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The role of the ventrolateral prefrontal cortex in emotional enhancement of memory: a TMS study

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Abstract

Negative stimuli are often remembered better than neutral stimuli, which is called the emotional enhancement of memory (EEM). We tested whether the role of the ventrolateral prefrontal cortex (VLPFC) in the EEM depended on stimulus valence and/or arousal, and attentional resources. Continuous theta burst stimulation (cTBS) was applied over the left VLPFC, right VLPFC and vertex before encoding ‘negative arousing,’ ‘negative nonarousing,’ and ‘neutral’ words under full and divided attention, followed by a recognition test. The vertex condition showed the EEM effect for ‘negative arousing’ and ‘negative nonarousing’ words. However, the right VLPFC condition showed no evidence of the EEM effect for ‘negative arousing’ or ‘negative nonarousing’ words, under full attention. In contrast, the left VLPFC condition showed the EEM effect for ‘negative arousing’ words, but not ‘negative nonarousing’ words, under full attention. Thus, the left and right VLPFC have different roles in the EEM, depending on valence and arousal.

Keywords

Emotion; Memory; TMS; VLPFC; Valence; Arousal

Introduction

Previous research has shown that negative stimuli can modulate memory, such that negative stimuli are better remembered than neutral ones (for review, Kensinger, 2009). The neural mechanisms supporting this *emotional enhancement of memory* (EEM) effect have been shown to differ based on arousal (Clark-Foos & Marsh, 2008; Kensinger & Corkin, 2004). For negatively valenced, highly arousing stimuli, the EEM was driven by an amygdalar-hippocampal route (Dolcos, LaBar & Cabeza, 2004a; Kensinger & Corkin, 2004), which was thought to occur automatically (for review, Kensinger & Schacter, 2008), whereas for negatively valenced, low arousal stimuli, the EEM was driven by a prefrontal-hippocampal route, specifically, a ventrolateral prefrontal cortex (VLPFC) – hippocampal route (Kensinger & Corkin, 2004), and was thought to be related to controlled processing (for

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review, Kensinger, 2004). These studies suggest that there are two routes to the EEM effect depending on stimulus arousal. The current experiment focused on the VLPFC-mediated route and tested whether the role of the VLPFC in the EEM depends on stimulus arousal and controlled processing. To determine the role of the VLPC in the EEM, the current experiment used continuous theta burst stimulation (cTBS), a patterned form of repetitive transcranial magnetic stimulation (TMS), which is thought to be inhibitory (Huang et al., 2005), to temporarily inhibit the VLPFC during an encoding task under full and divided attention in order to better understand the role of the VLPFC in the negative EEM effect, and whether this differed depending on the valence and arousal of the stimuli, and/or the amount of attentional resources available.

Evidence for the EEM effect is robust, with many studies showing enhanced memory for emotional compared to neutral stimuli (Adelman & Estes, 2013; Dolcos, LaBar & Cabeza, 2004a; Dolcos, LaBar & Cabeza, 2004b). In a typical experiment, participants study negative, positive, or neutral words, and more positive and negative words are later recalled than neutral words (Doerkson & Shimamura, 2001). Based on the multitudes of studies showing this effect (Steinmetz & Kensinger, 2013; Dolcos et al., 2013; for review, Kensinger, 2009), superior memory for emotional items has been dubbed the *emotional enhancement of memory* (EEM) effect (Talmi et al., 2008). Although the EEM effect occurs for both positive and negatively valenced stimuli, the EEM effect is typically more robust for negative stimuli (Maddox et al., 2012; Waring & Kensinger, 2009). Thus, the current experiment used negative stimuli to investigate the EEM effect.

To better understand the psychological mechanisms behind the EEM effect, previous research has investigated different aspects of the negative stimuli being studied, namely valence and arousal (Clark-Foos & Marsh, 2008; Gomes, Brainerd & Stein, 2013). Previous research has shown that there are two different mechanisms supporting the EEM based on valence and arousal; the EEM based on valence is thought to be dependent on controlled processing, whereas the EEM based on arousal is thought to be automatic (Kang et al., 2014; Kensinger & Corkin, 2004; for review, Kensinger, 2004). For example, one experiment examined the EEM effect when words varied based on valence and arousal (Kang et al., 2014). Participants encoded ‘negative arousing,’ ‘negative nonarousing,’ and ‘neutral’ words during full or divided attention blocks. Under full attention, both ‘negative arousing’ and ‘negative nonarousing’ words showed the EEM effect and were better remembered than ‘neutral’ words. In contrast, under divided attention, only ‘negative arousing’ words, and not ‘negative nonarousing’ words showed the EEM effect. Thus, it appears that in order to show the EEM effect, ‘negative nonarousing’ stimuli require additional attentional resources, whereas when the negative stimuli are high in arousal, the EEM effect seems to occur automatically. As such, it is important to consider valence, arousal, and attentional resources when understanding the psychological mechanism underlying the EEM effect.

