In France, current national policies in the field of mental health promote the development of early intervention but France has not yet met national standards of care for EIP.
A recent report from the London School of Economics (2016) comparing different European countries even mentioned the delay of France in this area, referring to only one EIP in the country.
However, different early intervention initiatives have emerged in France during the last decade without such information being centralized and therefore with no visibility on the current situation over the whole territory.
The aims of this study were to draw up a comprehensive inventory of existing or planned programs (in metropolitan France and in the overseas territories) in 2017 and to describe how they operate in 2016.
Methods: This was a two-phase study; phase one was to identify and create an inventory of existing initiatives, and phase two was to describe and conduct an analysis of each initiative.
To be included, identified initiatives had to offer an early, intensive and multidisciplinary approach with at least 0.5 dedicated full-time equivalent staff. A secondary inclusion criterion concerned the out-patient setting of the initiative.
Inventory was achieved through many contacts across the country, among physicians/psychiatrists, healthcare facilities (hospitals, clinics, adolescent centers…) or administrative institutions (Health Regional Agencies…) which may either provide this kind of care or know of such initiatives.
An online declarative survey was administered between March and July 2017 to the identified psychiatrists with questions that covered administrative and clinical topics: structure of attachment, dedicated team, funding, targeted population, activity in 2016, partners of the program, difficulties encountered and prospects.
Results: Between March and July 2017, 37 EIP for management of early psychosis were identified in France: 18 were operational, 8 were being established, and discussions were under way for the remaining 11.
The 18 identified operational programs were located throughout the country with a few regional disparities. All programs operated with multidisciplinary teams, including at least one psychiatrist and one nurse, and with a mean of 4.3 dedicated full-time equivalents healthcare workers (median: 3.7).
Most programs offered case management (12/18), with caseloads ranging from 4:1 to 22:1. The mean caseload was 10:1 (standard deviation 8:1).
All programs included 15 to 35 year-old early psychosis patients. Four programs also included patients at ultra-high risk for psychosis (UHR), while 4 others continued patient management during the chronic stages; 4 initiatives included all these stages of the disease.
Half of the programs had been existing for 2 to 5 years (50%); 89% were created less than 5 years ago.
The surveyed professionals described an increasing number of patients under their care.
Discussion: Numerous projects and discussions appear to be under way (some programs should open very soon).
A real dynamic has been launched in France with an increasing focus and this evaluation will help to improve visibility of the identified programs and promote the development of new programs.

T34. SUBMISSION WITHDRAWN .

T35. DIFFUSION MEASURES OF EXTRACELLULAR FREE WATER IN A NON-HUMAN PRIMATE MODEL OF MATERNAL IMMUNE ACTIVATION: EXPLORING NEUROIMMUNE MECHANISMS OF PSYCHIATRIC DISORDERS

Cameron Carter*[,1], Tyler Lesh[2], Costin Tanase[2], Jeffrey Bennett[2], Ana-Maria Iosif[2], Judy Van Der Water[2], Richard Maddock[2], David Amaral[2], Melissa Baumann[2]
[1]UC Davis Health System, Imaging Research Center; [2]UC Davis

Background: Evidence has been accumulating for an immune-based component of psychiatric disorder etiology, particularly schizophrenia. Early epidemiological studies found an increased incidence of schizophrenia in offspring of mothers who had an infection during pregnancy. Recent work has identified genetic links to the MHC complex, pro-inflammatory cytokine elevations in cerebrospinal fluid and plasma. We have developed a non-human primate (NHP) model of maternal immune activation (MIA) using a modified form of the viral mimic polyIC (polyICLC) examine the relationship between altered neuorimmune function may contribute to psychosis risk through effects on the developing brain and behavior of NHP offspring. In a previous cohort of MIA-exposed offspring, our group observed evidence for increased pre-synaptic dopamine levels in the striatum using 6-[18F]fluoro-L-m-tyrosine (FMT) positron emission tomography, in addition to pubertal-onset behavioral abnormalities, which may model part of the neurodevelopmental pathway towards psychosis. This study builds on this model and examines the effect of maternal immune activation on in vivo--extracellular free water--a diffusion magnetic resonance imaging measure obtained with a multi-shell acquisition. We sought to test the hypothesis that offspring of pregnant monkeys who received polyICLC injections at the end of the first trimester would show increased extracellular free water compared to control offspring.
Methods: Fourteen pregnant rhesus monkeys (Macaca mulatta) receiving polyICLC at the end of the first trimester were compared to 14 controls. The offspring from both groups underwent a multi-shell diffusion MRI scan at 3 Tesla. Diffusion data was collected when the offspring were one month, 6 months, and 12 months of age. Six month preliminary findings are currently presented. Diffusion images were aligned to individual subject MPRAGE scans. Individual subject structural scans were then nonlinearly aligned to generate a common group average template and the group average template was subsequently nonlinearly aligned to a neurodevelopmental rhesus atlas. For this preliminary analysis, the frontal cortex was selected as an a priori region of interest in addition to the more global whole-brain gray and white matter masks.
Results: Six month old MIA-exposed rhesus offspring showed a trend for increased whole-brain white matter extracellular free water ($p=.09$) with no significant difference in whole-brain gray matter free water ($p=.27$) compared to control offspring. However, analysis of the frontal ROI revealed significantly increased gray matter free water in the left hemisphere ($p=.013$) with a trend towards increased gray matter free water in the right hemisphere ($p=.081$). There were no significant differences between MIA-exposed and control offspring in basic motor and reflex development or growth trajectories.
Discussion: These data suggest that despite the lack of behavioral abnormalities at this early age, extracellular free water values are increased in MIA-exposed offspring, particularly in frontal gray matter. More global whole-brain free water group differences did not reach statistical significance, which may indicate some regional specificity to these changes early in development. The NHP MIA model complements the human schizophrenia literature in which extracellular free water increases have been repeatedly identified. Ultimately, these data provide validation of the clinical relevance of the NHP MIA model and improve our understanding of neuroimmune mechanisms in the development of psychiatric disorders, particularly schizophrenia.

