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Medial prefrontal cortex has a causal role in selectively enhanced consolidation of emotional memories after a 24-hour delay: An iTBS study

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Acknowledgments:
Preparation of this manuscript was supported by the National Science Foundation (Grant BCS-1539361 awarded to J.D.P and E.A.K., and CAREER Grant 1848440 awarded to N.S.R) and from the University of Notre Dame William P. and Hazel B. Collegiate Chair funds (awarded to N.S.R). The authors would like to thank Katie McGuckin, Willian De Faria, Clare Hannon, Shannon O'Hara, and Frank Calabrese for contributing to data collection and analysis.

Conflict of interest:
The authors declare no conflicts of interest.

Abstract

Previous research points to an association between retrieval-related activity in the medial prefrontal cortex (mPFC) and preservation of emotional information compared to co-occurring neutral information following sleep. Although the role of the mPFC in emotional memory likely begins at encoding, little research has examined how mPFC activity during encoding interacts with consolidation processes to enhance emotional memory. This issue was addressed in the present study using transcranial magnetic stimulation in conjunction with an emotional memory paradigm. Healthy males and females encoded negative and neutral scenes while undergoing concurrent TMS with an intermittent theta burst stimulation (iTBS) protocol. Participants received stimulation to either the mPFC or an active control site (motor cortex) during the encoding phase. Recognition memory for scene components (objects and backgrounds) was assessed after a short (30 minutes) and a long delay (24-hours including a night of sleep) to obtain measures of specific and gist-based memory processes. The results demonstrated that, relative to control stimulation, iTBS to the mPFC enhanced gist, but not specific, memory for negative objects on the long delay test. mPFC stimulation had no discernable effect on gist memory for objects on the short delay test nor on the background images at either test. These results suggest that mPFC activity occurring during encoding interacts with consolidation processes to selectively preserve the gist of negatively salient information.

Significance Statement

Understanding how emotional information is remembered over long delays is critical to understanding memory in the real world. The present study uses transcranial magnetic stimulation (TMS) to investigate the interplay between mPFC activity that occurs during memory encoding and its subsequent interactions with post-encoding consolidation processes. Excitatory TMS delivered to the mPFC during encoding enhanced gist-based memory for negatively valenced pictures on a test following a 24-hr delay, with no such effect on a test occurring shortly after the encoding phase. These results are consistent with the hypothesis that emotional aspects of memories are differentially subjected to consolidation processes, and that the mPFC might contribute to this “tag-and-capture” mechanism during the initial formation of such memories.

Introduction

Neuroimaging studies have established that increased levels of activation of the medial prefrontal cortex (Murty et al., 2010) and functional connectivity (Berkers et al., 2016; Kensinger & Corkin, 2004) between the medial prefrontal cortex (mPFC) and medial temporal lobe (MTL; amygdala and hippocampus) are associated with successful emotional encoding of negative information (cf. Payne & Kensinger, 2010, 2011, 2018; see also Goto & Grace, 2008). Emotional memory is often characterized by "trade-off effects", where superior recollection of emotional experiences, or emotional parts of an experience, occur at the expense of memory for neutral aspects of experience (Kensinger et al., 2007a). Sleep-based consolidation processes play a pivotal role in these emotional memory trade-off effects by selectively preserving negative information (Payne et al., 2008, 2012; Payne & Kensinger, 2011), especially gist-based, or general, aspects of negative information (Payne et al., 2008; Hu et al., 2006).

One account of emotional memory trade-offs proposes that processes that operating near the initial learning event can tag emotional aspects of an experience and set the stage for downstream sleep-based consolidation processes (Kim & Payne, 2020; Payne & Kensinger, 2018; also see, Richter-Levin & Akirav, 2003). This “tag and capture” mechanism has been proposed to explain how encoding and sleep-based consolidation processes interact to promote later stabilization of memories. Payne and Kensinger (2018) propose that successful emotional memory will be optimal with increased MTL and PFC activity near encoding, with sleep occurring shortly after. Critically, emotional tags can be set via stress- and arousal-related neuromodulators and reflect initial encoding activity between the MTL and PFC but require a consolidation delay containing sleep to ensure that these tags persist (Payne & Kensinger, 2018).

Thus, post-learning sleep is essential for transforming temporary synaptic changes into long-lasting systems-level ones, and for linking these distributed tags into an integrated memory trace.

Evidence from fMRI studies suggests that sleep leads to a refinement in the neural networks engaged in emotional memory retrieval. For example, studies have revealed that initial broad network activation observed during encoding is refined into a smaller network centered on the amygdala, hippocampus, and ventral mPFC following a sleep-filled consolidation delay, with greater connectivity among these regions correlating with enhanced memory for negative information compared to wakefulness (Bennion et al., 2015; Payne & Kensinger, 2011; Sterpenich et al., 2009). This refinement in emotional memory retrieval networks presumably occurs as memories are consolidated. Importantly, the processes (e.g., tag and capture mechanisms) that lead to refinements in emotional memory retrieval networks are established near the time of encoding. Thus, by modulating neural activity at encoding, we may be able to affect how emotional information is subsequently consolidated. The present work is therefore motivated to causally manipulate mPFC activity during encoding; this mPFC stimulation is expected to promote changes in MTL-mPFC connectivity that will in turn lead to preferential memory for emotional information following a consolidation delay. Thus, specifically, our *a priori* hypothesis is that, relative to control stimulation, mPFC stimulation will preferentially affect memory for negative objects, but only following sleep.

