Environmental cues are often reliable signals of motivationally significant outcomes allowing one to predict rewards and to perform appropriate behaviours based on this information. Neural activity in the orbitofrontal cortex (OFC) may form part of the representation of expected outcomes following predictive actions or cues (Rudebeck & Murray, 2014; Schoenbaum & Esber, 2010; Walton, Chau, & Kennerley, 2015) and has been found to increase in the presence of cues that reliably predict rewards {REF}.

The OFC has been hypothesised as a site that integrates sensory and motivational information to adaptively increase or inhibit behaviour based on the up-to-the-moment expected value of predicted rewards (Rudebeck & Murray, 2014; Walton et al., 2015). For example, in outcome devaluation procedures an intact OFC is required to appropriately reduce responding for predicted outcomes that are no longer rewarding (Gallagher, McMahan, & Schoenbaum, 1999; Pickens et al., 2003; Pickens, Saddoris, Gallagher, & Holland, 2005; Rudebeck & Murray, 2011; West, DesJardin, Gale, & Malkova, 2011). Conversely, in Pavlovian over-expectation procedures a functional OFC is required to selectively increase responding when two predictive cues are compounded to predict an increase in predicted reward value (Takahashi et al., 2009).

Surprisingly, disruption of OFC function does not disturb initial learning about cues that predict outcomes which is thought to be dependent on prediction-error signals that calculate the discrepancy between expected and actual outcomes {REF}. Instead, current hypotheses attribute OFC involvement to situations in which initial learning must be modified by changes in the value or likelihood of the reward change. For example, in extinction procedures when an expected reward is no longer delivered the expected value of the cue should be updated to reflect this new state of affairs {REF}, a process that is predicted to involve OFC function. In line with this prediction, Panayi & Killcross (2014) found that selectively inactivating OFC function during extinction results in abnormally persistent responding to a cue that no longer predicts reward.

While the findings of Panayi & Killcross (2014) are consistent with the hypothesis that the OFC is required to update behaviour based on the current value of predicted rewards, there are two alternative explanations of these results. One possibility is that the role of the OFC is to form inhibitory associations between events and expected outcomes, and therefore the rats never learn to inhibit their established behaviour. In the past simple inhibitory explanations of OFC function have been ruled out by evidence that subjects with OFC damage are ultimately able to inhibit inappropriate responding {REF}. However, the suppression of behaviour can occur via a number of alternative mechanisms that do not involve inhibition such as behavioural competition, attention and habituation (Panayi & Killcross, 2014). The objective of this work is to provide the first direct test of the role of the OFC in the acquisition of inhibitory associations.

Extinction learning has been argued to predominantly involve new context-dependent inhibitory learning rather than unlearning of the original association {REF}. Therefore, a more recent explanation of the role of the OFC in extinction learning is that the OFC representing a new state to support this new inhibitory learning {REF}. In the absence of this new state representation it is predicted that extinction will result in the unlearning of the original association which would retard the rate of extinction. Importantly, the OFC is proposed to only be involved in the representation of task states when the states are not explicitly signalled but instead require the use of memory to infer a new state.

Considered together, these hypotheses of OFC function provide three distinct predictions about the role of the OFC in the acquisition and expression of inhibitory associations in a Pavlovian conditioned inhibition task. If the OFC is simply involved in the acquisition of inhibitory associations, then OFC inactivation should disrupt the expression and subsequent learning of a conditioned inhibitor. If the OFC is involved in modulating behaviour based on the current expected value of predicted outcomes, then OFC inactivation should disrupt the expression but not the acquisition of a conditioned inhibitor. If the OFC is involved in representing the states of a task when changes in task contingencies are not explicitly signalled, then OFC inactivation should not disrupt the expression or acquisition of a conditioned inhibitor. Our findings indicate that OFC inactivation impairs the selective expression of behavioural inhibition during task acquisition. However, conditioned inhibition is acquired in rats when subsequently tested with functional OFC. These findings were also replicated when the conditions of training were matched to extinction learning tasks. These findings suggest that the OFC is not simply involved in the acquisition of inhibitory associations, but instead modulates behaviour when expected outcomes change.

SOP -> greater inhibition formed in a feature negative design if decay from A1->A2 is more rapid…?

The OFC has been hypothesised as a site that integrates sensory and motivational information to adaptively increase or inhibit behaviour based on the up-to-the-moment expected value of predicted rewards (Rudebeck & Murray, 2014; Walton et al., 2015). In outcome devaluation procedures an intact OFC is required to appropriately reduce responding for predicted outcomes that are no longer rewarding (Gallagher et al., 1999; Pickens et al., 2003, 2005; Rudebeck & Murray, 2011; West et al., 2011). Conversely, in Pavlovian over-expectation procedures a functional OFC is required to selectively increase responding when two predictive cues are compounded to predict an increase in predicted reward value (Takahashi et al., 2009).

Functionally the OFC is involved in number of tasks in which well-established behavioural control must be modified when the value of expected outcomes changes.

OFC expectation of outcomes + Neural activity

OFC and extinction? Outcome omission.

OFC Role Inhibitory [Maybe note necessary?]

