Dear handling editor,

We are submitting a manuscript entitled “The role of the rodent lateral orbitofrontal cortex in simple Pavlovian cue-outcome learning depends on training experience” for consideration as a research article in eLife. In this study, we used focal lesions and temporary inactivation of the rodent lateral orbitofrontal cortex (OFC) to test the role of this region in the acquisition of simple Pavlovian cue-outcome learning.

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). Indeed, the hallmark deficits reported following OFC damage are reversal learning and outcome devaluation, tests of behavioural flexibility when reward contingencies and values unexpectedly change (Panayi & Killcross, 2018. eLife). In contrast to these complex tasks, OFC dysfunction is reported to leave initial acquisition learning intact, particularly in simple tasks with a simple unambiguous cue-outcome relationship. Indeed, intact initial acquisition following OFC damage is a clear prediction of models of OFC function (Wilson, et al. 2014. Neuron). However, this basic finding has not been explored fully, and acquisition is often stopped prior to reaching asymptote. Here, we fully explored the role of OFC dysfunction during acquisition of a simple single cue-outcome relationship.

Our findings were simple, yet surprising. First, we found that pre-training OFC lesions significantly enhanced acquisition, but only after extended training. Next, we tested the effect of post-training inactivation and lesions on acquisition and found the opposite effect, post-training OFC dysfunction significantly impaired acquisition. Finally, using an associative blocking procedure, we found that this acquisition deficit did not prevent the target cue to effectively block subsequent learning to a new cue. This suggests that post-training OFC inactivation disrupted value-based performance but left the underlying learning about the predictive cue-outcome relationship intact.

We recently submitted a separate article in which we report a similar acquisition deficit to a control cue following OFC inactivation. All three reviewers of our submission considered this deficit in acquisition to be a major concern as it did not fit the prevailing OFC literature, and reasonable grounds for rejection. Given that these effects run counter to the prevailing view that OFC dysfunction should not disrupt initial acquisition, in the present manuscript we replicated these effects multiple times with different cue modalities to confirm their reliability. Although major theories of OFC function might be consistent with these effects, they currently do not predict them a priori, and the existence of these effects would be considered controversial among many OFC researchers.

Our findings provide the first evidence that the rodent lateral OFC is necessary for initial acquisition learning, even in simple unambiguous cue-outcome learning procedures. These findings challenge the prevailing understanding of OFC function, and we propose how OFC theories might be modified to accommodate them. eLife has published a growing number of articles focused on the OFC recently, and we believe that our data will be of considerable interest to the readership of eLife. We also believe that this work will be of general interest to work focusing on the reinforcement learning models of prefrontal function.

Sincerely,

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