannabis during adolescence can induce longlasting neurobiological changes that ultimately affect the function and behavior of the adult brain. Epigenetic mechanisms are thought to underlie these long-term neurobiological processes, as indicated by studies using crude brain extracts. However, the importance of epigenetic changes induced by cannabis in distinct neuronal subtypes remains largely unknown. In my laboratory, we address this challenge by applying novel methodologies that target distinct neuronal classes in the mouse brain. We have successfully used INTACT (isolation of nuclei tagged in specific cell types), coupled with high-throughput sequencing methods, to determine cell-type specific epigenetic and transcriptional changes. The INTACT method is based on expressing green fluorescent protein (GFP) fused to a nuclear envelope protein (Sun1) in a given neuronal population (e.g. excitatory or inhibitory neurons). This permits isolation of GFP-tagged nuclei using antibodies that recognize GFP. In this study, mice received daily injection of Δ9-tetrahydrocannabinol (Δ9-THC) during the adolescent period (P28-P48), and were evaluated with a battery of behavioral tests after 15 drug-free days. This chronic administration of Δ9-THC led to impairments in working memory capacity both in male and female mice. Isolated nuclei from animals treated with vehicle or Δ9-THC have been processed for epigenomic and transcriptomic profiling. The analysis of these sequencing datasets will allow us to correlate the observed behavioral phenotypes with transcriptional and epigenetic changes in specific neuronal populations. This approach will broaden our understanding of the cell-type specific effects of cannabinoids in the developing brain.

## Sunday 17th June 2018

## 14.45-16.30

## S10: Glutamate and mood disorders: All is not explained by NMDA

Chair: Mark Rasenick, USA
Co-Chair: Harald Sitte, Austria

---

### Speaker 1: Kenji Hashimoto, Japan

**Title:** *Comparison of (R)-ketamine and enantiomers of ketamine metabolites as rapid-onset and sustained antidepressants*

**Abstract**

The *N*-methyl-D-aspartate receptor (NMDAR) ketamine has rapid-acting and sustained antidepressant effects for treatment-resistant patients with major depressive disorder and bipolar disorder. The ketamine's antidepressant actions are the most important discovery in the field of depression research in half a century. However, the precise molecular mechanisms underlying ketamine's antidepressant actions are unknown. Previously, we reported that (*R*)-ketamine (Ki = 1.4 μM for NMDAR) has greater potency and longer-lasting antidepressant actions than (*S*)-ketamine (Ki = 0.30 μM for NMDAR) in rodents. Unlike (*S*)-ketamine, (*R*)-ketamine does not appear to cause psychotomimetic side effects, abuse potential, and loss of parvalbumin (PV)-positive cells in the prefrontal cortex. In addition, using a conscious monkey PET, we reported that (*S*)-ketamine, but not (*R*)-ketamine, caused a marked release of dopamine in the striatum, suggesting that (*S*)-ketamine-induced dopamine release might be associated with its acute psychotomimetic and dissociative symptoms in human. Taken all together, (*R*)-ketamine appears to be a potent, long-lasting and safe antidepressant, relative (*S*)-ketamine. In contrast, Zanos et al. (2016) reported that (2*R*,6*R*)-hydroxynorketamine (HNK), a metabolite from (*R*)-ketamine, is essential for ketamine's antidepressant actions. However, there is now the buzz about antidepressant actions of (2*R*,6*R*)-HNK. In this symposium, I would like to discuss the recent findings of the enantiomers of ketamine and its metabolites as rapid-acting and sustained antidepressants.

### Speaker 2: Maurizio Popoli, Italy

**Title:** *Restoration by ketamine of maladaptive plasticity induced by acute and chronic stress*

**Abstract**

Stressful events represent a major risk factor for stress-related neuropsychiatric disorders. We dissected the destabilizing effects of stress in the glutamate system and the consequences on brain structure/function. The footshock (FS) stress

protocol is used as model of inescapable acute stress and the chronic mild stress protocol (CMS, 5 weeks) is used as model of chronic stress.
Acute inescapable stress rapidly enhanced glutamate release/transmission in PFC, an effect sustained for 24 h. Unexpectedly, significant atrophy of apical dendrites was observed already at 24 h, and prolonged for at least 14 days. Chronic treatment with traditional antidepressants and single administration of ketamine (10 mg/kg) blocked most maladaptive effects of acute stress. Ketamine blocked enhancement of glutamate release when administered 24 or 72 hours before FS stress, or when administered 6 hours after FS stress.
In rats subjected to CMS, ketamine was acutely administered to vulnerable (CMS-V) rats. Glutamate release was reduced in HPC synaptosomes from CMS-V. Significant reduction in expression of total BDNF and BDNF splice variants was found in all CMS rats. Reduced dendritic trafficking of BDNF mRNA and atrophy of apical dendrites was found in HPC of CMS-V. Ketamine treatment, completely restored anhedonic behavior in CMS-V rats and most of the related changes, with the only exception of BDNF expression.
Acute and chronic stress induce typical signatures of behavioral, structural and functional changes, with overlapping features. Ketamine restores most maladaptive changes induced by stress. In particular, in both cases ketamine stabilizes the glutamatergic dysfunction, reducing glutamate release enhanced after acute stress and restoring that reduced after CMS.
Our results suggest that ketamine could be used as prophylactic treatment in traumatic events (e.g., for PTSD).

## Speaker 3: Mark Rasenick, USA

**Title:** *A rapid, Ketamine-induced antidepressant biosignature in primary and cultured glia reveals NMDA-Receptor independent increases in cAMP and BDNF*

**Abstract**

Nathan Wray, Harinder Singh, Jeff Schappi and Mark M. Rasenick

Departments of Physiology and Psychiatry, U. Ilinois College of Medicine, Chicago and the Jesse Brown VAMC, Chicago.

**Background:** Ketamine produces rapid and robust antidepressant, albeit transient, effects in depressed subjects within hours of administration, often when traditional antidepressant compounds have failed to alleviate symptoms. We hypothesized that, similarly to other antidepressants, ketamine would translocate $G\alpha_s$ from lipid rafts to non-raft microdomains, but with a distinct, abbreviated treatment duration. We also anticipated that this would result in a sustained increase in cAMP.
**Procedure and results:** C6 glioma cells or primary astrocytes were treated with 10 µM ketamine for 15 minutes, which translocated $G\alpha_s$ from lipid raft domains to non-raft domains. This lasted for 24 hours. Other NMDA antagonists did not translocate $G\alpha_s$ from lipid raft to non-raft domains. The ketamine induced $G\alpha_s$ plasma membrane redistribution increased functional coupling of $G\alpha_s$ and adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). Moreover, increased intracellular cAMP increased phosphorylation of cAMP response element-binding protein (CREB), which, in turn, increased BDNF expression in primary astrocytes. Other NMDA receptor antagonists were without effect and increase in intracellular cAMP occurred after knocking out the NMDA receptor, indicating and NMDA receptor independent effect. Furthermore, 10 µM of the ketamine metabolite (2R,6R)-hydroxynorketamine also induced $G\alpha_s$ redistribution and an increase in cAMP.
**Conclusion:** These results reveal a consistent cellular biosignature for antidepressant action and suggest a novel mode of action for acute ketamine treatment in astrocytes that may contribute to ketamine's powerful antidepressant effect. They also suggest a role for glia in the antidepressant action of ketamine.

## Speaker 4: Carrie Jones, USA

**Title:** *Optimizing Full and Partial mGlu5 Negative Allosteric Modulators for the Treatment of Depression, Anhedonia, and co-morbid Addiction Use Disorders*

**Abstract**

With the increasingly high comorbidity of depression and anhedonia associated with cocaine use disorder (CUD), there is a critical need to develop novel pharmacotherapies targeting multiple symptoms associated these indications to improved overall treatment success. One novel treatment mechanism involves modulation of glutamatergic neurotransmission through antagonism of the metabotropic glutamate (mGlu) receptor subtype 5 ($mGlu_5$). Over the last decade, selective inhibitors of $mGlu_5$, known as negative allosteric modulators (NAMs), have been developed that do not interact with the highly conserved orthosteric binding site of glutamate, but instead bind to an allosteric site in the seven transmembrane-spanning domain of $mGlu_5$ and inhibit coupling of the receptor to GTP-binding proteins. Multiple full $mGlu_5$ NAMs are

currently under clinical investigation for the treatment of symptoms associated with depression and anhedonia. However, complete blockade or inverse agonist activity by some full $mGlu_5$ NAMs has been associated with adverse effects, including psychosis in humans and psychotomimetic-like effects in animals, suggesting a narrow therapeutic window. In the current presentation, we will review the discovery and optimization of several novel partial $mGlu_5$ NAMs, characterized by their submaximal, but saturable levels of blockade that may represent a novel approach to broaden the therapeutic window of this mechanism. To understand potential therapeutic *vs* adverse effects in preclinical behavioral assays, we will describe studies that examined the partial $mGlu_5$ NAMs, M-5MPEP and Br-5MPEPy, in comparison with the full $mGlu_5$ NAM MTEP, across models of antidepressant- and/or anhedonic-like activity and CUD in rodents. Our data will demonstrate that both M-5MPEP and Br-5MPEPy produce robust antidepressant-like activity in a dose range that also decreases cocaine self-administration without induction of psychotomimetic-like activity. Taken together, these data suggest that partial $mGlu_5$ NAM activity is sufficient to produce therapeutic effects similar to full $mGlu_5$ NAMs, but with a broader therapeutic index.

**Sunday 17th June 2017**
**14.45-16.30**
**CP02: Schizophrenia**
Chair: Eileen Joyce, UK
Co-Chair: Ana Weidenauer, Austria

---

## Speaker: Carol Tamminga, USA

**Abstract**
Conventional diagnoses are based on phenomenological expression and are not know for neurobiological consistency. BSNIP investigators have examined brain-based markers of disease across psychosis diagnoses and used these to develop novel categories of psychotic disorders. Five sites in the US collected a dense biomarker battery (>40 distinct markers) on probands (N=988) with a range of diagnoses with psychosis and their family members; the data failed to find biomarkers which would identify conventional psychosis diagnoses. The biomarkers include measures from brain imaging, cognition testing, electrophysiological validators, and oculomotor movements, along with clinical and demographic personal characteristics, especially those known to be abnormal in psychotic disorders. We interpreted this failure to find distinguishing biomarker characteristics as an indication of gross neurobiological heterogeneity composing conventional diagnostic groups. Therefore, we moved to the next step of disgarding these diagnoses from the probands and computationally re-clustering them based on biomarker characteristics to achieve increased biological homogeneity; we used mainly cognitive and electrophysiological characteristics, developing two constructs, 'cognitive control' and 'sensorimotor reactivity'. We have been able to find additional validation for the constructs using brain imaging, family heritability and EEG as well as fMRI connectivity parameters. Once developed, we will use the characteristics as a whole to modify the computational base of the constructs themselves. We have yet to provide the strongset validators for this approach, either specific genetic fingerprints of the psychosis The consortium is working on these strong validation steps now by collecting an additional large group of probands for stronger genetic analyses and by postulating treatment approaches based on the Psychosis Biotype characteristics.

**Sunday 17th June 2018**
**16.45-17.30**
**PL02: Suicidal subtypes: improving phenotypes to uncover underlying biosignatures**
Chair: Siegfried Kasper, Austria

---

## Speaker: Maria A Oqendo, USA

**Abstract**
Despite advances in the assessment and management of suicidal behavior, suicide rates in the United States have increased dramatically over the past 30 years. There is ample evidence that suicidal thoughts and behaviors are transdiagnostic phenomena that can arise even in the absence of other diagnosable mental health disorders. Studies have identified genetic, neurobiological, and psychological factors that are associated with suicidal behavior, but these risk factors have modest statistical and limited clinical utility. Data suggests that, rather than being a unified construct, suicidal behavior likely represents a final common pathway of multiple separate pathological processes. The pattern of suicidal thinking helps distinguish at least two of these suicidal subtypes—two phenotypes with distinct biosignatures.

**Monday 18th June 2018**
**08.45-09.30**
**PL03: Molecular mechanisms of gene x environment interactions – implications for diagnosis and treatment of psychiatric disorders**
Chair: Elias Eriksson, Sweden

## Speaker: Elisabeth Binder, Germany

**Abstract**
Early adverse exposures, such as maternal stress during pregnancy and child abuse, are thought to result in long-lasting consequences on neural circuit function and stress hormone regulation and ultimately in an increased risk for psychiatric but also medical disorders later in life. The impact of these environmental risk factors is moderated by genetic variation. The biological mechanisms underlying this increased risk and these gene x environment interactions are still unclear. This lecture will focus on putative biological mechanisms that implicate the ability of the stress hormone cortisol, released in response to stress, to trigger a cascade of adaptive genomic and non-genomic processes through activation of its receptors and the moderation of these responses by genetic variation. These stress hormone receptors are intracellular and bind to the DNA where they act as transcription factors. In such, this system presents a unique set-up for gene x environment interaction.

Overall, the presentation will outline how stress-exposure can have lasting effects on cell and tissue function and how this relates to risk or resilience to stress-related disorders.

**Monday 18th June 2018**
**09.45-11.30**
**S11: Prediction of disease vulnerability and treatment response in mood and anxiety disorders**
Chair: Charles Nemeroff, USA
Co-Chair: Nicole Praschak-Rieder, Austria

## Speaker 1: Charles Nemeroff, USA

**Title:** *Childhood Adversity and Biological Predictors of Mood Disorder Vulnerability and Treatment Response*

**Abstract**
Over the last two decades, a burgeoning data base has provided overwhelming evidence that early life trauma in the form of child abuse and neglect is associated with a marked increase in the risk for development of major mood disorders (major depression and bipolar disorder) and certain anxiety disorders (post-traumatic stress disorder [PTSD]), as well. In addition, the course of these syndromal and severe psychiatric disorders is more malignant in patients who experience childhood adversity and moreover, their response to evidence-based treatments including psychopharmacology, psychotherapy and their combination is less robust compared to similarly diagnosed patients without a history of early life adversity.
This presentation will describe recent findings from our group and others concerning the neurobiological consequences of childhood abuse and neglect including structural and functional brain imaging studies, inflammatory markers and gene-environments interaction studies. The latter includes identification of gene variants that modulate the diathesis for development of depression and PTSD in the presence of early life trauma.
In addition, predictors of treatment response, both genomic and functional imaging will be described with a focus on the large iSPOT and PReDICT studies. Future research directions will be outlined.

## Speaker 2: Elisabeth Binder, Germany

**Title:** *Using multi-levels of biomarkers for prediction of depression outcome*

**Abstract**
Tania Carrillo-Roa[1], Tanja Brückl[1], Darina Czamara[1], Elisabeth B. Binder[1, 2]
[1]Department of Translational Psychiatry, Max-Planck Institute for Psychiatry
[2]Department of Psychiatry and Behavioural Sciences, Emory University.

Biomarkers to guide patient stratification for optimal treatment selection are lacking for major depression (MDD), possibly also because biomarkers are often used in isolation. This presentation will highlight approaches that combine multiple biomarkers from levels of investigation to inform patients stratification and predict treatment outcome. A first approach combines genetic association with brain structure and clinical information as a predictor of antidepressant response. Hippocampal (HC) structure and function have been implicated in the neurobiology of MDD and treatment outcome. Using a neuroimaging-based genomics approach, we investigated whether polygenic scores (PGS) derived from SNPs influencing HC volume from the ENIGMA study (Hibar et al., 2015, 2017) correlate with treatment outcomes in MDD as a whole or stratified by clinical subtypes previously related to treatment outcome as well as response

to specific treatments in 3 independent cohorts. While HC volume-PGS were unable to predict outcome overall, they significantly predicted outcome in non-anxious patients. Higher HC-PGS reflecting increased HC-volume correlated with better outcomes, agreeing with previous findings relating anxiety and reduced HC-volume with poor outcomes in MDD. Furthermore, HC-PGS predicted differential outcomes to CBT vs. medication. A second approach will highlight how large cohorts with multi-level information (brain imaging, immune markers, neurocognition, psychophathology, environmental exposures, omics measures) can give insights into the biological stratification of MDD patients, with a focus on comparing multidimensional correlates with previously established MDD subgroups related to typical vs. atypical features (Milaneschi et al,. 2016).
Overall this presentation highlights the importance of combining biomarkers for the stratification of MDD and in consequence the prediction of antidepressant response.

## Speaker 3: Linda Carpenter, USA

**Title:** *Cortisol Response to a Neuroendocrine Test for Predicting Future Onset of Depression and Anxiety Disorders*

**Abstract**
Posttraumatic stress disorder (PTSD) manifests after exposure to a traumatic event and is characterized by avoidance/numbing, intrusive symptoms and flashbacks, mood and cognitive disruptions, and hyperarousal/reactivity symptoms. These symptoms reflect dysregulation of the fear system likely caused by poor fear inhibition/extinction, increased generalization, and/or enhanced consolidation or acquisition of fear. These phenotypes can be modeled in animal subjects using Pavlovian fear conditioning, allowing investigation of the underlying neurobiology of normative and pathological fear. Preclinical studies reveal a number of neurotransmitter systems and circuits critical for aversive learning and memory that have informed the development of therapies used in human clinical trials. In this talk, I will discuss the evidence for genetic, neurobiological, and neural circuit mechanisms to understanding PTSD. Furthermore, I will discuss future approaches to pharmacotherapy and other treatments for posttraumatic stress disorder that have been developed via a bench to bedside translational models.

## Speaker 4: Gustavo Turecki, Canada

**Title:** *MicroRNAs 146a/b-5p, 425-3p and 24-3p are consistent markers of antidepressant response and regulate MAPK/Wnt system genes*

**Abstract**
Antidepressants (ADs) are the most common treatment for major depressive disorder (MDD). However, only about 30% of patients experience adequate response after a single AD trial, and this variability remains poorly understood. Genes can be regulated through the activity of several non-coding RNA (ncRNA) transcripts. Among ncRNAs, small non-coding RNAs, including microRNA (miRNA) and small nucleolar RNA (snoRNA), are particularly interesting because they play a key role in the regulation of essential brain processes, seem to mediate psychiatric treatments, and circulate freely in blood. Here we will present a series of complementary studies investigating small non-coding RNAs as possible biomarkers of antidepressant response.

We used a series of different methods, including small RNA-sequencing in a randomized placebo-controlled trial of duloxetine (N = 516). We then confirmed our results in an independent clinical trial of antidepressant (N =122), and subsequently, we investigated response to treatment in an animal model of depression (N=26). Further, we conducted a series of studies investigating postmortem brain samples and neural progenitor cells, in addition to RNA-IP, overexpression and downregulation experiments to test the interaction between small ncRNAs and their targets in vitro.

The small RNA-sequencing in the randomized placebo-controlled trial of duloxetine revealed differential expression of several miRNA and 31 snoRNAs (FDR < 0.05). Using bioinformatic analyses, we identified common target genes of the differentially expressed miRNAs, and found a significant dysregulation of genes involved in MAPK/Wnt signaling pathways. The snoRNA were characterized in a series of follow up experiments, including in vitro work and functional assays with induced serotonergic neurons.

Together, our results identify putative ncRNA biomarkers of AD response. These results provide important steps in the potential development of early diagnostic tools, preventive strategies, and effective pharmacological targets for MDD treatment.

**Monday 18th June 2018**
**09.45-11.30**

## S12: Translational research on etiopathogenesis of late-life cognitive impairment and depression: four different approaches toward the common goal

Chair: Gwenn Smith, USA
Co-Chair: Dietmar Winkler, Austria

---

### Speaker 1: Gwenn Smith, USA

**Title:** *Multi-Modality Imaging of Neurodegeneration in Late Life Cognitive Decline and Depression*

**Abstract**

Molecular imaging methods to visualize the neuropathology of Alzheimer's disease (AD) in vivo provide an unprecedented opportunity to understand the neuropsychiatric (NPS) and cognitive symptoms observed in early stage AD by testing hypotheses informed by human neuropathology and animal models. A fuller understanding of the neurobiology of early AD and its clinical progression is essential to identify individuals at risk and to identify targets for prevention and treatment. To maximize the benefit from disease-modifying therapies, individuals must be identified and treated in the early stages, including mild cognitive impairment (MCI). Only by doing so, is it possible to prevent progressive spreading of neuropathology and emergence of cognitive deficits and NPS. Multi-radiotracer PET studies of beta-amyloid (Aβ) and serotonin (5-HT) in amnestic, multi-domain, MCI (aMCI-MD) and cognitively normal elderly demonstrated progressive, cortical and limbic 5-HT degeneration, linked to network dysfunction, that was greater and more widespread than cortical Aβ, cerebral atrophy or cerebral blood flow deficits. Cortical and limbic 5-HT degeneration was a more powerful predictor of cross-sectional and longitudinal memory impairment than Aβ. Human data and animal models show the synergistic effect of Tau on both Aβ and 5-HT degeneration. Tau overlaps more than Aβ with loss of 5-HT in cortical and 5-HT-rich limbic regions, is more temporally linked to cognitive deficits and decline and is better correlated with cognitive impairment. Thus, in vivo imaging of 5-HT combined with Tau and Aβ, may represent a powerful predictor of cognitive decline and emergence of NPS. Lower 5-HT transporters (SERT) overlapped to a greater extent with Tau in limbic regions than Aβ. Elucidating the role of 5-HT in relation to Tau and Aβ in cognitive decline in aMCI-MD will have fundamental implications for the design of prevention and intervention studies targeting 5-HT and studies of other neurotransmitters vulnerable to neurodegeneration (norepinephrine).

### Speaker 2: John O'Brien, UK

**Title:** *PET imaging of tau and neuroinflammation in dementia*

**Abstract**

There is renewed interest in the potential importance of neuroinflammation as a pathophysiological mechanism in both neurodegenerative and psychiatric disorders. Neuroinflammation can be assessed using positron emission tomography (PET) with many different tracers, the best established of which is PK11195, a marker of microglial activation.

The ability to assess amyloid using PET imaging or CSF is well established, more recently several tracers have been proposed as potential markers of tau, including AV-1451. In the NIMROD (Neuroimaging of Inflammation in Memory and Related Other Disorders) study, we have utilised PK11195, AV-1451 and amyloid (PiB) imaging to investigate changes in neuroinflammation in different disorders and examine their association with tau and amyloid pathology.

In studies of Alzheimer's disease (a cortical tauopathy) and progressive supranuclear palsy (a subcortical tauopathy), we have shown alternations in AV-1451 which distinguish the two disorders and maps to known pathological accumulations of tau pathology. Binding of AV-1451 particularly mirrors the paired helical filament distribution of tau in Alzheimer's disease. Alzheimer's disease is associated with increases in PK11195 binding, and we found evidence of increased PK uptake in subgenual anterior cingulate cortex in late-life depression.

In Alzheimer's disease, assessment of the relationship between tau burden and brain functional connectivity, using resting state fMRI, indicated that strongly connected nodes displayed more tau pathology in Alzheimer's disease, independent of intrinsic network connectivity.

These results supported predictions of transneuronal spread of tau pathology in favour of alternative hypotheses that tau accumulation is a consequence of increased metabolic demand. Once tau accumulates, there is evidence that increasing tau burden then disrupts connectivity.

Results provide support for the transneuronal spread of tau in Alzheimer's disease and indicate neuroinflammation as a potential target of interest in late-life depression. Findings highlight the value

of PET imaging of neuroinflammation and tau in late-life cognitive and psychiatric disorders.

## Speaker 3: Masafumi Ihara, Japan

**Title:** *Bench to bedside: using mouse models to identify new treatment approaches for dementia*

**Abstract**

With the demographic shift in age in advanced countries inexorably set to progress in the 21st century, dementia will become one of the most important health problems worldwide. Vascular cognitive impairment, the second most common type of dementia, is frequently characterized by cerebrovascular white matter changes and responsible for the cognitive decline of the elderly. To investigate the underlying mechanisms involved in white matter changes, a mouse model of chronic cerebral hypoperfusion has been developed, which involves the narrowing of the bilateral common carotid arteries with microcoils. This model is used worldwide and evaluated to be one of the most promising models of vascular cognitive impairment. We have also used ameroid constrictors that gradually occlude the common carotid arteries to develop more faithful models of chronic cerebral hypoperfusion. These several hypoperfusion models show good reproducibility of the white matter changes characterized by blood-brain barrier disruption, glial activation, oxidative stress, and oligodendrocyte loss following chronic cerebral hypoperfusion with or without ischemic stroke. Detailed characterization of these hypoperfusion models may help to decipher the substrates associated with impaired memory and move toward a more integrated therapy of vascular cognitive impairment. In the lecture, the oral–brain axis will be also introduced as the pathogenic connection between the oral cavity and the cerebral blood vessels, which will be a future target for drug development of vascular cognitive impairment.

