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DO THIS:::::

Looking at the role of OFC in behavioural flexibility, something that is dysfunctional in disorders of compulsivity (DOC).

OFC dysfunction in DOC is thought to cause deficits in behavioural flexibility by disrupting representations of task space, which is commonly measured with reversal learning tasks.

However, in reversal learning tasks, the features of the task that identify task-state specific information are confounded with other features such as changes in reward value and behavioral inhibition, which have also been proposed as OFC functions.

Therefore, it is unclear whether the deficits the OFC deficits reflect impaired representations of task space or deficits in these other features.

You’re going use better task that can isolate that feature (representations of task space), called an OS task, to:

1) measure how representations in OFC (as measured by ephys) relate to flexible behaviour

2) investigate how a history of cocaine use, a manipulation to cause DOC, affects these representations and their relationship to OS task behaviour.

3) test whether these deficits (in representations and behaviour) can be treated by a novel drug.

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AIMS 1

Info

Aim 2

Info

Reversal learning is a measure of behavioral flexibility that is significantly impaired in many disorders of compulsivity (DOC) such as cocaine addiction and obsessive-compulsive disorder and is a promising translational model of DOC. Reversal learning tasks measure behavioural flexibility by changing the meaning of cues that signal when to act or withhold behaviour. Orbitofrontal cortex (OFC) dysfunction causes reversal learning deficits and is also a common neural disturbance in DOC. The OFC is thought to represent the identity and relationships between behaviorally relevant cues that make up a cognitive map of task space. A history of cocaine use, known to cause compulsivity, disrupts both behavior and task representations in OFC in reversal learning. 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 a typical reversal learning task, changes in task structure coincide with changes in cue-reward associations. Therefore, it is unclear whether cocaine use disrupts accurate representations of task states in OFC that are necessary for flexible behavior in reversal learning tasks. It is possible to isolate neural activity associated with unique task states from these other task variables using a procedure known as occasion setting (OS). Here I will record neural activity an OS task to identify the neural correlates of task state representation in rodent OFC, and how they relate to behavioral flexibility in neurotypical and cocaine experienced rats. Once established, the ability for a promising novel pharmacotherapy for cocaine addiction (a novel dopamine receptor D3-anatagonist) to restore neural function and behavioral flexibility will be tested. These experiments will clarify the role of prefrontal dysfunction in behavioral inflexibility common to many disorders of compulsivity and test whether neurotypical function can be restored using a novel candidate drug treatment.

Aim 1.

Aim 2.

Orbitofrontal cortex (OFC) dysfunction is a consistent neuropathology that underlies aberrant and inflexible behaviors that occur in many disorders of compulsivity (DOC) such as cocaine addiction, attention-deficit hyperactivity disorder, and obsessive-compulsive disorder. OFC function is thought to represent a cognitive map of state space, a mental map of the predictive relationships between cues, behavior, and outcomes that can guide behavior. Using a reversal learning task, subjects with a history of cocaine use have been found to have impoverished representations of task structure in OFC that correlated with repetitive and inflexible behavior. However, in a typical reversal learning task, features of the task that identify task-state specific information are confounded with other features such as changes in cue-reward relationships, temporal order, and behavioral inhibition, which have all been proposed as OFC functions. Therefore, it is unclear whether cocaine use disrupts accurate representations of task states in OFC that are necessary for flexible behavior in reversal learning tasks. Occasion setting (OS) tasks share many features with reversal learning tasks but can be used to isolate the neural correlates of cognitive map representations by using explicit cues to signal cognitive map changes.

Here I will address the question of whether a history of cocaine use disrupts cognitive map representations in OFC that are necessary for behavioral flexibility. I will combine experimental manipulation of cocaine use with electrophysiology to manipulate and record OFC activity during an OS task. This approach will clarify how OFC dysfunction contributes to inappropriate behavioral control in disorders of compulsivity. Once established, I will test whether behavioral activity and OFC function can be restored using a novel pharmacotherapy for cocaine addiction. Together, these experiments will further our understanding of the

Broad aims:

* Use an OS task to identify neural correlates of underlying task structure in OFC
* Confirm whether these representations are correlated with the behavioral flexibility/accuracy 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