CONTRIBUTIONS OF THE MEDIAL PREFRONTAL CORTEX TO MANAGING MEMORY AND RESOLVING MNEMONIC INTERFERENCE

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Abstract

Mnemonic interference is the failure to retrieve a target memory due to the presence of other memories. Interference indicates underlying principles of memory organization, most notably that there is an interdependent structure to memories. Interference is potentially problematic for retrieval in systems that store many memories, yet there is substantial evidence for neural mechanisms dedicated to managing interference in support of memory retrieval. This evidence indicates that the prefrontal cortex (PFC) is a critical structure for combatting interference. However, the majority of this evidence is derived from human imaging studies and behavior studies involving human subjects with non-specific PFC damage, which lack the experimental control to examine the precise neural operations that manage interference. Surprisingly, few animal models exist that explicitly examine the role of the PFC in managing mnemonic interference. This discrepancy may be due to a diverse literature on the functional contribution of the PFC, including its involvement in a variety of processes that fall under the broad category of executive control. Animal studies have modeled some of these other executive functions, particularly the PFC role in behavioral flexibility and task switching. This thesis argues that many executive functions attributed to the PFC and modeled in animals involve an underlying need to resolve conflict in neural representations developed over learning. This view may reduce the number of attributes needed to characterize PFC function. I test this hypothesis by examining the role of PFC in resolving mnemonic interference in rats and comparing this evidence to other animal models of PFC function. These studies provide strong evidence that the PFC is critical for the normal management of interference in rats, which is consistent with the human literature. Together this evidence indicates a fundamental role for PFC in managing mnemonic competition, which opens the door for detailed investigations of neural mechanisms of interference resolution in animal models of memory.

BIOGRAPHICAL SKETCH

Greg was born and raised in rural Connecticut. His parents, Joe and Ursula Peters, encouraged freethinking, inquiry and debate, and they always insisted that both of their sons spend the majority of their time exploring the natural world. Greg attended Edwin O. Smith High School in Storrs, Connecticut, which borders the main campus of the University of Connecticut. Always influenced by the nearby flagship, Greg made the short trip over to UConn as an undergraduate, which he soon realized was a familiar place with so much more to offer than he ever knew. Greg credits the diverse opportunities and a few great mentors at UConn for cultivating his academic potential, and for teaching him to channel a longstanding curiosity in the behavior of the creatures of our world. It was in Dr. Etan Markus' course in learning and memory that Greg realized his appreciation for the fundamental importance of memory to living things. In Dr. Markus' research lab, Greg learned that it was possible to observe neural activity that directly reflected memory, and he began to believe he might be able to make a career out of asking questions that came naturally to him. Greg graduated from UConn with a degree in Psychology and Neuroscience and took a technician job with Dr. Amy Griffin at the University of Delaware, where he helped her start up her neurophysiology lab. Seeing a lab grow from the ground up was a valuable experience, and Greg learned about the many little things that make a lab tick. Prior to graduate school, Greg focused mostly on research concerning hippocampal processing and its relation to memory. Both of Greg's prior mentors, Dr. Markus and Dr. Griffin, embraced the perspective that the rat hippocampus is essential for aspects of memory that go well beyond the more predominant spatial memory processing theories. Dr. David Smith's contextual view of hippocampal processing offered a perspective that Greg admired and believed in, and he was thrilled to be given the opportunity to pursue a graduate degree studying the neurobiology of memory at a Cornell University. Greg will be forever grateful that he was fortunate enough to land in such a great academic environment located in a beautiful college town, and to have gained so many wonderful friends and colleagues along the way.

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TABLE OF CONTENTS

CHAPTER 4

APPENDIX

Chapter 1

Introduction

Interest in mnemonic interference has had an important influence on psychology. Attention to interference peaked when mid 20th century cognitive scientists were immersed in the idea that interference indicated a plausible mechanism for how memories were adapted or forgotten. Interference is broadly defined as the failure to retrieve a target memory due to other memories, which demonstrates that memories are not stored or retrieved independently – new memories can impede the retrieval of older memories, and conversely, older memories can interfere with the formation of new memories. The logical and intriguing extension of this is that interference reveals underlying principles of memory organization, particularly how memories are altered or updated over time.

Yet for a variety of reasons, the study of interference has lost some traction in modern psychology. Interference is easy to reproduce in the lab, but it is not always clear how experimentally induced interference relates to the way memory is implemented in the real world. Furthermore, extending the investigation of interference to neural mechanisms is difficult using non-invasive methods in humans. Here I present research that spreads the study of interference to animal models of memory in order to establish more tractable ways of assessing neural mechanisms of interference. To this day, there is much to learn about how memory systems strike a balance between maintaining stable

memory representations and the ability to update or disregard other memories to make way for new memories. Interference reflects a part of these interdependent, internal features of memory, and we hope that the continued study of this phenomenon in model systems could reinvigorate interest in interference, and ultimately help reveal the important neural mechanisms that support encoding and retrieval dynamics.

Interference and Memory

The systems that achieve biological memory are intimidatingly complex. One practical approach to the study of memory has been to break it down into functionally distinguishable components. Some of these components, such as encoding and retrieval, are dissociable in many ways, yet it would be a mistake to view them in complete isolation. Retrieval is influenced by how memories are stored, since it is largely dependent on encoding conditions. Likewise, encoding processes are inherently prospective, since memory is built around how it will be implemented for future use. For sure, encoding and retrieval are two sides of the same coin.

The interplay between encoding and retrieval is further complicated by the fact that one heuristic of memory encoding appears to be the integration of new information with existing knowledge (McClelland et al. 1995). This is problematic if the properties of different memories are similar enough that it makes distinguishing them difficult at retrieval. The overlap between memories that

occurs during ongoing memory processes could sometimes lead to the retrieval of the wrong memories, which is presumably how interference occurs. In systems that store many memories, the integration of overlapping memory representations would appear to put pressure on memory systems to incorporate effective mechanisms for maximizing retrieval in a precise and contextually appropriate manner. How neural systems efficiently encode memories while distinguishing them during retrieval is fundamental to the adaptive value of memory as we know it.

Neurobiology of Interference Resolution

Mnemonic interference is informative of underlying memory processes. In some cases, interference reflects the constraints on processes that update memories. For example, proactive interference is defined by the cost of prior memory on forming new memory. Nevertheless, we are capable of resolving the interference from older memories in order to adopt new behaviors. Considering the vast of number of memories we store, it is remarkable that interference does not occur more regularly. How is it possible to effectively store and retrieve memories with pinpoint precision in the face of our cluttered mnemonic past? One view is that critical to accuracy during memory retrieval are mechanisms that manage potential interference from other memories. In fact, there is substantial imaging and behavioral evidence for neural mechanisms dedicated to resolving interference. Brain imaging studies consistently show that activity in the prefrontal cortex (PFC) is associated with interference resolution (D'Esposito et

al. 1999; Sylvester et al. 2003; Badre and Wagner 2005; Jonides and Nee 2006; Kuhl et al. 2011). Furthermore, damage to the PFC results in increased susceptibility to interference, while leaving many other mnemonic and cognitive abilities relatively intact (Luria 1971; Rocchetta and Milner 1993; Lou Smith et al. 1995; Shimamura et al. 1995). Despite the known relationship between the PFC and interference resolution in humans, few studies have looked at the role of the PFC in managing competing memories in animal models. My research seeks to determine whether experimental manipulation of PFC activity also affects the management of mnemonic interference in animal models of memory. A consistent role for the PFC in managing competing memories across species adds investigative power to the neural mechanisms of interference and interference resolution, and could lead to a more comprehensive understanding the neural substrates that support these important mnemonic processes.

An additional complexity to the study of mechanisms that manage memory is that memory-guided behavior is often adapted when it no longer leads to learned or expected outcomes. Memories are strongly associated with their encoding context, yet contextual conditions can remain relatively stable while the memories associated with those conditions can be altered. We know that, most of the time, we are not doomed to repeat established patterns of behavior guided by outdated memories. For example, if the department seminar has been held in the same room for many years but suddenly changes to a remodeled space down the hall, the frequency with which people will accidently wander into the old

empty room when heading to the seminar will likely decrease over time. This type of modification in memory-guided behavior is often referred to as behavioral flexibility, which is tightly associated with executive control mechanisms and known to be accomplished through operations of the PFC (Braver et al. 2009). Detailed studies of behavioral flexibility emphasize an underlying role for the PFC in managing switching between behavioral strategies or task sets (Monsell 2003; Sakai 2008). However, a survey of the vast literature on behavioral flexibility appears to show that studies of flexibility typically require the resolution of interference from conflicting behaviors (Vandierendonck et al. 2010). In this way, studies of flexible behavior tend to closely mirror studies of proactive interference, since they both examine the effect of previous memory on new learning. However, flexibility has received significantly more attention than interference resolution in animal models of PFC function (Dias and Aggleton 2000; Floresco and Magyar 2006; Gisquet-Verrier and Delatour 2006; Ragozzino 2007; Kesner and Churchwell 2011). My doctoral research has explored whether PFC involvement is also critical for managing interference within the domain of memory. One implication of this research is that the PFC role in behavioral flexibility could be explained by an underlying need to resolve competing representations that goes beyond changes in strategy requirements, since in many cases, interference can occur without overt changes in the strategic goals that guide behavior. We address this relationship by investigating whether the PFC is important for managing mnemonic interference, while minimizing or eliminating the need to alter strategies or behavioral requirements. Because the

PFC is also involved in managing mnemonic interference, this may indicate a broader role of the PFC in executive control by managing competition in neural systems across multiple cognitive domains.

There is an intriguing irony to the study of interference. Interference is observed as a memory failure due to the negative consequences of memory competition, but interference produced in experimental settings is likely caused by the very mechanisms that reduce competition between memories. Retroactive interference is a failure to retrieve a previous memory due to new memory, but this also reflects a system that highlights current memories and minimizes competitors. Thus, mechanisms associated with interference have often been connected to inhibitory control. For example, retroactive interference has been proposed to occur because newly formed memories exert an inhibitory influence on previous memories (McGeoch and McDonald 1931). Consistent with a role in managing interference, the PFC is also strongly associated with inhibitory control of behavior (Aron et al. 2004; Verbruggen and Logan 2008). Damage or dysfunction of the PFC often results in disinhibited behavior, which is thought to be caused by disruption in the normal inhibitory control circuitry modulated by connections with local inhibitory neurons in PFC projection sites, as well as internal regulatory mechanisms of the PFC (Barbas and Zikopoulos 2007). Interestingly, mechanisms thought to manage competition during memory retrieval have a strong inhibitory component, such as when extra study practice with a subset of category exemplars inhibits the retrieval of other exemplars

within the same study category (Anderson 2003). A careful consideration in my doctoral research is the theoretical perspective the inhibitory mechanisms are essential to managing competing memories in order to reduce interference.

Animal Models of PFC function

The most prominent theory of PFC function modeled in rats is behavioral flexibility. Modeling the role of the PFC in behavioral flexibility has been important because of the known association between the PFC and behavioral flexibility in humans. In fact, predominant clinical tests of PFC function are measures of flexibility, most notably the Wisconsin Card Sorting Task (WCST) (Drewe 1974; Bornstein 1986; Miyake et al. 2000). Impairments on the WCST due to PFC dysfunction typically involve an inability to adopt new card sorting rules once an initial sorting rule has been learned (Milner 1963). Thus, PFC subjects are capable of the mnemonic requirements necessary for sorting the cards, but have trouble flexibly altering their behavior to new sorting strategies. Animal models show a similar behavioral effect of PFC disruption on behavioral flexibility, which have given significant momentum to this attribute of PFC function (Ragozzino et al. 1999; Birrell and Brown 2000). A central argument supported by the research in this dissertation is that behavioral flexibility is intimately connected to adaptive mnemonic functions, and that many tests of behavioral flexibility in animals induce substantial mnemonic interference. When PFC subjects are impaired in adopting a new behaviors or strategies, their deficits in performance are not typically random, but indicate that they continue to follow some previously

learned pattern of behaviors. Subjects tend to perseverate, or continue to follow an existing pattern of behavior despite the fact that it no longer leads to the learned outcome. A consistent argument throughout this research is that a broader interpretation of the PFC involvement in flexibility may be a role in resolving interference from previously learned behaviors in order to adopt new behaviors.

Functional Anatomy of the PFC

The PFC is a good candidate for a modulatory role during memory retrieval. Not only is there imaging evidence that the PFC is central to the cognitive control of memory retrieval (Dobbins et al. 2002; Badre and Wagner 2007), but the anatomical position of the PFC strongly supports an integrative position ideal for executive functions. There are several comprehensive reviews on the functional anatomy of the PFC (Goldman-Rakic 1987; Barbas 2000; Dalley et al. 2004; Arco and Mora 2009). Most relevant to its role in managing neural competition, the PFC connects widely throughout the brain, with massive input from most sensory cortices, and output to motor regions as well as bi-directional connectivity to limbic regions important for memory and emotion (Barbas 2000). Within these diverse functional circuits, connections between the PFC and other regions are predominantly excitatory, but often connect to local inhibitory neurons and have been proposed to support inhibitory control of local populations important for minimizing distracting information (Barbas and Zikopoulos 2007).

The PFC is divided into three major subregions in primates, which include the lateral, orbital and medial subdivisions. These subregions vary in their specific sensory input and predominant output structures, which has contributed to theories of functional specialization of PFC subregions. Dorsalateral PFC (DLPFC) is most associated with mnemonic functions due to intimate connections with temporal lobe and limbic structures (Barbas and Zikopoulos 2007). However, The PFC posses substantial intrinsic connections thought to be important for the integration of diverse information across cognitive domains (Barbas 2000). Overarching cognitive control requires diverse integration, and as a whole, PFC subregions are notable for their integration of sensory input and common influence on motor output (Arco and Mora 2009). This anatomical feature is central to theories of the PFC role in executive control of behavior (Miller and Cohen 2001, Goldman-Rakic 1995). Furthermore, the intriguing relationship between PFC anatomy and function is that it appears well positioned to modulate both motor output associated goal-directed behavior due to connections with nucleus accumbens and premotor cortex, as well as mnemonic functions associated with the hippocampus and amygdala (Arco and Mora 2009). These diverse cortical to subcortical connections may reveal the neural circuitry that underlies the PFC involvement across multiple cognitive domains (Duncan and Owen 2000).

Considering the notable expansion of the primate PFC relative to rats (Uylings and van Eden 1990), it is no surprise that there may be critical variations in some regards between the anatomical relationship between rat and primate PFC, particularly with respect to homologous subregional specialization. However, widespread connectively is highly conserved in the PFC of primates and rats, and this is reflected in homologous functionality of the PFC across a variety of behavioral tasks (Vertes 2006). The regions of the rat PFC most commonly associated with cognitive functions homologous to the DLPFC in primates is the rat medial prefrontal cortex (mPFC) (Uylings et al. 2003), and as a result, rat models of behavioral flexibility have typically focused on the mPFC. For this reason, the research presented in this thesis also focuses on the mPFC of rats in managing interference. This rationale also allows for direct comparisons between the role of the mPFC in behavioral flexibility and a role in managing mnemonic interference.

Summary and Thesis Overview

This thesis presents experimental evidence for an important role of the rat PFC in managing mnemonic interference in rats. There is substantial evidence from humans that the PFC plays a central role in mnemonic interference, but few studies have translated this role to the study of mnemonic processes in animal models. The following chapters present evidence in support of the overarching hypothesis that the PFC is critical for rats to manage interference from competing memories, and that this underlies a broader role for the PFC in managing

competition that goes beyond behavioral flexibility or strategy selection. Across different tasks and behavioral requirements, we show a consistent involvement of the PFC whenever memory-guided behavior requires effective management of interference from other memories.

Chapter two is a multi-study behavioral analysis of the contribution of the PFC to different aspects of managing memory competition in odor discrimination memory in rats. We first test the hypothesis that the PFC is important for managing many memory items by comparing the role of the PFC in learning multiple discrimination problems against its role in learning the same number of problems presented individually. We then examine the role of the mPFC in the retrieval of multiple, concurrently learned discrimination memories to test the role of the PFC in managing memory while minimizing elements of perseverative responding. Central to the hypothesized role of the PFC in managing interference, we next test the role of the PFC in overcoming proactive interference from memories that overlap with a new set of discrimination problems. In a final experiment, we also demonstrate an interesting role for the PFC in ongoing memory formation that influences the likelihood that memories will lead to subsequent interference. Together, we show that the PFC involvement in managing mnemonic interference goes beyond a role in strategy selection or flexibility by isolating the need to manage interference in behavioral tasks that do not explicitly require changes in strategies or attention to cues typical of behavioral flexibility paradigms. These studies demonstrate that

behavioral deficits associated with PFC inactivation are consistently related to experimentally induced levels of mnemonic interference.

Chapter three extends the investigation of the role of the PFC in animal models of mnemonic interference presented in chapter two. One important criticism of the odor discrimination studies presented in chapter two is that, though they do not involve the strategic or modality specific changes associated with flexibility tasks such as the WCST, they still sometimes require rats to learn or adopt new memories in the face of previous learning. To address this concern, we tested the role of the PFC in managing interference without requiring rats to adopt any new memories or strategies to guide behavior. We developed a continuous match to sample task that allowed us to test rats on two levels of interference despite identical strategic requirements. The high interference version of the task involved multiple repetitions of stimuli, and over an entire training session, prior trials caused interference on subsequent trials if they occurred in close temporal proximity. On the low interference version, no repetitions of stimuli were presented within a session. This allowed us to train rats on a single rule, and then test the role of the PFC on performance of different levels of interference independent of changes in strategy or other rule-guided behaviors. Though the PFC is clearly important to adopt diverse strategies or flexibility alter behavior according to changing task demands, the involvement of the PFC is consistently greater when the potential for interference is high, even when no strategy or rule change is required. Thus, this work further

extends the role of the PFC in managing mnemonic interference to animal models, and supports a broader role for the PFC in dealing with mnemonic competition, whenever it occurs.

Chapter four is a commissioned review of the current state of knowledge on the PFC role in managing interference, with an emphasis on how evidence from humans is consistent with recent studies in animal models. Included is a comparison of predominant theories of PFC function and how they relate to issues of interference resolution. This review also includes a synthesis of perspectives on the relative anatomical position of the PFC within the brain and how this might reflect its functional role in managing competition across multiple cognitive domains. I conclude with an in depth discussion of emerging evidence of homologous functionality of the PFC across humans and rats, and how this reflects an important role for this region in managing neural competition.

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Chapter 2

The Medial Prefrontal Cortex is Critical for Memory Retrieval and Resolving Interference

Introduction

The prefrontal cortex (PFC) is thought to exert top down influence on a variety of psychological processes, a function generally referred to as executive control (Shallice and Burgess 1996; Smith and Jonides 1999; Miller and Cohen 2001). Some processes known to involve the PFC include strategy selection (Monsell 2003; Block et al. 2007), directing attentional resources (Banich et al. 2000; Daffner et al. 2000; Asplund et al. 2010) and inhibiting prepotent behavioral responses (Aron et al. 2004; Chambers et al. 2006; Verbruggen and Logan 2008; Jonkman et al. 2009). Recently, a growing body of research has shown that the PFC is involved in similar functions in rodents. For example, medial prefrontal (mPFC) lesions cause impairments in a rodent adaptation of the Wisconsin card sorting task and the pattern of impairments is similar to those seen in humans (Ragozzino et al. 1999b; Birrell and Brown 2000; Ng et al. 2007). Like humans, the rats are unimpaired in learning the initial rule (e.g. respond according to one stimulus feature, such as odor) but they are severely impaired in learning to switch to a different stimulus feature (e.g. texture). Consistent with this, studies of spatial memory have shown that rats with mPFC damage are impaired in switching strategies from a place to a response strategy although they are not impaired in reversals within a strategy, such as switching from a ‘go east’ to a ‘go west’ place strategy (Ragozzino et al. 1999a; Rich and Shapiro

2007). Other studies have also shown that reversal learning is not impaired by mPFC lesions (Aggleton et al. 1995; Floresco et al. 2008). A number of authors have also emphasized the mPFC role in attentional processes in rats (Birrell and Brown 2000; Ng et al. 2007). These studies demonstrate that the mPFC is critical in tasks that require rats to shift attention among competing stimulus features that indicate distinct behavioral responses. A common theme in this research is that the PFC contributes to behavioral flexibility, the ability to rapidly adopt new strategies or behavioral response patterns (Block et al. 2007; Ragozzino 2007).

Although its role in strategy selection and attentional set shifting has been studied extensively, less is known about the PFC role in memory processes. However, recent imaging studies of human subjects have suggested that executive control processes also apply to the domain of memory retrieval. Interestingly, these studies have focused primarily on inhibition of retrieval. For example, when subjects are instructed to suppress the retrieval of some items from a study list, the ability to subsequently retrieve those items is impaired, and the PFC is active during retrieval suppression (Anderson and Green 2001; Depue et al. 2007). The PFC is also thought to play a role in another kind of memory inhibition called the retrieval-induced forgetting effect, in which practice with some items on a study list inhibits the subsequent retrieval of non-practiced items, relative to a baseline condition (Anderson et al. 1994; Kuhl et al. 2007; Wimber et al. 2008). However, it is not clear from the human imaging data whether the PFC role is limited to the inhibition of retrieval or whether the PFC might also be involved in promoting the retrieval of target memories.

Recently, a number of investigators have begun to study the role of the PFC in memory processes in rodents. In these studies, the medial division of the PFC has been a primary target of interest because it is thought to be functionally similar to the dorsolateral PFC in primates (Uylings et al. 2003; Vertes 2006; Seamans et al. 2008), which is the region commonly found to be involved in memory processes in humans. In rodents, mPFC lesions impair various forms of spatial memory (Lee and Kesner 2003; Jo et al. 2007; Lee and Solivan 2008; Churchwell et al. 2010). The mPFC has also been shown to be involved in a number of nonspatial memory tasks, including fear conditioning and extinction (Sotres-Bayon and Quirk 2010), transitive inference (DeVito et al. 2010) and memory for sequential order (Devito and Eichenbaum 2011). Although these studies clearly suggest that the mPFC is involved in typical rodent memory tasks, there is currently no consensus about the precise contribution of the PFC to memory encoding and retrieval processes.

