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Running Head: MEDIAL PFC AND EMOTIONAL MEMORY CONSOLIDATION

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

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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 young adults encoded negative and neutral scenes while undergoing concurrent TMS with a modified short intermittent theta burst stimulation (sTBS) 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-minute) and a long delay (24-hour, including a night of sleep) to obtain measures of specific and gist-based memory processes. The results demonstrated that, relative to control stimulation, sTBS to the mPFC enhanced memory for negative objects on the long delay test (collapsed across specific and gist-based memory measures). mPFC stimulation had no discernable effect on 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 preferentially preserve negatively salient information.

Significance Statement

Understanding how emotional information is remembered over time is critical to understanding memory in the real world. The present study used noninvasive brain stimulation (repetitive transcranial magnetic stimulation, rTMS) to investigate the interplay between mPFC activity that occurs during memory encoding and its subsequent interactions with consolidation processes. rTMS delivered to the mPFC during encoding enhanced 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

Emotional memory is often characterized by "trade-off effects", where superior recollection of the emotional parts of an experience occur at the expense of memory for neutral aspects (Kensinger et al., 2007a; Payne et al., 2008). One account of emotional memory trade-offs proposes that synaptic processes operating near the initial learning event can "tag" emotionally salient aspects of an experience and set the stage for downstream preferential consolidation of these emotional aspects (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 subsequent consolidation processes interact to promote later stabilization of memories. While the synaptic tag has yet to be directly examined in humans, recent studies have observed network-level neural processes via functional MRI (Tambini et al., 2017) and behavioral outcomes (Ballarini et al., 2013; Dunsmoor et al., 2015; Patil et al., 2016) that are consistent with the theorized tagging mechanism.

An open question in memory research is whether these network-level neural processes can be utilized to causally manipulate the preferential encoding and consolidation of emotional information. Neuroimaging studies have established that increased levels of activation of the medial temporal lobe (MTL; including the amygdala and hippocampus) and the medial prefrontal cortex (mPFC) are associated with successful emotional encoding of negative information (cf. Murty et al., 2010; Payne & Kensinger, 2010, 2011, 2018; see also Goto & Grace, 2008). Functional connectivity between the MTL and mPFC is also associated with successful emotional memory encoding (Berkers et al., 2016; Kensinger & Corkin, 2004).

There is also evidence that longer consolidation delays (e.g., 24-hour delays) are crucial for emotion-related memory enhancements (Dunsmoor et al., 2015; see also Patil et al., 2016 for

89 reward-related memory). One probable reason for this delay-dependency is the presence of sleep
90 during the consolidation interval. Sleep-based consolidation processes play a pivotal role in
91 emotional memory trade-off effects by selectively preserving negative information (Payne et al.,
92 2008), especially gist-based aspects of negative information (Payne et al., 2008; Hu et al., 2006).
93 Evidence from fMRI studies suggests that sleep leads to a refinement in the neural networks
94 engaged in emotional memory retrieval. For example, studies have revealed that initial broad
95 network activation observed during encoding is refined into a smaller network centered on the
96 amygdala, hippocampus, and ventral mPFC following a sleep-filled consolidation delay, with
97 greater connectivity among these regions correlating with enhanced memory for negative
98 information compared to wakefulness (Bennion et al., 2015; Payne & Kensinger, 2011;
99 Sterpenich et al., 2009). This refinement in emotional memory retrieval networks presumably
100 occurs as memories are consolidated.

101 Importantly, the hypothesized tag-and-capture mechanisms that lead to refinements in
102 emotional memory retrieval networks are established near the time of encoding. Payne and
103 Kensinger (2018) proposed that successful emotional memory will be optimal with increased
104 MTL and PFC activity near encoding, with sleep occurring shortly after. Critically, emotional
105 tags can be set via stress- and arousal-related neuromodulators that reflect initial encoding
106 activity between the MTL and PFC. However, sleep is required to ensure that these tags persist
107 (Payne & Kensinger, 2018), suggesting that post-learning sleep is essential for transforming
108 temporary synaptic changes into long-lasting systems-level ones, and for linking these
109 distributed tags into an integrated memory trace.

110 Thus, by modulating neural activity at encoding, we may be able to affect how emotional
111 information is subsequently consolidated. The present work therefore sought to understand how

112 the mPFC might influence interactions between encoding and consolidation processes that are
113 thought to lead to selective preservation of negative memories (Payne & Kensinger, 2018).
114 During the encoding phase of an emotional memory trade-off task, we applied a short, modified
115 version of intermittent theta burst stimulation (sTBS) to either the mPFC or an active control site
116 (motor cortex; MC) (see the “Transcranial Magnetic Stimulation” section in the methods for
117 details about the sTBS protocol and the rationale for how we targeted the mPFC). A recognition
118 test assessed memory following a short (30-minute) delay and a long (24-hour) delay that
119 included sleep.