We sought to understand how the mPFC might influence interactions between encoding and consolidation processes that are thought to lead to selective preservation of negative memories (Payne & Kensinger, 2018). During the encoding phase of an emotional memory trade-off task (Payne et al., 2009), we applied intermittent theta burst stimulation (iTBS), which induces excitatory neural effects in the targeted and functionally connected areas (Huang et al.,

2005), to the mPFC or an active control site (motor cortex; MC) . A recognition test assessed memory following a short (30 minute) delay and a long (24-hour) delay that included sleep. Under the assumption that mPFC activity at encoding interacts with subsequent consolidation processes to refine the MTL-mPFC network associated with memory for negative information, we predicted that iTBS to mPFC during encoding should enhance memory for negative, but not neutral, information following a long delay.

Materials and Methods

Participants

Forty-five participants (aged 18-24; *M* = 19.71) were recruited from the University of Notre Dame. Participants identified as 71% Caucasian, 11% Asian, 9% African American, 7% Hispanic, and 2% who declined to state. All participants were fluent English speakers, had no history of sleep disturbances, and did not take medication known to impact sleep or present contraindications for TMS. The current sample size was selected to be in line with prior TMS work (Sack et al., 2009) that has detected significant behavioral effects when targeting cortical regions based on the 10-20 system (see TMS section below). Participants were randomly assigned to receive iTBS either to the mPFC (*N* = 23) or to motor cortex (MC; *N* = 22), which served as an active control site.

Participants were screened for contraindications for TMS following published criteria (Rossi et al., 2009), and were excluded if they self-reported any history of seizures, brain injuries (e.g., stroke, aneurysms, concussions, traumatic brain injury), severe headaches/migraines, fainting, metal implants, neurological/psychiatric disorders, potential pregnancy, or psychoactive medication use. Additionally, participants were instructed to get no less than six hours of sleep the night before and refrain from caffeine, alcohol, and tobacco three hours prior to the study.

Upon arrival, participants provided informed consent. Following completion of the study, they received either course credit or monetary compensation ($15/hour).

Materials

The stimuli have been used in previous work (Payne et al., 2008) with 448 total critical scene components (objects and backgrounds) selected in this study. The critical scene components were then partitioned into old (256) and new items (192). The encoding task consisted of 128 complex valenced scenes (64 negative, 64 neutral) that were created by placing a negative (e.g., snake) or neutral object (e.g., chipmunk) on a plausible neutral background (e.g., forest). The short and long delayed recognition tests each contained a unique set of old and new scene components (i.e., objects and background in isolation). Studied scenes consisted of the objects and the background from “whole” scenes, i.e., objects on backgrounds that were presented together during the study phase. New scene components were drawn from scenes that were not presented during the study phase. Each recognition test consisted of 224 total scene components: 32 previously viewed ("same") objects (16 negative, 16 neutral), 32 similar objects (16 negative, 16 neutral), 64 foil objects (32 negative, 32 neutral), 32 same backgrounds (16 shown with negative object, 16 shown with a neutral object), 32 similar backgrounds (16 similar objects were shown with a negative object, and 16 with a neutral object), and 32 foil backgrounds (all neutral). Same components were defined as the exact same background or object studied during encoding (e.g., identical snake). Similar components were defined as an alternative version of a background or object that differed in any number of visual features from those studied during encoding (e.g., a snake that differed in color, positioning, shape, species, etc.). Note, since backgrounds were always non-emotional, there are no negative backgrounds. The scene components were never presented twice (i.e., in both tests) and were counterbalanced.

Additionally, participants never saw both a same (e.g., same snake) and similar (e.g., similar snake) scene during the one test.

Overview of Experimental Procedure

Participants completed the experiment over the course of two sessions separated by approximately 24-hours. The first session included determination of active motor threshold (see section Transcranial Magnetic Stimulation below), the encoding task, and a recognition test after a 30-minute delay ("short delay" test). iTBS was administered during the encoding phase. After the first session, participants returned to the lab approximately 24-hours later to complete a recognition test on the remaining untested items ("long delay" test). Note that simultaneous electroencephalography recordings were obtained during the encoding and recognition memory tests during the first session (comprised of the encoding and short-delay recognition tasks). These data are not the focus of the present manuscript and therefore will not be discussed further.

Emotional Memory Trade-off Task

Encoding Phase (Figure 1a). Participants viewed 128 negative and neutral complex scenes. For each scene, they made an approach/avoid judgment using a 7-point scale (1 = move closer, 7 = move away) to facilitate incidental encoding. The scenes were presented pseudorandomized in 16 blocks with 8 images per block (4 negative, 4 neutral). Each trial began with a 100-200ms jitter prior to a 1000ms fixation cross. Following the fixation cross, a valenced scene was presented for 3000ms and was replaced with a self-paced avoid/approach judgment scale. Following the 8th trial of each block, participants underwent 2s of iTBS (30 pulses), for a total of 480 pulses over the entire encoding phase.

