results are also consistent with results from the rodent ketamine-challenge model. These results are promising for the potential use of AUT00206 in the treatment of disorders associated with reduced cortical inhibitory function, such as schizophrenia.

**T109. MODULATORY ACTIVITY OF THE NOVEL DRUG SEP-363856 ON BRAIN FUNCTION: POTENTIAL APPLICATION FOR THE TREATMENT OF SCHIZOPHRENIA**

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**Background:** Schizophrenia is a complex and heterogeneous psychiatric disorder. The core features comprise positive and negative symptoms, including hallucinations and impaired motivation, as well as cognitive impairment. Current evidence implicates dysfunctions of different brain circuits, involving several neurotransmitters, among which dopamine and glutamate may play a prominent role. So far, the main treatment approach consists of atypical antipsychotics, mostly dopamine-serotonin antagonists, although there is an active search for drugs with novel mechanisms of action. In this regard, the drug SEP-363856 has demonstrated broad antipsychotic activity in preclinical models. The mechanism of action of SEP-363856 is distinct from currently available antipsychotics as it does not have affinity for D2 or 5-HT2A receptors, but it acts as an agonist at 5-HT1A and trace amine-associated (TAAR1) receptors. The aim of the present study was to investigate the ability of SEP-363856 to modulate the functional activity of selected brain areas relevant for schizophrenia and to test its potential in counteracting behavioural and molecular alterations induced by acute phencyclidine (PCP) administration, to mimic a condition of hypo-glutamatergic in the rat.

**Methods:** In order to investigate brain region-specific transcriptional mechanisms, adult male Sprague Dawley rats were treated with vehicle or SEP-363856 (1, 3 or 10 mg/kg, PO) and sacrificed 1h later for the dissection of brain areas for molecular analysis. In order to test the ability of SEP-363856 to correct the alterations under a condition of reduced glutamate activity, adult female Lister Hooded rats were pre-treated with the drug (1, 3 or 10 mg/kg, PO) 60 minutes before an acute injection of PCP (2 mg/kg, i.p.). Locomotor activity was analysed during the following 90 minutes before sacrifice for the molecular analyses.

**Results:** We found that the prefrontal cortex (PFC) showed the most significant changes in response to acute administration of SEP-363856. Indeed, the drug induced a significant up-regulation of a number of activity-dependent genes, such as Arc, Zif268, c-Fos and Npas4. We also found that the expression of the pool of BDNF transcripts with the long 3’UTR, characterized by a prominent dendritic localisation, was significantly increased within the PFC of animals treated with SEP-363856. The prominent activation of PFC was associated with a significant increase of signalling pathways associated with glutamatergic and dopaminergic activity, including the phosphorylation levels of AMPA receptor subunit 1 (GluA1), protein kinase B (Akt) and, to a lesser extent, the MAP kinases ERK1/2. When investigating the activity of the drug in the acute PCP model, we found that SEP-363856 at all doses attenuated PCP-induced hyperlocomotion. At the molecular level, we found that acute PCP injection up-regulated mRNA levels of activity-dependent genes (Arc, Zif268, c-Fos and Npas4) as well as of BDNF within PFC and these changes were also prevented by SEP-363856 at all doses.

**Discussion:** In summary, the results of our studies indicate that SEP-363856 has a rather selective activity on prefrontal cortex, by promoting rapid transcriptional mechanisms that may be related to its ability in modulating glutamatergic as well as dopaminergic pathways. Moreover, we found that SEP-363856 was able to counteract the behavioural and molecular effects induced by NMDA receptor antagonism. Further studies will investigate its ability to restore cognitive functions known to be impaired in schizophrenia.

**T110. BIOEQUIVALENCE OF GENERIC AND BRAND NAME CLOZAPINE IN KOREAN SCHIZOPHRENIC PATIENTS: A RANDOMIZED, TWO-PERIOD, CROSSOVER STUDY**

Abstract not included.