120 Under the assumption that mPFC activity at encoding interacts with subsequent
121 consolidation processes to refine the MTL-mPFC network associated with memory for negative
122 information, we assumed that modulating mPFC with sTBS during an emotional memory
123 encoding task would, in turn, alter activity in an excitatory manner to both the targeted and
124 functionally connected areas (similar to the effects observed with standard intermittent TBS,
125 Hermiller et al., 2020; Huang et al., 2005; Tang et al., 2019) within an emotion–cognition
126 network, including changes in MTL-mPFC connectivity. Enhanced emotional memory
127 performance at the short delay would be suggestive of differences in encoding (and very early
128 consolidation processes) due to mPFC stimulation, while altered behavioral outcomes at the long
129 delay, especially in the absence of differences at the short delay, would indicate that TMS-related
130 modulation of this network prioritized certain items during encoding for *later* consolidation (e.g.,
131 post-sleep). Our *a priori* hypothesis was that mPFC relative to control stimulation would
132 preferentially enhance memory for negative, but not neutral, information following a long delay.
133 Furthermore, this study also examined the effects of mPFC stimulation during encoding on the

134 specificity of these emotional memory trade-off effects for specific and gist-like emotional
135 memories (cf. Bovy et al., 2020; Hu et al., 2006; Payne et al., 2008).

136 **Materials and Methods**

137 *Participants*

138 Forty-five participants (aged 18-24; $M = 19.71$; $N_{\text{females}} = 30$) were recruited from the
139 University of Notre Dame. Participants identified as 71% Caucasian, 11% Asian, 9% African
140 American, 7% Hispanic, and 2% who declined to state. All participants were fluent English
141 speakers, had no history of sleep disturbances, and did not take medication known to impact
142 sleep or present contraindications for TMS. The current sample size was selected to be in line
143 with prior TMS work (Sack et al., 2009) that has detected significant behavioral effects when
144 targeting cortical regions based on the 10-20 system (see TMS section below). Participants were
145 randomly assigned to receive sTBS either to the mPFC ($N = 23$) or to motor cortex (MC; $N =$
146 22), which served as an active control site.

147 Participants were screened for contraindications for TMS following published criteria
148 (Rossi et al., 2009), and were excluded if they self-reported any history of seizures, brain injuries
149 (e.g., stroke, aneurysms, concussions, traumatic brain injury), severe headaches/migraines,
150 fainting, metal implants, neurological/psychiatric disorders, potential pregnancy, or psychoactive
151 medication use. Additionally, participants were instructed to get no less than six hours of sleep
152 the night before and refrain from caffeine, alcohol, and tobacco three hours prior to the study.
153 Upon arrival, participants provided informed consent. Following completion of the study, they
154 received either course credit or monetary compensation (\$15/hour).

155 *Materials*

156 The stimuli have been used in previous work (Payne et al., 2008) with 448 total critical
 157 scene components (objects and backgrounds) selected in this study. The critical scene
 158 components were then partitioned into old (256) and new items (192). The encoding task
 159 consisted of 128 complex valenced scenes (64 negative, 64 neutral) that were created by placing
 160 a negative (e.g., snake) or neutral object (e.g., chipmunk) on a plausible neutral background (e.g.,
 161 forest). The short and long delayed recognition tests each contained a unique set of old and new
 162 scene components (i.e., objects and background in isolation). Studied scenes consisted of the
 163 objects and the background from “whole” scenes, i.e., objects on backgrounds that were
 164 presented together during the study phase. New scene components were drawn from scenes that
 165 were not presented during the study phase. Each recognition test consisted of 224 total scene
 166 components: 32 previously viewed (“same”) objects (16 negative, 16 neutral), 32 similar objects
 167 (16 negative, 16 neutral), 64 foil objects (32 negative, 32 neutral), 32 same backgrounds (16
 168 shown with negative object, 16 shown with a neutral object), 32 similar backgrounds (16 similar
 169 objects were shown with a negative object, and 16 with a neutral object), and 32 foil
 170 backgrounds (all neutral). Same components were defined as the exact same background or
 171 object studied during encoding (e.g., identical snake). Similar components were defined as an
 172 alternative version of a background or object that differed in any number of visual features from
 173 those studied during encoding (e.g., a snake that differed in color, positioning, shape, species,
 174 etc.). Note, since backgrounds were always non-emotional, there are no negative backgrounds.
 175 The scene components were never presented twice (i.e., in both tests) and were counterbalanced.
 176 Additionally, participants never saw both a same (e.g., same snake) and similar (e.g., similar
 177 snake) scene during the one test.