## Speaker 4: Hochang Benjamin Lee, USA

**Title:** *Cardiovascular surgery as an experimental model to test Vascular Depression Hypothesis and CATCH hypothesis*

**Abstract**

Dr. Hochang Lee of University of Rochester (USA) discusses cardiovascular surgery (e.g. coronary artery bypass graft surgery and left-ventricular assist device surgery) as a potential human experimental model to examine cerebrovascular aspects of late-life psychiatric syndromes (e.g. depression, delirium, and cognitive decline). "Vascular Depression" hypothesis posits that cerebrovascular disease predisposes, precipitates, or perpetuates late-onset depression and implicates etiopathogenesis and treatment strategies that are different from idiopathic, early-onset depression. The NIMH-sponsored Neuropsychiatric Outcomes after Heart Surgery (NOAHS) study utilizes Transcranial Doppler ultrasound (TCD) to detect and quantify the location and severity of Intracranial Atherosclerosis (ICA), as well as to assess for other putative pre-CABG risk factors (e.g. pre-CABG cognitive impairment and depression, neuroticism, low social and support) for post-CABG depression in CABG surgery patients at the time of cardiac catheterization. The NOAHS study tests the Vascular Depression Hypothesis by follow the subjects over the subsequent 12 months to assess for incidence, symptomatology and course of post-CABG depression, delirium and cognitive decline. The critically attained threshold of cerebral hypoperfusion (CATCH) hypothesis of AD posits that chronic cerebral hypoperfusion (CCH) adversely affect metabolic, anatomic, and cognitive function of brain based on multiple experimental, clinical, and epidemiological studies. However, few studies have examined the impact of reversing CCH on cognition and brain metabolism to investigate a potential venue for dementia prevention research. Approved as “destination therapy” for those with advanced heart failure (NYHS=4), left ventricular assist device (LVAD) restores the function of a failing left ventricle and could be a useful clinical model in understanding the impact of reversing CCH on cognition and brain metabolism

**Monday 18th June 2018**
**09.45-11.30**
**Presidential Symposium: Transformative Treatments for Psychiatry**
Chair: Barbara Sahakian, UK
Discussant: John Krystal, USA

## Speaker 1: David Nutt, UK

**Title:** *Drugs of abuse as novel therapeutics for the upcoming century*

**Abstract**
Many therapeutic drugs are also subject to abuse in recreational settings. This abuse has driven the international community to attempt to control it through controls such as the UN Conventions of 1960 and 1971. Almost invariably these controls have failed to limit recreational use but have severely impeded research. This is especially true for drug controlled in Schedule 1 of the conventions for example cannabis psychedelics and MDMA. I believe these controls represent the worst censorship of research in the history of science. My talk will focus on the lost opportunities for neuroscience research and treatment innovation that these bans produce. I will share our recent data on how human research with psychedelics and MDMA has given remarkable new insights into brain processes such as consciousness and mood regulation with exciting if preliminary data on treatment efficacy in conditions such as depression and addiction. Finally I will argue that an enlightened approach to the use of such drugs will open up a new era of neuroscience research, and one especially important given the pull-out of "big pharma" from brain research.

*Nutt DJ, King LA, Nichols DE (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. Nat Rev Neurosci. Aug;14(8):577-85. doi: 10.1038/nrn3530. Epub 2013 Jun 12.*

## Speaker 2: Matthew State, USA

**Title:** *From next generation genomics to gene therapy in psychiatry*

**Abstract**
The last decade has witnessed remarkable advances in the understanding of the genetics of complex neuropsychiatric disorders. For a number of common developmental syndromes, this progress has been dominated by the discovery of new (*de novo*) and rare mutations, in the coding portion of the genome, that confer very large biological effects. These findings contrast with some of the equally remarkable discoveries with regard to later onset disorders, where the lion's share of progress has been made in the identification of common single nucleotide risk polymorphisms, often in the non-coding regions of the genome, that carry small individual effect. These differences in the types of genetic contributors so far identified – that is in the emerging genetic architectures of these syndromes – holds different challenges for the path from gene discovery to therapeutics development. This talk with summarize recent progress in psychiatric genomics, with a particular focus on autism spectrum disorder, Tourette syndrome and other early onset disorders. It will contrast these findings conceptually with recent progress in the genetics of schizophrenia and will address both the opportunities and challenges in translating recent gene discoveries into an actionable understanding of pathophysiology and developing novel treatment strategies, including gene therapies

## Speaker 3: Hayriye Cagnan, UK

**Title:** *Closed loop DBS strategies for neuropsychiatric applications: lessons from movement disorders*

**Abstract**
Deep brain stimulation is an effective treatment used to reduce symptoms of wide range of neurological disorders such as Parkinson's disease, Essential Tremor, dyskinesia and dystonia. Stimulation at high frequencies (130-180 Hz) reduces excessive rhythmic neural activity when stimulation effectively reduces disease symptoms. State of the art deep brain stimulation devices deliver stimulation continuously throughout the day without accounting for patients' symptom severity. The link between excessive rhythmic activity and symptom severity has lead to the proposal that rhythmic neural activity could be used as a biomarker in order to control when and how much stimulation is delivered. Recent studies highlight that when stimulation is delivered only when excessive rhythmic activity is observed, patients' symptoms can be reduced significantly while common stimulation side effects observed during continuous stimulation are alleviated. Stimulation specificity could further be improved by temporally patterning the stimulation to selectively disrupt excessive rhythmicity. These advancements are essential to increase stimulation efficacy and specificity while reducing stimulation side effects such as impulsivity, speech and gate disturbances. I will provide an overview of the novel deep brain stimulation strategies developed to treat movement disorders and extrapolate how insights from treatment of common movement

disorders could inform treatment of neuropsychiatric disorders.

**Monday 18th June 2018**
**09.45-11.30**
**S13: A translational approach to reducing drug-related memories and enhancing self-control in drug addiction**
Chair: Rita Goldstein, USA
Co-Chair: Gabriella Gobbi, Canada

---

## Speaker 1: Rita Goldstein, USA

**Title:** *The prefrontal cortex in reducing drug memories and enhancing alternative behaviors in cocaine addiction*

**Abstract**
Addicted individuals continue seeking drugs despite severe negative consequences, suggesting they may have diminished ability to form and/or maintain new associations for stimuli previously associated with drug use. We used classical conditioning to examine extinction learning for drug cues in individuals with cocaine use disorders (iCUD) and demographically matched healthy controls. Subjects learned to associate a cue, the conditioned stimulus (CS), with a drug-related (CSD+) or pleasant (CSP+) image. Extinction training immediately followed acquisition and involved repeated presentation of the CS without the paired image. Retention of extinction learning was assessed 24 hours later. Results showed that like fear extinction, non-fear based extinction relies on the ventromedial prefrontal cortex (vmPFC). However, extinction-related changes in the vmPFC differed by cue valence and diagnosis. In controls, vmPFC activation to the CSD+ (which was unpleasant for participants) gradually increased as in fear extinction, while it decreased to the CSP+, consistent with a more general role of the vmPFC in flexible value updating. Supporting a specific role in extinction retention, we further observed a cross-day association between vmPFC activation and skin conductance, a classic index of conditioned responses. Finally, iCUD showed vmPFC abnormalities for both CSs, which, in the case of the CSD+, correlated with craving. These data suggest a global deficit in extinction learning in this group that may hinder extinction-based treatment efforts. More broadly, these data show that the vmPFC, when functionally intact, supports extinction learning in diverse contexts in humans. Results of other studies in the lab show morphological abnormalities in the vmPFC in iCUD, its recovery with abstinence and modulation by a dopamine indirect agonist (methylphenidate). This talk will also highlight the use of a multi-modality imaging approach in assessing drug-cue reactivity (including cue-induced incubation of craving) and designing pharmacologically-enhanced cognitive-behavioral interventions targeted at reducing craving and drug-seeking in cocaine addiction.

## Speaker 2: Karen Ersche, UK

**Title:** *Habitual behaviours in cocaine addiction: possible mechanisms and predisposing factors*

**Abstract**
“Just say no” was the slogan of a US anti-drug campaign, which although used thirty years ago still resonates with many people. The current opioid epidemic in America and the growing problem of stimulant drug use in Australia, Asia and Europe, clearly illustrate that this slogan oversimplifies a serious problem. Drug-addicted individuals cannot simply stop using. In fact, they are not even deterred from using by the devastating consequences of continued drug use, even though many report not liking the drugs as much as they used to. “Just say no” places all responsibility on the individual without acknowledging the available neuroscientific evidence that points towards impairments in brain regulatory control systems in addiction. Growing translational evidence indicates that regular use of stimulant drugs such as cocaine has profound effects on how individuals behave, as these drugs disrupt the balance of brain systems implicated in the control over behaviour. Behaviour is generally guided by the anticipated consequences of actions, but animal models have shown that cocaine exposure diminishes the individual’s ability to appropriately process information about consequences, leading to failures to optimally adjust behaviour accordingly. Moreover, and more importantly, growing evidence indicates that cocaine use facilitates the shift of control over behaviour from the conscious goal-directed system in the orbitofrontal cortex to the non-consciously operating habit system, which is subserved by corticostriatal circuits. As a result, regular behaviours such as drug-taking readily develop into automatic habits, which means that the behaviour is no longer guided by the motivation to obtain an anticipated outcome (or avoid a negative one), but is instead habitually triggered by environmental stimuli. In my talk, I will report on the translation of this animal work to humans with cocaine addiction, and touch on how changes to treatment practices could enable individuals to say no.

## S

## peaker 3: Carien Lansink, Netherlands

**Title:** *Modulation of goal-directed action by reward expectancy cues and hippocampal and ventral striatal synchronization*

**Abstract**

When we are thirsty we go to the fridge, open it and we take a soda. Such goal-directed action, in contrast to spontaneous action, is characterized by an active internal representation of the goal, its location and the action strategy that is required to reach the goal. These representations heavily depend on the integrity of the hippocampal-ventral striatal circuitry, mediating place-reward associations. We recorded the activity of neuronal ensembles in rat hippocampus and ventral striatum simultaneously recorded during a goal-directed and spontaneous action to test how this circuitry integrates the spatial-contextual information conveyed by the hippocampus to the ventral striatum to invigorate reward-directed behavior. We found that a reward-predictive cues, that is, cue lights that signals that reward will be available and trigger action to the goal, induced a firing rate change (remapping) in hippocampal and ventral striatal neurons. The cues induced an increase in spatial information transmission and sparsity in both structures. These effects were paralleled by an enhanced temporal specificity of ensemble coding and a more accurate reconstruction of the animal's position from population firing patterns. In addition, reward-predictive cues resulted in enhanced rhythmic activity in the hippocampal local field especially in the theta (6-12 Hz) and beta 15-25 Hz) frequency bands. Both hippocampus and ventral striatum showed increased synchronization between neuronal firing and local field potential activity during cued compared with spontaneous goal approaches. Together, these results suggest that the hippocampus may contribute to the selection of action strategy by providing contextual and spatial information that aids activation of a particular ventral striatal ensemble for invigorating a corresponding action appropriate fir that temporal phase and spatial context. Furthermore, cue-triggered reward expectancy intensifies hippocampal output to the ventral striatum, by which the hippocampus may gain prioritized access to these systems modulating motivated behaviors.

## Speaker 4: Bruce Hope, USA

**Title:** *Neuronal ensembles in drug-related memories in drug addiction*

**Abstract**

Addiction is a maladaptive learned behavior where drug-related cues guide drug-seeking and drug-taking. Like most learned behaviors, it is a complex behavior thought to be encoded with high resolution via alterations within highly specific patterns of neurons called 'neuronal ensembles' that are activated selectively by the drug-related cues. We have developed tools to identify, characterize and manipulate these neuronal ensembles in rat models of drug seeking and relapse. These tools are based on activation of the Fos gene in strongly activated neurons during behavior. In our self-administration models, only about 1% of neurons are activated enough to express Fos mRNA or protein. We begin with our Daun02 inactivation procedure where behavior induces beta-galactosidase (betaGal) enzyme in strongly activated neurons in transgenic Fos-LacZ rats. The inactive prodrug Daun02 injected into a brain area 90 minutes later. BetaGal catalyzes Daun02 to daunorubicin which kills only those Fos and betaGal-producing neurons that were activated during behavior. For example, unlike research based on inactivating whole brain areas, Daun02 inactivation has allowed us to find 'separate' Fos-expressing neuronal ensembles in the infralimbic prefrontal cortex that mediate recall of cocaine self-administration and extinction memories that increase or decrease cue-induced drug-seeking behavior. The identification of neurons that mediate these memories allows us to study the unique molecular and cellular alterations within these neurons that are capable of encoding the memories. We have found many unique IEG and neurotransmitter receptor genes are uniquely altered only with in the small number of Fos-expressing neurons, but not in the surrounding majority of Fos-negative neurons. We have also found many unique electrophysiological alterations, such as silent synapse formation and AMPA/NMDA ratios, induced only within the Fos-expressing neurons, but in the Fos-negative neurons. These unique alterations may provide unique targets for manipulating specific memories in learning disorders such as addiction and PTSD.

**Monday 18th June 2018**
**09.45-11.30**
**S14: Translational neuroscience of obsessive-compulsive disorders**
Chair: Dan Stein, South Africa
Co-Chair: Daniela Pollak, Austria

## Speaker 1: Dan Stein, South Africa

**Title:** *Nosology of obsessive-compulsive disorder: An international effort*

**Abstract**
Both DSM-5 (the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders and ICD-11 (the eleventh edition of the International Classification of Diseases) have included a new chapter on obsessive-compulsive spectrum disorders (OCRDs). During the DSM revision process there was a strong emphasis on constructs such as diagnostic validity and symptom dimensionality, and this emphasis arguably encouraged the inclusion of OCRDs in the manual. During the ICD revision process there was a strong emphasis on constructs such as clinical utility and global applicability, and this emphasis again likely fostered the inclusion of the OCRDs in the manual. At the same time, differences in the approach of DSM-5 and ICD-11 have led to some differences in the OCRDs included in these manuals, as well as in their conceptualization. The Research Domain Criteria (RDoC) framework provides yet another perspective on the assessment and evaluation of OCRDs, arguably further contributing to the consolidation of a translational approach to conceptualizing and investigating these conditions. This talk will provide an overview of this nosological research, as a foundation for the remaining talks in the symposium on the psychobiology of OCD.

## Speaker 2: Lea Davis, USA

**Title:** *Genetic Architecture of Obsessive-Compulsive Disorder and Tourette's Disorder*

**Abstract**
Obsessive-compulsive disorder (OCD) and Tourette Syndrome (TS) are genetically complex, comorbid neuropsychiatric disorders. In recent years, meta-analysis of genome-wide variation measured on thousands of cases and controls for each disorder has yielded significant insights into their genetic architecture. Evidence strongly suggests that both OCD and TS are highly polygenic such that genetic risk is largely due to the cumulative effects of many hundreds of small-effect risk loci. Studies by our group and others have shown that much of the heritability for each disorder can be accounted for by common genetic variation and that the genetic correlation between OCD and TS is strong; explaining in part, their highly comorbid presentation. However, despite their genetic correlation, differences in the genetic architecture between OCD and TS are also apparent. For example, recently published work suggests a significant role for rare variants in the development of TS as approximately 1% of individuals with TS harbor a rare risk-increasing deletion or duplication and two synaptic genes, neurexin 1 and contactin 6, have been specifically implicated. On the other hand, polygenic risk scores for OCD have been useful in predicting obsessive-compulsive symptoms in population-based cohorts. Current genomic efforts are focused on integration of additional "omics" datasets to improve the biological interpretation of statistically robust associations from common-variant studies. Additionally, predictive power of polygenic risk scores for both TS and OCD are yielding novel associations across the "phenome" (i.e., the complete medical catalogue of human diseases and conditions) in the context of a large biobank and electronic health record. Such findings have implications for future pharmacogenomic studies of both OCD and TS. This talk will focus on recent discoveries from genome-wide analyses of OCD and TS and how these results are being used in subsequent research to better understand symptomatology, comorbidity, and treatment response.

## Speaker 3: Premika Boedhoe, Netherlands

**Title:** *Neuroimaging of obsessive-compulsive disorder: Collaborative findings*

**Abstract**
Brain imaging studies of the neural correlates of OCD have yielded inconsistent results, partly because of limited statistical power, clinical heterogeneity, and methodological differences. In this context, we initiated the ENIGMA-OCD working group. Our aim is to elucidate brain abnormalities associated with OCD by performing meta- and mega-analysis using coordinated standardized image processing and statistical analysis protocols. Here, we present findings from the largest OCD studies to date. T1-weighted MRI scans of approximately 1900 OCD patients and 1800 controls from >25 sites worldwide were processed locally using FreeSurfer to assess subcortical volumes (Boedhoe et al., 2017a) and cortical thickness and surface area (Boedhoe et al., 2017b). These measures were also used to assess structural covariance networks using graph theoretical analysis (Yun et al., *in preparation*). We also investigated white matter integrity in a subset of the data (885 OCD patients and 774 controls) by performing image analysis of

DTI scans using Tract-Based Spatial Statistics (Piras et al., *in preparation*). We found a distinct pattern of subcortical abnormalities in adult and paediatric OCD. The results showed a larger thalamus in paediatric OCD patients and a larger pallidum – possibly a consequence of illness chronicity – in adult OCD. In contrast, the cortical results indicated that the inferior parietal cortex was implicated both in paediatric and adult OCD. DTI results revealed fractional anisotropy reduction in adult OCD patients in the posterior thalamic radiation and the sagittal stratum correlating negatively with illness duration, while no changes were found in paediatric OCD. Prolonged illness duration was also associated with abnormal brain network morphology, characterized by increased importance of regions relevant for self-referential information processing, and decreased importance of regions relevant for behavioural control and visuo-spatial processing. These studies are in line with the developmental nature of OCD and neuroplastic changes during the course of the illness.

### Speaker 4: Naomi Fineberg, UK

**Title:** *Pharmacotherapy of Obsessive-Compulsive Disorder: A Translational Approach*

**Abstract**

Obsessive compulsive disorder (OCD) and obsessive-compulsive related disorders (OCRDs) are distressing and disabling disorders with high rates of psychiatric comorbidity. They pursue a chronic relapsing course. Of the disorders, OCD is the most extensively researched. Treatment with cognitive behaviour therapy or selective serotonin reuptake inhibitor (SSRI) is effective in about 50% of cases. Continuation of SSRI provides protection against relapse and emerging evidence suggests this approach is cost effective.

For SSRI-resistant OCRD, nosological and neurobiological data have informed the selection of investigational drugs and cognitive remediation strategies. Adjunctive low dose antipsychotic is supported by the most robust data, but again the effect is highly variable. Novel pharmacological compounds are under investigation, including drugs acting to modulate glutamate neurotransmission. There is however considerable scope for translational research to identify treatments that produce better overall clinical outcomes, and for clinical or somatic markers to guide treatment selection at the level of the patient, to achieve better individualised outcomes. Highly Specialized Services are helpful for the most severe and enduring cases. For these individuals, experimental somatic treatments involving neuro-modulation or ablative neurosurgery may also be considered.

## Monday 18th June 2018
## 09.45-11.30
## S15: Schizophrenia: From genes to changed brain function

Chair: Brian Dean, Australia
Co-Chair: Matthaeus Willeit, Austria

---

### Speaker 1: Dan Rujescu, Germany

**Title:** *Towards understanding the genetics of schizophrenia*

**Abstract**

**OBJECTIVES:**

Schizophrenia is affecting about 1% of the general population. Evidence for a strong genetic component to the etiology of schizophrenia was first demonstrated by classical genetic epidemiology in the form of family, twin, and adoption studies. The heritability of the disease is one of the highest within psychiatric diseases estimated between 64–81%. The mode of inheritance is complex including large numbers of genes.

**METHODS:**

This talk summarizes recent efforts to identify genetic variants associated with schizophrenia. In parallel with the technological capabilities, approaches to complex disease genetics has extended from linkage studies to candidate association studies, genome wide association studies and currently, to exome or whole genome sequencing.

**RESULTS:**

The latest and largest genome wide association study on schizophrenia was published by the schizophrenia PGC team featuring a multi-stage GWA study of 36,989 cases and 113,075 controls. 128 associations in 108 independent loci were identified with strongest associated locus being an extended region of chromosome 6 containing a large number of genes including the MHC region ($p=3.48x10^{-31}$) (The Schizophrenia Psychiatric Genome Wide Association Study (GWAS) Consortium 2014). Dan Rujescu will give an update on current work of the schizophrenia subgroup of the PGC including much more samples. Furthermore, Dan Rujescu will highlight studies on structural genetic variants as risk factors for schizophrenia. Own studies as well as latest PGC efforts will be presented. Additionally, studies on exome and whole genome sequencing will be reported.

**CONCLUSIONS:**

Future studies will address especially the functional characterization of genetic variants. This will hopefully open the doors to our

understanding of the pathophysiology of schizophrenia. Complementary, integrated systems biology approaches to genomics, transcriptomics, proteomics and metabolomics may also play crucial roles in enabling a precision medicine approach to the treatment of individual patients.

## Speaker 2: Brian Dean, Australia

**Title:** *Understanding the impact of changes in cortical gene expression in schizophrenia*

**Abstract**

Schizophrenia is a psychiatric disorder defined by the presence of a constellation of symptoms that includes positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. anhedonia and social withdrawal) and cognitive deficits[1]. Significantly, studies in monozygotic twins show concordance rates for schizophrenia of approximately 50%[2], a level of concordance that is not consistent with a wholly genetic disorder. To accommodate the hypothesis that schizophrenia is heritable but not wholly genetic in nature, it is increasingly accepted that the disorder occurs in individuals with a genetic predisposition who encounter deleterious environmental factors that trigger functional changes in central nervous system (CNS)[3]. It is now understood that in disorders that involve interactions between genes and environment, the impact of the environment is through epigenetic mechanisms acting to change gene expression[4]. Hence, in schizophrenia it would be expected changes in gene expression in CNS would be reflective of both an altered genetic profile and the impact of epigenetic pathways. This has led to a number of studies on gene expression in the cortex from subjects with schizophrenia, as a dysfunctional cortex is recognised as making a major contribution to the pathophysiology of schizophrenia[6]. These studies argue for changes in presynaptic functioning, G-protein signalling, energy and metabolism, the control of gene expression, protein degradation, glutamate neurotransmission, GABA neurotransmission, synaptic plasticity, neuronal development, neurotransmission, signal transduction, myelination, apoptosis, cell signalling, glial functioning, apolipoproteins, synaptic function, inflammation and immunity and sphingolipid metabolism in the cortex from subjects with the disorder. In this presentation, these findings will be contextualised in the light of new data suggesting changes in gene expression in the frontal pole suggest, at least in that cortical region, that a breakdown in communication between inflammatory and neurodevelopmental pathways are making a major contribution to the pathophysiology of schizophrenia. Moreover, it will be suggested that there are viable drug targets in these disrupted pathways. Finally, the possibility that changes in cortical gene expression may allow the sub-division of different sub-groups with biological homogeneity within the syndrome of schizophrenia will be discussed.

## Speaker 3: Carol Tamminga, USA

**Title:** *The potential impact of changes in protein in the CNS from subjects with schizophrenia*

**Abstract**

Recent findings from human post-mortem hippocampal analyses, characterized by a focus on subfield-enriched samples in schizophrenia and healthy control cases, showed unexpected outcomes that provide a potential clue to aspects of disease pathophysiology in psychosis. As background, we know that the hippocampus in schizophrenia is characterized by *in vivo* human brain imaging perfusion studies and, generally, a reduction in activation to memory stimuli. We did a series of experiments in human post-mortem hippocampal tissue to search for the source of this hyperactivity. Initially, we reported not only *reduced* GluN1 RNA selectively in dentate gyrus (DG), and also selectively *reduced* GluN1 protein in DG; as the essential subunit of the NMDA receptor, this suggests *reduced* glutamatergic transmission from the DG to CA3 in the mossy fiber (MF) pathway. While we then postulated reduced neuronal activity in CA, we did not find this in the human tissue; instead, we found *increased* levels of GluN2b-containing NMDA receptors (the most activating of the NMDARs), *increased* PSD-95 (associated with increased regional LTP) and *increased* numbers of postsynaptic synaptic receptor sites (associated with increased synaptic remodelling). Hippocampal cell culture studies in animals (Lee et al, 2011) show that modulation of excitatory stimulation onto proximal pyramidal cell dendrites in CA3, acts to 'tune' down or up whole cell activity through homeostatic modulation, suggesting a mechanism for hippocampal hyperactivity in schizophrenia with excitatory failure of DG. Therefore, we back-translated the human tissue findings into a DG-selective GluN1 KO mouse and show upregulation of the NMDA and the AMPA receptors on CA3 pyramidal neurons, increased downstream tissue activation in CA3, CA1 and PFC and animal behaviours of psychosis in the KO in the DG GluN1 KO mouse. We will detail results from the animal model characterization and point up potential novel treatment directions.

### Speaker 4: Peter Falkai, Germany

**Title:** *Changes in cellular structure and function in schizophrenia: Possible contribution to pathophysiology*

**Abstract**

The pathophysiology of schizophrenia is so far not well understood at the cellular and molecular level. We have therefore implemented a brain bank for severe psychiatric disorders to be able to study the pathophysiology of these disorders from the cellular to the molecular level.

I a multi-center study gene expression profiles on 22.000 genes were performed in brains of patients with Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, Schizophrenia as well as healthy controls, in order to work out differences in gene expression profiles.

Focusing on the patients with schizophrenia it could be detected that about 800 genes were differentially regulated in this disorder. Gene set enrichment analysis showed that the largest group of these genes belonged to those genes involved in immune modulation. However, compared to Alzheimer's Disease, Parkinson's Disease and Multiple Sclerosis, 369 genes including 70 immune-related genes had most interestingly been down-regulated and not up-regulated in schizophrenia. From this fact and the well documented involvement of immune-related genes in synaptic function it was concluded that this change in immune modulation does not mirror a classical degenerative process but rather belongs to the strategy of the brain to cope with disturbed dysplasticity.

In a subsequent study using laser dissection spectrometry, 50 neurons were isolated from the frozen hippocampus of schizophrenic patients. Here, a very similar pattern of down-regulated immune modulated genes could be detected. I summary, these gene expression findings are in accordance with subtle cellular changes revealed in schizophrenia and point to a dysplastic and not a neurodegenerative process.

## Monday 18th June 2018
## 14.45-16.30
## S16: The antidepressant controversy: what do reanalyses of controlled trials reveal regarding the true efficacy of antidepressants?

