* Statement of the background, and why it is relevant
* Statement of the problem/gap in knowledge
* Statement of the solution/proposed plan to address this gap
* Aim 1.
  + Significance
  + Approach
    - Explicit statement about hypothesis and analysis
* Aim 2.
  + Significance
  + Approach
    - Explicit statement about hypothesis and analysis
* OFC function necessary for
  + 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.
  + Deficits in reversal learning, a task in which subjects must flexibly update learning and behaviour, underlie disorders of compulsion.
  + OFC function critically involved in disorders of compulsions
  + OFC/cocaine use/optogenetic recovery
  + Translational benefit of understanding OFC function in reversal learning tasks
  + Yet, very little has been done to explore this task further in drug development
* OFC is functionally heterogeneous
  + Most of our understanding comes from pLO
  + I have recently shown that aLO and pLO have dissociable roles in guiding flexible behaviour, and have anatomically distinct inputs.
* Expts:
  + 1) Compare well established pLO activity in reversal learning with aLO/pVO?
    - Modifying procedure to allow recent analyses of representation of task structure that have not been applied to OFC in reversal learning yet
  + 2) Establish how prior history of cocaine use disrupts these representations within these OFC subregions
  + And use novel-promising D3 antagonist to recover reversal behaviour and potentially OFC representations in this task.

Orbitofrontal Cortex (OFC) dysfunction is a well-established feature of the neuropathology underlying obsessive-compulsive disorder (OCD) and other psychiatric conditions involving a range of compulsivity such as, addiction, bipolar disorder, attention-deficit/hyperactivity disorder, and schizophrenia. One surprisingly consistent consequence of both OFC dysfunction and disorders of compulsion is an impairment in reversal learning tasks, i.e. the repetition of inappropriate behaviours caused by a failure to update learning and behaviour when the relationships between cues-actions-outcomes change. This has significant translational potential as reversal deficits are observed in both clinical populations and animal models. For example, in rodents, a prior history of cocaine use causes reversal learning deficits, disrupts OFC activity, and mild optogenetic activation of OFC activity can restore appropriate OFC dependent behaviour.

OFC function is necessary for appropriately updating and guiding behaviour based on mental models of the world that combine the relationships between cues, actions, and their outcomes. However, there are a number of OFC subregions which span large areas of cortex and emerging evidence now suggests that there is marked heterogeneity of function both within and between OFC subregions. In rodent studies, OFC activity is often only recorded from the posterior regions of the lateral OFC (pLO).

Reversal learning deficits, i.e. the repetition of inappropriate behaviours caused by a failure to update learning and behaviour when the relationships between cues-actions-outcomes change, are characteristic of both OFC dysfunction and these psychiatric conditions (particularly in OCD and addiction).

Understanding the role of the OFC in reversal learning procedures has significant translational potential for understanding compulsive behaviours in rodents and humans.

OFC function is necessary for appropriately updating and guiding behaviour based on mental models of the world that combine the relationships between cues, actions, and their outcomes.

Disruption of this function can lead to inappropriately persistent behaviour in the face of changing environmental contingencies.

Indeed, a prior history of cocaine use has been shown to disrupt the flexible updating of both behaviour and appropriate signaling within the OFC and can be rescued by optogenetic activation of the OFC.

Recent evidence suggests that there is marked heterogeneity of function both between and within classical parcellations of OFC subregions, suggesting distinct contributions of these subregions to the function of the OFC as a whole.

In studies of the rodent lateral OFC it is often the posterior region that is targeted.

Recently, I have demonstrated that lesions of anterior and posterior lateral OFC have dissociable effects on tasks involving value updating, including reversal learning, and receive distinct anatomical inputs.

Here I will address two key questions (1) Do the representations of task structure in the OFC that develop during reversal learning differ between the extensively studied posterior lateral OFC and the relatively unexplored anterior lateral OFC subregions? and (2) How are these OFC signals disrupted by prior history of cocaine use, a model known to lead to disrupted OFC activity and compulsive behaviours?