178 *Experimental design*

179 Participants completed the experiment over the course of two sessions separated by
 180 approximately 24-hours. The first session included determination of active motor threshold (see
 181 section Transcranial Magnetic Stimulation below), the encoding task, and a recognition test after
 182 a 30-minute delay (“short delay” test). sTBS was administered during the encoding phase with a
 183 30-minute delay occurring from the completion of the encoding phase to the onset of the
 184 recognition test. Note that simultaneous electroencephalography recordings were obtained during
 185 the encoding and short-delay recognition tasks, but not in the final (24-hour) delayed recognition
 186 test. These data are not the focus of the present manuscript and therefore will not be discussed
 187 further. After the first session, participants returned to the lab approximately 24-hours later to
 188 complete a recognition test on the remaining untested items (“long delay” test).

189 *Emotional Memory Trade-off Task*

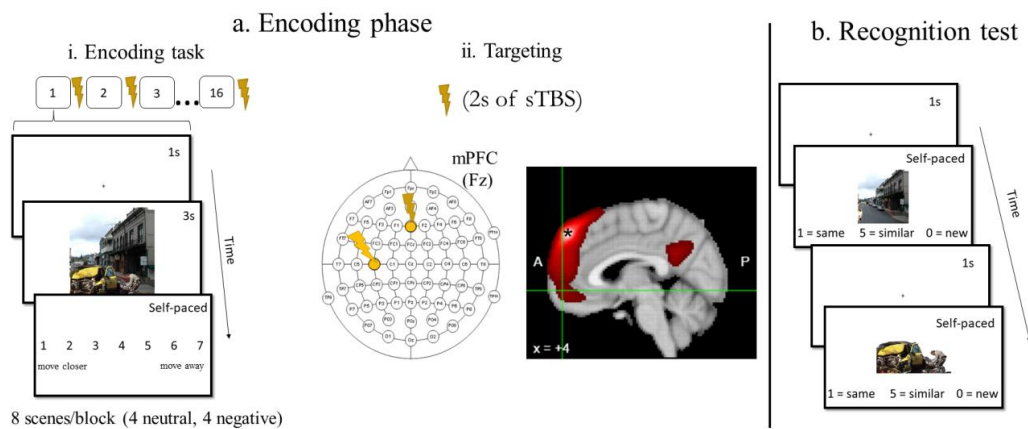
190 *Encoding Phase (Figure 1a).* Participants were instructed that they would be presented
 191 with a series of scenes and to imagine that they were coming across the scenes in real life.
 192 Participants viewed 128 negative and neutral complex scenes. For each scene, they made an
 193 approach/avoid judgment using a 7-point scale (1 = move closer, 7 = move away) to facilitate
 194 incidental encoding. The scenes were presented pseudorandomized in 16 blocks with 8 images
 195 per block (4 negative, 4 neutral). Each trial began with a 100-200ms jitter prior to a 1000ms
 196 fixation cross. Following the fixation cross, a valenced scene was presented for 3000ms and was
 197 replaced with a self-paced avoid/approach judgment scale. Following the 8th trial of each block,
 198 participants underwent 2s of sTBS (30 pulses), for a total of 480 pulses over the entire encoding
 199 phase.

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

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

208

209



210

211 *Figure 1.* (a) Encoding phase. (i) Encoding trial structure and timing. Participants viewed a
 212 fixation cross (1s), followed by a valenced image (3s) and an approach/avoid scale (self-paced).
 213 Stimulation occurred after every 8th image for a total of 128 images and 16 blocks. Participants
 214 underwent stimulation to only one site, which was randomly assigned. (ii) The Fz and C3
 215 electrodes were targeted for mPFC (N = 23) and motor control stimulation (N = 22),
 216 respectively. The Fz electrode was selected based on its proximity to the dorsal mPFC region
 217 (MNI: 4, 52, 46; indicated by *) that is functionally connected with the ventral mPFC region
 218 (MNI: 4, 56, -8; indicated by the green crosshair) that was linked to the selective preservation of
 219 negative objects in memory from Payne and Kensinger (2011). We targeted the dmPFC (Fz)
 220 under the assumption that sTBS would modulate neural activity in an excitatory manner (similar
 221 to iTBS) in both the target site and its associated networks. (b) Recognition task. Same, similar,
 222 and new objects (negative and neutral) and backgrounds (neutral) were presented individually.
 223 Participants responded "same", "similar", or "new". Scene components were presented in
 224 randomized order.