Recognition Memory Test. Participants were instructed to make same, similar, or new judgments to old and new scene components on both the short and long delayed recognition

tests. Participants completed a short practice phase to familiarize themselves with the recognition test and the same, similar, and new judgments before the recognition test (see Figure 1b). Same judgments were defined as the exact same background or object studied during encoding (e.g., identical snake). Similar judgments were defined as an alternative version of a background or object that differed in a specific visual detail from those studied during encoding (e.g., a snake that differed in color, positioning, species, etc.).

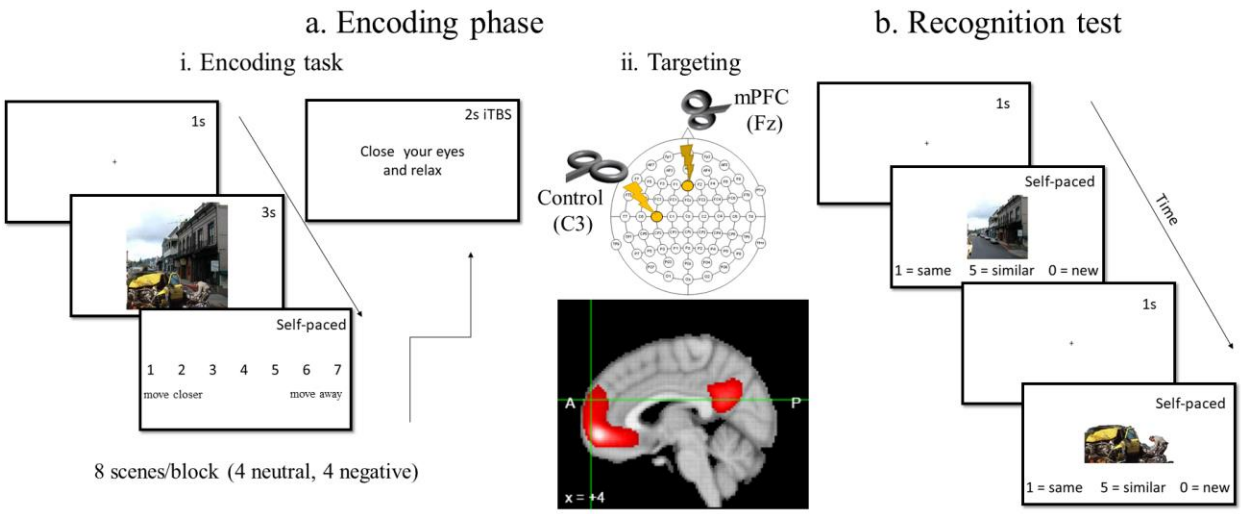

Figure 1. (a) Encoding phase. (i) Encoding trial structure and timing. Participants viewed a fixation cross (1s), followed by a valenced image (3s) and an approach/avoid scale (self-paced). Stimulation occurred after every 8th image for a total of 128 images and 16 blocks. Participants underwent stimulation to only one site, which was randomly assigned. (ii) The Fz and C3 electrodes were targeted for mPFC (N = 23) and motor control stimulation (N = 22), respectively. The Fz electrode was selected based on its proximity to the dorsal mPFC region (MNI: 4, 52, 46) that is functionally connected with the ventral mPFC region (MNI; 4, 56, -8) that was linked to the selective preservation of negative objects in memory from Payne and Kensinger (2011). **(b)** Recognition task. Same, similar, and new objects (negative and neutral) and backgrounds (neutral) were presented individually. Participants responded "same", "similar", or "new". Scene components were presented in randomized order.

Each trial began with a 100-200ms (10ms steps) jittered interval prior to a 1000ms fixation cross. Following the fixation cross, participants made self-paced same, similar, or new

judgments of individually presented negative objects, neutral objects, or neutral backgrounds. Objects and backgrounds were presented randomly, but only once, in either the short or long delay recognition test.

Transcranial magnetic stimulation

A PowerMag EEG 100 TMS stimulator (Mag & More GmbH., Munich, Germany) and a 70 mm figure-eight coil (PMD70-pCool) were used for administration of TMS. Active motor threshold was obtained by placing the coil over the left primary motor cortex and defined as the percentage of stimulator output that elicited visible movement in the right thumb on 5 out of 10 trials while participants maintained contraction of the right thumb and index finger. The mean motor threshold was matched between participants receiving mPFC and MC stimulation (mPFC: M = 59%, SD = 10%; MC: M = 59%, SD = 11%; $t(42) = -.25$, $p = .805$). As is standard, the iTBS protocol was administered at 80% of active motor threshold.

The stimulation site for the dorsal mPFC was determined using a large-scale meta-analysis of 340 fMRI datasets using Neurosynth.org (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) with a seed using the ventral mPFC coordinates identified by Payne and Kensinger (2011) to be associated with enhanced negative object recognition following sleep compared to wakefulness (MNI = 4, 56, -8). The rationale for targeting the dorsal mPFC is that TMS modulates neural activity in both the target site and its associated networks (for an example with TMS stimulation to angular gyrus modulating the hippocampus, which are part of the same network, see Nilakantan, Bridge, Gagnon, VanHaurents, & Voss, 2017). Thus, we reasoned that stimulating the dorsal mPFC would also affect the ventral mPFC activity, which is not readily accessible to TMS. The MNI coordinate with strong functional connectivity and coactivation with the vmPFC seed based on the Neurosynth meta-analysis was identified to be under

electrode Fz (Okamoto et al., 2004; Okamoto & Dan, 2005) using the International 10-20 system (Figure 1b; Jasper, 1958). For the control stimulation site, we targeted the MC under the C3 electrode because it is a common control site (e.g., Daskalakis et al., 2008; Fecchio et al., 2017) and, importantly, it does not have strong connectivity with the ventral mPFC region that has been implicated in emotional memory.

