* Here we show a significant effect of disrupting OFC function on Pavlovian acquisition in a simple single CS-US procedure.
* Furthermore, we find a dissociation between pre-and post-training OFC manipulations on Pavlovian acquisition such that pre-training OFC lesions enhance, whereas post-training manipulations impair, acquisition behaviour.
* Using an associative blocking procedure, we identified that impaired acquisition following post-training OFC inactivation does not disrupt the underlying learning about the predictive CS-US relationship. Instead it appears that behavioural control/performance to the CS is impaired.
* Finally, we assess whether this impaired behavioural control reflects an inability to update the current/relative value of the Pavlovian CS relative to the value of alternative behaviours. Indeed, OFC inactivation selectively disrupted the flexible control of Pavlovian CS approach behaviour, but did not disrupt sensitivity to the value of alternative behaviours in the environment.

The present studies tested the hypothesis that the rodent lateral OFC is not necessary for Pavlovian acquisition. Here we show that OFC lesions and inactivation significantly affects Pavlovian acquisition in a simple single CS-US procedure. Furthermore, we found a dissociation between pre- and post-training OFC manipulations on Pavlovian acquisition such that pre-training OFC lesions enhance, whereas post-training lesions and inactivation impairs acquisition behaviour. Next, using an associative blocking design, we tested whether impaired behaviour following post-training OFC inactivation reflects a disruption of learning or behavioural control. OFC inactivation did not disrupt the underlying learning about the predictive CS-US relationship, and instead disrupted the appropriate control of anticipatory behaviour to the CS. Finally, we assessed whether this impaired behavioural control reflects an inability to update the current value of the Pavlovian CS relative to the value of alternative behavioural options. Indeed, inactivation selectively disrupted the flexible control of Pavlovian CS approach behaviour when its relative value changed but did not disrupt sensitivity to the value of alternative/non-Pavlovian behaviours in the environment.

**Lateral OFC is necessary for Pavlovian acquisition**

* Why do we find an effect?
  + Parameters? Single Cue vs multiple cues/outcomes [most params very similar]
    - Length of training for pre-training lesions – task changes before asymptote reached [refs]; otherwise, in extended training there is some evidence of OFC lesion effects
      * Note that (even in our hands) multiple CS-US designs do not appear to reveal these acquisition differences [but did reveal differences in sign vs goal tracking in these same animals using CS+/CS- design]
      * Highlight the number of replications of the effect on disrupting acquisition, and the similarity of the effect of post-training lesions and muscimol – suggesting it is not simply some quirk of the manipulation technique used. Indeed, the specificity of the deficits we observed in the final experiment and the within subject saline controls, suggest that our infusion procedure is not itself causing general behavioural deficits.
    - Often cues are at asymptote for post-training OFC manipulations, so it is hard to see differences relative to controls. Here we saw small, but robust, differences after extended training that relied on continued acquisition in the control group. When manipulations were performed much earlier in training the effects were more pronounced, but few studies aim to disrupt function this early in acquisition.
    - OFC lesions have been shown to affect the balance of sign vs goal tracking behaviour [REFS] – It might be the case that the effects here are cue dependent in so far as different cues elicit different orienting and exploratory behaviours depending on their stimulus identity, and even US identity [REFS]
      * While not manipulated in the present study, anterior vs posterior lateral OFC lesions also differed in their effects on sign and goal tracking. Anterior lesions reduced sign tracking, and posterior lesions reduced sign tracking more while significantly increasing goal-tracking behaviour.
    - Are we targeting a different aspect of the OFC relative to other studies? Possible, however form a functional perspective, our lesions also disrupted Devaluation, and didn’t cause and

