Neural compensation during a novel operant devaluation task in rats.

by

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B.S., Oklahoma Christian University, 2014
M.S., Kansas State University, 2019

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

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Abstract

Reinforcer devaluation is a task often used to model flexible goal-directed action, the ability to adaptively modify behavior when the value of a reinforcer changes. Deficits in goal-directed action are reported in multiple neuropsychiatric conditions, including schizophrenia. We designed a novel devaluation task in which goal-directed action could be guided by stimulus-outcome (S-O) [presumably orbitofrontal cortex (OFC)-mediated] or response-outcome (R-O) associations [presumably prelimbic cortex (PL)-mediated] to maintain. Therefore, if our task is able to model neural compensation, damage to either PL or OFC should not impair devaluation because the non-damaged region can compensate for the loss using the alternate strategy. Additionally, we investigated whether the mediodorsal thalamus (MD) may be involved in neural compensation between these regions as MD is important for directing attentional resources to relevant stimuli in the environment. In Experiment 1, male and female rats (n = 59) received pre-training bilateral OFC, PL, combined OFC+PL, or sham lesions and then completed our devaluation task. Sham, OFC, and PL lesioned rats showed intact devaluation, whereas the OFC+PL lesion group exhibited impaired devaluation. In Experiment 2, male and female rats (n = 20) received pre-training bilateral PL or sham lesions and a unilateral infusion of cholera-toxin b (CTb), a retrograde tracer. Rats were perfused 75 minutes after the beginning of the final session of cued-trial training when Arc protein expression, an early immediate gene indicative of neural activity, is highest following neural activity. We double-labeled brains for Arc and CTb and assessed how PL lesions affected the number of Arc+ neurons in OFC and MD to assess changes in gross neural activity and the percent of CTb+ neurons that were also Arc+ in MD to assess how MD->OFC projecting neurons altered activation patterns when PL was lesioned. We found increased Arc+ neuron in OFC in PL lesioned rats, no change in Arc+ neurons in MD, and

a higher proportion of double-labeled neurons in MD. Our results suggest that our devaluation task can successfully model compensation between OFC and PL. Further, it shows that when PL is inactive, OFC increases neural activity, suggestive of the S-O strategy being learned. In addition, it suggests that MD may be involved in modulating which region is active and primarily used to guide learning. This research demonstrates a method to study how functional neural circuitry is subtly altered like in early stages of schizophrenia.

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a higher proportion of double-labeled neurons in MD. Our results suggest that our devaluation task can successfully model compensation between OFC and PL. Further, it shows that when PL is inactive, OFC increases neural activity, suggestive of the S-O strategy being learned. In addition, it suggests that MD may be involved in modulating which region is active and primarily used to guide learning. This research demonstrates a method to study how functional neural circuitry is subtly altered like in early stages of schizophrenia.

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Dedication

I would like to dedicate this to my family and friends. Your unwavering support is the only thing that has gotten me through this experience.

Chapter 1 - Introduction

Prodromal symptomatology, or symptoms that are below clinical threshold but signal the beginning of a disease, often appear in neuropsychiatric disorders including schizophrenia (SCZ) (Chung & Cannon, 2015; Conroy et al., 2018) and bipolar disorder (Berk et al., 2017; Conroy et al., 2018; Hafeman et al., 2016). In SCZ, these prodromal symptoms can be manifested as neurological soft signs, like decreased fine motor movements, or increased rates of affective symptomology like social withdrawal (Chan et al., 2018; Keshavan et al., 2011; Keshavan et al., 2005). With the advent of neuroimaging methods, we also know that altered neural activity patterns accompany these prodromal symptoms in SCZ, not only in these particular behavioral paradigms but also in higher order cognition. In humans, there can be alterations in neural activity in cases where the experimental group performs behaviorally similar to controls (Barbour et al., 2010; Keshavan et al., 2002; Morey et al., 2005; Yaakub et al., 2013).

Despite the neuronal degeneration that can be tracked through neuroimaging methods, it can be hard to detect reliable behavioral changes in populations with prodromal symptomology. One possible reason for unreliable or subtle behavioral effects is neural compensation, where activity in brain regions typically necessary for the task is increased to successfully complete the behavioral task or where brain regions not normally necessary to support learning for the task using alternative strategies are recruited. These compensatory mechanisms, while beneficial to the person, can hamper identification of disease states and delay diagnosis and treatment. In order to detect these compensatory responses, behavioral models that use different strategies must be developed in order to determine if the strategies shift when a brain area or circuit is incapacitated. Not only could these models provide a way to behaviorally identify subtle neurological shifts, they can also elucidate basic neurological mechanisms that mediate how

circuits interact with each other and how dysfunction in one circuit can affect connectivity in other areas. Validation of these models could provide reliable behavioral assays that can be implemented to predict and treat disease state onset.

Neural compensation

Neural compensation has been shown in animal models within the realms of fear conditioning, reversal learning, and spatial learning. In fear conditioning, lesions of the basolateral amygdala result in impaired fear conditioning acquisition with limited training but if the animal receives overtraining of the tone-shock pairings it can acquire a contextual fear response (Maren, 1999). Likewise, repeated training can lead to contextual fear memories being dependent on non-hippocampal structures (Lehmann et al., 2009). Finally, pretraining dorsal hippocampus lesions do not affect context fear conditioning when made before training (Maren et al., 1997), suggesting that the individual elements that make up a configural representation are stored in non-hippocampal structures and are sufficient for learning.

In reversal learning, methamphetamine exposure that results in partial dopamine loss in the striatum (Daberkow et al., 2008; Pastuzyn & Keefe, 2013), produces alterations in which brain regions showed correlations between reversal learning performance and *Arc* mRNA expression. Despite the brain-behavior correlations shifting to the nucleus accumbens shell from the dorsomedial striatum, reversal learning performance was unaffected between controls and methamphetamine-treated animals. Subsequent investigation showed that inhibiting *Arc* expression in the nucleus accumbens shell only impaired reversal learning performance in methamphetamine-exposed animals, showing that the brain region necessary for intact reversal learning shifted following methamphetamine exposure.

In a spatial learning task, rats learn a T-maze using a place strategy (i.e., turning based on location relative to cues in the room) but after extensive training rats exhibit a response strategy (i.e., turning left/right regardless of relative location within the room). The place strategy is dependent on the hippocampus whereas the response strategy is dependent on the striatum. When the striatum is inactivated, the rats continue to use the place strategy at both short and extensive training but when the hippocampus is inactivated, rats do not show a preference for either strategy following short training (Packard & McGaugh, 1996). Similarly, the strategy can be biased towards the place or response strategy regardless of training length by activating the hippocampus or striatum, respectively (Packard, 1999).

Novel devaluation task

One particular behavioral realm where identification of compensatory responses would be beneficial is flexible goal-directed action, as modeled by devaluation tasks. Devaluation is impaired across a number of psychiatric conditions, including autism spectrum disorder (Alvares et al., 2016; but see Geurts & de Wit, 2014), attention deficit hyperactivity disorder (Griffiths et al., 2014), schizophrenia (Morris et al., 2018; Morris et al., 2015; Waltz et al., 2015), obsessive compulsive disorder (Gillan et al., 2014; Gillan et al., 2011; Gillan & Robbins, 2014), and there is mixed evidence for impairments in substance use disorder (Ersche et al., 2016; but see Hogarth et al., 2018; Luijten et al., 2019; Sjoerds et al., 2013), suggesting devaluation performance could represent a valuable way to learn about these psychiatric conditions. In devaluation tasks, a subject learns that a response or a cue predicts a reward. The value of the reward is then reduced using motivational (e.g. selective satiety) or associative (e.g. conditioned taste aversion) methods. Devaluation is assessed by presenting the response option or cue that previously led to the devalued outcome and responding for that response option or cue is

typically reduced in a test session. Rodent goal-directed action tasks, as modeled by devaluation, typically seek to isolate one behavioral strategy by having either a response or a cue predict reward. This approach is valuable for isolating the circuitry of one particular strategy, but this approach does not model the complexity of real-world settings where cues and responses, mediated by different circuitry, may overlap and compete for attentional resources to produce the same goal-directed action. Further, the reductionist approach does not allow for the study of how circuits mediating separate strategies flexibly and dynamically interact to appropriately allocate attentional resources to the cues and responses used to encode the information needed for future goal-directed action. Therefore, the reductionist approach is likely insensitive to detecting neurological compensatory responses. To address this gap in knowledge, we developed an innovative devaluation task that can be solved using two dissociable strategies, potentially mediated by different prefrontal cortex (PFC) regions.

In our task (Fisher et al., 2017; Fisher et al., 2020, Pickens et al., 2017), rats receive two dissociable lever-light compounds that are associated with different food outcomes. Later, one of the outcomes is devalued using selective satiety and responding for the lever-light compound that predicts the devalued food is typically reduced. Therefore, rats can devalue using a stimulus-outcome (S-O) strategy by attending to the distinct cuelights, likely mediated by orbitofrontal cortex (OFC) (Ostlund & Balleine, 2007; Rhodes & Murray, 2013; Rudebeck & Murray, 2011), or by using a response-outcome (R-O) strategy by attending to the spatial lever location, likely mediated by prelimbic cortex (PL) (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Coutureau et al., 2009; Killcross & Coutureau, 2003; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009), to guide future behavior. This task allows us to study how circuits supporting different

behavioral strategies interact to promote adaptive behavior and how circuit dysfunction can alter cortical signaling.

The literature shows a dissociation between tasks that are dependent on OFC versus PL. In free-operant tasks (when there are no discrete cue presentations and reinforcers are associated with the same spatial lever location throughout training), OFC is not necessary for learning or performance of goal-directed action (Ostlund & Balleine, 2007; Panayi & Killcross, 2018; Parkes et al., 2018; but see Gremel & Costa, 2013 & Parkes et al., 2018), whereas PL is necessary for encoding the information necessary to guide future goal-directed action in free-operant tasks (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Coutureau et al., 2009; Killcross & Coutureau, 2003; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009). These pattern of data suggest PL, but not OFC, is necessary for the formation of R-O associations. Conversely, OFC is necessary for the formation and performance of S-O associations when discrete cues signal reinforcer identity (Baxter et al., 2000; Gallagher et al., 1999; Izquierdo et al., 2004b; Lichtenberg et al., 2017; Ostlund & Balleine, 2007; Panayi & Killcross, 2018; Pickens et al., 2005; Pickens et al., 2003; Rudebeck & Murray, 2011; West et al., 2011; West et al., 2013b). While the cues in our task do not uniquely signal reinforcer identity, other studies show that OFC can be recruited when cues signal reward availability (Fiuzat et al., 2017; Rhodes & Murray, 2013; Zeeb & Winstanley, 2013). This suggests that our task, where the cues are presented in conjunction with the lever during a trial when reward is available, could recruit OFC.

Preliminary data

Under normal circumstances, the two strategies likely compete for attentional resources. However, the strategies are not equally salient because rats naturally prefer a R-O strategy in our

task. We determined this using a behavioral cue switching experiment during which the cuelights used during training were switched for half of the rats during testing (e.g. the steady cuelight that was above the left lever during training was over the right lever during test) to determine whether rats primarily devalued based on the cuelight (S-O strategy) or the spatial lever location (R-O strategy). The other half of the rats received a test session where the cuelights used during training were not switched during test (e.g., the steady cuelight that was above the left lever during training was over the left lever during test). Rats devalued using the spatial lever location instead of the cuelights, suggesting rats naturally prefer a R-O strategy in our task (Fisher et al., 2020). We also investigated the role of OFC and PL in learning the associations needed to guide behavior since R-O and S-O strategies putatively rely on PL and OFC, respectively. To determine this, we implanted bilateral cannula over OFC or PL. Five minutes prior to the cued-trial training sessions, we infused either a GABA agonist muscimol/baclofen cocktail (to temporarily inactivate the region by activating the inhibitory neurons) or phosphate-buffered saline in our control groups. The rats did not receive infusions prior to selective satiety or devaluation test, so we limited our study to how these regions potentially encode the information needed to guide future devaluation. We found that the OFC and PL inactivation groups devalued similarly to controls. While these results could suggest that OFC and PL may be necessary only for performance or could be not necessary for our version of the devaluation task, we hypothesize that these results suggest our task can model compensation between these regions. We suggest that rats may be able to switch between attending to either strategy depending on the cortical substrates that are active during training to guide future goal-directed action (Fisher et al., 2020).

While the data are still preliminary, we ran a follow-up study investigating what strategy the rats use to guide devaluation performance when PL is inactive. We gave rats PL or sham lesions prior to training. Half of the rats in each group either received the test session where the cuelight location was switched from the training location (Cue-Switch) or whether the cuelight location remained the same for training and test (Cue-Normal). We replicated our finding that control/non-manipulated rats use the spatial lever location to guide devaluation behavior in the Cue-Switch condition. In the PL lesioned rats, we found intact devaluation in the Cue-Normal condition based on the spatial lever location but a reverse devaluation effect in the Cue-Switch condition based on the spatial lever location so responding was lower on the lever below the light associated with the devalued food, even though this spatial lever location was associated with the nondevalued food. Our data show that when PL is lesioned, the rats devalue using the cuelight location instead of the spatial lever location (Figure 1.1A). This pattern suggests that when PL is lesioned, the rats are using an S-O strategy to guide devaluation behavior, perhaps because the cue-based S-O strategy is a better competitor with the R-O strategy. This competition then results in a reverse devaluation effect, based on the lever value, when the spatial lever location and cuelight identities are in conflict but leaves devaluation intact when the cue identity and lever location predict the same outcome.

In a small subset of the Cue-Switch rats, we sacrificed animals 120 minutes after the beginning of the test session to quantify Fos protein expression, an early immediate gene indicative of neural activity. These data show that neural activity during testing, based on Fos expression, is increased in OFC when PL is lesioned, indicating a strategy with a different circuitry was used to guide devaluation behavior (Figure 1.1B). These data highly suggest our task can provide a way to determine how PFC circuits alter their function to compensate for

dysfunctional neural activity when other behavioral strategies are available. However, we have yet to confirm this possibility. Experiment 1 directly examines whether PL and OFC can compensate for each other in our task by lesioning PL, OFC, or both areas prior to training.

Role of MD in neural compensation

The ability to switch between strategies depending on the active neural substrates indicates there may be a separate brain region that actively directs resources to these regions to influence attention allocation to one strategy over the other. We propose that MD mediates this adaptive ability. In nonhuman primates, MD is necessary for devaluation (Mitchell et al., 2007; Wicker et al., 2018). However the time-course of the involvement is unclear. Pre-training MD lesions impair devaluation performance (Mitchell et al., 2007) and inactivation of MD prior to selective satiety or the devaluation test impaired performance (Wicker et al., 2018). Therefore, it is unclear from these studies if MD is necessary for learning the information needed for future goal-directed action in nonhuman primate tasks.

In rodents, MD only seems to be necessary when there are multiple responses to earn reinforcers (Corbit et al., 2003; Pickens, 2008) (but see one example where chemogenetic inactivation of MD did not impair devaluation performance in mice (Parnaudeau et al., 2015)), but not in tasks when only one response is trained (Pickens, 2008). However, a comparison of pre- and post-training MD lesions suggests MD is only required for encoding the information necessary to guide future devaluation but not for devaluation performance (in tasks where it is necessary at all) (Corbit et al., 2003). All together, the rodent and nonhuman primate literature suggest that task parameters, species differences, and/or type of MD manipulation may affect when MD is recruited during devaluation tasks. Despite these mixed findings, we have shown that pre-training inactivation of MD with a muscimol/baclofen cocktail impairs future

devaluation, suggesting MD is necessary to encode the information used for future devaluation in our task (Fisher et al., 2020). While our findings do not clarify the literature differences, they do provide evidence that MD is recruited during the training phase of our task.

We propose that MD modulates PFC connectivity such that, when PL or OFC activity is disrupted, MD is able to direct attentional resources to the brain region that remains active to encode the information needed for future goal-directed action. MD is part of the human salience network. Along with MD, the major nodes of the salience network are the anterior cingulate cortex and the insula with lesser nodes including the nucleus accumbens, substantia nigra, ventral tegmental area, amygdala, and hypothalamus (Menon & Uddin, 2010; Peters et al., 2016; Seeley et al., 2007). This network of brain structures is important for detecting salient events and directing attention (Menon & Uddin, 2010; Peters et al., 2016; Seeley et al., 2007). In addition, MD is a higher-order thalamic nucleus that is reciprocally connected to PL and OFC (Alcaraz et al., 2016; Groenewegen, 1988) and is proposed to relay salience information to the executive and default-mode networks to modulate attention and aid in task engagement (Bolkan et al., 2017; Rikhye, Gilra, et al., 2018; Rikhye, Wimmer, et al., 2018; Schmitt et al., 2017; Seeley et al., 2007). This attentional modulation would represent a highly adaptive function, as decreasing attention to learning a less salient or predictive strategy is more efficient than splitting attention between two strategies. Furthermore, this would represent a mechanism for how a neural compensation could occur if one of the PFC areas is degenerating due to disease or injury.