The typical offline protocol for iTBS follows 2s on/8s off cycles that deliver 600 pulses with each 2s of stimulation corresponding to 3 pulses at 50Hz with an inter stimulus interval of 200ms. We adopted a slightly modified iTBS approach with identical 2s periods of stimulation that was applied in a similar 2s on/8s off manner that was interleaved throughout the encoding phase. A similar approach has previously been shown to facilitate memory and, importantly, to not have cumulative effects on performance (Demeter et al., 2016). Prior to the start of the experimental task, participants received one 2s train of iTBS to become familiarized with the procedure. No participants reported any adverse response to iTBS.

Data Analysis

For the recognition data, participants' memory scores were calculated for general recognition (gist-familiarity) and specific recognition (recollection). The contrast between general and specific recognition scores was our focus because prior research suggests that overnight sleep exerts its strongest effects on gist-based familiarity, rather than specific recollection of memory details (Payne et al., 2008). In line with prior studies using a same-similar-new judgment at retrieval (Garoff et al., 2005; Kensinger et al., 2007b), general recognition parallels the independence-formulas score commonly used in Remember/Know paradigms (Yonelinas & Jacoby, 1995) with the following formula:

$$General\ recognition\ hits = \frac{P(\text{similiar}|\text{"same"})}{(1 - P(same|"same"))}$$

$$General\ false\ alarms = \frac{P(\text{similiar}|\text{"new"})}{(1 - P(same|"new"))}$$

Thus, general hits are calculated based on when participants respond “similar” to previously viewed items, taking into account when participants respond “same” to previously viewed items. General false alarms are measured when participants respond “similar” to new items, taking into account when they respond “same” to new items. Specific recognition was scored with the following formula:

$$Specific\ recognition\ hits = P(same|"same")$$

$$Specific\ false\ alarms = P(same|"new")$$

Thus, specific hits and false alarms are computed when participants respond “same” to previously viewed items and “same” to new items, respectively.

Since our primary aim was to investigate the effects of mPFC iTBS on emotional memory we computed recognitions scores for negative objects, neutral objects, the neutral backgrounds that were originally paired with a negative object, and the neutral backgrounds that were originally paired with a neutral object. Importantly, these calculations were repeated for the short and long delay tests. This enabled us to systematically compare how mPFC versus MC iTBS affected memory for negative and neutral objects, backgrounds in negative and neutral scenes, across the short and long delay tests. Analyses focused on memory performance for “same”, “similar”, and “new” responses to the same and new scene components (i.e., responses

to similar objects and background scenes were not analyzed), to be consistent with previous work using this paradigm (Kensinger et al., 2007a, 2007b; Waring et al., 2010).

There were statistically comparable ‘same’ (range = .038-.096) and ‘similar’ (range = .153-.258) false alarm rates between the cells in the experiment (all *p*’s > .05), which is consistent with previous work (Payne et al., 2008). All memory performance analyses were conducted on corrected recognition scores (hits – false alarms) to obviate issues with response bias effects. We will refer to these measures as recognition scores from this point forward.

Experimental Design and Statistical Analyses

We tested our *a priori* hypothesis that, relative to MC stimulation, mPFC stimulation will facilitate recognition for negative objects relative to neutral objects at a long delay using a series of 2 (stimulation site: mPFC, MC) x 2 (valence: negative, neutral) ANOVAs. Furthermore, we expected these stimulation site by valence interactions to be unique to recognition at the long delay (i.e., after sleep). To test this, we first had to establish if mPFC versus MC iTBS modulated memory for negative objects, but not neutral objects, at a short delay. Then, we examined if mPFC versus MC iTBS enhanced memory for negative objects, but not neutral objects, following a long delay that included sleep. Finally, we investigated if mPFC versus MC iTBS also influenced the (always neutral) backgrounds associated with these negative and neutral objects by analyzing the backgrounds at a short delay and then for backgrounds at a long delay.

ANOVAs were conducted in R (version 3.6.3.) using the *afex* (Singmann, Bolker, Westfall, Aust, & Ben-Shachar, 2020) package. Post-hoc comparisons on significant interactions between stimulation site and valence were conducted with the *emmeans* (Lenth, 2020) package with degrees of freedom estimated with the Kenward-Roger method. Results are considered significant at an alpha level of .05 unless otherwise noted.

Results

General recognition

Three participants (mPFC: 2, MC: 1) were excluded from the general recognition analysis due to no observations in one or more response categories. As shown in Figure 2 (a, c), iTBS to the mPFC preserved general recognition of negative objects after a long delay, but not after a short delay. This pattern of results was not observed for neutral objects, the background scenes, or the MC control condition (see Figure 2 a-d).