225

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 motor cortex (near the C3 electrode) and locating the site that produced visible movement in the right thumb from single pulses of TMS. Active motor threshold was defined as the lowest 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. Visible muscle twitches were determined by the first author in each session. This was done to obviate variability in what constitutes a visible muscle twitch across sessions and experiments. We determined active motor threshold and sTBS intensity while participants were wearing the EEG cap, so the coil distance from the stimulation site was the same during active motor thresholding and the encoding task sTBS. 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 sTBS 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 et al., 2011). The Fz electrode was selected as the dorsal mPFC stimulation site based on the Neurosynth meta-analysis that showed

the MNI coordinate under the Fz electrode (MNI: 4, 52, 46; Okamoto et al., 2004; Okamoto & Dan, 2005) had strong functional connectivity and coactivation with the ventral mPFC site identified by Payne and Kensinger (2011) that was associated with enhanced negative object recognition following sleep compared to wakefulness (MNI = 4, 56, -8; Figure 1b). 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 to cortical regions modulating the hippocampus, see Wang et al., 2014; Warren et al., 2019). Thus, we reasoned that stimulating the dorsal mPFC would also affect the ventral mPFC activity, which is not directly accessible to TMS. For the control stimulation site, we targeted the MC under the C3 electrode because it is both a common control site (e.g., Daskalakis et al., 2008; Fecchio et al., 2017) and, importantly, we are not aware of any evidence demonstrating a strong connectivity between the MC and the ventral mPFC region during emotional encoding.

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 sTBS approach with identical 2s periods of stimulation that was applied in a similar 2s on/8s off manner that was interleaved (between each encoding block) throughout the encoding phase. Specifically, following each encoding block (8 images), participants were instructed to close their eyes and relax while the TMS coil was positioned to either the mPFC or MC stimulation site location. For the mPFC condition, the coil was positioned at 0° from the midline pointing posteriorly to target the Fz electrode. For the MC condition, the coil was positioned at 45° from the sagittal plane to target the C3 electrode (Figure 1b). Following 2s of sTBS, participants were instructed to continue with the encoding task with a self-paced button press. The average time from the last TMS pulse to the onset of the first and

272 last image in the following encoding block was 8.28 seconds (range: 6.14 - 19.66) and 48.71
 273 seconds (range: 45.62 - 60.01), respectively.

274 A similar approach has previously been shown to facilitate memory and, importantly, to
 275 not have cumulative effects on performance (Demeter et al., 2016). Prior to the start of the
 276 experimental task, participants received one 2s train of sTBS to become familiarized with the
 277 procedure. No participants reported any adverse response to sTBS.

278 *Statistical analysis*

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

287

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

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

288

289 Thus, general hits are calculated based on when participants respond “similar” to
 290 previously viewed items, taking into account when participants respond “same” to previously
 291 viewed items. General false alarms are measured when participants respond “similar” to new

292 items, taking into account when they respond “same” to new items. Specific recognition was
 293 scored with the following formula:

294

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

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

295

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

298 Since our primary aim was to investigate the effects of mPFC sTBS on emotional
 299 memory we computed recognitions scores for negative objects, neutral objects, the neutral
 300 backgrounds that were originally paired with a negative object, and the neutral backgrounds that
 301 were originally paired with a neutral object. Importantly, these calculations were repeated for the
 302 short and long delay tests. This enabled us to systematically compare how mPFC versus MC
 303 sTBS affected memory for negative and neutral objects, backgrounds in negative and neutral
 304 scenes, across the short and long delay tests. Analyses focused on memory performance for
 305 “same”, “similar”, and “new” responses to the same and new scene components (i.e., responses
 306 to similar objects and background scenes were not analyzed), to be consistent with previous
 307 work using this paradigm (Kensinger et al., 2007a, 2007b; Waring et al., 2010).

308 There were statistically comparable ‘same’ (range = .038-.096) and ‘similar’ (range =
 309 .153-.258) false alarm rates between the cells in the experiment (all p ’s > .05), which is
 310 consistent with previous work (Payne et al., 2008). All memory performance analyses were
 311 conducted on corrected recognition scores (hits – false alarms) to obviate issues with response
 312 bias effects. We will refer to these measures as recognition scores from this point forward.

Analyses were conducted in R (version 3.6.3.) with the *afex* (Singmann et al., 2020) and *emmeans* packages (Lenth, 2020). Significant effects in the ANOVAs were followed-up with post-hoc contrasts as implemented in the *emmeans* package. Degrees of freedom for post-hoc contrasts were estimated using the Kenward-Rogers method. Three participants (mPFC: 2, MC: 1) were excluded from the analysis due to no observations in one or more response categories for the general recognition test. Results are considered significant at an alpha level of .05 unless otherwise noted and post hoc degrees of freedom were estimated with the Kenward-Roger method.

