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Dynamic changes in prefrontal cortex involvement during verbal episodic memory formation

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Highlights

- We investigated encoding-related post-stimulus brain activity in the prefrontal cortex with repetitive Transcranial Magnetic Stimulation (r-TMS)
- We delivered r-TMS during encoding while a word appeared on the screen, and at different points in time after its offset
- r-TMS over the ventrolateral prefrontal cortex shortly after stimulus offset decreased subsequent memory accuracy
- No effects were found when r-TMS was delivered over the dorsolateral prefrontal cortex at any time point
- The involvement of the ventrolateral prefrontal cortex may reflect offset-specific processes.

ABSTRACT

During encoding, the neural activity immediately before or during an event can predict whether that event will be later remembered. The contribution of brain activity immediately after an event to memory formation is however less known. Here, we used repetitive Transcranial Magnetic Stimulation (rTMS) to investigate the temporal dynamics of episodic memory encoding with a focus on post-stimulus time intervals. At encoding, rTMS was applied during the online processing of the word, at its offset, or 100, 200, 300 or 400 ms thereafter. rTMS was delivered to the left ventrolateral (VLPFC) or dorsolateral prefrontal cortex (DLPFC). VLPFC rTMS during the first few hundreds of milliseconds after word offset disrupted subsequent recognition accuracy. We did not observe effects of DLPFC rTMS at any time point. These results suggest that verbal encoding-related VLPFC engagement starts at a relatively late processing stage, and may reflect brain processes related to the offset of the stimulus.

Keywords: episodic memory, rTMS, prefrontal cortex, memory formation

1. INTRODUCTION

Laying down new memories involves a set of complex neural processes. The classical approach to the study of the neural basis of memory formation is to measure brain activity for an event during a learning or study phase, and to analyse this activity as a function of whether the event will be remembered or forgotten in a subsequent memory phase (subsequent memory procedure, Sanquist 1980). Several event-related functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) studies used this approach to reveal the network of brain regions implicated in successful memory formation (for early reviews, Friedman & Johnson, 2000; Paller & Wagner, 2002). More recently, non-invasive brain stimulation techniques (transcranial magnetic stimulation, TMS; transcranial direct current stimulation, tDCS) added to this literature by showing that the stimulation of selected regions of the prefrontal cortex during memory encoding affected later retrieval (Rossi et al., 2001, 2004, 2006, 2011; Köhler, Paus, Buckner & Milner, 2004; Machizawa, Kalla, Walsh & Otten, 2010; Javadi & Walsh, 2012; Blumenfeld, Lee & D'Esposito, 2014).

Most EEG, fMRI and TMS studies that used a subsequent memory approach focused on brain activity that unfold at an early stage of processing, that is, within the first few hundreds of milliseconds after the onset of a stimulus, and hence primarily during its online processing. In the last few years however, a number of studies have shown that the temporal dynamics of memory encoding are far more multifaceted. These investigations have revealed that the critical time for memory encoding is not restricted to the initial and online processing stages, and that peri-encoding brain activity, that is, brain activity immediately before or after an encoding event, can be equally predictive of successful episodic memory formation (Cohen et al., 2015). One line of research has demonstrated that brain activity engaged immediately before an event influences the effectiveness with which

that event is encoded into long-term memory (Adcock, Thangavel, Whitfield-Gabrieli, Knutson & Gabriel, 2006; Otten, Quayle, Akram, Ditewig & Rugg, 2006; Park & Rugg, 2010; Galli, Wolpe & Otten, 2011). This encoding-related anticipatory brain activity reflects preparatory mechanisms whose functional significance and specific brain correlates vary depending on the encoding task and the motivational characteristics of the stimulus.