First, we examined general recognition scores for objects in negative and neutral scenes at a short delay with a 2 (Stimulation site) x 2 (Valence) mixed factorial ANOVA. We found no evidence (i.e., stimulation by valence interaction) that mPFC versus MC iTBS modulated memory, see Figure 2a. Specifically, we found no significant effect of stimulation site, $F(1, 40) = .95$, $MSE = .11$, $p = .337$, $\eta_p^2 = .02$, valence, $F(1, 40) = 3.32$, $MSE = .07$, $p = .076$, $\eta_p^2 = .08$, or stimulation by valence interaction on general recognition scores, $F(1, 40) = .56$, $MSE = .07$, $p = .457$, $\eta_p^2 = .01$. Consistent with our prediction, these findings suggest that mPFC iTBS did not modulate memory for negative or neutral objects at a short delay. Next, to examine our primary aim if mPFC activity near encoding interacts with consolidation processes (i.e., enhanced memory for negative objects following mPFC versus MC iTBS only at a long delay) the same ANOVA was conducted on the general recognition scores of objects in negative and neutral scenes at a long delay that included sleep. This analysis revealed no main effect of valence, $F(1, 40) = 1.28$, $MSE = .03$, $p = .265$, $\eta_p^2 = .03$, a significant main effect of stimulation site, $F(1, 40) = 6.49$, $MSE = .05$, $p = .015$, $\eta_p^2 = .14$, and, importantly, a significant stimulation site by valence interaction, $F(1, 40) = 7.89$, $MSE = .03$, $p = .008$, $\eta_p^2 = .17$. In line with our prediction, follow up *t*-tests revealed that mPFC stimulation led to significantly higher general recognition of negative

objects at a long delay compared to MC stimulation, $t(72.7) = 3.70$, $p < .001$, $d = 1.39$. There were no significant differences between the mPFC and MC stimulation conditions on general recognition scores for the neutral objects, $t(72.7) = .42$, $p = .671$, $d = .16$ (see Figure 2c).

To further tease apart the influence of mPFC iTBS on emotional memory, we also conducted similar ANOVAs on general recognition scores for backgrounds in the negative and neutral scenes. The analysis of the short-delay test revealed a significant effect of valence, $F(1, 40) = 6.40$, $MSE = .04$, $p = .015$, $\eta_p^2 = .14$, which reflected higher general recognition scores for background images for negative compared to neutral scenes, see Figure 2b. Neither the main effect of stimulation site, $F(1, 40) = 2.84$, $MSE = .06$, $p = .100$, $\eta_p^2 = .07$, nor the interaction was significant on the short delay general recognition scores, $F(1, 40) = 1.27$, $MSE = .04$, $p = .267$, $\eta_p^2 = .03$. The ANOVA on the general recognition scores for backgrounds on the long delayed test revealed no significant effect of stimulation site, $F(1, 40) < .01$, $MSE = .06$, $p = .979$, $\eta_p^2 < .01$, valence, $F(1, 40) = .30$, $MSE = .02$, $p = .585$, $\eta_p^2 = .01$, nor a significant interaction, $F(1, 40) = .29$, $MSE = .02$, $p = .593$, $\eta_p^2 = .01$ see Figure 2d.

In summary, iTBS to the mPFC compared to MC significantly facilitated general recognition for negative objects at the long delay (that included a night of sleep) and we found no evidence that memory for the background scene components were affected. This effect was only found at the long delay, as no differences emerged for objects or backgrounds when memory was assessed at the short delay. Importantly, for neutral scenes, no differences between stimulation conditions emerged for objects or backgrounds when memory was assessed at either a short or long delay.