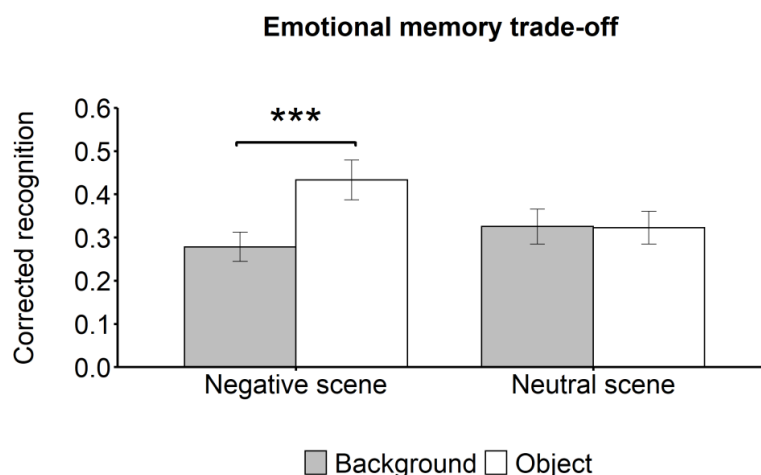
Results

We tested our *a priori* hypothesis that, relative to MC stimulation, mPFC stimulation would facilitate recognition for negative objects at a long delay using a 2 (stimulation site: mPFC, MC) x 2 (valence: negative, neutral) x 2 (scene component: object, background) x 2 (delay: short, long) x 2 (Memory score: general, specific) ANOVA. The analysis included a between-subjects factor (stimulation site) and within-subject factors (valence, scene component, delay, and memory score). The full results are reported in Table 1, and the primary results of interest are reported below.

The emotional memory trade-off effect

In line with prior work (e.g., Payne et al., 2008), we first examined the existence of the emotional trade-off effect and if this effect remained consistent over time. As expected, we replicated the emotional memory trade-off effect as our results revealed a significant valence x scene component interaction, $F(1, 40) = 43.81$ $MSE = .02$, $p < .011$, $\eta_p^2 = .523$ (Figure 2). Follow up *t*-tests revealed that for negative scenes, objects were better remembered than their accompanying backgrounds, $t(73.2) = 7.67$, $p < .001$, $d = .705$. Critically, this pattern was not

336 observed for neutral scenes, as memory performance did not differ between objects and
 337 backgrounds, $t(73.2) = .14$, $p = .890$, $d = .013$. Somewhat surprisingly, the scene component x
 338 valence x delay interaction revealed no evidence that the emotional memory trade-off differed
 339 between a short and long delay, $F(1, 40) = 2.19$, $MSE = .02$, $p = .147$, $\eta_p^2 = .052$.



340
 341 *Figure 2.* Corrected recognition scores (hits – false alarms) revealed an emotional memory trade-
 342 off effect with greater memory for objects compared to backgrounds in negative scenes.
 343 Additionally, no memory differences emerged for neutral scenes. Error bars represent 95%
 344 confidence intervals. *** $p < .001$. Note, this is collapsed across stimulation site, delay, and
 345 memory scores.

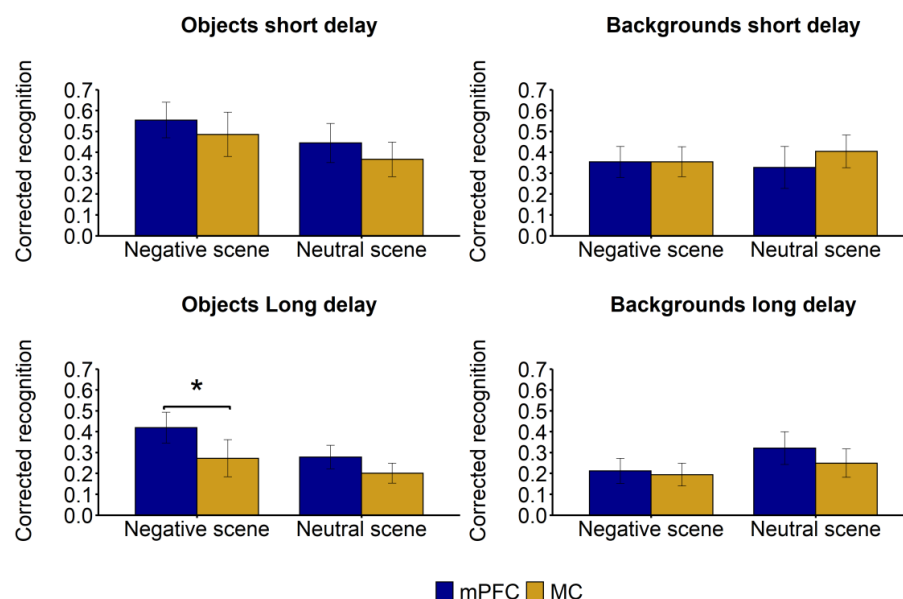
347 *mPFC activity modulates the emotional memory trade-off effect at a long delay*

348 We then examined the causal role of mPFC activity near the time of encoding interacting
 349 with consolidation processes (e.g., modulating the emotional memory trade-off effect). Because
 350 prior work has linked the mPFC in selectively preserving negative information following sleep,
 351 we anticipated that negative objects would be preferentially remembered following a long delay
 352 that included sleep in the mPFC condition relative to the MC condition. In line with our
 353 prediction, our analysis revealed a significant stimulation site x scene component x valence x

354 delay interaction, which suggests that mPFC compared to MC sTBS modulated the emotional
 355 memory trade-off effect, $F(1, 40) = 6.27$, $MSE = .02$, $p = .016$, $\eta_p^2 = .136$ (Figure 3).

