as rigorously and a clear understanding of the aetiology and risk of developing either adverse event remains elusive.

Aims: The current study aims to investigate changes in cardiac functioning in a group of patients treated with clozapine.

Method: Transthoracic echocardiograms were conducted on one hundred and four clozapine naïve patients, prior to commencing clozapine treatment (Time 1) and were repeated after 6 to 12 months (Time 2) of treatment, as part of routine cardiac monitoring. Patient psychiatric and medication history were documented, as were full white blood count, troponin 1 and creatinine kinase results.

Results: Preliminary analyses of the data set indicate a decrease in left ventricular shortening, a measure of ventricular contractility, from Time 1 (pre clozapine) to Time 2. Further analyses will be presented.

Conclusion: While there appears to be a trend towards a worsening of cardiac function with clozapine treatment, further investigations need to be carried out taking into account confounding factors that are known to be implicated in cardiac dysfunction to such as age, BMI, smoking, medical history, familial history, amongst others. Establishing a clearer understanding of the link between the two will help patients and clinicians balance the risk of cardiac problems and improved psychopathology and help to institute cardiac monitoring guidelines for patients treated with clozapine.

OP081   NOVEL ENVIRONMENT EXPLORATION IN RODENTS AND PATIENTS WITH BIPOLAR MANIA OR SCHIZOPHRENIA

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To differentiate the behavioral characteristics of schizophrenia (SCZ) and Bipolar Disorder (BD) and generate data suitable to validate putative animal models, we developed a human paradigm analogous to the rodent "open field". The human open field is a room in an inpatient psychiatric ward containing a desk, file cabinet, bookcase, 10 engaging objects, and no chair. The subject is asked to wait in the room and is monitored for 15 min. As in our rodent Behavioral Pattern Monitor, we quantify the amount of exploratory behavior, the sequential patterns of activity, and object interactions. Acutely decompensated BD (N = 15) and SCZ (N = 16) subjects were compared to healthy volunteers (N = 26). Studies of mouse models included pharmacological treatments with amphetamine or the selective dopamine transporter inhibitor GBR12909, and genetic knockdown of the dopamine transporter. Manic BD subjects demonstrated a unique exploratory pattern, namely high motor activity and object exploration. SCZ subjects failed to exhibit the expected habituation of motor activity. In mice, selective genetic or pharmacological inhibition of the dopamine transporter matched the mania phenotype better than the "gold standard" model of mania (amphetamine). These findings validate the human open field paradigm and identify defining characteristics of BD that are distinct from SCZ, even during highly psychotic states when they may otherwise be indistinguishable. This cross-species paradigm offers an innovative approach to recording exploratory activity in a novel environment, using procedures and multivariate assessments that have been validated in extensive studies of open field behavior in rodents.

OP082   ROLE OF SEROTONIN-1A RECEPTORS IN THE ACTION OF ANTIPSYCHOTIC DRUGS ON PRE-PULSE INHIBITION IN MICE

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Aims: The serotonin-1A ($5\text{-}HT_{1A}$) receptor has been implicated in the pathogenesis of schizophrenia, and some antipsychotic drugs have high affinity for this receptor. However the exact involvement of the $5\text{-}HT_{1A}$ receptor in schizophrenia and antipsychotic action remain unclear. We previously assessed the effect of antipsychotics on disruption of prepulse inhibition (PPI) by $5\text{-}HT_{1A}$ receptor stimulation in rats (1). PPI is a model of sensory information processing which is deficient in schizophrenia patients. To extend species comparison and to allow future studies in genetically-modified animals, we aimed to further explore the involvement of $5\text{-}HT_{1A}$ receptors in the action of antipsychotic drugs in mice.

Methods: Mice (n = 7–10/group) were pretreated with the typical antipsychotics and selective dopamine D_2 receptor (D_2R) antagonists, haloperidol or raclopride (both 0.05 or 0.25 mg/kg), the atypical antipsychotics, clozapine, olanzapine or risperidone (all 0.2 or 1 mg/kg), or the third generation antipsychotic, aripiprazole (1 or 5 mg/kg), which has partial agonist activity at both $5\text{-}HT_{1A}$ and dopamine D_2 receptors. Thirty minutes later, the mice were treated with either 1 mg/kg of the $5\text{-}HT_{1A}$ receptor agonist ($\pm$)-8-hydroxy-dipropyl-amino-tetralin (8-OH-DPAT) or saline and PPI was assessed using automated startle boxes.

Results: Treatment with 8-OH-DPAT dose-dependently increased PPI in Balb/c mice, but not in C57Bl/6 mice. Haloperidol, raclopride and aripiprazole pretreatment dose-dependently blocked the effects of 8-OH-DPAT on PPI. The atypical antipsychotics, clozapine, olanzapine and risperidone, had only minor effects on the action of 8-OH-DPAT on PPI.

Conclusion: These data suggest that stimulation of $5\text{-}HT_{1A}$ receptors by 8-OH-DPAT causes downstream activation of dopamine D_2 receptors leading to modulation of PPI. This effect appears to be opposite in mice (increased PPI) compared to rats (PPI disruption) which may be related to the differential activation of pre- and postsynaptic $5\text{-}HT_{1A}$ receptors, respectively (2). The ensuing changes in PPI can be blocked directly with antipsychotic drugs which have high affinity for $5\text{-}HT_{1A}$ receptors or indirectly by drugs which have high affinity for dopamine D_2 receptors. Further research is required to elucidate the exact mechanism of action of $5\text{-}HT_{1A}$ receptors in antipsychotic drugs, PPI, and by extrapolation possibly in schizophrenia.