At the neural level, previous evidence from fMRI studies suggests one model of how emotional stimuli might enhance item memory. The model suggests that arousing stimuli automatically activate a ‘bottom-up’ route, which includes the amygdala. In this way, arousal can lead to enhanced memory through amygdalar connections with the medial temporal lobe (MTL; Dolcos, LaBar & Cabeza, 2004b; Kensinger & Schacter, 2008). On the

other hand, negatively valenced low arousal stimuli activate a ‘top-down’ route, which includes connections between the prefrontal cortex and hippocampus, specifically the VLPFC and DLPFC (Dolcos, LaBar & Cabeza, 2004b; Mickley Steinmetz & Kensinger, 2009). This route can lead to enhanced memory through elaborative encoding (Dillon et al., 2007; Richards & Gross, 2000) and controlled processing (Kang et al., 2014), which correlate with activity in the VLPFC (Rygula et al., 2010). Thus, the current study used TMS to manipulate brain activity in the VLPFC and test the role of the VLPFC in the EEM effect.

Although bilateral VLPFC has been shown to be involved in these top-down EEM effects (for review, Jordan et al., 2013), there is also evidence of hemispheric differences between left and right VLPFC (Dolcos et al., 2013). For example, only the left VLPFC has been shown to correlate with the EEM effect for ‘negative nonarousing’ stimuli (Kensinger & Corkin, 2004). Left VLPFC activity was hypothesized to be involved in the EEM effect for ‘negative nonarousing’ stimuli through its role in elaborative encoding and controlled processing (Fletcher, Shallice & Dolan, 1998; for review, Fletcher & Hanson, 2001, Kensinger, 2004). In contrast, right VLPFC activity has been shown to correlate with the EEM effect broadly (Dolcos et al., 2013; Ritchey et al., 2011), but stimuli were not analyzed for separable effects of valence and arousal. Thus, there might be differences regarding which hemisphere of the VLPFC subserves the EEM effect for negative stimuli depending on valence and/or arousal. Although the previously mentioned fMRI studies reported activity differences in the left VLPFC in one case and right VLPFC in another case, laterality was not directly tested (Dolcos et al., 2013). Thus, one goal of this experiment is to compare the left versus the right VLPFC in the EEM effect.

Because we were specifically interested in the VLPFC, and TMS to more anterior and ventral regions of the PFC can be uncomfortable for participants, we used a continuous theta-burst stimulation (cTBS) protocol. cTBS can be applied for a short period of time (~20 sec) with effects lasting up to a half hour (Huang et al., 2005). Similarly, other experiments testing prefrontal regions have used cTBS to inhibit a prefrontal subregion of interest and showed impaired performance (Blumenfeld, Lee & D’Esposito, 2014; Bor et al., 2017; Lapate et al., 2017). Thus, we used cTBS to inhibit VLPFC activity during encoding. We stimulated participants before the encoding task in order to minimize the physical effects of stimulation (e.g., facial twitching) on the task.

For the current experiment, we applied cTBS over the left VLPFC, right VLPFC or vertex (a control region thought to have no impact on the task) immediately before participants encoded ‘neutral,’ ‘negative nonarousing,’ and ‘negative arousing’ words under full and divided attention. After a 25-minute delay, participants performed a recognition test for the words. We examined whether using cTBS to inhibit the left or right VLPFC during encoding would lead to changes in the EEM effect, and whether this depended on valence, arousal, and available attentional resources. Because VLPFC activity is thought to depend on attentional resources and correlate with controlled processing (Badre & Wagner, 2007; Ritchey et al., 2011; Lindquist et al., 2012), we predicted that inhibiting the VLPFC would reduce EEM effects only during full, but not divided attention. Because right VLPFC correlated with a general EEM effect (Ritchey et al., 2011), we predicted that inhibiting the

right VLPFC would reduce the EEM effect for both ‘negative arousing’ and ‘negative nonarousing’ words. In contrast, because left VLPFC activity previously correlated with the EEM effect only for ‘negative nonarousing’ and not ‘negative arousing’ words, we expected that inhibiting the left VLPFC would reduce the EEM effect for ‘negative nonarousing’ words.