Expt 1. Acquisition, reversals, intra-OFC comparison

* Describe Occasion setting design – allows more effective comparison of cue information because cue identity is identical in different situations.
  + Simple single cue control version embedded in the task for comparison with earlier data
  + Normally an internal representation of the context as an occasion setting latent state is assumed, here we make this explicit
  + Indeed, using an occasion setter, behaviour at the time of the Target cue must be guided by a latent state. If X->A->Go and Y->A->NoGo, then activity at the time of target cue A will differ between these conditions as a function of the latent state implied/cued by X and Y.
  + This allows us to extend analyses of state representation to the reversal learning task which have become common in understanding OFC function btu have yet to be applied to reversal learning situations due to the high correlation of task features when only using a simple 2 cue discrimination design.
  + Modelling of these data with RL models of state space
* Need some concrete predictions for activity – Model fit to Wilson et al?
* **Predictions:** OFC representations to target cues X and Y will contain representations of the upcoming response requirement and also unique information about the specific state they are in i.e. confusion matrices for odour representation, action/reward value representation, unique state representation.
  + **Error trials:** Predict that they will be the result of misclassified feature in activity to Target.
  + **Reversals:** Should result updating of firing to reflect new action/reward value representation and unique state representations.

Expt 2. The effect of prior cocaine use on intra-OFC representations and reversal behaviours

* Prior cocaine history has been shown to disrupt OFC representations and behaviours during reversal learning
* Here we will compare animals with a prior history of cocaine self-administration with controls with a matched history of sucrose pellet self-administration.
* Furthermore, we will attempt to causally manipulate/recover behavioural and OFC activity dysfunction using a promising D3 antagonist during the critical reversal stages.
* Predictions:
  + Behaviourally: (1) Reversals should be impaired in cocaine experienced group – take more trials to reach criterion accuracy. (2) D3 antagonist should restore performance in the cocaine group to learning rates similar to controls (no prior cocaine experience).
  + OFC representations: (1) During reversals, cocaine experience will disrupt the updating of unique state representations, (2) but this will not be the case in rats with prior cocaine use following treatment with a D3 antagonist.
    - After reversal, representations of state specific and Go-NoGo/Value will match pre-reversal activity.

1. OFC dysfunction is implicated in disorders of compulsive behaviour (OCD) and disorders of inappropriate behavioural regulation (e.g. addiction).
2. One task that intimately ties OFC dysfunction with these disorders is impaired reversal learning.
   1. Describe task
   2. Describe results of OCD patients
   3. Describe Drug use patients - <https://doi.org/10.3389/fnbeh.2016.00154>
   4. Relate to rodent research findings – i.e. OFC in reversal learning and a causal role in impaired reversal learning following cocaine use
      1. <https://www.nature.com/articles/s41467-020-17763-8>
   5. Grab some refs from here: <https://www.nature.com/articles/nn.3014>
3. OFC activation reverses cocaine impairments on overexpectation tasks
   1. <https://www.nature.com/articles/nn.3763.pdf>
4. Prior studies have looked at OFC in reversal learning tasks following cocaine use: <https://doi.org/10.1111/j.1460-9568.2006.05128.x>
5. However, there is recent evidence that the OFC is not a heterogeneous structure, and it is unclear how intra-OFC dynamics contribute to encoding associative structures necessary for flexible reversal behaviour.
   1. Propose VO vs LO or aLO vs pLO [given that I have shown dissociations on reversal deficits following OFC lesions]
   2. Angela Langdon – modelling of these dynamics
   3. Procedure will use conditional cues to enhance interpretability of Models
6. Next – how does cocaine exposure disrupt “normal” processing dynamics and can behaviour be rescued by D3 antagonists
   1. Amy Newman contribution
   2. Essentially study 2 will have cocaine vs saline and D3 antagonist vs vehicle during reversals
   3. Allows for the simultaneous comparison of behaviour and neural activity.

A: X+ | A: X-

A: Y- | A: Y+

B: X- | B: X+

B: Y+ | B: Y-

Would we use go/no-go behaviour? Or just rewarded/non-rewarded?

occasion setting - reversal learning

Amy Newman - D3/cocaine

Angela Langdon - modeling

Create a draft -

novelty = occasion setting - but sell it as a better version of the reversal task.