In the present study, we tested the hypothesis that the mPFC is involved in resolving interference. The idea that the PFC is needed for resolving competing response tendencies is central to theories about executive function. Consistent with this idea, memory retrieval often involves a process of selecting from among many competing retrieval targets, particularly in high interference situations. Evidence from neuropsychological and neuroimaging studies supports this hypothesis (for review see Blumenfeld and Ranganath 2007). Human subjects with PFC damage make more memory errors as study list length increases (Petrides and Milner 1982) and they are more susceptible to

interference (Incisa della Rocchetta and Milner 1993; Smith et al. 1995). Increased susceptibility to interference has also been reported in rodents with PFC damage (Granon et al. 1994). Indeed, interference is a prominent characteristic of many classic PFC tasks.

We used a recently developed high interference olfactory learning task to assess the mPFC role in memory (Butterly et al. 2012; Law and Smith 2012). In this task, rats learn an initial list of eight concurrently trained odor discrimination problems. After learning the first list, the rats are trained on a new list of eight discrimination problems. In order to induce interference, half of the odors from the first list also appear on the second list with their predictive values reversed. In a series of experiments, we examined whether rats with temporary inactivation of the mPFC (prelimbic and infralimbic cortex) could acquire and remember the initial list of concurrently trained discrimination problems, whether they were more susceptible to interference than controls when learning a new conflicting list of discrimination problems, and finally, whether mPFC involvement during the early stages of learning influences memory encoding and subsequent susceptibility to interference.

Results

Experiment 1

Acquisition of the Concurrent Discrimination Task. Extensive evidence indicates that the mPFC is not needed for simple discrimination learning

(Ragozzino et al. 1999b; Birrell and Brown 2000; Ragozzino et al. 2003; Ng et al. 2007). These studies suggested that the PFC is not needed for remembering which cues were associated with reward, but is instead only needed when the task requires behavioral flexibility, such as switching strategies or attentional set shifting. However, our hypothesis that the mPFC plays a key role in resolving interference suggests that the mPFC may be needed whenever subjects must manage many items in memory regardless of the specific task requirements. If so, the mPFC may be needed for discrimination learning when many problems must be learned and remembered at the same time.

We tested this hypothesis by giving control and muscimol rats (n=7 per group) concurrent training on a single list of eight odor discrimination problems. On each trial, the rats were presented with two cups containing odorized digging medium. Within each discrimination problem, one of the odors was always associated with a buried reward and the other was not. Each training session involved eight trials with each of the eight problems presented in a randomized sequence. The rats were given infusions prior to each of the first three training sessions. The percentage of trials with a correct response were submitted to a repeated measures ANOVA with inactivation condition (saline or muscimol) as a between subjects factor and training session (the three infusion sessions) as the within subjects factor (Figure. 2.1A). This analysis showed that muscimol inactivation significantly impaired learning (main effect of inactivation, $F_{(1,12)} = 11.83$, $P < 0.01$). Thus, the mPFC is important for discrimination learning when several problems must be acquired concurrently.

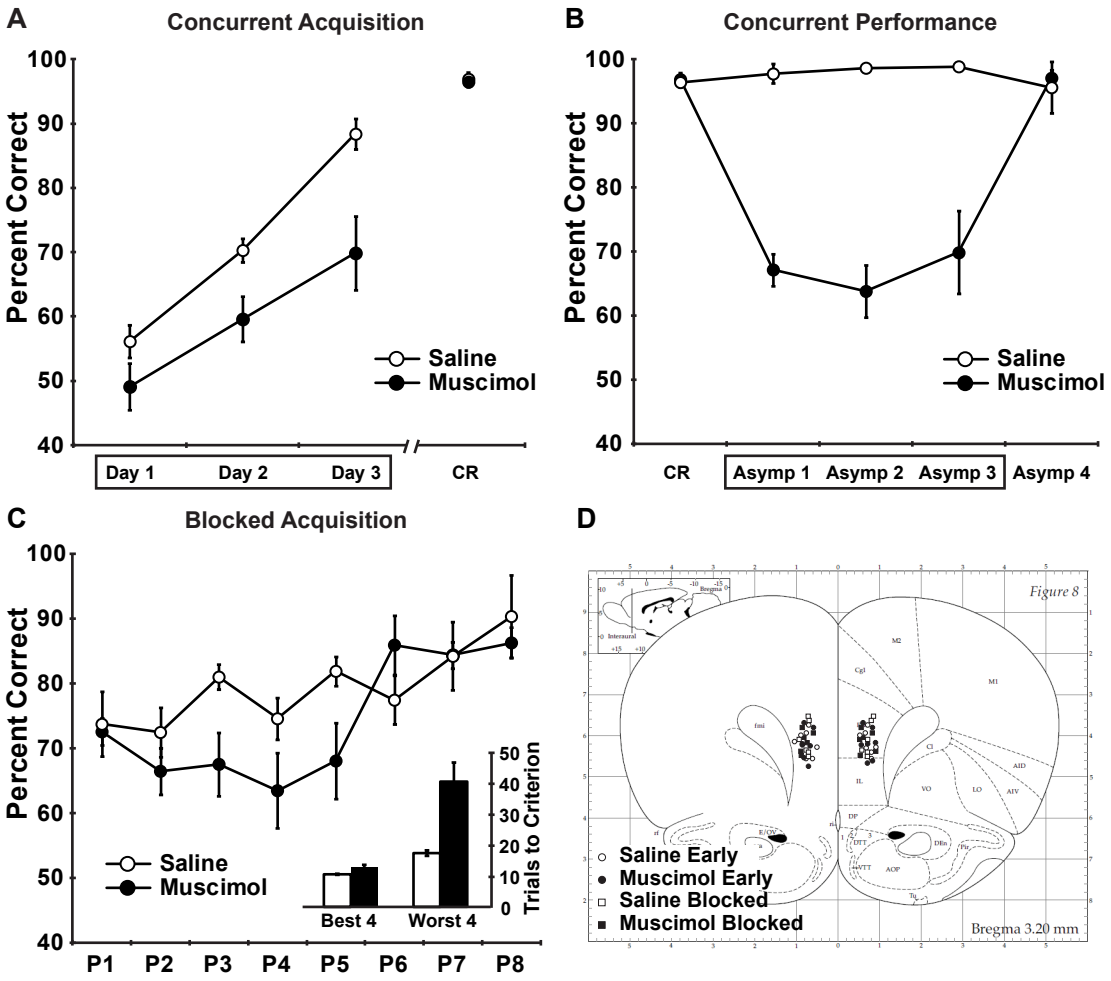

Figure 2.1. Inactivation of the mPFC during concurrent and blocked odor discrimination. (A) The percentage of trials with a correct response during the concurrent acquisition of eight odor discrimination problems are shown for saline and muscimol rats. Infusions were given prior to each of the first 3 training sessions (indicated by the box around Days 1-3). By the time the rats reached the behavioral criterion (CR session), the muscimol rats had caught up to the performance level of the controls. (B) The effects of muscimol on asymptotic performance of the concurrent discrimination task are shown. Infusions were given prior to the first 3 days of post-criterial asymptotic performance (Asymp 1-3). Data of the criterial session (CR) and fourth session, which did not involve infusions, are also shown for comparison. Error bars are not visible for some values because the SEM was smaller than the area covered by the data markers. (C) The percentage of trials with a correct response over the course of training to the criterion on each of the 8 odor discrimination problems (P1-P8) is shown for the blocked training procedure. The average number of trials needed to reach the criterion for the best and worst problems for each rat is shown in the inset. For this experiment, the rats were given saline control infusions or muscimol infusions prior to each training session. (D) Cannula placements are shown for the rats in experiment 1, including the concurrent training condition (Saline Early and Muscimol Early) and the blocked training condition (Saline Blocked and Muscimol Blocked).

Performance of the Concurrent Discrimination Task. Another prominent idea is that a key consequence of PFC damage is perseveration, wherein subjects are unable to abandon previously learned response tendencies when conditions change (Rubia et al. 2003; Verbruggen and Logan 2008; Jonkman et al. 2009). In contrast, our hypothesis that the mPFC plays a key role in resolving interference suggests that the mPFC may be needed whenever subjects need to manage many items in memory, regardless of whether memory failures take the form of perseveration or other kinds of errors. To test this hypothesis, we examined the effects of muscimol on performance of the well learned concurrent discrimination task.

After the early acquisition testing described above, the rats continued the concurrent discrimination training, without further infusions, until they reached a criterion of at least 90% correct for two consecutive sessions. Although they were initially impaired, rats that had been given muscimol during acquisition subsequently caught up to controls and their performance was equivalent during the criterial session ($t_{(12)} = -0.34$, $P = 0.74$). After achieving the criterion, the rats were given an additional four training sessions. The first three involved muscimol or saline infusions while the fourth session did not involve any infusions and served as a return to baseline check. Rats that had been given muscimol infusions during acquisition served as saline controls during asymptotic performance and the rats that received control infusions during acquisition were given muscimol during asymptotic performance. The percent correct data for the three infusion sessions were submitted to a repeated measures ANOVA with

inactivation condition (saline or muscimol) as the between subjects factor and training session as the within subjects factor (Figure 2.1B). Rats given muscimol were significantly impaired in performing the task (main effect of inactivation, $F_{(1,12)} = 60.44$, $P < 0.001$). However, both groups showed evidence of learning (main effect of training session: $F_{(2,24)} = 37.88$, $P < 0.001$, but no interaction of the inactivation and training session factors: $F_{(2,24)} = 1.85$, $P = 0.18$) and the performance of the muscimol rats returned to normal levels on the fourth session, when no infusions were given ($t_{(10)} = -0.41$, $P = 0.69$).

Acquisition of Blocked Discrimination Problems. The above results support our hypothesis that the mPFC is critical whenever subjects must manage many items in memory at the same time (i.e. concurrent discrimination). However, if this is correct then the mPFC should not be as important if rats were allowed to learn one discrimination problem at a time. To test this, we trained control and muscimol rats (n=6 per group) on the same odor discrimination problems in a blocked fashion. For these rats, training was similar to the concurrent training condition, except that the discrimination problems were presented one at a time and the rats only moved on to a new problem after reaching 90% correct on the current problem (Figure 2.1C).

On average, muscimol rats were impaired in learning the discrimination problems (trials to the criterion: $t_{(10)} = 3.93$, $P < 0.005$; percent correct: $t_{(10)} = -2.69$, $P < 0.05$). However, muscimol had no effect on learning the first discrimination problem (percent correct: $t_{(10)} = -0.22$, $P = 0.83$; trials to criterion: $t_{(10)} = 1.24$, $P = 0.24$), replicating previous findings of intact learning for single

discrimination problems (Birrell and Brown 2000; Ragozzino et al. 2003). In fact, although rats with temporary mPFC inactivation often performed poorly on some of the discrimination problems, they were typically able to learn several problems at a normal rate. For each rat, we separated the eight discrimination problems into the four best and four worst in terms of the number of trials needed to reach the criterion (Figure 2.1C, inset). These data were submitted to a repeated measures ANOVA with inactivation condition (saline or muscimol) as a between subjects factor and problem type (best or worst problems) as a within subjects factor. This analysis revealed a significant interaction of the inactivation condition and problem type factors ($F_{(1,10)} = 11.18$, $P < 0.01$). The muscimol rats were severely impaired in learning their worst odor discrimination problems, requiring more than twice as many trials as controls to learn each problem, but were relatively unimpaired on their best four problems (Figure 2.1C, inset). Thus, rats given temporary mPFC inactivation were able to learn several discrimination problems as long as they learned them one at a time.

This pattern of results was not present in the rats trained in the concurrent condition described above. A similar analysis of the best four and worst four odor discrimination problems did not find an interaction of the inactivation condition and problem type factors ($F_{(1,12)} = 17.29$, $P = 0.13$), indicating that although the muscimol rats were impaired in the concurrent task, as shown above, the impairment was not driven by very poor performance on some odor problems but normal performance on others. Instead, the magnitude of the impairment was similar for all odor discrimination problems in the concurrent condition.

Experiment 2

Managing Proactive Inteference. The finding that the mPFC is needed for the acquisition and retrieval of memory when many items are involved but not for only a few items provides suggestive evidence that the mPFC is involved in resolving interference. In the second experiment, we explicitly tested this hypothesis by training rats on two lists of odor discrimination problems that contain conflicting items. In this task, learning the first list causes significant proactive interference during learning of the second list (Butterly et al. 2012). However, the task does not require subjects to adopt a new strategy or shift attention from one stimulus feature to another. Thus, this experiment directly tests the hypothesis that interference alone, in the absence of strategic or attentional shifts, is sufficient to require mPFC involvement.

All of the rats (n=6 per group) were first trained on list 1 exactly as in experiment 1, except that there were no infusions, followed by training on a second list of eight odor discrimination problems in which each problem contained one novel odor paired with a previously presented odor from list 1 with its predictive value reversed. Half of the previously presented odors had been rewarded on the first list and half had not been rewarded. This ensured that the rats could not adopt a strategy of simply approaching the novel odors or avoiding the familiar odors. The rats were given muscimol or saline control infusions during the first 3 training sessions of the second list, followed by 2 additional sessions without infusions.

A previous study using this training procedure showed that temporary inactivation of the hippocampus selectively impaired the use of contextual information to resolve interference (Butterly et al. 2012). In that study, control rats performed better when they learned the two lists in different contexts whereas rats with temporary hippocampal inactivation showed no contextual learning advantage. In order to determine whether the mPFC plays a similar role in the use of contextual information to overcome interference, half the rats were trained on the second list in the same context where they learned the first list and the other half were trained in a different context. This yielded a 2X2 design with the following groups; control-different context, control-same context, muscimol-different context and muscimol-same context.

Rats in the four groups reached the same level of asymptotic performance on the first list before beginning the second list ($F_{(3,20)}$ = .33, P = .81). The percent correct data from the list 2 training sessions were submitted to a two-way ANOVA with inactivation condition (saline or muscimol) and context condition (same or different context) as the between subjects factors and training session (five levels) as the within subjects factor (Figure 2.2A). This analysis revealed a main effect of inactivation ($F_{(1,20)}$ = 29.94, P < 0.001), an interaction of the inactivation and context condition factors ($F_{(1,20)}$ = 6.62, P < 0.05) and an interaction of the inactivation condition and session factors ($F_{(1,20)}$ = 11.38, P < 0.001). The inactivation by context condition interaction was due to the fact that, as expected, control rats performed significantly better when they learned the two lists in separate contexts than when they learned the two lists in the same

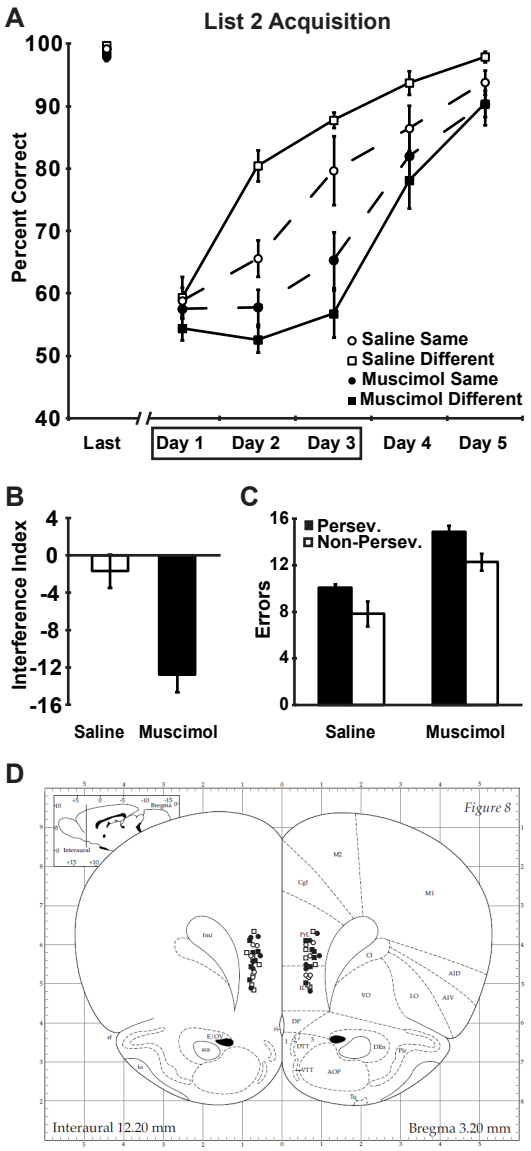

Figure 2.2. Inactivation of the mPFC during learning of a second list of conflicting odor discrimination problems. (A) Percent correct data are shown for the final day of training on list 1 (Last) and during the 5 training sessions of list 2, for control (open symbols) and muscimol rats (filled symbols) and for the different context (squares) and same context rats (circles). The rats were given infusions prior to the first 3 training sessions (indicated by the box). No infusions were given during the fourth and fifth sessions. (B) The interference index, reflecting the decline in performance from list 1 to list 2, is shown for control and muscimol rats. (C) The numbers of perseverative (black bars) and non-perseverative errors (white bars) made during the infusion sessions are shown for control and muscimol rats. (D) Cannula placements are shown for the rats in experiment 2 (symbols as in A).

context (main effect of context condition for controls, $F_{(1,10)} = 5.86$, $P < 0.05$) but rats with muscimol inactivation did not (main effect of context condition for muscimol rats, $F_{(1,10)} = 1.66$, $P = 0.23$). The inactivation condition by session interaction was due to the fact that control rats showed significant improvement in performance during the saline infusion sessions (ANOVA of performance during the first three training sessions: $F_{(2,22)} = 38.81$, $P < .0001$) while muscimol rats showed little evidence of learning ($F_{(2,22)} = 3.34$, $P = 0.07$). Thus, unlike the effects of hippocampal inactivation, which was highly specific to the different context condition (Butterly et al. 2012), mPFC inactivation impaired performance regardless of the context condition.

Our experimental design also allowed us to directly assess interference in the control and muscimol subjects. If proactive interference occurred, performance should decline when subjects had to learn a second list after having learned the first list. Therefore, an interference index reflecting the change in performance across lists was computed for each subject (average percent correct on list 2 minus the average percent correct on list 1) and the interference scores of control and muscimol subjects were compared. Muscimol rats showed significantly greater interference than controls ($t_{(22)} = -4.31$, $P < 0.001$, Figure 2.2B).

This task offers an additional test of the hypothesis that perseveration is the primary deficit in subjects with PFC damage. The second list presents the rats with two different kinds of problems. Half of the odor pairs contained a previously rewarded odor that was not currently rewarded and errors on these

trials could be caused by perseverative responding (i.e. perseverative errors). The other half of the odor pairs did not contain a previously rewarded odor. Instead, these trials contained a previously non-rewarded odor and a novel odor. Errors on these trials would be non-perseverative errors. We asked whether rats with temporary mPFC inactivation were more prone to make perseverative errors than controls by submitting the number of errors to a repeated measures ANOVA with the inactivation and context conditions as between subjects factors and error type (perseverative or non-perseverative) as a within subjects factor (Figure 2.2C). This analysis revealed a main effect of error type ($F_{(1, 22)} = 20.98$, $P < 0.001$), which indicated that all rats made more perseverative errors than non-perseverative errors, and a main effect of inactivation ($F_{(1, 22)} = 28.74$, $P < 0.001$), which confirmed that muscimol rats made more errors (of both types) than controls. However, there was no interaction of the error type and inactivation factors ($F_{(1,22)} = .12$, $P = 0.74$), indicating that the muscimol rats did not make disproportionately more perseverative errors than controls.

Experiment 3

Long-term influence from initial learning. In experiment three, the long term effects of muscimol inactivation during the early stages of learning were assessed. Observations during pilot experiments suggested that temporary inactivation at the outset of learning list 1 could have an effect on the subsequent learning of conflicting information during list 2. Specifically, subjects that had temporary inactivation of the mPFC during the early stages of learning list 1

appeared to exhibit *better* performance (less interference) on list 2. If correct, this would suggest an mPFC role at the time of encoding which alters the way that the memories are subsequently retrieved. In order to formally assess this, rats (n=6 per group) were given muscimol or control saline infusions prior to each of the first three sessions of list 1. They then continued daily training sessions until they reached the criterion, followed by four sessions of post-criterial training on list 1. They were then given five training sessions on list 2 (Figure 2.3). No infusions were given after the initial three sessions of list 1.

As in the first experiment, the rats that were given muscimol were impaired during the infusion sessions (Figure 2.3A, main effect of inactivation: $F_{(1,10)} = 26.65$, $P < 0.001$). In this experiment, the muscimol rats showed only marginally significant evidence of learning (ANOVA of performance across the three infusion session: $F_{(2,10)} = 3.72$, $P = 0.08$). After the initial infusion sessions, the performance of rats with temporary inactivations caught up to controls and they performed equivalently during the post-criterial training sessions ($t_{(10)} = .35$, $P = 0.73$). Importantly, both groups performed at very high levels for at least 5 sessions (the criterial session and the four post-criterial sessions, control mean = 99.11 ± 0.15 % correct, muscimol mean = 98.96 ± .31 % correct, Figure 1.3B). Remarkably, the rats that had been given muscimol infusions during the early sessions of list 1 performed significantly *better* on list 2 ($F_{(1,10)} = 6.47$, $P < 0.05$, Figure 1.3C). Thus, rats given early mPFC inactivation experienced less interference during list 2, suggesting that memories encoded without the mPFC do not exert as much proactive interference as normally encoded memories.