The contribution to memory formation of brain activity after the termination of a stimulus (hereafter referred to as "post-stimulus" activity") is instead less known. Researchers have generally assumed that brain activity that follows the termination of a stimulus is a mere continuation of earlier processing stages, or they have rather focused on more general consolidation processes lasting minutes or hours after an encoding episode. The specific contribution of post-stimulus brain activity to the formation of new memories has therefore largely been ignored. Yet, the link between post-stimulus processing and memory encoding is well represented in the psychological literature and is expressed in the concepts of retroactive interference (Dale, 1964; Dudai, 2004) and iconic memory (Sperling, 1960).

There are only a handful of fMRI studies that selectively focused on post-stimulus brain activity (Ben-Yakov & Dudai, 2011; Ben-Yakov, Eshel & Dudai, 2013; Elman, Rosner, Cohn-Sheehy, Cerreta & Shimamura, 2013). These studies have not only shown that this activity is crucial for memory formation, but also that brain activations after the offset of a stimulus are dissociable from those related to earlier, on-line processing. For instance, by time-locking fMRI responses to stimulus offset, Ben-Yakov and Dudai (2011) demonstrated that post-stimulus activity in the hippocampus and the left caudate nucleus predicted later retrieval, while encoding-related brain activations during stimulus presentation were found in the bilateral inferior frontal gyrus, the fusiform gyrus, and the temporo-parietal junction. By manipulating the duration of the stimuli it was further demonstrated that post-stimulus activations were specifically triggered by the offset of the stimulus, and not contingent upon an offset-invariant processing time (Ben-Yakov & Dudai, 2011). Elman et al. (2013)

additionally showed dissociations between online and post-stimulus processing in posterior parietal cortex activations.

These studies emphasized the relevance of post-stimulus brain activations for memory encoding, but given the correlational nature of fMRI data they did not clarify whether these activations were necessary for forming new memories. TMS may be better suited to investigate the temporal dynamics of memory formation for two reasons. First, it allows causal inferences on the involvement of targeted brain regions in successful memory encoding by temporarily interfering with neural activity in those regions. Second, the experimenter can manipulate with millisecond-precision the timing of the stimulation/interference, therefore also allowing causal inferences on the necessity of a given time interval for encoding (Pascual-Leone, Walsh & Rothwell, 2000; Rossi et al., 2011). Two TMS studies investigated the temporal dynamics of memory formation including a post-stimulus time interval. Machizawa et al. (2010) delivered double-pulse TMS to the ventrolateral prefrontal cortex (VLPFC) 350, 750 and 1150 ms after the onset of a one-second word, and found that the three stimulation times equally decreased subsequent memory performance compared to a control condition. Rossi et al. (2011) instead used a repetitive TMS (rTMS) approach and longer stimulation intervals. They stimulated the left dorsolateral prefrontal cortex (DLPFC) while subjects encoded visual scenes that were presented for one second. rTMS trains of 900 ms were delivered starting 100, 200, 300, 400 or 500 ms after the onset of the scene, therefore covering 0, 100, 200, 300 or 400 ms of the post-scene interval. The results showed a drop in memory accuracy when the stimulation covered the longest post-scene interval. While in this study the use of long trains of rTMS prevented a clear distinction between event and post-event processing, the results clearly indicated that the critical time window for memory formation started at a late stage of online processing and encompassed a large portion of offline, post-perceptual stimulus processing. Taken together, the studies by Machizawa et al. (2010) and Rossi et al. (2011) have provided evidence that post-stimulus brain activity plays a role in memory formation.

However, this evidence emerged in the context of general investigations of the temporal dynamics of memory formation. To the best of our knowledge, no previous studies have examined the specific temporal and spatial characteristics of post-stimulus brain activity.

