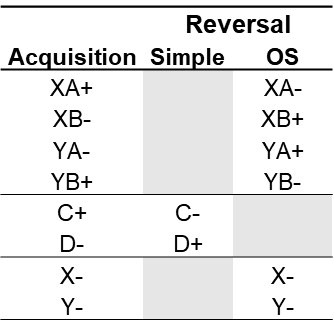
Broad aims –

* 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.

*Alternative strategies, pitfalls and future directions.* Cocaine history is expected to cause a significant reversal deficit to the simple reversal control cues in Expt 1, but this might not be true for the more complex conditional cues. This scenario will still provide interesting and meaningful behavioral and neural information addressing Aim 1 but would suggest that the experimental design is inappropriate for Expt 2. If this is the case, a simple reversal design will be employed in Expt 2 to test the efficacy of the D3-antagonist without losing any translational relevance. Cocaine history has been shown to disrupt both OFC function and behavior in the simple reversal design commonly used in this lab.