Dear handling editor,

We are submitting a manuscript entitled “Orbitofrontal Cortex is necessary for the behavioural expression, but not learning, of Pavlovian conditioned inhibition” for consideration as a research article in Cerebral Cortex. In this study, we used temporary inactivation of the orbitofrontal cortex (OFC) to test the role of this region in inhibitory learning that underlies behavioural flexibility and inhibitory control.

Over the past decade, there has been extensive interest in the function of the OFC as the neural substrate underpinning model-based behavioural flexibility. The best evidence for this comes from deficits in adapting to changes in predicted outcomes and goals following disrupted OFC function. For example, animals with OFC lesions can learn to discriminate between a rewarded and non-rewarded cue. However, if these cue-reward contingencies are reversed, OFC lesioned animals can not flexibly update their behaviour to inhibit irrelevant/incorrect behaviour (REFS). The earliest theories of OFC function posited it as the neural locus of inhibitory regulation of learning and behaviour (REFS). Modern theories of OFC function reject this simple inhibition hypothesis. However, the role of the OFC in inhibitory learning has never been directly tested and has been inferred from the successful reduction of behaviour in tasks designed to test other hypotheses.

A simpler interpretation of this reversal learning deficit is that the OFC is necessary for extinction learning when a cue or action is no longer reinforced. We have shown that this is the case (Panayi & Killcross, 2014), with OFC inactivation completely abolishing learning that a cue is no longer reinforced over several days. Here we extend this finding by directly testing whether OFC inactivation impairs the explicit acquisition of inhibitory associative learning i.e. learning that a cue predicts the absence of reward. Our results show that the OFC is indeed necessary for the expression of discriminative inhibitory control of behaviour. However, when OFC function was returned, learning about conditioned inhibitors was intact as revealed by standard tests of conditioned inhibition. We then extend these results to that the extinction learning deficits we have previously reported are not simply a failure to acquire conditioned inhibition.

We provide the first causal evidence for the role of the OFC in the learning and behavioural control of conditioned inhibition which has been a fundamental assumption of modern theories of OFC function. Unexpectedly our findings dissociate the role of the OFC in behaviour and learning

The function of the OFC is of particular interest to the readership of Cerebral Cortex, has often been the topic of Cerebral Cortex publications, and two of the journal’s most highly cited articles are about the connectivity and function of the OFC [REFS].

[Clarify Primate vs rodent differences?]

Specificity of OFC to LO – an issue that is starting to take prominence in the field.

Modelling suggests that the OFC is not simply the neural locus of behavioural inhibition but is necessary for tasks that require learning to inhibit behaviour. This has been rejected by evidence that OFC lesioned animals can suppress behaviour on some aspects of various behavioural tasks. However, the role of the OFC in conditioned inhibitory learning has never been tested directly.

following a reversal of reward contingencies these animals are impaired at inhibiting behaviour

We have recently shown that OFC inactivation during a simple Pavlovian extinction procedure

The hypothesis that the OFC is simply the neural locus of inhibitory behavioural control or learning has been rejected by most modern theories of OFC function, citing evidence that OFC lesions do not prevent the inhibition of behaviour in all circumstances [REF e.g. Extra dimensional shifts]. However the role of the OFC in the explicit acquisition of conditioned inhibition has never been explicitly tested.

Many theories of OFC function rely on modelling behavioural deficits in reversal learning, extinction, and outcome devaluation.

Models of OFC function rely heavily on a number of fundamental behavioural deficits following OFC lesions and functional inactivation, specifically deficits in reversal learning, extinction, and outcome devaluation

* OFC fundamental to behavioural flexibility
* Models assume that OFC not necessary for inhibition per se
  + Never directly tested role of OFC in learning inhibition
  + For example, extinction deficits suggest the inability to learn inhibitory associations
* We show