Methods

Participants

18 college students at an urban, public college on the East Coast (15 F; ages 18–35) participated in this experiment for \$15/hr. All participants were screened for any contraindications for TMS, including any history or family history of seizures, metal implants, neurological or psychiatric conditions, medication use, or if they were pregnant. Participants were also excluded if they were left-handed. All participants gave written informed consent in a manner approved by the Human Research Protection Program (HRPP) of the City University of New York.

TMS Procedures

A Magstim Rapid² Plus magnetic stimulator and air-cooled 70mm figure eight coil was used for TMS (Magstim Co., Whitland, Dyfed, UK). To determine motor threshold (MT), the figure eight coil was placed at a 45° angle over the left motor cortex. Participants lightly pinched their index and thumb together to obtain active MT. The coil was moved along the scalp and stimulation intensity increased (starting at 35% and was raised 5%) until a visible hand movement was observed. Motor threshold was determined by the lowest stimulus intensity needed to produce a visible finger movement 4/5 times.

The target sites were: left VLPFC, right VLPFC and the vertex. Neurotargeting was not available, so stimulation sites were approximated using the extended EEG electrode placement system, which has been used to effectively target other brain areas in TMS protocols (Sack et al., 2009). Within the VLPFC, previous fMRI studies have reported peak activations related to the EEM in the pars orbitalis portion of the inferior frontal gyrus, which also roughly corresponds to Brodmann’s Area 47 (Dolcos et al. 2013; Kensinger & Corkin, 2004; Ritchey et al. 2011). The nearest placements using the extended EEG system were AF7 and F7 (Figure 1), and we chose AF7 to approximate our target.

After the stimulation site was approximated and MT was determined, cTBS was administered. TBS involves delivering short bursts of 50 Hz repetitive TMS (rTMS) in the theta range (5 Hz; Rossi et al., 2009). In this protocol, participants were given 20 sec of TBS pulses (300 pulses) at 80% of active MT, which has been shown to produce inhibitory effects for ~20 min (Huang et al., 2005). This method is ideal for prefrontal stimulation, as it only requires a short period of stimulation and therefore minimizes participant discomfort (Blumenfeld, Lee & D’Esposito, 2014; Huang et al., 2005). Each participant completed 3 TBS sessions and received TBS to left VLPFC, right VLPFC, or the vertex in three different sessions, ~1 week apart.

Materials

Participants studied 360 words and were then tested on an additional 180 words from the Affective Norms for English Words (ANEW; Bradley & Lang, 1999). There were three types of words: 1) low valence and low arousal (which we call 'negative nonarousing' words; Kensinger & Corkin, 2004), 2) low valence and high arousal (which we call 'negative arousing' words) and 3) neutral valence and low arousal (which we call 'neutral' words). The words were categorized using the ratings given from the ANEW database. 'Negative nonarousing' words were defined by a valence rating <5 and an arousal rating <5 , the 'negative arousing' words were defined by a valence rating of <5 and an arousal rating of >6 , and the 'neutral' words were defined by a valence rating between 5 & 7 and an arousal rating <5 . A repeated measures ANOVA confirmed that the word types differed by valence, $F(2, 358)=1182.08$, $MSE=0.35$, $p<0.001$, with 'negative nonarousing' words ($M=3.03$, $SEM \pm 0.04$) and 'negative arousing' words ($M=2.93$, $SEM \pm 0.05$) rated as more negative than 'neutral' words ($M=5.62$, $SEM \pm 0.04$; both $t(179)'s > 40$, both $p's < 0.01$). Furthermore, there was no difference in valence ratings between the 'negative nonarousing' and 'negative arousing' words, $t(179)=1.50$, $p<0.20$. Similarly, a repeated measures ANOVA confirmed that the word types differed in arousal, $F(2, 358)=820.31$, $MSE=0.32$, $p<0.01$, with 'negative arousing' words ($M=6.50$, $SEM=0.03$) rated as more arousing than 'negative nonarousing' words ($M=4.43$, $SEM=.04$), $t(179)=44.67$, $p<0.01$, and 'neutral' words ($M=4.34$, $SEM=0.06$), $t(179)=32.80$, $p<0.01$. Moreover, there was no difference in arousal between the 'negative nonarousing' and 'neutral' words, $t(179)=.89$, $p<0.40$.