**Lateral OFC not necessary for learning the predictive CS-US relationship**

* Standard Expectancy account + VTA prediction error account + recent Mouse studies (Namboodiri?)
  + Extinction data?
* Associative blocking design was necessary to reveal that impaired behaviour, even when OFC function was returned, did not reflect a deficit in learning
  + Importance of using off-target cues to infer learning [Rescorla + Compound test issues]
  + At stage 2 - AB in the muscimol group started as low as the CD control in the saline group. So there was enough evidence of behavioural change to AB in the muscimol group to assume that it cue B would unblocked i.e. learning could occur. In some Pavlovian contexts, levels of behavioural expression can dictate whether learning occurs [Delamater – Extinction data].
* It is still possible that some aspect of learning was impaired

**Lateral OFC necessary for flexible value based Pavlovian control**

* We hypothesized that (1) since the deficits we observed did not disrupt learning about the CS-US contingency, and (2) the lateral OFC is often involved in value based behavioural control when expected values change, or need to be updated
* Putatively simple tasks can contain a lot of unconstrained behaviours that can compete with the target magazine approach behaviour. These behaviours are likely to be under the control of different behavioural systems (e.g. grooming), and the relative value of a behaviour (presumably determining its eligibility for dominating behavioural performance at any given moment) is likely to be highly variable within and between individual subjects. Our task successfully provided a way to direct the majority of these alternative behaviours in a value sensitive manner by relying on foraging/sampling behaviours, in a manner that was distinct but interacted with our standard Pavlovian CS-US behaviour.
* Mention specificity to Pavlovian, and not instrumental [but also see Parkes et al data – potentially the outcomes in their design become stimuli]
* Acknowledge that one possible alternative account of these data is that they represent an inability to integrate across USs of different sensory properties i.e. comparing apples to oranges [Neuroeconomics]. This is a possibility, but it is still noteworthy that the disruption observed here was specific to the relative value of Pavlovian expected behaviours, not simply all value based behaviours per se.

**Pre- vs Post-Training effects**

* Compensation of function with Pre-training lesions?
  + Differences in pre-vs post- training lesion on reversal learning deficits have been reported [Boulougouris studies]
* Relative Value integration account
  + Pre-vs post-training lesions might also differ in the opportunity for alternative behaviours to interfere with the expression of Pavlovian learning. Pre-training lesions might reduce interference at the start of learning in simple single CS-US designs where there are a lot of potential alternative behaviours.
* Sensory Specific US-expectancy account
  + Also mention general satiety motivation manipulation in pre-training lesions i.e. general sensitivity of behaviour to motivational vigour
* Latent state account
  + Prediction that under some conditions with multiple distinct states: Pre-training lesions might impair acquisition and post-training lesions might enhance acquisition