**T111. TOBACCO CIGARETTE SMOKING IS ASSOCIATED WITH REDUCTIONS IN FUNCTIONAL CONNECTIVITY, ANATOMICAL CONNECTIVITY AND CORTICAL THICKNESS IN LARGE-SCALE NETWORKS**

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**Background:** Abstinence from cigarette smoking is associated with disrupted interactions among the core cognitive resting state networks including the Salience (SN), Default mode (DMN) and Executive control (ECN). Unified multimodal methods [Resting state connectivity analysis, Diffusion Tensor Imaging (DTI) analysis, and cortical thickness analysis] were employed to test the hypothesis that the impact of cigarette smoking on the balance among these networks is due to alterations in white matter connectivity, functional connectivity and cortical thickness (CT) and that these metrics define fundamental differences between smokers and non-smokers.

**Methods:** Multimodal analyses of previously collected data via the Human Connectome Project were performed on 18 smokers and 18 age- and sex-matched nonsmoking controls. Resting state functional magnetic resonance imaging (fMRI) was used to compare SN-DMN and SN-ECN interactions between smokers and nonsmokers. The anatomy of these networks was then assessed using DTI and CT analyses. Finally, we computed a composite variable [resource allocation index (RAI)] that summated the combined strength of interactivity within these networks.

**Results:** Relative to control nonsmokers, resting state fMRI analysis revealed no difference in the coupling of networks. However, Resource Allocation Index computation of the inter-network coupling was significantly lower in the smokers. FA of right cingulum bundle was significantly lower in smokers as was thickness of left inferior parietal cortex, left and right precuneus, which are nodes of the ECN and DMN, respectively. Reduced RAI predicted lower cingulum bundle FA in smokers. Reduced thickness and FA were associated with degree of nicotine dependence as measured by the Fagerström score.

**Discussion:** Our results demonstrate that tobacco cigarette smoking is associated with alterations in all three independent metrics of brain function and anatomy. Whether these reductions are pre-existing, transient or permanent is not known. The observed disrupted salience in resting state networks, medial parietal thickness reductions and cingulum FA deficits may contribute to the cognitive and affective abnormalities that have been documented to occur in smokers.

**T112. LEVEL OF COMPLIANCE WITH LONG ACTING INJECTIONS AND RISK OF HOSPITALIZATION**

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**Background:** Previous studies showed a direct correlation between partial compliance with an oral antipsychotic medication and hospitalization risk among patients with schizophrenia across a continuum of compliance behavior. Long Acting Injections (LAIs) may enhance compliance and reduce
relapse. The aim of this study was to evaluate the relationship between compliance with LAI 1-monthly Paliperone Palmitate (PP1M) and risk of discontinuation and hospitalization.

Methods: This was a naturalistic, 6-year mirror-image study examining retention, compliance & hospitalization rates 3 years pre and 3 years post PP1M initiation. Compliance was divided in four groups: full (no missed dose/year), good (>6 injections/year), poor (<6 injections/year) and non-compliance (no injection/year).

Results: 173 consecutive patients were included. 120 (70%) patients had a primary diagnosis of schizophrenia and 53(30%) had other diagnosis. In total, 77% of patients continued PP1M for 1 year, 66% for 2 years and 55% for 3 years. Out of 173 patients, 122 patients (71%) were fully compliant, 21 (12%) were generally compliant, 13 patients (7%) were poorly compliant and 17(10%) were completely non-compliant. The discontinuation rate at 3 years was 37% for patients with full compliance, 33% with good and 70% with poor compliance.

The reduction in number and length of admissions was statistically significant for the group of patients that was fully compliant but not for the group with good or poor compliance. In the patients who were fully compliant the mean number of hospital admissions decreased from 1.9 to 0.6 and the mean number of bed days from 70 to 40 bed days per patient 3 years before and 3 years after PP1M initiation (P<0.001).

Discussion: There was a linear association between level of compliance and risk of re-hospitalization. More than two thirds of this naturalistic cohort were fully compliant. This group demonstrated the best outcomes in terms of reduced hospitalizations with more than half of the patients having no admission during 3 years follow up. Patients with poor compliance had the worst outcomes: they were twice as likely to have completely discontinued PP1M at 3 years as well as showing the highest hospitalization rates both before and after PP1M initiation.