For the auditory discrimination task used to divide attention, low (150 Hz; Talmi et al., 2007), medium (300 Hz) and high (450 Hz) pitched tones were created using the website (http://www.audiocheck.net/audiofrequencysignalgenerator_sinetone.php).

PsychoPy software (v. 1.84.0; Peirce, 2007; <http://www.psychopy.org/>) was used to present stimuli and record responses. Stimuli were presented on a PC.

Behavioral Paradigm

Immediately after receiving cTBS, participants encoded a list of words either under full or divided attention conditions (Figure 2). Participants were presented with words one at a time onscreen for 3 sec each. In each encoding session, there were 60 words (20 'negative arousing'; 20 'negative nonarousing'; 20 'neutral') that were passively encoded under full attention and 60 words (20 'negative arousing'; 20 'negative nonarousing'; 20 'neutral') that were encoded under divided attention. In the divided attention task, participants studied the word list while completing a standard auditory discrimination task (Talmi et al., 2007), in which participants identified whether a tone was low, medium or high pitched. The keyboard was labeled with 'Low,' 'Medium,' and 'High' buttons. Participants were told to do both tasks (i.e., encoding and tone discrimination) equally at the same time. The encoding trials were blocked, such that participants encoded all the words under full attention and then all the words under divided attention, or vice versa. The order of whether participants heard the list under full or divided attention was counterbalanced. After encoding, participants completed a delay task for ~25 minutes, in which they were given a non-verbal distractor task (i.e., coloring). They were told to relax and to color at their own pace.

Participants then performed a recognition task for the word lists ~25 minutes after encoding. The delay increased the likelihood that the cTBS effects had subsided (Huang et al., 2005) and would not affect the brain or performance during recognition. A 25-minute delay was chosen in order to have each of the encoding and retrieval sessions in one day, decreasing the likelihood of participant attrition for the 3 visits. During the task, participants were presented with a word onscreen for 3 sec and asked to identify if the word was presented during encoding by pressing 1 for 'old' or by pressing 2 for 'new.' Participants then had 2 sec to rate their confidence level on a scale from 1 ('Unsure') to 3 ('Very Sure'; Figure 2). Participants were presented with a total of 180 words (60 'negative arousing'; 60 'negative nonarousing'; 60 'neutral') during retrieval. 120 of the words were old and 60 were new.

Each subject received the same block order for full and divided attention blocks at each visit (i.e., under each stimulation site), with equal numbers receiving the full attention task first and the divided attention task first.

Statistical Analyses

The EEM effect was determined by difference scores in the proportion of 'hits' (i.e., 'old' responses to old items) for 'negative arousing' - 'neutral' (i.e., 'negative arousing EEM') and 'negative nonarousing' - 'neutral' ('negative nonarousing EEM'). Although it is typical to use corrected recognition scores (i.e., hits - false alarms) to characterize memory effects (Schacter, Verfaellie & Pradere, 1996), our attention manipulation was at encoding and therefore false alarms could not be attributed to either the full or divided attention conditions. Although the main interest was in the EEM effect, as measured by difference scores, the means for 'negative arousing', 'negative nonarousing', and 'neutral' words are reported for each attention and stimulation condition in Table 1.

Because this study was within-subjects, we used repeated measures ANOVAs to determine the effect of stimulation, stimulus type, and attention on the EEM effect. For significant effects, we conducted post-hoc follow-up ANOVAs and t-tests. Additionally, in order to verify that there was indeed an EEM effect, we conducted one-sample t-tests to show that performance was significantly different than zero. We also conducted separate analyses of false alarm rates by stimulation and stimulus type because they had the potential to be informative and to ensure that our results were not merely reflecting a bias for 'old' responses. False alarm rate was also analyzed using repeated measures ANOVA with post hoc testing.

