Running Head: The Medial Prefrontal Cortex and Interference.

The Medial Prefrontal Cortex is Needed for Resolving Interference Even When There are No Changes in Task Rules and Strategies.

Gregory J. Peters and David M. Smith
Department of Psychology
Cornell University
Ithaca, NY

Key Words: medial prefrontal cortex, memory, interference, matching to sample.

Corresponding Author:
David M. Smith, Ph.D.
Department of Psychology
236 Uris Hall
Cornell University
Ithaca, NY 14853
Office: (607)227-0045
Fax: (607)255-8433
dms248@cornell..edu

Acknowledgements: This work was supported by NIH grant MH083809 to D. Smith.

Abstract

The prefrontal cortex (PFC) plays a key role in behavioral flexibility, and the ability to resolve conflict from shifting strategies, task rules or attentional demands seems to be a hallmark of PFC function. Conflict also occurs in the domain of memory and the PFC plays an important role in the ability to cope with interference between competing retrieval targets. Previous studies often involved both interference and changes in task demands, which makes it difficult to determine the degree to which mnemonic interference per se engages PFC processing. We trained rats on a continuous matching to sample task in two conditions that varied in terms of the amount of interference present but not the task demands, and found that temporary inactivation of the medial PFC caused a greater impairment in the high-interference condition. This result suggests that the PFC plays an important role in resolving interference which can be distinguished from its role in shifting task demands.

Keywords: prefrontal cortex, memory, interference, rule learning, match to sample

Introduction

The prefrontal cortex (PFC) is involved in a variety of cognitive tasks and is thought to play a particularly important role in promoting behavioral flexibility, the ability to rapidly adopt new strategies, rules or behavioral response patterns (Block, Dhanji, Thompson-Tardif, & Floresco, 2007; M E Ragozzino, Detrick, & Kesner, 1999; Michael E Ragozzino, 2007). For example, human subjects with PFC damage have difficulty shifting their behavioral strategies in response to changing task rules (e.g. in the Wisconsin card sorting task, Demakis, 2003; Stuss et al., 2000) and rats with damage to the medial PFC (mPFC) show a strikingly similar pattern of results on a variety of conceptually similar tasks. Rats trained to dig for reward in one of two stimulus cups on the basis of odor are impaired in learning to respond instead on the basis of the digging medium (Birrell & Brown, 2000; Ng, Noblejas, Rodefer, Smith, & Poremba, 2007). Similarly, rats with mPFC damage are impaired in switching between place and response strategies on a plus maze task (Ragozzino et al., 1999; Rich & Shapiro, 2007) and in control rats, mPFC neurons become engaged at the time of the switch (Rich & Shapiro, 2009).

The need to resolve conflicting rules and responses is a prominent characteristic of these, and many other PFC-dependent tasks. A similar kind of conflict happens in the domain of memory, when subjects try to retrieve a particular target item from among many potential competitors, resulting in interference (Underwood, 1957). Interference is a major cause of retrieval failures in healthy subjects and PFC damage increases susceptibility to

interference in humans (Incisa della Rocchetta & Milner, 1993; Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995; Smith, Leonard, Crane, & Milner, 1995) and rodents (Granon, Vidal, Thinus-Blanc, Changeux, & Poucet, 1994). We have shown that the mPFC is involved in a proactive interference task that we developed for use in rats (Butterly, Petroccione, & Smith, 2012; Peters, David, Marcus, & Smith, 2013). In this task, rats learned a set of eight odor discrimination problems and after reaching asymptotic performance on that problem set, the rats were presented with a new set of eight discrimination problems that contained several novel odors along with old odors that had their predictive value reversed. Rats with muscimol inactivation of the mPFC were severely impaired relative to saline controls, suggesting heightened susceptibility to proactive interference. However, the switch from the first problem set to the second required that the rats learn a new set of discrimination rules. Additionally, we cannot be certain that the change in problem sets did not involve an unknown shift in the attentional or strategic characteristics of the task. For these reasons, we cannot fully rule out the possibility that the mPFC was engaged because of these factors, rather than interference per se.

In the present study, we sought to develop a task in which we could manipulate interference without altering the rules, strategies or attentional components of the task in order to test the hypothesis that the PFC plays a specific role in resolving interference. To accomplish this we trained rats on a continuous matching to sample task and we compared the effects of muscimol inactivation of the mPFC on high and low interference versions of the task. The

two tasks were identical except that each odor cue was repeatedly presented in the high-interference task, making it more difficult to remember whether the previous trial was a match or not, while the cues were not repeated at different times throughout the session in the low interference task.