T113. ULTRA-LOW DOSE OF RISPERIDONE GIVEN IN ADOLESCENCE PREVENTS STRUCTURAL BRAIN AND BEHAVIORAL ABNORMALITIES INDUCED BY GESTATIONAL OR LACTATIONAL EXPOSURE TO MATERNAL IMMUNE ACTIVATION

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Background: Pre-natal exposure to the viral mimic polyinosinic-polycytidyl acid (poly-I:C) has been shown to produce a wide spectrum of brain and behavioral abnormalities phenotypic of schizophrenia. We showed that pre-natal poly-I:C led to increasingly widespread volumetric abnormalities that preceded the emergence of behavioral deficits, and that an ultra-low dose of risperdone (RIS) given to male offspring prior to “symptom” emergence (on PNDs 34-47), prevented both behavioral and structural abnormalities. Recently, we established a new model in which poly-I:C is administered to the nursing dams on PND4. This manipulation leads in the offspring to only minor effect on behavioral phenotype and no effect on structural abnormalities.

Methods: Poly-I:C (4mg/kg) or saline, was injected to pregnant dams on GD 17, to nursing dams on PND4. This manipulation leads in the offspring to only minor effect on behavioral phenotype and no effect on structural abnormalities.

Results: Adult females prenatally exposed to poly-I:C had disrupted LI and excessive AIA, as well as enlarged lateral ventricles and smaller hippocampal, striatal and prefrontocortical volumes. In the lactational model, poly-I:C exposed males exhibited persistent LI and hypo-response to amphetamine, and poly-I:C-exposed females exhibited increased immobility in the FST and hyper-response to amphetamine. In vivo imaging revealed hippocampal and striatal volume reductions in both sexes at PND 70 and enlargement of LV at PND 200. Risperdone prevented poly-I:C-induced brain abnormalities as well as the emergence of behavioral abnormalities in both the prenatal and the lactational models.

Discussion: Ultra-low dose of risperdone administered in adolescence is effective in preventing both structural and behavioral consequences in the gestational immune activation model, and in both sexes in the lactational immune activation model. These findings provide the first evidence showing the efficacy of the same early intervention in preventing the emergence of distinct behavioral phenotypes caused by different early insults in the two sexes. Notably, the behavioral phenotypes are considered to model positive symptoms, whereas the structural abnormalities may correspond to negative symptoms and affective/hedonic deficit.

T114. IMPROVING THERAPEUTIC ADHEREENCE IN SCHIZOPHRENIA SPECTRUM DISORDERS - FROM NURSING APPROACHES TO NEW TECHNOLOGIES

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Background: Treatment adherence in patients with psychotic disorders is an important challenge for physicians and caregivers, and various methods have been suggested in order to improve this parameter. Therapeutic adherence is defined as the extent to which the patient’s behavior corresponds to the agreement between him or her and the prescribing physician. Monitoring this parameter is essential, because of its implications for the patient’s prognosis, evolution, risk of relapse, quality of life, and overall functioning. A large number of factors have been associated with the ability to influence therapeutic adherence, e.g. frequency of administration and number of daily medications, adverse events related to antipsychotics, lack of insight or partial insight. Finding new ways to improve therapeutic adherence may be of considerable help for clinicians and may improve patients’ functional prognosis.

Methods: Main electronic databases (PubMed, CINAHL, PsycINFO, Cochrane, EMBASE, Thomson Reuters/Web of Science) were searched using as keywords “therapeutic adherence”, “treatment adherence”, combined with “schizophrenia”, “schizoaffective disorder”, and “psychotic disorders”. All papers published between 1988 and 2018 were included in the review. RCTs, as well as meta-analyses, systematic reviews and narrative reviews, case reports, case series, and letters to the editor were included. Papers without specified diagnoses of psychotic disorders, which included poorly specified interventions, or which included patients under 18 years old were excluded from this review.

Results: A number of 288 papers were found after the primary search, and 41 remained after filtering out the rest of studies based on inclusion and exclusion criteria. Adherence therapy based on motivational interview,