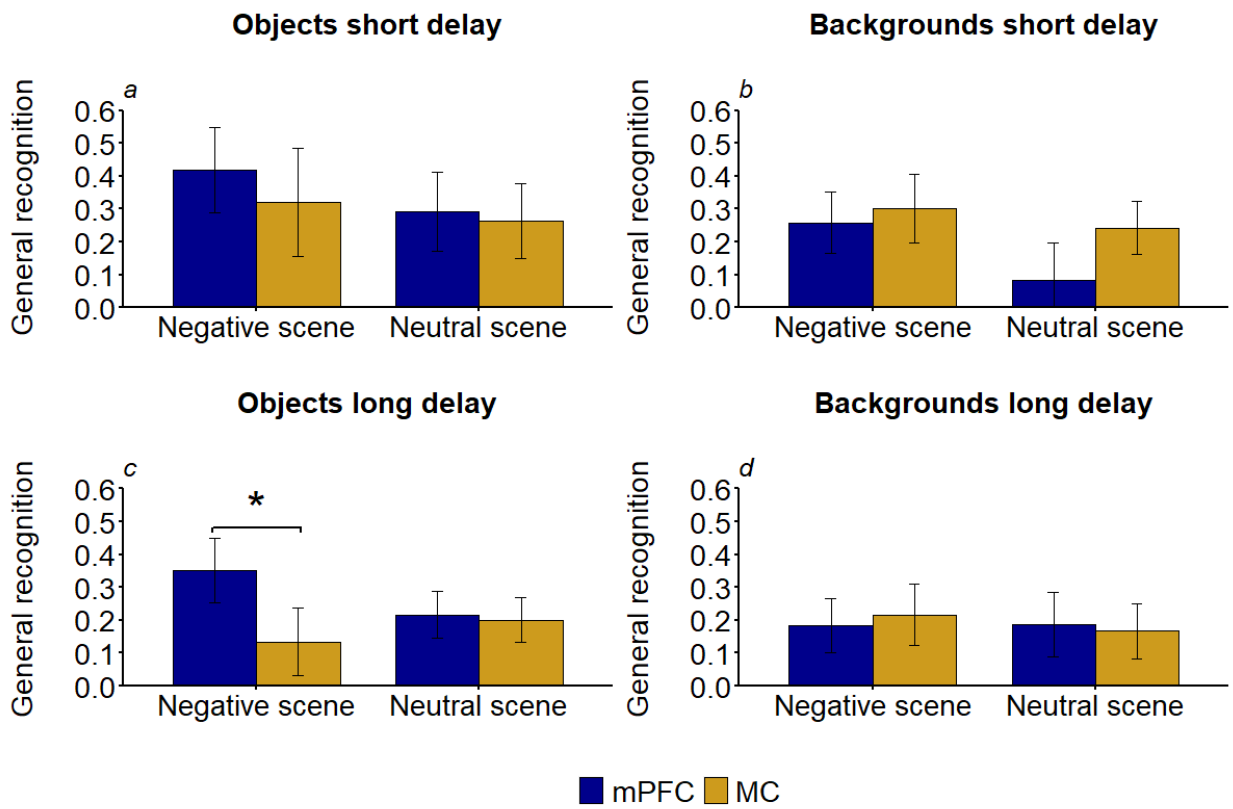

Figure 2. General corrected recognition scores (hits – false alarms) revealed that iTBS to the mPFC facilitated memory for negative objects at a long delay compared to MC stimulation. No general recognition differences were found between negative objects at a short delay for mPFC vs. MC control stimulation. Error bars represent 95% confidence intervals. *$p < .05$.

Specific Recognition

A similar set of analyses as those described in the preceding section were carried out on the specific recognition scores to specific recognition (see Figure 3a-d). The purpose of this analysis was to see if the results observed for gist memory extend to measures that index veridical recollection. To preface the results, these analyses provided little evidence that mPFC stimulation affected specific recognition of objects or backgrounds at a short or long delay.

The 2 (stimulation site) x 2 (valence) ANOVA on the specific recognition scores for objects in negative and neutral scenes from the short delay test only revealed a significant main effect of valence, $F(1, 43) = 36.62$, $MSE = .01$, $p < .001$, $\eta_p^2 = .46$, with higher specific

recognition for negative compared to neutral objects (see Figure 3a). The main effect of stimulation site, $F(1, 43) = 2.07$, $MSE = .07$, $p = .158$, $\eta_p^2 = .05$, and the stimulation site by valence interaction, $F(1, 43) = 3.67$, $MSE = .01$, $p = .062$, $\eta_p^2 = .08$, both failed to reach significance. These findings suggest that mPFC compared to MC iTBS did not affect specific recognition of negative or neutral objects at a short delay. Similarly, we found little evidence that mPFC iTBS modulated memory when the above ANOVA was conducted on specific recognition scores for objects in negative and neutral scenes on the long delay test. Specifically, there was a significant effect of valence, $F(1, 43) = 61.08$, $MSE = .01$, $p < .001$, $\eta_p^2 = .59$, with higher specific recognition of negative compared to neutral, see Figure 3c. The main effect of stimulation site, $F(1, 43) = 1.94$, $MSE = .08$, $p = .171$, $\eta_p^2 = .04$, and the stimulation site by valence interaction, $F(1, 43) = 2.25$, $MSE = .01$, $p = .141$, $\eta_p^2 = .05$, failed to reach significance. Thus, little evidence suggests that mPFC encoding activity interacted with consolidation processes on measures of specific recognition of negative and neutral objects at either delay.

Next, to examine if there was any evidence that mPFC activity at encoding interacted with consolidation processes to modulate memory for backgrounds, a similar analysis to that described above was conducted on specific recognition scores for backgrounds from negative and neutral scenes on the short and long delay test. The ANOVA conducted on the specific recognition scores for background images on the short delay test revealed a significant effect of valence, $F(1, 43) = 37.12$, $MSE = .01$, $p < .001$, $\eta_p^2 = .46$, with higher specific scores for backgrounds in neutral scenes compared to negative scenes, see Figure 3b. This analysis of the short delay test found no evidence that iTBS modulated specific recognition of backgrounds at a short delay. Specifically, we found no significant effect of stimulation site, $F(1, 43) = .21$, $MSE = .07$, $p = .648$, $\eta_p^2 = .01$, or stimulation site by valence interaction, $F(1, 43) = .97$, $MSE = .01$, p

= .331, η_p^2 = .02. The ANOVA conducted on the specific recognition scores for backgrounds in negative and neutral scenes on the long delay test revealed a similar pattern of results. There was a significant effect of valence, $F(1, 43) = 66.65$, $MSE = .01$, $p < .001$, $\eta_p^2 = .61$, with higher scores for backgrounds from neutral compared to negative scenes, see Figure 3d. There was no significant effects of stimulation site, $F(1, 43) = 2.47$, $MSE = .06$, $p = .123$, $\eta_p^2 = .05$, nor was the stimulation site by valence interaction significant, $F(1, 43) = 2.93$, $MSE = .01$, $p = .094$, $\eta_p^2 = .06$

In summary, iTBS to the mPFC did not significantly modulate specific recognition of negative or neutral scene components on either the short or long delay tests.