Thalamocortical projections modulate attention and compensation

I hypothesis that MD modulates information flow to PFC through feedback loops from PL and OFC. Thus, when MD loses feedback input from the PL, it increases activity to OFC. Analysis of the neuronal composition of the thalamus reveals that there are two main classes of

neurons: drivers and modulators, as Sherman and Guillery refer to them (Sherman & Guillery, 2013). Driver neurons are aptly named as they comprise a small percentage of the neurons in thalamocortical (TC) or corticothalamic (CT) pathways and "drive" neural activity. These neurons synapse onto ionotropic receptors whereas modulating neurons synapse onto metabotropic receptors and therefore produce more long-term changes in neuronal activity (Sherman & Guillery, 2013). In working memory tasks, evidence indicates CT pathways convey specific task rule-related information, suggesting this pathway is made up of driver neurons. Conversely, thalamocortical (TC) neurons do not convey task-specific information, suggesting this pathway is made up of modulator neurons (Bolkan et al., 2017; Schmitt et al., 2017). Despite sending nonspecific information, increasing TC activity increases performance whereas decreasing TC activity impairs working memory performance in a spatial delay non-match to sample T-maze task (Bolkan et al., 2017) and a two-alternative forced choice test (Schmitt et al., 2017). TC neurons (e.g., MD->PL) are proposed to have their effects by increasing bidirectional activity between MD and PL which results in increased attention and performance (Bolkan et al., 2017; Parnaudeau et al., 2018; Rikhye, Gilra, et al., 2018; Schmitt et al., 2017). While no one has directly tested the relationship between MD and OFC and S-O associations, MD and OFC are both implicated as necessary for updating associations in reversal learning tasks (Izquierdo, 2017; Izquierdo et al., 2016; Wolff & Vann, 2019), and one review proposes that MD->OFC may support and stabilize the representations necessary for reversal learning (Parnaudeau et al., 2018). We suggest a mirrored system in reward processing such that TC connections modulate attentional value assigned to S-O (MD->OFC) and R-O (MD->PL) strategies used to guide future devaluation performance. We propose the associative strength of the strategy would depend on TC modulatory connections between MD->OFC and MD->PL pathways instead of

relying on CT input, which may relay representations of the outcomes. There is some indirect evidence for a different role for TC pathways in goal-directed action. Selective PL->MD inactivation using DREADDs strongly impairs devaluation while MD->PL inactivation produces a weak devaluation effect (Alcaraz et al., 2018). Although that study did not directly measure neural activity, the weak devaluation effect is suggestive of a different role for MD->PL pathways in devaluation compared to the PL->MD pathways, perhaps a modulatory role more similar to working memory tasks.

Under normal circumstances, we propose MD increases attentional resources to PL across training and reduces excitatory input to OFC to promote the R-O strategy. Our data showing no effect of OFC and PL training inactivation on later devaluation (Fisher et al., 2020) and our pilot data showing a reverse devaluation effect (exhibiting devaluation based on the cues) in PL lesioned rats when the cues are switched during test, but intact devaluation when the cues are congruent between training and test, suggests these attentional resources are likely directed depending task demands and cortical availability. Our pilot neural data also support this idea. We believe this pattern of data emerges because, when PL is inactivated or lesioned, the thalamus loses input from PL via the CT pathways which subsequently decreases TC connectivity. We suggest that we see no effect of PL inactivation or lesion on devaluation when the test cues are congruent with training because, when PL is inactivated or lesioned, MD->OFC connectivity is increased during training to compensate for the loss of PL CT input. The increased connectivity results in more attentional resources directed to learning the S-O strategy to compensate for the loss of PL, which results in accurate devaluation performance only when the cues predict the same outcome as the spatial lever location. In Experiment 2, I measured neural activity following the last day of training, using Arc expression, in MD->OFC neurons

when PL is lesioned or not to determine whether MD may facilitate compensation by increasing neural activation in OFC projecting neurons when PL is damaged.

The last day of training was chosen to ensure that learning had taken place and maximize the likelihood of finding effects. If our hypothesis about MD increasing attentional resources based on task demands and cortical availability is correct, than examining neural activity during the last training session maximizes the likelihood that (1) MD is recruited in the learning process and (2) neural activity is increased in MD->OFC and OFC when PL is lesioned.

(1) As mentioned, at least in rats, MD is only necessary for learning the information needed to guide future goal-directed action, not for performance (Corbit et al., 2003) and for tasks where multiple responses earn reinforcers (Pickens, 2008). Thus, it is highly unlikely that assessing neural activity during the test session would reveal how MD may modulate attentional resources as MD would likely not be recruited (but see (Wicker et al., 2018) for an example of MD being necessary for devaluation performance in nonhuman primates). Furthermore, assessing activity during the test session would not show what happened during the learning phase. Differences in test activity would suggest changes while training occurred (according to some models of learning) but would not definitively show this as some models of learning suggest that simultaneously presented stimuli are learned at the same rate but differences seen in performance are due to stimuli comparisons that occur during performance, not learning (Miller & Matzel, 1988). In our task, each lever-light-pellet combination is trained separately across the four training sessions (2 sessions with each lever-light-pellet combination). Based on these previous studies, it is possible that MD does not become recruited until the second training session as this is when the second R-O association is presented. However, as the previous studies only used a free-operant (Corbit et al., 2003) task or a combination of S-O or R-O associations

presented separately (Pickens, 2008), it is unclear how MD may be recruited when there is attentional competition between two PFC regions, as is possibly occurring in our task where the cuelight (potentially recruiting OFC) and the spatial lever location (potentially recruiting PL) are presented simultaneously.

(2) Our criteria for PL lesion criteria was 60% damage or greater (see Methods for more details) and none of the lesions represented 100% damage. Thus, as our lesions left some of PL intact, it is likely that some of the PL->MD driver neurons were spared. It is unclear how big of an effect these spared driver connections would have on MD->PL function and the potential shift to increases in MD->OFC modulator connections. In order to allow for OFC, MD->OFC, and OFC->MD neuronal activity to outcompete PL and PL's bidirectional connections with MD, we decided to measure neural activity following the last training session when each lever-light - pellet combination had two sessions as opposed to the first session when the competition may not have fully occurred yet.

We decided to use the early immediate gene, activity-regulated cytoskeletal (Arc), for a few reasons. Unlike some early immediate genes, like c-Fos where the exact function is unclear, Arc has a well-characterized role in learning and memory (Gallo et al., 2018; Minatohara et al., 2015; Shepherd & Bear, 2011). The gene codes for a synaptic protein and is involved in the formation of new synapses and the maintenance of old synapses through mechanisms such as long-term potentiation (LTP) (Shepherd et al., 2006; Steward et al., 1998; Steward & Worley, 2001; Wang et al., 2016) and long-term depression (LTD) (Jakkamsetti et al., 2013; Park et al., 2008; Shepherd et al., 2006; Waung et al., 2008; Wilkerson et al., 2018). Additionally, Arc expression is necessary for long-term memory consolidation, such that blocking Arc expression impairs memory consolidation (Cao et al., 2015; McReynolds et al., 2014; Miranda et al., 2017;

Plath et al., 2006) and facilitating Arc expression aids consolidation of weak memories (Martinez et al., 2012). Furthermore, one study suggests that Arc expression may prime neurons to exhibit LTD or LTP based on initial activation so neurons that are weakly activated (e.g., a weak competitor – potentially like the cue-based strategy) may be primed for LTD. In contrast, strongly activated neurons (e.g., a strong competitor – potentially the spatial lever location strategy) are primed for LTP and retain their strong activation across training (Cao et al., 2015). Importantly, unpublished data from our lab show that a commonly used early immediate gene used in learning and memory studies, c-Fos, shows poor expression in MD. Arc, however, shows robust expression in MD, making it a better candidate to identify potential changes in early immediate gene expression (and indirectly, neural activity) in MD.

Hypotheses

Overall, we hypothesized that OFC and PL compensate for each other in our devaluation task and this compensation is made possible through connections with MD.

Experiment 1. Experiment 1 established the extent to which OFC and PL compensate for each other and whether these areas play a role in devaluation performance. Our overarching hypothesis was that the parameters of our devaluation procedure allow for rats to use either a PL-mediated or OFC-mediated strategy to successfully exhibit devaluation. As such, we believed the lack of PL and OFC effects we observed occurs because the brain area that was active during training is able to compensate for the inactivation of the other area (e.g. an OFC-mediated strategy was used when PL was inactivated). However, OFC and PL inactivation during training may not have impaired devaluation because neither area is involved in initial learning or these areas are only necessary for devaluation performance when the areas were active again. In order to test our hypotheses, we lesioned OFC, PL, or both OFC and PL combined (OFC+PL). This

methodology assessed whether OFC and PL compensate for each other in our task. We predicted (1) rats with sham lesions would show intact devaluation, (2) rats with OFC or PL lesions alone would show intact devaluation, and (3) rats with OFC+PL lesions would show impaired devaluation.

Experiment 2. Experiment 2 determined how functional activation patterns of MD->OFC projections change when attentional competition is removed during training by lesioning PL**.** We infused cholera-toxin b (CTb) into OFC in rats with or without PL lesions. CTb was taken up by the terminals in the OFC and transported back to the cell body. Therefore, any neurons that project to OFC were tagged with CTb. On the last session of training, brains were extracted to measure Arc at a time point that reflects neuronal activity during training. Therefore, areas with higher amounts of Arc protein are indicative of more activation and represent an indirect measure of neural activity. Double-labeling of a neuron for Arc and CTb indicates that the neuron projects to OFC and was active during the task. We predicted there will be (1) more Arc+ neurons in OFC, (2) no difference in Arc+ neurons in MD, and (3) a higher ratio of double-labeled CTb+Arc neurons in MD when PL is lesioned, suggesting that MD shifts attentional resources to OFC such that a S-O strategy is used to learn the contingencies needed for later devaluation when PL is damaged.

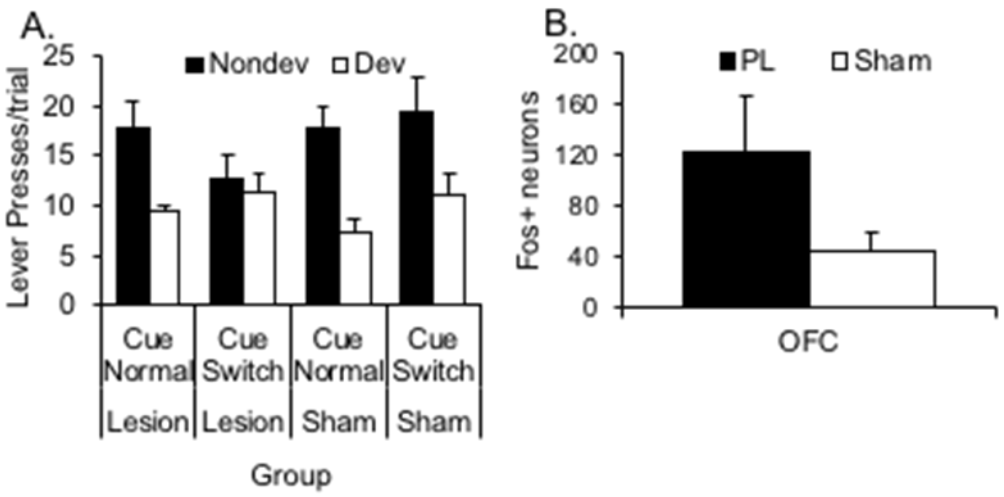

Figure 1.1. (A) Devaluation effect for the rats (6-10/grp – verified histology) that received PL or Sham pretraining lesions prior to receiving the Cue Switch or Cue Normal devaluation procedure. White bars = Nondevalued lever. Black bars = Devalued lever. NonDev = Nondevalued. Dev = Devalued. (B) Number of Fos+ neurons during devaluation performance in the lateral OFC following pretraining PL (n = 3) or Sham (n = 2) lesions. White bar = Sham. Black bar = Prelimbic cortex lesion. PL = Prelimbic cortex.

Chapter 2 - Methods

Subjects

Male and female naïve Long Evans rats (n = 79) bred in-house from parents from Charles River were used for all experiments. Group sizes for Exp. 1 were determined using power analyses (G*Power 3.1) using previous data to obtain statistically significant results at the $p < .05$ level (assuming effect sizes of ~.3 (Fisher et al., 2020) for Exp 1 or ~1.4 (unpublished data) for Exp 2 and an observed power of .80) with an estimated 75% surgical hit rate. Based on this analysis we required 12 rats per group for Exp. 1 and 10 rats per group for Exp. 2. Previous research in our lab found no sex differences in devaluation (Fisher et al., 2020), which is why we will use mixed-sex groups for all experiments. All animals were individually housed after surgery and maintained on a 12-hour reverse light-dark cycle (lights off at 7:00 AM) in a temperature and humidity controlled room.

The animals were free fed until they reached the surgery weight threshold (295 g for males and 215 g for females) and then received surgery. They remained on free feed for at least three days following surgery and until their weights met the pre-surgery weight threshold. They were then food-restricted to 85% of their free-feeding weight by daily feedings with a minimum of 5 g of food chow per day. Once rats reached their 85% target weights, the target body weight increased by 1 g/day for males or 0.25 g/day for females for the remainder of the experiment, such that the rats' target weights gradually increase by 7 g/week or 1.75 g/week. These values were based on unpublished data from our lab showing that this food restriction protocol maintains high rates of lever pressing for the duration of the experiment. Increases in target body weight for females is lower than the increases for males due to unpublished data from our lab that showed allowing females to gain more weight led to decreased lever pressing rats every 4-5

days. As these artificial decreases in lever press rates interfere with data integrity, males and females were allowed to gain weight at different rates. The rats were fed to maintain them at their target weights and water was available *ad libitum*. All procedures and animal care were in accordance with the Kansas State University Institutional Animal Care and Use Committee guidelines, the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and United States federal law.

Behavioral apparatus

Experiments were conducted in 12 standard self-administration chambers (Med Associates, St. Albans, VT). Each chamber is equipped with a pellet dispenser that delivers a 45-mg precision pellet (catalog #1811155; TestDiet, Richmond, IN), a 45-mg chocolate-flavored sucrose pellet (product #1811256; TestDiet, Richmond, IN), or a 45-mg grain pellet (catalog #1812127; TestDiet, Richmond, IN). The identity of the pellet dispensed is dependent on the task phase. The chambers have two retractable levers on either side of the food cup at approximately one third of the total height of the chamber, with a white cuelight located above each lever. A red houselight is mounted on the top-center of the back wall. A speaker for delivering auditory stimuli is located on the left side of the back wall of the chambers, on the opposite wall from the food cup. A Dell Optiplex computer, equipped with Med-PC for Windows, controls the equipment and records lever-presses.

General surgical methods

Rats underwent surgery for all experiments. Animals were anesthetized with 3-5% isoflurane in an induction chamber and then placed in a stereotaxic device (Kopf Instruments, Tujunga, CA) and maintained on 1-3% isoflurane for the duration of the surgery. Once the skull was exposed, bregma was used to determine injection placement, for which holes were burred

with a drill. All infusions (described below for each individual experiment) were at a rate of 0.1 µl/min. Following the infusion, the needle was left in place for 5-7 min to allow for diffusion. After the needle was removed, the incision was closed with wound clips and triple antibiotic ointment was applied. Animals were given 1 mg/kg flunixin (Norbrook, Overland Park, KS) subcutaneously upon completion of surgery and 24-h later during the post-op health check.

Devaluation task

Training (Experiments 1-2). After at least a 10-day recovery period, rats received 3 magazine training sessions, one with each pellet type. Then, they received 4 lever press training sessions (2 with each lever) on a fixed-interval-1 schedule earning grain pellets with no cuelights present. Here, lever presses could earn a reward with a press every one second. Grain pellets and no cuelights were used to prevent the formation of R-O and S-O associations that could be used to guide behavior prior to cued-trial training sessions. Next the rats received 4 once-daily cued-trial operant training sessions, two sessions for each cue-lever-reinforcer combination. Only one cue-lever-pellet compound was available during a session. Throughout training, left-lever presses earned precision pellets and were always associated with a steady cuelight. Right-lever presses earned chocolate pellets and were always associated with a flashing cuelight. Every cued-trial training session was 40 min long with 40 trials. All trials were 40 sec long and rats could earn up to two pellets per trial for lever-pressing, one in the first half and one in the second half of the trial at randomized times. During the inter-trial interval, the levers retracted and the cuelights turned off.

Devaluation Choice Test (Experiment 1 only). Following cued trial training, a choice test was administered. In the operant chambers, rats received a 1-hr satiation session with access to 30g of either chocolate or precision pellets (counterbalanced) presented in ceramic bowls.

Fifteen minutes after the satiation period, rats received a 12-min choice test with twelve 40-sec trials. During each trial, both levers with the associated cuelights were presented and responding was measured. The cuelights above the levers were in the same position as during training. Responding should be decreased for the cue-lever compound that earns the devalued reinforcer if rats devalue properly. Lever presses did not earn pellets to ensure the rats used their memory representations of the cue-lever combinations to guide behavior. Next, rats received two cued-trial training sessions, one with each lever-cue-food compound, to return lever pressing rates to baseline. Rats then completed another choice test with the opposite pellet devalued during the satiation period.