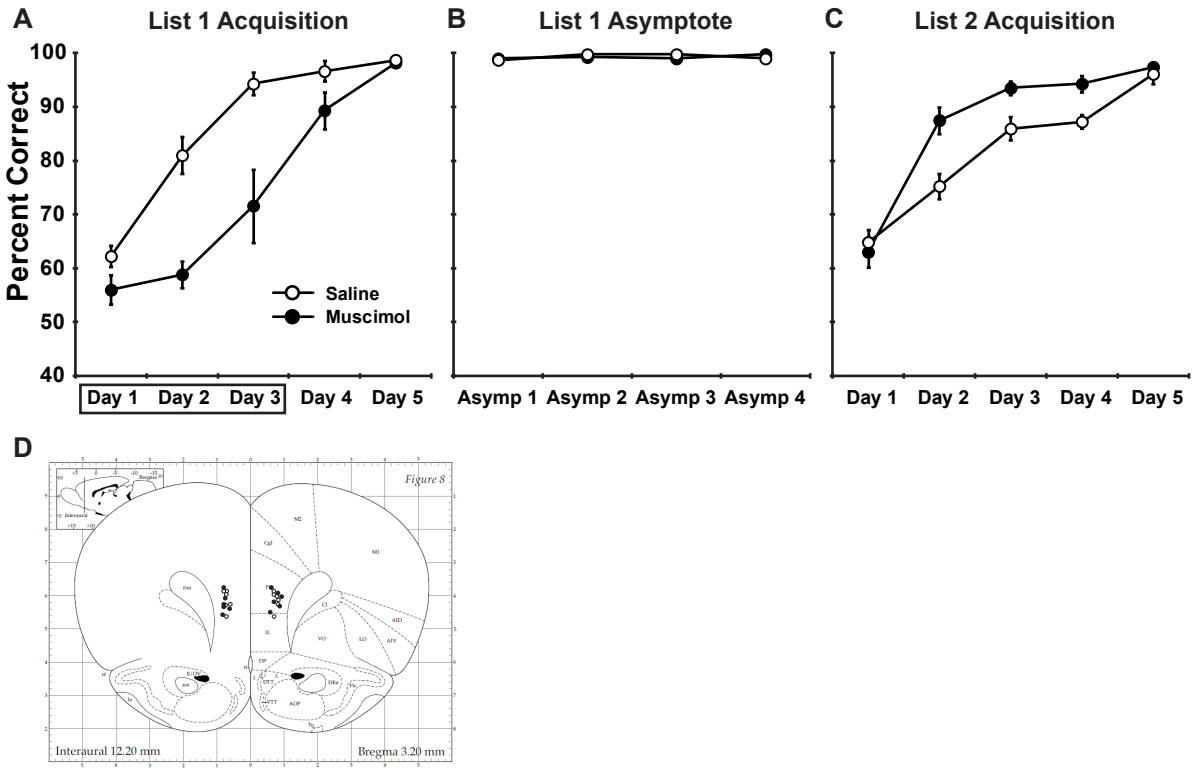

Figure 2.3 Effects of early mPFC inactivation on subsequent performance. (A) Percent correct for control and muscimol rats during the acquisition of the first list of odor discrimination problems. Infusions were given prior to the first 3 training sessions (indicated by the box), after which no additional infusions were given. As in experiment 1, temporary inactivation of the mPFC impaired learning but performance caught up to that of controls by the fifth training session. (B) Both groups of rats performed at high levels for the 4 asymptotic performance sessions. Error bars are not visible for some values because the SEM was smaller than the area covered by the data markers. (C) Performance during learning of the second list of conflicting odor discrimination problems. Rats that had been given muscimol infusions during the early acquisition of the first list performed better than controls. (D) Cannula placements are shown for the rats in experiment 3 (symbols as in A).

Discussion

Temporary inactivation of the mPFC impaired the acquisition and performance of the concurrent odor discrimination task, impaired the ability to learn a second list of conflicting odor associations after having learned the first list and affected the long term retrieval of memories. Since the odor memories are probably not permanently stored in the mPFC, these results are consistent with the idea that the PFC exerts top down executive control over processing in other brain regions (Miller and Cohen 2001) and that PFC executive control applies to the domain of memory (Wagner et al. 2001; Reber et al. 2002; Badre and Wagner 2007). As discussed above, prominent theories of PFC function hold that the PFC is involved in strategy selection, attentional set shifting and inhibiting prepotent response tendencies. Our results indicate that mPFC inactivation can produce severe deficits under conditions that do not require any of these functions. These results are consistent with the idea that the PFC is broadly involved in resolving interference (Badre and Wagner 2007; Blumenfeld and Ranganath 2007), regardless of whether the interference arises from competition among strategies, attentional targets, behavioral response tendencies or memory retrieval targets.

Previous studies have shown that the mPFC is not needed for simple discrimination learning (Birrell and Brown 2000; Ragozzino et al. 2003). In our experiments, muscimol rats were impaired in the concurrent acquisition of many odor discrimination problems although they were able to learn a few problems

normally as long as they were learned one at a time (see Figure 2.1C). Temporary inactivation of the mPFC also caused a striking impairment when they were given after the concurrent discrimination task was well learned, indicating that the mPFC role is not limited to learning but is also critical for retrieval. These results suggest that the mPFC is needed whenever subjects must simultaneously manage many items in memory, regardless of the particular type of task, and is consistent with an mPFC role in resolving interference. This role was directly confirmed in our second experiment, which was explicitly designed to induce high levels of interference (Butterly et al. 2012). Consistent with studies of human subjects (Incisa della Rocchetta and Milner 1993; Smith et al. 1995), muscimol rats were more susceptible to proactive interference than controls, resulting in severely impaired learning of the second list of conflicting odor discrimination problems.

Many authors have emphasized the idea that the PFC is critically involved in suppressing prepotent responses and that poor prefrontal control (e.g. in patients with lesions or children where PFC development is incomplete) results in perseveration (e.g. Tamm et al. 2002; Aron et al. 2003; Verbruggen and Logan 2008). Indeed, much of the work on executive control of memory processes in human subjects has focused on the inhibition of memory retrieval (Anderson and Green 2001; Depue et al. 2007). Our results indicate that the mPFC is not limited to inhibition, but is also involved in promoting the retrieval of desired responses and memories. The impaired performance of the well learned concurrent discrimination task could not have resulted from an inability to inhibit prepotent

responses. In fact, continued responding in previously established ways (i.e. perseveration) would have supported excellent performance. The results of experiment 2 also indicated that perseveration was not the primary problem in rats with temporary mPFC inactivation. When they were asked to learn a new list of conflicting items, muscimol rats made many more errors than controls. However, they did not make disproportionately more perseverative errors (erroneous responses to previously rewarded odors) than non-perseverative errors (erroneous responses to novel odors, Figure 2.2C).

In experiment three, rats given muscimol during the initial stages of learning were subsequently able to learn a new list of conflicting items faster than controls. This counterintuitive result is also consistent with the idea of an mPFC role in promoting memory retrieval. Although all of the rats learned the first list to equivalently high levels, intact controls experienced greater proactive interference on the second list than the rats given muscimol during the early learning sessions (see Figure 2.3). Apparently, having a functioning mPFC at the time of encoding results in memories that are particularly easy to retrieve in the future, and persistent intrusions of these old memories interferes with the subsequent acquisition of new conflicting memories. Consistent with this idea, human imaging studies have shown PFC activity during the successful encoding of memories (Reber et al. 2002; Ranganath et al. 2005; Spaniol et al. 2009). These findings suggest that the mPFC plays a critical role in the encoding and long term retrieval of important memories. In the present study, this lasted for

several days, with the average time from the last muscimol infusion to the beginning of list 2 training being more than six days.

Exactly how the mPFC promotes the long term retrieval of memories is not clear. During the initial stages of learning, as the odor memories are gradually laid down in their permanent storage site, mPFC neurons may become connected with the memory representations, possibly through interactions with the hippocampus (Anderson and Green 2001; Wagner et al. 2001). Later, retrieval of the memories could be triggered by any of several cues (e.g. return to the training context, presentation of one of the odor cues, etc.). However, the mPFC connections could serve as an additional source of excitatory input that primes the selective retrieval of the correct target memories. Neural network models suggest that this kind of top down excitatory input, combined with diffuse inhibition of other non-target representations, is an effective mechanism for resolving retrieval competition (Munakata et al. 2011).

This interpretation is consistent with each of our main findings. Learning a small number of discrimination problems in a blocked fashion is less sensitive to mPFC damage because there is little retrieval competition and non-PFC dependent sources of excitation (e.g. simple odor-reward associations) are sufficient to support performance. In the concurrent discrimination task, inactivation of the mPFC slowed acquisition because the presence of many partially encoded memories creates competition and one source of excitatory input to the correct memory targets is missing. Likewise, inactivation of the mPFC impaired asymptotic performance of the concurrent discrimination task

because a key mechanism of resolving retrieval competition has been lost. In our third experiment, temporary mPFC inacativation during acquisition prevented the formation of the excitatory connections from the mPFC, resulting in weaker long term retrieval of the memories and reduced capacity for them to cause proactive interference. Together, these findings support the hypothesis that the mPFC is critically involved in modulating memory retrieval processes.

There is ample evidence from studies of humans and animals that the mPFC and hippocampus interact during learning and memory processes (Anderson and Green 2001; Lee and Kesner 2003; Bunge et al. 2004; Wiltgen et al. 2004; Siapas et al. 2005) and there are anatomical connections between the two structures (Swanson 1981; Ferino et al. 1987; Hoover and Vertes 2007). Several authors have specifically proposed that the PFC exerts top down control of memory processes by influencing hippocampal retrieval processes (Anderson and Green 2001; Bunge et al. 2004; Munakata et al. 2011). Hippocampal neurons reliably respond to odor cues in similar tasks, suggesting that the hippocampus encodes odor memories (Wood et al. 1999; Manns et al. 2007) and a recent study of conditional discrimination found that temporary inactivation of the mPFC impaired memory and caused hippocampal responses to become less selective for particular odors (Navawongse and Eichenbaum 2012). This result is clearly consistent with the idea that mPFC input promotes the selective retrieval of specific odor memories via interactions with the hippocampus.

Previously, we showed that the hippocampus is critically involved in the olfactory memory task used here (Butterly et al. 2012). Using the same

procedures as experiment 2, we found that temporary inactivation of the hippocampus selectively blocked the ability to use contextual information to overcome interference but they had no effect on learning the second list in the same context. In contrast, temporary inactivation of the mPFC impaired learning regardless of the context condition (Figure 2.2A). These findings suggest that both structures are involved in resolving interference, but in different ways. An extensive literature has shown that the hippocampus is involved in encoding contexts (for reviews see Hirsh 1974; Wilson et al. 1995; Smith and Mizumori 2006) and we have suggested that associations of learned items with the learning context provides an automatic mechanism for interference free retrieval of the relevant memories whenever subjects revisit the familiar context (Butterly et al. 2012). However, this mechanism is only useful when the items to be remembered are strongly linked to a particular context. In other conditions, a more general interference resolution mechanism must be used. As described above, the mPFC seems to fulfill this need by exerting a top down influence on memory retrieval whenever there is retrieval competition.

The idea of conflict resolution is central to many theories of PFC function and, as other authors have noted (Badre and Wagner 2007; Blumenfeld and Ranganath 2007), a PFC role in resolving interference is consistent with that idea. This suggests that resolving mnemonic interference may be one facet of a broader conflict resolution function of the PFC. However, it is also possible that the classic deficits associated with PFC damage may reflect a failure to retrieve the appropriate strategy, attentional target or behavioral response from memory

due to poor interference resolution. The present results suggest that interference is sufficient to engage the PFC and studies of PFC interactions with the hippocampus may help determine the degree to which various kinds of conflict resolution may have mnemonic components (Anderson and Green 2001; Lee and Solivan 2008; Navawongse and Eichenbaum 2013). In any case, we suggest that prefrontal modulation of retrieval processes is an important mechanism for successfully resolving competition and that this is a key aspect of behavioral flexibility.

Materials and Methods

Subjects

62 adult male Long-Evans rats (Charles River Laboratories, Wilmington, MA) were individually housed and maintained on a 12 hour light-dark cycle. Rats were food restricted to 80%-85% of their ad libitum weight, and were given free access to water. All experiments were conducted in compliance with guidelines established by the Cornell University Animal Care and Use Committee.

Surgery and Microinfusions

Subjects were anesthetized with isoflurane and placed in a stereotaxic device (Kopf Instruments, USA). The skull was exposed, bilateral craniotomies were drilled and dual (bilateral) 22-gauge guide cannulae (Plastics One, Roanoke, VA) were implanted using standard stereotaxic techniques. The guide

cannulae were implanted so that infusion cannulae (26 ga), which protruded 0.5 mm beyond the tip of the guide cannulae, were positioned in the prelimbic/infralimbic cortex (3.2 mm anterior and 0.75 mm lateral to bregma, and 2.7 mm ventral to the cortical surface). The guide cannulae were secured to the skull with bone screws and dental acrylic. Rats were allowed to recover for 5-10 days before beginning behavioral training. Temporary lesions were induced with the $GABA_A$ agonist muscimol. Thirty minutes prior to the relevant training sessions, 0.5 µl of a solution containing 1 mg/ml of muscimol or an equivalent volume of saline solution was infused into each hemisphere. The infusion cannulae were left in place for 1 minute after the infusions. An injection volume of 0.5 µl was used based on previous studies of the mPFC inactivation during memory tasks (Lee and Kesner 2003; Rich and Shapiro 2007). The spread of 1.0 µl of injected muscimol in the cerebellum diffuses at a radius of 1.6-2.0 mm from the injection cite (Arikan et al. 2002), thus it is estimated that an injection of 0.5 µl is contained within the prelimbic/infralimbic borders with minimal diffusion to surrounding regions.

Apparatus

Details of the apparatus, odor stimuli and training procedures are given elsewhere (Butterly et al. 2012). Briefly, the rats were trained in Plexiglas chambers (45cm wide X 60cm long X 40cm deep) equipped with a removable divider, which separated the odor presentation area from an intertrial interval area. Thirty-two pure odorants served as cues. The amount of each odorant was

calculated to produce an equivalent vapor phase partial pressure when mixed with 50 ml of mineral oil (Cleland et al. 2002). These odorants were mixed into corncob bedding material and presented to the rats in ceramic cups (8.25cm in diameter, 4.5cm deep) that fit into circular cutouts cemented in the floor of the chamber.

Behavioral Training Procedures

Prior to training, all of the rats were acclimated to the training apparatus (two 15 min sessions in each of the two contexts, described below) and shaped to dig in cups of scented bedding material for buried rewards (45 mg sucrose pellets, Bioserve, Frenchtown, NJ).

Experiment 1 Methods: The first experiment was designed to assess the role of the mPFC in the acquisition and performance of a multi-problem concurrent discrimination task. The rats were given concurrent training on a list of 8 odor discrimination problems (16 individual odors). The two odors comprising each problem were always presented together, one odor in each cup. Within each discrimination problem, one odor was always rewarded and the other was not. At the start of each trial, the experimenter placed the two cups containing the odorized bedding in the apparatus, raised the divider and allowed the rat to dig until he retrieved the reward (corrections were always allowed following errors). A digging response was recorded if the rat displaced any of the bedding, except for incidental contact (e.g. stepping into the cup without digging). After consuming the reward, the rat was returned to the waiting area and the divider was replaced

for an inter-trial interval of approximately fifteen seconds while the experimenter prepared the cups for the next trial. The predictive value of the odors (rewarded or non-rewarded) was counterbalanced across subjects and their locations (left or right side of the chamber) were randomized. The rats were given daily training sessions consisting of 64 trials (8 trials with each discrimination problem, presented in an unpredictable sequence) until they reached a behavioral criterion of at least 90% correct on 2 consecutive sessions. After achieving this criterion, the rats were given an additional 4 post-criterial training sessions. Rats were given muscimol or saline control infusions during the first 3 training sessions (acquisition) and during the first 3 post-criterial sessions (asymptotic performance). The same cohort of rats was used in both tests. The rats that had been given muscimol infusions during acquisition served as saline controls during asymptotic performance and the rats that received control infusions during acquisition were given muscimol during asymptotic performance.

In order to determine whether the mPFC was needed for learning individual discrimination problems one at a time, two additional groups of rats (control and muscimol) were trained in a blocked learning condition. For these rats, the same 8 odor discrimination problems were used, but each problem was presented repeatedly until the rat reached the criterion before moving on to the next problem. In order to match the concurrent training condition as closely as possible, we used a criterion of 90% correct over 10 trials and the rats were allowed to complete as many problems as possible within any given session, except that no new problems were begun after the 64^{th} trial (i.e. the number of

trials per session in the concurrent condition). In most cases, each session continued until the rat achieved the critierion for the last problem of the day and training on the next problem of the list began on the following day. In a few cases, the rat failed to reach the criterion on the last problem after 20 trials and training was discontinued for the day but resumed with the same problem on the following day. Daily training sessions were given until the rat achieved the criterion for all 8 of the discrimination problems. None of the rats failed to reach the criterion for any of the problems. For consistency with the analysis of the concurrent training data, we computed the percentage of trials with a correct response over the course of training to the criterion on each of the discrimination problems. We also analyzed the number of trials needed to reach the criterion for each problem.

Experiment 2 Methods: Experiment 2 involved learning two lists of odor discrimination problems with conflicting items in order to assess the role of the mPFC in resolving interference. For this experiment, rats were trained on the first list of discrimination problems as described above, but with no infusions. After achieving the criterion and completing the four post-criterial training sessions (as in experiment 1) the rats were trained on a second list of 8 discrimination problems. Training on the second list was identical to the list 1 training sessions. However, in order to induce interference, each new discrimination problem consisted of a novel odor and an odor which had previously been presented on list 1. Thus, list 2 consisted of 16 odors, half of which had appeared previously on list 1. Of the eight odors taken from list 1, half had been rewarded previously and

half had not. For example, if the first two odor pairs on list 1 were A+/B- and C+/D-, the first two odor pairs on list 2 would be X+/A- and D+/Y-. This ensured that the rats could not adopt a strategy of simply approaching or avoiding the novel odor within each new odor pair.

Experiment 2 also involved a context manipulation in which half the rats were trained on the second list in the same context where they learned the first list (a white box) while the other half learned the second list in a new context (a black box). The two contexts differed along the following dimensions: color of the chamber (white or black), color of the curtains surrounding the training area (black or white), substrate in the chamber (Plexiglass floor or a black rubber mat), the 65 dB continuous background masking noise (white noise or pink noise) and the ambient odor left by wiping out the chamber with baby wipes prior to each training session (unscented or scented, Rite Aid, Inc). Additionally, the rats were transported in covered cages to the experimental area by different methods for the two contexts (via a cart or carried by hand). All of the rats were given 5 training sessions on the second list. The rats were given muscimol or saline control infusions prior to the first three training sessions. No infusions were given during the final 2 training sessions.

Experiment 3 Methods: In experiment 3, rats were trained on the two odor lists as in experiment 2. However, the rats were given muscimol or control saline infusions prior to the first 3 sessions of list 1, after which no more infusions were given. Daily training continued until they reached the criterion and had completed

4 additional post-criterial training sessions. This was followed by 5 training sessions on list 2 in the same context.

Data Analysis

For each subject and training session, the percentage of trials with a correct response and other dependent measures (e.g. trials to criterion, numbers of errors of various types, etc.) were computed and the data were submitted to ANOVA (SPSS, IBM Inc.). For all repeated measures analyses, Hyun-Feldt corrected p-values were automatically computed in order to adjust for violations of the sphericity assumption.

Histology

Following testing, all rats were anesthetized with isolflurane, transcardially perfused with 10% paraformaldehyde and their brains removed, frozen and sectioned at 40 μm, mounted on slides and stained with cresyl violet in order to identify the infusion locations.

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Chapter 3

The Medial Prefrontal Cortex Manages Working Memory Interference Independent of Changes in Strategy

Introduction

Mnemonic interference is a failure to retrieve a target memory due to the presence of other memories. Interference can result exclusively from problems at retrieval rather than encoding (Loftus and Patterson 1975) and typically manifests as the retrieval of related, non-target memories. For example, memory for where one has recently parked in the office lot can interfere with memory for where one has parked *today*, resulting in the temporary retrieval of the wrong parking spot. The fact that memory is susceptible to interference is suggestive of certain aspects of memory organization, namely that some memory traces have enough in common that they can compete during retrieval. Nevertheless, memories are often retrieved interference free. Critical to accurate memory retrieval are mechanisms that manage potential interference from other memories. If so, resolution mechanisms could underlie how target memories are effectively retrieved from an array of related memories.

In humans, the prefrontal cortex (PFC) is generally thought to play a major role in interference resolution (Nee et al. 2007). Behavioral studies show that PFC damage increases susceptibility to interference (Luria 1971; Rocchetta and Milner 1993; Lou Smith et al. 1995; Shimamura et al. 1995), and activity in PFC

subdivisions is associated with interference resolution in experimental settings (Sylvester et al. 2003; Badre et al. 2005; Kuhl et al. 2007; Wimber et al. 2009). Importantly, the PFC is not necessarily critical for memory retrieval per se, since PFC damage does not completely abolish the ability retrieve items from memory. Instead, the PFC appears to be more involved in a modulatory role concerning the control of memory retrieval, such as the retrieval of context-appropriate target memories or alternatively, avoiding the retrieval of unwanted memories.

Other research already suggests the PFC plays a specific role in managing competing memories. One mechanistic theory of interference resolution with considerable support proposes that inhibitory processes associated with executive control suppress competing memory traces (Anderson and Neely 1996; Anderson 2003). In support of this view, recent imaging evidence suggests that memory representations are inhibited by the retrieval of competing memories (Wimber et al. 2015). Crucially, this and other imaging studies show that PFC activity is associated with this type of memory suppression (Wimber et al. 2008, 2009; Crescentini et al. 2010), consistent with the classic role of the PFC in executive and inhibitory control (Miller and Cohen 2001; Yeung et al. 2004; Munakata et al. 2011) and the cognitive control of memory retrieval (Dobbins et al. 2002; Badre et al. 2005; Badre and Wagner 2007). Collectively, the PFC is an intriguing candidate for investigating the processes necessary for managing competing memories.

Despite significant advances in our understanding of the areas of the brain important for managing interference, precise brain mechanisms of interference resolution are difficult to derive from behavioral and imaging studies in humans alone. Fortunately, emerging evidence from tractable animal models may help further reveal how the PFC is involved in managing memory competition. Consistent with an mPFC role in establishing competing memories, we have shown that, like in humans, the mPFC is critical for rats to overcome proactive interference from prior learning (Peters et al. 2013). In the same study, we also demonstrate an important role for the mPFC in mnemonic processes associated with managing the acquisition and retrieval of many simultaneously learned, contextually-related memories. In support of a specific role for the mPFC in managing memories, we show that the mPFC is needed for concurrent discrimination learning but not blocked discrimination learning. Each of these findings is consistent with a role for the mPFC in managing interference, but it is not entirely clear whether each finding compels an interference interpretation over and beyond the possibility that the mPFC might also be involved in other critical executive functions such as strategy selection or rule-representation. In our proactive interference discrimination task, rats learn a new set of overlapping (high interference) discrimination problems and it is impossible to rule out that mPFC inactivation causes disruptions in the ability to adopt new memories beyond the effects of interference from previous memories. Despite substantial behavioral and neurophysiological support for an mPFC involvement in various mnemonic processes (Lee and Kesner 2003; Jo et al. 2007; DeVito and

Eichenbaum 2011) few studies have specifically isolated interference resolution in rats while controlling for other factors such as changes in strategy or flexibility requirements. In the currently study, we set out to test the role of the mPFC in managing interference by training rats on a single strategy, and then applying that strategy to different versions of a task that vary only in the level of within session interference.