356 To parse out the 4 way-interaction, follow up t -tests compared memory differences
 357 between the mPFC vs. MC stimulation conditions at each of the other factors (scene component,
 358 valence, delay). At the short delay, we observed no memory differences between the mPFC and
 359 MC stimulation site conditions for negative objects, $t(110) = 1.30$, $p = .196$, $d = .313$, or their
 360 backgrounds, $t(110) = -.02$, $p = .988$, $d = -.004$. Similarly, no memory differences emerged
 361 between the mPFC and MC stimulation site condition for neutral objects, $t(110) = 1.49$, $p = .139$,
 362 $d = .358$, or backgrounds, $t(110) = -1.46$, $p = .147$, $d = -.351$. Thus, we found no evidence that
 363 mPFC sTBS modulated the emotional memory trade-off effect at a short delay that did not
 364 include sleep (collapsed across memory score).

365 In line with our predictions, at a long delay, mPFC compared to MC stimulation
 366 facilitated memory for negative objects, $t(110) = 2.78$, $p = .006$, $d = .669$, with no differences
 367 emerging for their backgrounds, $t(110) = .33$, $p = .739$, $d = .081$. Importantly, we found no
 368 evidence for memory differences for neutral objects, $t(110) = 1.47$, $p = .145$, $d = .353$, or
 369 backgrounds, $t(110) = 1.36$, $p = .175$, $d = .328$. This pattern of results suggests that sTBS to the
 370 mPFC (compared to the MC) modulated the emotional memory trade-off effect by selectively
 371 preserving memory for negative objects, but not backgrounds, following a long delay that
 372 included a night of sleep (collapsed across specific and general memory scores). This effect was
 373 only found at the long delay, as no differences emerged for objects or backgrounds when
 374 memory was assessed at the short delay. Importantly, for neutral scenes, no differences between
 375 stimulation conditions emerged for objects or backgrounds when memory was assessed at either
 376 a short or long delay.



377

378 *Figure 3.* Corrected recognition scores (collapsed across memory score) revealed that mPFC
 379 compared to MC sTBS facilitated memory for negative objects at a long delay. No memory
 380 differences were found between negative objects at a short delay for mPFC vs. MC control
 381 stimulation. Error bars represent 95% confidence intervals. * $p < .05$.

382
 383 *The role of mPFC activity in memory specificity*

384 Next, we sought to address if mPFC stimulation differentially modulated the emotional
 385 memory trade-off effect at a short or long delay when assessed on specific vs. general memory.
 386 The 5 way interaction found no evidence that mPFC vs. MC stimulation at a short or long delay
 387 differentially modulated the emotional memory trade-off effect when memory was assessed on
 388 specific and general recognition scores, $F(1, 40) = .12$, $MSE = .02$, $p = .727$, $\eta_p^2 = .003$. Lastly,
 389 we examined if mPFC sTBS differentially modulated the emotional memory trade-off effect
 390 collapsed across delay when corrected recognition scores were assessed on specific vs. general
 391 information (gist). Our results revealed a marginally significant 4-way interaction among
 392 stimulation site, valence, scene component, and memory type, $F(1, 40) = 4.04$, $MSE = .02$, $p =$
 393 $.051$, $\eta_p^2 = .092$. Although this did not reach significance, there appeared to be a numeric trend

394 such that mPFC stimulation modulated the emotional memory trade-off effect for specific vs.
395 general recognition (collapsed across short and long delays).

396 *Summary of Results*

397 Collectively, the findings revealed that sTBS to the mPFC selectively facilitated
398 recognition of negative information after a long delay while no differences emerged for their
399 accompanying backgrounds. Critically, no memory differences emerged when memory was
400 assessed following a short delay in negative scenes or at either a short or long delay in neutral
401 scenes. Together, these findings suggest that modulating mPFC activity during encoding
402 selectively facilitated emotional memories.