Chair: Elias Eriksson, Sweden
Co-Chair: Hans-Peter Kapfhammer, Austria

---

### Speaker 1: Elias Eriksson, Sweden

**Title:** *Can the superiority of antidepressants over placebo in controlled trials be explained by their side effects breaking the blind?*

**Abstract**

When the first antidepressants were tested against placebo in the 60s, it was suggested that side effects of active treatment may break the blind, and that such an effect may enhance the placebo effect in patients and/or make the investigator more inclined to rate the patient as improved. To control for this, some early trials used atropine, mimicking the anticholinergic side effect, instead of inert placebo, but with diverging results; moreover, the interpretation of these data is rendered difficult by many of the trials being marred by significant methodological shortcomings (see Quitkin et al, Am J Psych 2000:157:327). More recently, the hypothesis that the superiority of selective serotonin reuptake inhibitors (SSRIs) over placebo in controlled trials is *exclusively* due to a side-effects-breaking-the-blind mechanism however has gained considerable attention (Kirsch et al, Basic Books, 2010), but without strong scientific basis; while one study report a correlation between side effects and efficacy (Greenberg et al, J Nerv Ment Dis 1994:182:547), a more extensive analysis did not confirm this (Barth et al, Br J Psychiatry, 2016:208:114). Importantly, however, both these studies addressed a possible association between side effects and outcome on trial-level rather than on patient-level. In recent patient-level analyses, based on all drug company-sponsored, placebo-controlled, Hamilton-depression-rating-scale-based trials in adult depression of citalopram or paroxetine, we found both active drugs to clearly outperform placebo also in the absence of adverse events, and that there was a slight association between presence of adverse events and effect size in patients on paroxetine but neither in those on citalopram nor those on placebo (Hieronymus et al, Mol Psych 2017, in press). Similarly, a follow-up analysis revealed no association between side effects and response in patients treated with escitalopram (unpublished). The results argue against side-effects-breaking-the-blind being a mechanism of significance for SSRIs outperforming placebo in controlled trials.

## Speaker 2: John Krystal, USA

**Title:** *Trajectories of response and relapse in placebo-controlled major depression trials*

**Abstract**

For patients with recurrent depression, many treatment guidelines recommend lifelong antidepressant treatment is recommended for all patients. How do we reconcile these recommendations with a growing body of data that question the magnitude of benefit provided by antidepressants to alleviate depression and to prevent relapse? Further, how do we understand the benefits of antidepressants within the context of repeated descriptions of robust placebo effects? The purpose of this presentation is to highlight results from trajectory-based analyses that take advantage of large samples of patient data that can be assembled by combining the results from several large placebo-controlled clinical trials to address these issues. **STUDIES OF ACUTE ANTIDEPRESSANT RESPONSE:** We conducted analyses of 7 studies (n=2515) conducted by Eli Lilly and Company using fluoxetine and duloxetine to treat episodes of depression. This analysis revealed that placebo did not have a rapid response trajectory. Instead the trajectory of placebo response was very similar to that of medication. Approximately 75% of patients randomized to active medication had a "responder" that was similar in timecourse but modestly larger in magnitude to that of placebo. However, approximately 25% of patients had a "non-responder" trajectory that was significantly worse than the placebo trajectory. In other words, we would have predicted that the patients in this group would have been better off on placebo than on the medications they received in these trials. This would suggest that treatment non-response is not an acceptable foundation for maintenance antidepressant treatment, i.e., patients should be evaluated for poor response on an ongoing basis and changes made to treatment accordingly. **STUDIES OF ANTIDEPRESSANT DISCONTINUATION AND RELAPSE:** Results from four double-blind placebo-controlled drug discontinuation studies of up to 26 weeks in length (n=1462) were analyzed to uncover trajectories of relapse during treatment with active antidepressant or placebo (blinded discontinuation). Analyses revealed three trajectories under each condition (stable recovery, unstable recovery, relapse). There were small differences in the rate representation in the relapse class (46% relapse on placebo, 33% relapse associated with the continuation of active medication). Thus, the actual protective effect of antidepressant treatment against relapse was only 13%. In summary, antidepressant clinical trials have a great deal of information that is not mined in traditional data analyses. The results of trajectory-based analyses provide new insights into treatment that inform our expectations for treatment-related outcomes, with implications for improving treatment outcomes.

## Speaker 3: Andrea Cipriani, UK

**Title:** *An update on the relative efficacy of different antidepressant in children and adults*

**Abstract**

There is debate in the literature whether inclusion of placebo arm may alter characteristics of antidepressant trials. However previous research has focused on response rates of various antidepressants on average only, ignoring potential differences among drugs or other aspects of trial findings. Little is known about the impact of placebo arm in all-cause dropout and dropout due to adverse events. We carried out a systematic review of published and unpublished double-blind RCTs for the acute treatment of unipolar major depression. The probability of being allocated to placebo (π) was the exposure of interest and we examined its influence on responders (efficacy), all-cause dropouts (acceptability) and dropouts due to adverse events (tolerability), whilst accounting for differences in drugs, trial and patient characteristics in the multivariate random effects meta-regression. 421 studies (68 305 participants) comparing 16 antidepressants or placebo were included. π ranged from 20% to 50%. Response rate was lower (RR 0.87; 95% CI 0.83, 0.92) and all-cause dropout rate higher (RR 1.19; 95% CI 1.08, 1.31) for the same antidepressants in placebo-controlled trials than in head-to-head trials. The probability of responding decreased by 3% (95% CI 2-5%) for every 10% increase in π, whereas the risk of all-cause dropout increased by 4% (95% CI 1-7%). Tolerability was unaffected by π. Response rate was inversely correlated with dropouts due to any cause (correlation coefficient -0.48; 95% CI -0.58, -0.36) and due to adverse events (-0.34; 95% CI -0.44, -0.23). For the same antidepressant, response rate was on average smaller and dropouts higher, when placebo was included; however no association was found with dropouts due to adverse events. Decreased patients' expectations, larger dropout rates and use of inappropriate statistical methods to impute missing data may explain this phenomenon. The findings call for caution in the integration of randomised evidence involving placebo arms.

### Speaker 4: Fredrik Hieronymus, Sweden

**Title:** *Influence of dose and baseline severity on the response to selective serotonin reuptake inhibitors*

**Abstract**

Two controversial issues regarding the effect of selective serotonin reuptake inhibitors (SSRIs) in depression are i) if it is dose-dependent and ii) if only subjects with severe depression experience a clinically meaningful response. In this lecture, these issues will be reviewed, and recent analyses shedding further light on them presented. Reviews regarding dose-escalation of SSRIs in the case of non-response suggest this to not be a productive strategy (Ruhe et al. Br J Psychiatry 2006;189:309), and several authors have reported the SSRI dose-response curve to be "flat". However, there are also meta-analyses claiming that the antidepressant effect of SSRIs is indeed dose-dependent (Papakostas et al. World J Biol Psychiatry 2010;11:300, Jakubovski et al. Am J Psychiatry 2016;173:174). In recent patient-level mega-analyses, based on all drug-company-sponsored, placebo-controlled, Hamilton-depression-rating-scale-based trials in adult depression of citalopram, paroxetine and sertraline, we found clear-cut evidence for low doses (citalopram ≤20mg/day, paroxetine ≤10mg/day and sertraline ≤50mg/day) being suboptimal, but no support for very high doses being more effective than 40mg/day, 20mg/day and 100mg/day, respectively. We conclude that recent meta-analyses have underestimated the efficacy of SSRI by including suboptimal dosage.With respect to the impact of baseline severity, several meta-analyses suggest the response to SSRIs to be positively associated with Hamilton scores at baseline, only those with severe depression displaying a meaningful response (Kirsch et al. PLoS Med 2008;5:e45); others however have seen no such association on either trial level (Melander et al. Eur Neuropsychopharmacol. 2008;18:623) or patient level (Rabinowitz et al. Br J Psychiatry. 2016;209:427). When addressing this issue using the above-mentioned data set we find i) the choice of outcome measure to be of considerable importance in this context and ii) that SSRIs are clearly effective also in the patients that are the least depressed at baseline, i.e. those with Hamilton-rating ≤18 points.

## Monday 18th June 2018
## 14.45-16.30
## S17: It's all in the wiring: Brain circuits involved in depression and antidepressant actions

Chair: Alan Frazer, USA
Co-Chair: Rupert Lanzenberger, Austria

---

### Speaker 1: Anthony Grace, USA

**Title:** *Quetiapine as an antidepressant medication: Activating effects on the mesolimbic dopamine system in a model of depression*

**Abstract**

Quetiapine as an antidepressant medication: Activating effects on the mesolimbic dopamine system in a model of depression Anthony A. Grace and Jared. The primary treatment used for depression for decades has relied on serotonin and/or norepinephrine uptake blockade. However, as with many drugs used to treat psychiatric disorders, these drugs were discovered by serendipity rather than on a firm neuropathological foundation. As a consequence, the current drug treatments are not as efficacious as one would prefer, with more than 30% of patients not deriving adequate treatment benefit. As a result, an effort has been made to discover alternate avenues of treatment. Emerging literature has suggested a role for the dopamine system in depression, based on the known involvement of dopamine in anhedonia and amotivational states; two key disruptions characteristic of major depressive disorder. Indeed, much basic research has found that in several animal models of depression, there is an attenuation of dopamine system responsivity that could account for such characteristics. One quandary this brings about is why second-generation antipsychotic medications, that are primarily dopamine antagonists, would be effective as adjunctive or monotherapeutic treatments for major depressive disorder. Using the chronic mild stress (CMS) paradigm, we have reported a substantial decrease in dopamine neuron responsivity, in which there is a decrease by more than 50% in the number of dopamine neurons spontaneously active. We now report that the D2 dopamine receptor antagonist quetiapine administered acutely increased DA neuron population activity in the VTA of control rats – but not in rats exposed to chronic mild stress model of depression. However, with repeated treatment with quetiapine at low, antidepressant doses (3 weeks at 10 mg/kg), the number of dopamine neurons firing in CMS rats was returned to normal levels of activity. These results suggest a novel mechanism for second generation antipsychotic

drugs in restoring DA system responsivity in anhedonia.

## Speaker 2: Alan Frazer, USA

**Title:** *The hippocampus as an initial target for novel antidepressants*

**Abstract**

The efficacy of ketamine for depression has broadened research from traditional studies of biogenic amine involvement to that of neurotransmitters such as glutamate and GABA and their circuitry. Previously, Dr. Frazer and his colleagues found a ventral hippocampus (vHipp)/medial prefrontal cortex (mPFC) circuit to be important for the antidepressant-like effect of ketamine in rats. It is likely though that a different circuit is involved in some of its adverse effects. To explore this, we initiated studies with negative allosteric modulators (NAMs) of α5-$GABA_A$ receptors, given that this subunit is expressed primarily in the hippocampus. Such drugs reduce GABAergic transmission in the hippocampus, as is so for ketamine- albeit by a different mechanism. One such drug, L655, 708, produced sustained antidepressant-like effects in the forced swim test, similar to those of ketamine, but unlike ketamine did not alter pre-pulse inhibition or startle nor have reinforcing effects as shown by intravenous self-administration. Mechanistically, L-655,708 differed from ketamine in that it did not activate the receptor for BDNF, namely TrkB, in the hippocampus. In addition, use was made of a PathScan approach that allows for the simultaneous detection of proteins including multiple receptor tyrosine kinases and signaling nodes when phosphorylated. The results confirmed that TrKB was not activated by L-655, 708, nor were other receptor tyrosine kinases. Of the proteins analyzed, only ERK activation increased in the vHipp and this was confirmed by western blot analysis. Furthermore, CamKII phosphorylation in the vHipp increased following L-655,708 administration. Similar to ketamine, though, blocking AMPA receptors in the mPFC prevented L-655, 708's sustained antidepressant-like effect.

By selectively acting on the hippocampus, drugs reducing GABAergic inhibition of output glutamatergic neurons to the mPFC may produce the beneficial effects of ketamine without its more serious adverse effects.

## Speaker 3: Christian Beckmann, Netherlands

**Title:** *Networks in the brain: using functional connectivity to characterise psychiatric disorders and guide treatment development*

**Abstract**

Large clinical and population cohort neuroimaging resources are increasingly coming online, forming a new field of imaging epidemiology. These offer a unified perspective that links brain connectional organization to behaviour and cognition. Currently, however, the full potential of these resources for understanding brain connectivity is not being realized. This is due to a lack of suitable analysis tools that explore relationships between and integrate across modalities, are sensitive to subtle changes in individual connectivity profiles and provide a means to move beyond simple case-control analysis towards understanding inter-individual differences in connectivity. In this talk I will outline novel approaches for charting the organisation of functional connectivity and introduce a 'normative modelling' strategy for utilising big cohort data for generating individualised predictions with application for imaging in psychiatric disorders.

## Speaker 4: Marie Spies, Austria

**Title:** *The default mode network and antidepressant treatment response prediction*

**Abstract**

**Objectives:**

Studies have shown that symptom improvement after two weeks of antidepressant treatment predicts later response and remission [1]. Functional magnetic resonance imaging (fMRI) studies demonstrate changes to brain activation patterns during emotion processing in major depressive disorder (MDD) and its treatment. Prediction of antidepressant response based on neuroimaging data is a current topic of great interest in translational neuroscientific research. This talk will present a recently published paper in which we used fMRI to assess whether brain activity during emotion processing predicts early antidepressant response in patients with MDD [2].

**Methods:**

In this study, 7T ultra high-field fMRI was used to assess brain activity during an emotion discrimination (EDT) task in 23 patients with MDD. Patients were then treated with Escitalopram. Response to SSRI treatment was assessed using the Hamilton Depression Rating Scale.

**Results:**

Deactivation within key regions of the default mode network (DMN) during emotion processing

predicted symptom improvement after two, but not four weeks of treatment.

**Conclusions:**

Previous studies suggest that deactivation of the DMN during cognitive and emotional tasks is inversely related to depressive symptoms [3]. In our study, more pronounced deactivation was associated with better early response. The correlation between DMN deactivation and two- but not four-week, symptom improvement may reflect that this finding predicts treatment effects that occur early on, but do not persist. On the other hand, treatment effects were only assessed after four weeks, and longer studies are necessary to elucidate how prediction of early response carries over to more long-term treatment effects. The ability to foresee antidepressant response early in treatment would allow psychiatrists to treat their patients more efficiently, hereby lowering patient burden.

## Monday 18th June 2018
## 14.45-16.30
## S18: Behavioural addiction: a research and clinical update

Chair: Sam Chamberlain, UK
Co-Chair: Christa Rados, Austria

---

### Speaker 1: Naomi Fineberg, UK

**Title:** *Introduction to the concept of behavioural addiction: how did we get here?*

**Abstract**

The term 'addiction' was traditionally used in relation to psychoactive substances. Addiction is not a unitary construct but incorporates several features. Core aspects, according to the Diagnostic and Statistical Manual Version 5 (DSM-5) (American Psychiatric Association 2013), include impaired control (e.g. craving increasingly large quantities, unsuccessful attempts to reduce intake), impairment (e.g. narrowing of interests, neglect of other areas of life), risky use (persisting intake despite awareness of damaging psychological or physiological effects), and pharmacological criteria (tolerance, withdrawal). Certain psychiatric syndromes characterised by repetitive habits share considerable phenomenological parallels with substance addiction, and have thus been argued to represent candidate 'behavioural addictions'. Accordingly, the DSM-5 introduced the category 'Substance Related and Addictive Disorders', and included gambling disorder as the first example of behavioural addiction. However, questions remain concerning whether this and other disorders, such as kleptomania, compulsive sexual behaviour, 'Internet addiction', hair pulling disorder, and skin-picking disorder, should also be conceptualized as addiction. Whereas many clinical aspects appear much like addiction, further characterisation of the psychopathology is required. Yet, there is a scarcity of centres with the skills and capacity to build studies to validate new findings based on reliable research methodology. This presentation explores what is meant by 'behavioural addiction', and critically considers the evidence for and against this conceptualisation in respect of the above conditions, from perspectives of aetiology, phenomenology, co-morbidity, neurobiology, and treatment. Research in this area has important implications for future diagnostic classification systems, neurobiological models, and interventions.

### Speaker 2: Jon Grant, USA

**Title:** *Neurobiology and treatment of gambling disorder and compulsive sexual disorder*

**Abstract**

Background: Gambling disorder and compulsive sexual behavior and compulsive shopping are common and yet under-treated problematic behaviors. Although not included in DSM-5 or the ICD-10, these behaviors have a long history in the medical literature.

Methods: Research on the neurobiology, clinical presentation and treatment of these behaviors are examined. Prevalence studies, phenomenology research, neurobiological/neurocognitive data, and treatment trials are presented.

Results: Gambling disorder and compulsive sexual behavior are common disorders based on prevalence studies with distinct clinical presentations. Randomized, placebo-controlled medication trials and cognitive behavioral studies have shown promising results.

Discussion: Mental health clinicians need to screen patients for gambling disorder and compulsive sexual behavior are common problematic behaviors, have significant associated distress, and can be treated.

### Speaker 3: Samuel Chamberlain, UK

**Title:** *Hair-pulling and excoriation disorders: obsessive-compulsive, impulsive, or addictive?*

**Abstract**

Hair-pulling disorder (trichotillomania) and excoriation (skin picking) disorder are poorly understood mental disorders, now listed in DSM-5 as Obsessive-Compulsive Related Disorders. Despite this current conceptualization, other evidence suggests features in common with impulse control disorders, or with the addiction

related disorders. This presentation will provide an overview of hair pulling disorder and excoriation disorder, from the perspectives of aetiology, phenomenology, co-morbidity, neurobiology, and treatment. The talk will have a special focus on existing neurobiological models including preclinical work, and shall present as-yet unpublished novel data revealing subcortical abnormalities in these conditions, along with pilot data indicative of immune and inflammatory dysfunction; as well as changes in pain regulation. We will see that these disorders often co-occur, and that translational research implicates dysregulation of reward circuitry (ventral striatum; impulsivity), shift over time to habitual acts (dorsal striatum; compulsivity), and a lack of top-down control (manifesting, for example, on stop-signal response inhibition tasks). Lastly, we shall consider existing evidence-based treatments as well as emerging novel avenues for treating, involving the glutamatergic system.

### Speaker 4: Brian Odlaug, Denmark

**Title:** *How to conceptualise and treat compulsive shopping, stealing, and Internet use*

**Abstract**

Compulsive buying, stealing (or "kleptomania"), and Internet use comprise three similar yet disparate psychiatric conditions. Each is associated with significant psychosocial and personal consequences, often inducing shame, embarrassment, and social isolation. While compulsive buying and kleptomania have a storied and well-documented literary foundation dating back over 100 years, only recently has the media and academia begun to recognize the deleterious impact these disorders may have on individual health and well-being.

What is known about these disorders from a psychiatric perspective, however, is far less than what is unknown at the present time.

While research has helped to illuminate neurobiological and neurocognitive profiles of these conditions, endophenotypic markers and the aetiology of these conditions are currently lacking. It appears, however, that each of these conditions shares similarities to other behavioral and substance addictions and obsessive-compulsive disorder as illustrated through clinical presentation and overlap (e.g., comorbidities) and data from functional and structural neuroimaging studies.

Gaining a better understanding of these conditions is both prudent and timely. Given the atmospheric rise of the Internet over the past 20 years and nearly exponential expansion of access to smart phones and devices worldwide, how individuals interact in cyberspace and how unfettered access impacts the individual (and in particular the developing adolescent brain) is becoming an area of increasing interest to mental and public health professionals. Access to online content and goods poses concerns for both compulsive Internet use and compulsive buying although the short- and long-term impact on both are areas is both unknown and in urgent need of examination.

With this and further research, one can hope to identify potentially safe and efficacious psychological and pharmacologic treatments for compulsive buying, kleptomania, and compulsive Internet use and decrease their subsequent burden on the individual and society.

## Monday 18th June 2018
## 14.45-16.30
## S19: Dopamine signal intensity in neuropsychiatric disorders: etiology and therapy

Chair: Kazutaka Ikeda, Japan
Co-Chair: Gabriele Sachs, Austria

---

### Speaker 1: Kazutaka Ikeda, Japan

**Title:** *Neuropsychiatric phenotypes in dopamine deficient mice and dopamine-transporter knockout mice*

**Abstract**

Dopamine (DA) plays an essential role in brain function, including motor control, reward, and psychosis. Low levels of DA and the blockade of DA neurotransmission generally cause hypolocomotion. By contrast, high levels of DA and enhanced DA neurotransmission generally cause hyperlocomotion that is considered to be relevant to psychosis. Some disorders, such as drug addiction and schizophrenia, have been reportedly associated with DA neuron activation in the mesocorticolimbic system. Almost all antipsychotic drugs block DA neurotransmission. However, several phenomena that are inconsistent with this theory have been clinically reported. Effective movement in Parkinson's disease in certain situations (i.e., kinesia paradoxia) indicates locomotor ability even at low DA levels. Typical antipsychotic drug-resistant and atypical antipsychotic drug-sensitive positive symptoms in schizophrenia indicate that at least a subgroup of positive symptoms is untreatable by the blockade of DA neurotransmission. To reveal

the mechanisms that underlie these phenomena, we analyzed DA-deficient mice and DA transporter knockout mice. Interestingly, DA-deficient mice exhibited hyperlocomotion that was ameliorated by clozapine but not by haloperidol. Hyperlocomotion in DA-deficient mice was also ameliorated by the muscarinic acetylcholine receptor agonist oxotremorine and the choline esterase inhibitor donepezil. Hyperactivity at ultra-low levels of DA may be a model of typical antipsychotic-resistant and clozapine sensitive psychotic symptoms. By contrast, DA transporter knockout mice exhibited hyperactivity that was ameliorated by methylphenidate. Hyperactivity at high levels of DA in the striatum may underlie the etiology of attention-deficit/hyperactivity disorder (ADHD), and the amelioration of hyperactivity at high levels of DA in the frontal cortex may underlie the mechanisms of pharmacotherapy of ADHD.

## Speaker 2: Naoshige Uchida, USA

**Title:** *Multiple dopamine systems*

**Abstract**

**Dopamine-related drugs have been used t**o treat various psychiatric disorders. However, the actions of these drugs have been difficult to understand and largely anecdotal, preventing rational treatment methods. Much of the work on dopamine has been guided by the dogma that dopamine neurons encode reward prediction errors (RPE = actual minus expected reward) and that they do so in a uniform manner. However, work from several groups, including ours, has indicated that dopamine neurons projecting to different targets exhibit distinct properties and serve distinct functions. Interestingly, dopamine neurons projecting to the posterior 'tail' of the striatum (TS) differ in many ways from dopamine neurons projecting to the ventral striatum (VS) and other regions. VS-projecting dopamine neurons, which signal 'canonical' RPEs, are activated by reward and inhibited by negative events. By contrast, TS-projecting dopamine neurons are activated by novel stimuli and by a subset of negative events. In this talk, I will discuss novel functions of TS-projecting dopamine neurons. These recent results point to the presence of multiple dopamine systems defined by their projection targets, which are different with regard to anatomy, activity and function. I will then discuss potential implications of our findings in various psychiatric disorders such as autism and bipolar disorders.

## Speaker 3: Tetsuro Kikutchi, Japan

**Title:** *The pharmacological and clinical implications of the dopamine D2 receptor partial agonists aripiprazole and brexpiprazole*

**Abstract**

Based on the dopamine hyperactive theory of schizophrenia, Otsuka Pharmaceutical Co. firstly researched on OPC-4392, a dopamine autoreceptor agonist in the 1980s. This research evolved into studying novel compounds that exhibit agonistic and antagonistic activities at presynaptic dopamine autoreceptors and at postsynaptic dopamine $D_2$ receptors, respectively. This led us discovering aripiprazole, a novel antipsychotic with dopamine $D_2$ receptor partial agonistic activity. Aripiprazole is the first antipsychotic proven to be clinically effective without belonging to a class of $D_2$ receptor antagonists. Then, we recently succeeded in developing the second dopamine $D_2$ receptor partial agonist, brexpiprazole. Compared to aripiprazole, brexpiprazole is more potent at serotonin 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors and displays less intrinsic activity at dopamine $D_2$ receptors. I will review the history of the research and development of aripiprazole and brexpiprazole, and will show the pharmacological activities and clinical implications.

## Speaker 4: Junhee Lee, Korea

**Title:** *The neurobiology of treatment resistant schizophrenia in aspect of dopaminergic systems in the brain*

**Abstract**

Schizophrenia is thought to be a heterogeneous disorder in terms of underlying neurophysiological mechanisms. In particular, it has been proposed that schizophrenia could be subclassified on the basis of dopamine dysfunction into a hyperdopaminergic form that responds well to first-line antipsychotics and a normodopaminergic form that shows limited response to these treatments, which is considered to be treatment resistant.

Indeed, molecular imaging studies have reported that treatment resistant patients show lower striatal dopamine synthesis capacity compared to that of patients who have responded well to first-line antipsychotic drugs, which supports the idea that there are neurobiologically distinct subtypes in schizophrenia linked to treatment response. Moreover, the differences were most marked in the part of the striatum functionally linked to dorsolateral frontal cortical regions; termed the associative striatum. In addition, recent data demonstrated that the striatal dopaminergic

activity was related with the frontostriatal connectivity in patients with schizophrenia who responded well to the first-line while the treatment resistant schizophrenia did not show the relationship. Together with the difference in dopamine synthesis capacity, the different patterns of relationship between striatal dopamine capacity and fronto-striatal connectivity support different pathophysiology underlying schizophrenia according to the responsiveness to antipsychotic drugs.
We will review all the molecular imaging studies regarding treatment responsiveness and discuss about the neurobiology of treatment resistant schizophrenia in aspect of dopaminergic systems in the brain.