Devaluation Consumption Test (Experiment 1 only). Finally, at least one day after the final choice test, animals in Experiment 1 completed 2 consumption tests. Each consumption test included a 60-min satiation period for one of the two pellet types (counterbalanced across group), identical to the satiation periods that preceded the choice tests. Fifteen minutes following the end of the satiation period, the animals had access to two ceramic bowls in the operant chambers. One bowl contained 10g of precision pellets and the other bowl contained 10g chocolate pellets. The consumption test lasted 10 min. After completion of the test, the remaining pellets were sorted by type and weighed to determine consumption. Animals received at least one day off after the first consumption test before completing the second consumption test identical to the first, except that animals were sated on the opposite pellet type as in the first consumption test.

Individual experiments

Experiment 1 (Figure 2.1). Male and female rats (n = 59; 12-20/group; Table 2.1) received neurotoxic lesions and/or sham lesions of PL and OFC. There were four surgical

groups: PL (13 rats; 6 male, 7 female), OFC (14 rats; 7 male, 7 female), OFC+PL (20 rats; 10 males, 10 females), and Sham (12 rats; 6 males, 6 females). The PL and OFC groups received a bilateral lesion of PL or OFC, respectively. The OFC+PL group received two bilateral lesions: a bilateral OFC lesion and a bilateral PL lesion. All excitotoxic lesions were created by infusing 0.4 µl (OFC) of 20 mg/ml NMDA and/or 0.3 µl (PL) of 10 mg/ml NMDA in phosphate-buffered saline (PBS). The Sham group received infusions of PBS to OFC and PL. Single lesion groups also received an infusion of PBS (0.4 µl or 0.3 µl) into the non-lesioned area. The OFC infusion was at the following coordinates relative to bregma: anterior-posterior (AP): +3.5 mm, medial-lateral (ML): +3.3 mm, dorsal-ventral (DV): -5.4 mm. The PL infusion was at the following coordinates relative to bregma: AP: +3.2 mm, ML: +0.7 mm, DV: -3.6 mm. Following surgery, the rats began cued-trial training, and then completed devaluation choice tests and devaluation consumption tests as described above.

Experiment 2. Male and female rats (n = 20; 8-12/group; Table 2.2) received neurotoxic lesions or sham lesions of PL. Rats in the PL lesion group (12 rats; 6 males, 6 females) received bilateral infusions of 0.3 µl of 10 mg/ml NMDA. Rats in the PL sham group 8 rats; 3 males, 5 females) received infusions of 0.3 µl of PBS. In addition, all rats in both groups received a unilateral, side counter-balanced, 0.2 µl infusion of 1% CTb conjugated with Alexa Fluor 488 in PBS in OFC (Marchant et al., 2016). The OFC infusion was at the following coordinates relative to bregma: AP: +3.5 mm, ML: $\pm$3.3 mm, DV: -5.4 mm. The PL infusion was at the following coordinates relative to bregma: AP: +3.2 mm, ML: $\pm$0.7 mm, DV: -3.6 mm. Following surgery, the rats began cued-trial training at least 3 weeks later to allow for retrograde transport and were perfused 75 min following the start of the last session of training to optimize Arc expression (Lonergan et al., 2010).

Histological Procedures

Perfusions. 75 minutes following the beginning of the last session of training (Experiment 2) or after the completion of behavioral testing (Experiment 1), the rats were deeply anesthetized with pentobarbital and perfused with 100 ml of 0.1-M PBS followed by 400-500 ml of 4% paraformaldehyde (PFA). The interval between the behavioral session and training was determined in order to maximize Arc expression (Lonergan et al., 2010). The brains were removed, post-fixed in PFA for 2 hr, and stored in 0.1-M PBS with 30% (w/v) sucrose for 48-72 hr until dehydrated. Sections (40-μm) were taken from each brain using a cryostat, and every section was collected.

Experiment 1 and 2. Every 3rd (Exp. 1) or 4th (Exp. 2) brain section was mounted and Nissl stained using thionin. Lesions were verified using a light microscope (model BX41, Olympus) and SPOT 5.1 Advanced Software. Only rats with bilateral lesions with 60% or more damage of the target area on a section were included in the data analyses.

Experiment 2. Immunohistochemistry (IHC) using an immunofluorescence method was performed to label for Arc and CTb (Experiment 2) by adapting the IHC procedure used by Marchant and colleagues (Marchant et al., 2010).

The tissue was gently agitated on a plate shaker throughout. First, the free-floating tissue was washed repeatedly with 0.1-M PBS (pH 7.4). The sections were blocked for 1 hr with 10% normal horse serum (NHS), 0.5% Triton-X, and 5% bovine serum albumin (BSA) in PBS and incubated at room temperature for 48 hr in rabbit anti-Arg 3.1 (1:4,000; Cell Signaling) and goat anti-CTb (1:5,000; ListLabs) diluted with 10% NHS, 0.5% Triton-X, 5% BSA, and 0.1% sodium azide in PBS. After three PBS rinses, sections incubated for 6 hr at room temperature in donkey anti-rabbit Alexa Fluor 594 (1:200) and donkey anti-goat Alexa Fluor 488 (1:200) diluted with

10% NHS, 0.5% Triton-X, and 5% BSA in PBS. The tissue was rinsed in PBS and incubated for 10 min at room temperature in DAPI (1:25,000) in PBS. The tissue was rinsed twice for 1 min each and then stored in PBS at 4°C until they were mounted on charged slides and coverslipped with mounting medium (90% glycerol and 0.5% n-propyl gallate in 20mM Tris, pH 8.0). Uniform stitched images (Zeiss 700) at 40X magnification for each area at the following coordinates, relative to bregma, were used for the analyses: OFC (+4.2), and MD (-2.9).

Statistical analyses

For the behavioral data, multilevel poisson regressions were run with a log link function on the number of lever presses (Training and Testing) and the number of rewards earned (Training). The best fitting models were chosen via model comparisons that employed the Akaike Information Criterion (AIC), which took into account the number of parameters entered into the model and penalized more complex models (Kuha, 2004). For neurological analyses, the dependent variable was the number of Arc+ neurons in OFC and MD or total number of CTb+Arc neurons divided by the total number of CTb+ neurons in MD.

Experiment 1. For the training data, possible predictors included the between-subjects variables PL (Sham, PL) and OFC (Sham, OFC) and the within-subjects variables Training Day (Day 1, Day 2, Retrain) and Pellet Type (Precision, Chocolate). The random effects structure included Subject, Training Day, and Pellet Type. For the test data, possible predictors included the between-subjects variables PL (Sham, PL) and OFC (Sham, OFC) and the within-subjects variables Lever (Nondev, Dev) and Trial. The random effects structure included Subject, Lever, and Trial. Planned comparisons were run for significant interactions including PL and OFC using Type I Sums of Squares.

Experiment 2. The training data included the possible predictors: PL (Sham, PL), Training Day (Day 1, Day 2, Retrain), and Pellet Type (Precision, Chocolate). Planned comparisons were run for significant interactions including PL and OFC using Type I Sums of Squares. The neurological data were analyzed with a Student's independent samples *t*-test with the variable Group (PL, Sham) on the ratio of double-labeled CTb+Arc neurons to the number of CTb+ neurons in MD or on the number of Arc+ neurons in each MD and OFC.

All data were analyzed with R (R 3. 3. 1). Significant interactions ($p < 0.05$) of the highest order with the variables PL and OFC (Exp. 1) or PL (Exp. 2) were followed by planned comparisons using emmeans for interactions with only categorical variables or emtrends for interactions with a continuous variable.

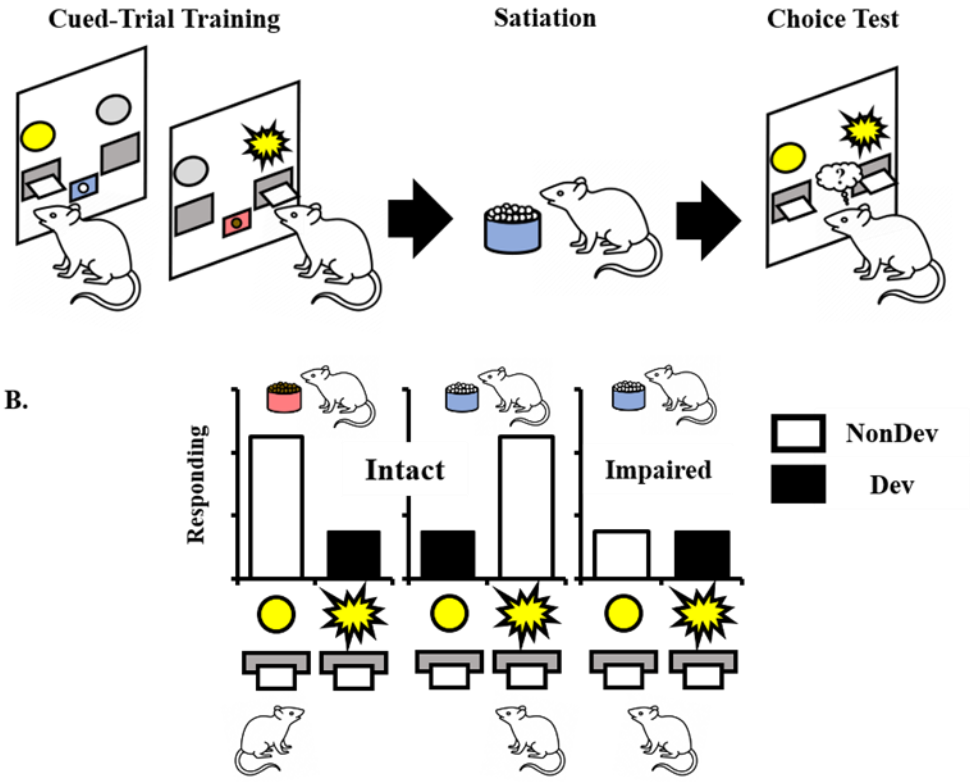

Figure 2.1. Schematic of our devaluation task procedure for Experiment 1. The *top* panel represents the three task phases: cued-trial training, satiation period, and choice test. The rats received four days of cued-trial training, two with each light-lever-pellet combination (steady-left-precision or flashing-right-chocolate). The rats are selectively sated on one of the pellets and

then received a choice test where both light-lever compounds are simultaneously presented but lever presses do not earn food. Not pictured: two days cued-trial retraining or the second satiation and choice test. The *bottom* panel represents the possible patterns of data for intact and impaired devaluation responding as a function of the pellet type devalued during the satiation period. On the top panel: Blue background represents precision pellets. Pink background represents chocolate pellets. On the bottom panel: Blue bowls represent sated on precision pellets. Pink bowls represent sated on chocolate pellets. White bars = Nondevalued lever. Black bars = Devalued lever. NonDev = Nondevalued. Dev = Devalued.

Table 2.1. Summary of surgical groups for Experiment 1.

		PL	
		Sham	Lesion
OFC	Sham	$Sham_o$+$Sham_p$ (Sham) (n = 12)	PL+$Sham_o$ (PL) (n = 9)
	Lesion	OFC+$Sham_p$ (OFC) (n = 13)	OFC+PL (OFC+PL) (n = 10)

Note. Table represents the infusions each of the four surgical groups received that were included in the study. Each group received two infusions, one into the orbitofrontal cortex (OFC) and one into the prelimbic cortex (PL). $Sham_o$ represents rats that received an OFC sham lesion by infusing PBS into OFC. $Sham_p$ represents rats that received a PL sham lesion by infusing PBS into PL. PL represents rats that received a PL lesion by infusing NMDA into PL. OFC represents rats that received an OFC lesion by infusing NMDA into OFC. Parenthetical represents the group abbreviation used throughout the proposal and group sizes.

Table 2.2. Summary of surgical groups for Experiment 2.

	PL	
	Sham	Lesion
CTb	Sham (n = 9)	PL (n = 7)

Note. Table represents the infusions each of the two surgical groups received that were included in the study. Sham represents rats that received a PL sham lesion by infusing PBS into PL. PL represents rats that received a PL lesion by infusing NMDA into PL.

Chapter 3 - Results

Experiment 1

Histological exclusions. For both PL and OFC, lesions had to damage at least 60% of the region. Based on these criteria, 15 rats (1 Male-OFC, 2 Male-PL, 2 Female-PL, 5 Male-OFC+PL, 5 Female-OFC+PL) were excluded. The final group sizes in Experiment 1 were as follows: OFC, n = 13 (6 Males, 7 Females); PL, n = 9 (4 Males, 5 Females); OFC+PL, n = 10 (5 Males, 5 Females); and Sham, n = 12 (6 Males, 6 Females).

Training. The Sham, OFC, and PL groups increased responding for both pellet types across the training days whereas the OFC+PL group maintained responding for precision pellets across training and decreased responding for chocolate pellets across training (Figure 3.1). A multilevel Poisson regression was used to analyze the data. Comparing AICs, the best fitting model (AIC = 7821.4) was about 300 points better than the next best model (AIC = 8130.8). The best fitting model included OFC × PL × Pellet × Day and all lower effects. Intercept, Pellet, and Day were added as random effects. There was significant OFC × PL × Pellet × Day interaction (b = -0.03, z = -7.81, $p < 0.01$). Other lower level effects are shown in Table 3. The OFC × PL × Pellet × Day interaction revealed that for the chocolate pellet type, the Sham (z = 6.92, $p < .01$), PL (z = 6.78, $p < .01$), and OFC (z = 5.83, $p < .01$) all increased responses across the training days whereas the OFC+PL group decreased responses (z = -2.77, $p < .01$). For the precision pellet type, the Sham (z = 9.15, $p < .01$), PL (z = 4.34, $p < .01$), and OFC (z = 4.83, $p < .01$) all increased responses across the training days whereas the OFC+PL group maintained responding (z = -1.55, p = .12).

The number of rewards earned increased across the training days but there were no group differences in this effect (Figure 3.2). A multilevel Poisson regression was used to analyze the

data. We used the same model structure as that used for the number of responses which included OFC × PL × Pellet × Day and all lower effects. Intercept, Pellet, and Day were added as random effects. There was a significant main effect of Day (b = 0.04, z = 5.00, p < 0.01). No other effects or interactions were significant (all p > .05; Table 4).

Devaluation test. The Sham, OFC, and PL groups made more responses on the nondevalued lever compared to the devalued lever, indicative of a devaluation effect, but the OFC+PL group did not (Figure 3.3). A multilevel Poisson regression was used to analyze the data. Comparing AICs, the best fitting model (AIC = 4810.90) was about 55 points better than the next best model (AIC = 4866.0). The best fitting model included OFC × PL × Lever × Trial and all lower effects. Intercept, Lever, and Trial were added as random effects. There was a significant OFC × PL × Lever interaction (b = -0.07, z = -3.54, p < 0.01) and a significant OFC × PL × Trial interaction (b = 0.03, z = 2.21, p = 0.03). Other lower level effects are shown in Table 5. The OFC × PL × Lever interaction revealed that the Sham (z = 4.70, p < 0.01), OFC (z = 5.54, p < 0.01), and PL (z = 3.48, p < 0.01) groups responded on the nondevalued lever significantly more than the devalued lever while the OFC+PL group (z = -1.59, p = 0.11) did not. The OFC × PL × Trial interaction revealed that the OFC+PL (z = -5.08, p < 0.01) and PL (z = -7.02, p < 0.01) groups decreased responding, averaged across the levers, across the trials but the OFC (z = -1.05, p = 0.29) and Sham (z = 0.217, p = 0.82) groups did not.

Consumption test. The rats ate significantly more of the pellet type they were not sated on (i.e. the nondevalued pellet type) regardless of what group they were in (Figure 3.4). A multilevel Gaussian regression was used to analyze the data. The model structure included OFC × PL × Satiation and all lower effects. Intercept and Satiation were added as random effects. There was a significant effect of Satiation (b = 0.55, t = 4.01, p < 0.01). There was no significant

interaction of OFC × PL × Satiation (b = -0.11, t = -0.81, p = 0.42). No other effects or interactions were significant ($p > 0.05$; Table 6). The rats ate more of the nondevalued pellet type (M = 2.97, SE = 0.21) compared to the devalued pellet type (M = 1.83, SE = 0.16).

Experiment 2

Histological exclusions. For PL, lesions had to damage at least 60% of the region. Based on these criteria, 4 rats (1 Female, 3 Males) were excluded. In addition, 1 Sham Male was excluded due to extensive cortical damage that was not the result of the brain extraction. The final group sizes in Experiment 1 were as follows: PL, n = 9 (4 Males, 5 Females); Sham, n = 7 (2 Males, 5 Females).

Training. PL lesioned rats increased responding for the precision pellet across the two training days while the Sham rats did not. Both groups pressed more for the precision pellet compared to the chocolate pellet (Figure 3.5). A multilevel Poisson regression was used to analyze the data. Comparing AICs, the best fitting model (AIC = 965.2) was about 2 points better than the next best model (AIC = 968.5). The best fitting model included PL × Pellet × Day and all lower effects. The next best model included PL × Pellet, Pellet × Day, and all lower effects. We chose to use the best fitting model that was more complex because it was more similar to the model for the training data in Experiment 1. In addition, we wanted to use the same model structure to analyze Responses and Rewards Earned and the more complex model performed substantially better than the less complex model. The PL × Pellet × Day interaction revealed that PL lesioned rats increased responding for precision pellets across the training days (z = 3.61, $p < 0.01$) but not the chocolate pellet type (z = -1.17, p = 0.24). The Sham group did not alter lever pressing rats across days for either the precision (z = 1.17, p = 0.24) or the chocolate (z = -1.41, p = 0.15) pellet type. The PL (z = 10.92, $p < 0.01$) and Sham (z = 5.31, $p <$

0.01) groups both responded more for the precision pellet type than the chocolate pellet type. No other effects including PL were significant. Other lower level effects are shown in Table 7.