In the current investigation, we sought to characterize the relationship between post-stimulus brain activity and verbal memory formation by systematically manipulating the onset of rTMS stimulation with respect to the post-stimulus interval. rTMS was delivered over two brain regions, the left DLPFC (Brodmann area 9, 46, and 9/46; Petrides, 2005) and the left VLPFC (Brodmann area 44, 45, 47; Petrides, 2005). Both regions have been implicated in successful episodic encoding. A discrepancy exists however between fMRI and TMS studies. fMRI studies have consistently shown an engagement of the left VLPFC, especially when the encoding task involves semantic processing (Fletcher, Shallice & Dolan, 1998; Blumenfeld & Ranganath, 2007; Galli, 2014), whereas only few studies reported DLPFC activations (Savage et al., 2001; Blumenfeld & Ranganath, 2006). On the contrary, most TMS and tDCS studies of episodic memory found an effect of left DLPFC stimulation on subsequent retrieval (Rossi et al., 2001, 2004, 2006, 2011; Epstein, Sekino, Yamaguchi, Kamiya & Ueno, 2002; Sandrini, Cappa, Rossi, Rossini & Miniussi, 2003; Skrdlantová et al., 2005; Turriziani et al., 2008; Turriziani, Smirni, Oliveri, Semenza & Cipolotti, 2010; Elmer, Burkard, Renz, Meyer & Jancke, 2009; Gagnon, Schneider, Grondin & Blanchet, 2010; Innocenti et al., 2010; Javadi & Walsh 2012; Javadi, Cheng & Walsh, 2012; Javadi & Cheng, 2013; Manenti, Brambilla, Petesi, Ferrari & Cotelli, 2013) whereas only a few targeted the left VLPFC (Floel et al., 2004; Köhler et al., 2004; Kahn et al., 2005; Machizawa et al., 2010; Blumenfeld et al., 2014; Vidal-Pinero et al., 2014). A further complication in integrating fMRI and non-invasive brain stimulation findings is that most TMS and tDCS studies targeted the DLPFC by delivering the stimulation over F3 of the International 10-20 EEG system, which is more dorsal than the maximum DLPFC peak of activation reported in fMRI studies (Blumenfeld et al., 2014). The diversity of findings and procedures invites further work

involving a direct contrast between these two brain regions to better disentangle their relative contribution to successful episodic memory encoding. Blumenfeld et al. (2014) previously compared the effects of left DLPFC and VLPFC TMS during encoding on subsequent retrieval and found a decrease in memory accuracy when the stimulation targeted the VLPFC. Their study however used offline theta burst stimulation and hence prevented an examination of the differential effects of the two brain regions as a function of the time of the stimulation.

Here, participants received rTMS over the left dorsolateral or ventrolateral prefrontal cortex while they performed an encoding task involving deep and shallow judgements on words (Craik & Lockhart, 1972). Words were presented for one second and we delivered trains of 500 ms 20 Hz rTMS at the offset of the word, and 100, 200, 300 and 400 ms thereafter. We also included a stimulation starting 500 ms after the onset of the word, therefore covering the second half of the word online processing. These stimulation conditions were compared to a vertex stimulation and a no-TMS condition.

2. MATERIALS AND METHODS

2.1 Subjects

Twenty-four subjects took part in the experiment. Subjects were assigned to one of two groups. One group (N=12, 6 males, mean age 24 years, range 20-27 years) received rTMS over the dorsolateral PFC, the other (N=12, 6 males, mean age 24 years, range 21-31 years) received rTMS over the ventrolateral PFC. All subjects were right-handed, Italian native speakers and without a history of neurological or psychiatric diseases. The two groups did not differ in age (independent samples t-test, p=0.630). The study was approved by the local ethical committee.

2.2 Materials

Stimuli were 368 Italian words, ranging in length between four and ten letters, which have previously been used in similar experiments in our lab (Innocenti et al., 2010; Cioncoloni et al., 2014). Four stimulus lists of 88 words each were constructed from this pool. The first list contained words that referred to animate entities, the second list words that referred to inanimate entities, the third and fourth lists contained words with or without the letter “e”, respectively, and included an equal number of animate and inanimate words. From each list, eight groups of 11 words were randomly selected and assigned to eight experimental blocks of 44 words each (see rTMS protocol below). In each block, 28 words were randomly designated as old items for the study phase, and 16 as new items for the test phase. An additional 16 words were selected from the pool to create practice lists for the study and test tasks.