## Monday 18th June 2018
## 14.45-16.30
## S20: D-lysergic acid diethylamide (LSD) and classical hallucinogens: preclinical and clinical studies in psychiatric disorders

Chair: Gabriella Gobbi, Canada
Co-Chair**:** Johannes Tauscher, USA

### Speaker 1: Gabriella Gobbi, Canada

**Title:** *D-lysergic acid diethylamide (LSD) and classical hallucinogens: mechanism of action and pharmacology*


**Abstract**

Background: The hallucinogen D-lysergic diethilamide (LSD) has been recently used at low doses as an antidepressant and "creativity enhancer", but at the same time it can also produce pseudo-hallucinations or "bad trips". The mechanism of action underlying these different effects is still unknown. The goal of this study was to understand the effect of LSD on serotonin (5-HT) system and its potential interactions with the dopamine (DA) neurons and the trace-amine associated receptor 1 ($TAAR_1$). Methods: Using *in vivo* electrophysiology, we studied the effects of cumulative doses of LSD (5-120 ug/kg, i.v.) on both DRN 5-HT and VTA DA neurons in rodents. The dopamine D2 antagonist haloperidol (50 µg/kg, i.v.), the 5-HT1A antagonist WAY-100,635 (500 µg/kg, i.v.), the 5-HT2A antagonist MDL100907 (500 µg/kg, i.v.), and the trace amine-associate receptor 1 ($TAAR_1$) antagonist EPPTB (5 mg/kg, i.v.) were also tested. The p-chlorophenylalanine (PCPA) (350 mg/kg, i.p.) was used for 5-HT depletion. Results: Low doses of LSD (5-20 µg/kg, i.v.) induced a significant decrease of DRN 5-HT firing activity, compared to vehicle ($P$ < 0.001), through $5\text{-}HT_{2A}$ and $D_2$ receptors. At these doses, LSD did not alter VTA DA neuronal activity ($P$ = 0.463). On the contrary, higher doses of LSD (30-120 µg/kg, i.v.) dose-dependently decreased VTA DA firing activity, as compared to vehicle ($P$<0.001). The depletion of 5-HT synthesis with PCPA did not affected the effects of LSD on DA firing activity. The inhibitory effects of LSD on VTA DA firing activity were prevented by D2, 5-HT1A and TAAR1 antagonists. Discussion: These results suggest that LSD at low doses affects 5-HT system, while at high doses the DA mesolimbic neuronal activity in a 5-HT independent manner, and with a pleiotropic mechanism involving $5\text{-}HT_{1A,}$ $D_2$ and $TAAR_1$ receptors. This dual mechanism may explain the effects of LSD on mood at low doses, and its psychotic-like effects at higher doses.


### Speaker 2: Danilo De Gregorio, Italy

**Title:** *Low doses of d-lysergic acid diethylamide (LSD) exerts antidepressant-like effect and modulates serotonergic neurotransmission*


**Abstract**



De Gregorio D.[1,2], Enns J.[1], Posa L.[1], Aguilar-Valles A.[2], Lopez-Canul M.[1], Sonenberg N.[2], Gobbi G.[1]
1 Department of Psychiatry, McGill University, Montreal, QC, Canada
2 Department of Biochemistry, The Goodman Cancer Centre, McGill University, Montreal, QC, Canada



Introduction: D- lysergic diethylamide acid (LSD) is a hallucinogen that is used for his effects on mood and creativity. We have recently shown that low doses LSD (5-20 µg/kg) decreased the activity of serotonin (5-HT) neurons in Dorsal Raphe Nucleus (DRN) while at higher doses (60-120 µg/kg) it induced a cessation of DA neurons in Ventral Tegmental Area (VTA). Thus, we have hypothesized that low doses LSD could reverse depressive symptoms and increase the 5-HT firing activity. Methods: A 14 day chronic stress (CS) paradigm was performed in C57BL/6J mice. From 7th to 14th day of stress, CTL and CS mice received subcutaneous LSD (30 µg/kg/day) or vehicle and tested on 15th day. *In vivo* extracellular recordings of 5-HT DRN neurons and behavioral tests (Open Field (OF), Forced Swim (FS) and Novelty Suppressed Feeding (NSF)) were employed. Results: CS mice showed a decreased mean firing activity of 5-HT DRN neurons compared to CTL (p<0.05). LSD (15 and 30, µg/kg/day, for 7 days) restored firing rates to CTL group levels (p<0.05). In the OFT, CS mice spent less time in the center of the arena, compared to CTL group (p<0.05). Frequency of the entrancies in the center was also reduced

($p<0.05$). Treatment with LSD (30 µg/kg/day, for 7 days, s.c) normalized time spent and the frequency of the entrancies in the center to CTL levels ($p=0.024$). The CS group showed increased immobility time compared to CTL mice in the FST ($p = 0.009$), while LSD (30 µg/kg/day,s.c., for 7 days ) reversed this immobility. Moreover, the NSFT revealed that LSD (15 and 30, µg/kg/day, s.c) reduced the latency to feed in CS mice ($p<0.001$), increased after 14 days of CS.
Discussion: This study reports that low doses of LSD reverses depression and 5-HT activity.

This study was supported by The Fonds de recherche du Québec – Santé (FRQS)

## Speaker 3: Katrin Preller, Switzerland

**Title:** *LSD-induced states: behavioral and neuroimaging studies in humans*

### Abstract

Due to their unique effects on consciousness, psychedelics such as LSD offer the opportunity to investigate the neuropharmacological mechanisms underlying alterations in perception and cognition important for increasing our understanding of psychiatric disorders. Furthermore, renewed interest in the potentially beneficial clinical effects of psychedelics warrants a better understanding of their underlying neuropharmacological mechanisms. However, since research with LSD has been stalled since the late 1960s, major knowledge gaps remain regarding LSD's neurobiology in humans.
By combining behavioral and neuroimaging methods with the administration of LSD with and without pretreatment with the serotonin 2A receptor antagonist Ketanserin, we show that LSD modulates brain connectivity and subjective effects via agonistic activity on the serotonin 2A receptor in humans. In particular, LSD-induced alteration in brain connectivity are characterized by a synchronization of sensory functional networks and dis-integration of associative networks. Furthermore, we elucidate the neuropharmacology of self-relevance and meaning processing, as well as the intertwined relationship between self-processing and social cognition. LSD induces attribution of personal relevance to previously meaningless stimuli and modulates the processing of meaningful stimuli in cortical midline structures. Moreover, LSD attenuates the differentiation between self- and other processing within a real-time social interaction paradigm affecting basic social interaction abilities.
Our results thus attenuate major knowledge-gaps regarding the neurobiology and neuropharmacology of LSD. Furthermore, they increase our mechanistic understanding of personal relevance processing and social cognition. Therefore, they offer important directions regarding the development of novel therapeutics for the treatment of psychiatric illnesses characterized by trans-diagnostic alterations in personal relevance attribution and social cognition.

## Speaker 4: David Nutt, UK

**Title:** *Psylocibin and serotonin hallucinogens: a new avenue for treatment resistant-depression*

### Abstract

Many therapeutic drugs are also subject to abuse in recreational settings. This abuse has driven the international community to attempt to control it through controls such as the UN Conventions of 1960 and 1971. Almost invariably these controls have failed to limit recreational use but have severely impeded research. This is especially true for drug controlled in Schedule 1 of the conventions for example cannabis psychedelics and MDMA. I believe these controls represent the worst censorship of research in the history of science. My talk will focus on the lost opportunities for neuroscience research and treatment innovation that these bans produce. I will share our recent data on how human research with psychedelics and MDMA has given remarkable new insights into brain processes such as consciousness and mood regulation with exciting if preliminary data on treatment efficacy in conditions such as depression and addiction. Finally I will argue that an enlightened approach to the use of such drugs will open up a new era of neuroscience research, and one especially important given the pull-out of "big pharma" from brain research.

*Nutt DJ, King LA, Nichols DE (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. Nat Rev Neurosci. Aug;14(8):577-85. doi: 10.1038/nrn3530. Epub 2013 Jun 12.*

**Monday 18th June 2018**
**14.45-16.30**
**CP03: Treatment Resistant Depression**
Chair: Lakshmi Yatham, Canada
Co-Chair: Shih-Ku Lin, Taiwan

**Speaker: Siegfried Kasper, Austria**

**Abstract**
Ketamine, the first rapid-acting antidepressant, is generating both excitement and concern within the treatment community. The purpose of this clinical perspective is to consider the current status of ketamine as a treatment for depression. It will begin by briefly highlighting limitations of current antidepressant treatment that create interest in ketamine. It will then review the current state of the clinical results with ketamine in clinical trials for unipolar and bipolar depression, OCD, and PTSD. It will highlight its rapid efficacy, robust effects in treatment-resistant populations, efficacy for suicide, and potential use for special populations (comorbid pain, psychotic depression, etc.). It will also review safety issues including its dissociative effects and abuse liability and consider strategies to manage these effects. This presentation will also consider ketamine within the context of long-term treatment. Lastly, it will consider the question, "how does ketamine work?" as the answer to this question may point to other rapid-acting antidepressant mechanisms.

**Monday 18th June 2018**
**14.45-15.45**
**Special Lecture**
Chair: Brian Dean, Australia

**Speaker: Josh Gordon, USA**
**Title:** *From gene to behavior; analysis of the 22q11 microdeletion*

**Abstract**
Advances in our understanding of the genetic basis of psychiatric illness have helped guide mechanistic studies of the neurobiological functions of genes and disordered behavior. Rare genetic variants that confer significant risk for developing psychiatric illness can uniquely inform the complex relationship between genetics and behavior. The 22q11.2 microdeletion variant confers a 20-30 fold increased risk of developing schizophrenia, and is associated with profound cognitive deficits; comparable to those seen in the disorder. Dr. Gordon will discuss research conducted in his lab and through collaborations, on the molecular and neural circuit basis of cognitive deficits in mouse models of the 22q11.2 microdeletion. His talk will focus on evidence that abnormal connectivity and miscommunication between two brain structures,(the prefrontal cortex and hippocampus), underlies working memory impairments in mice deficient for genes within the 22q11.2 locus. He will also discuss pharmacological interventions during development that may reverse these neural connectivity and behavioral abnormalities.

**Monday 18th June 2018**
**16.45.17.30**
**PL04: Modeling and predicting developmental trajectories of neuropsychiatric dimensions**
Chair: Shigeto Yamawaki, Japan

**Speaker: Noboru Hiroi, USA**

**Abstract**
Various cognitive capacities, such as executive functions and social cognition, continually develop from childhood to adulthood and the developmental trajectories of these dimensions derail in individuals with neuropsychiatric disorders. However, it is not well understood how such atypical cognitive dimensions contribute to the onset of neuropsychiatric disorders. Moreover, the mechanistic basis through which genetic variants determine the trajectories of cognitive dimensions is still poorly understood. Knowledge of these two aspects is essential to develop mechanism-based therapeutic options. I will present the latest advances in our understanding of 1) how variants of individual genes encoded in 22q11.2 copy number variants alter the developmental trajectories of cognitive dimensions and 2) potential neuronal substrates underlying such processes in mouse and cell models.

# CINP 2018 – Speaker Abstracts

**Tuesday 19th June 2018**
**08.45-09.30**
**The Arvid Carlsson Lecture**
**PL05: A circuits-first approach to mental illness**
Chair: Pierre Blier, Canada

---

**Speaker: Amit Etkin, USA**
**Title:**

**Abstract**
Over the past two decades, neuroimaging studies have defined a set of distributed brain systems that contribute to cognition, emotion, mood and other mental processes. Perturbations in these circuits have been identified in different ways across psychiatric disorders. The challenge ahead of us is how to use these insights to: 1) understand the nature of neural circuit deficits in mental illnesses and their relevance for existing treatments, and 2) to develop novel circuit-based therapeutics. I will discuss work in the lab defining the neural circuit abnormalities associated with psychiatric disorders as a whole, as well as specific changes associated with particular mood and anxiety disorders (and subgroups within them). I will then examine the mechanisms of current medication, psychotherapy and brain stimulation treatments within the context of a circuit-based understanding. Finally, I will describe new methods for direct and non-invasive probing and manipulation of circuits and insights that this brings for the development of new circuit-targeting therapeutics. Together, these data suggest that we are now on the brink of innovations in "rational" circuit-based diagnosis and treatments for mental illness. Success down this path will take us beyond use of symptom checklists for diagnosis, and one-size-fits all treatment with the psychopharmacological and psychotherapeutic tools currently available.

**Tuesday 19th June 2018**
**09.45-11.30**
**S21: Understanding the mechanism of action of ketamine-like drugs in mood disorders and their implementation in the clinic.**
Chair: Jennifer Phillips, Canada
Co-Chair: Richard Frey, Austria

---

**Speaker 1: Gerard Sanacora, USA**
**Title:** *Molecular and cellular mechanisms for the rapid-onset of antidepressant-like effects*

**Abstract**
The discovery of ketamine's rapid onset of antidepressant action has infused new optimism into the field of antidepressant drug development and opened new areas of research into mechanisms of antidepressant drug action and mood disorders pathophysiology. This presentation will summarize the results of several studies employing novel Carbon-13 magnetic resonance spectroscopy methods designed to explore the molecular and cellular mechanisms by which various agents induce rapid onset antidepressant effects. Specifically, data showing dose and time dependent changes in amino acid neurotransmitter 13C-labeling following exposure to ketamine and other drugs targeting the NMDA receptor in rodent models will be discussed. We will discuss the relationship between these effects on 13C-labeling, reflecting altered glutamate/glutamine cycling and neuroenergetics, and behavior as it pertains to both the rapid onset of antidepressant effects and possibly the alterations in cognition and perception that are associated with ketamine. Additional, early stage work will be presented suggesting the 13C-methodology could be adapted for use in human studies to examine the effects of ketamine and other putative rapid onset antidepressant drugs on glutamate neurotransmission. Lastly, an attempt will be made to synthesize the data produced by these studies with other findings suggesting activation of AMPA receptors and neurotrophic pathways are necessary for the sustained antidepressant-like effects of these drugs.

## Speaker 2: Milan Scheidegger, Switzerland

**Title:** *Exploring the antidepressant effects of ketamine: Insights from multimodal neuroimaging*

**Abstract**

Recent work will be presented, investigating the differential effects of racemic vs. S-ketamine in healthy subjects and patients with major depressive disorder (MDD) using multimodal neuroimaging of brain function, perfusion, and glutamatergic metabolism. Specifically, ketamine effects on glutamatergic neuroreceptor plasticity, brain network connectivity, cognition-emotion interaction and amygdala reactivity will be described in detail. Combining molecular and functional brain imaging approaches in a multimodal way opens up novel possibilities of integrating findings from different levels of neuronal organization in order to build systems-level models of brain function and dysfunction that characterize affective disorders such as depression.

## Speaker 3: Bashkim Kadriu, USA

**Title:** *Behavioural, peripheral, and central nervous system biomarkers for treatment response of ketamine-like drugs*

**Abstract**

Specific objective: The use of the rapid-onset antidepressant ketamine could facilitate our understanding of the neurobiology of the response and relapse processes found in mood disorders. To determine the biomarkers involved in response to ketamine. Methods: We present data on the recently completed Ketamine "MOA" study in where 34 drug-free MDD/TRD patients and 25 healthy controls completed a crossover trial with i.v. ketamine 0.5 mg/kg or placebo 2 weeks apart. Multi-modal biological assessments were collected longitudinally throughout the study to capture the neurobiology of response and relapse. Biological assessments included sMRI, fMRI, DTI, MRS, polysomnography, magnetoencephalography, metabolomics, and miRNA. Significant decreases in depressive, anxiety, and anhedonia symptoms were seen with ketamine compared to placebo. Results: We found that ketamine produces pan-therapeutic effects and distinct behavioral effects in depressed and healthy subjects, supporting the concept of depression as a disorder of homeostatic dysregulation. Our results suggest that ketamine induces a normalization of aberrant brain activity, both at a cellular level (gamma power) and at a systems level (cognitive and emotional task based fMRI; resting state fMRI). Our observed resting state connectivity changes in the insula in TRD subjects suggest that ketamine may normalize the interaction between the default mode network and salience networks, supporting the triple network dysfunction model of MDD. Our MRS results also hinted at a potential subgroup effect, where subjects with the highest glutamate levels at baseline tended to show decreases in glutamate following ketamine infusion. Our multimodal results, while preliminary and somewhat speculative, indicated that subgroups may be quite complex, and related less to a single aspect of neuronal function, and more to the interplay of those measurements. Finally, our results suggest that a single dose of ketamine not only improves depression symptoms in TRD patients, but may also correct critical abnormal neuroinflammatory pathway aberrant in mood disorders. Conclusions: Our findings have advanced the study of ketamine as a glutamatergic modulating intervention for MDD, a well as our overall understanding of TRD.

## Speaker 4: Jennifer Phillips, Canada

**Title:** *Cumulative and sustained effects of ketamine on depressive symptoms and suicidal ideation in treatment-resistant depression*

**Abstract**

**Background**: Repeated administration of subanaesthetic doses of intravenous ketamine may prolong the rapid decrease in depressive symptoms and suicidal ideation (SI) elicited in patients with treatment-resistant depression (TRD). The purpose of this study was to evaluate the antidepressant and antisuicidal effects of a single ketamine infusion, a series of repeated ketamine infusions, and prolongation of response with maintenance infusions. Cognitive, biological, and electrophysiological markers were also evaluated during the trial. **Methods**: Forty-two participants with TRD completed a randomized trial of ketamine. Participants received a single ketamine infusion during a double-blind crossover with midazolam (an active placebo). Following relapse of depressive symptoms, participants received 6 open-label ketamine infusions administered thrice-weekly over two weeks (repeated administration phase). Responders, participants obtaining ≥ 50% decrease in Montgomery-Åsberg Depression Rating Scale (MADRS) scores, received four further infusions administered once-weekly (maintenance phase). Changes in symptoms were assessed with the MADRS and the MADRS suicide item (item 10, MADRS-SI). **Results**: Compared to midazolam, a single ketamine infusion elicited a larger reduction in depressive symptoms ($p < .001$) and SI ($p = .009$) at 24 hours post-infusion. Repeated

measures ANOVAs examining the cumulative effects of repeated infusions revealed significant main effects of time, with reductions in MADRS ($p < 0.001$) and MADRS-SI scores ($p < 0.001$) with each successive infusion. Fifty-six percent of participants met response criteria following repeated infusions. During maintenance, there was no further change in MADRS ($p = 0.73$) or MADRS-SI scores ($p = 0.69$). **Conclusions**: Ketamine was superior to midazolam for both depression and SI. Repeated ketamine infusions had cumulative antidepressant and antisuicidal effects in participants. Reductions in depression and SI were sustained among responders through once-weekly infusions. This study provides novel data on the efficacy of this treatment approach, which has important implications for improving treatment response times and rates in TRD.

## Tuesday 19th June 2018
## 09.45-11.30
## S22: Deep brain stimulation for severe OCD: effect and mechanisms of STN and nucleus accumbens targets

Chair: Eileen Joyce, UK
Co-Chair:

### Speaker 1: Suzanne Haber, USA

**Title:** *The functional neuroanatomy of cortico-basal ganglia thalamic systems: relevance for OCD DBS*

**Abstract**

DBS is an effective therapeutic approach for treatment resistant OCD. The two main targets used by various groups are the anterior limb of the internal capsule/ventral striatum (ALIC/VS), and the subthalamic nucleus (STN). Both targets receive inputs from frontal cortex. This presentation will delineate the course of frontal cortical fibers that pass through each contact in both the ALIC/VS and STN. The first part of the talk will focus on tracing studies in the nonhuman primate which outlines the precise trajectory and location of fibers from different cortical regions in the ALIC/VS and STN of the NHP. Using this information, we segment the ALIC/VS and STN, based on the location of fibers from specific cortical locations. The second part of the talk will use diffusion MRI in NHPs and in humans to identify a similar segmentation in the human brain and use that information to predict the location of each contact.

### Speaker 2: Damiaan Denys, Netherlands

**Title:** *DBS of the nucleus accumbens for OCD: clinical experience*

**Abstract**

OCD is considered one of the most disabling psychiatric disorders, causing serious impairment in patients' daily functioning and affecting professional, social, and personal lives. Thanks to a wide range of available pharmacologic treatments and cognitive behavioural therapy (CBT), most patients can be treated to a satisfactory level. However, 10% of patients experience inadequate response and remain severely ill. In the last decades, neuromodulating techniques have emerged as promising alternatives for the treatment of OCD. Different from the rather aspecific pharmacologic modulation of drug therapy, neuromodulation techniques enable modulation of distinct neuronal circuits by targeting specific brain structures. OCD may be particularly suitable for these interventions because of its strong link to discrete neuro-anatomic networks. Neuroimaging studies have consistently related OCD to aberrant activity within the orbitofronto-striato-thalamo-cortical (CSTC) network. A major advantage of neuromodulation is its potential of adjustable and reversible brain network manipulation. This lecture reviews studies on DBS for OCD.

### Speaker 3: Hagai Bergman, Israel

**Title:** *The neurophysiology of the subthalamic nucleus and nucelus accumbens.*

**Abstract**

The basal ganglia (BG) use actor/critic architecture that enables multi-objective optimization of behavioral policy. The BG modulators (critics, e.g., dopamine) encode the mismatch between prediction and reality; whereas the BG main axis (actor) provides the connection between state and action. The striatum and the subthalamic nucleus (STN) constitute the input stage of the BG main axis (actor) network. Both the STN and striatum can be divided to three main territories encoding motor, cognitive and emotional information (putamen, caudate and nucleus accumbens respectively in the striatum). The STN and the striatum together innervate BG downstream structures. Our recent studies indicate that subthalamic rather than striatal activity shapes the main features of BG downstream activity, whereas the striatum provide the fine details. This STN modulation of BG downstream activity occurs both before (in health) and after intoxication by 1-methyl-4-phenyl-

1,2,3,6-tetrahydropyridine (MPTP) which leads to striatal dopamine depletion and parkinsonian clinical symptoms. This explains why the STN is such an effective site for deep brain stimulation (DBS) in Parkinson's disease and other BG disorders (e.g., OCD). Finally, today DBS systems are manually adjusted every 1-3 months. However, the abnormal beta synchronized oscillations in the STN are episodic, and long (> 2 seconds) episodes can be detected only in the disease state. We therefore suggest that we can better treat BG disorders by closed-loop adaptive DBS that would inactivate the basal ganglia only when they "misbehave", i.e., following detection of STN long beta events.

### Speaker 4: Eileen Joyce, UK

**Title:** *DBS for OCD: Comparison of STN and nucleus accumbens targets*

**Abstract**

**Background**: Deep brain stimulation (DBS) is an emerging treatment for severe OCD. Previous studies implicate two principal targets: ventral internal capsule/ventral striatum (VC/VS) and anteromedial subthalamic nucleus (amSTN). Symptom response during DBS is variable with no clear indication of the optimal target. We undertook the first pilot trial comparing VC/VS and amSTN DBS in the same patients.

**Methods**: Six patients with treatment-refractory OCD entered double-blind counterbalanced phases of 12 weeks amSTN or VC/VS DBS, followed by open phases when amSTN and VC/VS were stimulated together, optimal stimulation parameters achieved and adjunctive inpatient CBT delivered. OCD symptoms, mood, disability and cognition (CANTAB ) were assessed. Prior to surgery, participants underwent high resolution diffusion weighted 3T MRI. The precise location of activated DBS electrode contacts was determined from intraoperative stereotactic MRI and the volume of tissue activated (VTA) estimated using established modelling algorithms. Probabilistic tractography was generated, for all participants in native space, using each DBS-VTA as a seed mask. Resulting streamlines were transformed to MNI space and group averages generated.

**Results**: DBS at each site significantly reduced OCD symptoms, the magnitude of change being equivalent between them with little additional gain during concurrent stimulation at both sites. Significant differential effects were found with amSTN improving cognitive flexibility and VC/VS improving mood. Volumes of tissue activation showed that the effective VC/VS site was the ventral capsule not the nucleus accumbens. Average VC VTA streamlines were connected to medial orbitofrontal cortex, mediodorsal thalamus, amygdala and habenula. Streamlines from amSTN VTAs were connected to lateral orbitofrontal cortex, dorso-anterior cingulate cortex and dorsolateral prefrontal cortex.

**Conclusions.** The positive effect of VC DBS on mood is mediated by connectivity to medial orbitofrontal cortex, amygdala and habenula. Improved cognitive flexibility with amSTN DBS is secondary to modulation of lateral orbitofrontal, dorsolateral prefrontal and dorsal anterior cingulate cortices.

## Tuesday 19th June 2018
## 09.45-11.30
## S23: Recent updates on controversial issues in the management of schizophrenia

Chair: Hiroyuki Uchida, Japan
Co-Chair: Damiaan Denys, Netherlands

---

### Speaker 1: Takefumi Suzuki, Japan

**Title:** *Resistance to antipsychotic treatment, including clozapine*

**Abstract**

A sizable of people with schizophrenia do not adequately respond to a series of monotherapies with currently available antipsychotics; then they are classified as treatment resistant schizophrenia (TRS). In this presentation the following points are to be addressed: historical background of TRS, epidemiology of TRS, putative background of TRS, possible management of TRS and finally how better to define “TRS” in the real-world clinical practice. Traditionally TRS has been defined as a failure to respond to two or more antipsychotics from different chemical classes for an adequate treatment duration (frequently at least six weeks) at an adequate dosage (usually chlorpromazine equivalent daily dose of 600mg or higher). Since the pivotal study by Kane et al. (1988) clozapine has been identified to be a gold standard antipsychotic for TRS. Nevertheless clozapine is not always perfect and refractory patients even with clozapine are occasionally termed ultra-resistant schizophrenia. However, until recently, there have been no universal definitions of TRS and treatment response criteria among patients with TRS. A consensus paper on the definition of TRS and treatment response has lately been published (Howes et al., 2017) and this is expected to provide the touchstone for future studies on TRS in an effort to enhance interchangeability and interpretability of the results. Positive symptoms have been the main treatment target but various aspects within the illness (e.g., cognition, functioning, side effects

and subjective perspectives) that need to be taken into thoughtful account for the treatment to be successful. Suboptimal adherence to oral antipsychotic treatment should be proactively monitored to rule out “pseudo-resistant” cases. These issues are discussed together with future directions on this highly challenging but clinically relevant topic.

