

Dear 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, which forms a key aspect of behavioural flexibility and inhibitory control. Here we show for the first time that the OFC is necessary for inhibiting behaviour, but not for the underlying learning about cues that act as conditioned inhibitors.

Over the past decade, there has been extensive interest in the function of the OFC as the neural substrate underpinning model-based behavioural flexibility (Jones et al. 2012. Science; Wilson, et al. 2014. Neuron). A key aspect of behavioural flexibility is learning when to appropriately inhibit behaviour, and OFC dysfunction often results in an inability to learn to inhibit behaviour (Murray & Rudebeck, Nature Reviews Neuroscience, 2018; Panayi & Killcross, eLife, 2018). Most theories of OFC function argue that these deficits reflect a failure to update learning rather than simply a failure to learn inhibitory associations e.g. learning that a cue predicts that an outcome will be omitted. It is therefore surprising that no studies have directly tested whether the OFC is necessary for learning about conditioned inhibition. Here we test whether OFC inactivation impairs the explicit acquisition of inhibitory associative and show that the OFC is indeed necessary for the expression of discriminative inhibitory control of behaviour. However, when OFC function is returned, the underlying learning about conditioned inhibition is intact as revealed by standard tests of 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, but never explicitly tested. Furthermore, our findings dissociate the role of the OFC in the learning and behavioural expression of conditioned inhibition. 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 (e.g. Bechara et al, 2010; Ongur & Price, 2000). Therefore, we believe that these findings will be of considerable interest to the readership of Cerebral Cortex.

Sincerely,

Marios Panayi

Post-doctoral Researcher

National Institute on Drug Abuse, Cellular Neurobiology Research Branch