*The goal of this grant is to understand the role of task representation in OFC in flexible behavior and how it is disrupted by cocaine use, a disorder of compulsivity.*

*Backgrounds*

Reversal learning is a measure of behavioral flexibility that is significantly impaired in many disorders of compulsivity (DOC) such as obsessive-compulsive disorder and cocaine addiction, and is a promising translational model of DOC.

Reversal learning procedures have significant potential to further understanding and treatment of disorders of compulsivity (DOC) such as obsessive-compulsive disorder and cocaine addiction. Reversal learning tasks measure behavioural flexibility by changing the meaning of cues that signal when to act and when to withhold behaviour. Impairments in reversal learning are a reliable feature of both clinical and translational models of DOC. Reversal learning provides an important method to understand and test pharmacological treatments of DOC. Orbitofrontal cortex (OFC) dysfunction causes reversal learning deficits and is a common neural disturbance in DOC. In neurotypical subjects, a distinct subpopulation of *reversal neurons* selectively responds to cues that signal when to perform or withhold behavior, and flexibly update this selectivity when contingencies change. The proportion of these reversal neurons reliably predicts the speed of reversal learning. This is consistent with a mental representation of task structure being updated in OFC, which is the general function proposed by current computational reinforcement learning models of OFC. A history of cocaine use, known to cause compulsivity, significantly impairs reversal learning and reduces the number of reversal neurons in OFC. Therefore, prior cocaine use impairs representations of task structure in OFC that are necessary for flexible reversal behavior.

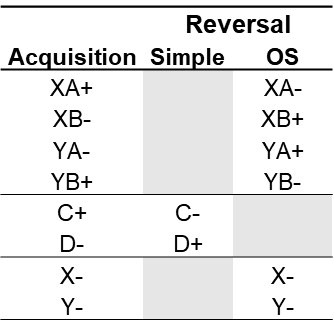
However, reversal tasks conflate changes in predicted cue value (rewarded -> non-rewarded) with changes in task specific cue meaning (respond->withhold).

Compulsive and neurotypical behaviours do not occur in a vacuum, but instead are elicited and informed by informative cues in our environment. Reversal learning procedures model this with discrete cues (e.g. odors) that indicate whether a behaviour (e.g. checking a location) will lead to a biologically meaningful outcome (e.g. food). In a typical procedure, subjects first learn to discriminate responding to a rewarded (A+) and non-rewarded (B-) cue, and then these cue-outcome relationships are reversed i.e. A- and B+. A reversal deficit is characterized by subject’s taking significantly longer to reach a threshold of behavioural accuracy following reversal. Distinct populations of neurons in OFC increase firing to rewarded and non-rewarded cues before and after reversal. This is consistent with a mental representation of task structure being updated in OFC, which is the general function proposed by current computational reinforcement learning models of OFC. Prior use of cocaine significantly impairs reversal learning behaviour and the flexibility of OFC activity to adapt to the new contingencies, suggesting that cocaine use impairs flexible updating of task representations in OFC. However, in this simple task the identity and value (average reward history) of each cue are significantly correlated. The meaning and identity of cues in the task can be separated by making cue-reward relationships conditional on other information/cues i.e. A is rewarded when preceded by cue X, but not cue Y (X->A+, Y -> A-), and B is rewarded when preceded by cue Y, but not X (X->B-, Y -> B+). Neural activity to cues A and B are now meaningful only in the context of preceding cues X and Y. A reversal of these contingencies (i.e. X->A- / Y -> A+ and X->B+ / Y -> B-), allows for an analysis of updating neural representations of task structure that can be dissociated from cue identity and value.

More generally, OFC activity is thought to reflect an internal cognitive model of a task/our environment. Prior history of cocaine use has been found to disrupt the flexible use and updating of these OFC representations, and optogenetic stimulation of OFC during learning effectively treats this impairment in rodents. This suggests that cocaine use impairs flexible updating of an internal model of the task within the OFC, leading to inflexible and persistent behaviour in reversal learning. However, in the reversal learning tasks commonly used, representations of internal cognitive maps cannot be disentangled from simple task features such as the presence or absence of reward. This is because the implementation designed to enforce the introduction of alternative maps utilizes the reward associations themselves. That is, the reversal is signaled to the subject by a change in cue-reward associations. Further, this approach confounds time and recognition of its passage, and leaves the decision whether to even create alternative maps up to the subject. The argument is that OFC function is necessary for rapid reversal learning because it facilitates the creation, maintenance or use of these alternative maps; however it could equally well be argued (and in fact has) that this deficit, viewed in isolation, is simply due to slower learning or deficits in response inhibition. To resolve these issues, it is necessary to use a behavioral approach that dissociates the cue that triggers changes in the map being used from these other features and requires mapping for successful performance. One such task that still shares many of the features of reversal learning that makes it so popular is an occasion setting task.