Results

We first compared overall performance on the recognition task between the full and divided attention conditions. Contrary to our expectations, there was no difference in the proportion correct (hits + correct rejections) at recognition between full (0.61 ± 0.02) and divided (0.60 ± 0.02) attention. Despite no differences in recognition, participants did engage in the tone discrimination task, with a proportion correct score of 0.93 ± 0.01 , showing that they divided their attention towards this task. However, it appeared that, unlike in pilot testing, this tone-discrimination task was insufficient to diminish encoding of the words such that performance differences were evident.

The Emotional Enhancement of Memory Effect

We next examined whether the EEM effect depended on stimulus type, stimulation, attention condition, and any interactions between them. Results of a 2 ('negative arousing EEM', 'negative nonarousing EEM') x 3 (stimulation site: left VLPFC, right VLPFC, vertex) x 2 (attention: full, divided) ANOVA showed a significant main effect of stimulus type, $F(1, 17)=23.76$, $MSE=0.01$, $p<0.001$, and a main effect of stimulation site, $F(2, 34)=3.37$, $MSE=0.05$, $p<0.05$. These main effects were qualified by a stimulus type x stimulation site x attention interaction, $F(2, 34)=3.78$, $MSE=0.01$, $p<0.04$ (Figure 3).

To follow up on the significant stimulus type x stimulation site x attention interaction, we separated the data by attention condition. For full attention, results of a 2 ('negative arousing EEM', 'negative nonarousing EEM') x 3 (stimulation site: left VLPFC, right VLPFC, vertex) ANOVA showed a main effect of stimulus type, $F(1, 17)=5.57$, $MSE=0.01$, $p<0.04$, such that participants had a greater 'negative arousing EEM' effect ($M=0.09$, $SEM\pm0.03$) than 'negative nonarousing EEM' effect ($M=0.04$, $SEM\pm0.02$). There was also a main effect of stimulation site, $F(2, 34)=3.86$, $MSE=0.03$, $p<0.04$, such that right VLPFC stimulation showed a lower EEM effect ($M=-0.004$, $SEM\pm0.03$) compared to vertex ($M=0.09$, $SEM\pm0.04$, $p<0.04$) and left VLPFC stimulation ($M=0.09$, $SEM\pm0.04$, $p<0.04$). Reduced EEM effects with inhibition of the right VLPFC are consistent with a role of the right VLPFC in encoding both 'negative arousing' and 'negative nonarousing' stimuli. Lastly, there was a marginal stimulus type x stimulation interaction, $F(2, 34)=2.93$, $MSE=0.01$, $p<0.07$.

Although the stimulus type x stimulation interaction was marginal, we conducted exploratory analyses to test whether the EEM differed for 'negative arousing' and 'negative nonarousing' stimuli based on stimulation. When comparing within stimulation sites, paired t-tests showed no difference in the EEM for 'negative arousing' and 'negative nonarousing' stimuli after vertex or right VLPFC inhibition. However, after left VLPFC inhibition, the EEM effect for 'negative nonarousing' stimuli ($M=0.04$, $SEM\pm0.04$) was reduced compared to the EEM effect for 'negative arousing' stimuli ($M=0.15$, $SEM\pm0.04$), $t(17)=3.35$, $p<0.01$, suggesting that the left VLPFC may play a specific role in the EEM effect for 'negative nonarousing' stimuli.

Turning to the divided attention condition, a 2 ('negative arousing EEM', 'negative nonarousing EEM') x 3 (stimulation site: left VLPFC, right VLPFC, vertex) ANOVA for the EEM effect showed a only main effect of stimulus type, such that participants had a greater EEM for 'negative arousing' stimuli ($M=0.14$, $SEM\pm0.04$) than 'negative nonarousing' stimuli ($M=0.08$, $SEM\pm0.03$), $F(1, 17)=9.01$, $MSE=0.02$, $p<0.009$.