403

404 General Discussion

405 This study investigated the causal role of the mPFC in the preferential encoding and
406 consolidation of emotionally salient information. Our results provide preliminary evidence that
407 the mPFC is causally involved in the encoding of negatively valenced scenes. Specifically,
408 stimulating the mPFC, but not the MC, during encoding with sTBS enhanced memory for
409 negative objects only after a 24-hour delay (filled with sleep). Moreover, sTBS to the mPFC had
410 no detectable effect on memory for negative stimuli on the short delay (30 minute) test, on
411 neutral information on either test, or on the background scene component in any condition.
412 Notably, false alarm rates did not differ between any of the conditions, which provides evidence
413 that our results are due to effects on recognition, rather than differences in response bias between
414 the mPFC and MC groups. We interpret these findings as being consistent with the idea that
415 mPFC activity near the time of encoding potentiates subsequent consolidation processes, which
416 together facilitate memory for negative information (Payne & Kensinger, 2010, 2011, 2018).

417 The results reported here also partially converge with recent work suggesting a causal
418 role for the mPFC in gist-based false memories (Bovy et al., 2020; for related findings, see
419 Berkers et al., 2017). Bovy and colleagues (2020) examined the relationship between gist-based
420 emotional false memories and mPFC by stimulating the mPFC using an inhibitory TMS
421 protocol, specifically continuous theta-burst stimulation (cTBS). Prior to encoding in an
422 emotionally-valenced Deese-Roediger-McDermott paradigm, participants underwent a negative
423 mood induction and received TMS to the mPFC with either a cTBS or control (i.e., 5Hz rTMS)
424 protocol. They found that cTBS to mPFC during encoding reduced false recognition of negative
425 critical lures on a test after a ~24-hour delay (including a night of sleep). The authors took these
426 findings as evidence that the mPFC plays an important role in extracting schematic (or gist)
427 information during encoding. Our findings extend the results described above. Here, we
428 observed that sTBS – a TMS protocol thought to be associated with increased excitation (“long-
429 term potentiation”, Wischniewski & Schutter, 2015) of the stimulated region – delivered to the
430 mPFC during encoding facilitated memory for negative objects on a 24-hour delayed test.
431 Moreover, we demonstrate that mPFC sTBS benefits emotional episodic memory by using a
432 memory task consisting of complex emotional scenes as opposed to semantically related word
433 lists. Most importantly, in addition to the 24-hour delayed test, we also included a short (30
434 minute) delayed memory test to better establish that mPFC activity during encoding interacted
435 with subsequent consolidation processes. We observed that mPFC sTBS at encoding selectively
436 enhanced negative memory only on the 24-hour delayed memory test. Our findings suggest that
437 mPFC activity near the time of encoding interacts with downstream consolidation processes to
438 support retention of emotional memories.

439 The present results also provide support for theories of the selective consolidation of
440 emotional information (Kim & Payne, 2020; Payne & Kensinger, 2018; Richter-Levin & Akirav,
441 2003). Specifically, stimulation (i.e., neuromodulation) of the dorsal mPFC during encoding may
442 have affected subsequent memory performance by upregulating regions important for emotional
443 memory encoding and retrieval, including the ventral mPFC, amygdala and hippocampus
444 (Bennion et al., 2015; Kensinger & Corkin, 2004; Murty et al., 2010; Payne & Kensinger, 2010).
445 Future work could directly test this possibility by examining the effects of TMS in conjunction
446 with fMRI measures of activity and connectivity.

447 There are some limitations of the present study that warrant mention. First, sTBS was
448 interspersed throughout the encoding task to attempt to modulate brain regions, specifically the
449 MTL, that are functionally connected with the mPFC and critically involved in the encoding of
450 emotional information. Although we aimed to modulate mPFC-MTL activity during the
451 encoding phase it is possible that our stimulation procedure may have also altered neural activity
452 during early consolidation and/or retrieval processes (i.e., during the short delay recognition test)
453 due to potentially long-lasting effects that extend 20-60 minutes following stimulation. Even
454 though we are unaware of any evidence to suggest that the modified sTBS protocol implemented
455 in the present study would have modulated neural activity beyond the encoding phase (e.g.,
456 modulating retrieval related processes), different stimulation protocols may provide further
457 insights into the role of the mPFC activity near the time of encoding in selectively preserving
458 negative information following a sleep filled delay. Furthermore, it is unclear if our results would
459 differ had we used a different TMS protocol. For example, as described above, Bovy and
460 colleagues found a causal role of the mPFC in gist-based false memories implementing cTBS
461 while our sTBS protocol revealed a causal role of the mPFC in emotional memory (collapsed