**Conclusions**

* Null result consistently reported. Latent state and specific outcome expectancy theories predict no effect in
* simple, single cue-outcome design where the outcome identity is irrelevant to the task and all task states are explicitly cued and stable.
* In contrast to these predictions and the extant literature, we observed a significant and replicable effect of OFC lesions and inactivation on acquisition behaviour.
  + Why did we find this effect? The majority of studies never trained animals to asymptote, notably at around 9-12 days when most procedures proceed to a new phase of learning, we did not observe differences. Instead, differences emerged only later in the asymptote of conditioning (around 15-21 days in this procedure).
  + This effect is consistent with the finding that after extensive acquisition training in a discrete choice go-nogo task, Schoenbaum et al [REFS] observed significant effects of OFC lesions on response vigour as measured by latency to respond, but not on choice accuracy.
* We modelled these deficits within the framework of the OFC representing some aspect of outcome expectancy that informs a full reward prediction-error. Loss of this information would lead to systematic under expectation of reward and therefore increase the asymptote of learning. This model predicted a similar increase in learning following post-training OFC inactivation. However, this hypothesis was not confirmed, and instead post-training OFC inactivation suppressed any further learning. This finding was replicated with post-training lesions, and post-training inactivation at an earlier time point during acquisition.
  + Therefore, the dissociable effects of pre- and post- training OFC lesions/inactivation were not simply differences between lesions and inactivation via muscimol infusions.
  + Reference inhibition paper here? Control cue Z?
* Next, we tested whether the suppressed behaviour following post-training inactivation of the OFC reflected a disruption of learning or performance. Using an associative blocking design, we confirmed that the disruption of behaviour to a single Pavlovian cue did not affect the ability of this cue to effectively block learning about a novel cue. This suggests that OFC inactivation did not disrupt learning about the cue-outcome relationship but instead disrupted the ability to modulate behaviour based on the current learned value of the cue.
  + Maybe refer to Kieflin et al study with Hierarchical stuff to indicate that you rule out a possible account of this effect being a state dependent learning effect.
  + Discuss the importance of not simply relying on performance levels to a target cue to indicate how much learning has occurred
* We concluded from these studies that the OFC was indeed important in simple Pavlovian cue-outcome behaviour even when the cue-outcome contingencies remain stable and the identity of the outcome is not relevant to task performance. Furthermore, it appeared that these effects likely reflected impaired behavioural control rather than impaired learning. To explain these effects, we proposed that the OFC was critical for calculating the current value of an expected outcome relative to the value of other options in the environment.
  + We created a task in which the relative value of alternative behaviours is integrated into Pavlovian expected outcomes to test this hypothesis. As predicted, the OFC was necessary for the integration of the relative value of alternative behaviours into the flexible control of Pavlovian expected value.
  + One possibility is that the failure to integrate between the Pavlovian and non-Pavlovian values is due to the different outcome identities of each of the outcomes i.e. pellet vs liquid sucrose [REFS]. However, it is still the case that the OFC was not necessary for flexibly modulating non-Pavlovian foraging behaviours, but impaired at modulating specifically Pavlovian behaviour based on the expected value of the outcome.
  + This adds to the finding that the OFC does not appear to be involved in other non-Pavlovian learned behaviours such as instrumental action-outcome learning (REFS). The specificity of this neural deficits supports the idea that Pavlovian cue-outcome behaviours are psychologically separate from instrumental action-outcome behaviours [Refs – Omission; SD vs CS in blocking].