2.3 Procedure

The experiment consisted of an incidental memory task followed by a recognition memory test after a delay of approximately 5 minutes. At study, participants viewed a total of 224 words, presented one at the time. The words were presented in eight consecutive blocks of 28 words each, corresponding to eight stimulation conditions (see rTMS protocol below). Each word was preceded by a cue, which consisted of the presentation of the letter *O* or the letter *X*. When an *O* appeared, subjects were instructed to report whether the following word referred to a living or a non-living entity (animacy judgement). When an *X* preceded a word, subjects had to decide whether the word contained the letter “e” or not (alphabetical judgement). Animacy and alphabetical judgements were equi-probable and randomly intermixed within each stimulation block. In both tasks, subjects responded by pressing one of two buttons with their right or left index finger. The hand with which each judgement was made was counterbalanced across participants to prevent rule effects. Each trial started with the presentation of the cue, which had duration of 2600 ms, and was followed by a 100 ms blank screen and by the presentation of the word, which remained on the screen for one

second. The time in between the offset of each word and the onset of the next cue was 2300 ms plus a random delay between 0 and 1500 ms.

In the test phase, the 28 words from each study block were interspersed with 16 new words and presented again for the recognition memory task, resulting in eight test blocks of 44 items each. The presentation of blocks followed the same order of the study phase (e.g., words that were presented in the first block in the study phase, were presented in the first block of the test phase). A plus sign presented before each word replaced the cue and served as warning stimulus. For each word, participants had to decide whether or not they had seen the word during the study phase by pressing one of two keys with their right or left index fingers. The assignment of old responses to the left or right hand was counterbalanced across subjects. Each trial started with the presentation of the warning stimulus, which had duration of 2600 ms, and was followed by a 100 ms blank screen and by the presentation of the word, which remained on the screen for one second. The time in between the offset of each word and the onset of the next cue was 4000ms plus a random delay between 0 and 1500 ms. The time in between the presentation of a word in the study phase and its repetition in the test phase was approximately 30 minutes. At both study and test, cues and words were presented in white uppercase Helvetica on a gray background. At a viewing distance of approximately 55 cm, words subtended a visual angle of 1.6° vertically, and 4.3° to 11.6° horizontally. Cues measured 1.6° x 1.4° of visual angle.

2.4 TMS protocol

Repetitive TMS was delivered through a MagStim Super Rapid stimulator with a biphasic current waveform (Magstim, UK). A figure-of-eight, 70-mm coil was used for the stimulation. The coil was placed tangentially to the scalp, with the handle pointing backwards and laterally at a 45° angle of the middle sagittal axis of the participants' head. Prior to rTMS, single magnetic pulses were delivered by the same coil and stimulator to the hand area of the left motor cortex to establish the individual excitability threshold for the first dorsal

interosseous muscle (Rossini et al. 2015). For each subject, the intensity of the stimulation during the experiment was set to 90% of the individual motor threshold.

20 Hz rTMS was delivered for 500 ms during the study phase. As shown in Figure 1, there were six PFC stimulation conditions, corresponding to six timings of rTMS administration. In the first condition, the stimulation was delivered 500 ms after the onset of the word. In the second condition, rTMS was delivered at the offset of the word. In the third, fourth, fifth and sixth stimulation conditions rTMS was administered 100, 200, 300 and 400 ms after the offset of the word, respectively. These timings were chosen to ensure that the stimulation covered the last 500 ms of word presentation, and five different intervals of post-stimulus processing with a 100-ms shift in time. Both groups additionally received a vertex stimulation, and performed one block of task without TMS, which made eight experimental conditions in total. The order of these conditions was randomized across subjects. No rTMS was delivered during the test phase.