Broad aims –

* Use an OS task to identify neural correlates of underlying task structure in OFC
* Confirm whether these representations are correlated with the speed of behavioral flexibility in control animals
* Test whether a history of cocaine use impairs behavioral flexibility in OS task and its correlates in OFC
* Test whether a novel D3-antagonist can effectively recover impaired behavioral flexibility and its neural correlates in OFC in cocaine treated rats

***Table 1.*** *Experimental design. X and Y are auditory cues, cues A-D are odors, and pairs of cues reflect sequential presentation of an auditory occasion setting (OS) cue followed by a target odor cue. Rewarded Go trials are indicated by “+”, and non-rewarded NoGo trials are indicated by “-”. Simple reversal and OS reversal sessions conducted separately. Reversals begin with corresponding trials from acquisition before reversal.*



***Table 2.*** Patterns of cue selectivity in OFC that reflect representations of reversal, specific state space, and OS value. Expected patterns of neural selectivity to odors in each of these categories are represented by matching colors. A reversal neuron in a simple reversal design will change cue selectivity before and after reversal. Reversal neurons might reflect expected value or the underlying task state. A state space neuron in the OS task will reflect the unique underlying identity of the same target odor in different states depending on the auditory OS. An OS value neuron will change odor selectivity before and after reversal to reflect the predicted value of the auditory OS on that trial.

**Expt 1.** **Determine whether remapping of task representations in OFC during OS are disrupted in rats with a history of cocaine use.**

Hypothesis: In neurotypical controls, the strength of neural correlates of task structure in OFC will correlate with speed of OS acquisition and reversal learning; Prior cocaine use will reduce neural correlates of task structure in OFC and retard OS acquisition and reversal of OS.

Procedure: Long Evans rats (N = 16) will undergo intrajugular catheter surgery followed by a standard cocaine (n = 8) or sucrose (n = 8) control self-administration protocol for 2 weeks followed by 30 days of withdrawal. Rats will then be water deprived and given standard behavioral pretraining to become familiar with responding for odors and 10% sucrose reward in behavioral testing chambers. Next, a drivable bundle of microelectrodes will be implanted in OFC to record neural activity. Following recovery, rats will be water deprived again and trained to with a novel set of cues on the OS outlined in **Figure 1**. On each trial, the rat will initiate cue presentation by entering and staying in the odor port, then an odor or brief auditory cue (1000 ms) followed by an odor (500 ms) will be presented. On rewarded odor trials, responding to the food well below the odor port will be rewarded with water. Correct performance will be defined as entering the food port on rewarded trials and withholding responding on non-rewarded trials. Trial order will be randomized. Once acquisition behavior reaches a criterion of 90% correct responding over 20 consecutive trials with OS cues (X, Y, A, B) and Simple cues (C, D), reversal learning manipulations will occur: first for simple and then OS cues in separate sessions. Each reversal manipulation will involve presenting the original odor-reward contingencies until criterion performance accuracy, and then a reversal of these odor-reward contingencies until behavior reaches criterion accuracy. This will allow a within-session comparison of acquisition and reversal behavior and neural activity.

The primary behavioral measure will be the number of trials to criterion accuracy (TTC). TTC will be compared between acquisition vs. reversal, simple vs. OS, and control vs cocaine rats using a Poisson mixed-effects ANOVA model appropriate for count data.

Neural activity will be processed using standard methods. It is difficult to discuss all the possible results from an electrophysiological experiment such as this, so only key analyses and predictions will be presented below. Neural analyses will focus on activity during cue presentation to identify cue selective neurons by comparing different trial conditions. A neuron will be considered cue selective if activity increases during one condition. Significant differences in firing rate will be tested using a number of standard analysis techniques including parametric and non-parametric statistics as appropriate. In addition to this neural analysis, a full analysis of all trial epochs using a variety of standard analysis techniques including single-unit and population decoding techniques will also be performed to address other predictions raised by this experimental procedure.

The relationship between the proportion of cue selective neurons and behavioral flexibility (i.e. TTC) will be compared by Pearson correlation, or a non-linear or non-parametric alternative if appropriate.

Verification of electrode placement will occur post-hoc using blinded histological processing techniques. Verification of the long-term effects of cocaine history will be confirmed by testing for sensitized (i.e. increased) locomotor activity in cocaine rats relative to sucrose rats in response to ascending doses of cocaine (7.5, 15.0, and 30.0 mg/kg cocaine injected i.p.).

Expected outcomes.

The simple reversal is a control replication of previous work published by the Schoenbaum lab and is expected to yield the same three key results. (1) Cocaine rats will take longer to learn the reversal to cues C and D than controls. (2) The proportion of reversal neurons which change cue selectivity after reversal will be lower in cocaine rats. (3) Across both groups, a high proportion of reversal neurons will correlate with faster reversal (lower TTC). Given the hypothesis that these reversal deficits caused by cocaine use reflects disrupted encoding of task specific states in OFC, I predict expect to see fewer neural correlates of task states in cocaine rats during OS learning.

If the deficits found in simple reversal learning are due to impoverished representations of task state space, then I expect cocaine rats to take significantly longer than controls to learn OS acquisition and reversal.

During OS acquisition neurons representing state space (Table 2) are expected to show differential cue selective activity to the same odor depending on whether it follows OS X or Y i.e. differential cue selectivity to A on XA and YA trials, or differential cue selectivity to B on XB and YB trials. This firing is task state specific because it cannot simply reflect odor cue identity (it is the same physical cue identity) or expected value (it is not selective to all rewarded OS trials). I also expect that some neurons will show odor cue selectivity that reflects the specific value of the auditory OS e.g. a “rewarded after X” neuron with selectivity to A during acquisition to XA+ that switches after reversal to B during XB+ trials.

I predict that I the proportion of both specific state space neurons and OS value neurons will be significantly reduced in cocaine experienced rats and will predict the speed of behavioral acquisition and reversal in all rats. One alternative outcome is that state space representations are not disrupted in cocaine rats, and OS acquisition behavior is not impaired in cocaine rats. If this is the case, then simple reversal learning deficits and reversal neurons reflect impaired value updating in OFC.