The current study builds on other research showing a functional homology between dorsolateral prefrontal cortex (DLPFC) in primates and the rat mPFC, with these respective regions each playing a role in strategy selection, attention switching, rule-based learning and similar executive functions (Birrell and Brown 2000; Ragozzino et al. 2003; Ng et al. 2007; Rich and Shapiro 2007, 2009). However, we argue that the PFC role in strategy selection and rule-learning includes an underlying need to resolve mnemonic competition. In both humans and animals, performance shown to be sensitive to PFC damage is often dependent on the requirement that subjects learn successive tasks that contain overlapping task-relevant information, thus producing conflict between the cue-associated memories that guide performance. For example, in the Stroop switching task, both color and procedural cues – necessary for identifying the color or reading the word – are continually present during the execution of either rule. Switching between rules requires subjects to resolve the conflict between these cues in order to actively maintain the relevant strategy. Similar competing strategies exist in other PFC sensitive tasks, such as the ongoing presence of

stimuli of different modalities in Wisconsin Card Sorting Task, as well as animal adaptations of these tasks. Together, evidence from task-switching, strategy selection, rule-learning and other PFC tasks suggests a major processing contribution of the PFC is to resolve potential interference from conflicting memories.

The PFC is also known to be important for working memory (Goldman-Rakic 1995), including a role in managing interference in working memory tasks (Badre and Wagner 2005; Jonides and Nee 2006). In fact, greater working memory capacity in humans is associated with less susceptibility to proactive interference (Rosen and Engle 1997; Kane and Engle 2000; Shipstead and Engle 2013), and this effect has been functionally linked to activity in the DLPFC (Burgess et al. 2011). Likewise, the rat mPFC is known to be involved in working memory (Delatour and Gisquet-Verrier 1996; Kesner et al. 1996; Seamans et al. 1998). If our hypothesis that the PFC is important for managing interference is correct and the rat mPFC is functionally similar to human DLPFC, then the mPFC should also be involved in managing proactive interference during working memory tasks for rats. We capitalized on this logic in order to develop a task for rats that allowed us train rats on a single rule or strategy under different levels of interference. In the current study, we trained rats on a continuous match-to-sample (CMTS) task (Wood et al. 1999) and then inactivating the mPFC during performance of the task. We suspected that the mPFC would play an important role in resolving working memory interference inherent to the demands of the

task. To this end, we first show behavioral evidence that the CMTS task induces interference. Next, we observed a greater involvement of the mPFC in the CMTS task when the stimulus presentation order induces greater interference. Importantly, this task also allowed us to train rats on a single rule, and then perform a within subjects test of the mPFC role in both high and low interference versions of that rule. This allowed us to assess the contribution of the mPFC to resolving interference without introducing changes in strategy or rule requirements needed to perform the task.

Results

Repeated items in a continuous match to sample task cause interference

We trained rats on a continuous match-to-sample task using a pool of olfactory stimuli as cues. Rats were trained to dig to retrieve a buried reward in single ceramic cups containing odorized bedding whenever the current odor stimulus matched the odor from the previous trial (figure 3.1A). Odors that did not match the previous cue were never rewarded, and we recorded errors whenever rats attempted to retrieve a reward in an unbaited stimulus cup. The olfactory stimuli were repeatedly drawn from a pool of 12 odors, presented one trial at a time, for daily sessions consisting of 96 trials. Interestingly, we observed a pattern of errors consistent with interference from previous within session memory for recent presentations of repeated olfactory cues.

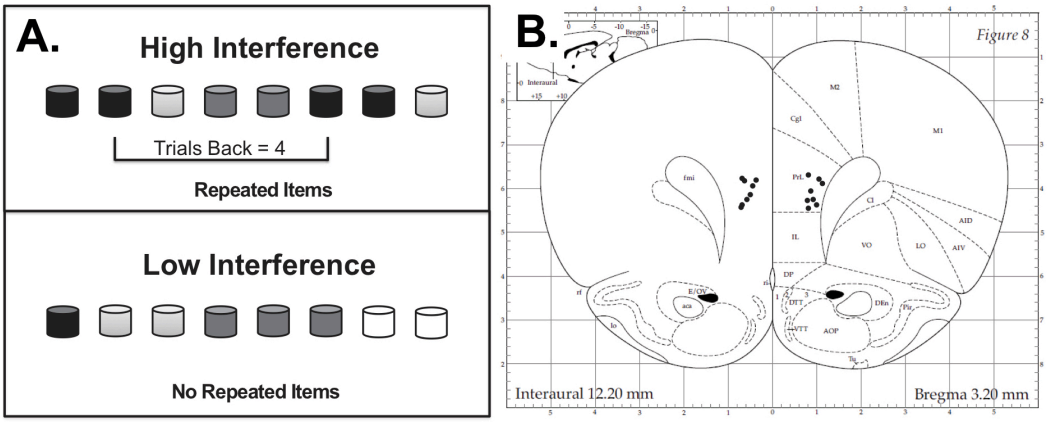

Figure 3.1. Schematic of high and low interference versions of the CMTS task. (A) Left to right cylinders reflect trial order of cups of odorized bedding, colors indicate unique odors. Rats are given a series of presentations of cups containing odorized bedding, one at a time, and must dig to retrieve a buried reward if the current odor matches the odor on the previous trial. In the high interference version of the task, the same odor is presented multiple times throughout the session. Trials back values represent the number of intervening trials since that last presentation of current trial odor for individual nonmatch trials. In the low interference version, each nonmatch trial consists of a unique odor to that session and is not repeated after subsequent match trials. (B) Cannula placements targeting the prelimbic/infralimbic border of the mPFC.

Rats first required 4-8 training sessions on the CMTS rule to reach an asymptotic performance criterion of 80% correct choices for two consecutive sessions. Unpublished data suggest that rats asymptote around 80% correct choice performance on our training list of odor cues, although maximal performance on this task is subject to manipulation depending on the precise structure of overlapping odor presentations (see discussion). After reaching the performance criterion, we tested the role of the mPFC on high interference version of the CMTS task using an inactivation procedure that followed a within subjects, saline(1)-muscimol(1)-saline(2)-muscimol(2) design (see methods).

Thus, each rat was tested on the high interference list during two saline injection sessions and two muscimol injection sessions, for a total of four testing sessions. Paired t-tests revealed no difference in choice performance between the two saline sessions ($t(7) = -1.159$, $p = .281$) or the two inactivation sessions ($t(7) = .172$, $p = .868$), so saline and inactivation sessions were combined, respectively, in all analyses.

A long history of research on mnemonic interference has shown that prior training trials cause proactive interference in working memory tasks under a variety of circumstances, such as when there are perceptual or conceptual repetitions in the stimuli that guide performance over the course of a task (Underwood 1957; Keppel and Underwood 1962; Brainerd and Dempster 1995; D'Esposito et al. 1999; May et al. 1999). In our CMTS task, we computed a "trials back" measure of recent experience with repetitions of odor stimuli by determining for each non-match trial (excluding the trials involving first presentation of each odor per session) the number of intervening trials since the last presentation of the same odor cue (Figure 3.1A, see "trials back"). This produced for each non-match trial an instantaneous value for the number of trials back since the last presentation of same odor. We next computed the average error rate for all subjects for each non-match trial during the control (saline) testing sessions on the high interference list only. Trials back values and average error rate were negatively correlated ($r=-0.765$, $P<.001$) during the control sessions, indicating that memory for recently presented odors interfered with the rats' ability to match the current odor cue to the previous trial (figure 3.2).

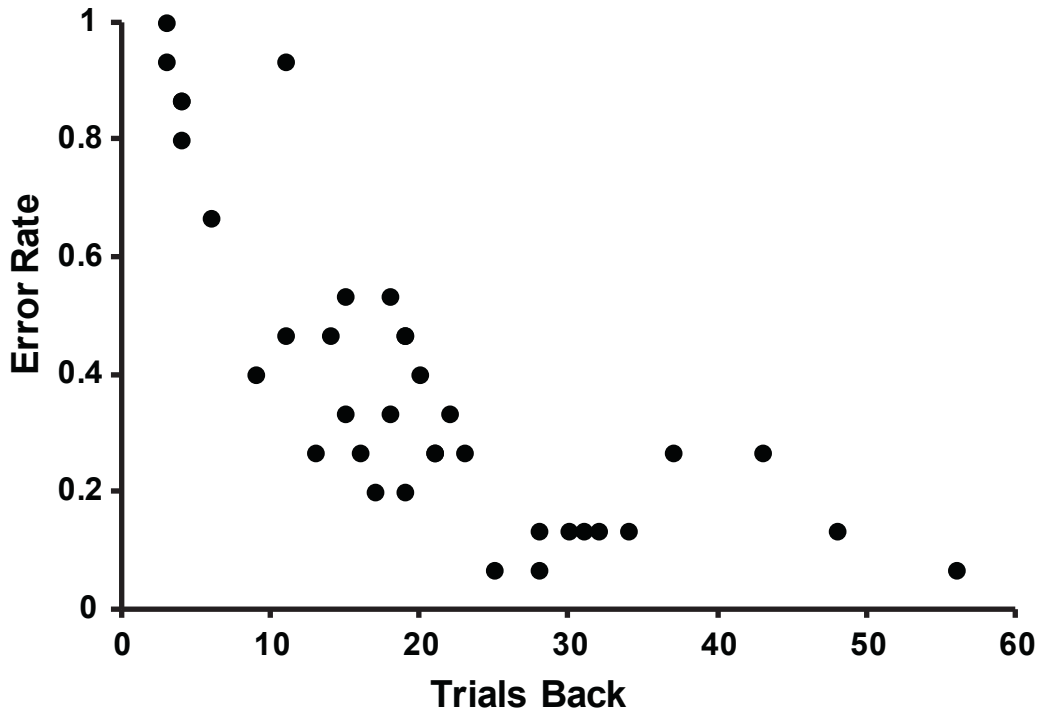

Figure 3.2. Relationship between error rate and trials back values indicates mnemonic interference. Control data for error rate on individual trials averaged across all animals on the high interference list. The percentage of errors for each nonmatch trial (error rate) is plotted against the number of intervening trials since last presentation of the current trial odor (trials back). A strong relationship between trials back and error rate indicates that memory for recently presented odors interferes with matching performance of the adjacent trial odor ($r=-0.765$, $P<.001$).

Differential involvement of the mPFC during varying levels of interference

Following training to criterion on the CMTS rule, each rat performed both the high and low interference versions of the task under both control and inactivation conditions. Rats were injected with either saline or muscimol on alternating daily sessions 30 minutes prior to testing. Rats were tested on 4 sessions of the high interference list following this ABAB schedule (saline-muscimol-saline-muscimol) and on two sessions of the low interference list (saline-muscimol). The same match-to-sample rule was required in both high and low interference versions of the task. What distinguished high and low interference was whether or not olfactory stimuli were repeated within a single session. In the high interference version, we used a pool of 12 odors, where each odor was reused at total of 8 times throughout the session. For the low interference version, we increased the number of odors to 24, and no odor was repeated, except on match trials (rewarded). The percentage of correct choices in the both the high and low interference versions of the task for each inactivation condition were submitted to a 2 way repeated measure ANOVA, with interference category (low or high) and inactivation condition (saline or muscimol) as within subjects factors. A main effect of inactivation ($F(1,7)=17.888$, $p<.005$) indicated that inactivation of the mPFC impaired performance on the CMTS task. A main effect of interference category ($F(1,7)=37.290$, $p<.001$) showed that the rats performed better on the low interference list in both control and inactivation conditions, indicating that mPFC inactivation does not render rats incapable of

performing the CMTS rule, per se. Importantly, a significant interaction between inactivation and interference conditions indicated a differential impairment due to mPFC inactivation across both levels of interference in the task ($F(1,7)=7.541$, $p<.05$) (figure 3.3A). Next we compared the average magnitude of impairment due to mPFC inactivation in the high interference version of the task to the impairment in the low interference version, which revealed that the decrease in performance due to inactivation was greater in the high interference version of the test ($t(7) = 2.746$, $p < .05$). This confirms the results of the two-way ANOVA and indicates a greater role for mPFC in high interference conditions (figure 3.3B).

Discussion

Several results of this study are noteworthy. First, the olfactory CMTS task is a practical rat model of working memory interference. Rats learn the task readily and perform well, yet memory for previous within task trials is shown to induce interference on subsequent trials when the same cues are reused within a short temporal window throughout the session. When rats are required to match the current trial odor to the previous odor in order to retrieve a reward, they are much more likely to erroneously dig for the reward if the non-match (non-rewarded) trial odor has been presented recently but not on the previous trial. This result indicates that memory for recent presentations of odors interferes with memory for the odor on the previous trial, and is analogous to the well-known effect that prior trial stimuli cause proactive interference in human working

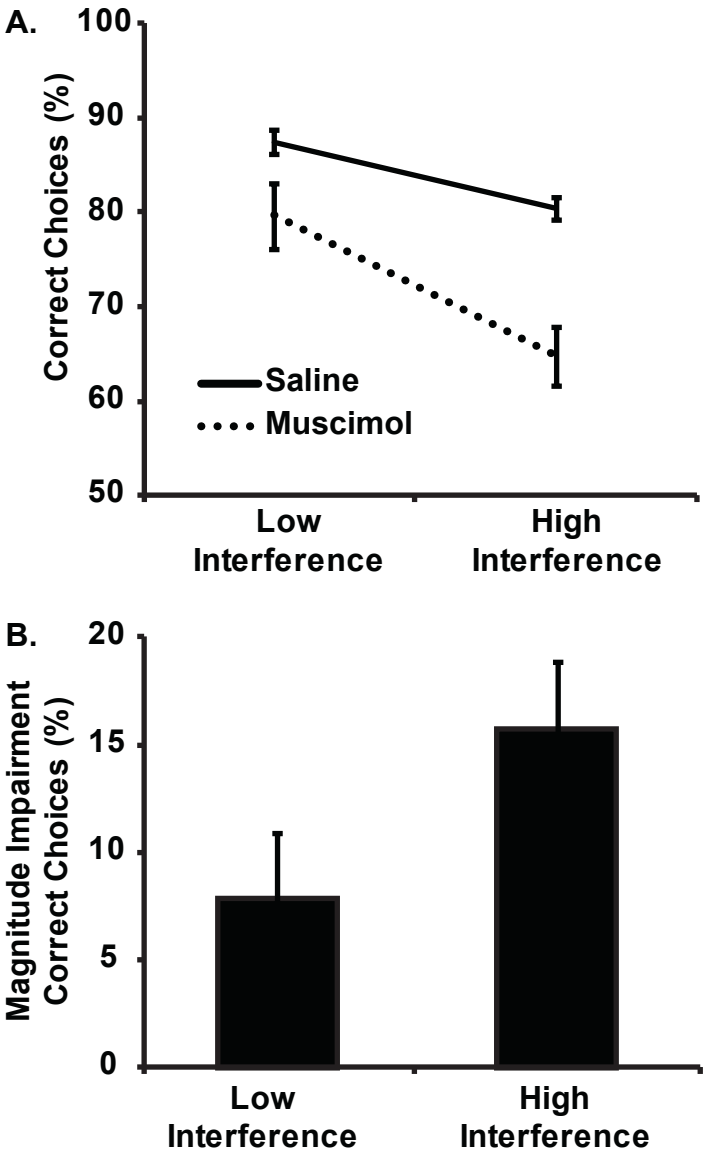

Figure 3.3. Performance impairment due to mPFC inactivation interacts with interference level in continuous match to sample. (A) Average performance on the high and low versions of the continuous match to sample task is shown for high and low interference versions of the CMTS task. All subjects perform better on the low interference version. Inactivation of the mPFC impairs performance on both high and low interference versions of the task, but an interaction between the inactivation condition and interference condition indicates that loss of the mPFC differentially affects performance across interference versions ($F(1,7)=7.541$, $p<.05$). (B) A comparison of the difference in performance due to mPFC inactivation between the high and low interference versions of the CMTS task reveal a greater impairment in the high interference condition ($t(7) = 2.746$, $p < .05$).

memory tasks. Furthermore, if enough odor stimuli are used in the CMTS task so that there are no repetitions of odor presentations on non-match trials during a single session, rats make fewer errors, further supporting that interference from recent odor presentations affects working memory performance. To our knowledge, this is the first report of behavioral evidence from rats of working memory interference that specifically examines the ongoing influence of prior stimuli on performance of subsequent trials in a matching-to-sample task. Further assessment of the brain mechanisms that help manage working memory interference in the CMTS task should provide a better understanding of how the brain copes with competing memories during retrieval.

Second, the mPFC is important for performing the CMTS task, consistent with the known involvement of the mPFC in working memory (Delatour and Gisquet-Verrier 1996; Kesner et al. 1996; Seamans et al. 1998). However, working memory deficits alone do not fully account for our results. Using a within subjects design, we show that although mPFC inactivation impairs performance in both high and low interference conditions of the task, there is a significant interaction between interference and inactivation conditions, indicating that mPFC inactivation results in a stronger deficit in the high interference version of the task. This suggests a greater role for the mPFC when overlapping memory cues must be managed to maximize performance, particularly when the potential for interference among memories is high. This is consistent with influential experiments in humans that demonstrate a functional relationship between

working memory and resistance to proactive interference (Kane and Engle 2000; Shipstead and Engle 2013).

A large body of work shows an important role for the PFC in task switching and attentional set-shifting critical for behavioral flexibility (Monsell 2003). Research on the mPFC of rats has often convincingly modeled the established role of the human PFC in these executive functions (Ragozzino et al. 1999; Birrell and Brown 2000; Ragozzino et al. 2003; Ng et al. 2007). However, similar to the mPFC role in working memory, our results are not fully accounted for by a role for the mPFC in strategy selection or task-switching. We trained rats on a match-to-sample rule and then tested rats on that rule using stimuli presented in two different orders, which corresponded to different levels of within session interference. Thus, the rules, strategies, relevant stimulus modality and working memory requirements are all equivalent in both versions of the task. Therefore, none of these other factors associated with PFC function can fully account for the differential involvement of the mPFC in the CMTS task. What varied between task versions was simply whether repetitions of odor stimuli were presented over a single session. It has long been known that previous trial stimuli can cause interference in later trials of working memory tasks (Keppel and Underwood 1962). We show that rats make more errors on the repeating items version of the task, and those errors reflect interference from recent repetitions. Moreover, if we eliminate repetitions during the session, rats make fewer errors. Therefore, the critical difference between the two versions of the task is the level within-session interference from prior trials. Inactivation the mPFC differentially affects

performance of each version of the task, with inactivation causing a greater impairment in high interference situations.

Inactivation of the mPFC during the CMTS likely interrupts the normal memory circuitry that mediates performance of the CMTS rule. Because, inactivated rats make more errors overall in both versions of the CMTS task, we cannot rule out the possibility that the mPFC participates in some aspect of the rule or strategy representation that guides performance. In fact, we believe the mPFC must be important for certain aspects of acquiring rules or strategies. Previously, we have shown the mPFC is involved in the acquisition and retrieval of odor discrimination memories, particularly when many discrimination problems are learned simultaneously. However, mPFC inactivated rats showed some evidence of learning during acquisition and did not drop to chance levels during retrieval, demonstrating that some aspects of memory persisted in both conditions. In the same study, mPFC inactivation caused the greatest impairment – with no evidence of learning during the inactivation condition – when rats were required to overcome proactive interference. We suspect this indicates an organizational role of mPFC role during memory formation and retrieval. This role would be consistent with our view that the mPFC is strongly involved in managing competing memories. Similarly, in the current CMTS study, mPFC inactivation caused impairments in memory performance, but resulted in a stronger impairment in the high interference version of the task. Collectively, these studies suggest that a critical contribution of the mPFC is to manage potential interference generated by competition from related memories.

Methods

Subjects

Eight adult male Long-Evans rats (Charles River Laboratories, Wilmington, MA) were housed singly and maintained with a 12 hour light-dark cycle. Rats were food restricted to 80%-85% of their ad libitum weight, and were given free access to water. All experiments were conducted in compliance with guidelines established by the Cornell University Animal Care and Use Committee.

Surgery and Microinfusions

Prior to behavioral training, subjects were anesthetized with isoflurane and placed in a stereotaxic device (Kopf Instruments, USA). The skull was exposed, bilateral craniotomies were drilled and dual (bilateral) 22-gauge guide cannulae (Plastics One, Roanoke, VA) were implanted using standard stereotaxic techniques. The guide cannulae were implanted so that infusion cannulae (26 ga), which protruded 0.5 mm beyond the tip of the guide cannulae, were positioned in the prelimbic/infralimbic cortex (3.2 mm anterior and 0.75 mm lateral to bregma, and 2.7 mm ventral to the cortical surface). The guide cannulae were secured to the skull with bone screws and dental acrylic. Rats were allowed to recover for 5-10 days before beginning behavioral training. Temporary lesions were induced with the $GABA_A$ agonist muscimol. Thirty minutes prior to the relevant training sessions, 0.3 µl of a solution containing 1 mg/ml of muscimol or an equivalent volume of saline solution was infused into

each hemisphere. The injectors were left in place for 1 minute after the infusions. The volume of 0.3 µl of muscimol injected in each hemisphere was reduced from a previous study from our lab (Peters et al. 2013) to increase the control over diffusion of muscimiol to surrounding regions and was based on existing evidence for an effect on working memory of mPFC inactivation at a volume of 0.3 µl per hemisphere (Yoon et al. 2008).

Apparatus

Rats were shaped to dig for reward in a single Plexiglas chambers (45cm wide X 60cm long X 40cm deep) equipped with a removable divider, which separated the odor presentation area from an intertrial interval area. A single odor was always used during the shaping procedure.

Following shaping, rats were trained on the CMTS task in a 33.5 inch by 19 inch rectangular wood open chamber with 20 inch high angled walls. Four cup locations were marked by circular cutouts located at each corner of the box. A combination of visual (black or white), textural (wood or plastic-covered walls) and olfactory (cleaned with scented or unscented baby wipes) cues distinguished each half of the box.

Twelve or Twenty-four pure odorants served as cues, depending on the level of interference category. The amount of each odorant was calculated to produce an equivalent vapor phase partial pressure when mixed with 50 ml of mineral oil (Cleland et al. 2002). These odorant solutions were mixed into corncob bedding material at a ratio of 5 mL odor solution: 1 L of bedding, and

presented to the rats in ceramic cups (8.25cm in diameter, 4.5cm deep) that fit into circular cutouts attached to the floor of the chamber.

Behavioral Training Procedures

Details of the odor stimuli and shaping procedures are given elsewhere (Butterly et al. 2012). Briefly, the rats were shaped to dig in a single cup containing odorized bedding material. The rats were first acclimated to the shaping apparatus (two 15 min sessions) and then shaped to dig in a single cup of scented bedding material for buried rewards (45 mg sucrose pellets, Bioserve, Frenchtown, NJ).