462 across specific and gist-based memories). Of relevance to this point, a recent meta-analysis of
463 TMS effects on episodic memory found that offline 1 Hz rTMS led to larger enhancing effects
464 on episodic memory compared to other stimulation protocols, including iTBS (Yeh & Rose,
465 2019). In addition, our excitatory assumption was based on the study by Demeters and
466 colleagues (2016) that applied a similar sTBS protocol to the DLPFC and found enhanced word
467 recognition. Coupled with our own enhanced memory for negative objects at a long delay results,
468 we find it likely that sTBS had excitatory effects. Relatedly, if sTBS had inhibitory effects (like
469 cTBS), then mPFC stimulation would have been expected to reduce memory performance (as
470 observed by Bovy and colleagues, 2020), which we did not find. Our assumption that sTBS has
471 similar effects to iTBS protocols despite the differences in the stimulation parameters (e.g.,
472 timing) is a limitation that is present across the literature. For example, the excitatory effects of
473 iTBS are primarily based on stimulating the motor cortex but are often assumed to have similar
474 effects when stimulating other cortical regions. Future work will be needed to probe if sTBS has
475 similar excitatory effects as iTBS protocols.

476 Second, we only examined the effects of mPFC stimulation during memory encoding. It
477 is possible that mPFC stimulation during a different stage of memory, such as during post-
478 encoding periods, would lead to a different pattern of results. To draw stronger causal claims
479 about the role of mPFC in emotional memory, we used an active control stimulation site (left
480 MC) instead of another common control site (i.e., vertex) or sham stimulation. Prior findings
481 have suggested vertex stimulation may modulate activity in the default mode network (Jung et
482 al., 2016), which is involved in emotion (Sheline et al., 2009) and memory processes (Rugg &
483 Vilberg, 2013). Although we cannot rule out the possibility that MC stimulation contributed to
484 the effects on memory by impairing recognition of negative objects, we find this possibility

485 unlikely for two reasons. First, memory performance in the MC stimulation group reported here
486 was comparable to memory performance in a no-stimulation control group in a pilot study (not
487 reported). Second, and most importantly, MC is not associated with emotional memory. Lastly,
488 future work is needed to determine if different stimulation protocols (e.g., frequency, intensity,
489 control stimulation site, stage of memory) will contribute to further insights about the role of
490 encoding-consolidation interactions involving the mPFC and its associated network.

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

500 In conclusion, the results of this study provide preliminary evidence for a causal role of
501 the mPFC in selectively preserving negative memories. The current work moves beyond
502 correlational findings and provides initial causal support for theories suggesting that activity and
503 connectivity in an emotional memory network (e.g., mPFC-MTL) near the time of encoding
504 interact with subsequent consolidation processes (perhaps during sleep) to form long-lasting
505 emotional memories (Kim & Payne, 2020; Payne & Kensinger, 2018).

506

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664
665 Table 1. *ANOVA results*

Effects	MSE	F(1, 40)	η_p^2	p
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Main effects				
Stimulation site	.27	1.42	.034	.241
Valence	.03	6.17	.134	.017*
Scene component	.04	21.77	.352	< .001***
Delay	.03	109.87	.733	< .001***
Memory score	.09	86.98	.685	< .001
Two-way interactions				
Stimulation site x Valence	.03	.62	.015	.434
Stimulation site x Scene component	.04	7.64	.160	.009**
Stimulation site x Delay	.03	5.01	.111	.031
Stimulation site x Memory score	.09	.95	.023	.336
Valence x Scene component	.02	43.81	.523	< .001***
Valence x Delay	.02	2.79	.065	.103
Valence x Memory score	.03	5.97	.130	.019*
Scene component x Delay	.03	4.51	.101	.040*
Scene component x Memory score	.03	.35	.009	.555
Delay x Memory score	.04	34.02	.460	< .001***
Three-way interactions				
Stimulation site x Valence x Scene component	.02	.15	.004	.697
Stimulation site x Valence x Delay	.02	.30	.007	.589
Stimulation site x Valence x Memory score	.03	5.13	.114	.029*
Stimulation site x Scene component x Delay	.03	.79	.019	.381
Stimulation site x Scene component x Memory score	.03	3.43	.079	.071
Stimulation site x Delay x Memory score	.04	.20	.005	.655
Valence x Scene component x Delay	.02	2.19	.052	.147
Valence x Scene component x Memory score	.02	37.40	.483	< .001***
Valence x Delay x Memory score	.03	1.76	.042	.192
Scene component x Delay x Memory score	.03	< .01	< .001	.959
4-way interactions				
Stimulation site x Valence x Scene component x Delay	.02	6.27	.136	.016*
Stimulation site x Valence x Scene component x Memory score	.02	4.04	.092	.051
Stimulation site x Valence x Delay x Memory score	.03	.09	.002	.760
Stimulation site x Scene component x Delay x Memory score	.03	.01	< .001	.917
Valence x Scene component x Delay x Memory score	.02	1.10	.027	.301
5-way interaction				
Stimulation site x Valence x Scene component x Delay x Memory score	.02	.12	.003	.727

666 Note. Degrees of freedom were the same for all effects. * $p < .05$, ** $p < .01$, *** $p < .001$.