Accounting for the pre vs. post training lesion differences

* The dissociable effects of pre- vs post-training lesions are important to understand.
* Updating the value of sensory-specific outcome expectancies
  + From an associative learning framework, the even putatively “simple” single cue-outcome Pavlovian learning can involve a number of different processes (REFS; Hall; Dickinson; Rescorla content of learning; Holland nature of responding; Delamater). Take for example a 10s light cue that reliably predicts the delivery of a pellet reward. A rat can learn that the cue predicts the sensory-specific properties of the outcome (e.g. taste, texture, sweetness, colour, size, location etc...), or the general motivational value of that reward, or simply develop a stimulus-response habit to approach the reward location when the cue is presented. Indeed, there is experimental evidence for these multiple aspects of learning occurring during Pavlovian conditioning [REFS].
  + It is possible that pretraining OFC lesions disrupt the balance of these different aspects of Pavlovian learning and behavior. If the OFC is necessary for the representation of the sensory specific properties of expected outcomes, then OFC lesions might allow a stimulus-response habit system to dominate behavioural control. This may lead to an unconstrained learning system (REFS; Adams and Dickinson chapter) that is not bounded by the actual value of the outcome and is instead limited by a behavioural ceiling and overly sensitive to the current general motivation (e.g. overall hunger levels) of the organism.
  + However, once initial learning occurs with an intact OFC, the initial encoding of the identity of the expected outcome is likely to have occurred (REFS; Delamater- shows this can occur very rapidly). Now, a post-training lesion or inactivation of the OFC is likely to affect the flexible updating of this information. Here we propose that the impaired acquisition behaviour we observed following post-training inactivation reflects an inability to update the current motivational value of the specific outcome that is expected.
* Inflexible Latent states
  + The latent state representation account of the OFC might also be able to account for the differences observed dissociation between pre- and post-training OFC lesions on acquisition.
  + Computational modeling has made the assumption, for simplicity, that in a simple single cue-outcome procedure, the cue state (e.g. “light on”) is stable throughout acquisition. Given that the same cue is presented, and it always leads to the pellet outcome, this stable representation is a reasonable assumption. However, it is also likely that during acquisition this state representation is not stable in healthy control animals. How can the animal be certain that the light cue, the testing chamber context, or the reward pellet that they see on each trial is identical to the trials they have already experienced within the session, and from previous days? The subjective experience of these states is very likely to be different within and between sessions such as the ambient noises, odours, temperature etc.. of the context, the location and intensity of the light cue based on where the rat happens to be located when it turns on, and the gradual onset of sensory specific satiety to the pellet. Informally, how does the rat know that this light is the same light that they saw at the start of the session, or the day before? The perception and recognition of these states is therefore subject to differences in such as generalization, confidence and certainty etc.…
  + Paradoxically, in a simple and stable cue-outcome training procedure pre-training OFC lesions may result in relatively rapid and inflexible formation of task states. The inability to integrate partially observable latent state information about the task could allow for an inflexible and certain representation of the CS state early in training. In this stable and simple training context this would lead to enhanced Pavlovian acquisition. However, in a task with multiple or uncertain cue-outcome contingencies pretraining OFC lesions should impair acquisition [REFS- Walton; Certainty Paper; Hiro’s gambling].
  + However, post-training inactivation of the OFC would disrupt the ability to update the state representation at whatever stage of certainty/stability that it has currently achieved. In the stable single cue-outcome learning situation employed in the present studies, this would result in disruption of further acquisition. Again, in a task with interference from multiple cue-outcome relationships, post-training lesions might actually significantly improve performance.
* Discussion of multiple subregions of OFC/homology [look at Mark’s paper]
  + Bring in Devalaution result as positive control
* Discussion of connectivity of OFC
  + BLA effects – Shauna/Juan Carlos?
* In general – need to cite specific studies to back up statements
  + Consider the new studies claiming OFC effects on learning but not showing it?

The orbitofrontal cortex (OFC) is critical to behavioural flexibility when learning and behaviour need to be updated to reflect a change in the environment [REFS]. In a range of learning situations, neural activity within the OFC initially tracks the value of rewards, and cues that have reliably predicted these rewards [REFS]. This suggests that the OFC represents the expected value of rewards based predictive stimuli in the environment. Expected values play an integral in prediction-error learning theories in which learning is based on the difference between predictions and actual experienced outcomes i.e. actual experienced value – expected value. Indeed, expected value information within the OFC has been tied to mid-brain dopaminergic prediction-error activity [REFS].

Consistent with a role for the OFC in representing expected values involved in prediction-error learning, OFC lesions and inactivation disrupt learning when rewards are no longer available (extinction), when cue-outcome contingencies change (reversal learning), and when multiple outcomes are expected (over-expectation). However, it is also clear that the OFC does not simply represent all information about the expected value of outcomes since OFC lesions do not affect initial, prediction-error dependent, cue-outcome learning. Instead the OFC has been proposed to represent specific aspects of outcome expectancy information. Take for example a putatively simple Pavlovian cue-outcome experiment in which a 10s light cue is immediately followed by a grain pellet reward. An animal can learn that the cue predicts a reward of a certain motivational value, but also about the sensory-specific properties of the outcome (e.g. taste, texture, sweetness, colour, size, location etc...), or simply develop a stimulus-response habit to approach the reward location when the cue is presented. Indeed, there is strong experimental evidence for learning about these multiple aspects of expected outcomes [REFS]. For example, if after learning about the light-pellet contingency, the value of the pellet was reduced by pairing consumption with

We will briefly consider three alternative accounts of pre- vs post-training OFC lesion differences based on theoretical accounts of OFC function. First, if the OFC is necessary for flexible control of Pavlovian behaviours relative to the value of alternative behaviours (i.e. consistent with Experiment 5), it is likely that the relative value of alternative behaviours changes over the course of training. Pre- vs post-training lesions might differ in the opportunity for alternative behaviours to interfere with the expression of Pavlovian learning. Pre-training lesions might reduce interference at the start of learning in simple single CS-US designs when there are a lot of potential alternative behaviours.