The number of rewards earned did not differ across any variable (Figure 3.6). A multilevel Poisson regression was used to analyze the data. When we examined model fits for the model analyzing Rewards Earned, the PL × Pellet × Day and all lower effects model structure had a substantially lower AIC than the PL × Pellet, Pellet × Day, and all lower effects model. We used the same model structure as that used for the number of responses which included PL × Pellet × Day and all lower effects. Intercept, Pellet, and Day were added as random effects. There were no significant effects or interactions of any variable (all $p > .05$; Table 8).

Neurological analyses. Student's independent two samples *t*-tests were used to analyze the overall number of Arc+ neurons in MD and OFC or the percentage of CTb+ neurons that were also Arc-positive in MD. While the numbers of Arc+ cells in MD were not different between the PL lesioned rats ($M = 335.06$, $SE = 44.44$) compared to Sham rats ($M = 271.86$, $SE = 28.96$), $t(14) = 1.11$, $p = .28$ (Figure 3.7), there were more Arc+ neurons in the lateral OFC in PL lesioned rats ($M = 197.94$, $SE = 8.84$) compared to Sham rats ($M = 144.86$, $SE = 11.45$), $t(14) = 3.74$, $p < .01$ (Figure 8). There was a higher percentage of overlap between Arc+ and CTb+ neurons in the PL lesioned group ($M = 84.62$ $SE = 2.63$) compared to the Sham group ($M = 56.09$, $SE = 7.44$), $t(14) = 3.98$, $p < .01$ (Figure 3.8).

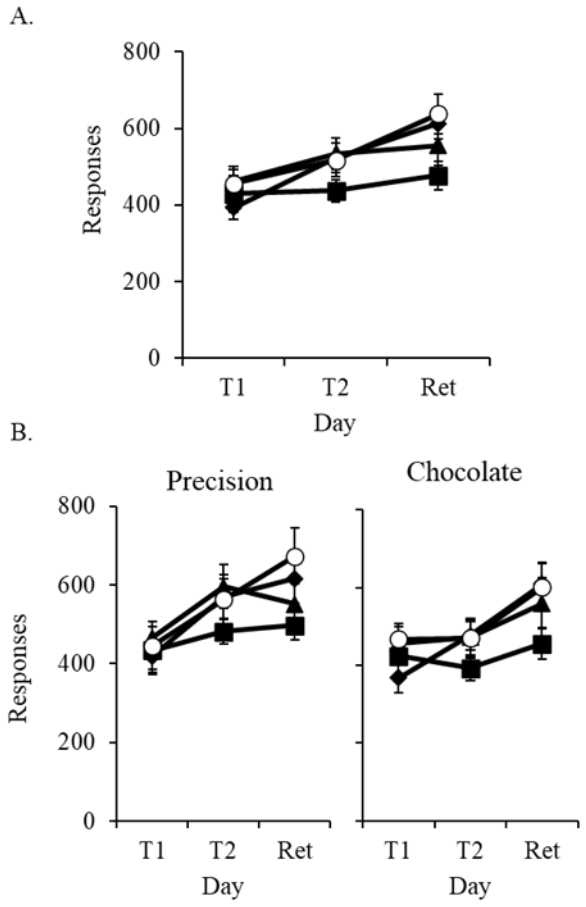

Figure 3.1. (A) Lever presses/session (mean ± SEM) made during training for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions over the course of three training days, collapsed across pellet type. (B) Lever presses/session (mean ± SEM) made during training for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions over the course of three training days for Precision (Left) or Chocolate (Right) pellet types. Black squares represent rats that received OFC+PL lesions. Black diamonds represent rats that received PL lesions. Black Triangles represent rats that received OFC lesions. White circles represent rats that received Sham lesions. T1 and T2 represent the first and second day of cued trial training for each pellet type and Ret represents the retraining day for each pellet type (averaged across the first, second and retraining day for each pellet in A and presented separately for each pellet on in B)

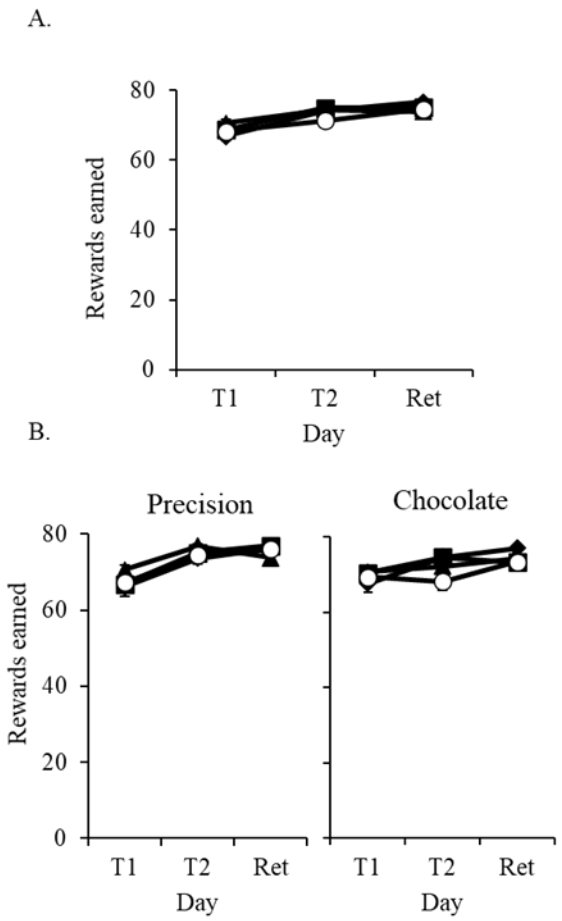

Figure 3.2. (A) Rewards Earned/session (mean ± SEM) made during training for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions over the course of three training days, collapsed across pellet type. (B) Rewards Earned/session (mean ± SEM) made during training for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions over the course of three training days for Precision (Left) or Chocolate (Right) pellet types. Black squares represent rats that received OFC+PL lesions. Black diamonds represent rats that received PL lesions. Black Triangles represent rats that received OFC lesions. White circles represent rats that received Sham lesions. T1 and T2 represent the first and second day of cued trial training for each pellet type and Ret represents the retraining day for each pellet type (averaged across the first, second and retraining day for each pellet in A and presented separately for each pellet on in B).

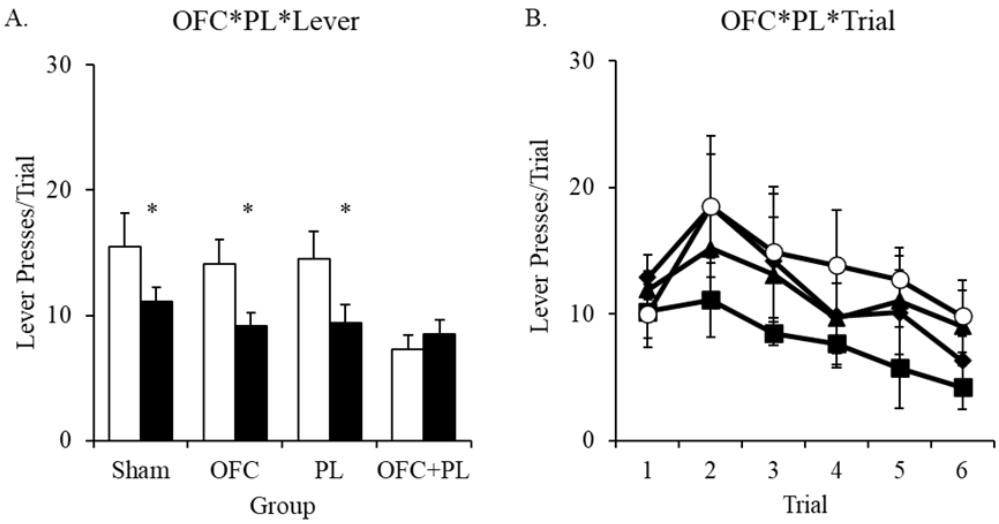

Figure 3.3. (A) Lever Presses/trial (mean ± SEM) made during the devaluation choice test for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions averaged across trials. White bars represent responding on the lever associated with the nondevalued outcome. Black bars represent responding on the lever associated with the devalued outcome. (B) Lever Presses/trial (mean ± SEM) made during the devaluation choice test for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions averaged across levers. Black squares represent rats that received OFC+PL lesions. Black diamonds represent rats that received PL lesions. Black Triangles represent rats that received OFC lesions. White circles represent rats that received Sham lesions.

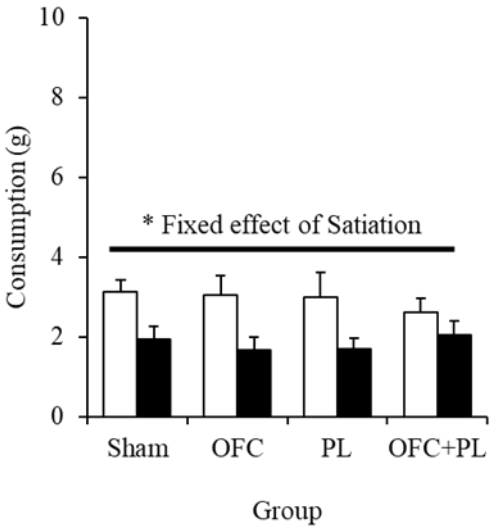

Figure 3.4. (A) Consumption (mean ± SEM) of the pellet types during the consumption test for the rats that received OFC, PL, OFC+PL, or Sham pretraining lesions. White bars represent consumption of the nonsated (nondevalued) pellet type. Black bars represent consumption of the sated (devalued) pellet type.

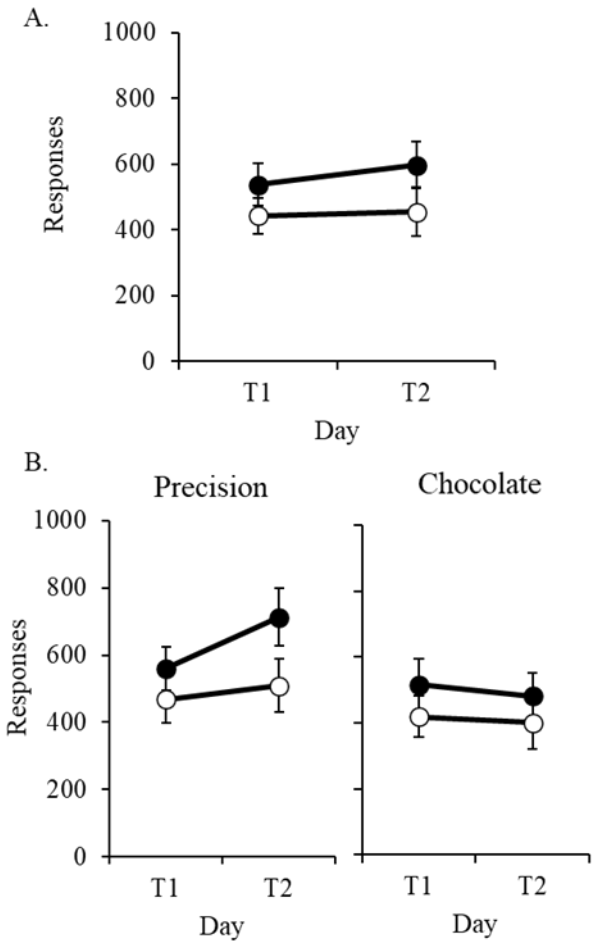

Figure 3.5. (A) Lever presses/session (mean ± SEM) made during training for the rats that received PL or Sham pretraining lesions over the course of two training days, collapsed across pellet type. (B) Lever presses/session (mean ± SEM) made during training for the rats that received PL or Sham pretraining lesions over the course of two training days for Precision (Left) or Chocolate (Right) pellet types. Black Circles represent rats that received PL lesions. White circles represent rats that received Sham lesions. T1 and T2 represent the first and second day of cued trial training for each pellet type (averaged across the first and second training day for each pellet in A and presented separately for each pellet on in B).

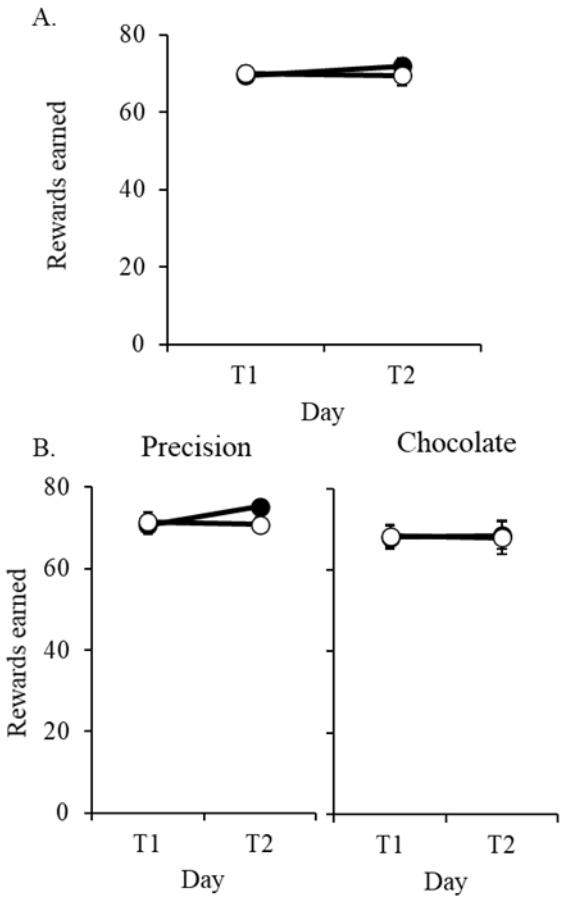

Figure 3.6. (A) Rewards Earned/session (mean ± SEM) made during training for the rats that received PL or Sham pretraining lesions over the course of two training days, collapsed across pellet type. (B) Rewards Earned/session (mean ± SEM) made during training for the rats that received PL or Sham pretraining lesions over the course of two training days for Precision (Left) or Chocolate (Right) pellet types. Black Circles represent rats that received PL lesions. White circles represent rats that received Sham lesions. T1 and T2 represent the first and second day of cued trial training for each pellet type (averaged across the first and second training day for each pellet in A and presented separately for each pellet on in B).

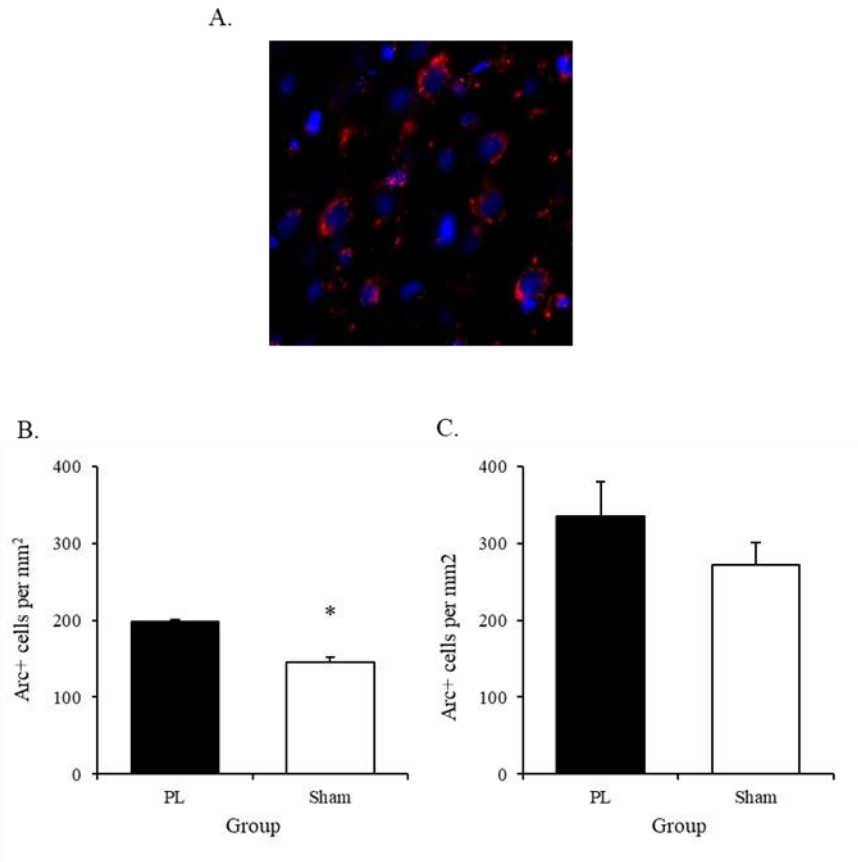

Figure 3.7. (A) Representative image of Arc+ neurons (in red) neuronal nuclei (in blue). (B) Arc+ cells per mm^2 in OFC. Black bars represent rats that received PL lesions. White bars represent rats that received Sham lesions. * = $p < 0.05$ (C) Arc+ cells per mm^2 in MD. Black bars represent rats that received PL lesions. White bars represent rats that received Sham lesions.