In both groups, the coil was positioned according to the standard cranial landmarks of the International 10-20 EEG system, a common approach used in our and other laboratories (Rossi et al., 2001, 2004, 2006, 2011; Sparing, Buelte, Meister, Paus & Fink, 2008; Beam, Borckardt, Reeves & George, 2009). In the DLPFC group, the stimulation was delivered by placing the wings junction of the coil on the scalp region corresponding to F3 of the international EEG 10-20 system. In the VLPFC group, the stimulation targeted a point on the scalp corresponding to F7. The vertex stimulation site was defined as a point midway between the inion and the nasion and equidistant from the left and right intertragal notches. Since this region is not involved in learning and memory processes, it was considered a control site for possible unspecific somatosensory, acoustic, or arousal effects of active TMS (Rossi et al., 2011). It has been previously reported that the stimulation of the lateral aspects of the prefrontal cortex may be uncomfortable for some participants (Machizawa et al., 2010). Before the start of the experiment, we delivered trains of rTMS to the targeted locations and encouraged participants to report any excessive distress in order to ensure

that all participants were comfortable with the TMS stimulation. Four participants reported excessive discomfort and did not continue with the experiment. The twenty-four participants who completed the experiment and compose the final sample reported only minor discomfort at the end of the encoding phase.

2.5 Statistical analysis

The statistical analyses were conducted on the within-subject factors Encoding Task (deep, shallow) and Onset of Stimulation (6 different onsets of rTMS plus the control conditions), and the between-subjects factor Group (DLPFC and VLPFC), for both accuracy and hits response times. Preliminary analyses were performed contrasting the two control conditions (vertex, no-TMS), separately for each group and collapsed across Encoding Task. In the absence of significant differences between vertex and no-TMS, subsequent analyses were performed on data collapsed across the two conditions, separately in each group.

The effects of rTMS on encoding and retrieval were analysed using mixed linear modelling. This approach has been used in previous rTMS studies (e.g., Berman et al., 2000; Fregni et al., 2006; Lesage, Morgan, Olson, Meyer & Miall, 2012). In addition, as one participant in the VLPFC group did not complete one block at retrieval, we opted for an approach that offers more statistical power in the presence of missing data. Mixed linear modelling provides less biased estimates of variance and covariance which can be explicitly modelled and dealt with efficiently with missing data (e.g., West, Welch & Galecki, 2014). We implemented a top-down model-building strategy for repeated-measures models (West et al., 2014). First, we started with a model with a well-specified mean structure by including all the fixed effects and their interactions into a random intercept model to account for the systematic variation before exploring covariance structures. We then modelled a maximal random structure allowed by our design (i.e., including random slopes for all within subject factors using unstructured) following the recommendations of Barr, Levy, Scheepers and Tily (2013) as well as West et al (2014). However, the models featuring random slopes did not

converge (G matrix featured negative or close to zero values). This might indicate, among other issues, a lack of variance in the data to be explained by adding random slopes. Therefore, the random slopes causing failure were removed from the model as recommended in West et al (2014). Third, we modelled the appropriate covariance structure for the residuals and test it using a likelihood ratio test. Finally, we reduced the model by removing non-significant interaction effects parameters based on the F tests. The descriptive and inferential analyses were conducted using SPSS (mixed modelling with mixed function and REML estimates).

3. RESULTS

3.1 Encoding task

Encoding accuracy did not vary substantially as a function of the time of stimulation, encoding strategy and stimulated area (Table 1). Statistical analyses were performed on the percentage of correct encoding judgements. The percentage of correct encoding judgements did not differ between the vertex and the no-TMS conditions in both groups (two-tailed t-test, DLPFC: p = .210; VLPFC: p = .772), therefore further analyses were conducted on data collapsed across the two control conditions, separately in each group. In the initial random intercept model – including all factors and their interactions – the main effect of Onset of Stimulation was marginally significant ($F_{6,\ 334.000}$ = 2.19, p = 0.044). No other main effect or interaction emerged (all ps > 0.262). In the final model of the top-down level model building strategy, the main effect of Onset of Stimulation was not significant (p = 0.135), and no other main effect or interaction emerged (all ps > 0.218). This model included a diagonal heterogenous variance structure fitting the data better than the model with homogenous variance structure, $\chi^2_{change}(1) = 33.6$, $p < 0.001$.