## Speaker 2: Rene Kahn, USA

**Title:** *Do antipsychotics make the brain shrink? Neuroprotective vs. neurotoxic effects*

**Abstract**

Abnormal volumes in various brain structures are well-established in schizophrenia, particularly reductions in prefrontal cortex and temporal lobes, and enlargement of lateral and third ventricles and the subarachnoid space. Brain volume is reduced in patients at ultra-high risk and is further reduced with progression to the first episode of psychosis, prior to exposure to medication. Unaffected twins in monozygotic and dizygotic twin pairs discordant for schizophrenia also exhibit reductions in gray matter and, based on these data, it has been estimated that most of the gray matter loss in schizophrenia is explained by genetic liability (especially white matter), although environmental factors also contribute (in gray matter). Whether medication plays a role in gray matter volume change, either protective or causative, remains uncertain. Antipsychotic drug dose at the time of scanning and duration of illness correlated significantly with gray matter volume loss in a meta-analysis of over 18,000 subjects with schizophrenia. But because medication dose may be a marker for severity of psychosis or refractoriness to treatment, correlations between medication dose and brain volume loss are difficult to interpret, although the relationship has remained significant after controlling for symptom severity in most studies. Indeed, we have reported that brain volume decreases are related to poor outcome, number of relapses, duration of psychosis and need for care. Moreover, in a recent study in bipolar patients, antipsychotics did not have an effect on brain volumes. All in all, the evidence suggests that brain volume loss in schizophrenia is related to poor outcome not to the use of antipsychotic medication.

## Speaker 3: Jun Soo Kwon, Republic of Korea

**Title:** *Impact of dopamine supersensitivity on brain, psychopathology, and treatment*

**Abstract**

Pharmacotherapy using antipsychotic drugs has been the cornerstone of treatment of schizophrenia, especially mitigating positive symptoms of schizophrenia. The main mechanism of action of antipsychotic drugs has been regarded as the antagonism of dopamine D2 receptors in the brain. However, many of the schizophrenia patients show non-adherence to the medication and experience relapses. After the relapse, the patient usually needs a higher dosage of antipsychotic drugs, and sometimes the patient gets poor responses to multiple antipsychotic medications over time. The development of treatment resistance after relapse episodes has been addressed partly by the dopamine supersensitivity. Studies suggest that long-term exposure to antipsychotic drugs may cause the up-regulation of dopamine D2 receptors, manifesting as a dopamine supersensitivity phenomenon. It has been recently postulated that the dopamine supersensitivity could worsen the prognosis of schizophrenia, and may be partly involved in the development of treatment resistant schizophrenia.

We will review the potential mechanisms underlying the development of dopamine supersensitivity, its impact on the symptoms, psychopathology, and treatment of schizophrenia, and the literatures describing the neuroimaging findings regarding the dopamine supersensitivity in the brain.

## Speaker 4: Wolfgang Fleischhacker, Austria

**Title:** *Is antipsychotic necessary for maintenance treatment?*

**Abstract**

The relapse preventive effect of antipsychotic maintenance treatment is one of the best documented outcomes research findings in psychiatry. NNT´s amount to between 3-6. For most patients relapse prevention translates into improved or at least stable psychosocial functioning. Although longer term psychosocial outcomes appear to correlate better with improvement in negative symptoms and cognitive dysfunctions than with positive symptoms, the latter, given their disruptive effects on psychosocial integration are also relevant in this context. More recently, concerns have been raised that the treatment with antipsychotic medication might adversely affect long-term

outcomes for schizophrenia patients. These assumptions are based on a few observational studies, which have to be interpreted with a note of caution, given the methodological challenges inherent in this type of study. Nevertheless, it appears that a small subgroup of patients may stay well after an acute episode despite discontinuing antipsychotics. Unfortunately, it is as yet impossible to reliably predict such positive outcomes following a first episode of psychosis. Consequently, all available guidelines suggest maintenance treatment for at least a year after a first episode of the illness. In addition, there are first hints from neuroimaging studies that it may be possible to categorize patients with high or low relapse risk via machine learning algorithms in anatomical MR studies or, alternatively, by quantifying dopamine release in PET imaging protocols.

References:
W.W. Fleischhacker, C. Arango, P. Arteel, T.R.E. Barnes, W. Carpenter, K. Duckworth, S. Galderisi, L. Halpern, M. Knapp, S.R. Marder, M. Moller, N. Sartorius, P. Woodruff
Schizophrenia – Time to Commit to Policy Change
**Schizophrenia Bulletin**, 40 (3): 165-194, 2014

## Tuesday 19th June 2018
## 09.45-11.30
## S24: Neuroimaging in the treatment of depression – acute neuronal response, treatment effects and recurrence prediction

Chair: Andreas Hahn, Austria
Co-Chair: Kamilla Miskowiak, Denmark

---

### Speaker 1: Annette Bruhl, Switzerland
**Title:** *Using real-time fMRI neurofeedback to enhance treatment in mood and anxiety disorders*

### Speaker 2: Andreas Hahn, Austria
**Title:** *Effects of acute ketamine and citalopram challenge assessed with pharmacological fMRI*

**Abstract**
Major depression is a severely disabling disorder with recurrence rates of more than 50% within 10 years. It is therefore of high importance to understand the underlying neuropathological aspects and how the different treatment strategies affect human brain function.
This presentation will focus on the acute effects of the antidepressant treatment agents citalopram and ketamine assessed with functional magnetic resonance imaging (fMRI). In such investigations the baseline and challenge scans are often separated by hours or even days due to various issues such as logistics and time to peak effects after oral administration. This implies the major drawback of potential differences in motivation, mood or attention between the two scans, resulting in an increased within-subject variance.
To avoid the above disadvantages, we employed pharmacological fMRI with an intravenous challenge during the scan in a double blind, placebo controlled study design. Continuous data acquisition of up to 60min before, during and after the administration of the study drug enabled a thorough assessment of acute pharmacological effects. Different data analysis strategies will be presented, which include modeling of the fMRI signal with pharmacokinetic data of ketamine and citalopram blood plasma levels, conventional and dynamic functional connectivity analyses as well as data driven methods. Finally, the challenges of this technique and implications of the obtained results in major depression will be discussed.

### Speaker 3: Kamilla Miskowiak, Denmark
**Title:** *Neuronal correlates of electroconvulsive therapy in depression*

**Abstract**
Negative neurocognitive bias is a core feature of major depressive disorder (MDD) that is reversed by pharmacological and psychological treatments. This double-blind functional magnetic resonance imaging (fMRI) study investigated for the first time whether electroconvulsive therapy (ECT) modulates negative neurocognitive bias in MDD. Twenty-nine patients with treatment-resistant MDD were randomized to one active or sham ECT session at the beginning of their ECT course in a double-blind, between-groups design. The following day, they underwent whole-brain fMRI at 3T while viewing emotional faces, emotional self-referent words and affective pictures. A single ECT session modulated neuronal response during the three emotional processing tests in ways that are compatible with antidepressant actions. During emotional face processing, ECT produced no change in amygdala or cortical response using a conservative cluster-forming threshold of $Z>3.1$ ($p<0.001$). However, a less conservative exploratory cluster-corrected whole-brain analysis revealed ECT-induced changes in parahippocampal and superior frontal responses to fearful vs. happy faces as well as fear-specific functional connectivity between amygdala and occipito-temporal regions. Across all patients, greater fear-specific amygdala–occipital coupling correlated with lower fear vigilance. During

retrieval of emotional self-referent words, ECT-treated patients displayed reduced retrieval-specific neural response for positive self-referent words in the left frontopolar cortex in the primary analysis using FSL 'randomize' that involves permutation-based nonparametric inference (n=5000). This effect may reflect increased memory efficiency for positive self-referent information. Finally, the same analysis method revealted ECT-related reduction in neural response to unpleasant vs. pleasant pictures in the medial prefrontal cortex, a region showing increased response in more depressed patients. These effects of ECT occurred in the absence changes between treatment groups in mood symptoms. The findings are remarkably similar to neurocognitive effects of antidepressant drug treatment. Together, this points to early reduction in negative neurocognitive bias as a putative common mechanism of distinct biological treatments for depression.

## Speaker 4: Henricus Ruhe, Netherlands

**Title:** *Brain connectivity markers in recurrence of depression*

*Henricus G Ruhe[1,2,3,4], Caroline A. Figueroa[3,4], Roel JT Mocking[3], Michelle N Servaas[5], Joana Cabral[4,6], Harriette Riese[5], Marieke Wichers[5], Gustavo Deco[7], Morten L Kringelbach[4,8], Aart H Schene[1,2]*

**Abstract**

Background

Recurrence in Major Depressive Disorder (MDD) is common (50-80% in 5 years) and causes a large burden on society, patients and relatives/friends. Neurobiological mechanisms underlying recurrence are poorly understood and not used to predict recurrences or guide specific preventive treatments.

**Aim**

To increase understanding of aberrant brain functioning associated with recurrence in MDD.

**Methods**

Using a well-phenotyped cohort of 69 drug-free, remitted (Hamilton-scores ≤7) rMDD-patients, highly vulnerability for recurrence (≥2 episodes of depression), followed-up for 2.5 years, and 44 healthy age, IQ and sex matched controls, we investigated the potential of high dimensional symptomatology ratings (experience sampling), neuropsychological measurements and resting-state functional connectivity to understand and predict vulnerability for recurrence.

**Results**

Patients and controls differed in Hamilton-scores (median 2 vs 1, respectively), cognitive reactivity (median LEIDS-R 41 vs 9, respectively) and rumination (median RRS 35 vs 25, respectively), all p<0.001. For 63 rMDD-patients ≥1 follow-up visit was completed. Fifty-two rMDD-patients (82.5%) completed 2.5 years of follow-up; recurrence occurred in 35 (55.5%) patients.

Increased variability of negative affect and decreased variability of positive affect were associated with recurrence (p<0.05). Higher variability in depressed mood-ratings was associated with decreased connectivity of the Salience Network (SN) with other networks (p=0.023) and with increased within Default Mode Network (DMN)-connectivity (p=0.053). An Independent Component Analysis of resting state MRI-scans before and after an autobiographical memory mood induction, showed reduced connectivity between the posterior anterior cingulate and hippocampus (vs. controls; p=0.006). Ongoing analyses consider how switching dynamics between whole brain connectivity patterns (states) differ between rMDD-patients and controls. Beyond different switching patterns (p<0.05), rMDD-patients consistently show decreased probability of occurrence and duration of a frontal-DMN-SN-striatal control-network (p<0.005).

**Conclusion**

Disrupted functional connections in highly vulnerable rMDD-patients, although in remission, reveal important pathways involved in emotional regulation. This may serve as markers for preventive and therapeutic applications.

**References**

- Figueroa, C. A. et al. Aberrant default-mode network-hippocampus connectivity after sad memory-recall in remitted-depression. Soc. Cogn. Affect. Neurosci. 2017;12:1803–1813.
- Lande, H. et al. Associations of positive and negative affect with physical activity in drug-free patients in remission of recurrent major depressive disorder (P291). Bipolar Disord.2016;18 Suppl.:160–161.
- Mocking, R. J. T. et al. Vulnerability for new episodes in recurrent major depressive disorder: protocol for the longitudinal DELTA-neuroimaging cohort study. BMJ Open 2016;6:e009510.
- Servaas, M. N. et al. Associations Between Daily Affective Instability and Connectomics in Functional Subnetworks in Remitted Patients with Recurrent Major Depressive Disorder. Neuropsychopharmacology 2017;42:2583–2592.

Author's affiliations

1. Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands
2. Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, The Netherlands

3. Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
4. Department of Psychiatry, University of Oxford, Oxford, United Kingdom
5. University of Groningen, University Medical Center Gromingen, ICPE, Groningen, the Netherlands
6. Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
7. Center for Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain
8. Center for Music in the Brain, Aarhus University, Aarhus, Denmark

## Tuesday 19th June 2018
## 09.45-11.30
## S25: NMDAR dysfunction, neuromodulatory dysfunction and glutathione deficit in schizophrenia pathogenesis

Chair: Daniel Javitt, USA
Co-Chair: Ulrich Sauerzopf, Austria

---

### Speaker 1: Hsien-Yuan Lane, Taiwan

**Title:** *Roles of D-amino acid oxidase (DAO), DAOA (G72), and cystine/glutamate antiporter in NMDAR hypofunction, glutathione deficit, and schizophrenia pathogenesis*

**Abstract**

**Background**: All current treatments for schizophrenia principally function by blocking dopamine D2 receptors. Given the limitation of these medications, substantial efforts have been made to identify novel targets. Two such targets, glutamate and glutathione (GSH), are interdependently linked to schizophrenia pathogenesis. In addition, cystine/glutamate antiporter system xc(-) may be also implicated in the pathogenesis of schizophrenia via regulating extracellular glutamate and GSH that may prevent the brain from oxidative damage. Lately, the pivotal D-amino acid oxidase (DAO) inhibitor, sodium benzoate, was found to be beneficial for patients with chronic schizophrenia. We also found that peripheral makers including DAO activator (DAOA, or G72) and cystine/glutamate antiporter system xc(-) may be able to identify unique subgroups of patients with schizophrenia. However, it remains unclear whether benzoate can also improve clozapine (the last-line antipsychotic agent)-resistant schizophrenia. **Methods:** In a randomized, double-blind, 6-week trial, 60 schizophrenia inpatients that had been stabilized with clozapine were allocated into three groups to receive add-on treatment of 1-g/d sodium benzoate, 2-g/d sodium benzoate, or placebo. **Results:** Both doses of benzoate generated better improvement than placebo in Scales for the Assessment of Negative symptoms (SANS). Two-g/d benzoate also excelled placebo in Positive and Negative Syndrome Scale (PANSS) total score, PANSS-positive score, and Quality of Life Scale. Benzoate was well tolerated without evident side-effects. The changes of catalase, an antioxidant, were different among three groups and correlated with the improvement of PANSS-total and PANSS-positive scores in the benzoate group.
**Discussion**: Our findings suggest that benzoate adjuvant therapy improved symptomatology of clozapine-resistant schizophrenia. Further studies are warranted to elucidate the optimal dose, treatment duration, and the mechanisms of benzoate for clozapine-resistant schizophrenia.

### Speaker 2: Akira Sawa, USA

**Title:** *Interplay of glutathione and glutamate: relationship of blood glutathione, MRS glutamate, and cognition*

**Abstract**

Involvement of oxidative stress in the pathophysiology of schizophrenia (SZ) is suggested by studies of peripheral tissues. Nonetheless, it is unclear how such biological changes are linked to relevant, pathological neurochemistry and brain function. We designed a multi-faceted study by combining biochemistry, neuroimaging, and neuropsychology to test how peripheral changes in a key marker for oxidative stress may associate with central neurochemicals or neuropsychological performance in health and in SZ. Fifty healthy controls and 46 patients with SZ were studied cross-sectionally. Peripheral levels of total glutathione (GSH) within extracellular (plasma) and intracellular (lymphoblasts) compartments were measured. Furthermore, we examined the levels of Glx (glutamate and glutamine) in the dorsal anterior cingulate cortex (dACC) using 3-Tesla proton magnetic resonance spectroscopy ($^1$H-MRS). We observed lower peripheral total GSH in SZ compared to controls, in extracellular and intracellular pools. Across the total population, positive correlations were found between peripheral total GSH levels and cognition. Within the entire population, plasma and lymphoblast total GSH levels positively correlated with dACC Glx levels, the latter after controlling for age and smoking status. Furthermore, within the entire population and in patients alone, dACC Glx levels positively correlated with visuospatial memory after controlling for age and smoking status.

Based on these data, we have conducted a new study using 7-Tesla MRS for another cohort (81 patients with first episode psychosis and 91 age-matched control subjects): we confirmed a significant reductoin of glutamate and GSH in the ACC of the patients with first episode psychosis. Exploring the relationship between systemic oxidative stress, central glutamate, and cognition in SZ will benefit further from assessment of patients with more varied neuropsychological performance. Furthermore, studying GSH in lymphoblasts from patients may facilitate discovery of molecular and cellular mechanisms that link oxidative stress, cellular dysfunction, and cognitive deficits in SZ.

## Speaker 3: Kim Do, Switzerland

**Title:** *Linking early-life oxidative stress, inflammation and NMDAR hypofunction in schizophrenia pathogenesis*

**Abstract**

**Background**. Oxidative stress, coupled with dysregulation of inflammation, NMDAR and dopamine, is involved in schizophrenia (SZ) pathophysiology, affecting integrity of parvalbumin interneurons (PVI) critical for cognition. Various SZ animal models present an elevated oxidative stress prevented by antioxidant N-acetyl-cysteine (NAC). These preclinical results suggest a convergence of various genetic and environmental risk factors on oxidative stress induced PVI impairment. In earlier trial in chronic SZ, NAC improved negative symptoms, mismatch negativity and local synchronization.

**Methods**. Early psychosis patients (EP, NAC=32, placebo=31) were supplemented with NAC (2.7g/day, 6 months) in a double-blind randomized placebo-controlled trial. Outcome measures at trial start and end: PANSS; neurocognition (MATRICS); quantification of medial prefronfal cortex glutathione (GSHmPFC) by 1H-magnetic-resonance-spectroscopy, of white matter diffusion properties estimated by generalized fractional anisotropy (gFA) computed from diffusion spectrum imaging, of blood cells GSH (GSHBC) and GSH peroxidase activity (GPxBC)

**Results.** PANSS negative and positive were not affected by NAC. NAC improved Processing Speed (F(1, 30)=5.849, p=.022), favoring 2 of 3 processing speed tasks (Trail Making A, F(1, 30)=4.279, p=.048 & Verbal Fluency, F(1, 30)=5.749, p=.023). GSH**mPFC** (+23%, p=0.005) and GSH**BC** (+19%, p=0.05) were increased. In patients with high-baseline GPxBC (>22.3U/gHb), NAC improved PANSS positive versus placebo (p=0.02). PANSS positive change correlated negatively with that of GPxBC activity, showing improvement parallel to redox status restoration. NAC group showed 11% increase in fornix white matter integrity (gFA), correlating with GSHmPFC increase.

**Conclusion**. This is the first clinical trial assessing the potential predictive role of peripheral biomarkers of redox dysregulation, allowing identifying a subgroup of patients with improved positive symptoms. NAC induced GSHmPFC increase demonstrates target engagement. NAC improved Processing Speed shows a therapeutic enhancement of cognition. NAC improved fornix integrity, in association with brain GSH elevation, demonstrates for the first time that a redox regulator can enhance structural connectivity.

## Speaker 4: Daniel Javitt, USA

**Title:** *NMDAR - glycine modulatory site as pharmacological target in schizophrenia: translational biomarkers and novel clinical findings*

**Abstract**

Deficits in neurotransmission at N-methyl-D-aspartate-type glutamate receptors (NMDAR) have been extensively demonstrated in schizophrenia. As yet, however, there are no treatments that reverse NMDA-related symptomatic impairments in schizophrenia, in part due to lack of models capable of translating between rodent and human studies. This presentation focuses on mismatch negativity (MMN) both as a clinical marker of NMDAR dysfunction in schizophrenia, and as a translational biomarker for NMDAR-based treatment development in rodents.

MMN is elicited most commonly in an auditory “oddball” paradigm and reflects pre-attentive processing of stimulus “deviance” at the level of auditory cortex. Despite the simplicity of the paradigm, schizophrenia patients show large effect-size deficits in MMN generation that correlate strongly with impaired functional outcome. Schizophrenia-like deficits in MMN generation are reproduced by administration of NMDAR antagonists (e.g. PCP, ketamine) in healthy human volunteers and in animal models. In schizophrenia, MMN deficits persist despite antipsychotic treatment. Here we present results of both rodent and human studies evaluating effects of potential NMDAR modulators, including the amino acids glycine and D-serine that bind to the glycine modulatory site of the NMDAR.

MMN-related neural activity maps to the theta (4-7 Hz) frequency range in both humans and rodents. In rodents, chronic treatment with PCP leads to a significant inhibition of MMN-related theta activity. Moreover, effects are prevented by concurrent treatment with glycine at doses that significantly enhance brain glycine levels. These findings support both the use of MMN for preclinical drug

evaluation and NMDAR/glycine-site enhancement for treatment of schizophrenia. In schizophrenia, treatment with the NMDAR agonist D-serine leads to enhanced MMN response along with improved clinical symptoms.
Overall, these findings strongly support the role of NMDAR dysfunction in schizophrenia and encouraging further development of potential NMDAR enhancing agents for treatment of persistent symptoms and neurophysiological impairments.

**Tuesday 19th June 2017**
**09.45-11.30**
**CP04**
***The Paul Kielholz Lecture***
**Rapid Acting Antidepressants**
Chair: Helena Calil, Brazil

## Speaker: John Krystal, USA

**Abstract**
Ketamine, the first rapid-acting antidepressant, is generating both excitement and concern within the treatment community. The purpose of this clinical perspective is to consider the current status of ketamine as a treatment for depression. It will begin by briefly highlighting limitations of current antidepressant treatment that create interest in ketamine. It will then review the current state of the clinical results with ketamine in clinical trials for unipolar and bipolar depression, OCD, and PTSD. It will highlight its rapid efficacy, robust effects in treatment-resistant populations, efficacy for suicide, and potential use for special populations (comorbid pain, psychotic depression, etc.). It will also review safety issues including its dissociative effects and abuse liability and consider strategies to manage these effects. This presentation will also consider ketamine within the context of long-term treatment. Lastly, it will consider the question, “how does ketamine work?” as the answer to this question may point to other rapid-acting antidepressant mechanisms.

**Tuesday 19th June 2018**
**13.00-13.45**
**PL06: Glutamatergic GABAergic and dopaminergic abnormalities in antipsychotic-naive first- episode schizophrenia patients: connected disturbances or independent biomarkers for outcome?**
Chair: Barbara Sahakian, UK

## Speaker: Birte Glenthoej, Denmark

**Abstract**
We have collected multimodal longitudinal data from four cohorts of antipsychotic-naïve first-episode schizophrenia patients and matched healthy controls (HC). In two cohorts we found that the effect of treatment was associated with either low dopamine D2 receptor binding potentials (BP) in the caudate nucleus or high D2 receptor BP in the frontal cortex. Our dopamine data are in line with the literature supporting a relation between treatment response and increased dopamine synthesis capacity (SC). Other data have pointed to an association between non-response and glutamatergic and/or GABAergic abnormalities. The clinical findings are, however, inconsistent and the animal literature rather supports that glutamatergic and GABAergic abnormalities are primary to dopaminergic dysfunction. In our ongoing study on initially antipsychotic-naïve patients we are assessing glutamate levels in the anterior cingulate cortex (ACC) and thalamus and GABA levels in the ACC (MRS) as well as dopamine SC in the caudate nucleus (PET). Participants are examined at baseline, at 1.5 and 6 months and after 2 years of treatment. The data, based on the first included 44 patients and 36 HC, show increased baseline glutamate levels in the thalamus and decreased GABA levels in the ACC – and an association between high thalamic glutamate levels and low GABA levels in the ACC and treatment response. Glutamate and GABA levels in the ACC are positively associated in the patients and in the whole sample at a trend level. Examinations of dopamine SC started up later than the MRS examinations. Analyses of the PET data are ongoing. In conclusion, data from our group combined with data from the literature support the involvement of dopaminergic, glutamatergic and GABAergic dysfunction in the pathophysiology of schizophrenia – and an association between these disturbances and treatment outcome. To what extent the reported neurochemical disturbances represent separate clinically relevant biotypes will be discussed.

**Tuesday 19th June 2017**
**13.45-15.30**
**S26: Microbiome and neuropsychiatry – moving towards mechanisms**
Chair: Caitlin Cowan, Ireland
Co-Chair: Hans-Jurgen Möller, Germany

## Speaker 1: Caitlin Cowan, Ireland

**Title:** *The Microbiota-gut-brain axis across the lifespan modulates stress and cognitive behaviours*

**Abstract**
The brain-gut-microbiota axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of neurodevelopmental, age-related and neurodegenerative disorders. The routes of communication between the gut and brain include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or by way of microbial metabolites such as short chain fatty acids. Studies in animal models have shown that the development of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. At the other extreme of life, individuals who age with considerable ill health tend to show narrowing in microbial diversity. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. Recently, the gut microbiota has been implicated in a variety of conditions including autism, schizophrenia and Parkinson's disease. Moreover, fundamental brain processes from adult hippocampal neurogenesis to myelination to microglia activation have been shown to be regulated by the microbiome. Further studies will focus on understanding the mechanisms underlying such brain effects and developing nutritional and microbial-based intervention strategies.