Method

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

Prior to training, the rats were anesthetized with isoflurane, placed in a stereotaxic device (Kopf Instruments, USA), and the skull was exposed so that craniotomies could be drilled to accommodate bilateral guide cannulae (22 gauge, Plastics One, Roanoke, VA). The guide cannulae were positioned so that the tip of the infusion needle (26 gauge), which protruded 0.5 mm beyond the guide, would be near the prelimbic/infralimbic boundary (3.2 mm anterior and 0.75 mm lateral to bregma, and 2.7 mm ventral to the cortical surface). Some of the more dorsal infusions may have primarily inactivated the prelimbic cortex but no conspicuous differences in behavioral effects were seen in those subjects. 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. 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.

Training took place in a rectangular wood chamber (85 cm X 50 cm X 50 cm deep) equipped with four cup holders located near the corners of the box. Twenty-four pure odorants served as cues. The specific odorants were selected because they have been used previously in studies of memory and olfactory perception (e.g. see Butterly, Petroccione, & Smith, 2012; Cleland, Morse, Yue, & Linster, 2002) and the amount of each odorant could be calculated to produce an equivalent vapor phase partial pressure when mixed with 50 ml of mineral oil in order to hold the stimulus intensity as constant as possible. Then 5 ml of each odor solution was mixed into 1 L of corncob bedding material to be used as odorized digging medium. The odors included: propyl butyrate, ethyl isovalerate, furfuryl proprionate, n-butyl glycidyl ether, n-amyl acetate, ethyl butyrate, propionic acid, benzaldehyde, 1-octanol, pentanol, trans-2-hexenyl acetate, propenoic acid, heptanol, ethyl valerate, 1,8-cineole, anisole, 5-methylfurfural, ethyl acetate, (+/-) limonene, methyl butyrate, 2-phenylethanol, 1-butanol, methyl 2-furoate, and butyl butyrate.

Rats were first shaped to dig for a reward (45 mg sucrose pellets, Bioserve, Frenchtown, NJ) in a ceramic cup of bedding material (8.25 cm in diameter, 4.5 cm deep), followed by training on the matching to sample task. We used a matching to sample rule, rather than the non-matching rule of previous studies (Wood et al. 1999), because we reasoned that attempting to retrieve the

specific memory for the previously presented odor might cause greater interference than simply judging the dissimilarity from the previous odor. However, we did not test a non-matching rule so we do not know whether a similar result might have been obtained. All rats were initially trained on a high interference version of the task involving repeated presentations of each odor cue, followed by testing with muscimol infusions. Then, in order to determine whether any impairments caused by mPFC inactivation were specific to high interference conditions, each rat was tested on a low interference version of the task in which the odors appeared for only one bout of trials and did not appear again later in the session (Fig. 1A).

During each session, the rats were presented with a sequence of odors, one at a time, in a cup placed at one of four randomized locations within the chamber. The first cup of the day always contained a buried reward, but on subsequent trials a reward was available only if the current odor matched the odor of the previous trial. A correct response was scored when the rat retrieved a reward or when he made a correct rejection by investigating and turning away from an unbaited cup without digging. An error was recorded if the rat dug in an unbaited cup. Omission errors (i.e. failure to dig in a baited cup) were also possible, but they were very rare after the first few training sessions. Immediately after the completion of each trial, either by a correct response or an error, the cup was removed. The next trial was initiated as soon as the experimenter could place the cup for the new trial, resulting in an intertrial interval of approximately 10 sec.

High interference training sessions involved 96 trials, with 12 odor cues presented 8 times each in a randomized sequence. Half of the trials for each session were matching trials and half were non-matching, and each odor cue was presented an equal number of times as a match and a non-match. Rats were given daily training sessions until they reached a performance criterion of 80% correct on two consecutive sessions. They were then given four test sessions with intracranial injections in an ABAB sequence (saline, muscimol, saline, muscimol). Performance did not differ on the two saline sessions ($t(7) = -1.159$, $p = .281$) or the two muscimol sessions ($t(7) = .172$, $p = .868$), so the data for each rat was averaged to produce one performance measure for the saline condition and one for muscimol.