T36. THE ANTIPSYCHOTIC-LIKE PROPERTIES OF EVENAMIDE (NW-3509) REFLECT THE MODULATION OF GLUTAMATERGIC DYSREGULATION

Marco Bortolato*[,1], Laura Faravelli[2], Ravi Anand[3]
[1]University of Kansas; [2]Newron Pharmaceuticals S.p.A.; [3]Anand Pharma Consulting

Background: The lack of adequate benefit with current 5HT2 / D2 antipsychotics in large proportions of schizophrenic patients suggests it is essential to modulate other mechanisms for improving symptoms of schizophrenia (SCZ). Increasing evidence implicates NMDAr hypofunction, and hippocampal hyperactivity, in the dysregulation not only of mesolimbic DA neurons but also of Glu neurons, leading to increasing synaptic activity of Glu in the PFC. Injection of NMDAr antagonists (PCP, ketamine) at doses that produce psychotomimetic effects lead to a downstream increase of Glu neurotransmission at non-NMDAr. The excessive firing and the hyper-glutamatergic tone represent alternative targets of treatment for SCZ ultimately affecting positive, negative, cognitive symptoms. The addition of Glu release inhibitors may augment the benefits of the antipsychotics in patients showing inadequate response.
Evenamide uniquely does not interact with monoaminergic (DA, 5-HT, NA, H) pathways affected by current antipsychotics, or with more than 130 different targets that are involved in CNS activity, except sodium channels. Preclinical data suggests that by the modulation of the firing abnormalities, evenamide normalizes the aberrant spread of Glu excitatory transmission that occurs in the brains of patients with SCZ. Evenamide showed efficacy in animal models relevant to SCZ (sensory motor gating, mania, psychosis, depression, impulse control, cognition, social interaction), in monotherapy and as an add on to first or second generation antipsychotics irrespective of whether impairment was either spontaneous, induced by amphetamine or NMDAr antagonists or stress. Evenamide, has also shown significant benefit in a p.c phase 2 trial as an add-on to risperidone and aripiprazole in patients worsening on dopaminergic/serotoninergic antagonist medication, suggesting it acts through other mechanisms. New animal data further confirm evenamide's activity in reducing SCZ symptoms provoked by Glu alteration.
Methods: Effects of evenamide (EVE 1.25, 5, 15 mg/kg PO) to restore the impaired information processing (a deficit observed in SCZ), were evaluated in the rat model of the Pre-Pulse Inhibition (PPI) deficit induced by injection of the NMDAr antagonist ketamine (KET 6 mg/kg, SC). Clozapine (CLO 7.5 mg/kg, IP) was used as a positive control.
Results: PPI analysis showed significant main effects for KET to lower PPI levels [$F(1,264)=139.67$, $P<0.0001$], for EVE [$F(3,264)=3.14$, $P<0.05$] and CLO to enhance PPI levels [$F(1,98)=30.89$, $P<0.001$]. Notably, significant EVE x KET [$F(3,264)=2.79$, $P<0.05$] and CLO x KET interactions [$F(1,98)=5.45$, $P<0.05$] were found.
Post-hoc analyses (Tukey's) revealed that KET significantly lowered PPI ($P<0.0001$) for each group; both EVE (5 mg/kg) and CLO significantly increased PPI in KET-treated rats ($P=0.02$; $p<0.001$).
Discussion: Evenamide as monotherapy has similar effect to clozapine in reversing ketamine- induced worsening of PPI. Together with previously demonstrated effects to reverse PCP-induced PPI and social interaction deficits, this further supports its potential to affect both positive and negative symptoms of SCZ by targeting altered Glu transmission.
Efficacy of evenamide as an add-on to antipsychotics would revolutionize development of novel antipsychotics that would target aberrant firing and Glu transmission in SCZ. Two clinical trials have been planned to support the hypothesis that the addition of evenamide should add a non-dopaminergic mechanism for augmenting antipsychotic efficacy in patients who are not responding adequately to current antipsychotic, and in patients with treatment resistant SCZ who are not responding/worsening on clozapine.