The CMTS task was adapted from a previous continuous *non-match* to sample task (Wood et al. 1999). Following shaping to dig for reward, rats were acclimated to the CMTS training apparatus for a single 10 min session immediately prior to the first training session. Rats then began training on the CMTS rule. Twelve odors were used as cues during training. For each trial, a single cup containing bedding mixed with one of the 12 odors was placed in one of four cup locations within the rectangular arena. Each training session was composed of 96 trials, and each odor was presented 8 times over the course of the entire session. For each trial, the cup placed in the chamber contained a buried reward if its odor matched the odor presented on the previous trial. If the current odor did not match the previous trial, the cup was not baited. Rats progressed through all 96 trials one odor presentation at a time, where each trial was rewarded based on whether it matched the previous trial. Half of the match

trials within a session followed a nonmatch trial and the other half followed a match trial. Additionally, rats were never presented with more than 4 nonmatch trials in a row. A 10 s intertrial interval separated each trial.

Odors were presented in a pseudorandom fashion that was designed to maximize the equivalent distribution of trials back values (trials back defined above). A total of three lists were used to guide the odor presentation order during training, with each session alternating between one of the three lists. The purpose of the different session lists was so that on consecutive sessions, different odors appeared at different positions within the list, but the relative distribution of odors was identical on each list. Thus, the order of odor identity was different for adjacent sessions. This ensured that the rats did not learn a consistent order of odor presentation. However, the relative structure of the list was the same for each session, but different odors could appear at different positions of the list on different sessions. For example, if odor A was seen on trials 1, 15 and 20, and odor B was seen on trials 4, 17 and 45 during session 1, session 2 might involve presenting odor B in place of odor A for trials 1, 15 and 20 and vice versa. The key is the individual odor presented at trial position 1, 15 and 20 was always the same within a given session, but odor identity at these positions could change during different session. This pattern was consistent across all trials and all sessions. This produced 3 lists with equivalent trial back values despite different orders of odor presentation, which ensured that any effects observed by the presentation order were not due to the odor identities themselves.

Each trial consisted of single cue presented in 1 of 4 cup locations. Presentation locations were counterbalanced for total number of presentations in each location, as well as for the number of rewarded and non-rewarded presentations for each location. In addition, each trial alternated between the north and south pair of cup locations. Together, this ensured that rats could not predict the precise cup location for the current trial, but made it easier for the experimenter to distinguish adjacent trials during training.

Error responses were recorded whenever a rat dug in an unbaited cup by displacing any bedding material with its nose or paw, or conversely, when rats rejected a baited up. Correct responses were recorded when rats retrieved a buried reward or correctly rejected an unbaited cup. To complete each trial, the rat was required to approach the cup so that its nose crossed the vertical cylindrical extent above the cup rim. If the rat removed its nose from the rim without displacing any bedding, it was scored as a rejection and the cup was immediately removed. If the rat dug, he was allowed to dig until he retrieved the reward or stopped digging if no reward was present.

High and low interference Versions of the CMTS Task

Rats were trained in the CMTS rule on daily sessions until they reached a criterion of 80% correct choices for 2 consecutive sessions. Each rat was then tested on the repeated items list using a within subjects design. All rats were injected with either saline or muscimol 30 minutes prior to testing on alternating

testing sessions following an ABAB design, for a total of 4 testing sessions (saline 1 - muscimol 1 - saline 2 – muscimol 2).

Following testing on the interference list, all rats were trained on the low interference, no-repeating items list. This training was limited to provide rats with exposure to the additional odors (24 vs. 12). Rats were trained on the low interference list until they performed the list at 80%. The CMTS rule transferred quickly to the new list, with rats performing at 80% within 1-3 days of training. Following criterion performance, all rats were tested for 2 sessions of the low interference list. For the first low interference testing session, all rats were injected with saline and for the second session, all rats were injected with muscimol prior to testing.

Data Analysis

For each training session, we computed the percentage of trials with a correct response. Trials back values were computed for all non-match trials (except for the first presentation of each odor for each session) by determining the number of intervening trials since the last presentation of the same odor. Error rates were computed by averaging the percentage of errors made by each rat for each trial. All data were analyzed using SPSS (SPSS, IBM Inc.). For all repeated measures analyses, Hyun-Feldt corrected p-values were automatically computed in order to adjust for violations of the sphericity assumption.

Histology

Following testing, all rats were anesthetized with isolflurane, transcardially perfused with 10% paraformaldehyde and their brains removed, frozen and sectioned at 40 μm, mounted on slides and stained with cresyl violet in order to identify the infusion locations.

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Chapter 4

Contributions of the Prefrontal Cortex to Resolving Mnemonic Interference

The adaptive benefit of increasing memory capacity depends on effective memory retrieval. We store all sorts of memories and routinely retrieve them with remarkable precision, yet much of how memories are accessed is a mystery. How do neural systems accomplish the seemingly ordinary process of locating specific memories? A critical feature of memory retrieval appears to be processes that actively manage interference from other memories (Anderson 2003). If so, memory selection could be strongly influenced by the processes that cope with potentially competing memories, which would ultimately allow for target memories to be effectively retrieved from the crowd.

Though processes that manage competition during memory retrieval have received significant attention in humans (Levy and Anderson 2002; Johnson and Anderson 2004; Shipstead and Engle 2013), but less is known about whether similar processes can be studied in animal models. This review highlights evidence of homologous neural structures in primates and rats that are involved in managing competing memories. We hope to illuminate the common ground between the human memory literature and animal models of memory in an effort to promote future investigations into the neural substrates that manage mnemonic competition.

Some clues about the need to manage competing memories during retrieval come from instances when memory fails. To illustrate, consider that memory for where one has recently parked in the office lot can interfere with memory for where one has parked today, resulting in a fruitless search at the wrong end of the parking lot, only to retrieve the correct spot moments later. These relatively infrequent retrieval failures under certain circumstances reveal some aspects of how memories are organized, with a key feature being that related memories have enough in common that they sometimes *interfere* with one another. Presumably, the storage of many related memories involves overlap in memory traces, and one consequence of this organization is that target memories can sometimes be susceptible to *interference* from other memories. Problems certainly ensue when memory interference causes the retrieval of unintended and counterproductive memories. However, memories are more often retrieved interference free. This may be because memory retrieval involves mechanisms that manage the retrieval of related competitors. Here we discuss evidence for processes that manage interference as well as the neural mechanisms associated with interference resolution with a focus on emerging evidence from animal models.

Mnemonic Interference

Interference could be written off as a result of inefficient memory encoding (e.g. failing to encode today's parking location), which might then lead to the retrieval of alternative memories. However, interference has been well

characterized in experimental settings and is often isolated to problems at retrieval rather than simply reflect encoding failures (Loftus and Patterson 1975). In fact, experimental research on interference has an important history in the study of learning and memory. Interference theory pointed to memory interference as the critical culprit in forgetting, whereas competition driven theories suggested that original memories are not lost but masked by new learning (Postman and Underwood 1973). This debate was an influential factor in theoretical models of associative learning and memory. Despite many arguments, it was generally agreed upon that central to the generation of interference is the relationship between memory items. Memories that are similar are much more likely to interfere with one another both retroactively (McGeoch and McDonald 1931) and proactively (Wickens et al. 1963). For example, during interpolated learning subjects perform multiple iterations of study-retention memory tests, and interference causes decreased memory performance when items on successive lists are semantically related to items from previous study lists (McGeoch 1932). If the semantic content of a subsequent list is changed, subjects typically demonstrate a rebound for memory items (release from interference) in the new semantic category, further demonstrating that the relationship between memories is critical to interference (Wickens 1970).

Neural Mechanisms of Interference

Early cognitive studies of interference provided a critical foundation on which to guide future investigations into the neural mechanisms of interference

and interference resolution. Numerous studies indicate that damage to the prefrontal cortex increases susceptibility to interference (Luria 1971; Rocchetta and Milner 1993; Shimamura et al. 1995; Lou Smith et al. 1995). Generally, PFC subjects tend to erroneously retrieve previously relevant memory items (false-positive responses) on successive memory tasks that contain overlapping items, suggesting PFC damage causes impairments in the ability to withhold the retrieval of or otherwise appropriately monitor previous memories items (Milner 1963; Iversen and Mishkin 1970; Barceló and Knight 2002). This effect also indicates that relatively isolated PFC damage does not impair memory retrieval *in toto*, since memory errors tend to reflect inaccurate retrieval of previous memories at a greater rate than controls. Instead, it is generally agreed that PFC subjects have problems managing or monitoring the retrieval of previous memories. Conditions such as Alzheimer's disease, fronto-temporal dementia and schizophrenia that are known to involve PFC dysfunction (Levin 1984; Konrad and Winterer 2008) also exacerbate susceptibility to memory interference (Cornblatt and Keilp 1994; Levy and Chelune 2007; Gleichgerrcht et al. 2011).

In agreement with behavioral studies, brain imaging studies consistently point to an important role for the PFC during interference resolution (D'Esposito et al. 1999; Sylvester et al. 2003; Badre and Wagner 2005; Jonides and Nee 2006; Kuhl et al. 2011). Furthermore, a recent meta-analysis of imaging studies specifically evaluated the overarching PFC involvement in resolving interference (Nee et al. 2007). This study found that despite consistent PFC activity

associated with interference resolution, different PFC subdivisions are often selectively active depending on the cognitive domain associated with the interference task. For example, activity in the dorsolateral PFC is more associated with interference resolution during cognitively oriented response selection, whereas inferior frontal gyrus is more active when conflict resolution is required during behaviorally oriented response execution. One possible explanation for this dissociation is that interference resolution processes are recruited for different representaitonal domains, and predominant connections between the PFC and other brain regions associated with specific domains dictate subregional involvement. There is disagreement over whether PFC subdivisions are recruited for similar computational operations in support of conflict resolution, or if the differential activity in various PFC subdivisions across tasks in more indicative of functional specificity (Miller and Cohen 2001; Duncan and Owen 2000). We address this issue throughout this review and suggest that current evidence tends to favor of a domain general role for the PFC in resolving neural competition.

The ability to determine the precise mechanisms of managing competing memories during memory retrieval is limited by the constraints of behavioral and imaging studies in humans alone. If the evidence strongly indicates that the PFC is critical for managing mnemonic interference in humans, then it is reasonable to suspect that it will be involved in similar processes in other species. However, few studies to date have specifically examined the role of the PFC in resolving

mnemonic interference during memory retrieval in animal models, despite numerous studies of other theories of PFC function in rats (Birrell and Brown 2000; Hok et al. 2005; Ng et al. 2007; Ragozzino 2007; Jonkman et al. 2009) and non-human primates (Goldman-Rakic 1987; Fuster 1991; Dias et al. 1997). An important factor in this discrepancy may be that the PFC is most commonly associated with a variety of other executive functions, and existing animal models often echo these theoretical perspectives. For example, the PFC is highly associated with cognitive flexibility needed for task-switching operations, and animal models have explored the role of the PFC in task-switching in other species. The following section highlights predominant views of the role of the PFC in executive functions that have been translated to animal models, and how we believe this evidence ultimately reflects an important role for the PFC in managing interference.

Anatomical and Functional Relationship between Primate and Rat PFC.

The anatomical position of the PFC is consistent with a modulatory role necessary for complex cognition (Robbins 2000; Goldman-Rakic 1995; Arco and Mora 2009). Central to this view is that the PFC connects widely throughout the brain and in a way that is thought to integrate diverse information for goal-directed action (Miller and Cohen 2001). The PFC receives substantial input from cortical sensory regions (Goldman-Rakic 1987; Cavada and Goldman-Rakic 1989; Barbas 2000), and projects to multiple limbic regions including the hippocampus and amygdala, as well as cortical and subcortical motor areas

(Amaral and Price 1984; Öngür and Price 2000; Gabbott et al. 2005). The integrative position between the sensory input and motor output through direct projects to premotor cortex, as well as direct and indirect (via limbic regions) projections to nucleus accumbens, makes it an ideal candidate for top-down processes associated with cognitive control of behavior (Arco and Mora 2009; Atallah et al. 2004). Importantly, though functional theories derived from anatomical mapping of the PFC have received greater attention in primates, there is considerable anatomical and structural evidence for conservation of PFC function across primates and rats (Öngür and Price 2000; Uylings et al. 2003; Vertes 2006). One substantial cytoarchitectural difference between the PFC of rats and primates is that the rat PFC lacks the granular layer that has been considered a defining feature of the PFC in primates (Levin et al. 1991). However, this is just one of many features taken into account when determining homologous brain structures, and taken collectively, the overall consensus in the field accepts that the relationship between patterned connectivity, functional attributes and developmental factors, among others, that support the homology between rodent and primate PFC (Uylings et al. 2003).

The PFC and Executive Control

There are a number of important processes associated with the PFC contribution to executive functions. Some of these include planning (Morris et al. 1993; Koechlin et al. 2000), decision making (Bechara et al. 1999; Clark et al. 2004), behavioral flexibility (Barbas and Zikopoulos 2007; Ragozzino 2007),

goal-directed processing (Corbetta and Shulman 2002), rule-related processing (Wallis et al. 2001), inhibition (Aron et al. 2004), working memory (Goldman-Rakic 1995), general fluid intelligence (Kane and Engle 2002; Gray et al. 2003), conflict monitoring (Yeung et al. 2004; Botvinick et al. 2001), memory monitoring (Moscovitch and Winocur 2002) and other, often overlapping operations that tend to fit under the umbrella of executive control. Much of this work suggests that PFC subdivisions are preferentially involved in one or more of these specific executive processes. However, there is some controversy concerning the plausibility of the distribution of so many specific functions across PFC subdivisions. Though these PFC subdivisions are clearly involved in all these processes, recent theories have adopted a more domain general view of PFC function (Miller and Cohen 2001; Rajah et al. 2008; Kan et al. 2013) in an attempt to bridge the functional gap between various operations attributed to the PFC. Common to these overarching theories is a focus on the consistent involvement of the PFC in functions that require reconciling neural competition or conflict. Since PFC subdivisions are partly defined by their differential connections with brain networks associated with diverse cognitive domains, these subdivisions may be recruited for the common purpose of resolving competing representations within their respective cognitive domains (Duncan and Owen 2000). This, in turn, could underlie a more general role for the consistent involvement of the PFC across overlapping executive functions, particularly when selection among potential alternatives in required.

Executive control broadly implies the top down modulation of other cognitive processes. In the domain of memory, anatomical evidence suggests the PFC is a good candidate for top-down modulation since PFC projections influence activity in limbic regions that are commonly associated with mnemonic functions (Barbas 2000). Though the precise nature of the interplay between the PFC and limbic structures is not fully understood in humans, there is neural evidence in support of PFC influence within the domain of memory. Notably, Wagner and colleagues have consistently demonstrated that PFC activity is associated with selective control during memory retrieval (Wagner et al. 2001; Dobbins et al. 2002; Badre and Wagner 2007). In what appears to be a complimentary process, recent evidence suggests the PFC is associated with the suppression of population activity that reflects competing memory representations (Wimber et al. 2015). This modulatory influence on competing memory appears to be a strong candidate for a mechanistic account of executive control in memory retrieval since it suggests that activity in the PFC might act to selectively suppress portions of memory networks, thereby potentially reducing conflict between competing memory representations in an effort to select specific, targeted memory representations.

The modulatory role for the PFC on limbic processing is supported in animal models of memory. Critical work on functional circuitry involving the mPFC is already revealing specific mechanisms that indicate a modulatory influence of mPFC projections on limbic structures in rats. In fear conditioning

paradigms, subdivisions of the medial prefrontal cortex are critical for both fear memory (Quirk et al. 2006; Burgos-Robles et al. 2009) and extinction (Milad and Quirk 2002), and this has been shown to reflect a functional mPFC influence on the amygdala (Quirk et al. 2003; Sotres-Bayon et al. 2004). Recent work suggests that though the mPFC in critical for the formation of competing fear extinction memories, it is not critical for their retrieval, indicating a facilitation in memory formation in support of a modulatory influence on fear memory (Do-Monte et al. 2015). In agreement with the mPFC as a modulatory node within different cognitive domains, Smith et al. (2012) shows that transient optogenetic stimulation of infralimbic (mPFC) cortical activity blocks habitual responding mediated by the striatum, further indicating that infralimbic cortex is important for initiating behaviors that contradict prior learning (Smith et al. 2012). Futhermore, in the mPFC-hippocampal circuit important for spatial memory, mPFC inactivation does not abolish spatial memory representations, but renders them less specific (Navawongse and Eichenbaum 2013), indicating additional evidence for an important modulatory role of the mPFC in memory representations in other brain regions. Together, these behavioral investigations on the functional circuitry of the mPFC suggest a supervisory role for the mPFC rather than an absolute role in memory formation. Further work on the functional circuitry between the mPFC and other major projection sites has great potential to reveal specific neural operations that guide memory, particularly during extinction, which is known to involve the suppression of competing memories.

Despite exciting circuit level evidence for a modulatory role for the mPFC in memory-guided behavior, the precise contribution of the PFC to executive control of memory retrieval remains unclear. Comparatively, much more is known about the overt influence on behavior caused by PFC damage, which has contributed several alternative theories on the contribution of the PFC to executive functions. Hallmarks of executive control include abilities such as task switching or behavioral flexibility and the inhibitory regulation of behaviors. In the following sections, we review some of these theories and argue that at the core of these processes is the need to resolve mnemonic competition.

Task Switching and Behavioral Flexibility

Influential work on operations of the PFC has shown that it is critical for task switching (Dove et al. 2000; Rushworth et al. 2002; Monsell 2003). Classic examples of experimental paradigms that require task switching include the Stroop task and the Wisconsin Card Sorting Task (WCST) (Herd et al. 2006; Banich 2009). Task switching involves moving between task sets, and the level of interference between these sets is a critical factor known to affect switching performance (Kiesel et al. 2010; Vandierendonck et al. 2010). Task switching performance is influenced by the relationship or overlap between physical and conceptual properties of meaningful stimuli within each task (Rogers and Monsell 1995). For example, in the stroop task, both color and procedural cues – necessary for identifying the color or reading the word – are continually present during the execution of either rule. Switching between rules requires subjects to

resolve the conflict between these cues in order to actively maintain the relevant strategy. There is a cost between switches, and that these costs are informative about neural processes underlying switching performance. Typical switch costs include slowed reaction time and decreased accuracy in task performance immediately following a switch. Importantly, switch costs have long been thought directly reflect interference between tasks, as switch costs decrease when interference is minimal (Allport et al. 1994; Rubinstein et al. 2001; Waszak et al. 2003).

Switching tasks, particularly the WCST, have proven to reliably diagnose PFC damage (Drewe 1974; Bornstein 1986; Miyake et al. 2000). The notable capacity needed to perform normally in these tasks is that ability to abandon prepotent or learned, rule-based responses in order to adopt new response contingencies. Importantly, damage to the PFC does not typically impair many of the complex associative learning requirements needed to perform these tasks, such as learning the initial rules of the task (Milner 1963). For example, in the WCST, PFC subjects are not impaired in the perceptual requirements of the task (such as distinguishing and sorting cards based on their content, e.g. colors, shapes, or quantities), nor are subjects impaired in learning or remembering the basic rules of the task. Instead, it is only after certain behavioral responses within the context of the task have been established that damage to the PFC results in performance that is most distinguishable from controls. When the requirements of the task are suddenly changed without the subjects' immediate awareness,

competition is created between the previously acquired rule and a new rule, and PFC subjects are typically impaired in the ability to pick up on or adopt these new rules (Milner 1963; Stuss et al. 2000; Demakis 2003).

Task switching requirements have been adopted in animal models of PFC function. Tasks designed for other species that mimic the requirements of the WCST have shown similar deficits due to PFC damage in non-human primates (Dias et al. 1996; Moore et al. 2009) and rats (Birrell and Brown 2000; Ragozzino et al. 2003; Floresco and Magyar 2006; Durstewitz et al. 2010). Birrell and Brown (2000) show that, in tasks which mimic the requirements of the WCST but are designed for rats, lesions of the medial prefrontal cortex (mPFC) impair the ability of rats to make extradimensional shifts in behavioral responses to stimulus modalities that were previously irrelevant but now cue an new adaptive response. Specifically, the mPFC is critical when rats must cease a learned response to stimuli of a particular sensory dimension (e.g. texture) in order to respond to cues of different perceptual dimension, such as odor. Rats are typically not impaired in acquiring the rule association between the initially learned cue and the response, and are only impaired when they must switch to the use of cues of a different perceptual dimension. This finding parallels human studies using the WCST, which show that people with PFC damage are not typically impaired in learning or following the initial rules of the task, but are severely impaired in the ability to switch to newly imposed rules. Collectively, humans, other primates and rodents with PFC lesions often continue to perform switching tasks as though they are

following the initially learned rule. The similar results observed across species has strengthened the claim that the PFC is needed for behavioral flexibility, or the ability to overcome existing patterns of behavior in order to adopt new patterns of behavior (Milner 1963; Mishkin 1964; Butter 1969; Nelson 1976; Ragozzino 2007). This is typically referred to as perseveration, or the persistent execution of a previous reinforced behavior that no longer leads to the learned outcome.

Further work in rats supports a role for the PFC in the acquisition of strategies needed to overcome conflicting memories, but also show that it is not necessarily critical for flexibility between strategies. In a clever study, Rich and Shapiro (2007) trained rats on multiple switches between two navigational strategies on a plus maze (i.e. place versus response strategy). In some cases, both strategies involved overlapping navigational routes (i.e. when the rat is placed on the west arm, the “go south” strategy conflicts with the “go right” strategy). They show that temporary inactivation of the rat mPFC impairs memory for switching to a new strategy, but interestingly, does not impair the ability to switch between two familiar strategies. Furthermore, inactivation of the mPFC during training on a new conflicting strategy caused rats to perform the original strategy 24 h later, whereas controls were more likely to perform the newly acquired strategy, indicating an important role for the mPFC in surpressing competing responses (Rich and Shapiro 2007). In a later study, the same authors confirm that mPFC activity is associated with changes in strategies on

the plus maze (Rich and Shapiro 2009). Overall, this suggests that the mPFC is not necessarily needed to switch between strategies needed to solve different tasks, but is critical for memory for newly adopted strategies in the face of previous conflicting memories. Similar to other studies involving PFC lesions, when the mPFC is inactivated, subsequent memory tests reveal that rats tend to follow previously adopted strategies.

Task Switching or Interference?