After testing in the high interference condition, each rat was trained and tested on a low interference version of the task. This task was the same in all respects, except that the number of odor cues was increased from 12 to 24 and the number of training trials was reduced from 96 to 48 so that each odor could be presented for a single sequence of trials and then not used again within the same session. Because the odors were not encountered earlier in the session, intrusions of erroneous memories from earlier trials was not possible. After reaching at least 80% correct on this task (1-3 sessions), the rats were given a test session with saline and one with muscimol. We wanted to keep the pre-test baseline training consistent, so we trained all the rats to asymptote on the high interference task first, rather than counterbalancing the high and low interference

training and test sessions. However, we note that any effects of testing order cannot be fully ruled out by our design.

For each training session, we computed the percentage of trials with a correct response and subjected these data to paired sample t-test or repeated measures ANOVA with Hyun-Feldt corrected p-values to account for violations of the sphericity assumption (SPSS, IBM Inc.). Following testing, the 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 (Fig 1B).

Results

We expected that repeated exposure to the odor cues within a session would cause interference and the observed pattern of errors confirmed this. Rats rarely made omission errors on match trials, so nearly all of the errors occurred on non-matching trials. That is, errors occurred when the rats incorrectly judged the current odor to be a match with the previous odor. These errors were common when the current odor had been presented recently, but much less common when the current odor had not been seen for many trials. This suggests that recent exposure to an odor cue impaired the rats the ability to distinguish memory for the previous trial from memories associated with earlier trials. To assess this, we plotted the error probability against the number of intervening trials since the current odor cue was last presented and found that these values were negatively correlated (Fig. 2A, $r=-0.765$, $p=.00000006$). This occurred

despite the fact that the rats were only required to remember the odor from one trial back and all previous trials were irrelevant.

In order to compare the effects of mPFC inactivation on the high and low interference tasks, we submitted the percentage of correct choices to a 2 way repeated measure ANOVA, with interference category (low or high) and inactivation condition (saline or muscimol) as within subjects factors (Fig 2B). This analysis revealed a main effect of inactivation ($F(1,7)=17.888$, $p=.004$), a main effect of interference level ($F(1,7)=37.290$, $p=.0005$), with better performance on the low interference task, and a significant interaction of the inactivation and interference conditions ($F(1,7)=7.541$, $p=.029$). This pattern of results suggested that mPFC inactivation caused a greater impairment on the high interference version of the task, so we examined the magnitude of the impairment in the high and low interference conditions directly by computing the difference in performance between saline and muscimol sessions for each rat. We found that the magnitude of the impairment was significantly greater in the high interference task ($t(7) = 2.746$, $p=.014$, Fig 2C). Interestingly, performance on the low interference task was also significantly impaired by the muscimol infusions ($t(7) = 2.53$, $p=.040$, Fig 2C left bar, one sample test compared to zero), but the impairment was more severe in the high interference condition.

Discussion

Inactivation of the mPFC impaired continuous matching to sample performance, a task which involves substantial mnemonic interference. The impairment was significantly more severe in a high interference version of the

task than in a low interference version of the same task, suggesting that the mPFC is specifically engaged by the presence of interference. Importantly, the high and low interference tasks involved the same match-to-sample rule, and there was no requirement for an attentional shift or a shift in behavioral strategy, as in previous studies. The two tasks also had the same working memory demands, to remember the odor from one trial ago, so the greater impairment in the high interference task could not have been due to a selective deficit in working memory. Thus, the present results indicate that the mPFC plays a role in high interference conditions that is not attributable to these factors.

The PFC is known to be involved in inhibitory control, and perseverative or impulsive responding are a commonly reported consequence of PFC damage (e.g. Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Ragozzino, Kim, Hassert, Minniti, & Kiang, 2003; Verbruggen & Logan, 2008). In the present study, mPFC inactivation caused increased responding on non-match trials, which might appear to be an impairment of response inhibition. However, the high and low interference conditions both required that the rats inhibit responding on half of the trials (i.e. the non-match trials). If muscimol had simply made the rats more impulsive, then the two tasks should have been equally impaired but they were not. The smaller impairment seen in the low interference task might reflect impulsive responding, or other factors such as working memory deficits (Levy & Goldman-Rakic, 2000; Thompson-Schill et al., 2002), but the *greater* impairment in the high interference task cannot be attributed to impaired response inhibition. Consistent with this idea, our previous results indicate that

heightened susceptibility to proactive interference after mPFC inactivation was not due to perseverative responding (Peters et al., 2013).