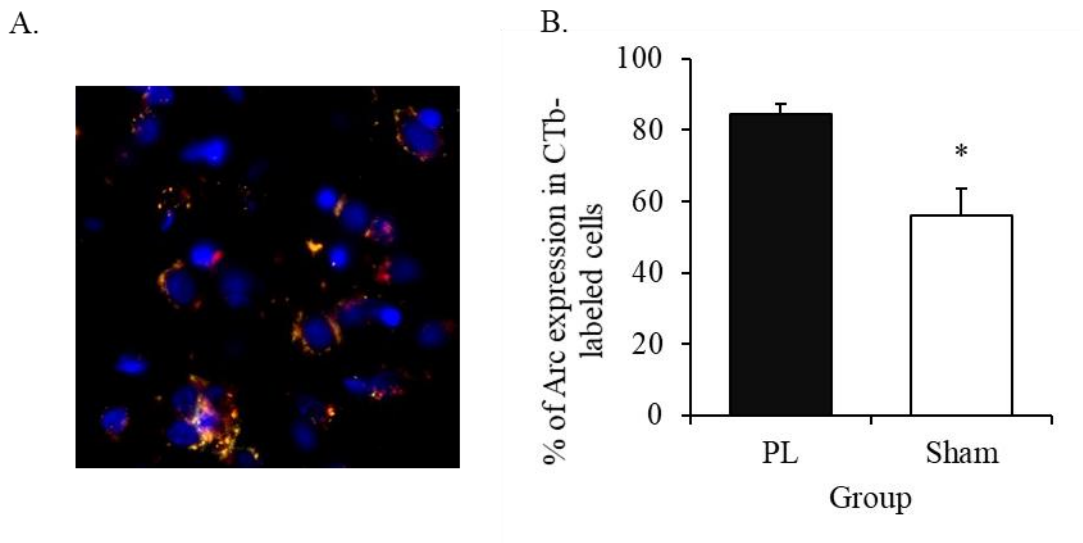

Figure 3.8. (A) Representative image of Arc+CTb+ neurons (in yellow), Arc+ neurons (in red), and neuronal nuclei (in blue). (B) Percentage of Arc+ neurons in CTb+ cells in MD. Black bars represent rats that received PL lesions. White bars represent rats that received Sham lesions. * = $p < 0.05$

Table 3.1. Results of multilevel Poisson regression for fixed effects and interactions for the training data (Lever Presses/session) in Experiment 1.

	b	*z*-value	*p*
Intercept	6.16	128.87	**<0.01**
PL	-0.09	-13.56	**<0.01**
OFC	0.09	16.14	**<0.01**
Pellet	-0.05	-2.21	**0.03**
Day	0.13	4.62	**<0.01**
PL*OFC	0.06	11.35	**<0.01**
PL*Pellet	0.02	3.84	**<0.01**
OFC*Pellet	0.009	1.71	0.09
PL*Day	-0.07	-10.07	**<0.01**
OFC*Day	-0.083	-12.30	**<0.01**
Pellet*Day	0.0005	0.13	0.90
PL*OFC*Pellet	0.002	0.36	0.73
PL*OFC*Day	-0.04	-6.21	**<0.01**
PL*Pellet*Day	0.01	2.76	**<0.01**
OFC*Pellet*Day	-0.003	-0.74	0.46
PL*OFC*Pellet*Day	-0.03	-7.81	**<0.01**

Note. Bold values represent significant effects ($p < 0.05$).

Table 3.2. Results of multilevel Poisson regression for fixed effects and interactions for the training data (Rewards Earned/session) in Experiment 1.

	b	*z*-value	*p*
Intercept	4.28	551.16	**<0.01**
PL	0.002	0.33	0.74
OFC	0.007	0.98	0.33
Pellet	-0.004	-0.54	0.59
Day	0.04	5.00	**<0.01**
PL*OFC	-0.004	-0.53	0.59
PL*Pellet	0.008	1.04	0.30
OFC*Pellet	-0.0005	-0.07	0.95
PL*Day	0.01	1.25	0.21
OFC*Day	-0.01	-1.25	0.21
Pellet*Day	-0.01	-1.16	0.25
PL*OFC*Pellet	-0.004	-0.48	0.63
PL*OFC*Day	-0.0003	-0.04	0.97
PL*Pellet*Day	-0.003	-0.37	0.71
OFC*Pellet*Day	-0.001	-0.13	0.90
PL*OFC*Pellet*Day	-0.01	-1.09	0.28

Note. Bold values represent significant effects ($p < 0.05$).

Table 3.3. Results of multilevel regression for fixed effects and interactions for the devaluation test data in Experiment 1.

	b	*z*-value	*p*
Intercept	2.27	25.02	**<0.01**
PL	-0.38	-11.97	**<0.01**
OFC	0.01	0.31	0.76
Lever	0.13	4.68	**<0.01**
Trial	-0.14	-4.49	**<0.01**
PL*OFC	0.10	3.35	**<0.01**
PL*Lever	-0.08	-3.91	**<0.01**
OFC*Lever	-0.05	-2.47	**0.01**
PL*Trial	-0.12	-7.73	**<0.01**
OFC*Trial	0.01	0.55	0.58
Lever*Trial	0.004	0.46	0.65
PL*OFC*Lever	-0.07	-3.54	**<0.01**
PL*OFC*Trial	0.03	2.21	**0.03**
PL*Lever*Trial	-0.004	-0.52	0.61
OFC*Lever*Trial	0.02	1.84	0.07
PL*OFC*Lever*Trial	-0.002	-0.23	0.82

Note. Bold values represent significant effects ($p < 0.05$).

Table 3.4. Results of multilevel regression for fixed effects and interactions for the consumption test data in Experiment 1.

	b	*t*-value	*p*
Intercept	2.40	17.21	**<0.01**
OFC	-0.05	-0.36	0.72
PL	-0.05	-0.38	0.71
Satiation	0.56	4.01	**<0.01**
OFC*PL	0.04	0.26	0.79
OFC*Satiation	-0.07	-0.49	0.63
PL*Satiation	-0.09	-0.68	0.50
OFC*PL*Satiation	-0.11	-0.81	0.42

Note. Bold values represent significant effects ($p < 0.05$).

Table 3.5. Results of multilevel Poisson regression for fixed effects and interactions for the training data (Lever Presses/session) for Experiment 2.

	b	*z*-value	*p*
Intercept	6.14	69.03	**<0.01**
PL	0.11	1.28	0.20
Pellet	-0.11	-3.09	**<0.01**
Day	0.03	0.71	0.48
PL*Pellet	-0.01	-0.40	0.69
PL*Day	0.04	0.91	0.36
Pellet*Day	-0.12	-10.91	**<0.01**
PL*Pellet*Day	-0.03	-2.53	**0.01**

Note. Bold values represent significant effects ($p < 0.05$).

Table 3.6. Results of multilevel Poisson regression for fixed effects and interactions for the training data (Rewards Earned/session) for Experiment 2.

	b	*z*-value	*p*
Intercept	4.25	199.74	**<0.01**
PL	0.006	0.30	0.76
Pellet	-0.03	-1.68	0.09
Day	0.01	0.42	0.68
PL*Pellet	-0.006	-0.34	0.73
PL*Day	0.02	0.69	0.49
Pellet*Day	-0.01	-0.42	0.67
PL*Pellet*Day	-0.01	-0.48	0.63

Note. Bold values represent significant effects ($p < 0.05$).

Chapter 4 - Discussion

In the current experiments, we showed that rats can exhibit normal goal-directed action in our multi-response/multi-reinforcer devaluation task with cued trials when either PL or OFC is functional but are impaired when both PL and OFC are damaged. We also showed that OFC neural activity increases and MD->OFC projecting neurons show increased activity during training when PL is lesioned. Below, we discuss how the effect of OFC+PL lesions on devaluation and the lack of effect of OFC or PL lesions on devaluation suggests our task can model neural compensation. We also discuss the increased neural activity in lateral OFC and MD during training and the role of MD in modulating neural compensation.

OFC+PL lesions impaired devaluation but OFC or PL lesions did not impair devaluation

We found evidence that OFC or PL lesions did not impair devaluation but double OFC+PL lesions did impair devaluation. The lack of effect of OFC or PL lesions suggests that OFC and PL are not individually necessary for learning the necessary associations for future goal-directed action or performance of goal-directed action in our devaluation task. However, in conjunction with the impairments found in the double lesion condition, the lack of OFC or PL lesion effect suggests at least one of these regions is necessary for training and/or performance in our devaluation task.

Our task is designed in such a way that it can be solved using an S-O strategy by paying attention to the unique cuelights above the levers, likely mediated by OFC, or an R-O strategy by paying attention to the spatial lever location, likely mediated by PL. Previously, we have shown that OFC or PL inactivation during training does not impair future devaluation in our task, despite rats preferring to use an R-O strategy (Fisher et al., 2020). As such, we suggested that the

pattern of data we found indicated that, while the R-O strategy was the default strategy learned, the cue-based strategy could be learned and used to express normal goal-directed action if PL was inactive. This is suggestive of overshadowing taking place between the spatial lever location and the cuelights.

Overshadowing refers to the process by which a conditioned stimulus (CS) (e.g., a tone) gains preferential conditioning over another, less salient CS (e.g., a light) when the two CSs are presented in compound. The result is that the more salient CS elicits a greater conditioned response than the less salient CS. Overshadowing can be explained in terms of attentional processes (Mackintosh, 1975; Pearce & Hall, 1980) or error correction leading well-predicted outcomes to be less effective unconditioned stimuli (Rescorla & Wagner, 1972). We propose that the spatial lever location is a more salient CS than the cuelights in our task, so the spatial lever location strategy overshadows the cuelights when both are presented simultaneously, despite either strategy being capable of developing outcome-specific associations. Thus, the S-O strategy is learned secondarily to the R-O strategy under normal conditions but the R-O strategy cannot be learned or overshadow the S-O strategy when PL is inactivated or lesioned. An inactive PL allows for the S-O strategy to be learned and guide behavior. We have preliminary data showing that, when PL is lesioned prior to training, devaluation (based on the spatial lever location) is intact when the cuelights and the lever-location predict the same outcome, which mirrors the pattern found in the PL group in Exp. 1. However, when the cuelights and lever-location predict different outcomes, PL lesioned rats devalue using the cuelight value instead of the lever-location (unpublished data; Figure 1). This pattern of data indicates that the S-O strategy was learned and used to guide goal-directed action when PL was inactive.

We hypothesize that the compensation, in which the normal overshadowing is not observed and the normally overshadowed cue now guides behavior, occurs during training. The data from our first experiment are unable to differentiate whether the training phase or performance phase is the phase in which competition/compensation is occurring between OFC and PL. Most models of associative learning tend to ascribe cue-competition to processes occurring either predominantly during acquisition or performance. For example, cue competition could affect what is learned during the acquisition phase, in which case behavior during performance could be simply a direct read-out of what was learned during the acquisition phase, with all complex processing due to cue competition limited to the learning phase. A learning model, such as the Rescorla-Wagner model (Rescorla & Wagner, 1972), posits that associative value, and therefore learning, is a finite resource such that every stimulus present competes for associative value. A learning model would say that the R-O strategy has a faster learning rate than the S-O strategy because it is more salient during training. Conversely, a performance model, such as the Comparator Hypothesis (Miller & Matzel, 1988), posits that the learning rate is constant across stimuli and behavior is determined at the time of performance. A performance model would say that the R-O and S-O strategies are learned equally well, but the R-O strategy out-competes the S-O strategy to guide behavior during test. Our results are unable to definitively differentiate which theoretical process (i.e., learning or performance process) is responsible for our results because OFC and PL were both lesioned during training and testing.

Previous literature supports our hypothesis that training is the important phase for compensation between OFC and PL primarily because PL seems to only be necessary for the acquisition phase of devaluation tasks. A pre- versus post-training lesion study (Ostlund & Balleine, 2005) and an inactivation study (Tran-Tu-Yen et al., 2009) found that PL is not

necessary for *performance* of free operant devaluation tasks where the strategy being learned is the R-O strategy but is necessary for *learning* R-O strategies (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Coutureau et al., 2009; Killcross & Coutureau, 2003; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009). Conversely, OFC is likely necessary for both acquisition and performance. Chemogenetic inactivation of OFC during training impairs devaluation when there is a shift in instrumental contingencies (i.e., the outcomes are switched such that the lever that previous earned Outcome A now earn Outcome B) (Parkes et al., 2018). Results of experiments with lesions or inactivations made before (Parkes et al., 2018; Pickens et al., 2003; West et al., 2011) or after selective satiety/taste aversion (Gardner et al., 2017; Pickens et al., 2005; West et al., 2011) show that OFC is necessary for devaluation performance. While OFC may be necessary for both acquisition and performance, PL's time-limited role in free-operant devaluation tasks makes it likely that compensation between OFC and PL primarily occurs during acquisition of the contingencies needed for future devaluation. One way to determine whether the regions are important for compensation during training and/or testing would be to inactivate OFC and PL during training or during testing using chemogenetics or an inactivating agent like a muscimol/baclofen cocktail. This design would differentiate whether the compensation between the regions primarily occurs during training and/or performance of the task.

Even if compensation is primarily occurring during the acquisition phase, the role of OFC in devaluation performance suggests that when overshadowing does not occur (like when PL is lesioned), OFC plays a bigger role in performance as well as acquisition. We have pilot data suggesting that this is the case. We gave three rats PL lesions and two rats Sham lesions prior to any training and 120 minutes after the second choice test, we perfused rats so that we could

quantify Fos expression. We found a trend towards higher Fos expression in OFC when rats had PL lesions, suggesting that OFC is more active during performance when PL is damaged prior to training (Figure 1B).

One other limitation of the data is that the OFC+PL condition has double the lesion volume, so one possibility is that impairments occurred not because OFC and PL are both necessary for the task but because there was more brain damage. The mass action principle suggests that the proportion of brain damage is directly proportional to the decreased ability of memory function (Lashley, 1950). In search of a memory engram, Lashley conducted maze experiments where rats received cortical lesions of varying size. Lashley found that location of the lesion did not affect performance but the amount of cortex lesioned affected the degree of impairment in maze performance (Lashley, 1950). He concluded that any neurons in any cortical region could support learning and memory (equipotentiality) and that many areas act together to support learning and memory (mass action principle). Studies have since shown that while many regions act in concert to support learning and memory, there is functional specificity among these regions. There are many types of memories like declarative, emotional, and habit memories that are specialized to rely on distinct brain regions and pathways like the hippocampus, amygdala, and striatum (Squire, 2004; White et al., 2013). These functional specializations of the brain refute Lashley's claims because each individual brain region is not equally likely to be involved in any given memory and therefore the same amount of damage can have differing effects depending on where that damage occurs.

Based on Lashley's data, we could possibly conclude that devaluation performance was only impaired in the double-lesion condition due to two brain regions being damaged instead of one as in the single-lesion condition. While our data cannot definitely say the devaluation

impairment observed in the double-lesion group was not simply due to more cortical damage, our training and consumption test data and understanding of OFC and PL function from previous literature makes this conclusion unlikely. Studies of OFC and PL function show that these regions support distinct behaviors. As mentioned previously, PL seems to support R-O associations (Balleine & Dickinson, 1998; Corbit & Balleine, 2003; Coutureau et al., 2009; Killcross & Coutureau, 2003; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009) while OFC seems to support S-O associations (Baxter et al., 2000; Gallagher et al., 1999; Izquierdo et al., 2004a; Lichtenberg et al., 2017; Panayi & Killcross, 2018; Pickens et al., 2005; Pickens et al., 2003; Rudebeck & Murray, 2011; West et al., 2011; West et al., 2013a). Similarly, in attentional set-shifting tasks, OFC is necessary for reversal learning while PL is not, and PL is necessary for extradimensional set-shifting while OFC is not (Birrell & Brown, 2000; Bissonette et al., 2013). These functional specializations that OFC and PL exhibit make it unlikely that our devaluation impairment was only due to more cortical damage.

The test data reveal a deficit in devaluation performance, but the OFC+PL group did decrease responding to the levers across trials suggesting that group does not show deficits in extinction learning. Decreases in responding to both levers could represent that the rats were exhibiting a *non*-selective satiety effect, in which rats were less hungry and were not able to guide their behavior through *selective* satiety since they did not have outcome specific associations. However, the consumption test data showed that all rats were able to devalue properly when the outcome was presented suggesting the rats can exhibit selective satiety during consumption. The decrease in consumption of the sated food in the consumption tests shows that the value of the reward is able to be updated once the food is tasted so there are not overt deficits selective satiety. Therefore, the OFC+PL group has the ability to devalue rewards and use that

ability to guide behavior when the outcomes are present (at least in consumption). In summary, our data suggest that the OFC+PL group do not show overt deficits in basic learning or deficits in selective-satiety guiding consumption when the outcomes are present, and the impairment is selective updating value representations. It is unlikely that the increased cortical damage in the OFC+PL group can alone explain the selective performance in the devaluation choice test.