Because there were reductions in the EEM effect under certain stimulation and stimulus parameters, we further examined whether the EEM effect existed under full and divided attention in the different conditions by testing whether the EEM effect differed from zero in each condition using a one-sample t-test. Under vertex stimulation and full attention, there was a significant EEM effect for both 'negative arousing' stimuli, $t(17)=2.35$, $p<0.04$, and 'negative nonarousing' stimuli, $t(17)=p<2.16$, $p<0.05$. Under vertex stimulation and divided attention, there was a significant EEM effect for 'negative arousing' words, $t(17)=4.84$, $p<0.01$, and a marginal EEM effect for 'negative nonarousing' words, $t(17)=p<1.96$, $p<0.07$. In contrast, and consistent with the other reported analyses, under right VLPFC stimulation

and full attention the EEM effect did not differ from zero, whereas under divided attention, there was a significant EEM effect for ‘negative arousing’ words, $t(17)=2.43$, $p<0.03$, but no EEM effect for ‘negative nonarousing’ ($p<0.60$). Lastly, under full attention and left VLPFC stimulation, there was a significant EEM effect for ‘negative arousing’ words, $t(17)=3.80$, $p<0.01$, but no EEM effect for ‘negative nonarousing’ words ($p<0.40$). In contrast, under divided attention, there was a significant EEM for ‘negative arousing’ words, $t(17)=2.91$, $p<0.02$ and ‘negative nonarousing’ words, $t(17)=2.53$, $p<0.03$. Thus, we verified that there was an EEM effect in some conditions, depending on attention and stimulation site.

Because we used difference scores to define the EEM, one potential concern is that the effect could be driven by differences between the stimulation conditions in the hit rate for neutral words. Therefore, we compared hit rate for neutral items in a 3 (stimulation site: left VLPFC, right VLPFC, vertex) $\times$ 2 (attention: full, divided) ANOVA, which showed no effect of stimulation site, $F(2, 34)=1.75$, $MSE=0.04$, $p>0.18$, no effect of attention, $F(1, 17)=0.48$, $MSE=0.04$, $p>0.49$, nor a stimulation $\times$ attention interaction, $F(2, 34)=0.29$, $MSE=0.05$, $p>0.74$. The raw hit rates for each condition are reported in Table 1.

False Alarms

One possible concern is that the EEM effects, which were based on the proportion of hits, were driven by biased responding to call negative words ‘old,’ and that this differed by stimulation site. Evidence for biased responding would be an increased false alarm rate for ‘negative arousing’ and ‘negative nonarousing’ words. We chose not to include FAs in our characterization of the EEM effect because ‘new’ items at retrieval cannot be specifically attributed to either the full or divided attention condition at encoding, which means that if we used corrected recognition scores that incorporate false alarms, we would be subtracting the same number from each of those conditions. Nevertheless, false alarms may be potentially informative and we tested whether the false alarm rate differed by stimulation site and by stimulus type. A 3 (stimulus type: ‘neutral,’ ‘negative nonarousing,’ ‘negative arousing’) $\times$ 3 (stimulation site: left VLPFC, right VLPFC, vertex) ANOVA showed a main effect of stimulus type, $F(2, 34)=13.83$, $MSE=0.02$, $p<0.001$, with fewer FAs for ‘neutral’ ($M=0.26$, $SEM\pm 0.03$) than ‘negative arousing’ ($M=0.40$, $SEM\pm 0.03$), $t(17)=6.28$, $p<0.01$, and ‘negative nonarousing’ ($M=0.37$, $SEM\pm 0.03$), $t(17)=3.83$, $p<0.01$. Although there was a bias to call either type of negative stimulus ‘old,’ there was no effect of cTBS on false alarms, nor was there a stimulation $\times$ stimulus type interaction, $F(2, 34)=13.83$, $MSE=0.02$, suggesting that the effects of cTBS on the EEM effect were not solely driven by biased responding.

General Discussion

In this experiment, we tested the roles of the left VLPFC and right VLPFC in the negative EEM effect, and whether these roles depended on valence, arousal, and/or the amount of attentional resources available (Kensinger & Corkin, 2004; Kang et al., 2014). Consistent with previous neuroimaging work (Ritchey et al., 2011), cTBS over the right VLPFC, which is thought to be inhibitory, reduced the EEM effect for both ‘negative arousing’ and ‘negative nonarousing’ stimuli under full attention. In contrast, and consistent with other

fMRI studies (Kensinger & Corkin, 2004), again under full attention, cTBS over the left VLPFC reduced the EEM effect for ‘negative nonarousing’ words, yet the EEM effect for ‘negative arousing’ words was intact. These findings suggest that if there are enough attentional resources, the VLPFC plays a role in the EEM effect (for review, Iordan et al., 2013), with different roles for the left and right VLPFC depending on stimulus arousal.

