unknown. A possible explanation for the co-morbidity between schizophrenia and addiction is that the rewarding properties of cocaine reverse the diminished motivational drive caused by chronic antipsychotic regimen. Moreover, chronic antipsychotic treatment can sensitize and amplify cocaine rewarding effects and exacerbate psychoses.
Methods: The rewarding properties of cocaine are attributed to the differential effects of dopamine on D1 and D2 receptor-expressing medium spiny neurons (MSNs) in the nucleus accumbens (NAc). Using in vivo Ca2+ miniature microscopic imaging, we characterize the role of D1 and D2 MSN in mono- and a cross- sensitization paradigms. D1- and D2-Cre mice were injected with a Cre dependent calcium indicator (gCaMP6f) and implanted with a gradient index (GRIN) lens above the nucleus accumbens and calcium activity was recorded using a head mounted miniature microscope. Cocaine sensitization was measured after a classic repeated cocaine regiment and antipsychotic and psychostimulant cross-sensitization was measured by a single cocaine injection after chronic pre-treatment with haloperidol.
Results: We found that both D1-MSN and D2-MSN populations are modulated by initial cocaine experience and further modulated during the expression of cocaine sensitization. A subpopulation of D1-MSN displayed initial activation, but reduced activity during the expression of sensitization. By contrast, the majority of D2-MSNs were suppressed by initial cocaine experience, but became active during the expression of sensitization. Furthermore, activity of D1- and D2-MSNs bidirectionally related with the observed behavioral responses to cocaine. Cross-sensitization following haloperidol treatment led to increased behavioral responses to psychostimulants. Current experiments are set out to investigate the neuronal responses of D1 and D2-MSN during cross sensitization between haloperidol and cocaine.
Discussion: Cocaine sensitization leads to differential neuronal responses in D1- and D2-MSN and these responses are differentially correlated with the magnitude of the sensitized behavioral response. These results reveal important new insights in the neurobiological processes in the nucleus accumbens that underlie psychostimulant sensitization and provide an important new model for studying the pharmacology of antipsychotic effects on striatal function and its potential role in increasing the susceptibility of schizophrenic patients to developing drug addiction.

S37. STATE-DEPENDENT EFFECTS OF D2 PARTIAL AGONIST ARIPIPRAZOLE ON DOPAMINE NEURON ACTIVITY IN THE MAM NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

Susan Sonnenschein*[,1], Kathryn Gill[1], Anthony Grace[1]
[1]*University of Pittsburgh*

Background: Aripiprazole is an antipsychotic drug characterized by partial agonist activity at D2 receptors that impacts both hyperdopaminergic and hypodopaminergic states. It is unclear whether aripiprazole reduces dopamine neuron activity via inhibition or by excitation-induced depolarization block, the latter being characteristic of D2 antagonist administration, and how aripiprazole interacts with D2 antagonist-induced reduction in dopamine neuron activity.
Methods: Adult offspring of saline and MAM-treated rats received aripiprazole (10 mg/kg), or vehicle, p.o. and dopamine neuron activity was examined 2h following acute treatment, or after 1d or 7d withdrawal from 21d repeated treatment. Dopamine neuron activity in the VTA was measured using in vivo extracellular recordings from anesthetized rats. After electrophysiological sampling, apomorphine (200 µg/kg i.p. or 20 µg/kg i.v.) was administered, followed by resampling the VTA to test for the presence of depolarization block. Additional recordings were conducted in MAM rats 1 h following acute haloperidol treatment (0.6 mg/kg, i.p). After electrophysiological sampling, aripiprazole (1mg/kg, i.p.) was administered to examine its effect on haloperidol-induced depolarization block.
Results: Both acute and repeated administration of aripiprazole reversed the increased number of spontaneously active dopamine neurons in MAM rats without impacting control rats. The reduction in dopamine neuron activity persisted after 7d withdrawal from repeated aripiprazole treatment and was not impacted by administration of apomorphine. In contrast, aripiprazole increased dopamine neuron activity in haloperidol-treated MAM rats.
Discussion: This study establishes that aripiprazole rapidly reduces hyperdopaminergic activity in MAM rats, without impacting dopamine neuron population activity in normal rats. The reduction is not due to depolarization block and persists 1 week following withdrawal from repeated treatment. Aripiprazole also removes haloperidol-induced depolarization block in MAM rats, which may underlie the acute psychotic symptoms observed clinically following the switch from D2 antagonist to aripiprazole treatment.

S38. CHARACTERISING THE COGNITIVE CONSEQUENCES OF DISRUPTED BDNF-TRKB SIGNALLING AT PARVALBUMIN-EXPRESSING INTERNEURONS

Adrienne Grech*[,1], Xin Du[1], Rachel Hill[1]
[1]*Monash University*

Background: Schizophrenia is a debilitating syndrome characterised by three main symptom categories: positive, negative and cognitive. Cognitive symptoms emerge first, and currently do not have appropriate treatments, despite being a strong predictor of the severity and progress of the illness. Cognitive deficits are thought to be partly attributed to impaired synchronization of gamma frequency oscillatory activity. Gamma oscillations are generated by a subclass of GABAergic interneuron that expresses the calcium binding protein, parvalbumin (PV). PV-interneurons are supported by Brain Derived Neurotrophic Factor (BDNF) and recent evidence has found that cessation of BDNF support in PV- interneurons impairs gamma oscillations. All of these factors have been demonstrated to have a role in cognitive processing, but their dynamic relationship is not completely understood.
Methods: The aims of this study were: 1) To generate transgenic mice where 50% of BDNF receptor (TrkB) gene is excised from PV-expressing neurons using the cre-lox recombination system and 2) To investigate the cognitive and behavioural consequences of disrupted BDNF signalling at inhibitory PV-expressing interneurons. Male and female mice underwent a battery of tests including: Y-Maze, Novel Object Recognition Task (NORT), Elevated Plus Maze, Locomotor and Cheeseboard Maze.
Results: Sex-specific spatial memory impairments were found in PV-Cre x TrkB floxed mice with only males showing no preference for the novel arm in the Y-maze paradigm. Furthermore, male PV-Cre x TrkB floxed mice displayed a lack of cognitive flexibility in the cheeseboard maze for long term spatial memory. No significant differences were observed in measures of anxiety and activity, indicating that these were not confounding variables for cognitive measures.
Discussion: This mouse line has not been cognitively characterised before and the results are of major interest. Subtle changes to cognition were observed and were sex-dependent. Interestingly, only males were observed to have changes in cognition, in line with human data. Human males with schizophrenia tend to exhibit more severe cognitive symptoms. Overall, the evidence from this study supports a role for BDNF-TrkB signalling at PV interneurons in regulating spatial memory performance. Future work will be investigating spatial search strategies of the Cheeseboard Maze, in order to elucidate further any cognitive differences between the genotypes. Additionally, future work will aim to specifically disrupt BDNF-TrkB signalling in the hippocampus and/or prefrontal cortex, as these two areas are highly implicated in both cognition and schizophrenia. It would also be of interest to use this genotype in a two-hit model, to further investigate the interaction of multiple factors and their impact on cognitive functions.