Our devaluation task presumably uses a mixture of S-O and R-O responses and our results indicate that either strategy can be used to guide behavior depending on strategy saliency and whether the strategy neural correlate is available during the task. This does not invalidate other devaluation procedures where S-O (e.g., Pavlovian) or R-O (e.g., free-operant) strategies are used exclusively to guide behavior. Indeed, our interpretation of our data is based heavily on results of these simplified tasks showing a dissociation between tasks that are OFC or PL dependent. However, our findings and task may be more representative of how devaluation occurs in humans where cue-based and response-based strategies are often intermixed. Our task represents one possible way to model devaluation in complex environments while leveraging the control gained from use of animal models. Parkes et al. (2018), recently found that OFC was required for a free-operant devaluation task when the outcomes were switched after a period of pretraining. This task represents another way to model more complex environments when the same action may predict a different reward over time. Similarly, Gremel and Costa (2013) found that the same action, when presented in different contexts with different reinforcement schedules, required OFC. Therefore, our task represents one of a few new devaluation task variants that can model more complex environments that may in turn better model devaluation and the underlying neural substrates in humans.

One methodological consideration is the training data revealed that the OFC+PL lesioned group decreased responding for the chocolate pellet and maintained responding for the precision pellet across training while the other groups increased responding for both pellet types. While response rates diverged for the OFC+PL lesioned group, they earned as many rewards as the other three groups. Our rats were conditioned using a variable-interval schedule during cued-trial training. Rats could only earn a max of two pellets during a trial that were available (following a lever press) at randomized times. Thus, rats could, in theory, press only twice during the trial and earn just as many pellets as a rat that presses twenty times during the trial. While the OFC+PL group may have had lower motivation to respond (as evidenced by lower response rats) for the two pellet types than the other three groups, they still earned just as many rewards. Since the groups all receive the same number of rewards, the differences in lever press rates are likely negligible in terms of learning the light-lever association with the pellet type.

Neural activity in lateral OFC and MD during training

Analysis of the Arc+ neurons in OFC and MD found increased numbers of Arc+ neurons in OFC in PL lesioned rats and no differences between groups in MD during training. Broadly, these findings suggest that increased neural activity in OFC may represent increased learning of the S-O strategy to guide behavior in the absence of PL competition. In addition, the lack of effect in MD is likely due to different populations of neurons (MD->OFC versus MD->PL) being active when PL is lesioned or not.

We found more Arc+ neurons in lateral OFC when PL was lesioned during training. These data suggest that when PL is damaged, OFC becomes more active so that the S-O strategy is learned in order to guide behavior. However, due to the nature of the study we cannot say for certain that the increase in OFC activity would result in the S-O strategy being used to guide

behavior. Studies have found increased neural activity in OFC, measured by *in vivo* electrophysiology or functional magnetic resonance imaging, during acquisition go/no-go discrimination (Schoenbaum et al., 1998), go/no-go reversal learning (Schoenbaum et al., 2000), and sensory preconditioning (Sadacca et al., 2018; Wang et al., 2020), which related to better performance. In addition, we have data showing that when PL is lesioned, rats devalue based on the S-O strategy (unpublished data; Figure 1A), suggesting that if the current study had allowed for testing, we would have observed that PL lesioned rats used the S-O strategy to guide behavior. Future studies should use a chemogenetic manipulations, such as exciting OFC during training to determine whether rats devalue using the R-O or S-O strategy when OFC activity is increased during training.

We did not find a difference between the number of Arc+ neurons in MD in PL lesioned rats compared to Sham rats. MD has strong projections to OFC and PL (Alcaraz et al., 2016). Therefore, we did not expect to see an overall difference in Arc+ neurons. It is likely that in the Sham group, MD->PL neurons were more active whereas in the PL lesion group, MD->OFC neurons were more active. The lack of difference is most likely due to different populations being active in our different groups. MD->PL and MD->OFC projecting neurons are segregated in MD (Alcaraz et al., 2016) so it is likely that we would have seen differences in MD if we had subdivided MD when counting Arc+ neurons.

The increase in MD->PL or MD->OFC potentially depends on the driver input from the PL->MD and OFC->MD neurons. When PL is intact, there are likely stronger driver inputs to MD that are reflective of the greater saliency of the response options. These inputs compete with the OFC->MD input and the decrease in OFC activity is likely driven by less input from the MD->OFC modulating neurons. However, when PL is lesioned, the OFC->MD driver inputs are

stronger and therefore outcompete any remaining PL->MD driver inputs, which are severely diminished in the lesion condition (≥60% PL damage). PL activity then decreases as MD->PL activity is inhibited and the MD->OFC activity increases in order to increase OFC activity and maintain the thalamocortical/corticothalamic circuits. In a spatial working memory task and a two-alternative forced choice task, MD->PL activity during delays was necessary for intact performance (Bolkan et al., 2017; Schmitt et al., 2017). *In vivo* electrophysiology also found that individual neurons did not remain active during the entire delay period. Instead, there was sequential activation across the population of PL neurons that was dependent on MD activity, suggesting that PL activity alone is insufficient to maintain activity across the delay period (Bolkan et al., 2017; Schmitt et al., 2017). It is conceivable that the opposite would also occur (i.e., decreases in PL->MD driver activity decreased MD->PL activity). Future experiments should use circuit-specific manipulations to determine whether increasing MD->OFC and OFC->MD activity biases rats towards using the S-O strategy even when PL is intact.

The role of MD in modulating neural compensation

We found a higher ratio of Arc+CTb+ neurons in MD when PL is lesioned, revealing that MD->OFC projecting neurons are more active when PL is lesioned prior to training. This is indirect evidence for our overshadowing hypothesis that the S-O and R-O strategies compete for attentional resources. Based on our data, the R-O strategy is more salient as it is the preferred strategy used when the two strategies are pitted against each other (Fisher et al., 2020). Therefore, we predict that when PL is active, OFC receives less excitatory input from MD to reduce attentional competition between the two strategies, whereas when PL is inactive or damaged there is no competition so attentional resources are shifted to OFC so the S-O strategy can be learned. As such, our finding that MD->OFC neurons are more active when PL is

damaged provides indirect, but compelling evidence that when PL is damaged, MD directs attentional resources to OFC so that strategy is learned preferentially.

A previous study has found that increased MD->PL activity increased neural activity in PL during a two-alternative forced choice task (Schmitt et al., 2017). Interestingly, they found that only fast-spiking inhibitory neurons increased spiking, not excitatory neurons. Follow-up analysis found that the maintenance of excitatory spiking but increase in inhibitory spiking was due to increased local connectivity amongst excitatory neurons (i.e., greater coherence between excitatory neuron spiking). This increased connectivity/coherence was enhanced by MD input and disrupted by suppression of MD input during the task. These data are in line with the modulating role of thalamocortical neurons (Sherman & Guillery, 2013). Furthermore, these studies revealed that MD excitability recruits additional neurons to the task adding evidence that MD inputs to PL increase local connectivity (Schmitt et al., 2017). These results provide a framework for how MD may interact with OFC. We found increased neural activity in OFC but we have yet to investigated the type of neurons that are exhibiting increased activity. If MD and OFC interact in a task-dependent manner in the same way as MD and PL, then the increase in MD->OFC activity is predicted to increase inhibitory activity in OFC and increased coherence between excitatory neurons. One caveat is that the Schmitt et al. paper examines a task where PL does not compete with other brain regions, therefore it is possible that in our circumstance we would also observe increased excitatory neural activity along with increased inhibitory neural activity because when PL is intact, OFC would not exhibit as much excitatory activity. Future studies should determine what cell types in OFC are active with PL is lesioned, intact, and in a task where OFC outcompetes PL.

While we hypothesize that MD coordinates activity across PL and OFC, this process likely does not happen exclusively in MD. Anatomically, MD->PL and MD->OFC projecting neurons do not overlap, so it is unlikely that MD computes the saliency information and modulates MD->PL and MD->OFC as a result. One region that likely coordinates MD, PL, and OFC activity to enable optimal performance is the thalamic reticular nucleus (TRN). TRN is a thin nucleus of GABAergic neurons that surrounds the dorsal thalamus. It receives axon collaterals from corticothalamic and thalamocortical projections including OFC and PL (Zikopoulos & Barbas, 2006, 2012), but only projects to thalamic nuclei. TRN has well-characterized roles in the generation of sleep spindles, sensory gating, and top-down mediated sensory selection (Krol et al., 2018; Luthi, 2014; Pinault, 2004). Little is known about how TRN coordinates activity in associative higher-order nuclei, like MD, and their cortical targets. TRN is thought to be an attentional spotlight by coordinating activity across prefrontal cortex and thalamus to increase activity of relevant regions and decrease activity of irrelevant regions to increase signal-to-noise ratio (Crabtree, 2018; Krol et al., 2018; Zikopoulos & Barbas, 2006), as it does to modulate activity across different sensory modalities. For example, first-order sensory thalamic nuclei, meaning they receive the majority of their input from direct sensory connections (e.g., retinal projections), also modulated neural activity based on attentional demands. In these studies, a signal indicates whether mice should use an auditory or visual stimulus to guide their behavior. When recording in the lateral geniculate nucleus, a first-order visual thalamic nucleus, neural activity quantified by *in vivo* electrophysiology is increased when mice receive the signal to attend to the visual stimulus (Halassa et al., 2014; Nakajima et al., 2019; Wimmer et al., 2015). Importantly, manipulation of TRN using TRN-specific genetic knock-out of ErbB4

(Ahrens et al., 2015) or PTCHD1 (Wells et al., 2016) or activation of visual-projecting TRN (Wimmer et al., 2015), impairs the ability to attend to the reward-predictive cues.

Thus, one explanation for the current data is that TRN directs MD to enhance or suppress OFC or PL activity depending on cortical availability. If this were the case, it is possible that TRN is sensitive to the strength of incoming messages and inhibits weaker responses to enhance the signal-to-noise ratio of the stronger signal. Therefore, when PL is inactivated or damaged, TRN loses PL->MD driver input so the OFC signal is increased. However, research investigating the role of TRN modulating OFC, PL and MD to support flexible decision-making is lacking. One other alternative is that MD and/or TRN receive input from other regions that direct neural activity.

One possible region is the basolateral amygdala (BLA), although strong evidence for is lacking. Like MD, BLA is part of the salience network (Menon & Uddin, 2010; Peters et al., 2016; Seeley et al., 2007). BLA has connections to both MD and TRN (Zikopoulos & Barbas, 2012). In addition, BLA neurons form synapses closer to the cell body than OFC and MD synapses in TRN and there are more numerous large and efficient terminals from BLA->TRN than from OFC and MD (Zikopoulos & Barbas, 2012). Anatomically, this configuration would aid attentional shifts to salient events that occur in the environment. Functionally, BLA influences TRN to indirectly amplify cortical activity. In an auditory study, activating BLA->TRN increased tone-evoked response in the auditory thalamus and auditory cortex (Aizenberg et al., 2019). Notably, activating this pathway did not increase tone-related activity but instead it suppressed spontaneous activity, therefore increasing the signal-to-noise ratio. The lack of an increase in cortical activity suggests that BLA may not be responsible for our pattern of results where we observed increases in MD->OFC projecting neurons and increased activity

in OFC. While it is possible that BLA may have different effects for non-sensory nuclei, the increase in signal-to-noise ratio makes this an unlikely mechanism for the activation patterns observed in MD.

Our findings suggest an exciting new area of behavioral neuroscience in which compensation effects may be observed. Neural compensation between single regions has been documented in other behavioral tasks including fear conditioning, reversal learning, and spatial learning. In fear conditioning, lesions of the basolateral amygdala result in impaired fear conditioning acquisition with limited training but if the animal receives overtraining of the tone-shock pairings it can acquire a contextual fear response (Maren, 1999). Likewise, repeated training can lead to contextual fear memories being dependent on non-hippocampal structures (Lehmann et al., 2009). Finally dorsal hippocampus lesions do not affect context fear conditioning when made before training (Maren et al., 1997). In reversal learning, after methamphetamine exposure that results in partial dopamine loss in the striatum (Daberkow et al., 2008; Pastuzyn & Keefe, 2013), there were alteration in which brain regions showed correlations between reversal learning performance and *Arc* mRNA expression. Despite the brain-behavior correlations shifting to the nucleus accumbens shell, reversal learning performance was unaffected. Subsequent investigation showed that inhibiting *Arc* expression in the nucleus accumbens shell only impaired methamphetamine-exposed animals, showing that the brain region necessary for intact reversal learning shifted following methamphetamine exposure. In a spatial learning task, rats learn a T-maze using a place strategy (i.e., turning based on location relative to cues in the room) but after extensive training rats exhibit a response strategy (i.e., turning left/right regardless of relative location within the room). The place strategy is dependent on the hippocampus whereas the response strategy is dependent on the striatum. When the

striatum is inactivated after short or extensive training, the rats continue to use the place strategy but when the hippocampus is inactivated, rats do not show a preference for either strategy after short training (Packard & McGaugh, 1996). Our study is the first instance to show compensation occurring during a devaluation task. This leads to exciting hypotheses about how circuits interact with each other to promote cognition and how external insults to the system can alter these circuits.

Conclusions

Our results indicate that our multi-response/multi-reinforcer devaluation task with cued trials can successfully model neural compensation between OFC and PL. This indicates that observation of behavioral alterations in neuropsychiatric disorders or neural injury could be obscured by neural compensation and our task could be a way to detect subtle alterations of PL and/or OFC function. These results provide a strong basis for future research examining the mechanisms of how OFC and PL actively compensate for each other in our task. We also found indirect evidence for our overall hypothesis that MD regulates neural compensation and attentional activity based on the salience of the strategies available and cortical availability. Further, this suggests MD dynamically regulates attentional control of complex learning strategies between PFC brain regions. Together, these studies form the basis of a program of research validating a behavioral task that can be used to identify subtle shifts in behavioral strategies used to guide behavior following neural injury or other disorders. This research will elucidate basic mechanisms that underlie how circuits interact with each other to guide behavior and how the circuits alter as a compensatory response to neural dysfunction. Future studies should provide a causal link that MD modulates neural compensation and determine whether this

compensation may be occurring in disorders/models of disorders that affect function of PL, OFC, or both.

References

Ahrens, S., Jaramillo, S., Yu, K., Ghosh, S., Hwang, G. R., Paik, R., Lai, C., He, M., Huang, Z. J., & Li, B. (2015, Jan). ErbB4 regulation of a thalamic reticular nucleus circuit for sensory selection. *Nat Neurosci, 18*(1), 104-111. https://doi.org/10.1038/nn.3897

Aizenberg, M., Rolon-Martinez, S., Pham, T., Rao, W., Haas, J. S., & Geffen, M. N. (2019, Oct 29). Projection from the Amygdala to the Thalamic Reticular Nucleus Amplifies Cortical Sound Responses. *Cell Rep, 29*(5), 1396. https://doi.org/10.1016/j.celrep.2019.10.036

Alcaraz, F., Fresno, V., Marchand, A. R., Kremer, E. J., Coutureau, E., & Wolff, M. (2018, Feb 6). Thalamocortical and corticothalamic pathways differentially contribute to goal-directed behaviors in the rat. *Elife, 7*. https://doi.org/10.7554/eLife.32517 10.7554/eLife.32517.

Alcaraz, F., Marchand, A. R., Courtand, G., Coutureau, E., & Wolff, M. (2016, Aug). Parallel inputs from the mediodorsal thalamus to the prefrontal cortex in the rat. *Eur J Neurosci, 44*(3), 1972-1986. https://doi.org/10.1111/ejn.13316 10.1111/ejn.13316. Epub 2016 Jul 12.

Alvares, G. A., Balleine, B. W., Whittle, L., & Guastella, A. J. (2016, Dec). Reduced goal-directed action control in autism spectrum disorder. *Autism Res, 9*(12), 1285-1293. https://doi.org/10.1002/aur.1613

10.1002/aur.1613. Epub 2016 Mar 21.

Balleine, B. W., & Dickinson, A. (1998, Apr-May). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology, 37*(4-5), 407-419. https://www.ncbi.nlm.nih.gov/pubmed/9704982

Barbour, T., Murphy, E., Pruitt, P., Eickhoff, S. B., Keshavan, M. S., Rajan, U., Zajac-Benitez, C., & Diwadkar, V. A. (2010). Reduced intra-amygdala activity to positively valenced faces in adolescent schizophrenia offspring. *Schizophrenia Research, 123*(2-3), 126-136. https://doi.org/10.1016/j.schres.2010.07.023

Baxter, M. G., Parker, A., Lindner, C. C., Izquierdo, A. D., & Murray, E. A. (2000, Jun 1). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci, 20*(11), 4311-4319. https://www.ncbi.nlm.nih.gov/pubmed/10818166

Berk, M., Post, R., Ratheesh, A., Gliddon, E., Singh, A., Vieta, E., Carvalho, A. F., Ashton, M. M., Berk, L., Cotton, S. M., McGorry, P. D., Fernandes, B. S., Yatham, L. N., & Dodd, S. (2017). Staging in bipolar disorder: from theoretical framework to clinical utility. *World Psychiatry, 16*(3), 236-244. https://doi.org/10.1002/wps.20441

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *The Journal of Neuroscience, 20*(11), 4320-4324. https://www.ncbi.nlm.nih.gov/pubmed/10818167

Bissonette, G. B., Powell, E. M., & Roesch, M. R. (2013, Aug 1). Neural structures underlying set-shifting: roles of medial prefrontal cortex and anterior cingulate cortex. *Behav Brain Res, 250,* 91-101. https://doi.org/10.1016/j.bbr.2013.04.037

Bolkan, S. S., Stujenske, J. M., Parnaudeau, S., Spellman, T. J., Rauffenbart, C., Abbas, A. I., Harris, A. Z., Gordon, J. A., & Kellendonk, C. (2017, Jul). Thalamic projections sustain prefrontal activity during working memory maintenance. *Nat Neurosci, 20*(7), 987-996. https://doi.org/10.1038/nn.4568

10.1038/nn.4568. Epub 2017 May 3.