## Speaker 2: Anna Cattaneo, UK

**Title:** *Gut microbiome pro-inflammatory and anti-inflammatory mediators in brain functioning and behaviour: identification of possible pathways and treatment strategies*

**Abstract**
Stressful events experienced during infancy and adolescence have been seen affecting the physiological brain maturation towards a potentially pathological trajectory that might lead to the development of several psychiatric disorders later in life. During the last years, the role of the gut microbiota has been investigated as one of the principal actor in regulating brain development and maturation. For example, it has been observed that a complete lack of microbiome in animals enhanced the activity of the stress response system, whereas the restoration of microbiome in GF mice or probiotics supplementation in microbiome-depleted rodents reinstated physiological brain development and normal response to stress. Also, several stress paradigms, such as prenatal stress, maternal separation or stress during adolescence have been found able to alter microbiome composition.
During the talk, I will show data on the impact of social isolation during adolescence that has been performed from PND21 to PND 49, and the following reinstatement of a normal non-stressful condition, the social reintegration, on the microbiome composition, and possible influence of these changes on brain inflammation. To evaluate changes in microbiota composition, metagenomic analyses have been performed on stool DNA samples by using Miseq Illumina platform at different time points: at PND 28 and 49 to evaluate the effect of isolation and, at PND63 and PND 84 to evaluate the effect of social reintegration.
The comparison of the microbiota composition across groups identified two main effects: a time and a regrouping effect. We found that microbiota composition changes over time during neurodevelopment, but in a different way in animals exposed to isolation as compared to grouped animals. At phylum level, for example, we observed an opposite oscillation in Firmicutes and Bacteroidetes abundances along time between the two groups. To evaluate whether changes in the microbiome composition could also be reflected in changes in brain immune parameters, I will also show data on brain levels of the main pro-inflammatory cytokines as well as of several microglia related markers in different brain regions.
In general, I will discuss how exposures to stress during adolescence can affect the physiological development of microbiome and in turn may influence the immune system development, influencing the vulnerability to develop, later in life, several kinds of diseases characterized by alterations in the immune/inflammatory responses, such as psychiatric disorders. A better clarification of the impact of the microbiome composition on human vulnerability could open new frontiers for the development of prevention strategies.

### Speaker 3: Rochellys Diaz Heijtz, Sweden

**Title:** *Bacterial peptidoglycans as novel signalling molecules from microbiota to brain*

**Abstract**

Recent animal studies have revealed that the gut microbiota has much wider effects on host physiology and development than originally believed, including the early-life programming of brain circuits involved in the control of emotions, motor activity, and social behavior. The current challenge is to understand the precise molecular mechanisms mediating the communication between the microbiota and the brain. In this presentation, I will cover new evidence from my laboratory suggesting that one of the mechanisms mediating the influence of the gut microbiota on brain development and behavior involves the direct actions of gut-derived microbial molecules within the brain.

### Speaker 4: Premsyl Bercik, Canada

**Title:** *Microbiota as a key modulator of generalized anxiety disorder- Towards mechanisms*

**Abstract**

Increasing evidence suggests that gut microbiota, apart from shaping host's immune system and impacting its metabolism, plays also an important role in the formation of normal behavior and brain chemistry. There are multiple pathways by which intestinal bacteria could communicate with the central nervous system, including immune, humoral and neural mechanisms. Gnotobiotic mouse models offer an unique opportunity to study the complex interactions between the host and the microbiome, which may be difficult to discern in conventional mouse models or in vitro systems.

The pathophysiology of Generalized Anxiety Disorder (GAD) is poorly understood but clinical studies showed that some patients with GAD display signs of low grade inflammation. We have studied gut microbiome in a cohort of well-characterized patients with Generalized Anxiety Disorder (GAD) and sex/ age matched healthy controls and found slightly but statistically different composition in their microbiota profiles. Using stool samples from selected patients with signs of immune activation, we colonized NIH Swiss germ-free mice and studied their behavior using a battery of standard tests. We found that microbiota transplantation from patients with GAD induced immune activation and anxiety-like behavior, accompanied by changes in brain chemistry, compared to mice colonized with microbiota from healthy individuals. In this presentation, we will discuss possible mechanisms underlying the microbiota-brain communication which lead to abnormal behavior in this humanized mouse model.

## Tuesday 19th June 2018
## 13.45-15.30
## S27: Psychedelic medicine: the therapeutic potential of mind- altering substances

Chair: Kim Kuypers, The Netherlands
Co-Chair: Georg Psota, Austria

---

### Speaker 1: David Erritzoe

**Title:** *Clinical, brain imaging, and personality data from studies with psychedelics at Imperial College*

**Abstract**

Data from our clinical pilot trial in treatment-resistant depression with psilocybin and from our online study about psychedelic experiences will be presented. The focus will be on clinical and personality results from both data sets – but some pre- to post-psilocybin fMRI results will also presented.

### Speaker 2: Kim Kuypers, Netherlands

**Title:** *The effects of psychedelics on empathy and creative thinking- implications for its use in therapy*

**Abstract**

Decades ago MDMA and LSD entered the therapeutic setting and already then showed their therapeutic potential in the treatment of psychiatric disorders. Since thousands of years another psychedelic, ayahuasca, is being used by tribes in the western Amazonia for healing and divination, and in recent years its use has expanded worldwide.

Research into the therapeutic potential of these substances has re-emerged and (preliminary) findings are promising. Depression and anxiety disorders are amongst the disorders of focus. Since both are characterized by cognitive rigidity and disturbed empathy our aim was to investigate whether psychedelics can change and improve this behavior acutely and with a longer duration. To that end, we conducted a series of studies assessing the acute and longer term effects of ayahuasca and psilocybin on creative thinking and empathy in both a naturalistic and an experimental setting.

Findings from these studies will be presented and compared to findings from another series of studies we have conducted into the effects of classical 'stimulants' (cocaine, MDMA) and novel

psychoactive substances (4-FA, 2C-E) on creative thinking and empathy. This will enable us to conclude whether classic psychedelics (psilocybin, ayahuasca) have a specific behavioral profile that differentiates them from other psychoactive substances, explaining their therapeutic potential.

## Speaker 3: Matthias Liechti, Switzerland

**Title:** *Acute effects, pharmacokinetics and concentration-effect relations of Lysergic Acid Diethylamide in healthy subjects and cancer patients*

**Abstract**

Lysergic acid diethylamide (LSD) is experimentally used in Switzerland in the treatment of patients with anxiety associated with life-threatening diseases. Studies using psilocybin treatment in patients with anxiety and depression secondary to life-threatening cancer showed that the acute subjective effects of psilocybin and in particular greater acutely induced mystical experiences predicted anxiolytic and anti-depressant effects. LSD has been shown to produce similar alterations in mind and mystical-type experiences in patients with cancer and healthy subjects. Two placebo-controlled, double-blind, cross-over studies using oral administration of 100 and 200 µg LSD were conducted to better define the acute subjective, emotional, and pharmacokinetic effects of LSD in healthy subjects. The subjective effects lasted (mean) 8 and 12 h for the 100 and 200 µg LSD doses, respectively. LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 µg compared with 100 µg. Maximum plasma concentration ($C_{max}$) was reached after 1.5 h and the plasma half-life was 2.6 h. A close relationship was observed between the LSD plasma concentration and subjective response. LSD produced feelings of trust, closeness to others, and enhanced emotional empathy. LSD impaired the recognition of sad and fearful faces and reduced reactivity of the left amygdala relative to placebo during the presentation of fearful faces. These effects of LSD on emotion processing and sociality may be useful for LSD-assisted treatment of anxiety in patients with cancer.

## Speaker 4: Jordi Riba, Spain

**Title:** *Long-term use of psychedelic drugs- the effects on brain structures and personality in humans*

**Abstract**

Psychedelic drugs have a long history of use by humankind for their capacity to profoundly modify our ordinary state of consciousness. At the molecular level they display agonist activity at the 5-HT2A receptor and have been shown to stimulate neurotrophic and transcription factors associated with synaptic plasticity. Recent clinical trials have demonstrated that single doses of psilocybin, LSD and the N,N-dimethyltryptamine-containing preparation ayahuasca can induce lasting antidepressant effects. Regular ayahuasca intake has also been reported to facilitate recovery from alcohol, opiate and stimulant addiction. Using a broad range of methodologies, we have tried to improve our still incomplete knowledge of the biological and psychological mechanisms underlying the therapeutic potential of psychedelics. At the neural level, converging evidence indicates that psychedelics induce immediate and sustained modifications of both the function and plasticity of the medial parietal cortex (mPC). This area, with its extensive connections to the rest of the brain, plays a key role in self-referential thought processes. The mPC consistently shows modifications in spontaneous oscillatory activity during the acute inebriation, and neurometabolic inhibition during the post-acute phase. The intensity of this inhibition correlates with improvements in certain psychological capacities, like non-judgemental thinking. Crucially, its promotion is a central goal of mindulness psychotherapy. In line with this finding, personality assessments have yielded greater life satisfaction and psychosocial well-being in regular ayahuasca users. Coincidentaly, structural MRI data from users has revealed reduced cortical thickness in the mPC. These reductions were inversely correlated with life-time ayahuasca use and with scores on self-transcendence, a measure of the positive aspects of religiousness and spirituality. Taken together, the available data suggests that psychedelics have the capacity to exert beneficial effects, through multiple-level interactions with the brain-mind complex. Adequately managed, psychedelics could prove useful tools to help patients who do not find relief in currently available treatments.

**Tuesday 19th June 2018**
**13.45-15.30**
**S28: Developing new medications for the treatment of schizophrenia: failures and hopes**
Chair: Wolfgang Fleischhacker, Austria
Co-Chair: Istvan Bitter, Hungary

## Speaker 1: Wolfgang Fleischhacker, Austria

**Title:** *Pharmacological treatment of schizophrenia: Still barking up the wrong tree?*

**Abstract**
Although effective treatments for schizophrenia exist since mid-last century, their efficacy / safety profiles leave much to be desired. Given the increasing knowledge about the neurobiological underpinnings of the disorder and its subsyndromes, rational drug development is attempting to target relevant sites of action. Next to others, dopaminergic, glutamatergic and cholinergic targets have been explored in clinical trials.
A broad range of targets based on presumptive pathophysiological mechanisms of schizophrenia and its subsyndromes have been evaluated with respect to symptom relief. Next to antipsychotic effects, more specific trials have looked into the potential of improving negative symptoms and cognitive deficits. After promising findings in pilot studies, large scale replication efforts with molecules acting on various sites of the glutamatergic systems have been disappointing. Results of studies targeting cholinergic receptors, both through nicotinergic and muscarinergic (partial) agonists, are still ambiguous. The most promising results so far have been obtained in clinical trials with partial D3/D2 agonists, such as brexpiprazole and cariprazine.
Drug development based on neurobiological findings in schizophrenia is making slow but steady progress.

## Speaker 2: Carol Tamminga, USA

**Title:** *Focusing on hippocampal (CA3/CA1) hyperactivity and/or dentate gyrus hypoactivity to modulate psychosis in schizophrenia*

**Abstract**
Hippocampal function has long been known to be abnormal in persons with schizophrenia and postulated to be associated with its psychotic and cognitive manifestations. Declarative memory, which is the hallmark cognitive feature of hippocampus, is disordered in the illness; hippocampal size is altered; hippocampal resting state function is abnormal; and hippocampal pathology has been described. We have contributed to this literature by describing remarkable hippocampal pathological changes in its cellular and molecular elements which is subfield-specific. The molecular and cellular alterations compromise the very features of the subfield's function, particularly in the dentate gyrus (DG) and appear to generate even more disruptive functional changes downstream from DG, in CA3/CA1 and in structures efferent from hippocampus. We have studied this psychosis-related hippocampal pathology based on an *a priori* model, postulating a counterintuitive CA3 upregulation resulting from a failure in afferent DG stimulation from the mossy fiber pathway onto the glutamatergic long-tract CA3 pyramidal neuron; we will show clear evidence of both the DG failure and of increased molecular and cellular activity in CA3 derived from human postmortem tissue. We have taken this human disease pathology and reverse translated it into a mouse model and show clearly (as has already been shown in dispersed hippocampal neurons) that decreasing afferent stimulation through knocking out GluN1 specifically in DG generates increased sensitivity of NMDA and AMPA receptors in CA3 and animal behaviors characteristics of psychosis, along with increased activity of pyramidal neurons in CA3 and in CA1. We have postulated that this constellation of tissue pathology generates a failure of 'pattern separation' in a person with psychosis (which we have already demonstrated in persons with schizophrenia) and mistaken association of stimuli in CA3, due to the hyperactivity resulting in psychotic elements in constructing hippocampally-related memories. We have taken the hippocampal subfields in persons with schizophrenia and analyzed the transcriptomes to show additional molecular elements altered in schizophrenic psychosis.

### Speaker 3: Charles Large, USA

**Title:** *Kv3 channel modulation with AUT00206, a novel rational approach for the treatment of schizophrenia*

**Abstract**

Fast-spiking, parvalbumin-positive GABAergic interneurons in corticolimbic circuits orchestrate the firing of pyramidal neurons to enhance gamma synchrony that underpins certain cognitive processes. Increasing evidence from post-mortem studies and animal models support the suggestion that dysfunction of this class of interneuron may contribute to the pathophysiology and selective symptoms of schizophrenia, notably cognitive and negative symptoms. Furthermore, data suggest that PV interneuron dysfunction may occur early in the disease process, perhaps even prior to the emergence of positive symptoms that lead to a formal diagnosis of schizophrenia.

Kv3.1 and Kv3.2 potassium channels are specifically expressed on PV interneurons and contribute to the rapid firing and transmitter release that is required to synchronise cortical networks. We have shown that positive modulation of Kv3.1 and Kv3.2 channels with a novel drug, AUT00206 can enhance the activity of PV interneurons and rescue cognitive dysfunction in rodent models. Furthermore, the molecule prevents the aberrant activation of corticolimbic brain circuits induced by the psychotomimetic drug, ketamine. Clinical evaluation of the potential of AUT00206 to treat schizophrenia includes assessment of the ability of the drug to modulate relevant neural circuitry and neurocognitive function, first in healthy volunteers, and subsequently in patients. The importance of translational biomarkers of central pharmacodynamic effect will be discussed, including the selection of clinical cognitive and electrophysiological measures based on results from preclinical animal models.

### Speaker 4: Robert Schwarcz

**Title:** *Inhibition of kynurenic acid synthesis in psychiatric diseases*

**Abstract**

Kynurenic acid (KYNA) is an astrocyte-derived metabolite of the kynurenine pathway of tryptophan degradation and antagonist of alpha7 nicotinic acetylcholine and N-methyl-D-aspartate receptors, and its levels are elevated in the prefrontal cortex of individuals with schizophrenia. Because endogenous KYNA modulates extracellular glutamate, dopamine and GABA levels in the brain, these increases may be pathophysiologically significant. The presentation will review the latest insights into KYNA neurobiology and provide an update on translationally relevant approaches to lower KYNA levels in the mammalian brain under both physiological and pathological conditions.

## Tuesday 19th June 2018
## 13.45-15.30
## S29: Genes epigenome and environment in pathophysiology of brain illness

Chair: Maurizio Popoli, Italy
Co-Chair: Johannes Berger, Austria

---

### Speaker 1: Marija Kundakovic, USA

**Title:** *Sex-specific Neuroepigenomics: Implications for Anxiety Disorders and Depression*

**Abstract**

Anxiety and depression affect ~20% of the world's population and are two times more prevalent in women than men. Sex-hormone fluctuation is likely the major risk factor for the female's increased vulnerability, although the mechanism(s) are poorly understood. Sex hormones regulate gene expression via changes in chromatin organization, which remains underexplored in the brain. Moreover, epigenetic mechanisms are implicated in anxiety-related behavior. An understanding of how fluctuating estrogen levels affect chromatin and gene expression in the brain will provide critical insights into the mechanisms underlying sex- and hormone-dependent variations in anxiety-related behaviors. To address this question, we examined female mice in two phases of the estrous cycle: diestrus (low estrogen) and proestrus (high estrogen), and compared them to males using anxiety tests (open-field, light-dark-box, elevated-plus maze) in young adulthood. Female mice in diestrus exhibited increased anxiety-like behavior compared to proestrus females and males, implying that a physiological drop in estrogen increases anxiety risk. We then assessed the effects of fluctuating estrogen levels on neuronal chromatin organization in the ventral hippocampus, an area implicated in anxiety. For each group, we performed the assay for transposase-accessible chromatin using sequencing (ATAC-seq) on FACS-purified neuronal nuclei from the ventral hippocampus. We detected differential chromatin accessibility in: >20,000 genomic regions in diestrus vs. proestrus

females; >19,000 regions in diestrus females vs. males; >20,000 regions in proestrus females vs. males. Estrous-cycle- and sex-related chromatin (re)organization was detected in gene regulatory regions and is associated with differential gene expression, including genes important for synaptic function, neurotransmission, neuroplasticity, and behavior. These data provide candidate genes and pathways contributing to within- and between-sex differences in anxiety-related behavior. Unraveling the mechanisms through which sex hormones dynamically affect brain function and behavior will increase our understanding of brain sexual dimorphism and help tailor sex-specific approaches to treat anxiety and depression.

## Speaker 2: Nicolas Singewald, Austria

**Title:** *Genetic and epigenetic mechanisms targeting fear extinction dysfunction in anxiety pathology*

**Abstract**

Although there have been advances in the treatment of fear-, anxiety- and trauma-related disorders, a considerable proportion of patients still shows only partial long-term therapeutic benefit with existing treatments. A promising option for improving therapy outcome is the pharmacological boosting of inhibitory learning in exposure-based therapy (Singewald et al Pharmacol & Ther 2015). Epigenetic mechanisms are known to play a role in neuronal plasticity, including the formation of long-lasting extinction memories, a central mechanism underlying successful exposure-based therapy.

To study the role of epigenetic mechanisms in fear extinction failure and its therapeutic rescue, we used rat and mouse models, which display a profound deficit in fear extinction learning mimicking aspects of anxiety patients with similar deficits who do not or only insufficiently respond to exposure therapy.

Comparing extinction-impaired to normally extinguishing mice, we revealed a number of aberrantly expressed histone marks, chromatin remodeling factors and miRNAs in fear extinction learning-associated brain areas. Rescue of impaired fear extinction was associated with an altered expression of a number of learning and memory-related coding genes, increased histone acetylation in some of these genes and changes in miRNA regulation. Among these, the increased expression of particular miRNAs was specific for extinction learning positively regulating plasticity-related signaling cascades. Finally, as a proof of principle we show that targeting these epigenetic mechanisms indeed normalized deficits in the formation of enduring fear extinction memories. These findings may pave new ways for the development of biomarkers and improved treatment strategies in anxiety and trauma-related disorders.

*Supported by the Austrian Science Fund FWF:SFB F4410 and SPIN W1206.*

## Speaker 3: Iiris Hovatta, Finland

**Title:** *Gene-environment interactions in anxiety-like behavior in mice*

**Abstract**

Chronic psychosocial stress is a well-established risk factor for anxiety disorders. Mechanisms by which chronic stress impacts susceptibility and resilience to psychiatric disorders are largely unknown. The chronic social defeat stress (CSDS) mouse model allows identification of factors underlying resilience and susceptibility to chronic psychosocial stress, in a controlled manner not possible in human settings. We have investigated the effect of genetic background on behavior and brain gene expression patterns after CSDS. Genetic background influences the susceptibility and resilience on the behavioral level, as 69% of the innately non-anxious C57BL/6NCrl (B6) mice but only 11% of innately anxious DBA/2NCrl (D2) mice were resilient to stress, the remainder being susceptible to CSDS-induced social avoidance. We carried out RNA-sequencing on three anxiety-associated brain regions: the medial prefrontal cortex (mPFC), ventral hippocampus (vHPC), and bed nucleus of the stria terminalis (BNST). The mPFC and BNST transcriptomic response to stress was largely non-overlapping between the strains, but there was a significant overlap in the vHPC transcriptomic stress-response between the strains. We discovered an over-representation of oligodendrocyte-related genes in the differentially expressed genes of all three brain regions. Because oligodendrocytes myelinate axons, we used electron microscopy to measure myelin thickness and found significant region and strain-specific differences. For example, in resilient D2 mice the mPFC axons had thinner myelin than controls, whereas susceptible B6 mice had thinner myelin than controls in the vHPC. Our unbiased genetic screen suggests that myelin plasticity is one of the major responses to chronic psychosocial stress in mammals, varies across brain regions, and is genetically controlled. We established inbred mouse strains as a valuable model to investigate gene-environment interactions in stress-induced anxiety. These results have important implications for translation of mouse findings to human anxiety disorders and suggest that biological basis of anxiety should be tested in mice from several genetic backgrounds.

### Speaker 4: Laura Musazzi, Italy

**Title:** *Modulation of epigenome and microRNAs in animal models of acute and chronic stress*

**Abstract**

Background

Dysfunction of the glutamate system has been associated to stress-related neuropsychiatric disorders. Although the NMDA receptor antagonist ketamine (KET) was consistently reported to exert a fast antidepressant effect, the mechanisms involved are still largely unknown.

MicroRNAs (miRNAs) have recently emerged as regulators of complex patterns of gene/protein expression changes in the brain, and recent studies showed that miRNAs are involved in the pathophysiology of mood disorders and in the action of drugs.

Methods

Rats were subjected to CMS for 5 weeks. Sucrose Preference Test (SPT) was used to distinguish stress-resilient (CMS-R) from vulnerable (CMS-V) rats. 10 mg/kg KET was acutely administered to CMS-V. Changes in mRNA and miRNA levels were measured by qPCR. RNA dendritic trafficking was analysed by in-situ hybridization. Dendritic morphology was examined in Golgi-Cox stained sections.

Results

A significant reduction of BDNF expression levels was found in HPC of all CMS rats, while in situ hybridization showed reduced dendritic trafficking of BDNF mRNAs exclusively in CMS-V. KET, although not reversing changes in BDNF levels, completely rescued dendritic trafficking in CA3 of CMS-V. Morphological analysis of CA3 pyramidal neurons showed a reduction in total length and branching of apical dendrites; KET restored these changes.

The expression profile of 17 miRNAs, selected for their involvement in the modulation of synaptic plasticity, showed selected changes induced by CMS and KET. In particular, the levels of miR-9, a brain enriched miRNA previously associated with changes in neuronal morphology, are selectively decreased in the HPC of CMS-V; KET partially recovered the reduction.

Conclusions

A single administration of KET rescued most of the alterations induced by CMS in CMS-V. Further investigation of the mechanisms underlying individual resilience/vulnerability to stress and fast KET antidepressant action could help to clarify the neurobiological underpinnings of depression and to identify new pharmacological targets for faster antidepressants.

## Tuesday 19th June 2018
## 13.45-15.30
## S30 (Late Breaking): Clinical, genetic, and molecular determinants of mood fluctuations in bipolar disorder: focus on circadian rhythms

Chair: Stefano Comai, Italy
Co-Chair: Mirko Manchia, Canada

### Speaker 1: Thomas G. Schulze, Germany

**Title:** *Clinical Response to Lithium in Bipolar Disorder is associated with Circadian Clock Gene-Sets*

**Abstract**

Sergi Papiol & Thomas G. Schulze for the Consortium on Lithium Genetics (ConLiGen)

*Background:* The link between a disruption of the circadian rhythms and mental disease has been consistently observed and reported over the last two centuries. Disturbances in the timing and architecture of the sleep/wake cycle, partially regulated by the circadian clock, have been comprehensively documented in different psychiatric disorders. The stabilization of circadian rhythms has been suggested as part of the mechanism of action of lithium in bipolar disorder. Nonetheless the relationship between circadian genes and psychiatric phenotypes has not yet been fully understood.

*Methods:* We carried out gene-set association analyses based on circadian clock genes using MAGMA and INRICH. We used GWAS summary statistics of The International Consortium on Lithium Genetics (ConLiGen) and an independent Sweden lithium response cohort, several major psychiatric disorders and chronotype as target phenotypes. We defined three main categories of curated gene-sets: clock modulator genes, core clock genes and genes following a circadian pattern of expression.

*Results:* As regards lithium response, MAGMA analyses reported a significant association of a core clock gene-set with dichotomous lithium response (corrected competitive P=0.0005). INRICH analyses showed a similar result with several core clock gene-set definitions at a clumping P-value threshold of 0.01 (corrected competitive P=0.0006). We did not observe a consistent enrichment for the other analyzed traits, except for chronotype. The core clock enrichment was consistently replicated in an independent lithium response GWAS using, again, both methods (MAGMA: corrected competitive P=0.036; INRICH: corrected competitive P=0.006).

*Conclusions:* Our results suggest the influence of core clock machinery gene-sets on the clinical response to lithium in bipolar disorder patients. A better understanding of potential links between circadian mechanisms, genetic risk factors, and the response to lithium treatment may open new avenues into the clinical management of bipolar disorder.

## Speaker 2: Michael J. McCarthy, USA

**Title:** *Cellular circadian rhythms in bipolar disorder patients: implications for pharmacotherapy.*

### Abstract

Bipolar disorder (BD) is a serious mood disorder associated with circadian rhythm abnormalities. Risk for BD is largely genetically encoded, and may overlap with the biological systems that maintain circadian rhythms, while the mood stabilizers lithium and valproic acid have effects on circadian rhythms, indicating alterations in circadian effects may underlie treatment response. We hypothesized that lithium-responsive BD patients (Li-R) would show characteristic differences in circadian rhythms compared to lithium non-responsive individuals (Li-NR). Selecting patients from a prospective, multi-center, pharmacogenetic clinical trial of lithium monotherapy, we examined morning/evening preference (chronotype) Li-R and Li-NR patients with BD. In a subset of patients, we measured circadian rhythms in fibroblasts longitudinally over 5 consecutive days using a bioluminescent reporter gene (*Per2-luc*). In this manner, we estimated circadian rhythm parameters (amplitude, period, phase) in living cells from Li-R and Li-NR donors. Compared to Li-NR subjects, Li-R subjects showed a difference in chronotype, with higher levels of trait morningness. Evening chronotype was associated with increased mood symptoms at baseline, especially depression and insomnia. Cells from Li-R patients were more likely to exhibit a short circadian period, a period shortening effect of lithium and a linear relationship between period and phase. We conclude that circadian rhythms may influence response to lithium in maintenance treatment of BD.