As evident in Table 1, the mean reaction times in the encoding task across all conditions ranged from 704 ms to 829 ms, with standard deviations ranging from 92 ms to

233 ms. In the random intercept model, we found no significant main effect or interaction involving Onset of Stimulation (all *p*s > 0.108).

3.2 Memory task

Table 2 shows the percentage of hits and false alarms in the memory task. For statistical analyses, the accuracy of recognition memory judgements was established with the discrimination index Pr (the proportion of hits minus the proportions of false alarms; Snodgrass & Corwin, 1988). As in both groups Pr values did not differ between vertex and no-TMS (two-tailed t-test, DLPFC: p = 0.154; VLPFC: p = 0.665), we collapsed the two control conditions in each group to obtain a single baseline measure.

As evident in Figure 2, rTMS over the VLPFC during encoding impaired retrieval considerably if delivered within few hundreds of milliseconds after the offset the word. When the stimulation was active later in the post-word interval, or during the online processing of the word, subsequent memory was not impaired. The stimulation of the DLPFC instead did not significantly affect retrieval.

Inferential statistical analyses confirmed these preliminary observations. In the final model with a diagonal heterogeneous structure that fitted the data better than the initial model with homogeneous structure ($\chi^2_{change}(1)$ = 19.0, p < 0.001), and with a reduced number of non-significant interaction terms, the main effect of Encoding Task was significant ($F_{1,\ 295.778}$ = 96.64, p < 0.001). As expected, recognition memory accuracy was higher for items encoded using a deep encoding strategy (M_{dif} = 0.177, 95% CI [0.142, 0.213]). We also found a marginally significant main effect of Onset of Stimulation ($F_{6,\ 88.654}$ = 2.45, p = 0.031). Bonferroni-corrected pairwise comparisons between each stimulation interval and the baseline revealed that recognition memory accuracy decreased when the onset of rTMS corresponded to the offset of the word (M_{dif} = -0.083, 95% CI [-0.163, -0.003], p = 0.036).

Crucially, Onset of Stimulation significantly interacted with Group ($F_{6,\ 83.162}$ = 3.04, p = 0.010). To assess at which point in time DLPFC and VLPFC rTMS at encoding affected subsequent memory retrieval, we compared each stimulation interval with the baseline,

separately in each group. These contrasts (corrected for multiple comparisons) revealed that VLPFC rTMS had detrimental effects on retrieval accuracy if administered at word offset (M_{dif} = -.148, 95% CI [-.261, -.035], p = 0.004), and 100 ms after word offset (M_{dif} = -.157, 95% CI [-.275, -.038], p = 0.004), thus when the stimulation interfered with the first 600 milliseconds after word offset (Figure 2). Figure 3 shows that the disruption of retrieval accuracy when VLPFC rTMS was administered during this early post-stimulus interval was very consistent across subjects. rTMS instead did not affect retrieval if the stimulation interfered with later post-word intervals, or during the online processing of the word (ps > 0.059). When rTMS targeted the DLPFC, no effects on retrieval were observed (for all rTMS onsets, ps> 0.799).

We further examined the effects of DLPFC and VLPFC stimulation by using the same top-down model-building strategy on the percentage of hits and false alarms, separately. In both analyses, the final model included a diagonal heterogeneous variance structure that fitted the data better than the initial model with homogeneous structure ($\chi^2_{change}(1) = 8.5$, p = 0.009 and $\chi^2_{change}(1) = 8.7$, p = 0.008, respectively). For hits, only the main effect of Encoding Strategy was significant ($F_{1,335.447} = 172.17$, $p < 0.001$). For false alarms, we found a significant main effect of Onset of stimulation ($F_{6,40.578} = 2.79$, p = 0.023). Bonferroni-corrected pairwise comparisons between each stimulation interval and the baseline condition indicated an increase in false alarm rates only when the stimulation was delivered at 300 ms after word offset (M_{dif} = 11.19, 95% CI [0.218, 22.156], p = 0.044). No other interval was significant (ps > 0.088).