An alternative interpretation for the effect of PFC lesions on behavior flexibility paradigms is that subjects fail to effectively resolve interference between tasks or learning sets, which has been noted by several authors (Kane and Engle 2002; Blumenfeld and Ranganath 2007; Kiesel et al. 2010; Vandierendonck et al. 2010). A key feature of the WCST and other tests of flexibility is that at the time of impairment – when subjects much switch to a new rule that is guided by newly relevant cues – the cues that guide performance of the initially learned rule continue to be present despite new contingencies that indicate a change in behavior is required. For example, if subjects initially learn to sort based on “shape,” when the sorting strategy is changed to “color,” the shapes are still present on the cards. The continued presence of previously relevant cues is a source of interference, and PFC subjects are susceptible to this interference in predictable ways. Subjects tend to perseverate – that is they tend to continue to respond as though they are following the cues relevant to a rule previously learned rather than adopting a new rule guided by a different set

of cues. Importantly, in order to observe this deficit, the associative cues that initially guided performance on the previously acquired rule must still be present when subjects are required to adopt a new rule. In the above example, if shapes were removed from the cards, it would be impossible to determine whether subjects are following the initial strategy or responding randomly. However, subjects do tend to follow previously established rules, and we suggest that the pattern of deficits typical of switching tasks occur because subjects fail to correctly resolve interference from previous learning in order to adopt the new behaviors.

In sum, normal performance on switching tasks across species reflects the adaptive capability to adopt behavioral solutions to changing circumstances within familiar contextual conditions. However, damage to the PFC severely disrupts this ability. Thus, substantial evidence indicates that the PFC is not as critical for many aspects of associative learning, and that it plays a much more important role in dealing with the presence of competition between learned responses, once it arises. One possible mechanism by which the PFC might accomplish this is by inhibiting previously learned or established patterns of behavior.

Inhibitory Mechanisms that Manage Memory Competition

The fact that PFC subjects often perseverate, or fail to cease the execution of a previously learned behavior, suggests an important role for the

PFC in behavioral inhibition, or the ability to alter or inhibit the retrieval of learned behaviors, particularly when they no longer lead to an expected outcome (Mishkin 1964). Inhibition is a critical component of executive control (Verbruggen and Logan 2008), and the PFC has been shown to have a substantial inhibitory role on behavior in multiple cognitive domains (Aron et al. 2004; Ridderinkhof et al. 2004; Munakata et al. 2011). Furthermore, PFC dysfunction often results in a loss of inhibition (Milner 1982; Levin et al. 1991; Rocchetta and Milner 1993; Casey et al. 1997), which typically manifests as contextually inappropriate or prepotent behaviors. In this way, inhibition appears to play an important role in contextually guided selection of alternative behaviors. Consistently, there is convincing evidence that the PFC is also involved in the inhibition within the domain of memory retrieval (Wimber et al. 2008, 2009; Crescentini et al. 2010), and it is thought that this is a critical mechanism for modulating memory selection. The ability to inhibit the retrieval of competing but inappropriate retrieval targets is proposed to be a mechanism that modulates memory retrieval selection in accordance with contextual information (Anderson 2003). Overall, convergent evidence suggests the PFC is involved in similar selection functions that are guided by means of inhibition across different cognitive domains (Miller and Cohen 2001), which might depend on the specific connections of PFC subdivisions to other areas of the brain.

Within the domain of memory, the importance of inhibition has received significant attention (Levy and Anderson 2002; Anderson 2003; Johnson and

Anderson 2004; Aslan et al. 2007; Medalla and Barbas 2010). A classic demonstration of inhibition during retrieval is observed in the Retrieval Induced Forgetting (RIF) effect. In RIF, extra practice with a subset of within category exemplars from a study list not only improves memory for these extra studied items, but also inhibits memory retrieval of the within category items that did not receive extra practice, relative to a baseline condition (items that were practiced equally as the to be inhibited items) (Anderson et al. 1994). What is particularly relevant to those interested in studying mechanisms of memory interference is that the RIF effect is specific to conditions that involve competing memory targets. During a typical RIF task, subjects study exemplars within a limited set of categories. For example, the categories might include “fruits” and “drinks,” and subjects are asked to remember many exemplars within each category (e.g. fruits: apple, banana, orange; drinks: bourbon, gin, vodka). There are two interesting findings associated with this categorization procedure. First, the inhibitory effect on non-practiced items is specific to the within category items. For example, extra practice on items such as orange and apple inhibit memory for non-practiced items such as banana, but do not affect memory for bourbon or vodka. This means the inhibitory effect is strongest for related items. In other words, RIF is most prominent when items might potentially *interfere* with one another. The second important finding is that the RIF effect is most robust for typical or common exemplars of a given category. In other words, the RIF inhibition is more pronounced for commonly associated items of fruit such as *orange* or *apple*, and less pronounced for items such as *kiwi*. If it is assumed that

common exemplars of a given category have similar, stronger and more well-established routes of activation and share more elements within the representational memory network, then the fact that RIF is stronger for items that are commonly associated appears to reflect inhibitory mechanism that promote interference resolution. Importantly, it has been repeatedly demonstrated that PFC activity is associated with memory suppression in RIF (Johansson et al. 2007; Spitzer et al. 2008; Wimber et al. 2008, 2009; Crescentini et al. 2010).

The mPFC and Interference

The involvement of the PFC in suppressing competing memories suggests an important role in managing neural competition within the domain of memory. Additionally, there is consistent evidence for functional similarities between the PFC of primates and rodents. These two lines of evidence have led us to test the hypothesis that the rat PFC is involved in managed mnemonic interference. We have suggested that the PFC appears most critical when interference is present. Thus we expect that the PFC will be engaged whenever interference is high and that PFC lesions will impair the ability to effectively resolve interference. In a series of experiments, we tested the role of the PFC is resolving interference and managing memories in a task that does not explicitly require attentional or strategic shifts in order to guide behavior (Peters et al. 2013).

We suspected that inducing proactive interference during learning would be sufficient to require PFC involvement. An important feature of our interference

task is that it does not require extradimentional shifts in attention to changes in the perceptual quality of stimulus cues. Many researchers have shown the mPFC is critical for extradimensional shifts rather than intradimensional shifts or reversals (Birrell and Brown 2000; Ragozzino et al. 2003; Ng et al. 2007). However, these studies typically require rats to learn just a few discrimination problems, thus minimizing the number of relevant cues needed to be remembered in order to guide behavior. In these tasks, and consistent with studies in humans and other primates, it has been well demonstrated that the rat mPFC is not needed for initial discrimination learning (Dias et al. 1997; Ragozzino et al. 1999; Birrell and Brown 2000). We have replicated this finding by showing that the mPFC is not needed for learning a few discrimination problems one at a time, such as when discriminations are presented in blocks, but we also learned that mPFC lesions do impair acquisition when rats are required to learn many discrimination problems concurrently. Concurrent learning creates sources of interference (Shapiro and Olton 1994), and together, these experiments indicate that the mPFC is differentially needed for discrimination learning as interference increases, such as when rats must manage multiple items in memory simultaneously.

We have also shown that the mPFC is needed for the normal memory retrieval of many concurrently learned discriminations, even when no changes in strategy are required. When rats are trained to asymptotic performance on a list of discrimination problems, subsequent inactivation of the mPFC on the same set

of problems impairs but does not abolish memory retrieval of these discriminations. This result is inconsistent with the claim that the critical impairment associated with PFC lesions is strictly perseveration, since perseverative responding would be not be expected to cause an impairment on the well-learned discrimination problems. Perseveration is an indicator of interference, but perseverative responding does not explain whether PFC dysfunction causes deficits in effectively inhibiting past memories, or impairs other requirements associated with adopting competing memories. For example, preservative responding may indicate an inability to direct attention to new cues rather than problems inhibiting old responses. Nevertheless, our results demonstrate that the mPFC is needed for memory retrieval even when perseveration is not a factor, indicating deficits associated with PFC dysfunction cannot be attributed to preservative responding alone.

In another set of experiments we explicitly tested the role of the mPFC in resolving interference. In our proactive interference task, previous learning of one set of discrimination problems causes proactive interference on the second set of problems (Butterly et al. 2012). Temporary inactivation of the mPFC during acquisition of the second set of problems significantly impairs the rats' performance on the second set (Peters et al. 2013) (Figure 4A). In fact, rats perform at near chance levels when the mPFC is inactivated during the switch to the high interference problem set, indicating severe interference from the previous set. Importantly, though this task induces significant proactive

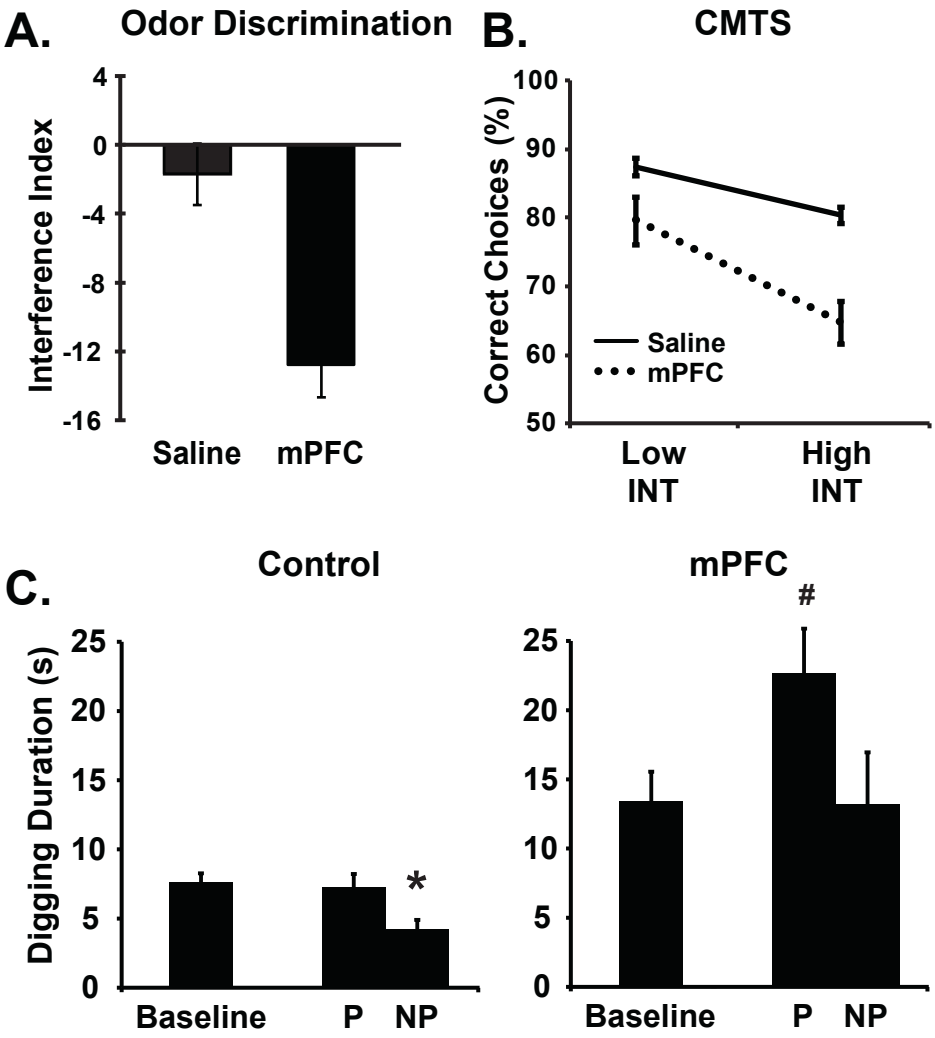

Figure 4. (A) Inactivation of the mPFC causes greater interference in discrimination learning. The interference index reflects the decline in performance due to interference when rats learn a second set of conflicting discrimination problems following training on an initial set of problems. By subtracting average performance on the first set of problems from the second set, negative values represent slower learning on the second set of problems. Inactivation of the mPFC increases susceptibility to interference from previous memory items. (B) Inactivation of the mPFC differentially impairs match to sample performance. High and low interference versions of match to sample differed in whether odor stimuli were repeated over the course of a training session. All rats make more errors on the high interference version of the task due to increased rates of responding to recent presentations of repeated cues on nonmatch trials. It can be inferred from the interaction between the interference condition and the inactivation condition that the mPFC is more critical when interference is high. (C) A rat model of retrieval induced forgetting indicates that the mPFC is critical for memory suppression of related memories. Control rats responded less to non-practiced odors (NP) relative to baseline when extra-practice is given on a subset of the other odors (baseline bar vs. NP bar). mPFC inactivation eliminates this suppression of memory despite equal experience with NP odors and baseline odors in both condtions. P indicates responding to practiced odors.

interference, there was no change in the strategy or rule that guided performance, thus it does not require the extradimensional shift previously thought to be critical for mPFC engagement in discrimination learning (Birrell and Brown 2000; Ng et al. 2007; Ragozzino 2007). This suggests that the presence of interference along is sufficient to require the mPFC in order to effectively adapt behavior.

We conducted a final odor discrimination study that may have important implications for the involvement of the PFC in interference resolution. Preliminary observations of performance on our odor discrimination task indicated that temporary inactivation of the mPFC early in training on an initial set of discrimination problems was affecting performance when rats switched to the subsequent, high interference set of problems. This observation led us to hypothesize that the mPFC might have an important influence during early stages of learning. We formally tested this hypothesis by inactivating the mPFC in one group of rats, while performing control injections in the other group, during the first three days of training on the initial set of problems. After the first three days of training, we then continued to train both groups, without further infusions, until they were performing the task well. All rats eventually performed the task at greater than 95% accuracy, with no difference between groups. We then trained both groups on a new, high interference set of problems. Surprisingly, rats with the mPFC inactivated during training on the first three days of learning the initial set performed significantly better on the second set of high interference

problems. This improvement was present despite the fact that both the inactivation group and controls learned the second list with an intact mPFC, with neither group receiving any more infusions into the mPFC since the first three days of training on the initial problems. We suspect that this result has important implications for understanding the role of the mPFC during learning and its influence on the susceptibility to interference during later learning. One possibility is the engagement of the mPFC modulates the strength of memories by potentiating routes of retrieval, leading to greater activation of these memories. Inactivating the mPFC at the onset of learning a set of problems that would eventually be used to induce interference on subsequent set of problems "released" rats from some of the effects of this interference, possibly by decreasing memory intrusions associated with previous learning. Other evidence has recently been reported that suggests that interactions during the initial stages of learning between the PFC and other structures important for memory are important for the lasting formation of memories, and it is possible that this "tagging for consolidation" mechanism was interrupted in our study (Lesburguères et al. 2011). This effect appears to further support an organization role for the mPFC in during acquisition that ultimately influences the strength that memories will exert in conflicting circumstances.

Despite strong evidence that the rat mPFC is critical to overcome interference and manage memories, it is difficult to completely rule out the possibility that the impairments due to mPFC inactivation in our odor

discrimination task were a result of a disruption in an existing strategy representation. For example, it is possible that rats develop a strategic representation that is mediated by the mPFC during initial acquisition of the task, and that subsequent inactivation of the mPFC during the switch to the high interference list disrupts that existing network, or the ability to adopt a new strategic response. Though impairments caused by mPFC inactivation during acquisition of conflicting discrimination problems was more severe than inactivation of the mPFC during initial acquisition of a set of discrimination problems with an identical number of problems, we sought to determine whether inactivation of the mPFC caused impairments in managing interference in tasks that did not require rats to adopt new competing strategies or memories. We trained rats on a simple continuous match to sample rule using a pool of olfactory stimuli as cues. Just as in our olfactory discrimination task, rats were required to dig in cups containing odorized bedding to retrieve a reward. However, rats were only presented with one odor at a time, and learned to retrieve a reward whenever the current odor stimulus matched the odor on the previous trial. Rats quickly learned to dig in the current stimulus cup when its odor matched the previous stimulus, and avoid digging when the current trial odor did not match the odor on the previous trial. However, because a pool of repeated odor stimuli were used, all rats made significantly more errors on non-match trials when the current odor was presented recently but not on the previous trial (analogous to interference caused by experience with prior stimuli in working memory tasks in humans). Thus, memory for recently presented odors interfered with memory for

the most recent odor. Importantly, we were able to adapt the task in order to present rats with either many repetitions of odor stimuli (high interference) or no repetitions by using unique odors for each successive non-match trial (low interference). We then inactivated the mPFC during performance of both high and low interference versions of the task, and found that this manipulation differentially affected performance – the magnitude of impairment was much greater on the high interference version of the task than the low interference version (figure 4B). An exclusive mPFC role in strategy representation does not fully account for these results since the strategy needed to perform both versions of the task was the same. The difference between versions was only the amount of interference caused by repeated presentations of familiar stimuli. This further strengthens the claim that the mPFC is most critical when the potential for interference is high.

Since there is strong evidence that suppression of competing memories during memory retrieval may be a mechanism that manages potential interference, and the PFC appears to be involved in this effect, we wondered whether a similar function could be observed in rats. In another set of experiments, we tested the role the mPFC in the suppression of contextually related memories by developing a task analogous to the human RIF task (Wu et al. 2014). Rats learned that several odors were associated with reward by pairing each odor with a reward an equivalent number of times. We then divided the rats into two groups. One group of rats was given additional pairings (analogous to

extra practice in the RIF task) on a subset of these odor-reward pairings. The other group was not given extra practice on the items and served as a baseline control. Like in human RIF, normal rats that received extra practice on a subset of the memory items showed suppressed memory for non-practiced items relative to the baseline controls. Importantly, temporary lesions of the mPFC eliminated this suppression effect (Figure 4C). This finding supports a role for the rat mPFC in memory suppression, consistent with studies of human memory. This supports the view that PFC is important for the suppression of competing memories and strengthens the claim that the human and rat PFC are involved in similar functions, particularly within the domain of memory retrieval.

In sum, we have explored the role of the rat mPFC in managing multiple memories in the face of mnemonic interference across multiple tasks. Our results are consistent with the human literature on the role of the PFC in interference resolution. In addition to an important role for the mPFC in memory acquisition and retrieval, we observed that the mPFC is needed when rats must manage proactive interference from previous odor discrimination memories, despite no explicit changes in strategy or rule requirements. In direct support of this, we also observed a preferential role for the mPFC in working memory tasks when interference is high. Furthermore, consistent with a suppression mechanism for managing competing memory in the humans (Anderson 2003), we show the mPFC is needed for the suppression of contextually learned memories in a rat model of RIF. Collectively, these results provide convergent evidence for a

common role for the mPFC in the ability to effectively making use of new information by combating interference from previous memories across a variety of task requirements.

Conclusion

A number of related theories exist on the functional contribution of the PFC to cognition. Common to many of these theories is the observation that the PFC is critical for adjusting appropriate behavioral as conflict arises between new and old memories, responses, strategies or learned patterns of behavior or thought. Though we do not fully understand the precise contribution of the PFC to these circumstances, animal models of PFC function are extremely consistent with the human literature and have great potential to further knowledge on the basic neural mechanisms that underlie PFC role in these critical adaptive functions. Such research should ultimately lead to be better characterizing of the functional contribution of the PFC to cognition. We suggest that an important function of the PFC is to modulate memory retrieval by resolving interference between related memory representations. Evidence for a similar contribution of the PFC in other cognitive domains indicates that the PFC may be recruited for domain general functions that manage competition in mammalian neural systems, facilitating the ability to continually add and update representational elements throughout experience.

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Appendix

The following appendix item is a study of the mPFC and hippocampal role in a rat model of the retrieval-induced forgetting effect which was referenced in chapter four. The RIF effect is well-characterized in humans and is believed to reflect underlying mechanisms that actively inhibit competing memories during memory retrieval. However, it has been difficult to pinpoint the precise mechanisms of inhibition in RIF despite clear suppression of memory for competing items in human performance. The study below shows a complimentary involvement of the mPFC in the suppression competing memories in a rat model of RIF, further establishing a role for the mPFC in managing competing memories, while adding another experimental tool for assessing neural mechanisms of RIF.

The hippocampus, medial prefrontal cortex and selective memory retrieval: Evidence from a rodent model of the retrieval-induced forgetting effect.

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Abstract

Inhibition is an important component of many cognitive functions, including memory. For example, the retrieval-induced forgetting (RIF) effect occurs when extra practice with some items from a study list inhibits the retrieval of the non-practiced items relative to a baseline condition that does not involve extra practice. Though counterintuitive, the RIF phenomenon may be important for resolving interference by inhibiting potentially competing retrieval targets. Neuroimaging studies suggest that the hippocampus and prefrontal cortex (PFC) are involved in the RIF effect, but controlled lesion studies have not yet been performed. We developed a rodent model of the RIF training procedure and trained control rats and rats with temporary inactivation of the hippocampus or mPFC. Rats were trained on a list of odor cues, presented in cups of digging medium with a buried reward, followed by additional practice trials with a subset of the cues. We then tested the rats' memories for the cues and their association with reward by presenting them with unbaited cups containing the test odorants and measuring how long they persisted in digging. Control rats exhibited a robust RIF effect in which memory for the non-practiced odors was significantly inhibited. Thus, extra practice with some odor cues inhibited memory for the others, relative to a baseline condition that involved an identical amount of training. Inactivation of either the hippocampus or the mPFC blocked the RIF effect. We also constructed a computational model of a representational learning circuit to simulate the RIF effect. We show in this model that 'sideband suppression' of similar memory representations can reproduce the RIF effect and that alteration of the suppression parameters and learning rate can reproduce the lesion effects seen in our rats.

Our results suggest that the RIF effect is widespread and that inhibitory processes are an important feature of memory function.

Introduction

Inhibition is an important component of many cognitive functions, including attention, perception, language, thought and action (Dagenbach and Carr, 1994). A common pattern in the literature is that the processing of one item is facilitated while the processing of potentially competing items is inhibited. For example, selective attention to one item is accomplished, in part, by inhibiting attention to distractors (Tipper, 1985). Similarly, semantic cueing with one homophone (e.g. bank-money) inhibits cueing with another (bank-river, Simpson and Kang, 1994). These examples of selective inhibition based on feature-similarity may be functionally analogous to the visual system's center-surround receptive field mechanism of contrast enhancement, except that it is not constrained to a clearly-defined two-dimensional topology of similarity. A comparable form of inhibition occurs in the domain of memory. The retrieval-induced forgetting (RIF) effect (Anderson et al., 1994) occurs when retrieval practice with some items from a study list inhibits the retrieval of the non-practiced items relative to a baseline condition that does not involve retrieval practice.