## Speaker 3: Mirko Manchia, Canada

**Title:** *Alterations of circadian rhythms in diverse stages of bipolar disorder*

### Abstract

Mirko Manchia[1,2]

[1]Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[2]Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of mood disturbances of opposite polarity (hypomania/mania or depression) interspersed with periods of relative well-being. Modifications of circadian rhythms are core symptoms in BD. These include altered sleep patterns as well as infradian or ultradian manifestations of affective symptoms. Importantly, as pointed out in several prospective studies of individuals at high genetic risk for BD (i.e. offspring of one biological parent with BD), these alterations can antecede the diagnosis of the disorder. For instance, specific sleep problems such as frequent nighttime awakenings, inadequate sleep, and increased difficulty falling asleep predict conversion to BD among non-BD offspring of BD parents. Further, sleep alterations can predate mood episodes during the illness course. This presentation has a twofold aim: 1) to selectively review the findings on the presence of altered sleep patterns in early and later stages of BD; 2) to present findings of a large cohort of Italian patients with either BD or major depressive disorder (MDD) on sleep alterations during mood episodes. Concerning the first aim, data from prospective longitudinal high-risk studies will be reviewed to highlight the role of circadian alterations in different stages of BD. Secondly, the analysis of a clinical dataset of about 4,900 patients showed that patients in the early course of the illness had significantly higher scores at the item 4 of the Hamilton Depression Rating Scale (HDRS) ($F = 10.9$, $p = 0.0009$). Moreover, BD patients showed higher severity of insomnia (items 4, 5, and 6 of the HDRS) compared to MDD patients ($p < 0.0001$ for each comparison). Taken together these findings show the relevance of circadian rhythm alterations in BD, particularly in the early course of the illness. Consideration for possible treatments of sleep disturbances as preventive strategies in BD will be made.

### Speaker 4: Stefano Comai, Italy

**Title:** *Melatonin MT1 receptors: neurobiological and psychopharmacological implications for drug discovery in bipolar disorders.*

**Abstract**

S. Comai[1,2], L. Posa[2], D. De Gregorio[2], M. López-Canul[2], Spadoni G.[3], G. Gobbi[2].

[1] Division of Neuroscience,San Raffaele Scientific Institute and Vita-Salute University, Milan, Italy; [2]Department of Psychiatry, McGill University, Montreal, Canada; [3]Department of Biomolecular Sciences, Università degli Studi di Urbino "Carlo Bo", Urbino, Italy.

**Background:** Bipolar disorder (BD) is characterized by mood swings. The circadian system is a key to behaviors that are regularly performed on a 24-hour cycle, and is known to be extensively disrupted in BD. The suprachiasmatic nucleus (SCN) regulates most of the circadian rhythms in the body. The neuromodulator melatonin (MLT) through its two G-protein coupled receptors, MT1 and MT2, controls the activity of the SCN. Here we discuss our preclinical findings on the possible role of MLT receptors in BD.

**Methods:** We examined in rodents the effects of MT1 and MT2 genetic inactivation (MT1 and MT2 knockout (KO) mice) and pharmacological activation (using the selective MT1 partial agonist UCM871 and MT2 partial agonist UCM924) upon core symptoms of BD including altered mood (mania/depression), sleep/wake cycle (particularly rapid eye movement sleep (REMS)), and serotonin (5-HT) activity, being 5-HT one of the main neurotransmitters involved in the manifestation of mood.

**Results:** MT1KO but not MT2KO mice showed a depressive like-phenotype mostly in the dark/night phase while during the light/day phase they showed hyperlocomotion, an index of mania-like behavior. Compared to controls, MT1KO mice had reduced 24-hour REMS and no REMS difference between light and dark phases, while MT2KO had reduced non-REMS during the light phase. In keeping, UCM871 increased REMS and UCM924 increased non-REMS duration. Using in-vivo electrophysiology, we found that during the light phase MLT via MT1 receptors and UCM871 reduced the activity of most (70%) of dorsal raphe 5-HT neurons.

**Conclusions:** MT1KO but not MT2KO mice show depressive-like behavior and hyperactivity depending on the phase of the day, and sleep/wake cycle and REMS impairments. UCM871 affects REMS and 5-HT activity in a phase of the day dependent manner. These results suggest that MT1 rather than MT2 receptors are likely implicated in circadian manifestation of behavior occurring in BD.

**Tuesday 19th June 2018**
**13.45-15.30**
**CP05: Anxiety Disorders**
Chair: Michael Bach, Austria
Co-Chair: Alexandra Schosser, Austria

---

### Speaker: Naomi Fineberg, UK

**Abstract**

Anxiety disorders and obsessive compulsive and related disorders are common, disabling, lifespan illnesses associated with significant comorbidity, chronicity and relapse and responsible for considerable health-economic cost and burden. Timely intervention and effective relapse prevention represent key therapeutic goals. Yet, despite the introduction of evidence based guidelines, these disorders are often poorly recognized and inadequately treated. This interactive session will address the clinical art of treating these challenging disorders from a research-enhanced perspective, using clinical vignettes supplemented by epidemiological, health-economic and treatment-trial data. We will start by considering some of the major clinical challenges associated with lifespan treatment (patient preference, tolerability, interactions, perinatal issues etc), and move on to discuss the management of severe refractory illness, focusing on obsessive compulsive disorder, including novel psychopharmacological and neuro-stimulation strategies. An international consensus statement proposing new clinical standards of care for obsessive compulsive and related disorders will be presented. Audience participation will be encouraged and there will be plenty of time for questions.

**Tuesday 19th June 2018**
**13.45-15.30**

## S31: (Late Breaking) Advances in non-invasive brain stimulation approaches targeting prefrontal, cingulate and insular cortices for treatment of OCD and addictions:

Chair: Joseph Zohar, Israel
Co-Chair: Diana Martinez, USA

### Speaker 1: Livio Luzi, Italy

**Title:** *Deep TMS of the prefrontal and insula cortices reduces food craving and body weight in obese subjects*

**Abstract**

BACKGROUND: Growing evidence highlights that a dysfunctional dopamine system is the main neurophysiological mechanism activating the reward pathway and stimulating feeding behavior, and therefore, promoting obesity. Deep Transcranial Magnetic Stimulation (dTMS) is a well known method for non-invasive stimulation of neural circuits and modulation of dopamine system in neuro-psychiatric disorders.
In this study, we hypothesized that dTMS reduces appetite and causes weight loss via modulation of the dopaminergic reward pathway.
METHODS: A total of 40 obese patients (11 males, 29 females, age 48.0±9.9, BMI 36.3±4.5) were enrolled in the study: 17 obese subjects underwent a 5-week treatment with high frequency dTMS (18 Hz, HF), 10 were treated with low-frequency dTMS (1 Hz, LF), and 13 were Sham-treated. After the 5-week treatment, all patients were followed up to 1 year. Food Craving Questionnaires-Trait was used to evaluate the food craving. Metabolic, physical activity, and neuro-endocrine parameters were assessed at baseline, after the 5-week treatment, and at the follow-up visits.
RESULTS: Following 5 weeks of dTMS treatment, body weight significantly decreased in HF compared with both LF and Sham groups ($p<0.01$). The body weight loss persisted up to 1 year of follow-up. Difference in food craving decrease was found significant at 6-month follow-up ($p<0.05$). In HF, a significant improvement of physical activity parameters, specifically an increase of activity energy expenditure ($p<0.05$), was found.
CONCLUSION: These findings demonstrated the efficacy of a 5-week treatment of HF dTMS in reducing appetite and body weight in obesity, up to 1 year follow-up period. Activation of dopaminergic neurons with modulation of the reward pathway, and stimulation of physical activity are hypothesized as the possible mechanisms underlying dTMS effects.

### Speaker 2: Diana Martinez, USA

**Title:** *Transcranial Magnetic Stimulation of Medial Prefrontal and Cingulate Cortices and Cocaine Self-Administration.*

**Abstract**

Previous studies have shown that repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex may serve as a potential treatment for cocaine use disorder (CUD). The goal of this pilot study was to investigate the effect of rTMS using the H7 coil on cocaine self-administration in the laboratory. The H7 coil provides stimulation to the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC). In the self-administration sessions, CUD participants chose between cocaine and an alternative reinforcer (money) in order to directly measure cocaine-seeking behavior.

Volunteers with CUD were admitted to an inpatient unit and assigned to one of three rTMS groups: high frequency (10 Hz), low frequency (1 Hz), and sham. Six participants were included in each group and the rTMS was delivered on weekdays for three weeks. The cocaine self-administration sessions were performed at three time points: at baseline (pre-TMS, session 1), after 4 days of rTMS (session 2), and after 13 days of rTMS (session 3). During each self-administration session, the outcome measure was the number of choices for cocaine.

The results showed a significant group by time effect ($p = .02$), where the choices for cocaine decreased between sessions 2 and 3 in the high frequency group. There was no effect of rTMS on cocaine self-administration the low frequency or sham groups.
Taken in the context of the existing literature, these results contribute to the data showing that high frequency rTMS to the prefrontal cortex may serve as a potential treatment for CUD.

### Speaker 3: Abraham Zangen, Israel

**Title:** *Deep transcranial magnetic simulation of the prefrontal and insula cortices induces smoking cessation in heavy smokers*

**Abstract**

The pathophysiology of addiction involves impaired excitability and function of reward-related circuitries. The combination of transcranial magnetic stimulation (TMS) and EEG measures revealed reduced cortical excitability in various forms of addiction. Repeated electromagnetic

stimulation of these circuitries can induce lasting alterations in excitability and function of these networks, thereby becoming a potential therapeutic approach. Our animal studies since 2007 revealed that multiple sessions of localized stimulation of the prefrontal cortex can alter molecular, electrophysiological and behavioral features of cocaine addiction, and recently also relapse rates. Our new animal model data on relapse to cocaine seeking following prelimbic and infralimbic stimulation will be presented. Furthermore, in order to translate animal studies, that utilized implanted electrodes with TMS-like temporal patterns of stimulation, to application in human addicts, we have used conventional and deep TMS coils to affect the relevant circuitries in heavy smokers and alcoholics. Multiple sessions using high, but not low, frequency of stimulation with an H-coil version targeting the prefrontal and insular cortices in heavy smokers induced smoking cessation, particularly when combined with activation of the craving-related circuitries by presentation of smoking cues just prior each stimulation session. This study led to a large multi-center sham-controlled study, ongoing in the past 3 years in 15 centers worldwide, which is now in completion phase. Initial results using high-frequency rTMS targeting the medial PFC and cingulate cortices in alcoholic patients indicate relapse prevention coupled with increased resting state functional connectivity between an anterior cingulate seed and the medial frontal gyrus.
Optimization of stimulation parameters for addiction treatments requires further investigation into mechanisms, utilizing imaging and electrophysiological techniques.

### Speaker 4: Joseph Zohar, Israel

**Title:** *dTMS in OCD -targeting the ACC– a new therapeutic tool, a new concept of stimulation.*

**Tuesday 19th June 2018**
**13.45-15.30**

## PL07: Differential influence of pre- and early postnatal cannabis exposure on the developing brain

Chair: Toshikazu Saito, Japan

---

### Speaker: Tibor Harkany, Austria

**Abstract**
Plant-derived and synthetic cannabinoids are commonly consumed, most notably by teenagers and young adults. Most alarming is the frequency of cannabis use during pregnancy, which is justified by its antiemetic action and the public perception that cannabis is neither addictive nor powerful enough to cause lasting harm to the adult brain. Here, I will discuss that even though cannabinoids, particularly □□9-tetrahydrocannabinol (THC, the primary psychoactive component of Cannabis spp.) invariably engage cannabinoid receptors in foetal, neonatal and adult brains, their developmental action vastly differs from adult outcomes due to the activation of precisely-timed signal transduction cascades. I will present evidence for THC to misroute axons and disrupt synaptogenesis by modulating endocannabinoid signaling in subcellular domains that sustain neurite outgrowth. I highlight the coupling of cannabinoid receptors to dynamic cytoskeletal reorganization as critical to detrimental cannabis effects. Thus, miswiring of neuronal circuits can underpin life-long modifications to social behaviours and cognition in affected offspring. Next, I will expand these concepts towards postnatal, primarily adolescent, periods by reviewing data on THC effects in relevant experimental models and longitudinal human studies. Cannabinoids will be shown to negatively affect both the survival of neurons that migrate and differentiate postnatally and the refinement of experience-dependent synaptic organization and plasticity. A case will be made for impaired cellular bioenergetics, particularly mitochondrial function, to compromise the assembly of and information processing within neuronal networks, manifesting as stereotyped and depressive behaviours experimentally. Overall, cannabinoids will be recognized to adversely impact both the formation and activity-dependent plasticity of neuronal circuits until after adolescence, thus provoking irreparable modifications to the brain's wiring diagram that underlies high-order cognitive processes.

# CINP 2018

# Satellite Symposium Abstracts

**Sunday 17th June 2018**
**13.00-14.30**
**Satellite Symposia 1**

***Otsuka & Lundbeck Sponsored Symposium***

## The place of long-acting injectables in severe mental health disorders - bipolar disorder and schizophrenia

Chair: Wolfgang Fleischhacker, Austria

**Chair's introduction: why we have LAIs, their benefits and convenience**
Wolfgang Fleischhacker, Austria

It is hoped that newer antipsychotics, with differing pharmacological profiles and improved tolerability, will provide much needed functional benefits for individuals with severe mental health disorders. However, while the individual pharmacology of antipsychotics results in differing efficacy and tolerability profiles, many factors contribute to outcomes for patients, including adherence to medication.
Long-acting injectable (LAI) antipsychotics were developed to improve treatment adherence. The evidence suggests that, through improved adherence, LAIs are, in general, more effective than oral antipsychotics in preventing relapse and, consequently, hospitalisation, and can help eliminate the abrupt loss of efficacy that can occur if oral doses are missed. For most individuals, each relapse leads to worsening of symptoms, progressive cognitive deterioration, impaired functioning, and reduced quality of life. Consequently, LAI antipsychotics have become important for maintenance treatment and may help to achieve improved functioning and quality of life, factors that are increasingly important goals of treatment.
In this symposium we will focus on functioning in individuals with severe mental health disorders and the impact of relapse prevention on functioning. We will present data on relapse prevention with LAIs for both bipolar disorder and schizophrenia. We will also discuss patient perspectives of treatment, patient management, and the importance of shared decision-making.

### Speaker 1: Eduard Vieta, Spain

**Title:** *Relapse prevention and functioning in patients with BP-I disorder*

**Abstract**
The concept of functioning in bipolar I disorder (BP-I) is complex. The main functioning problems presented by individuals with BP-I include cognitive impairment, reduced capacity to work/study and to live independently, difficulties with interpersonal relationships and participating in recreational activities, and sexual dysfunction.[1]
The FAST (Functioning Assessment Short Test) was developed for the clinical evaluation of real-world functional impairment presented by patients with mental health disorders, including BP-I.[1] It is a simple instrument that is sensitive to different mood states, easy to apply, and only requires a very short time for administration.[1]
A number of studies have reported high rates of functional impairment in individuals with bipolar disorder. FAST scores have been shown to be equally high in patients in manic and depressive phases.[1] Impaired function has even been shown in those with euthymia.[2] Tohen et al. (2000) showed that, although 97.5% of patients achieved syndromal recovery after a first episode, only 37.6% achieved functional recovery.[3]
Persistent symptoms and relapses can lead to worsening of functional impairment.[4,5] Long-acting injectable (LAI) antipsychotics have been shown to reduce relapse rates in BP-I.[6,7] Furthermore, improvements in function can be maintained long term with LAI treatment, even in euthymic patients.[8]
It is important to optimise the health and wellbeing of patients by use of individualised treatments involving coordination of pharmacological, psychosocial, and educational resources in order to achieve full functional recovery – the ultimate goal of treatment.

**References**
1. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health 2007; 3: 5.
2. Rosa AR, Franco C, Martínez-Aran A, et al. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom 2008; 77: 390–392.
3. Tohen M, Hennen J, Zarate CM Jr, et al. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry 2000; 157: 220–228.
4. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. Nat Rev Dis Primers 2018; 4: 18008.

5. López-Jaramillo C, Lopera-Vásquez J, Gallo A, et al. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 2010: 12: 557–567.
6. Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 2012; 22: 825–835.
7. Lähteenvuo M, Tanskanen A, Taipale H, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry 2018; 75 (4): 347–355.
8. Madera JJ, Jin N, Such P, et al. Effect on functioning with aripiprazole once-monthly (AOM 400) in the long-term treatment of bipolar I disorder (BD-I). Poster presented at the 30th annual US Psychiatric & Mental Health Congress, 16–19 September 2017, New Orleans, LA, USA.

## Speaker 2: Joseph Calabrese, USA

**Title:** *The place of LAIs in BP-I disorder*

**Abstract**

The highly recurrent nature of bipolar I disorder (BP-I) can be very difficult to manage. Recurrent episodes of mania are commonly associated with unfavourable outcomes, including poorer cognitive performance and greater number of hospitalisations.[1] Furthermore, poorer social and occupational functioning, an episode in the last 2 years, and history of rapid cycling are all associated increased caregiver burden.[2] Another major contributor to caregiver burden is their responsibility for overseeing medication intake.[2] Poor adherence to treatment is a significant problem in BP-I. Long-acting injectable (LAI) antipsychotics have the potential to improve medication adherence;[3] thereby, potentially improving patient outcomes and relieving family burden.[4]

Aripiprazole once-monthly and risperidone every 2 weeks are the only LAI atypical antipsychotics approved for maintenance treatment of BP-I. Aripiprazole LAI significantly delayed the time to recurrence of any mood episode compared with placebo ($p<0.0001$) and the risk of recurrence of any mood episode was approximately halved (hazard ratio: 0.45; 95% CI: 0.30, 0.68; $p<0.0001$).[5] Furthermore, aripiprazole LAI significantly delayed time to hospitalisation for any mood episode over 1 year ($p<0.001$).[6] Patients also showed improvement and maintenance of manic symptoms, and maintained overall functional improvements versus placebo ($p<0.05$).[6]

Compounds that possess prophylactic efficacy during maintenance therapy are the mainstay treatment for BP-I. However, the tolerability profile of a therapeutic agent is important in guiding long-term treatment decisions, and side-effect profiles may differentially affect adherence. Aripiprazole LAI is generally safe and well tolerated by patients with BP-I during long-term treatment with few discontinuations due to adverse events.[5]

**References**

1. López-Jaramillo C, Lopera-Vásquez J, Gallo A, et al. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 2010; 12: 557–567.
2. Reinares M, Vieta E, Colom F, et al. What really matters to bipolar patients' caregivers: sources of family burden. J Affect Disord 2006; 94: 157–163.
3. Gigante AD, Lafer B, Yatham LN. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs 2012; 26: 403–420.
4. Bates JA, Whitehead R, Bolge SC, et al. Correlates of medication adherence among patients with bipolar disorder: results of the Bipolar Evaluation of Satisfaction and Tolerability (BEST) study: a nationwide cross-sectional survey. Prim Care Companion J Clin Psychiatry 2010; 12: e1–e8.
5. Calabrese JR, Sanchez R, Jin N, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry 2017; 78: 324–331.
6. Calabrese JR, Sanchez R, Jin N, et al. Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. J Affect Disord 2017; 227: 649–656.

## Speaker 3: Wolfgang Fleischhacker, Austria

**Title:** *Planning and initiating an LAI in patients with recent-onset schizophrenia*

**Abstract**

A good functional outcome for individuals with schizophrenia is a key objective desired by patients, their families, and society. Long-term symptom control, relapse prevention, and tolerability of medication underpin functional improvement. These outcomes are particularly important to achieve early in the course of schizophrenia, given the greater capacity for

change, the relatively better social and family support during this period, and the marked impact of relapse in early adulthood on psychosocial consequences in terms of education or work opportunities.

The major advantage associated with long-acting injectable (LAI) antipsychotics is the impact on treatment adherence. Potential benefits for aripiprazole once-monthly over the oral formulation have been observed for time to all-cause discontinuation and Positive and Negative Syndrome Scale (PANSS) scores, in addition to non-inferiority for prevention of relapse.[1] These findings are in line with the comparable results between LAI risperidone and any oral antipsychotic therapy observed in a controlled clinical study in the USA.[2] Differences between oral and LAI formulations detected in controlled clinical trials are likely to be an underestimate of those in clinical practice as adherence is usually enhanced in the clinical trial situation. Results from mirror-image studies in patients eligible for clinical use of LAIs showed strong superiority of LAIs compared to oral antipsychotics in preventing hospitalisation.[3] These findings are further supported by a within-individual analysis of comparative effectiveness of antipsychotic treatments which showed that the risks of rehospitalisation, treatment failure, and death were lower with LAI treatment compared with an equivalent oral formulation in a very large cohort of patients with schizophrenia.[4-6] The lower risks were also observed in an incident cohort of newly diagnosed individuals.[4-6]

The goals of treatment in schizophrenia are changing. With an expectation of functional recovery from the first episode, we need to address how best to achieve this.

**References**

1. Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry 2014; 205: 135–144.

2. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. N Engl J Med 2011; 364: 842–851.

3. Kishimoto T, Nitta M, Borenstein M, et al. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry 2013; 74: 957–965.

4. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry 2017; 74 (7): 686.

5. Taipale H, Mehtälä J, Tanskanen A, Tiihonen J. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia-a nationwide study with 20-year follow-up. Schizophr Bull 2017; 10.1093/schbul/sbx176.

6. Taipale H, Mittendorfer-Rutz E, Alexanderson K, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. Schizophr Res 2017; 10.1016/j.schres.2017.12.010.

## Speaker 4: Ofer Agid, Canada

**Title:** *The benefits achieved in early-episode patients' functioning when treatment with an LAI is implemented early*

**Abstract**

Schizophrenia is unquestionably a potentially disabling and severe mental illness. A critical period has been postulated of 2–5 years following onset of psychosis during which future trajectories of functional outcome may be set and when interventions are likely to have a maximum beneficial effect.[1] Therefore, preventing relapse in the early stages by using an appropriate multidisciplinary and integrated treatment approach can make achieving a fulfilling and productive life possible.

Early initiation of treatment may help to protect patients from subsequent deterioration in functioning.[2,3] Treatment with aripiprazole once-monthly showed superior improvements compared with paliperidone palmitate on health-related quality of life as measured with the clinician-rated Heinrichs–Carpenter Quality-of-Life Scale (QLS), Clinical Global Impression — Severity scale, and Investigator's Assessment Questionnaire scores.[4] These significantly greater improvements were consistently demonstrated in young patients (≤35 years), indicating that patients in the early stage of schizophrenia may benefit in particular from aripiprazole long-acting injectable (LAI).[4]

With the known adherence benefits of LAI antipsychotics, and associated favourable relapse prevention and functioning data, their apparent underuse raises the question as to whether these medications are being given due consideration in the early phase of illness?

There is evidence to suggest that psychiatrists underestimate patient acceptability of injectable formulations, and tend to reserve LAIs for those with established nonadherence, poor insight, and multiple relapses.[5] Where resistance to LAIs does occur, the use of a shared decision-making approach, i.e., a collaborative process in which the role of the psychiatrist is to educate the patient concerning evidence-based treatments, to share their clinical experience, to acknowledge and clarify patient preferences and values, and to empower patients, may increase the likelihood of

LAI acceptance.[6] Physicians should set aside any preconceptions and make time to address an individual's specific reservations, ideally early in the course of schizophrenia.[5]

**References**
1. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl 1998; 172: 53–59.
2. Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. Schizophr Res 2013; 148: 117–121.
3. Stahl SM. Long-acting injectable antipsychotics: shall the last be first? CNS Spectr 2014; 19: 3–5.
4. Naber D, Hansen K, Forray C, et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res 2015; 168 (1–2): 498–504.
5. Cahling L, Berntsson A, Bröms G, Öhrmalm L. Perceptions and knowledge of antipsychotics among mental health professionals and patients. BJPsych Bull 2017; 41: 254–259.
6. Kreyenbuhl J, Medoff D, McEvoy JP, et al. The RAISE Connection Program: psychopharmacological treatment of people with a first episode of schizophrenia. Psychiatr Serv 2016; 67: 1300–1306.

## Sunday 17th June 2018
**13.00-14.30**
**Satellite Symposia 2**

### *Janssen Sponsored Symposium*

### Treating depression today and tomorrow
Chair: Siegfried Kasper, Austria

**Speaker 1: Peter Falkai, Germany**
**Title:** *Treating depression today*

**Speaker 2: John Krystal, USA**
**Title:** *Treating depression tomorrow*

## Sunday 17th June 2018
**18.00-19.30**
**Satellite Symposia 3**

### *AsCNP and Sumitomo Dainippon Sponsored Symposium*

### Schizophrenia Today: Review of pharmacology, metabolics and cognition across the lifespan
Chair: Wolfgang Fleischhaker - Austria

**Speaker 1: Wolfgang Fleischhacker, Austria**
**Title:** *Approaches to pharmacological treatment of schizophrenia across lifespan*

**Abstract**
Schizophrenia is a chronic condition that, for most patients, requires long-term pharmacological treatment that is tailored to individual response in order to achieve an optimum balance of efficacy and tolerability. Alongside this, current recommendations for schizophrenia management highlight the importance of addressing patients' physical as well as mental health in order to encourage long-term treatment adherence and optimise overall health and quality of life. Key goals of early intervention in schizophrenia include the prevention of harm, control of disturbed behaviour, and reduction of the severity of psychosis and its associated symptoms. During stabilisation and maintenance treatment, the primary goals are to continue to reduce symptoms, achieve and maintain remission, promote recovery, maintain or improve functioning and quality of life, and monitor for adverse treatment effects. Choosing the correct antipsychotic from the outset of treatment is crucial since patients often continue long-term maintenance treatment with the antipsychotic that was effective for them in the acute setting. Moreover, although antipsychotics are generally similar in terms of efficacy, they vary greatly in their adverse effect profiles, including their relative propensities for causing extrapyramidal symptoms and cardiometabolic, neurocognitive, endocrinological and sexual adverse effects. Certain stages of life (e.g. adolescence, late life) present additional challenges, which must also be considered when selecting treatment. The benefits and risks of an antipsychotic must therefore be considered when starting treatment and regularly monitored and reassessed within the context of each patient's specific and evolving needs. Treatment may need to be stopped, adapted or changed, not only to optimise symptom control, but also to ensure that physical

health, functioning and quality of life are optimised and not compromised by the potential adverse effects of treatment. Proactive monitoring for potential adverse effects and informed patient choice are essential in mitigating treatment non-adherence and optimising outcomes over the long term.