Cao, V. Y., Ye, Y., Mastwal, S., Ren, M., Coon, M., Liu, Q., Costa, R. M., & Wang, K. H. (2015, Jun 17). Motor Learning Consolidates Arc-Expressing Neuronal Ensembles in Secondary Motor Cortex. *Neuron, 86*(6), 1385-1392. https://doi.org/10.1016/j.neuron.2015.05.022

Chan, R. C. K., Cui, H. R., Chu, M. Y., Zhang, T. H., Wang, Y., Wang, Y., Li, Z., Lui, S. S. Y., Wang, J. J., & Cheung, E. F. C. (2018, Feb). Neurological soft signs precede the onset of schizophrenia: a study of individuals with schizotypy, ultra-high-risk individuals, and

first-onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci, 268*(1), 49-56. https://doi.org/10.1007/s00406-017-0828-4
10.1007/s00406-017-0828-4. Epub 2017 Jul 31.

Chung, Y., & Cannon, T. D. (2015, May). Brain imaging during the transition from psychosis prodrome to schizophrenia. *J Nerv Ment Dis, 203*(5), 336-341. https://doi.org/10.1097/NMD.0000000000000286
10.1097/NMD.0000000000000286.

Conroy, S., Francis, M., & Hulvershorn, L. A. (2018, Mar). Identifying and treating the prodromal phases of bipolar disorder and schizophrenia. *Curr Treat Options Psychiatry, 5*(1), 113-128. https://doi.org/10.1007/s40501-018-0138-0
10.1007/s40501-018-0138-0. Epub 2018 Jan 22.

Corbit, L. H., & Balleine, B. W. (2003). The role of prelimbic cortex in instrumental conditioning. *Behavioural Brain Research, 146*(1-2), 145157. https://doi.org/10.1016/j.bbr.2003.09.023

Corbit, L. H., Muir, J. L., & Balleine, B. W. (2003). Lesions of mediodorsal thalamus and anterior thalamic nuclei produce dissociable effects on instrumental conditioning in rats. *European Journal of Neuroscience, 18*(5), 1286-1294. https://doi.org/10.1046/j.1460-9568.2003.02833.x

Coutureau, E., Marchand, A. R., & Di Scala, G. (2009, Apr). Goal-directed responding is sensitive to lesions to the prelimbic cortex or basolateral nucleus of the amygdala but not to their disconnection. *Behav Neurosci, 123*(2), 443-448. https://doi.org/10.1037/a0014818 10.1037/a0014818.

Crabtree, J. W. (2018). Functional Diversity of Thalamic Reticular Subnetworks. *Front Syst Neurosci*, *12*, 41. https://doi.org/10.3389/fnsys.2018.00041 10.3389/fnsys.2018.00041. eCollection 2018.

Daberkow, D. P., Riedy, M. D., Kesner, R. P., & Keefe, K. A. (2008). effect of methamphetamine neurotoxicity on learning-induced arc mRNA expression in identified striatal efferent neurons. *Neurotoxicity Research, 14*(4), 307-315. https://doi.org/10.1007/bf03033855

Ersche, K. D., Gillan, C. M., Jones, P. S., Williams, G. B., Ward, L. H., Luijten, M., de Wit, S., Sahakian, B. J., Bullmore, E. T., & Robbins, T. W. (2016, Jun 17). Carrots and sticks fail to change behavior in cocaine addiction. *Science, 352*(6292), 1468-1471. https://doi.org/10.1126/science.aaf3700 10.1126/science.aaf3700.

Fisher, H., Bright, N., Gallo, M., Pajser, A., & Pickens, C. L. (2017, Oct). Relationship of low doses of alcohol voluntarily consumed during adolescence and early adulthood with

subsequent behavioral flexibility. *Behavioural Pharmacology, 28*(7), 531-544. https://doi.org/10.1097/FBP.0000000000000331

10.1097/FBP.0000000000000331.

Fisher, H., Pajser, A., & Pickens, C. L. (2020, Jan 27). Pre-training inactivation of basolateral amygdala and mediodorsal thalamus, but not orbitofrontal cortex or prelimbic cortex, impairs devaluation in a multiple-response/multiple-reinforcer cued operant task. *Behav Brain Res, 378*, 112159. https://doi.org/10.1016/j.bbr.2019.112159

10.1016/j.bbr.2019.112159. Epub 2019 Oct 9.

Fiuzat, E. C., Rhodes, S. E., & Murray, E. A. (2017, Mar 1). The Role of Orbitofrontal-Amygdala Interactions in Updating Action-Outcome Valuations in Macaques. *J Neurosci, 37*(9), 2463-2470. https://doi.org/10.1523/JNEUROSCI.1839-16.2017

10.1523/JNEUROSCI.1839-16.2017. Epub 2017 Feb 1.

Gallagher, M., McMahan, R. W., & Schoenbaum, G. (1999, Aug 1). Orbitofrontal cortex and representation of incentive value in associative learning. *J Neurosci, 19*(15), 6610-6614. https://www.ncbi.nlm.nih.gov/pubmed/10414988

Gallo, F. T., Katche, C., Morici, J. F., Medina, J. H., & Weisstaub, N. V. (2018). Immediate Early Genes, Memory and Psychiatric Disorders: Focus on c-Fos, Egr1 and Arc. *Front Behav Neurosci, 12*, 79. https://doi.org/10.3389/fnbeh.2018.00079

Gardner, M. P. H., Conroy, J. S., Shaham, M. H., Styer, C. V., & Schoenbaum, G. (2017, Dec 6). Lateral Orbitofrontal Inactivation Dissociates Devaluation-Sensitive Behavior and Economic Choice. *Neuron, 96*(5), 1192-1203 e1194. https://doi.org/10.1016/j.neuron.2017.10.026

Geurts, H. M., & de Wit, S. (2014, May). Goal-directed action control in children with autism spectrum disorders. *Autism, 18*(4), 409-418. https://doi.org/10.1177/1362361313477919 10.1177/1362361313477919. Epub 2013 Sep 26.

Gillan, C. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Voon, V., Apergis-Schoute, A. M., Fineberg, N. A., Sahakian, B. J., & Robbins, T. W. (2014, Apr 15). Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry, 75*(8), 631-638. https://doi.org/10.1016/j.biopsych.2013.02.002 10.1016/j.biopsych.2013.02.002. Epub 2013 Mar 16.

Gillan, C. M., Papmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., & de Wit, S. (2011, Jul). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry, 168*(7), 718-726. https://doi.org/10.1176/appi.ajp.2011.10071062

Gillan, C. M., & Robbins, T. W. (2014, Nov 5). Goal-directed learning and obsessive-compulsive disorder. *Philos Trans R Soc Lond B Biol Sci, 369*(1655). https://doi.org/10.1098/rstb.2013.0475

10.1098/rstb.2013.0475.

Gremel, C. M., & Costa, R. M. (2013). Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. *Nature Communications*, *4*, 2264. https://doi.org/10.1038/ncomms3264

Griffiths, K. R., Morris, R. W., & Balleine, B. W. (2014). Translational studies of goal-directed action as a framework for classifying deficits across psychiatric disorders. *Front Syst Neurosci*, *8*, 101. https://doi.org/10.3389/fnsys.2014.00101 10.3389/fnsys.2014.00101. eCollection 2014.

Groenewegen, H. J. (1988, Feb). Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. *Neuroscience*, *24*(2), 379-431. https://doi.org/10.1016/0306-4522(88)90339-9 10.1016/0306-4522(88)90339-9.

Hafeman, D. M., Merranko, J., Axelson, D., Goldstein, B. I., Goldstein, T., Monk, K., Hickey, M. B., Sakolsky, D., Diler, R., Iyengar, S., Brent, D., Kupfer, D., & Birmaher, B. (2016). Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths. *American Journal of Psychiatry*, *173*(7), 695-704. https://doi.org/10.1176/appi.ajp.2015.15040414

Halassa, M. M., Chen, Z., Wimmer, R. D., Brunetti, P. M., Zhao, S., Zikopoulos, B., Wang, F., Brown, E. N., & Wilson, M. A. (2014, Aug 14). State-dependent architecture of thalamic reticular subnetworks. *Cell, 158*(4), 808-821. https://doi.org/10.1016/j.cell.2014.06.025 10.1016/j.cell.2014.06.025.

Hogarth, L., Lam-Cassettari, C., Pacitti, H., Currah, T., Mahlberg, J., Hartley, L., & Moustafa, A. (2018, May 22). Intact goal-directed control in treatment-seeking drug users indexed by outcome-devaluation and Pavlovian to instrumental transfer: critique of habit theory. *Eur J Neurosci*. https://doi.org/10.1111/ejn.13961 10.1111/ejn.13961.

Izquierdo, A. (2017, Nov 1). Functional Heterogeneity within Rat Orbitofrontal Cortex in Reward Learning and Decision Making. *J Neurosci, 37*(44), 10529-10540. https://doi.org/10.1523/JNEUROSCI.1678-17.2017 10.1523/JNEUROSCI.1678-17.2017.

Izquierdo, A., Brigman, J. L., Radke, A. K., Rudebeck, P. H., & Holmes, A. (2016). The neural basis of reversal learning: An updated perspective. *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2016.03.021

Izquierdo, A., Suda, R. K., & Murray, E. A. (2004a, Aug 25). Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward

contingency. *J Neurosci, 24*(34), 7540-7548. https://doi.org/10.1523/JNEUROSCI.1921-04.2004

Izquierdo, A., Suda, R. K., & Murray, E. A. (2004b, Aug 25). Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. *Journal of Neuroscience, 24*(34), 7540-7548. https://doi.org/10.1523/Jneurosci.1921-04.2004

Jakkamsetti, V., Tsai, N. P., Gross, C., Molinaro, G., Collins, K. A., Nicoletti, F., Wang, K. H., Osten, P., Bassell, G. J., Gibson, J. R., & Huber, K. M. (2013, Oct 2). Experience-induced Arc/Arg3.1 primes CA1 pyramidal neurons for metabotropic glutamate receptor-dependent long-term synaptic depression. *Neuron, 80*(1), 72-79. https://doi.org/10.1016/j.neuron.2013.07.020

Keshavan, M. S., Delisi, L. E., & Seidman, L. J. (2011). Early and broadly defined psychosis risk mental states. *Schizophrenia Research, 126*(1-3), 1-10. https://doi.org/10.1016/j.schres.2010.10.006

Keshavan, M. S., Diwadkar, V. A., Montrose, D. M., Rajarethinam, R., & Sweeney, J. A. (2005). Premorbid indicators and risk for schizophrenia: A selective review and update. *Schizophrenia Research, 79*(1), 45-57. https://doi.org/10.1016/j.schres.2005.07.004

Keshavan, M. S., Diwadkar, V. A., Spencer, S. M., Harenski, K. A., Luna, B., & Sweeney, J. A. (2002). A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 26*(6), 1143-1149. https://doi.org/10.1016/s0278-5846(02)00249-x

Killcross, S., & Coutureau, E. (2003). Coordination of actions and habits in the medial prefrontal cortex of rats. *Cerebral cortex (New York, N.Y. : 1991), 13*(4), 400-408. https://www.ncbi.nlm.nih.gov/pubmed/12631569

Krol, A., Wimmer, R. D., Halassa, M. M., & Feng, G. (2018, Apr 18). Thalamic Reticular Dysfunction as a Circuit Endophenotype in Neurodevelopmental Disorders. *Neuron, 98*(2), 282-295. https://doi.org/10.1016/j.neuron.2018.03.021 10.1016/j.neuron.2018.03.021.

Kuha, J. (2004, 2004/11/01). AIC and BIC: Comparisons of Assumptions and Performance. *Sociological Methods & Research, 33*(2), 188-229. https://doi.org/10.1177/0049124103262065

Lashley, K. S. (1950). In search of the engram. In *Physiological mechanisms in animal behavior. (Society's Symposium IV.).* (pp. 454-482). Academic Press.

Lehmann, H., Sparks, F. T., Spanswick, S. C., Hadikin, C., McDonald, R. J., & Sutherland, R. J. (2009, Jul). Making context memories independent of the hippocampus. *Learn Mem, 16*(7), 417-420. https://doi.org/10.1101/lm.1385409

Lichtenberg, N. T., Pennington, Z. T., Holley, S. M., Greenfield, V. Y., Cepeda, C., Levine, M. S., & Wassum, K. M. (2017, Aug 30). Basolateral Amygdala to Orbitofrontal Cortex Projections Enable Cue-Triggered Reward Expectations. *J Neurosci, 37*(35), 8374-8384. https://doi.org/10.1523/JNEUROSCI.0486-17.2017
10.1523/JNEUROSCI.0486-17.2017. Epub 2017 Jul 25.

Lonergan, M. E., Gafford, G. M., Jarome, T. J., & Helmstetter, F. J. (2010). Time-dependent expression of Arc and zif268 after acquisition of fear conditioning. *Neural Plast, 2010*, 139891. https://doi.org/10.1155/2010/139891

Luijten, M., Gillan, C. M., De Wit, S., Franken, I. H. A., Robbins, T. W., & Ersche, K. D. (2019, Feb 15). Goal-Directed and Habitual Control in Smokers. *Nicotine Tob Res*. https://doi.org/10.1093/ntr/ntz001
10.1093/ntr/ntz001.

Luthi, A. (2014, Jun). Sleep Spindles: Where They Come From, What They Do. *Neuroscientist, 20*(3), 243-256. https://doi.org/10.1177/1073858413500854

Mackintosh, N. J. (1975). *A theory of attention: Variations in the associability of stimuli with reinforcement* [doi:10.1037/h0076778]. American Psychological Association.

Marchant, N. J., Campbell, E. J., Whitaker, L. R., Harvey, B. K., Kaganovsky, K., Adhikary, S., Hope, B. T., Heins, R. C., Prisinzano, T. E., Vardy, E., Bonci, A., Bossert, J. M., & Shaham, Y. (2016, Mar 16). Role of Ventral Subiculum in Context-Induced Relapse to Alcohol Seeking after Punishment-Imposed Abstinence. *J Neurosci, 36*(11), 3281-3294. https://doi.org/10.1523/JNEUROSCI.4299-15.2016

10.1523/JNEUROSCI.4299-15.2016.

Marchant, N. J., Furlong, T. M., & McNally, G. P. (2010). Medial Dorsal Hypothalamus Mediates the Inhibition of Reward Seeking after Extinction. *The Journal of Neuroscience, 30*(42), 14102-14115. https://doi.org/10.1523/jneurosci.4079-10.2010

Maren, S. (1999, Oct 1). Neurotoxic basolateral amygdala lesions impair learning and memory but not the performance of conditional fear in rats. *J Neurosci, 19*(19), 8696-8703. https://www.ncbi.nlm.nih.gov/pubmed/10493770

Maren, S., Aharonov, G., & Fanselow, M. S. (1997, Nov). Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav Brain Res, 88*(2), 261-274. https://doi.org/10.1016/s0166-4328(97)00088-0

Martinez, M. C., Alen, N., Ballarini, F., Moncada, D., & Viola, H. (2012, Sep). Memory traces compete under regimes of limited Arc protein synthesis: implications for memory interference. *Neurobiol Learn Mem, 98*(2), 165-173. https://doi.org/10.1016/j.nlm.2012.05.007

McReynolds, J. R., Holloway-Erickson, C. M., Parmar, T. U., & McIntyre, C. K. (2014, Jul). Corticosterone-induced enhancement of memory and synaptic Arc protein in the medial prefrontal cortex. *Neurobiol Learn Mem, 112*, 148-157. https://doi.org/10.1016/j.nlm.2014.02.007

Menon, V., & Uddin, L. Q. (2010, Jun). Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct, 214*(5-6), 655-667. https://doi.org/10.1007/s00429-010-0262-0
10.1007/s00429-010-0262-0. Epub 2010 May 29.