In typical studies of the RIF effect, subjects are trained on a list of category-exemplar word pairs (e.g., FRUIT – apple, FRUIT – orange, etc.). After the initial training trials, subjects are given additional retrieval practice with some of the items from the list (e.g., FRUIT – a___, in response to which the subject is expected to retrieve 'apple'). Subjects then undergo retrieval testing in which they are asked to recall as many of the exemplars from the training list as possible. Unsurprisingly, recall of the practiced items generally is improved, relative to a baseline condition in which no retrieval practice was given. However, recall of the non-practiced items is significantly *inhibited* relative to baseline.

Importantly, this retrieval inhibition occurs even though the non-practiced items are given the same amount of training as the baseline items, indicating that it is the retrieval practice with some items that causes poorer retrieval of the non-practiced items (Anderson et al., 1994).

Experimentally, the RIF effect is manifested as a retrieval failure, wherein recall of the non-practiced items is poorer than baseline. Indeed, the phrase "retrieval-induced forgetting" implies a memory failure. However, the RIF phenomenon may be a highly adaptive mechanism for resolving interference. Interference is a critical problem for high volume memory systems in which many items have mutual associations. In everyday situations, successful memory retrieval depends on the ability to retrieve the correct target item from memory while inhibiting the retrieval of potentially competing, inappropriate memories. For example, remembering where I parked my car this morning requires that I retrieve today's parking spot without retrieving all the other places that I have parked recently.

Inhibiting the retrieval of competing memories is an effective strategy for reducing interference, and experimental evidence suggests that RIF serves this purpose. The RIF effect occurs specifically in response to retrieval competition (for review see Levy and Anderson, 2002). Consistent with this interpretation, words that are strong exemplars of a category (e.g., apple) produce greater retrieval competition and are inhibited more strongly than weak exemplars (e.g., kiwi). Moreover, the inhibition of non-practiced items is time-limited, persisting for at least one hour but less than twenty-four hours in Levy and Anderson's (2002) paradigm, suggesting that the RIF effect provides an

ongoing mechanism for highlighting recently- or frequently used memories for easy retrieval.

The RIF phenomenon has been extensively studied in humans. In addition to the cue-recall task described above, it has been demonstrated with recognition memory (Spitzer and Bauml, 2007), implicit memory (Veling and van Knippenberg, 2004), semantic memory (Johnson and Anderson, 2004), visuospatial object memory (Ciranni and Shimamura, 1999), eyewitness memory (MacLeod, 2002) and even foreign language acquisition (Levy et al., 2007). Previous neuroimaging studies have implicated the hippocampus and the prefrontal cortex (PFC) in the RIF effect (Anderson and Green, 2001; Wimber et al., 2008) and several other kinds of retrieval inhibition (Crescentini et al., 2010; Depue et al., 2007; Wagner et al., 2001). Some authors have argued that retrieval inhibition involves direct interactions between the hippocampus and PFC, with the PFC exerting executive control over hippocampal retrieval processes (Anderson and Green, 2001; Bunge et al., 2004; Munakata et al., 2011). However, to date there has not been an animal model of the RIF effect, and no controlled lesion studies of retrieval inhibition have been performed. In the present study, we adapted the RIF procedure for use in rodents by presenting rats with a list of odor cues, followed by extra practice with some of the odors (or no extra practice in the baseline condition) and then testing of their memory for the odors. We then used temporary neurochemical inactivation to examine the respective roles of the hippocampus and the medial prefrontal cortex (mPFC) in mediating the RIF effect.

In order to examine possible mechanisms of the RIF effect and inform our interpretation of temporary inactivation data, we also constructed a computational model

of a representational learning circuit and trained it on the RIF task. Because RIF functions to suppress retrieval of similar memories that may compete with the target memory, while sparing dissimilar memories that do not threaten interference, we based our model on a high-dimensional metric of similarity. Consequently, suppression of potentially competing memories could be achieved via sideband suppression within this high-dimensional metric space, a technique that we previously have used to model the processing of perceptually similar odorants (Cleland and Linster, 2012; Cleland et al., 2009). Importantly, in this model framework, similarity is conceptualized broadly to include learned associations among odor cues and contexts encountered during the training experience. That is, it includes all of the shared elements that could lead to interference between memories. After modeling the RIF effect, we manipulated appropriate model parameters to simulate the effects of hippocampal or prefrontal cortical inactivation.

Methods

Overview. We trained rats on a rodent version of the RIF task which involved training on a list of odor cues, followed by extra practice with some of the odors (or no extra practice in the baseline condition) and then testing of the odor memories. We conducted three experiments: 1) to determine whether the RIF effect can be seen in rodent olfactory memory, 2) determine whether hippocampal inactivation disrupts the RIF effect and 3) determine whether mPFC inactivation disrupts the RIF effect. We then assessed our results using a computational model.

Subjects, Surgical Procedures and Infusions. Subjects were 64 adult male Long-Evans rats (Charles River Laboratories, Wilmington, MA). Rats were assigned to either a hippocampal inactivation group (n=16), an mPFC inactivation group (n=16), an unoperated control group (n=16), or hippocampal (n=8) or mPFC (n=8) saline control groups. Unoperated controls and rats given saline infusions did not differ on any measure of performance, so they were combined into a single control group. For rats assigned to infusion groups, bilateral guide cannulae (one injection site in each hemisphere, Plastics One, Roanoke, VA) were stereotaxically positioned just above the target location so that the infusion cannula, which protruded 1.0 mm beyond the tip of the guide cannula, would be positioned in the target area (Fig. 1, dorsal CA1: 3.6 mm posterior and 2.6 mm lateral to bregma, 2.2 mm ventral to the cortical surface; mPFC: 3.2 mm anterior and 0.5 mm lateral to bregma, 2.7 mm ventral to the cortical surface). The guide cannulae were secured to the skull with bone screws and dental acrylic. The rats were given an antibiotic (5 mg/kg Baytril) and an analgesic (5 mg/kg ketoprofen) prior to surgery. After at least one week of recovery, the rats were placed on a restricted feeding regimen (80-85% of free feeding weight) and began training. Temporary inactivation of the hippocampus or mPFC was induced by infusing the $GABA_A$ agonist muscimol into the corresponding region of the brain. Specifically, thirty minutes prior to the relevant training sessions, 0.5 μl of a 1 mg/ml muscimol solution in saline, or the same volume of saline vehicle, was infused into each hemisphere at a rate of 0.5 μl/min. The infusion cannulae were left in place for 1 minute after the infusions. All procedures complied with guidelines established by the Cornell University Institutional Animal Care and Use Committee.

Apparatus and Behavioral Training Procedures. Details of the apparatus and odor stimuli have been published elsewhere (Butterly et al., 2012). Briefly, the rats were trained in a white Plexiglass chamber (45 cm X 60 cm X 40 cm deep) equipped with a removable divider which separated the chamber into an odor presentation area and an intertrial interval area. Prior to training, the rats were shaped to dig for buried rewards (45 mg sucrose pellets, Bioserve, Inc., Frenchtown, NJ) in ceramic cups (8.25 cm in diameter, 4.5 cm deep) filled with corncob bedding material. A list of six pure odorants served as the odor cues (propyl butyrate, ethyl acetate, anisole, ethyl isovalerate, furfuryl propionate and n-butyl glycidyl ether). A seventh odorant (1-butanol) was used as a distractor stimulus that was never rewarded. In each case, a volume of each odorant calculated to generate an equivalent vapor phase partial pressure after dilution was mixed with 50 ml of mineral oil (10 Pa, Cleland et al., 2002; Cleland et al., 2009). 10 ml of each odorant solution was then mixed with 2 liters of corncob bedding material and stored in air-tight containers. For all training and testing procedures, the odorants were presented one at a time, alongside an identical cup containing bedding scented with the distractor odor, which was never baited.

Within each of the inactivation conditions described above, half the rats were assigned to the baseline condition and the other half were assigned to the extra practice condition. Training and testing took place in a single session incorporating all three phases: training, extra practice (or a delay of equivalent duration), and testing. During training, all of the rats were given 6 trials with each of the 6 odor cues, presented in an unpredictable sequence. For each trial, the cups containing the odor cue with a buried reward and the distractor odor were placed into the chamber, the divider was raised and

the rat was allowed to approach the cups and dig until he retrieved the reward. For rats in the extra-practice condition, three of the six odors were designated P (practiced), and the other three were designated NP (non-practiced). Subjects in this group received 4 additional training trials with each P odor, but did not receive any additional training with the NP odors. Rats in the baseline condition were not given extra practice on any of the odors. The extra practice trials required 5 min, so rats in the baseline condition were given a 5 min delay after training in order to produce an equivalent delay prior to testing, which occurred immediately thereafter. The test trials were identical to the training trials, except that neither cup was baited. The amount of time the rat spent digging in the unbaited cup containing the target odor served as our measure of how well the rats remembered the odor and its association with reward (Cleland et al., 2009). Digging times were measured with a stopwatch by an experimenter blind to the rat's condition. The rats were given four test trials, two with P odors and two with NP odors. The selection of the test odors from the training list and the order of presentation of the P and NP odors were counterbalanced across subjects. Each rat in the baseline condition was yoked to a rat in the extra practice condition for the selection of test odors, such that the two groups were tested with identical odors.

Data Analysis. In order to correct for potential differences in perseverative tendencies or overall responsiveness, the amount of time spent digging in the distractor cup was subtracted from the time spent digging in the test odorant for each trial. Thus, our digging time score reflects how much more time the rats spent digging in the target odor than in the distractor odor. Distractor effects were minor: control rats spent 0.59±0.18 sec digging in the distractor cups, mPFC inactivation rats spent 1.28±0.27 sec,

HPC inactivation rats spent 0.18±0.06 sec. In each experiment, our goal was to determine whether extra practice affected memory for the odors (i.e. improved memory for the P odors or impaired memory for the NP odors), relative to the baseline condition which did not involve extra practice. We used Welch's t-tests to compare digging times for the practiced and non-practiced odors separately to the baseline condition, with Bonferroni correction for two comparisons (i.e. $\alpha = 0.025$). For significant outcomes, we report effect size (Cohen's *d*).

Computational modeling. We constructed a computational model of a representational learning circuit to model the RIF effect. In this class of circuit, neural representations of external stimuli are high-dimensional and can be arbitrarily complex, yet retain quantifiable similarity relationships with one another. The RIF effect in the model is based on sideband suppression generated by each of these representations – that is, representations generate "surround" inhibition of similar (neighboring) representations in their high-dimensional similarity space. Hence, training on some items from a list will suppress memories of other items from that list to the degree that they are similar to the trained items, but will not suppress memories of dissimilar items (e.g. items drawn from dissimilar lists or learned in a different context). Note that we use the term 'similarity' broadly to include not only perceptual similarity but also similarities derived from learned associations such as those formed when items are part of the same learning experience, which might lead to retrieval competition and interference. This conforms to experimental observations in which memory for items drawn from different categories was not impaired by the RIF effect (Anderson et al., 1994). Extra training on half of the elements from a list of odors therefore should actively impair memories for other

odorants from the same list that do not also receive additional training, whereas parameter changes intended to simulate the effects of hippocampal or mPFC inactivation should reduce or eliminate the RIF effect, reflecting experimental data.

We used the NEST simulator (Diesmann and Gewaltig, 2001; Gewaltig and Diesmann, 2007, http://www.nest-initiative.org) and the PyNN model specification package (Davison et al., 2008, http://neuralensemble.org/PyNN) to implement a network of 100 leaky integrate-and-fire (LIF) pyramidal neurons (Fig. 2A; *Pyr*) that received analogue excitatory input (specific to a given odor cue) as well as global periodic inhibition in the gamma band (40 Hz) generated by an oscillator process (*Osc*). Cue representations comprised spatial patterns of excitatory input to these pyramidal neurons (temporal profiles of input were not manipulated). This input generated action potentials in pyramidal neurons that were phase-constrained to periods of disinhibition. Higher levels of input generated correspondingly phase-leading action potentials within phases of declining inhibition (phase or precedence code, Linster and Cleland, 2010; Panzeri et al., 2010). Pyramidal cells delivered this spiking output onto a layer of 100 output layer neurons (*OLN*s). Connectivity between the pyramidal cell layer and the OLN layer was pseudorandom and uniformly distributed with a 50% probability of connection. Pyr-to-OLN synapses were sensitive to pyramidal cell spike timing according to a spike timing-dependent plasticity (STDP) rule implemented as described in Linster and Cleland (2010, Fig. 2B, Table 1). Briefly, earlier pyramidal cell spikes (preceding the evoked postsynaptic spike, if any) yielded increased Pyr-to-OLN weights after conditioning, whereas later Pyr spikes (following the OLN spike) progressively produced lower, eventually negligible weights, thereby sparsening the OLN-level representation.

To generate a metric in which greater neuronal activity levels and sparser spatial representations in the OLN layer both reflect greater learning, we measured learning as follows. A cue-evoked barrage of phase-constrained Pyr spikes produced either zero or one spike per cycle in any given OLN. The mean spike phase (in ms) of the activated OLN population was calculated for each oscillation period, and the reciprocal of this mean phase was used as the learning metric. Specifically, the strengthening of Pyr-to-OLN synapses produced an increased phase lead in follower OLNs. Sparsening the OLN representation by reducing the number of activated OLNs via learning also generated an increased phase lead, as the most lagging OLNs were the ones eliminated. Increased phase leads, corresponding to increased values in the reciprocal mean spike phase in ms^{-1}, indicate greater learning. The ordinates in Fig. 3D-F denote a reasonable range for values of this metric after substantial learning, corresponding to a difference in mean spike times of roughly 1 ms.

Neural representations of odor cues consisted of 100-dimensional vectors corresponding to the levels of input to the 100 pyramidal neurons. To generate a list of random high-dimensional odor cue representations (HDRs) with consistent statistical relationships (probability distributions of similarity), we sampled 100 points from a sigmoidal distribution of unit amplitude to generate a "source HDR". To produce each of the odorant stimulus HDRs used for training, we added Gaussian noise to each point of the source HDR, set all resulting negative values to zero, and scaled the distribution linearly so that the maximum value was unity. Hence, each cue HDR was similarly related to the source HDR, and also consistently related to one another. The source HDR itself was not used as a cue. The average similarity among the HDRs in a given list can

be estimated as the mean radius of a hypersphere containing all of the HDRs in that list. The interrelatedness of the HDRs can be manipulated by increasing or decreasing this radius, making the group of HDRs less or more similar to one another, respectively. The HDRs used for additional practice (P) in each simulation were randomly selected, and 18 separate simulations were performed and averaged together to comprise each figure.

Results

RIF in Controls. Intact control rats showed robust evidence of the RIF effect in the form of inhibited memory for the NP odors compared to the baseline condition ($t_{(30)} = 3.63$, $p < 0.001$, $d = 1.09$, Fig. 3A). Importantly, the extra-practice rats were given the same number of trials with the NP odors as were the rats in the baseline condition with their odors; the only difference was that rats in the extra-practice condition were given four additional training trials with the P odors. Thus, consistent with previous studies in human subjects, extra practice with some items from a study list of odors inhibited the retrieval of the non-practiced items on that list. Contrary to expectations, control rats did not show significantly stronger memories for the P odors, relative to the baseline condition ($t_{(30)} = 0.31$, $p = 0.76$), suggesting that the initial six training trials were sufficient to form asymptotically strong memories that were not measurably strengthened by the four extra practice trials.

We simulated these results using a computational model of a representational learning circuit (see Methods). In order to match the rat training procedures, baseline learning was achieved after training the simulated circuit with six presentations of each of six HDR stimuli in a pseudorandomized order. Subsequently, the circuit was given four

additional training presentations with a randomly-selected set of three of the HDRs (the "P" HDRs), while the other three HDRs (the "NP" HDRs) were not presented again. Under control conditions, the P-type HDRs were not learned significantly better than baseline, because learning was nearly asymptotic after the six baseline training trials (Fig. 3D, P *vs* baseline, $t_{(34)} = 2.00$, $p = 0.054$). However, the additional training significantly suppressed memory for the NP-type HDRs relative to the baseline HDRs (NP *vs* baseline, $t_{(34)} = 3.79$, $p < 0.001$, $d = 2.22$).

Effects of Hippocampal Inactivation on the RIF Effect. Temporary inactivation of the dorsal hippocampus completely blocked the RIF effect. Specifically, digging times for the NP odors were not reduced relative to the baseline condition ($t_{(14)} = -0.14$, $p = 0.89$) and digging responses to the P odors were not elevated relative to the baseline condition ($t_{(14)} = -0.55$, $p = 0.59$, Fig. 3B). That is, the performance of rats with hippocampal inactivation was unaffected by the extra practice trials.

Items are strongly associated with the context in which they occur, and the hippocampus is involved in this associative process (e.g. Butterly et al., 2012). Accordingly, we treated contextual associations as shared features of the HDRs in our model and simulated hippocampal inactivation by reducing context-based feature similarity (i.e. by decreasing the average similarity of the HDRs). Specifically, the radius of the hypersphere enclosing the six randomly generated HDRs was increased by a factor of five (Table 1, see Methods), such that the overlap and interactions among HDRs were substantially reduced. As a result, the *NP* representations were not significantly suppressed by the additional training of the *P* items relative to the baseline (Fig. 3E, P *vs* baseline, $t_{(34)} = 0.49$, $p = 0.63$). As in the control group, asymptotic learning of the

baseline items prevented significant additional learning and memory for the *P* items was not improved by additional training relative to the baseline HDRs (NP *vs* baseline, $t_{(34)} = 1.39$, $p = 0.17$).

Effects of mPFC Inactivation on the RIF Effect. Temporary inactivation of the mPFC also blocked the inhibitory component of the RIF effect (Fig. 3C). Rats with mPFC inactivation did not exhibit reduced memory for the NP odors relative to baseline ($t_{(14)} = 0.05$, $p = 0.96$). Interestingly, the rats showed some evidence of improved memory for the P odors compared to the baseline condition, but this effect did not achieve significance with our Bonferroni-corrected alpha level of 0.025 ($t_{(14)} = 2.36$, $p = 0.033$, $d = 0.28$). Thus, mPFC inactivation may have produced a more selective impairment in the inhibition of the NP items than hippocampal inactivation. The apparent increase in overall digging time is discussed below.

Although the PFC is thought to influence memory in a variety of tasks (e.g. Lee and Solivan, 2010; Smith et al., 1995), the specific mechanism by which the PFC participates in the RIF effect is not known. One possibility is that the PFC responds to retrieval conflict by sending feedback to the memory network in order to dynamically enhance sideband suppression and thereby achieve optimal inhibition of potential competitors. Additionally, recent evidence indicates that overall learning is delayed by mPFC inactivation (Peters et al., 2013). Therefore, we simulated mPFC inactivation by reducing the STDP-mediated learning rate (i.e. reducing the values of W+ and W-), and by modestly decreasing the sideband overlap (increasing σ, Table 1). These manipulations produced a pattern of results very similar to rat behavioral data (Fig. 3F). Specifically, they enabled additional practice to improve cue memory above baseline (P

vs baseline, $t_{(34)} = 3.70$, $p < 0.001$, $d = 2.19$; increasing W+ to 0.2 rendered this difference non-significant) while also eliminating the inhibitory component of the RIF effect (NP *vs* baseline, $t_{(34)} = 1.55$, $p = 0.124$).

Group Differences in Digging Response Rates. The key question tested in these experiments was whether additional practice with some odors from the list impaired memory for the non-practiced odors in control rats and in rats with hippocampal or mPFC inactivation. We used odor-cued digging responses to assess memory and showed inactivation-induced changes in responding to the NP odors in control animals. However, hippocampal and PFC lesions have also been shown to produce a non-specific increase in behavioral responses (i.e. perseverative responding, Mishkin, 1964; Whishaw and Tomie, 1997). To examine this, we submitted the baseline response rates for control rats and rats in the hippocampal and mPFC inactivation conditions to a one-way ANOVA ($F[2,29] = 9.69$, $p < 0.001$). Post hoc comparisons using Tukey's honestly significant difference showed that inactivation of the mPFC was associated with elevated digging times compared to controls ($p < 0.005$). The digging times of rats given hippocampal inactivation were not significantly different from controls ($p = 0.31$). Thus, in addition to blocking the inhibitory component of the RIF effect, mPFC inactivation caused perseverative responding. We did not include perseveration in our simulation, so Fig. 3F does not show the globally elevated response levels observed in rats with mPFC inactivation (Fig. 3C).

Discussion

Like human subjects (Anderson et al., 1994), rats exhibited a robust RIF effect in which practice with some items from a study list inhibited the retrieval of the non-practiced items. These results suggest that RIF is a widespread phenomenon, occurring in many learning situations and in different species, and they join a growing body of research indicating that inhibitory processes are an important aspect of memory function. We suggest that these inhibitory processes play a critical role in resolving interference. Interference is a critical problem for high volume memory systems, and one mechanism for resolving interference is to inhibit the retrieval of potentially competing memory targets. Previous neuroimaging studies of human subjects have suggested an involvement of the PFC and the hippocampus in these processes (Anderson and Green, 2001; Wimber et al., 2008). The current results confirm this involvement via targeted temporary inactivation of each of these areas, demonstrating that the RIF effect depends on the integrity of both the mPFC and the hippocampus.

The behavioral tasks used to evoke the RIF effect in this new animal model have potentially important procedural differences as well as similarities when compared to the classic human studies of RIF. In typical human studies (e.g. Anderson et al., 1994), subjects are trained on category-exemplar pairs (e.g. FRUIT-apple) and there is no explicit reinforcement. In our studies, rats were trained to associate odor cues with a buried reward. Because the P and NP odors had identical reinforcement histories, differential reinforcement of these cues cannot account for the current results. However, we cannot be certain that the reduced responses to the NP items observed in the animal and human tasks are supported by the same underlying mechanism. Nevertheless, the same adaptive outcome is achieved in each case: the less-frequently encountered items

are inhibited in a manner that facilitates retrieval of the more frequently encountered items. Moreover, observation of practice-induced inhibition across many different kinds of memory (see Introduction, Ciranni and Shimamura, 1999; Johnson and Anderson, 2004; MacLeod, 2002; Spitzer and Bauml, 2007; Veling and van Knippenberg, 2004) supports the idea that the RIF effect is a general function relevant to many kinds of memory.