A growing literature suggests that the PFC role in inhibitory control also extends to the domain of memory. Several findings suggest that the PFC can act to inhibit memory retrieval (Anderson & Hanslmayr, 2014; Depue, Curran, & Banich, 2007; B. J. Levy & Anderson, 2002; Wimber, Alink, Charest, Kriegeskorte, & Anderson, 2015), particularly in situations that involve competition among potential retrieval targets. As described above, the mPFC is critical for our proactive interference task, where rats had to inhibit previously learned items in order for new learning to take place (Peters et al., 2013). The PFC has also been implicated in the retrieval-induced forgetting effect, which is thought to enhance the retrieval of recently used memory items by suppressing competitor items. The PFC is involved in this form of retrieval inhibition in both humans (Johansson, Aslan, Bauml, Gabel, & Mecklinger, 2007; Wimber et al., 2015) and rats (Bekinschtein, Weisstaub, Gallo, Renner, & Anderson, 2018; Wu, Peters, Rittner, Cleland, & Smith, 2014). The continuous matching to sample task is characterized by the need to remember the previous trial but to inhibit potentially interfering memories from earlier trials. Inactivation of the mPFC impaired the ability to suppress the influence of those previous trials on the match/non-match judgements during the current trial, so these results are consistent with a PFC role in retrieval inhibition.

The mPFC role is not strictly limited to retrieval inhibition, although that may be its dominant role in the continuous matching to sample task. Our

previous work indicates that the mPFC is also needed to promote memory retrieval. For example, the mPFC is needed for acquisition of a concurrent discrimination task and mPFC inactivation during the early stages of learning results in weakened memory traces more than a week later (Peters et al., 2013). Together, these results suggest a more general role for the mPFC in modulating memory retrieval in either direction, by promoting or inhibiting the retrieval of particular memories, which is consistent with the idea of executive control over retrieval processes (Badre & Wagner, 2002; Depue, 2012; Munakata et al., 2011). We suggest that the PFC role in memory retrieval is one facet of a broad role in resolving conflict in a variety cognitive domains, including strategy switching and response inhibition tasks, and similarities with studies of human subjects suggests that this role is conserved across a variety of species. Given the growing interest in the role of the mPFC in memory and its functional interactions with the hippocampus (Guise & Shapiro, 2017; Jadhav, Rothschild, Roumis, & Frank, 2016; Jayachandran et al., 2019; Navawongse & Eichenbaum, 2013), we suggest that the presence of mnemonic interference should be considered as a possible causal factor in tasks that engage prefrontal processing.

References

Anderson, M. C., & Hanslmayr, S. (2014). Neural mechanisms of motivated forgetting. *Trends in Cognitive Sciences*, *18*(6), 279–292. https://doi.org/10.1016/j.tics.2014.03.002

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, *6*(2), 115–116. https://doi.org/10.1038/nn1003

Badre, D., & Wagner, A. D. (2002). Semantic retrieval, mnemonic control, and prefrontal cortex. *Behavioral and Cognitive Neuroscience Reviews*, *1*(3), 206–218. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17715593

Bekinschtein, P., Weisstaub, N. V., Gallo, F., Renner, M., & Anderson, M. C. (2018). A retrieval-specific mechanism of adaptive forgetting in the mammalian brain. *Nature Communications*, *9*(1), 4660. https://doi.org/10.1038/s41467-018-07128-7

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J Neurosci*, *20*(11), 4320–4324. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10818167

Block, A. E., Dhanji, H., Thompson-Tardif, S. F., & Floresco, S. B. (2007). Thalamic-Prefrontal Cortical-Ventral Striatal Circuitry Mediates Dissociable Components of Strategy Set Shifting. *Cerebral Cortex*, *17*(7), 1625–1636. https://doi.org/10.1093/cercor/bhl073

Butterly, D A, Petroccione, M. A., & Smith, D. M. (2012). Hippocampal context

processing is critical for interference free recall of odor memories in rats. *Hippocampus*, *22*(4), 906–913. https://doi.org/10.1002/hipo.20953