OFC Role modulatory (value)

OFC Role Hidden States [model based system involved in generating the model – also consistent with correct attribution of reward with events e.g. Walton]

Evidence suggests that OFC not necessary for learning/performance to novel cues, only when learning about the cue needs modification. Role of this work was to clarify the role of the OFC in behavioural expression and the learning of inhibitory associations between cues and the omission of outcomes i.e. a conditioned inhibitor.

The hypothesis that the OFC is required for updating behaviour based on the current value of predicted outcomes would predict that OFC inactivation would impair the ability to selectively inhibit behaviour in the presence of a conditioned inhibitor. In contrast, the hidden state view of the OFC would predict that conditioned inhibition tasks are not OFC dependent because the conditioned inhibitor is a clear external stimulus to map a change in the task state.

Our findings indicate that selective suppression of behaviour when learning about a conditioned inhibitor is abolished by OFC inactivation in rats. However, when the OFC is functional there is clear evidence that OFC-inactivated rats had acquired the conditioned inhibition trained in this task.

Environmental cues are often reliable signals of motivationally significant outcomes allowing one to predict rewards and to appropriately perform behaviour to acquire the expected reward. \* However, after learning a predictive cue-outcome relationship, environmental contingencies may change such that the cue no longer predicts reward and thus the learning must be updated and learned behavioural responses inhibited. Historically, the orbitofrontal cortex (OFC) has been proposed as the neural locus of this inhibitory behavioural control, responsible for suppressing prepotent or learned responses when cue-outcome relationships change (Butter, 1969; Murray, O’Doherty, & Schoenbaum, 2007). For example, disruption of OFC function results in persistent responding to a cue when it no longer predicts reward (Panayi & Killcross, 2014; Rudebeck & Murray, 2011) i.e. in experimental extinction.

More recently the role of the OFC has been expanded to include adaptively increasing and inhibiting behaviour based on the up-to-the-moment expected value of predicted rewards (Rudebeck & Murray, 2014; Walton et al., 2015) \*\*\*. In outcome devaluation procedures an intact OFC is required to appropriately reduce responding for predicted outcomes that are no longer rewarding (Gallagher et al., 1999; Pickens et al., 2003, 2005; Rudebeck & Murray, 2011; West et al., 2011). Conversely, in Pavlovian over-expectation procedures a functional OFC is required to selectively increase responding when two predictive cues are compounded to predict an increase in predicted reward value (Takahashi et al., 2009).

However, while it has been demonstrated that the OFC is not simply involved in behavioural response inhibition when expected outcomes change, it has not been shown whether the OFC is involved in the acquisition of inhibitory cue-outcome associations per se. Specifically, is the OFC involved in learning about a predictive cue that is an explicit signal of reward omission? In a typical appetitive Pavlovian conditioned inhibition procedure (Rescorla, 1969) subjects are presented with a cue (A) that reliably predicts the delivery of reward (A+) unless it is presented in compound with a separate cue (X) that predicts the omissions of reward (AX-). Typically, this procedure will render X as a conditioned inhibitor for the delivery of reward such that X is learned to be associated with the absence of the reward. If X acquires an inhibitory association with the reward, then X should inhibit responding when presented in compound with other predictive cues (a summation test) and it should be more difficult to learn that X now predicts the presence of the reward (X+) relative to a novel cue (a retardation test).

For example, disruption of OFC function impairs the appropriate reduction in responding to predictive cues when rewarding outcomes are omitted i.e. extinction (REFS), when contingencies between rewarded and non-rewarded cues change i.e. reversal (REFS), and when predicted outcomes are no longer desirable i.e. devaluation (REFS).

Recent evidence has been used to successfully argue that the OFC is not simply involved in inhibitory control processes as originally suggested. Specifically, it has been argued that [Behavioural inhibition can occur in OFC damaged animals; Reversal learning may not be a characteristic deficit of OFC damage].

However, there are a number of ways in which behavioural inhibition can be defined -

As such, there is no direct evidence that the OFC is not involved in the formation of inhibitory associations.

* Explain Pavlovian conditioned inhibition; Feature negative design

Rather, the OFC has been proposed to represent the specific identity and current motivational value of predicted rewards and is functionally involved in adaptively increasing or decreasing responding based on this up-to-the-moment expected value (Rudebeck & Murray, 2014). [This is supported by outcome devaluation studies; over-expectation studies show a failure to increase behaviour in the presence of increased expected reward].

* Prediction of what would happen in a conditioned inhibition task
  + Behavioural expression of inhibition should be impaired
  + Learning of conditioned inhibition may be intact if OFC is functional

More recently, Wilson et al. (2014) have proposed that the OFC is involved in representing the underlying structure of behavioural tasks as states. [Define hidden task states; Give example of extinction to support it].

* Prediction: The explicit addition of the conditioned inhibitor should provide a clear external stimulus to define a new task state i.e. the change of phase does not involve a hidden state.
* Therefore, behaviour should not be perturbed during the inhibitory discrimination, and consequently inhibitory association will be formed.
* However, if it is argued that the change in phase is a partially hidden state (involving the integration of information that the cue was previously rewarding) then the inverse is predicted i.e. inhibition of behaviour should be slower than controls during acquisition.