In human subjects the RIF effect seems to depend on the subject actively engaging in a retrieval search. For example, a robust RIF effect is seen when subjects are given partial cuing of the retrieval target (e.g. FRUIT-a_____) during the practice trials, but not when additional training trials are presented with the target item provided (e.g. FRUIT-apple) (Anderson et al., 2000). Indeed, such additional training trials are sometimes used as a control condition that is not expected to produce RIF (e.g. Johansson et al., 2007). In contrast, additional training trials produced significant retrieval inhibition with our procedure. This apparent discrepancy may be explained by the sequence of events in our trials. During each trial, the rats approach the cup, investigate the odor and then dig for the reward, which often takes several seconds. Presumably, the rat retrieves the odor-reward association during this time and this supports the digging response, since the rats generally do not dig in the unrewarded distractor cup. Thus, each trial likely involves a significant retrieval component as well as constituting an additional reinforced training trial. In contrast, additional training trials in humans involve the simultaneous presentation of the cue and the target (e.g. FRUIT-apple) and there is little opportunity for the subject to engage in retrieval. Thus, the extra practice trials in our procedure likely

involve a retrieval component that is not present in additional training trials used with human subjects.

Although our control subjects showed significant inhibition of the memory for the non-practiced odors, they did not show the commonly observed improvement in memory for the practiced items, relative to the baseline condition (Fig. 3A). This result suggests that in control rats, the initial six training trials may have been sufficient to form relatively strong memories which were not measurably strengthened by the additional four practice trials. Consistent with this interpretation, previous experience in our laboratory suggests that rats can reliably remember a rewarded odor after only three or four training trials.

Rats given temporary inactivation of the hippocampus did not show enhanced memory for the practiced items nor did they show inhibition of memory for the non-practiced items. The fact that the muscimol rats responded to the test odors as much as control rats, and much more strongly than they responded to the distractor odor, suggests that they did not simply forget the odors. Rather, the rats given hippocampal inactivation were insensitive to the inhibitory effects of the extra practice trials. Widely accepted theoretical accounts suggest that hippocampal encoding processes are rapid and automatic whereas learning in extra-hippocampal systems proceeds through the slow accumulation of information across trials (e.g. McClelland et al., 1995). However, our results suggest that hippocampal processing may also be sensitive to the subtle effects of additional training trials on memory retrieval.

So why does the hippocampus play a role in the RIF effect? The answer may lie in the well-known hippocampal role in processing contextual information (for review see

Smith, 2008). As discussed above, the RIF effect is thought to be triggered by retrieval competition. Although the odor cues used were not chemically or perceptually similar (i.e. they do not cross-generalize), they were related by virtue of being presented within the same distinctive training context and rats are known to spontaneously associate odors that are presented together (Devito and Eichenbaum, 2011) or within the same environment (Butterly et al., 2012). Within this interpretation, hippocampal processing likely resulted in the association of each odor with the training context, such that any cue that evoked the memory of one odor also would have activated memory representations of the other odors, resulting in retrieval competition. The loss of contextual associations in rats with hippocampal inactivation would result in reduced retrieval competition and, consequently, weaker suppression of the non-practiced odors (see also Norman et al., 2007). This interpretation was supported by the results of our computational model. Hippocampal inactivation was modeled as a reduction in the average contextual similarity among cues, mediated by an increased hypersphere radius during cue (HDR) generation (see Methods). This reduction in cue competition resulted in a failure to suppress the non-practiced items, just as hippocampal inactivation did in our rats.

Inactivation of the mPFC completely blocked the inhibitory effect of the extra practice trials and memory for the practiced odors was not significantly better than for the baseline odors. Inactivation of the mPFC also caused an overall increase in responding during the memory test. This overall increase may simply have been due to behavioral perseveration, which is known to result from PFC lesions (Mishkin, 1964). However, perseveration alone cannot explain the selective loss of inhibition, *relative to baseline*, seen in rats with mPFC inactivation, and we have shown that this inactivation procedure

produces severe memory deficits that cannot be attributed to perseveration (Peters et al., 2013). Our results demonstrate a critical role of the mPFC in retrieval inhibition and provide support for neuroimaging studies suggesting that the PFC exerts inhibitory control over memory retrieval processes (Anderson and Green, 2001; Depue et al., 2007; Wimber et al., 2008).

The loss of inhibition in the rats with mPFC inactivation is consistent with studies showing that PFC activity is correlated with stronger retrieval inhibition (Kuhl et al., 2007; Wimber et al., 2008), suggesting that the PFC monitors ongoing retrieval processes and resolves conflict by suppressing the retrieval of inappropriate memories. Retrieval conflict arises when several representations are activated without a single clearly differentiated retrieval target emerging. We suggest that the PFC responds to such conflict by sending feedback to the memory network to boost sideband suppression such that the strongest retrieval target is maintained and its chief competitors are more strongly inhibited. This includes competitors that are perceptually similar and those with similarity due to shared context or other contributing factors. Further supporting this interpretation is a recent study showing that mPFC input to the hippocampus via the nucleus reuniens increases the specificity of memories, while inactivation of the same pathway causes broader generalization (Xu and Sudhof, 2013), the latter of which has been associated with reduced learning (Cleland et al., 2009). Simulations performed with our computational model are consistent with these interpretations. We modeled mPFC inactivation as a reduction in sideband suppression (increased value of σ) along with a reduction in the STDP learning rate (reduced values of W+ and W-, Table 1). Note that

the reduced sideband suppression could also arise from a reduction of mPFC effects on hippocampal function.

Our simulations modeled the mechanisms underlying the RIF effect as sideband suppression – essentially similar to those underlying contrast enhancement in sensory systems. Specifically, both mechanisms regulate the deployment of competitive inhibition according to the similarity between representations, with the important caveat that cue similarity in the present model is not constrained by sensory metrics: quantitative similarity relationships between cues in the model are arbitrary (and of arbitrarily high dimensionality) and incorporate feature-similarity, cue familiarity, contextual relationships, and any other features of cue presentation or history that contribute to perceived similarity relationships among cues. Our simulations of lesion effects on rat behavior suggest that the hippocampus and mPFC may modulate retrieval processes by regulating these sideband suppression mechanisms and their associated learning processes. The underlying algorithm hence may reflect a common neural mechanism in the brain for the management of representations, whether arising from basic sensory processes or from complex cognitive functions.

The RIF phenomenon and related problems in the control of cortical inhibition have been modeled by others, emphasizing data from human subjects. One recent model of inhibitory control presents the PFC as delivering sophisticated, competitive inhibition of other neocortical regions by identifying favored representations and delivering inhibition so as to bias the computational outcome toward these favored representations (Munakata et al., 2011). In the model, this was achieved by a specific activation of favored representations coupled with a diffuse inhibition of non-activated representations. This

model is consistent with research suggesting that PFC biases competition by selectively activating the contextually appropriate response (e.g. Egner and Hirsch, 2005; Miller and Cohen, 2001), and also with our recent findings that the mPFC is not limited to delivering inhibition, but is also involved in promoting memory retrieval (Peters et al., 2013). However, it is not clear that this model can produce the specific inhibition of strong retrieval competitors that is a hallmark of the RIF effect (Anderson et al., 1994).

A second computational model, specifically designed to replicate the complex characteristics of the RIF effect as reported in human subjects, has been presented by Norman and colleagues (2007). It shares several features with our present model, including an overall strategy of selectively suppressing the strongest competitors, a learning framework in which learning results in memory representations becoming progressively more distinct from one another in order to reduce retrieval competition, and a mechanistic dependence on a global, oscillating inhibitory input to all principal neurons (albeit in the theta frequency band rather than the gamma band). However, other features of the two models are quite different. The Norman et al (2007) model is a rule-based artificial neural network that incorporates certain relevant priors into its design, such as a global awareness of whether the oscillating level of inhibition is above or below a baseline level, which qualitatively changes the operative learning rule. In contrast, our model is a leaky integrate-and-fire network with fully localized synaptic plasticity rules and no global state-dependent singularities. The Norman et al (2007) model is a four-part associative memory network in which representations are in danger of triggering one another via shared excitatory links among neurons commonly activated by both representations; RIF acts to solve this problem by weakening the problematic links,

damaging the integrity of the competitor representation in the process. Our present model is a two-layer feed-forward representational learning network, in which repeated representational activation of Layer 1 (Pyr) neurons entrains a representation-specific pattern of Layer 2 (OLN) neurons via a spike timing-dependent plasticity (STDP) rule (it is the Layer 2 representation that is durably affected by learning in this model). All cue representations are strengthened by repeated presentation of their cues during initial training, and weaken one another during this phase because weakly activated Pyr neurons will have their output synapses weakened owing to STDP. During subsequent "extra practice" with the P cues, the weakly activated elements of competitor (NP) representations will continue to be weakened, but without the opportunity to reassert themselves via presentation of their primary cues. Notably, the P cues are in competition with one another as well, but gain more weight via direct learning than they lose via competition. Ultimately, in this model, cues that remain important (i.e. continue to be presented) while competing strongly with one another will become progressively more distinct from one another in Layer 2 (cf. Cleland et al., 2009; Linster and Cleland, 2010; Weinberger, 2007), eventually minimizing or eliminating this retrieval competition. Our model demonstrates that a relatively simple algorithm based on the principles of competitor suppression can reproduce the RIF effect – irrespective of whether it is implemented in semantic or episodic memory networks – and can replicate the observed effects of PFC and hippocampal inactivation.

Our results join a growing body of research showing that the hippocampus and PFC are involved in resolving mnemonic interference. Neuroimaging studies with human subjects have shown that the PFC and hippocampus both contribute to the RIF effect

(Anderson and Green, 2001; Wimber et al., 2008), and many rodent studies have shown that these structures work cooperatively in various learning and memory tasks (Lee and Solivan, 2008; Navawongse and Eichenbaum, 2013; Xu and Sudhof, 2013). In previous studies, we have shown that inactivation of either the mPFC or hippocampus impairs the ability of rats to resolve interference (Butterly et al., 2012; Peters et al., 2013). High levels of interference are characteristic of many tasks known to be sensitive to hippocampal damage. For example, the hippocampus is required for transitive inference (Dusek and Eichenbaum, 1997), transverse patterning (Dusek and Eichenbaum, 1998) and cue sequence learning (Agster et al., 2002; Fortin et al., 2002), all of which require subjects to select a cue that previously has been rewarded on some trials but not on others, resulting in substantial interference. The PFC has also been directly implicated in resolving interference in humans and rodents (Incisa della Rocchetta and Milner, 1993; Peters et al., 2013). The PFC role in resolving interference is consistent with a number of accounts of PFC function that emphasize its role in the top-down control of memory retrieval processes (Anderson and Green, 2001; Bunge et al., 2004; Munakata et al., 2011). Additional research will be needed to investigate the specific interactions of the hippocampus and PFC in resolving interference.

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Figure Captions

Figure 1. Locations of the infusion cannulae in the dorsal hippocampus and medial prefrontal (prelimbic and infralimbic) cortex are shown on images adapted from (Paxinos and Watson, 1998). Cannula placements for rats in the baseline condition are indicated by filled circles while placements for rats in the extra practice condition are indicated by open diamonds.

Figure 2. Computational model features. A. Schematic of the model. Input representations (cues, HDRs; see text) excite the 100-neuron population of spiking pyramidal neurons (*Pyr*; four depicted) comprising layer 1 of the network. Oscillatory inhibitory input (*Osc*; 40 Hz gamma) also is delivered to these same neurons, shaping the timing of action potentials such that each Pyr neuron fires either one or zero spikes per gamma oscillation, with greater input excitation producing a corresponding phase lead within the low-inhibition window. Pyr spikes excite output layer neurons (OLNs; Layer 2) via plastic synapses that follow the STDP learning rule (Song et al., 2000, see text). The pattern of OLN activation comprises the output representation that is shaped by learning. B. The spike timing-dependent plasticity rule. The abscissa denotes the time difference between a presynaptic Pyr spike and a postsynaptic OLN spike across a given synapse; if the Pyr spike precedes the OLN spike, the time difference is negative and the synapse is strengthened, whereas if the OLN spike precedes the Pyr spike, the time difference is positive and the synapse is weakened. The amount of strengthening or weakening per cycle depends on this spike time difference as well as on the absolute

vertical scale values W+ (for the positive wing of the rule) and W- (for the negative wing) and on the characteristic time constants for each curve (τ+, τ-).

Figure 3. Average digging duration in response to the test odors is shown for control (A), hippocampal inactivation (B) and mPFC inactivation groups (C). Digging durations (time spent digging in the test odor cup minus the time spent digging in the distractor cup, see Methods), are shown for rats in the baseline condition and rats that were given extra practice trials, with responses to the practiced (P) and non-practiced (NP) odors shown separately. Results from our computational model are shown for the simulated controls (D), hippocampal inactivation (E) and mPFC inactivation conditions (F). Parameter changes associated with each inactivation condition are listed in Table 1. Ordinate values are reciprocal mean spike phases (in ms^{-1}) measured in output layer neurons (see Methods). For each plot, the practiced and non-practiced odors were compared to the baseline condition. Digging times for the non-practiced odors were significantly reduced only for the control experiment (A and B, * indicates $p < 0.025$ see Methods). Values were significantly increased for the practiced odors only in the model of the mPFC inactivation (F). Digging times for the practiced odors were numerically increased in the rats with mPFC inactivation, relative to baseline, although this difference did not reach our corrected alpha level of 0.025 (C, #, $p = 0.033$). All other comparisons were not significant.

	Control	HPC lesion	mPFC lesion
σ	1	5	2.5
W+	0.5	0.5	0.1
W-	0.6	0.6	0.06
τ+	5	5	5
τ-	5	5	5

Table 1. Model parameters. The σ parameter denotes the relative similarity of cues on a list (i.e. the radius of the hypersphere containing a family of HDRs) and hence their degree of competitive overlap and sideband suppression. Values are scaled to control; lower values represent higher similarity and stronger competition. The STDP scale variables W+ and W- determine the scale of weight increases and reductions (respectively) produced via spike timing-dependent plasticity (STDP); together they instantiate learning rate within the model. The STDP time constants τ+ and τ- are in ms; σ and W are unitless. Other model parameters (not shown) were unchanged across conditions.

Figure 1

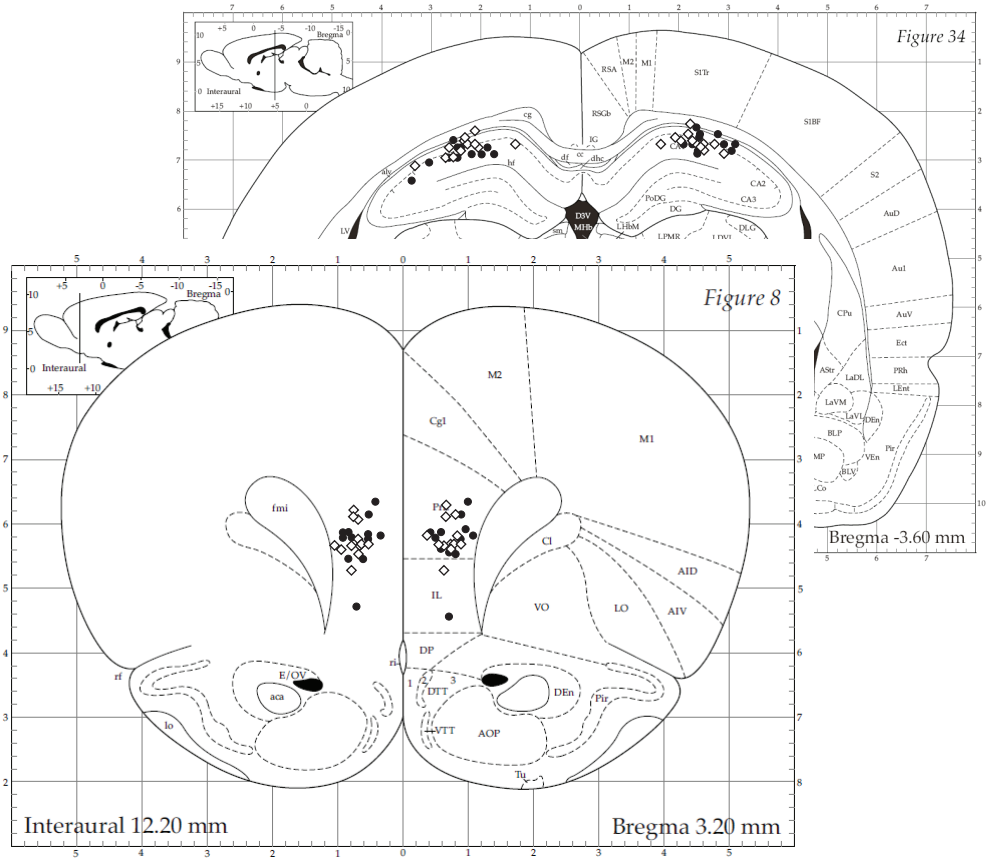


Figure 34
Bregma -3.60 mm
Figure 8
Interaural 12.20 mm
Bregma 3.20 mm

Figure 2

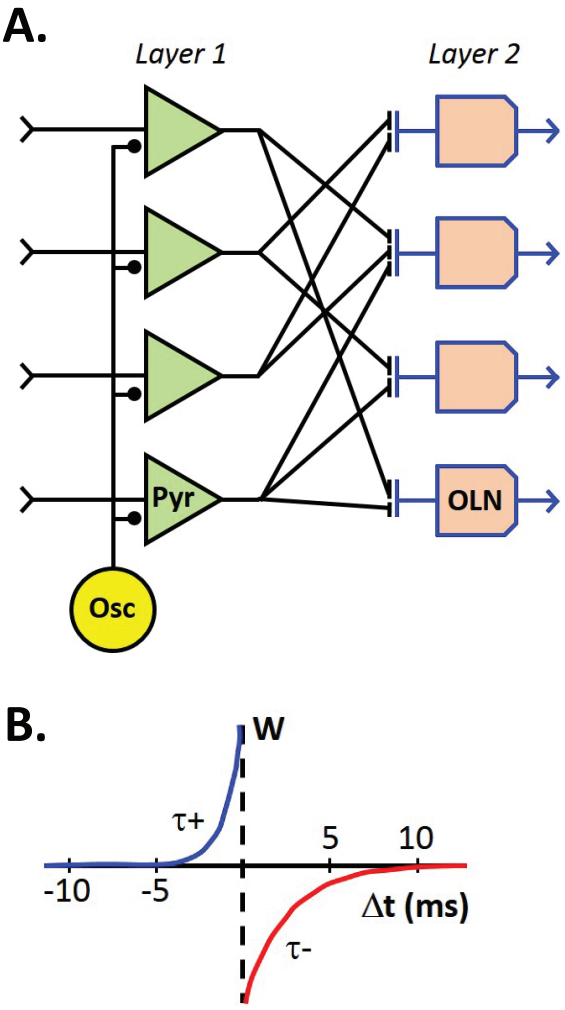
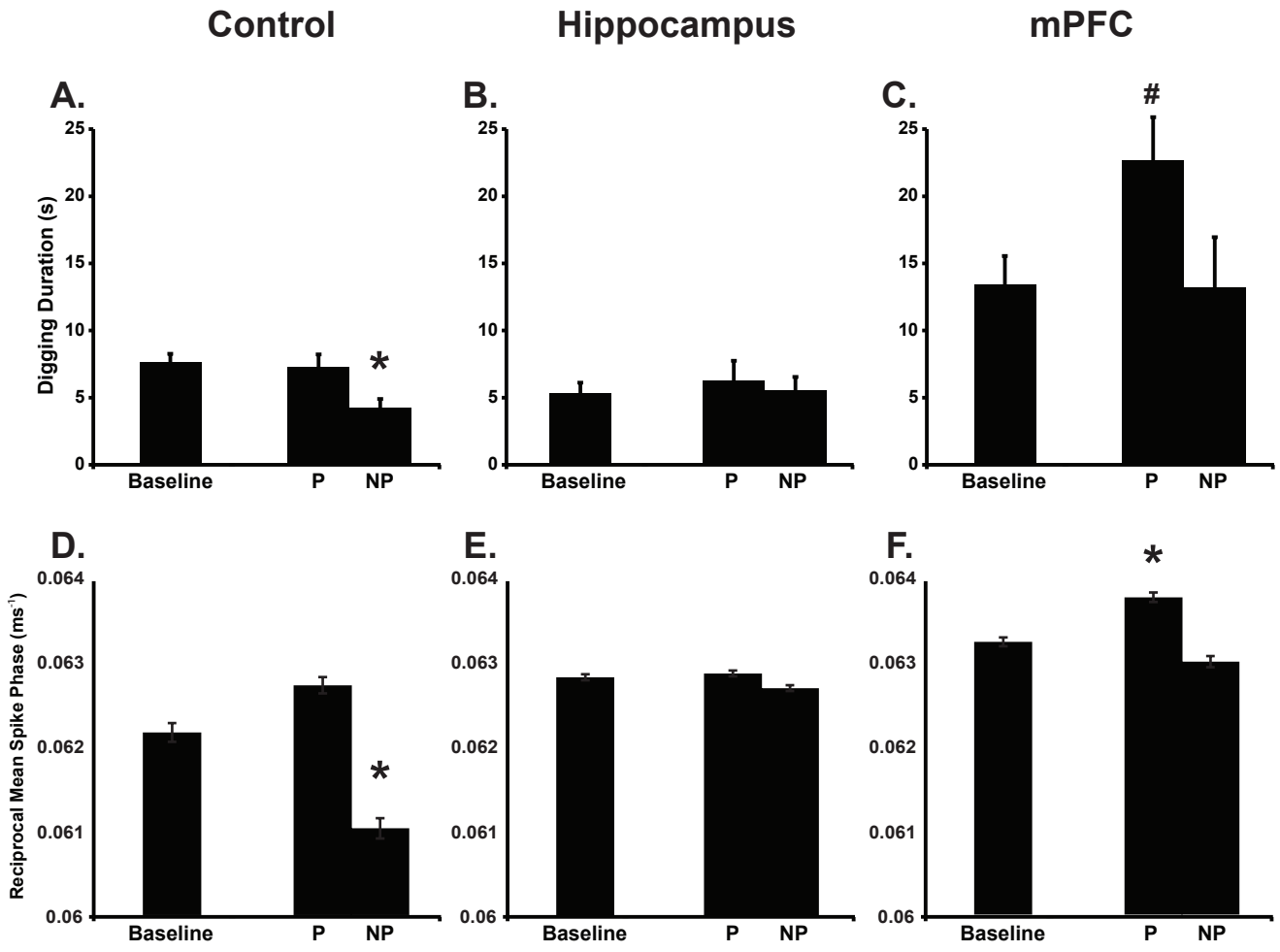


Figure 3


Control
Hippocampus
mPFC
A.
B.
C.
Digging Duration (s)
25
20
15
10
5
0
*
#
Baseline
P
NP
D.
E.
F.
Reciprocal Mean Spike Phase (ms-1)
0.064
0.063
0.062
0.061
0.06