T37. THE LONELY MOUSE: A MODEL FOR STUDYING MATERNAL PSYCHOLOGICAL STRESS AND ITS CONSEQUENCES IN THE OFFSPRING

Joseph Scarborough[1], Flavia Müller[1], Annamaria Cattaneo[2], Juliet Richetto*[,1]
[1]Institute for Veterinary Pharmacology and Toxicology, University of Zurich; [2]IRCCS Fatebenefratelli San Giovanni di Dio

Background: It is well established that antenatal psychopathology affects obstetric outcomes and maternal behavior, and that it has long-term consequences on the offspring's wellbeing and mental health, which are relevant for multiple psychiatric disorders. Against this background, it is of pivotal importance to investigate the precise mechanisms that underlie such association, and evaluate the potential beneficial and/or detrimental impact of pharmacological treatment during pregnancy and the postpartum period. To date, rodent models rely mainly on exposure to chronic or acute unpredictable stress during pregnancy, which is mainly based on physical stressors characterized by medium translational value. Therefore, we propose the use of a social isolation-rearing paradigm to investigate the effects of antenatal maternal stress on the offspring. This model has the advantage of implementing psychological stressors, as opposed to physical stressors, to induce depressive-like behaviours in female mice. Moreover, the depressive-like state can be induced and assessed before pregnancy, thus eliminating possible confounding factors that arise from physical stressful manipulations applied during pregnancy.
Methods: C57BL/6 female mice were socially isolated, or group housed, from weaning (PND21) to adulthood (PND91). After 5 weeks of social isolation, the animals were tested to confirm the development of a depressive-like phenotype. At PND91, both group housed and socially isolated mice were bred and left undisturbed during pregnancy. The offspring were subjected to cognitive and behavioral testing in adulthood. A subgroup of socially isolated and grouped females were treated with the antidepressant Fluoxetine (10mg/kg) for the last 3 weeks of social isolation, pregnancy and weaning, and the offspring were once again subjected to cognitive and behavioral testing in adulthood.
Results: Social isolation rearing induced weight gain, basal plasma corticosterone reduction and depressive-like behavioural traits, such as reduced social interaction and increased anxiety. Both female and male offspring of socially isolated mothers displayed a variety of behavioural abnormalities relevant to different psychiatric disorders, such as increased anxiety and altered fear expression. Male offspring also presented metabolic alterations and cognitive deficits in the form of spatial working memory and recognition memory. Prenatal fluoxetine was effective in rescuing some of the above-mentioned behavioural abnormalities but detrimental for others.
Discussion: Our results demonstrate, for the first time, that long-lasting psychological stress preceding pregnancy is sufficient for inducing long-term behavioural and metabolic alterations in the offspring. Specifically, social isolation can be considered a strong etiological factor for stress in rodents, just as loneliness is a significant precursor to depression in humans. The social isolation-rearing model could thus offer a translationally-relevant setting in which to further investigate the mechanisms underlying the association between prenatal stress and psychopathology in the offspring, and the contribution of pharmacological treatments.

T38. SUBMISSION WITHDRAWN

T39. NEURAL MECHANISMS OF METABOTROPIC GLUTAMATE RECEPTOR 3 MEDIATED ENHANCEMENT OF SYNAPTIC PLASTICITY AND COGNITION

Branden Stansley*[,1], Max Joffe[1], Samantha Yohn[1], Craig Lindsley[1], Colleen Niswender[1], P. Jeffrey Conn[2]
[1]Vanderbilt University; [2]Vanderbilt University Medical Center

Background: The group II metabotropic glutamate receptor 3 (mGlu3) is an emerging therapeutic target for schizophrenia, as research has demonstrated a link between mutations in the human gene encoding for mGlu3, GRM3, and clinical diagnosis of schizophrenia. Schizophrenia is known to be accompanied by debilitating cognitive impairments that negatively impact the overall quality of life of the patient. While current pharmacological