Orbitofrontal Cortex (OFC) dysfunction is a well-established feature of the neuropathology underlying and other psychiatric conditions involving a range of compulsivity such as obsessive-compulsive disorder (OCD), addiction, bipolar disorder, attention-deficit/hyperactivity disorder, and schizophrenia.

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?

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.