Right VLPFC and Emotional Memory Under Full Attention

We used cTBS to understand if the right VLPFC contributes to the EEM effect overall, and whether this differs based on stimulus arousal. Our control site, the vertex, showed evidence for the EEM effect for ‘negative arousing’ and ‘negative nonarousing’ items under full attention. In contrast, after cTBS over the right VLPFC during full attention there was no evidence of the EEM effect. This finding is consistent with previous neuroimaging findings suggesting a role of the right VLPFC in processing negatively valenced stimuli at all levels of arousal (Dolcos, LaBar & Cabeza, 2004a; Garcia-Pacios et al., 2017), potentially leading to the EEM for all negative stimuli (Dolcos et al., 2013; Ritchey et al., 2011). Our finding that cTBS over the right VLPFC eliminated evidence of the EEM effect for both ‘negative arousing’ and ‘negative nonarousing’ stimuli is consistent with an enhanced role for the right VLPFC in successful encoding of negatively valenced stimuli (Ritchey et al., 2011), at least under full attention.

Left VLPFC and Emotional Memory Under Full Attention

Unlike the right VLPFC condition, which showed no evidence of the EEM effect for either ‘negative arousing’ or ‘negative nonarousing’ stimuli under full attention, the left VLPFC condition showed evidence for the EEM effect for ‘negative arousing’ but not ‘negative nonarousing’ stimuli, under full attention. One interpretation is that cTBS over the left VLPFC eliminated the EEM effect for ‘negative nonarousing’ but not ‘negative arousing’ words, demonstrating a specific role of the left VLPFC in the EEM for ‘negative nonarousing’ words, potentially because ‘negative arousing’ words might rely more on automatic processing (Kang et al., 2014; Kensinger & Corkin, 2004). Previous work has shown that activity in the left VLPFC has correlated with measures of cognitive control, including elaborative encoding (for review, Blumenfeld & Ranganath, 2007). Indeed, one meta-analysis found consistent activity of the left VLPFC during instances in which participants were actively attending to emotional stimuli, which is a controlled process (Lindquist et al., 2012). Thus, one interpretation of our findings is that inhibiting the left VLPFC led to a decrease in elaboration of low arousal words resulting in a decrease of the EEM effect for ‘negative nonarousing’ words. Indeed, elaborative encoding has been proposed as a potential mechanism that underlies the EEM effect (Steinmetz & Kensinger, 2013). Furthermore, the EEM effect for ‘negative nonarousing’ words has also been shown to rely more heavily on cognitive control (Kang et al., 2014). Thus, our results suggest a role of the left VLPFC in EEM effect through controlled processing rather than arousing stimuli/automatic processing.

Divided Attention

One of the main goals was to compare the roles of the left and right VLPFC under full and divided attention, but our ability to make inferences based on the available attentional

resources is limited because there was no evidence that our divided attention task depleted attentional resources. Other experiments using a tone-discrimination task have found lower performance for stimuli encoded under divided attention (Talmi et al., 2007), and our pilot experimental sample showed lower performance, it is thus surprising that we did not find this difference. However, other experiments have suggested that a harder concurrent tone-discrimination task is necessary to see performance differences (Kang et al., 2014). Our secondary task was therefore not strong enough to substantially deplete attentional resources and result in worse performance in the divided attention condition in this sample. Thus, our main inferences focus on the full attention condition.

However, given that our interpretation of the role of the VLPFC in the EEM effect focuses on cognitive control and elaborative encoding, and dividing attention would presumably diminish cognitive control and elaborative encoding, it is worth considering how the EEM remains robust under divided attention for all stimulation conditions. One possibility is that when full cognitive resources are less available, such as under divided attention, the main neural pathway supporting the EEM is the more automatic route, the amygdalar-hippocampal route (Dolcos, LaBar & Cabeza, 2004a; Kensinger & Corkin, 2004; for review, Kensinger & Schacter, 2008). Thus, the role of the left VLPFC in the EEM effect for ‘negative nonarousing’ words is one route to the EEM and is used only when there are adequate attentional resources available. Future work should test these possibilities more directly.