The present experiments tested the functional role of the OFC in initial acquisition learning. Latent state and sensory-specific outcome-expectancy theories of OFC function predict that the OFC is not necessary when appropriate performance is not dependent on latent task states or the sensory-specific properties of the outcome. Therefore, OFC lesions should not affect the acquisition of a simple and Pavlovian single cue-outcome relationship. In contrast to this prediction, OFC lesions and inactivation reliably disrupted Pavlovian acquisition behaviour.

First, pre-training OFC lesions (Experiment 1) significantly enhanced acquisition resulting in a significantly higher asymptotic behaviour than controls. OFC lesions have previously been reported to have no significant effect on initial acquisition learning in tasks with similar single cue-outcome, and even multiple cue-outcome contingencies [REFS]. However, the majority of these studies did not train subjects to asymptote, or employed discrete choice measures of behaviour which lack the sensitivity to detect differences above a behavioural ceiling or differences in the vigour of the response. For example, using similar parameters, many studies employing OFC lesions stop acquisition training after around 9 sessions [REFS – Deval and Unblocking Schoenbaum], before proceeding to a new phase of learning in the experiment. Indeed, the present also suggest that there is no reliable difference between OFC and controls after 9 days of acquisition. Instead, differences only emerged later at the asymptote of conditioning (around 15-21 days in the present paradigm). In a discrete trial go-nogo choice procedure, Schoenbaum and colleagues [REFS] also reported no effect of OFC lesions on acquisition, however they did report significant differences in response latencies.

We modelled these deficits within the framework of the OFC representing some aspect of outcome expectancy that informs a full reward prediction-error [REFS – supplementary as well]. Loss of this information would lead to systematic under expectation of reward and therefore increase the asymptote of learning. This model predicted a similar increase in learning following post-training OFC inactivation. However, this hypothesis was not confirmed, and instead post-training OFC inactivation suppressed any further learning (Experiment 2). This finding was replicated with post-training lesions (Experiment 3) to rule out differences between muscimol inactivation and NMDA excitotoxic lesions, and post-training inactivation (Experiment 4) at an earlier time point during acquisition. These findings replicate a similar post-training disruption of acquisition reported by Panayi & Killcross (REF Inhibition paper 2020), observed to a control cue in a more complex conditioned inhibition experimental design.

Next, we tested whether the suppressed behaviour following post-training OFC inactivation reflects a disruption of learning or performance. Using an associative blocking design (REFS), we confirmed that the disruption of behaviour to a single Pavlovian cue did not affect the ability of this cue to effectively block learning about a novel cue (Experiment 5). This suggests that OFC inactivation did not disrupt learning about the cue-outcome relationship but instead disrupted the ability to modulate behaviour based on the current learned value of the cue. This dissociation of learning and performance even when OFC function is returned, highlights the potential issues with inferring differences in learning based on performance to a target cue. Performance is often assumed to be some monotonic function of underlying learning (REFS). This finding also rules out any accounts of post-training OFC inactivation as state-dependent learning effects similar to those reported in measures such as sucrose preference (REFS – Kieflin et al).

We concluded from these studies that, contrary to our initial prediction, the OFC is indeed important in simple Pavlovian cue-outcome behaviour even when the cue-outcome contingencies remain stable and the identity of the outcome is not relevant to task performance. Furthermore, these effects likely reflect impaired behavioural control rather than impaired learning. To explain these effects, we proposed that the OFC was critical for calculating the current value of an expected outcome relative to the value of other behavioural options in the environment.

Given that there are very few obvious sources of interference that might occur in our single cue-outcome Pavlovian procedure, we reasoned that there must be an array of alternative behaviours of varying values that the rat can engage in at any point in time e.g. grooming, exploration, sleeping etc...