(1) Van den Buuse & Gogos, J Pharmacol Exp Ther 320, 1224–1236, 2007
(2) Gogos, Kusljic & Van den Buuse, Pharmacol Biochem Behav 81, 664–672, 2006

OP083   THE ROLE OF TNF IN AGING-ASSOCIATED COGNITIVE PERFORMANCE – A MOUSE MODEL

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Aims: Although the age-dependent neurobiological processes leading to cognitive decline in the elderly remains to be fully understood, there is now growing evidence to suggest that age-dependent increases in pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF), might play a role in such age-associated cognitive decline. The aim of this work was to examine, using a mouse model, the effect of a deficiency of TNF ($TNF^{-/-}$) on cognitive function throughout aging.

Methods: A standardized survey on cognition-like behaviour assessing learning and retention, spatial learning/memory, and cognitive flexibility was used to measure the cognitive-behavioural profile of TNF knockout and wildtype mice, across three age periods; 3, 6 and 12 months of age, respectively.

Results: All studied mice strains demonstrated successful exploration and learning processes during the training phases of the tests, which made the specific cognition like tests valid in these mice strains. In the specific cognition-like tests, the $B6.TNF^{-/-}$ mice demonstrated, at 3 months of age, significantly poorer learning and retention in the novel object test as compared to B6.WT mice. In addition, spatial learning and learning effectiveness were significantly poorer in $B6.TNF^{-/-}$ mice, at 3 months of age, as compared to B6.WT mice. While the absence of TNF was correlated with poor cognitive functioning in early adulthood, over time the deletion of TNF resulted in better cognitive performance compared to B6.WT mice.

Conclusion: Low-levels of TNF under non-inflammatory immune conditions appear essential for normal cognitive function. Moreover, the absence of TNF with age appears to protect against age-associated cognitive decline. Collectively, these findings suggest a possible role for TNF in the molecular and cellular mechanisms subserving age-related changes in learning, memory and cognition.

OP084 INTERACTION OF ESTROGEN WITH CENTRAL SEROTONERGIC MECHANISMS IN SENSORY PROCESSING: MISMATCH NEGATIVITY AND LOUDNESS DEPENDENCE OF THE AUDITORY EVOKED POTENTIAL

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Background and purpose: The sex steroid hormone, estrogen, has been proposed to be protective against schizophrenia. This study aimed to explore whether this effect of estrogen occurs via a modulation of the serotonin-1A (5-HT$_{1A}$) receptor, which is strongly implicated in the pathophysiology of schizophrenia. Schizophrenia is associated with impairments of sensory processing as measured using mismatch negativity (MMN). Further, the loudness dependence of the auditory evoked potential (LDAEP) has been suggested as a non-invasive electrophysiological marker of central 5-HT function, with reduced serotonergic activity thought to increase the LDAEP slope. This study aimed to examine the effect of estrogen treatment on modulation of MMN and LDAEP by the 5-HT$_{1A}$ receptor partial agonist, buspirone, in healthy humans. We previously found (Gogos *et al*. 2006, Neuropsychopharmacology), in the same subjects, that buspirone caused a significant disruption of prepulse inhibition (a measure of sensory gating) and pretreatment with estrogen prevented this disruption.

Approach: In a double-blind, placebo-controlled, repeated-measures design, 16 healthy female volunteers were treated with placebo/placebo, estrogen (2 mg)/placebo, placebo/ buspirone (5 mg) and estrogen/buspirone. MMN was measured at the Fz electrode and LDAEP was measured using dipole source localization analysis.

Key Results: There was no significant effect of either drug treatment on MMN amplitude or latency. However, buspirone treatment significantly enhanced LDAEP slope in the placebo condition but was without any effect in the estrogen condition. Further, estrogen treatment alone resulted in a marked and significant increase of LDAEP slope.

Conclusion: These results suggest that buspirone treatment increased LDAEP by inhibiting 5-HT function and that this inhibition was prevented by estrogen pretreatment. In addition, estrogen was found to increase LDAEP, possibly by a direct action on cortical pyramidal cells or by an interaction with 5-HT$_{1A}$ receptors. However, neither 5-HT$_{1A}$ receptor activation nor estrogen is involved in the modulation of MMN. These results could be important for our understanding of the mechanism by which estrogen protects against schizophrenia.

OP085 IMPAIRED MISMATCH NEGATIVITY IN THE SCHIZOPHRENIA PRODROME

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Background: Mismatch negativity (MMN) to tone duration deviants has consistently been shown to be reduced in schizophrenia. Here we report on MMN data obtained from 19 healthy control subjects and 72 referrals to a specialized mental health service for the identification of individuals at ultra-high risk (UHR) of developing schizophrenia.

Methods: MMN was derived as subtraction waveforms of event related potentials (ERPs) to frequent short (50 ms) or long-duration (100ms) standard tones minus ERPs to infrequent long or short-duration deviant tones, respectively.

Results: The largest MMN amplitudes were recorded in control subjects compared with MMN from 12 referrals meeting criteria for first-episode psychosis and 27 UHR referrals with significant effects of duration type and group. Approaching significance, reduced MMN was recorded in 5 UHR individuals making a confirmed transition to schizophrenia one year after UHR identification in comparison to 13 UHR individuals who did not make such a transition.

Conclusion: Our preliminary findings suggest impaired MMN appears to be associated with prodromal schizophrenia.