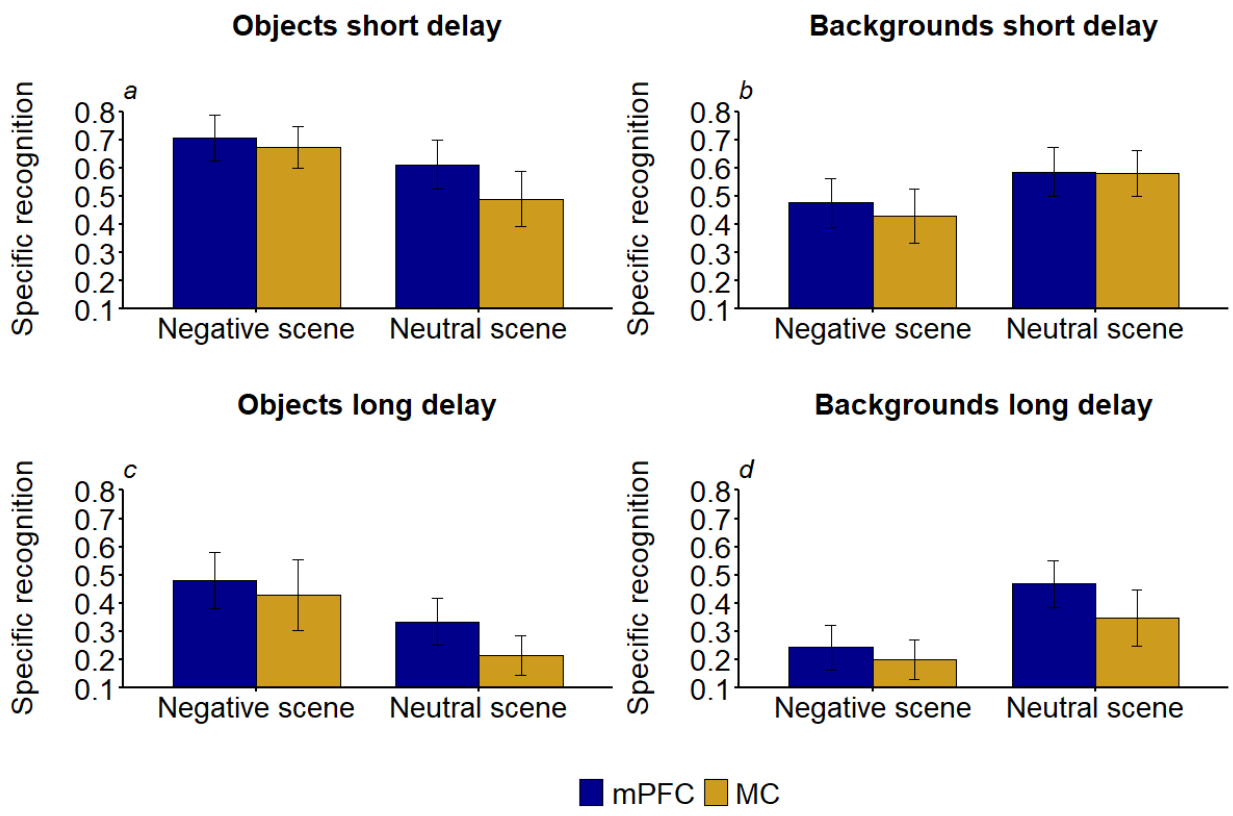

Figure 3. Specific corrected recognition scores (hits – false alarms) revealed no differences between negative objects at a delay (short or long) for the mPFC vs. MC control stimulation site. Error bars represent 95% confidence intervals.

Summary of Results

Collectively, the findings revealed that iTBS to the mPFC selectively facilitated general recognition of negative information after a long delay while no differences emerged for specific recognition. Critically, for general recognition, memory was facilitated for negative objects while memory for their accompanying backgrounds was unaffected. In addition, no memory differences emerged when memory was assessed following a short delay in negative scenes or at either delay in neutral scenes. Together, these findings suggest that modulating mPFC activity during encoding selectively facilitated gist-based representations of emotional memories.

General Discussion

This study investigated the causal role of the mPFC in the preferential encoding and consolidation of emotionally salient information. Our results provide preliminary evidence that the mPFC is causally involved in the encoding of negatively valenced scenes. Specifically, stimulating the mPFC, but not the MC, during encoding with iTBS enhanced general recognition memory for negative objects only after a 24-hour delay (filled with sleep). We found no evidence that this effect was present for specific recognition. Moreover, iTBS to the mPFC had no detectable effect on memory for negative stimuli on the short delay (30 minute) test, on neutral information on either test, or on the background scene component in any condition. We interpret these findings as being consistent with the idea that mPFC activity near the time of encoding potentiates subsequent consolidation processes, which together facilitate memory for negative information (Payne & Kensinger, 2010, 2011, 2018).

The finding that iTBS to the mPFC during encoding enhanced general recognition for negative objects on the long delay test suggests that the mPFC facilitates consolidation of gist-based memory for negative information. The present findings converge with previous work

showing that overnight sleep facilitates the consolidation of emotional gist memory over detail memory (see Hu et al., 2006; Payne et al., 2008). Notably, false alarm rates did not differ between any of the conditions, which argues against the idea that our results are due to differences in response bias between the mPFC and MC groups.