cTBS Limitations

One limitation of this experiment relates to TMS coil positioning because we used the extended EEG system and not precise neurotargeting. Although our goal was to target areas of the VLPFC previously implicated in the EEM (Dolcos et al. 2013; Kensinger & Corkin, 2004; Ritchey et al. 2011), we must acknowledge that our AF7 target was near the area of interest, but cannot be considered a precise target (Figure 1). It would be beneficial for future work to more precisely target specific coordinates and use neurotargeting based on individual anatomy. Given that AF7 was merely near the pars orbitalis portion of the inferior prefrontal gyrus, we must also consider other nearby prefrontal regions that may have been influenced by cTBS. It is possible that other parts of the inferior frontal gyrus, middle frontal gyrus, and more rostral prefrontal regions were affected by cTBS. Thus, our results may best be interpreted as regions influenced by cTBS over AF7. However, even if there are limitations to our ability to specifically target the VLPFC, our results show clear hemispheric differences in the EEM based on arousal in response to cTBS at AF7, and these laterality differences are important, even if we can only approximate this to the VLPFC.

Another potential caveat relates to the premise that cTBS is inhibitory. Continuous TBS has shown inhibitory responses in motor cortex (Huang et al., 2005), and we assume this extends to VLPFC, but we cannot be certain that all participants showed inhibition in the VLPFC (Wassermann, 2002). Indeed, a recent study showed variability in cTBS effects, with some participants showing facilitation after cTBS (Jannati et al., 2017). Nevertheless, we used a protocol for stimulation that has been used before and has shown to lead to behavioral (Blumenfeld, Lee & D’Esposito, 2014) and neural effects (Tupak et al., 2013), specifically

inhibition (Huang et al., 2005). Still, a future study compare VLPFC activity pre- and post-cTBS using fMRI to ensure that the VLPFC was in fact inhibited.

Conclusions

This study sought to determine whether the VLPFC was involved in the EEM effect based on stimulus valence and/or arousal and available attentional resources. Under full attention, inhibiting the left or right VLPFC via cTBS led to a decrease in the EEM effect; specifically, cTBS over the left VLPFC led to a decrease in memory for ‘negative nonarousing’ words, whereas cTBS over the right VLPFC led to a decrease in memory for both ‘negative arousing’ and ‘negative nonarousing’ words, or all words negatively valenced. These results suggest that the left VLPFC is involved in the EEM effect for ‘negative nonarousing’ stimuli specifically, whereas the right VLPFC is involved in the EEM effect for *all* negative stimuli.

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Figure 1:

Depiction of the inferior frontal gyrus pars orbitalis (green), which previous fMRI studies have implicated in the emotional enhancement of memory effect, on a 3D brain surface. The yellow disks represent the locations of scalp electrodes placed using the extended EEG system. Placement AF7, which was used to approximately target the region of interest, is shown in red.

Figure 2: Sample trials of the encoding and retrieval tasks. Participants first encoded words (top) under both full (left) and divided attention (right). Participants then performed a recognition task for the words (bottom).

Figure 3:

The emotional enhancement of memory (EEM) effect under full (A) or divided (B) attention. Under full attention, vertex stimulation showed the typical EEM effect of enhanced memory for ‘negative arousing’ and ‘negative nonarousing’ stimuli, whereas right VLPFC stimulation led to a decrease in both EEM effects and left VLPFC stimulation led to a decrease in the EEM effect for ‘negative nonarousing’ words only. Under divided attention, there was a larger EEM for ‘negative arousing’ compared to ‘negative nonarousing’ words ($p < 0.01$). Error bars were computed on a within-subjects basis in accordance with Loftus and Masson (1994).

Table 1:

Mean (SD) proportion of hits for each condition.

	Full Attention			Divided Attention		
	Left VLPFC	Right VLPFC	Vertex	Left VLPFC	Right VLPFC	Vertex
Negative Arousing	0.68 (0.19)	0.61 (0.21)	0.67 (0.20)	0.66 (0.22)	0.66 (0.14)	0.69 (0.17)
Negative Nonarousing	0.57 (0.18)	0.60 (0.21)	0.64 (0.18)	0.63 (0.18)	0.58 (0.18)	0.60 (0.23)
Neutral	0.53 (0.21)	0.61 (0.22)	0.56 (0.22)	0.52 (0.24)	0.56 (0.22)	0.51 (0.21)