## Speaker 2: Christoph Correll, USA

**Title:** *Review of metabolic challenges in the treatments of schizophrenia: an overview of evidence over last decade*

**Abstract**

Current guidelines for the management of schizophrenia highlight the importance of addressing the physical as well as mental healthcare needs of patients. Guidelines also promote the routine screening and monitoring of patients for cardiometabolic risk. Such recommendations have arisen because of an increasing recognition of the disease- and treatment-related impact of schizophrenia on patients' physical health. Compared with the general population, individuals with schizophrenia have an increased risk of cardiovascular and other metabolic diseases that is not only related to the disease itself, but also to the fact that those with schizophrenia are less likely to receive primary and secondary prevention than those without schizophrenia. Lifestyle factors associated with schizophrenia (e.g. smoking, inactivity and poor diet) can further increase the risk of cardiometabolic problems, such as diabetes. Crucially, a growing body of evidence has additionally demonstrated that although antipsychotics are generally rather similar in terms of efficacy, at least at group levels, they vary greatly in their propensities for causing adverse effects that may cause and/or exacerbate physical health problems, particularly in relation to cardiometabolic risk. For example, there is clear evidence that atypical antipsychotics vary greatly in terms of their likelihood for causing weight gain, dyslipidaemia, hyperglycaemia and the metabolic syndrome. Furthermore, adverse cardiometabolic effects also negatively impact on quality of life and adherence. Moreover, studies have shown that patients who experience adverse cardiometabolic effects with a particular antipsychotic may benefit if switched to an antipsychotic with a lower propensity for metabolic adverse effects. Taken together, this review demonstrates that clinicians can improve patients' cardiometabolic health, not only by using appropriate behavioural and pharmacological prevention and intervention approaches, but also by prioritising the use of antipsychotics with a relatively low risk of adverse cardiometabolic effects, aiming to add years of life and life to years in this population.

## Speaker 3: Philip Harvey, USA

**Title:** *Cognition in schizophrenia: how to evaluate and adapt treatment for best functional outcomes?*

**Abstract**

The goal of schizophrenia treatment is not only the management of psychotic symptoms but also the achievement of functional recovery. This encompasses a broad range of functional outcomes, including occupational, educational and social activities, and the attainment of meaningful interpersonal relationships, independence and a good quality of life. Evidence has demonstrated a clear link between neurocognition and functional outcomes in schizophrenia and, more recently, social cognition has emerged as an important mediator between neurocognition and social functioning. There are many tools available to assess cognitive and functional capacity in patients with schizophrenia, such as the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, Brief Assessment of Cognition in Schizophrenia (BACS) and UCSD Performance-based Skills Assessment (UPSA). Some antipsychotics are associated with neurocognitive adverse effects, which may cause or exacerbate problems in cognitive function. Studies have suggested that the cognitive benefits observed following treatment with antipsychotics may not exceed those anticipated from practice effects. Nevertheless, evidence for the potential neurocognitive benefits of certain atypical antipsychotics is more robust. For example, clinical trials of the atypical antipsychotic lurasidone have demonstrated clinically relevant cognitive improvement at higher doses (up to 148 mg/day), compared to placebo. Long-term treatment with lurasidone was not associated with deleterious effects on cognitive function in either adolescent or adult patients, and, even at high doses, lurasidone does not appear to induce sleepiness or sedation. Further research is required to determine whether the potentially beneficial neurocognitive effects of some antipsychotics translate into benefits in terms of improved functional outcomes and overall recovery.

**Monday 18th June 2018**
**13.00-14.30**
**Satellite Symposia 4**

***Lundbeck Sponsored Symposium***

## Why do we need new treatments for major depressive disorder and schizophrenia?

Chair: Philip Gorwood, France

### Chair's welcome

Philip Gorwood, France

Why do we need new treatments for major depressive disorder and schizophrenia?
Many patients suffering from major depressive disorder (MDD) do not fully respond to antidepressant treatment (ADT). One efficacious option to help patients with an inadequate response to ADT is to add an atypical antipsychotic to their treatment regimen. In schizophrenia, atypical antipsychotics are generally efficacious at controlling positive symptoms when taken as prescribed, and there is some evidence of a beneficial effect on negative symptoms. In MDD and schizophrenia, however, antipsychotics as a group can be limited by a high side-effect burden, which can cause harm to patients and can lead to poor treatment adherence.
Dopamine $D_2$ receptor partial agonists – aripiprazole, cariprazine, and brexpiprazole – have been developed in the context of a need for antipsychotics with improved tolerability profiles. Each of these agents has shown efficacy in the short- and long-term treatment of schizophrenia; aripiprazole and brexpiprazole are also effective in, and approved for, the adjunctive treatment of MDD. Importantly, aripiprazole, cariprazine, and brexpiprazole are associated with low levels of side effects.
The objectives of this symposium are to discuss the need for new adjunctive treatments for MDD, and new treatments for schizophrenia; and to consider the advantages of $D_2$ partial agonist antipsychotics in the treatment of these disorders.

### Speaker 1: Philip Gorwood, France

**Title:** *MDD and schizophrenia – addressing unmet needs with newer antipsychotic treatments*

**Abstract**
Despite the availability of effective antidepressants, a large proportion of patients with major depressive disorder (MDD) do not achieve an adequate clinical response or remission.[1] In these patients, the efficacy of treatment augmentation with an atypical antipsychotic is supported by high-quality evidence.[2] For patients with schizophrenia, atypical antipsychotics are the mainstay of treatment.
Most antipsychotics are associated with adverse effects – to varying degrees – which can result in a substantial impairment of a patient's subjective well-being and quality of life.[3-5] Of particular concern are activating effects (e.g., akathisia, restlessness, insomnia, and agitation), sedating effects (e.g., somnolence and sedation), and metabolic effects (e.g., weight gain).
Partial agonism at $D_2$ receptors is thought to have a modulating effect on dopamine neurotransmission – dependent on the level of endogenous dopamine present – leading to fewer undesirable side effects.[6] A key factor for the therapeutic use of $D_2$ partial agonists is the determination of the optimal level of intrinsic activity at that receptor.[6,7] Aripiprazole, cariprazine, and brexpiprazole act as partial agonists at $D_2$ receptors, though each agent has a distinct receptor binding profile. Aripiprazole preferentially binds to $D_2$ receptors, whereas cariprazine demonstrates greatest affinity for $D_3$ receptors.[8] Brexpiprazole is a partial agonist at 5-$HT_{1A}$ and dopamine $D_2$ receptors, and an antagonist at 5-$HT_{2A}$ and noradrenaline $\alpha_{1B/2C}$ receptors, all at subnanomolar potency.[9]
Compared with aripiprazole, brexpiprazole has approximately 10-fold higher affinity for 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors, >10-fold higher affinity for $\alpha_{1B}$ and $\alpha_{2C}$ receptors, and a lower intrinsic activity at the $D_2$ receptor.[7,9,10]
Thus, the pharmacological profile of newer antipsychotics suggests a low propensity to induce adverse events that are typically associated with dopamine antagonism, or to induce activating or sedating adverse events.

**References:**

1. Wang SM, Han C, Lee SJ, et al. Chonnam Med J 2016; 52 (3): 159–172.
2. Connolly KR, Thase ME. Drugs 2011; 71 (1): 43–64.
3. Leucht S, Cipriani A, Spineli L, et al. Lancet 2013; 382 (9896): 951–962.

4. Citrome L. J Clin Psychopharmacol 2017; 37 (2): 138–147.
5. Bobes J, Garcia-Portilla MP, Bascaran MT, et al. Dialogues Clin Neurosci 2007; 9 (2): 215–226.
6. Stahl SM. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications. Fourth Edition. © Cambridge University Press, 2013.
7. Citrome L, Stensbøl TB, Maeda K. Expert Rev Neurother 2015; 15 (10): 1219–1229.
8. Kiss B, Horváth A, Némethy Z, et al. J Pharmacol Exp Ther 2010; 333 (1): 328–340.
9. Maeda K, Sugino H, Akazawa H, et al. J Pharmacol Exp Ther 2014; 350 (3): 589–604.
10. Citrome L. Int J Clin Pract 2015; 69 (11): 1211–1220.

## Speaker 2: Anita Clayton, USA

**Title:** *New adjunctive treatment opportunities for patients with MDD*

**Abstract**

For the many patients who do not achieve an adequate response to antidepressant treatment (ADT), addition of a non-antidepressant is a recommended treatment option. Aripiprazole, brexpiprazole, and quetiapine extended- and prolonged-release are approved for adjunctive use in major depressive disorder (MDD). Quetiapine exhibits antagonism at the $D_2$ receptor, while aripiprazole and brexpiprazole act as $D_2$ receptor partial agonists.

In a pooled analysis of three short-term studies, adjunctive aripiprazole produced a greater improvement in Montgomery–Åsberg Depression Rating Scale (MADRS) Total score compared with antidepressant monotherapy.[1] In a pooled analysis of four short-term studies, adjunctive brexpiprazole also showed greater improvement in MADRS Total score compared with antidepressant monotherapy. Improvements in social functioning, as measured by the Sheehan Disability Scale (SDS) Mean score, have also been observed with adjunctive aripiprazole,[2] and with adjunctive brexpiprazole. Cariprazine – the third D2 partial agonist antipsychotic; not approved for use in MDD – has shown efficacy as adjunctive treatment in one short-term Phase II study.[3]

In long-term studies (up to 52 weeks), sustained improvement in clinical symptoms was observed with adjunctive aripiprazole,[4] and with adjunctive brexpiprazole.

As adjunctive treatment for MDD, aripiprazole has been shown to be similarly associated with activating and sedating events, and brexpiprazole has been shown to be neither activating nor sedating.[5] In pooled analyses of short-term studies, the most common treatment-emergent adverse event (TEAE) with adjunctive aripiprazole was akathisia.[1] Whilst akathisia was also the most common TEAE with short-term adjunctive brexpiprazole treatment, the incidence was substantially lower than with aripiprazole (aripiprazole, 23%; brexpiprazole, 8%), which may reflect differences in pharmacological profiles.

In long-term adjunctive treatment, the most common TEAE associated with aripiprazole was akathisia,[4] and with brexpiprazole was weight increase; however, the mean increase in body weight throughout long-term treatment was slightly smaller with brexpiprazole than with aripiprazole. Long-term treatment, with aripiprazole[6] or brexpiprazole, was associated with an improvement in sexual functioning, as measured by the Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ).

Thus, adjunctive treatment with aripiprazole or brexpiprazole is a valuable treatment option for patients with MDD and an inadequate response to ADT.

**References:**

1. Dunner DL, Laubmeier KK, Manos G, et al. Prim Care Companion CNS Disord 2012; 14 (6): PCC.12m01380.
2. Fabian TJ, Cain ZJ, Ammerman D, et al. Prim Care Companion CNS Disord 2012; 14 (6): PCC.12m01394.
3. Durgam S, Earley W, Guo H, et al. J Clin Psychiatry 2016; 77 (3): 371–378.
4. Berman RM, Thase ME, Trivedi MH, et al. Neuropsychiatr Dis Treat 2011; 7: 303–312.
5. Citrome L. J Clin Psychopharmacol 2017; 37 (2): 138–147.
6. Clayton AH, Baker RA, Sheehan JJ, et al. BMC Res Notes 2014; 7: 459.

## Speaker 3: Christoph Correll, Germany/USA

**Title:** *The role of partial agonists in the treatment of schizophrenia*

**Abstract**

In the treatment of schizophrenia, most antipsychotics are associated with adverse effects; activating, sedating, and metabolic-related events are common causes of concern. Compared with $D_2$ receptor antagonism that is exhibited by most antipsychotics, $D_2$ partial agonism – as shown by aripiprazole, cariprazine, and brexpiprazole, each of which displays a different receptor profile – is thought to result in a lower side-effect burden in relevant domains.

In the short-term treatment of schizophrenia, each of these agents has demonstrated efficacy on the Positive and Negative Syndrome Scale (PANSS),[1-3] as well as on the Personal and Social

Performance scale (PSP; a measure of patient functioning).[3-5]
In addition to effectiveness as acute treatment, each agent has also demonstrated efficacy in preventing relapse over the long term,[6-8] as well as long-term effectiveness in improving, or maintaining improvements in, patient functioning.[4,7,8]
Overall, the $D_2$ partial agonists have shown favourable tolerability in the short-term treatment of schizophrenia. However, the distinct receptor profile of each drug leads to differences in tolerability profiles. Activating and sedating events can be burdensome side effects of antipsychotic treatment. Aripiprazole has been shown to be similarly associated with activating and sedating events, cariprazine is primarily activating, and brexpiprazole has been shown to be neither activating nor sedating.[9] In short-term treatment, each agent has shown a low propensity to induce weight gain.[3,10,11] Effects on laboratory parameters (such as increases in prolactin, and changes in glucose, cholesterol, and triglyceride levels) were also generally small, and comparable to changes observed with placebo.[3,10,11]
Long-term treatment with these $D_2$ partial agonists was also generally well tolerated, with no new or unexpected adverse events compared to the short-term studies, and only small mean changes in metabolic parameters.[6-8]
Thus, antipsychotics with $D_2$ partial agonist activity are valuable treatment options for the acute and maintenance treatment of schizophrenia; additional, head-to-head studies would shed further light on their comparative effectiveness.

**References:**

1. Kane JM, Assunção-Talbott S, Eudicone JM, et al. Schizophr Res 2008; 105 (1–3): 208–215.
2. Zhao MJ, Qin B, Wang JB, et al. J Clin Psychopharmacol 2018; 38 (1): 55–59.
3. Correll CU, Skuban A, Hobart M, et al. Schizophr Res 2016; 174 (1–3): 82–92.
4. Fleischhacker WW, Baker RA, Eramo A, et al. Schizophr Res 2014; 159 (2–3): 415–420.
5. Németh G, Laszlovszky I, Czobor P, et al. Lancet 2017; 389 (10074): 1103–1113.
6. Pigott TA, Carson WH, Saha AR, et al. J Clin Psychiatry 2003; 64 (9): 1048–1056.
7. Durgam S, Earley W, Li R, et al. Schizophr Res 2016; 176 (2–3): 264–271.
8. Fleischhacker WW, Hobart M, Ouyang J, et al. Int J Neuropsychopharmacol 2017; 20 (1): 11–21.
9. Citrome L. J Clin Psychopharmacol 2017; 37 (2): 138–147.
10. Marder SR, McQuade RD, Stock E, et al. Schizophr Res 2003; 61 (2–3): 123–136.
11. Earley W, Durgam S, Lu K, et al. Int Clin Psychopharmacol 2017; 32 (6): 319–328.

## Monday 18th June 2018
**13.00-14.30**
**Satellite Symposia 5**

***AsCNP and Sumitomo Dainippon Sponsored Symposium***

## Neuropsychopharmacology to the next generation: New wave from Asia
Chair: Siegfried Kasper, Austria

### Speaker 1: Andi J Tanra
**Title:** *New trends on prescription pattern of anti-psychotic in Asia: Result from the Research on Asia Psychotropic Prescription (REAP) study 2016*

**Abstract**
Antipsychotics remain the core of treatment for schizophrenia and related disorders although other psychotropic medications and non-pharmaceutical interventions have been used adjunctively in some patients and settings. Regular surveys on access to and prescription patterns of psychotropic medications in clinical practice are an important and efficient way of examining the use and time trends of treatments in a given population and region.
Recently, we conducted the psychotropic prescription studies, in coordination with the International Collaborative Studies on psychotropic prescription (REAP-Asia), as the largest and the longest international collaborative research project in Asia in the field of psychiatry. The aim of the study was to investigate the pattern of psychotropic prescription, to evaluate the factor that affect and the impact of the pattern, and finally to suggest the way to improve the quality of the pattern of prescription.
The prescription patterns of 579 schizophrenia patients in 10 centers in Indonesia (research institute and hospital) were investigated during March – May 2016. The total of 15 countries in Asia were joined the survey with the total of 3744 samples. The patients' socio-demographic and clinical characteristics and their prescriptions for psychotropic drugs were recorded using a standardized protocol and data collection procedure.
The results showed that there was a significant higher frequency of polypharmacies (34.7%) in the antipsychotics prescription pattern. The combined uses with other medication or psychotropic were common, with the highest frequency (43.5%) was combination with anti-parkinson drugs. In Indonesia itself, there has been a major shift in the prescriptions from first-generation antipsychotics (FGAs) to second-

generation antipsychotics (SGAs), which was also reflected in the incidence and severity of drugs induced EPS. Tobacco use posed greater challenge compared to other medical comorbidities and other non-psychiatric drug use.
The results above provide a great challenge and also opportunity in order to provide a better of mental health services in Indonesia and other countries in Asia. A better collaboration and network between countries in Asia are urgently needed. The Asian College of Neuropsychopharmacology (AsCNP) is dedicated to develop the field of neuropsychopharmacology in the Asian region, with the mission to raise awareness of developments at the level of clinical, translational, and basic science. In the future, we hope that AsCNP can embrace and strengthen the potential and collaboration of Asian countries in the field of neuropsychopharmacology.

## Speaker 2: Kazuyuki Nakagome, Japan

**Title:** *New Multimodal Therapeutic Approach to Realize Recovery in Patients with Schizophrenia*

**Abstract**

The treatment goal of schizophrenia has been shifted from mere alleviation of psychotic symptoms to attaining recovery in terms of both clinical and personal aspects. Clinical recovery represents improvement in functioning which can be assessed objectively, and personal recovery represents subjective QOL. Cognition has been focused on because it is more closely related to functioning than other symptoms. Many candidate compounds have been developed with the aim of improving cognitive impairment but no drug has been approved for that indication so far. Meanwhile, cognitive remediation therapy, which is a psychosocial treatment program, showed significant efficacy on cognitive impairment with an effect size of approximately 0.4-0.5. More interestingly, it showed significant effect on functioning in case it was combined with other psychosocial treatments.
Many studies failed to show direct relationship between functioning and subjective QOL. Brekke et al. (2001) indicated that executive functioning was a moderator of the relationship between functioning and subjective QOL. Specifically, patients with impaired executive functioning showed a significant positive relationship between social functioning and subjective QOL and for those with intact executive functioning, social functioning was negatively associated with subjective QOL. In fact, subjective QOL is more closely related to depression, dysphoria and motivation rather than cognition. Interestingly, motivation is one of the mediators between cognition and functioning. Improvement in motivation either by enhancing cognition, sense of autonomy, self-efficacy, relatedness, or direct approach on brain reward system, may lead the patients to both clinical and personal recovery. New drugs that not only reduce positive symptoms but that are effective in enhancing cognition and/or motivation are essential in combination with psychosocial treatment programs to attain clinical and personal recovery. I think it is time for us to reconsider the outcome measures used in clinical trials for drug approval for the sake of well-being of the patients.

# Index of Authors


| Last | First | Page Number |
|---|---|---|
| Beckmann, | Christian | 31 |
| Bellivier, | Frank | 13 |
| Bercik, | Premsyl | 49 |
| Bergman, | Hagai | 40 |
| Binder, | Elisabeth | 18 |
| Blier, | Pierre | 38 |
| Blumberg, | Hilary | 12 |
| Boedhoe, | Premika | 25 |
| Borg, | Jackie | 2 |
| Brühl, | Annette | 43 |
| Cagnan, | Hayriye | 22 |
| Calabrese, | Joseph | 61 |
| Carpenter, | Linda | 10, 19 |
| Cattaneo, | Anna | 48 |
| Chamberlain, | Samuel | 32 |
| Cipriani, | Andrea | 29, 65 |
| Clayton, | Anita | 66 |
| Comai, | Stefano | 54, 56 |
| Correll, | Christoph | 64, 66, 67 |
| Cowan, | Caitlin | 48 |
| Cryan, | John | 1 |
| Davis, | Lea | 26 |
| De Gregorio, | Danilo | 35, 56 |
| Dean, | Brian | 26, 27, 37 |
| Denys, | Damiaan | 40, 41 |
| Diaz Heijtz, | Rochellys | 49 |
| Do, | Kim | 47 |
| Dunlop, | Katharine | 10 |
| Eriksson, | Elias | 18, 28 |
| Erritzoe, | David | 49 |
| Ersche, | Karen | 23 |
| Etkin, | Amit | 38 |
| Falkai, | Peter | 7, 28, 63 |
| Fineberg, | Naomi | 26, 32, 56 |
| Fleischhacker, | Wolfgang | 42, 43, 51, 60, 61, 62, 63, 67 |
| Frank, | Ellen | 3, 4 |
| Franke, | Barbara | 5, 7 |
| Frazer, | Alan | 30, 31 |
| Gelernter, | Joel | 5 |
| George, | Mark | 10 |
| Glenthoej, | Birte | 47 |
| Gobbi, | Gabriella | 23, 35, 56 |
| Goldstein, | Rita | 23 |
| Grace, | Anthony | 30 |
| Gordon, | Josh | 37 |
| Gorwood, | Philip | 65 |
| Grant, | Jon | 32 |

# Index of Authors


| | | |
|---|---|---|
| Haber, | Suzanne | 40 |
| Hahn, | Andreas | 43 |
| Halldin, | Christer | 8 |
| Harkany, | Tibor | 13, 58 |
| Harvey, | Philip | 64 |
| Hashimoto, | Kenji | 15 |
| Hieronymus, | Fredrik | 28, 30 |
| Hiroi, | Noboru | 37 |
| Hoogman, | Martine | 6 |
| Hope, | Bruce | 24 |
| Hovatta, | Iiris | 53 |
| Howes, | Oliver | 1, 2 |
| Hurd, | Yasmin | 13, 14 |
| Ihara, | Masafumi | 21 |
| Ikeda, | Kazutaka | 33 |
| Javitt, | Daniel | 45, 46 |
| Jones, | Carrie | 16 |
| Joyce, | Eileen | 40, 41 |
| Kadriu, | Bashkim | 39 |
| Kahn, | René | 43 |
| Kasper, | Siegfried | 10, 17, 37, 63, 67 |
| Kikutchi, | Tetsuro | 34 |
| Kranz, | Georg | 10 |
| Krystal, | John | 1, 22, 29, 47, 62, 63 |
| Kundakovic, | Marija | 54 |
| Kuypers, | Kim | 49 |
| Kwon, | Jun-Soo | 42 |
| Lane, | Hsien-Yuan | 45 |
| Lansink, | Carien | 24 |
| Large, | Charles | 52 |
| Laviolette, | Steven | 13 |
| Lee, | Hochang Benjamin | 21 |
| Lee, | Junhee | 34 |
| Liechti, | Matthias | 50 |
| Luykx, | Jurjen | 4 |
| Luzi, | Livio | 57 |
| Manchia, | Mirko | 55 |
| Manzoni, | Olivier | 13 |
| Martinez, | Diana | 57 |
| McCarthy, | Michael J. | 55 |
| Meyer-Lindenberg, | Andreas | 1, 3 |
| Miskowiak, | Kamilla | 43 |
| Moeller, | Hans Jurgen | 48 |
| Morilak, | David | 11 |
| Musazzi, | Laura | 54 |
| Nakagome, | Kazuyuki | 68 |
| Nemeroff, | Charles | 18 |

# Index of Authors


| | | |
|---|---|---|
| Nutt, | David | 22, 36 |
| O'Brien, | John | 3, 20 |
| Odlaug, | Brian | 33 |
| Agid, | Ofter | 62 |
| Oqendo, | Maria A | 17 |
| Phillips, | Jennifer | 38, 39 |
| Popoli, | Maurizio | 15, 52 |
| Preller, | Katrin | 36 |
| Rasenick, | Mark | 15, 16 |
| Reif, | Andreas | 5, 11 |
| Riba, | Jordi | 50 |
| Ribases, | Marta | 6 |
| Robbins, | Trevor | 12 |
| Ruhe, | Henricus | 30, 44 |
| Rujescu, | Dan | 26 |
| Sahakian, | Barbara | 2, 3, 22, 47 |
| Saito, | Toshikazu | 9, 58 |
| Sanacora, | Gerard | 38 |
| Sawa, | Akira | 45 |
| Scheidegger, | Milan | 39 |
| Schulze, | Thomas G. | 54, 60 |
| Schwarcz, | Robert | 52 |
| Singewald, | Nicolas | 53 |
| Smith, | Gwenn | 20 |
| Sotres-Bayon, | Francisco | 11 |
| Spies, | Marie | 31 |
| State, | Matthew | 22 |
| Stein, | Murray | 4 |
| Stein, | Dan | 25 |
| Suhara, | Tetsuya | 7 |
| Suzuki, | Takefumi | 41 |
| Tamminga, | Carol | 17, 27, 51 |
| Tanra, | Andi | 67 |
| Tauscher, | Johannes | 8, 35 |
| Telese, | Francesca | 15 |
| Turecki, | Gustavo | 19 |
| Uchida, | Hiroyuki | 41 |
| Uchida, | Naoshige | 34 |
| Vieta, | Eduard | 13, 60, 61 |
| Winstanley, | Catharine | 11 |
| Yamawaki, | Shigeto | 7, 37 |
| Yatham, | Lakshmi | 37, 61 |
| Young, | Allan | 13 |
| Zangen, | Abraham | 57 |
| Zohar, | Joseph | 4, 57, 58 |