Miller, R. R., & Matzel, L. D. (1988). The Comparator Hypothesis: A Response Rule for The Expression of Associations. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 22, pp. 51-92). Academic Press. https://doi.org/https://doi.org/10.1016/S0079-7421(08)60038-9

Minatohara, K., Akiyoshi, M., & Okuno, H. (2015). Role of Immediate-Early Genes in Synaptic Plasticity and Neuronal Ensembles Underlying the Memory Trace. *Front Mol Neurosci, 8*, 78. https://doi.org/10.3389/fnmol.2015.00078

Miranda, M., Kent, B. A., Morici, J. F., Gallo, F., Weisstaub, N. V., Saksida, L. M., Bussey, T. J., & Bekinschtein, P. (2017, Sep-Oct). Molecular Mechanisms in Perirhinal Cortex Selectively Necessary for Discrimination of Overlapping Memories, but Independent of Memory Persistence. *eNeuro, 4*(5). https://doi.org/10.1523/ENEURO.0293-17.2017

Mitchell, A. S., Browning, P. G. F., & Baxter, M. G. (2007). Neurotoxic Lesions of the Medial Mediodorsal Nucleus of the Thalamus Disrupt Reinforcer Devaluation Effects in Rhesus Monkeys. *The Journal of Neuroscience, 27*(42), 11289-11295. https://doi.org/10.1523/JNEUROSCI.1914-07.2007

Morey, R. A., Inan, S., Mitchell, T. V., Perkins, D. O., Lieberman, J. A., & Belger, A. (2005). Imaging Frontostriatal Function in Ultra-High-Risk, Early, and Chronic Schizophrenia During Executive Processing. *Archives of General Psychiatry, 62*(3), 254. https://doi.org/10.1001/archpsyc.62.3.254

Morris, R. W., Cyrzon, C., Green, M. J., Le Pelley, M. E., & Balleine, B. W. (2018, Mar 3). Impairments in action-outcome learning in schizophrenia. *Transl Psychiatry, 8*(1), 54. https://doi.org/10.1038/s41398-018-0103-0

10.1038/s41398-018-0103-0.

Morris, R. W., Quail, S., Griffiths, K. R., Green, M. J., & Balleine, B. W. (2015). Corticostriatal control of goal-directed action is impaired in schizophrenia. *Biological Psychiatry, 77*(2), 187-195. https://doi.org/10.1016/j.biopsych.2014.06.005

Nakajima, M., Schmitt, L. I., & Halassa, M. M. (2019, Aug 7). Prefrontal Cortex Regulates Sensory Filtering through a Basal Ganglia-to-Thalamus Pathway. *Neuron, 103*(3), 445-+. https://doi.org/10.1016/j.neuron.2019.05.026

Ostlund, S. B., & Balleine, B. W. (2005). Lesions of medial prefrontal cortex disrupt the acquisition but not the expression of goal-directed learning. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 25*(34), 7763-7770. https://doi.org/10.1523/JNEUROSCI.1921-05.2005

Ostlund, S. B., & Balleine, B. W. (2007). Orbitofrontal cortex mediates outcome encoding in pavlovian but not instrumental conditioning. *The Journal of Neuroscience, 27*(18), 4819-4825. https://doi.org/10.1523/JNEUROSCI.5443-06.2007

Packard, M. G. (1999, Oct 26). Glutamate infused posttraining into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proc Natl Acad Sci U S A, 96*(22), 12881-12886. https://doi.org/10.1073/pnas.96.22.12881

Packard, M. G., & McGaugh, J. L. (1996, Jan). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol Learn Mem, 65*(1), 65-72. https://doi.org/10.1006/nlme.1996.0007

Panayi, M. C., & Killcross, S. (2018, Jul 25). Functional heterogeneity within the rodent lateral orbitofrontal cortex dissociates outcome devaluation and reversal learning deficits. *Elife, 7*. https://doi.org/10.7554/eLife.37357

10.7554/eLife.37357.

Park, S., Park, J. M., Kim, S., Kim, J. A., Shepherd, J. D., Smith-Hicks, C. L., Chowdhury, S., Kaufmann, W., Kuhl, D., Ryazanov, A. G., Huganir, R. L., Linden, D. J., & Worley, P. F. (2008, Jul 10). Elongation factor 2 and fragile X mental retardation protein control the dynamic translation of Arc/Arg3.1 essential for mGluR-LTD. *Neuron, 59*(1), 70-83. https://doi.org/10.1016/j.neuron.2008.05.023

Parkes, S. L., Ravassard, P. M., Cerpa, J. C., Wolff, M., Ferreira, G., & Coutureau, E. (2018, Jul 1). Insular and Ventrolateral Orbitofrontal Cortices Differentially Contribute to Goal-Directed Behavior in Rodents. *Cereb Cortex, 28*(7), 2313-2325. https://doi.org/10.1093/cercor/bhx132

10.1093/cercor/bhx132.

Parnaudeau, S., Bolkan, S. S., & Kellendonk, C. (2018, Apr 15). The Mediodorsal Thalamus: An Essential Partner of the Prefrontal Cortex for Cognition. *Biol Psychiatry, 83*(8), 648-656. https://doi.org/10.1016/j.biopsych.2017.11.008

Parnaudeau, S., Taylor, K., Bolkan, S. S., Ward, R. D., Balsam, P. D., & Kellendonk, C. (2015, Mar 1). Mediodorsal thalamus hypofunction impairs flexible goal-directed behavior. *Biol Psychiatry, 77*(5), 445-453. https://doi.org/10.1016/j.biopsych.2014.03.020 10.1016/j.biopsych.2014.03.020. Epub 2014 Mar 26.

Pastuzyn, E. D., & Keefe, K. A. (2013). Changes in neural circuitry regulating response-reversal learning and arc-mediated consolidation of learning in rats with methamphetamine-induced partial monoamine loss. *Neuropsychopharmacology, 39*(4), 963-972. https://doi.org/10.1038/npp.2013.296

Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review, 87*(6), 532. https://doi.org/10.1037/0033-295X.87.6.532

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. *Front Syst Neurosci, 10,* 104. https://doi.org/10.3389/fnsys.2016.00104 10.3389/fnsys.2016.00104. eCollection 2016.

Pickens, C. L. (2008). A limited role for mediodorsal thalamus in devaluation tasks. *Behavioral Neuroscience, 122*(3), 659-676. https://doi.org/10.1037/0735-7044.122.3.659

Pickens, C. L., Aurand, L., Hunt, J., & Fisher, H. (2017). Subchronic anesthetic ketamine injections in rats impair choice reversal learning, but have no effect on reinforcer devaluation. *Behavioural Pharmacology, 28*(4), 294. https://doi.org/10.1097/FBP.0000000000000289

Pickens, C. L., Saddoris, M. P., Gallagher, M., & Holland, P. C. (2005, Feb). Orbitofrontal lesions impair use of cue-outcome associations in a devaluation task. *Behav Neurosci, 119*(1), 317-322. https://doi.org/10.1037/0735-7044.119.1.317

Pickens, C. L., Saddoris, M. P., Setlow, B., Gallagher, M., Holland, P. C., & Schoenbaum, G. (2003, Dec 3). Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. *J Neurosci, 23*(35), 11078-11084. http://www.ncbi.nlm.nih.gov/pubmed/14657165

Pinault, D. (2004, Aug). The thalamic reticular nucleus: structure, function and concept. *Brain Res Brain Res Rev, 46*(1), 1-31. https://doi.org/10.1016/j.brainresrev.2004.04.008 10.1016/j.brainresrev.2004.04.008.

Plath, N., Ohana, O., Dammermann, B., Errington, M. L., Schmitz, D., Gross, C., Mao, X., Engelsberg, A., Mahlke, C., Welzl, H., Kobalz, U., Stawrakakis, A., Fernandez, E.,

Waltereit, R., Bick-Sander, A., Therstappen, E., Cooke, S. F., Blanquet, V., Wurst, W., Salmen, B., Bosl, M. R., Lipp, H. P., Grant, S. G., Bliss, T. V., Wolfer, D. P., & Kuhl, D. (2006, Nov 9). Arc/Arg3.1 is essential for the consolidation of synaptic plasticity and memories. *Neuron, 52*(3), 437-444. https://doi.org/10.1016/j.neuron.2006.08.024

Rescorla, R. A., & Wagner, A. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In (Vol. Vol. 2).

Rhodes, S. E. V., & Murray, E. A. (2013). Differential effects of amygdala, orbital prefrontal cortex, and prelimbic cortex lesions on goal-directed behavior in rhesus macaques. *The Journal of Neuroscience, 33*(8), 3380-3389. https://doi.org/10.1523/JNEUROSCI.4374-12.2013

Rikhye, R. V., Gilra, A., & Halassa, M. M. (2018, Dec). Thalamic regulation of switching between cortical representations enables cognitive flexibility. *Nat Neurosci, 21*(12), 1753-1763. https://doi.org/10.1038/s41593-018-0269-z
10.1038/s41593-018-0269-z. Epub 2018 Nov 19.

Rikhye, R. V., Wimmer, R. D., & Halassa, M. M. (2018, Jul 8). Toward an Integrative Theory of Thalamic Function. *Annu Rev Neurosci, 41*, 163-183. https://doi.org/10.1146/annurev-neuro-080317-062144
10.1146/annurev-neuro-080317-062144. Epub 2018 Apr 4.

Rudebeck, P. H., & Murray, E. A. (2011, Jul 20). Dissociable effects of subtotal lesions within the macaque orbital prefrontal cortex on reward-guided behavior. *J Neurosci, 31*(29), 10569-10578. https://doi.org/10.1523/JNEUROSCI.0091-11.2011 10.1523/JNEUROSCI.0091-11.2011.

Sadacca, B. F., Wied, H. M., Lopatina, N., Saini, G. K., Nemirovsky, D., & Schoenbaum, G. (2018, Mar 7). Orbitofrontal neurons signal sensory associations underlying model-based inference in a sensory preconditioning task. *Elife, 7*. https://doi.org/10.7554/eLife.30373

Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M. M. (2017, May 11). Thalamic amplification of cortical connectivity sustains attentional control. *Nature, 545*(7653), 219-223. https://doi.org/10.1038/nature22073 10.1038/nature22073. Epub 2017 May 3.

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (1998, Jun). Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nat Neurosci, 1*(2), 155-159. https://doi.org/10.1038/407

Schoenbaum, G., Chiba, A. A., & Gallagher, M. (2000, Jul 1). Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. *J Neurosci, 20*(13), 5179-5189. https://www.ncbi.nlm.nih.gov/pubmed/10864975

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007, Feb 28). Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci, 27*(9), 2349-2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007 10.1523/JNEUROSCI.5587-06.2007.

Shepherd, J. D., & Bear, M. F. (2011). New views of Arc, a master regulator of synaptic plasticity. *Nature Neuroscience, 14*(3), 279. https://doi.org/10.1038/nn.2708

Shepherd, J. D., Rumbaugh, G., Wu, J., Chowdhury, S., Plath, N., Kuhl, D., Huganir, R. L., & Worley, P. F. (2006, Nov 9). Arc/Arg3.1 mediates homeostatic synaptic scaling of AMPA receptors. *Neuron, 52*(3), 475-484. https://doi.org/10.1016/j.neuron.2006.08.034

Sherman, S. M., & Guillery, R. W. (2013). *Functional connections of cortical areas: A new view from the thalamus*. MIT Press.

Sjoerds, Z., de Wit, S., van den Brink, W., Robbins, T. W., Beekman, A. T., Penninx, B. W., & Veltman, D. J. (2013, Dec 17). Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients. *Transl Psychiatry, 3*, e337. https://doi.org/10.1038/tp.2013.107 10.1038/tp.2013.107.

Squire, L. R. (2004, Nov). Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem, 82*(3), 171-177. https://doi.org/10.1016/j.nlm.2004.06.005

Steward, O., Wallace, C. S., Lyford, G. L., & Worley, P. F. (1998, Oct). Synaptic activation causes the mRNA for the IEG Arc to localize selectively near activated postsynaptic sites on dendrites. *Neuron, 21*(4), 741-751. https://doi.org/10.1016/s0896-6273(00)80591-7

Steward, O., & Worley, P. F. (2001, Apr). Selective targeting of newly synthesized Arc mRNA to active synapses requires NMDA receptor activation. *Neuron, 30*(1), 227-240. https://doi.org/10.1016/s0896-6273(01)00275-6

Tran-Tu-Yen, D. A., Marchand, A. R., Pape, J.-R. R., Di Scala, G., & Coutureau, E. (2009). Transient role of the rat prelimbic cortex in goal-directed behaviour. *The European Journal of Neuroscience, 30*(3), 464-471. https://doi.org/10.1111/j.1460-9568.2009.06834.x

Waltz, J. A., Brown, J. K., Gold, J. M., Ross, T. J., Salmeron, B. J., & Stein, E. A. (2015, Sep). Probing the Dynamic Updating of Value in Schizophrenia Using a Sensory-Specific Satiety Paradigm. *Schizophr Bull, 41*(5), 1115-1122. https://doi.org/10.1093/schbul/sbv034

10.1093/schbul/sbv034. Epub 2015 Apr 1.

Wang, F., Schoenbaum, G., & Kahnt, T. (2020, Jan). Interactions between human orbitofrontal cortex and hippocampus support model-based inference. *PLoS Biol, 18*(1), e3000578. https://doi.org/10.1371/journal.pbio.3000578

Wang, H., Ardiles, A. O., Yang, S., Tran, T., Posada-Duque, R., Valdivia, G., Baek, M., Chuang, Y. A., Palacios, A. G., Gallagher, M., Worley, P., & Kirkwood, A. (2016, Feb 3). Metabotropic Glutamate Receptors Induce a Form of LTP Controlled by Translation and Arc Signaling in the Hippocampus. *J Neurosci, 36*(5), 1723-1729. https://doi.org/10.1523/JNEUROSCI.0878-15.2016

Waung, M. W., Pfeiffer, B. E., Nosyreva, E. D., Ronesi, J. A., & Huber, K. M. (2008, Jul 10). Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. *Neuron, 59*(1), 84-97. https://doi.org/10.1016/j.neuron.2008.05.014

Wells, M. F., Wimmer, R. D., Schmitt, L. I., Feng, G., & Halassa, M. M. (2016, Apr 7). Thalamic reticular impairment underlies attention deficit in Ptchd1(Y/-) mice. *Nature, 532*(7597), 58-63. https://doi.org/10.1038/nature17427

West, E. A., DesJardin, J. T., Gale, K., & Malkova, L. (2011, Oct 19). Transient inactivation of orbitofrontal cortex blocks reinforcer devaluation in macaques. *J Neurosci, 31*(42), 15128-15135. https://doi.org/10.1523/JNEUROSCI.3295-11.2011 10.1523/JNEUROSCI.3295-11.2011.

West, E. A., Forcelli, P. A., McCue, D. L., & Malkova, L. (2013a, Jun 1). Differential effects of serotonin-specific and excitotoxic lesions of OFC on conditioned reinforcer devaluation and extinction in rats. *Behav Brain Res, 246*, 10-14. https://doi.org/10.1016/j.bbr.2013.02.027

West, E. A., Forcelli, P. A., McCue, D. L., & Malkova, L. (2013b). Differential effects of serotonin-specific and excitotoxic lesions of OFC on conditioned reinforcer devaluation and extinction in rats. *Behavioural Brain Research, 246*, 10-14. https://doi.org/10.1016/j.bbr.2013.02.027

White, N. M., Packard, M. G., & McDonald, R. J. (2013, Dec). Dissociation of memory systems: The story unfolds. *Behav Neurosci, 127*(6), 813-834. https://doi.org/10.1037/a0034859

Wicker, E., Turchi, J., Malkova, L., & Forcelli, P. A. (2018, May 31). Mediodorsal thalamus is required for discrete phases of goal-directed behavior in macaques. *Elife, 7*. https://doi.org/10.7554/eLife.37325

Wilkerson, J. R., Albanesi, J. P., & Huber, K. M. (2018, May). Roles for Arc in metabotropic glutamate receptor-dependent LTD and synapse elimination: Implications in health and disease. *Semin Cell Dev Biol, 77*, 51-62. https://doi.org/10.1016/j.semcdb.2017.09.035

Wimmer, R. D., Schmitt, L. I., Davidson, T. J., Nakajima, M., Deisseroth, K., & Halassa, M. M. (2015, Oct 29). Thalamic control of sensory selection in divided attention. *Nature, 526*(7575), 705-709. https://doi.org/10.1038/nature15398 10.1038/nature15398. Epub 2015 Oct 21.

Wolff, M., & Vann, S. D. (2019, Jan 2). The Cognitive Thalamus as a Gateway to Mental Representations. *J Neurosci, 39*(1), 3-14. https://doi.org/10.1523/JNEUROSCI.0479-18.2018 10.1523/JNEUROSCI.0479-18.2018. Epub 2018 Nov 2.

Yaakub, S. N., Dorairaj, K., Poh, J. S., Asplund, C. L., Krishnan, R., Lee, J., Keefe, R. S. E., Adcock, R. A., Wood, S. J., & Chee, M. W. L. (2013, Nov). Preserved Working Memory and Altered Brain Activation in Persons at Risk for Psychosis. *American Journal of Psychiatry, 170*(11), 1297-1307. https://doi.org/10.1176/appi.ajp.2013.12081135

Zeeb, F. D., & Winstanley, C. A. (2013, Apr 10). Functional disconnection of the orbitofrontal cortex and basolateral amygdala impairs acquisition of a rat gambling task and disrupts animals' ability to alter decision-making behavior after reinforcer devaluation. *J Neurosci, 33*(15), 6434-6443. https://doi.org/10.1523/JNEUROSCI.3971-12.2013 10.1523/JNEUROSCI.3971-12.2013.

Zikopoulos, B., & Barbas, H. (2006, Jul 12). Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *Journal of Neuroscience, 26*(28), 7348-7361. https://doi.org/10.1523/Jneurosci.5511-05.2006

Zikopoulos, B., & Barbas, H. (2012, Apr 11). Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *J Neurosci, 32*(15), 5338-5350. https://doi.org/10.1523/JNEUROSCI.4793-11.2012 10.1523/JNEUROSCI.4793-11.2012.