Butterly, Dan A., Petroccione, M. A., & Smith, D. M. (2012). Hippocampal context processing is critical for interference free recall of odor memories in rats. *Hippocampus*, *22*(4), 906–913. https://doi.org/10.1002/hipo.20953

Cleland, T. A., Morse, A., Yue, E. L., & Linster, C. (2002). Behavioral models of odor similarity. *Behavioral Neuroscience*, *116*(2), 222–231. https://doi.org/10.1037/0735-7044.116.2.222

Demakis, G. J. (2003). A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage. *Neuropsychology*, *17*(2), 255–264. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12803431

Depue, B. E. (2012). A neuroanatomical model of prefrontal inhibitory modulation of memory retrieval. *Neuroscience & Biobehavioral Reviews*, *36*(5), 1382–1399. https://doi.org/10.1016/j.neubiorev.2012.02.012

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science (New York, N.Y.)*, *317*(5835), 215–219. https://doi.org/10.1126/science.1139560

Granon, S., Vidal, C., Thinus-Blanc, C., Changeux, J. P., & Poucet, B. (1994). Working memory, response selection, and effortful processing in rats with medial prefrontal lesions. *Behavioral Neuroscience*, *108*(5), 883–891. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7826511

Guise, K. G., & Shapiro, M. L. (2017). Medial Prefrontal Cortex Reduces Memory

Interference by Modifying Hippocampal Encoding. *Neuron*, *94*(1), 183-192.e8. https://doi.org/10.1016/j.neuron.2017.03.011

Incisa della Rocchetta, A., & Milner, B. (1993). Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia*, *31*(6), 503–524. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8341411

Jadhav, S. P., Rothschild, G., Roumis, D. K., & Frank, L. M. (2016). Coordinated Excitation and Inhibition of Prefrontal Ensembles during Awake Hippocampal Sharp-Wave Ripple Events. *Neuron*, *90*(1), 113–127. https://doi.org/10.1016/j.neuron.2016.02.010

Jayachandran, M., Linley, S. B., Schlecht, M., Mahler, S. V, Vertes, R. P., & Allen, T. A. (2019). Prefrontal Pathways Provide Top-Down Control of Memory for Sequences of Events. *Cell Reports*, *28*(3), 640-654.e6. https://doi.org/10.1016/j.celrep.2019.06.053

Johansson, M., Aslan, A., Bauml, K.-H., Gabel, A., & Mecklinger, A. (2007). When Remembering Causes Forgetting: Electrophysiological Correlates of Retrieval-Induced Forgetting. *Cerebral Cortex*, *17*(6), 1335–1341. https://doi.org/10.1093/cercor/bhl044

Levy, B. J., & Anderson, M. C. (2002). Inhibitory processes and the control of memory retrieval. *Trends in Cognitive Sciences*, *6*(7), 299–305. https://doi.org/10.1016/S1364-6613(02)01923-X

Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research*, *133*(1), 23–32. https://doi.org/10.1007/s002210000397

Munakata, Y., Herd, S. A., Chatham, C. H., Depue, B. E., Banich, M. T., & O'Reilly, R. C. (2011). A unified framework for inhibitory control. *Trends in Cognitive Sciences*, *15*(10), 453–459. https://doi.org/10.1016/j.tics.2011.07.011

Navawongse, R., & Eichenbaum, H. (2013). Distinct Pathways for Rule-Based Retrieval and Spatial Mapping of Memory Representations in Hippocampal Neurons. *Journal of Neuroscience*, *33*(3), 1002–1013. https://doi.org/10.1523/jneurosci.3891-12.2013

Ng, C. W., Noblejas, M. I., Rodefer, J. S., Smith, C. B., & Poremba, A. (2007). Double dissociation of attentional resources: prefrontal versus cingulate cortices. *J Neurosci*, *27*(45), 12123–12131. https://doi.org/10.1523/JNEUROSCI.2745-07.2007

Paxinos, G., & Watson, C. (1998). *The rat brain in stereotaxic coordinates*. Retrieved from https://books.google.com/books/about/The_Rat_Brain_in_Stereotaxic_Coordinates.html?id=9nXEtwEACAAJ

Peters, G. J., David, C. N., Marcus, M. D., & Smith, D. M. (2013). The medial prefrontal cortex is critical for memory retrieval and resolving interference. *Learning and Memory*, *20*(4), 201–209. https://doi.org/10.1101/lm.029249.112

Ragozzino, M E, Detrick, S., & Kesner, R. P. (1999). Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *J Neurosci*, *19*(11), 4585–4594.

Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10341256

Ragozzino, M E, Kim, J., Hassert, D., Minniti, N., & Kiang, C. (2003). The contribution of the rat prelimbic-infralimbic areas to different forms of task switching. *Behav Neurosci*, *117*(5), 1054–1065. https://doi.org/10.1037/0735-7044.117.5.1054

Ragozzino, Michael E. (2007). The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Annals of the New York Academy of Sciences*, *1121*(1), 355–375. https://doi.org/10.1196/annals.1401.013

Rich, E. L., & Shapiro, M. (2009). Rat Prefrontal Cortical Neurons Selectively Code Strategy Switches. *Journal of Neuroscience*, *29*(22), 7208–7219. https://doi.org/10.1523/jneurosci.6068-08.2009

Rich, E. L., & Shapiro, M. L. (2007). Prelimbic/Infralimbic Inactivation Impairs Memory for Multiple Task Switches, But Not Flexible Selection of Familiar Tasks. *Journal of Neuroscience*, *27*(17), 4747–4755. https://doi.org/10.1523/JNEUROSCI.0369-07.2007

Shimamura, A. P., Jurica, P. J., Mangels, J. A., Gershberg, F. B., & Knight, R. T. (1995). Susceptibility to Memory Interference Effects following Frontal Lobe Damage: Findings from Tests of Paired-Associate Learning. *Journal of Cognitive Neuroscience*, *7*(2), 144–152. https://doi.org/10.1162/jocn.1995.7.2.144

Smith, M. L., Leonard, G., Crane, J., & Milner, B. (1995). The effects of frontal- or temporal-lobe lesions on susceptibility to interference in spatial memory.

Neuropsychologia, *33*(3), 275–285. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7791996

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., … Izukawa, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia*, *38*(4), 388–402. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10683390

Thompson-Schill, S. L., Jonides, J., Marshuetz, C., Smith, E. E., D'Esposito, M., Kan, I. P., … Swick, D. (2002). Effects of frontal lobe damage on interference effects in working memory. *Cognitive, Affective & Behavioral Neuroscience*, *2*(2), 109–120. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12455679

Underwood, B. J. (1957). Interference and forgetting. *Psychological Review*, *64*(1), 49–60. https://doi.org/10.1037/h0044616

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends in Cognitive Sciences*, *12*(11), 418–424. https://doi.org/10.1016/j.tics.2008.07.005

Wimber, M., Alink, A., Charest, I., Kriegeskorte, N., & Anderson, M. C. (2015). Retrieval induces adaptive forgetting of competing memories via cortical pattern suppression. *Nature Neuroscience*, *18*(4), 582–589. https://doi.org/10.1038/nn.3973

Wu, J. Q., Peters, G. J., Rittner, P., Cleland, T. A., & Smith, D. M. (2014). The hippocampus, medial prefrontal cortex, and selective memory retrieval:

Evidence from a rodent model of the retrieval-induced forgetting effect. *Hippocampus*, *24*(9), 1070–1080. https://doi.org/10.1002/hipo.22291

Figure Captions

Figure 1. Behavioral Task and Infusions. A) Schematic of the continuous matching to sample task. Each letter represents a unique odor cue. In the high interference task, the odor cues were repeatedly presented at varying intervals. Two such instances (8 trials back and 2 trials back) are highlighted. In the low interference task, the odor cues were presented for a single run of trials and they did not appeared again within the session. B) Cannula placements targeting the mPFC (adapted from Paxinos & Watson, 1998).

Figure 2. Performance in the continuous matching to sample task. A) Trials from the control sessions were sorted according the how recently the current odor was last presented (see Fig 1A) and the probability of an error for each lag was computed. The error rate was high when the current odor had been presented recently and systematically declined with increasing trial lag (Trials Back). B) Average performance (+/- SEM) is shown for the high and low interference versions of the continuous matching to sample task for the saline and muscimol sessions. C) The average loss in performance due to mPFC inactivation is shown for the high and low interference conditions. The difference in performance (% correct) between muscimol and saline sessions was computed separately for each subject.

Figure 1

A.

High Interference

8 trials back

A A B C C C D A A A B A B

2 trials back

Low Interference

A B B C C C D D E E F G G

B.

