Deficits in reversal learning, a measure of flexible learning and behaviour, are fundamental features of clinical populations and animal models of obsessive-compulsive disorder (OCD) and other psychiatric conditions involving a range of compulsivity such as, addiction, bipolar disorder, attention-deficit/hyperactivity disorder, and schizophrenia. Reversal learning is an orbitofrontal cortex (OFC) dependent task in rodents and humans, and a cortical region involved in the neuropathology of these disorders. In rats, prior history of cocaine can disrupt task representations within OFC and cause reversal deficits. Optogenetic OFC stimulation can also restore flexible learning and behaviour in cocaine experienced rats. Theories of OFC function

The OFC is necessary for appropriately updating and guiding behaviour based on mental models of the world, and OFC dysfunction results in an inability to update the relationships between cues, actions, and their outcomes in reversal learning.

Orbitofrontal cortex (OFC) function is disturbed in many disorders of compulsion and provides an important neural target with significant translational potential for understanding compulsive behaviours and developing pharmacological treatments.

use a modified reversal learning procedure that can dissociate cognitive models of task representations from simple behavioural features.

in that can combination with electrophysiology and a prior history of cocaine use to directly test the contribution of cognitive model representations in OFC to reversal learning deficits. I will then use then test the efficacy of a novel drug to restore behavioural flexibility in reversal learning in rats with a

I will then use test the efficacy of a new drug to restore flexible reversal learning in this task to establish

I will then use this reversal task to test the translational potential of a novel and promising candidate drug for treating addiction.

* Talk about cues as signals to start and stop behaviours [cybernetic model of compulsions]

Orbitofrontal cortex (OFC) dysfunction is a key neuropathology underlying both DOC and reversal learning deficits. A prior history of cocaine use impaired reversal learning is accompanied by impaired updating in OFC firing.

Also

A prior history of cocaine impairs reversal learning behaviour and impairs updating representations .

In a recent study, rats with a history of cocaine use were unable to update their mental model of a task represented within OFC. This resulted in inappropriate behaviour which was effectively treated by optogenetic activation of the OFC. This was shown in behaviour that was not directly relevant to DOC.

Measure behavioural flexibility

Understanding OFC function and dysfunction in reversal learning tasks

**Aim 1. Determine whether OFC representations of task space differ between anterior and posterior LO in reversal learning**

Here I will extend previous findings in the lab showing the involvement of pLO activity in reversal learning and compare this within-subjects comparison to aLO activity. This will happen in a task that combines an established simple go-nogo reversal learning design with a modified conditional go-nogo task that will allow for a more sophisticated analysis of task-state representation. This experiment will test the hypothesis that anterior and posterior LO represent distinct aspects of task-state representations.

Given that behaviour in reversal learning is sensitive to disorders of compulsive behaviour, and the OFC is considered a key cortical substrate of compulsive behaviour and reversal learning, here I aim to increase our understanding of the role the OFC plays in reversal learning. Furthermore, I will test whether these representations differ within a single subregion of the OFC which I have previously shown to have dissociable roles in reversal learning.

**Significance**

* OFC/reversal learning – fundamental to understanding compulsive behaviour and have high translational potential
* Describe task modification and how this can help integrate task-state models with reversal learning procedures.
  + A well-studied reversal learning task that has been used in the lab involves initially training a rat to discriminate between an odour cue signaling that going to the fluid well will be rewarded (A -> Go), and a separate odour will not be rewarded (B -> NoGo), and then reversing these cue-response relationships (i.e. A -> NoGo, B -> Go). Deficits in reversal learning present as a significant increase in the number of trials needed to reach pre-reversal levels of accuracy (relative to a control group). This lab has shown that both OFC lesions and prior history of cocaine use are sufficient to cause reversal deficits, and prior history of cocaine use significantly impairs the updating of neurons selectively firing to the rewarded cue.
  + The dominant theory of OFC function developed in this lab using a variety of complex learning tasks to show that activity within the OFC represents environmental and task states i.e. contexts, cues, action, rewards and their relationships in a mental model of the task-state space akin to a cognitive map of the task.
  + Unfortunately, the reversal task described above does not allow for an analysis of task-state representation because the identity of the cues and the response-outcome relationships are correlated. Here I will employ a conditional reversal design that can tease apart the separate task-state information from cue and action-outcome representations.
  + The conditional task will involve the presentation of two odours (C and D) which will be rewarded (Go/NoGo) depending on an auditory cue (auditory cues X and Y) presented immediately prior to the odour. Specifically, odour C will be rewarded after auditory cue X but not Y (X -> C -> Go, Y -> C -> NoGo), whereas odour D will be reinforced after auditory cue Y but not X (X -> D -> NoGo, Y -> D -> Go). Once this is acquired, the unique meaning of auditory cues X and Y will be reversed (See figure XXX).
  + This task effectively separates the task-specific meaning of the odour cues from their physical identity and allows for a comparison activity during Go and NoGo trials to the same odour cue before and after reversal.
  + Isolating representations of task-state space within a reversal learning task will allow me to relate OFC activity in reversal learning in the context of the broader theory of OFC function.
  + How do representations of task-state space following reversal differ within the OFC? I will use single unit recording to directly compare anterior and posterior subregions of LO in this reversal task to determine whether there these subregions.
  + RL modeling with Angela Langdon – Now possible given this design.

**Approach**

**Expt. 1.**

Planned analysis and expected outcomes.

Alternative strategies, pitfalls, and future directions:

Aim 2. Determine how prior history of cocaine use disrupts OFC representations of task space in reversal learning and whether pharmacological intervention with D3 antagonists can restore reversal behaviour and OFC representations.

Prior history of cocaine use provides a translationally relevant model of a disorder of compulsive behaviour that has been shown to cause reversal deficits in clinical populations and in reversal learning tasks commonly used in this lab. Comparing OFC activity between subjects with and without a prior history of cocaine use will allow me to establish how disrupting representations of task-state space within the OFC can lead to reversal deficits. I will simultaneously assess the efficacy of a promising new class of dopamine D3 receptor antagonists to treat the effects of cocaine use on reversal learning.

**Significance.**

**Approach.**

**Expt. 2.**

First, two cohorts of animals will be given prior history of cocaine self-administration, or a control sucrose self-administration procedure for 2 weeks. Following 4 weeks drug free, these rats will undergo the same behavioural training and implantation of tetrode arrays described above in experiment 1. During the reversal period, half the rats in the cocaine and the sucrose exposed groups will receive an i.p. injection of the D3 antagonist prior to reversal sessions, and the other half will receive a vehicle injection.

Behaviourally, I predict that cocaine rats will take significantly more trials to reach criterion levels of accuracy during reversal but not during acquisition. Furthermore, it is hypothesized that the D3 antagonist will selectively reduce the number of trials to criterion during reversal in the cocaine rats to levels comparable to controls.

Neural representations: It is predicted that during initial acquisition, sucrose and cocaine treated rats will show similar patterns of task-state space encoding in the OFC to those found in Expt 1. Following reversal, it is expected that in cocaine treated rats these task-state space representations will fail to update to reflet the new contingencies, and this deficit will be by administration of the D3- antagonist in cocaine treated rats.