The results reported here also extend recent work suggesting a causal role for the mPFC in gist-based false memories (Bovy et al., 2020; for related findings, see Berkers et al., 2017). Bovy and colleagues (2020) examined the relationship between gist-based emotional false memories and mPFC by stimulating the mPFC using an inhibitory TMS protocol, specifically continuous theta-burst stimulation (cTBS). Prior to encoding in an emotionally-valenced Deese-Roediger-McDermott (DRM) paradigm, participants underwent a negative mood induction and received TMS to the mPFC using the above mentioned cTBS or a control (i.e., 5Hz rTMS protocol). They found that cTBS to mPFC during encoding reduced false recognition of negative critical lures on a delayed test (~24-hour) that included a sleep interval. The authors took these findings as evidence that the mPFC plays an important role in extracting schematic (or gist) information during encoding. Our findings converge with and extend the above described results. Here, we observed iTBS – a TMS protocol thought to be associated with increased excitation ("long-term potentiation", Wischnewski & Schutter, 2015) of the stimulated region – delivered to the mPFC during encoding facilitated memory for negative objects on a 24-hour delayed test. Moreover, we demonstrate that mPFC iTBS benefits emotional episodic memory by using a memory task consisting of complex emotional scenes as opposed to semantically related word lists. Most importantly, in addition to the 24-hour delayed test, we also included a short (30 minute) delayed memory test to better establish that mPFC activity during encoding interacted with subsequent consolidation processes. We observed that mPFC iTBS at encoding selectively

enhanced negative gist-based memory only on the 24-hour delayed memory test. Our findings suggest a causal role the mPFC activity near encoding interacts with downstream consolidation processes to support retention of gist-based memories.

The present results also provide support for theories of the selective consolidation of emotional information (Kim & Payne, 2020; Payne & Kensinger, 2018; Richter-Levin & Akirav, 2003). Specifically, excitatory stimulation (i.e., neuromodulation) of the dorsal mPFC during encoding may have affected subsequent memory performance by upregulating regions important for emotional memory encoding and retrieval, including the ventral mPFC, amygdala and hippocampus (Bennion et al., 2015; Kensinger & Corkin, 2004; Murty et al., 2010; Payne & Kensinger, 2010). Future work could directly test this possibility by examining the effects of TMS in conjunction with fMRI measures of activity and connectivity.

There are two limitations of the present study that warrant mention. First, iTBS was interspersed throughout the encoding task to attempt to modulate brain regions, specifically the MTL, that are functionally connected with the mPFC and critically involved in the encoding of emotional information. It is unclear if our results would differ had we used a different TMS protocol, such as 1Hz rTMS. Of relevance to this point, a recent meta-analysis of TMS effects on episodic memory found that offline 1 Hz rTMS led to larger enhancing effects on episodic memory compared to other stimulation protocols, including iTBS (Yeh & Rose, 2019). Second, we only examined the effects of mPFC stimulation during memory encoding. It is possible that mPFC stimulation during a different stage of memory, such as during post-encoding periods, would lead to a different pattern of results.

To draw stronger causal claims about the role of mPFC in emotional memory, we used an active control stimulation site (left MC) instead of another common control site (i.e., vertex) or

sham stimulation. Prior findings have suggested vertex stimulation may modulate activity in the default mode network (Jung et al., 2016), which is involved in emotion (Sheline et al., 2009) and memory processes (Rugg & Vilberg, 2013). Although we cannot rule out the possibility that MC stimulation contributed to the effects on memory by impairing recognition of negative objects, we find this possibility unlikely for two reasons. One, memory performance in the MC stimulation group reported here was comparable to memory performance in a no-stimulation control group in a pilot study (not reported). Two, and most importantly, MC is not associated with emotional memory. Future work is needed to determine if different stimulation protocols (e.g., frequency, intensity, control stimulation site, stage of memory) will lead to further insights about the role of encoding-consolidation interactions involving the mPFC and its associated network.

Future work should conduct a more direct investigation of the relationship between mPFC activity during encoding and sleep-based consolidation in emotional memory. Sleep affords an ideal environment for offline consolidation to transform, integrate, and preserve salient and future relevant information (Payne, 2011). Synchronous neural oscillations during sleep (e.g., theta oscillations, slow oscillations, spindles) have been observed in the amygdala, hippocampus, and prefrontal cortex, and may facilitate synaptic plasticity and selective memory consolidation during sleep (Kim & Payne, 2020; Rasch & Born, 2013). Examining the macro and microarchitecture of sleep in conjunction with causal methods like TMS will provide critical insight into the neural mechanisms of emotional memory encoding and consolidation.

In conclusion, the results of this study provide preliminary evidence for a causal role of the mPFC in selectively preserving negative memories. The current work moves beyond correlational findings and provides initial causal support for theories suggesting that activity and

connectivity in an emotional memory network (e.g., amygdala-hippocampus-mPFC) near the time of encoding interact with subsequent consolidation processes (perhaps during sleep) to form long-lasting emotional memories (Kim & Payne, 2020; Payne & Kensinger, 2018).

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