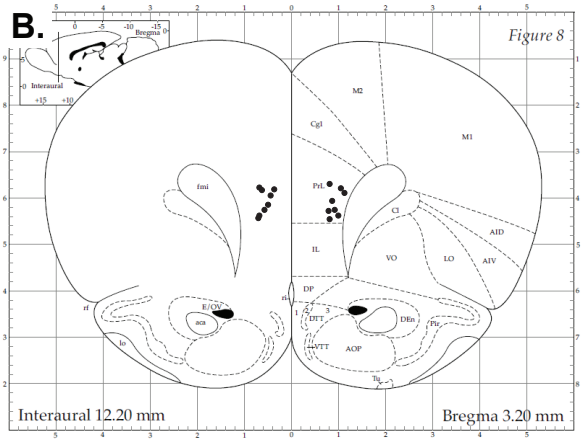
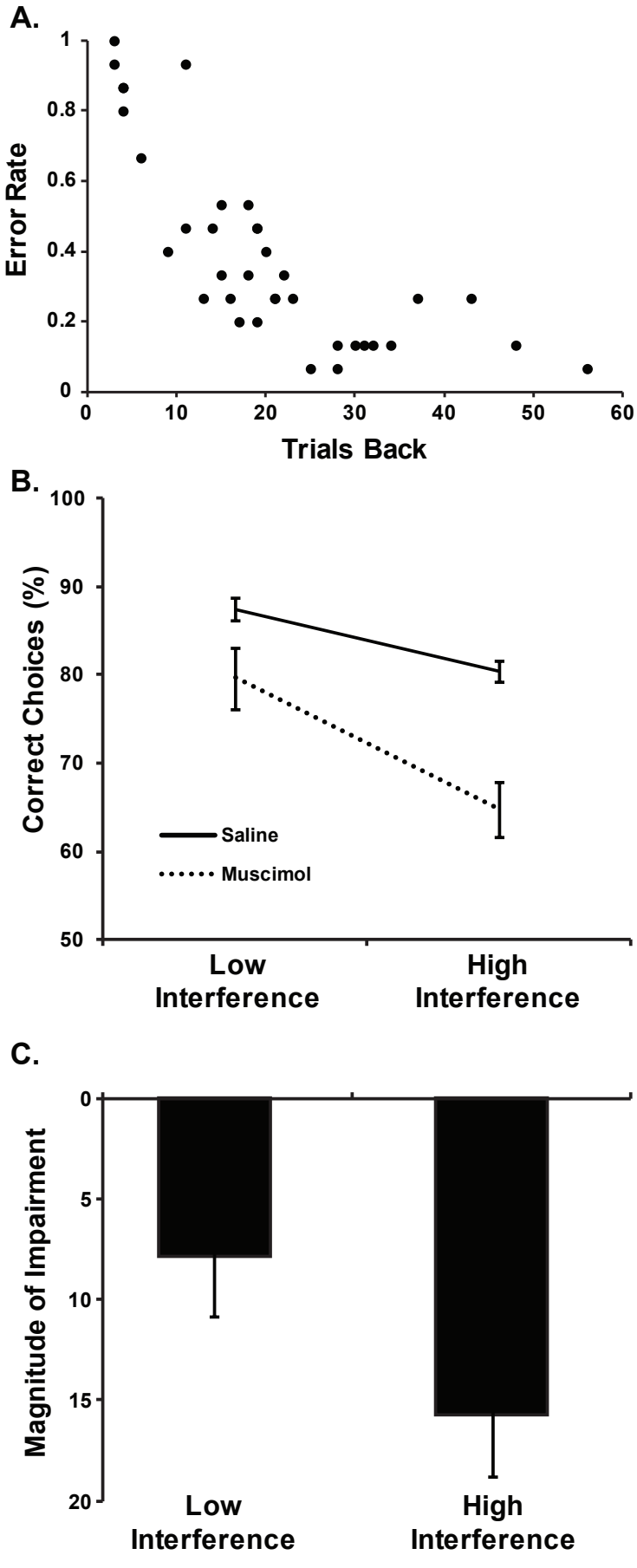


Figure 2


A.
Error Rate
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Trials Back
B.
Correct Choices (%)
100
90
80
70
60
50
Saline
Muscimol
Low Interference
High Interference
C.
Magnitude of Impairment
0
5
10
15
20
Low Interference
High Interference