Table 2 shows reaction times for hits in the recognition memory task. The estimated mean reaction times across all conditions ranged from 1313 ms to 1712 ms with standard deviations ranging from 271 ms to 715 ms. In the random intercept model, we found no significant main effects or interactions involving Onset of Stimulation (all ps > 0.189).

4. DISCUSSION

Our data support the notion that post-stimulus processing in the left VLPFC is crucial for the formation of new verbal memories. rTMS delivered after the offset of the words at encoding

decreased subsequent recognition accuracy, particularly when the stimulation interfered with the first few hundreds of milliseconds after offset. We did not observe any significant difference from baseline when the stimulation was delivered during the online processing of the words. The selective decrease of retrieval accuracy was specifically related to memory discriminability rather than overall hit rate, and cannot be explained by rTMS effects on the encoding task. Neither accuracy nor response times at encoding differed as a function of rTMS onset. Moreover, the observation that encoding judgements were taken on average well ahead the offset of the stimulus indicates that our results are not dependent upon rTMS effects on encoding-related decision-making processes. This suggests that, at least in the context of the present experiment, post-stimulus processing is more relevant for memory formation than online processing.

In general, it is reasonable to assume that post-stimulus processing reflects an early stage of memory consolidation that transforms short-term representations into long-term memory traces. However, the exact mechanisms that support memory formation at this stage of processing are not yet clear. One possible candidate is episodic binding, that is, the binding of event features into a cohesive memory episode. Episodic binding is a central feature of memory encoding that has consistently been associated with medial temporal lobe structures, especially the hippocampus (Davachi & Wagner, 2002). Very little is known about the temporal dynamics of episodic binding, but recent data suggest that this mechanism may occur at a post-stimulus processing stage. fMRI studies that allowed for a clear separation between stimulus and post-stimulus activations found encoding-related brain activity in the hippocampus after the stimulus offset, but not during online processing (Ben-Yakov & Dudai, 2011). One hypothesis is that in the current study VLPFC stimulation after word offset interfered with post-stimulus episodic binding through an indirect effect on medial temporal lobe structures. In this respect, one should note that while the depth of TMS prevents a direct stimulation of these brain regions, recent studies have shown that PFC stimulation can modulate network dynamics and propagate to distant brain regions, including the hippocampus (Li et al., 2004; Bilek et al., 2013). Our findings could also be consistent with

the notion of episodic buffer, a multidimensional storage system that provides a temporary interface between working memory and long-term memory by integrating information from different sources into a unitary episodic representation (Baddeley, 2000). This integration is thought to be an automatic process (Allen, Baddeley & Hitch, 2006), and can therefore contribute to memory formation even when encoding is incidental as in the current experiment.

Although we could demonstrate a causal link between brain activity immediately after an event and memory formation, we cannot establish on the basis of this dataset alone whether we disrupted a post-stimulus process *per se*, or a memory encoding process that begins after one second of stimulus presentation, regardless of the time of its offset. In the former scenario, we would have interfered with brain and cognitive processes that are specifically induced by the termination of the stimulus. For instance, the event boundary may trigger the automatic episodic binding and VLPFC-hippocampus connectivity that helps transform the trace into a long-term representation, as outlined above. In the latter scenario, we would have interfered with processes that start after one second from stimulus onset, and are a continuation of online processing. Further studies will need to disentangle between these two hypotheses by varying the duration of the stimulus while keeping the onset of rTMS constant. However, the observation that in a previous fMRI study post-stimulus brain activity was independent of stimulus length (Ben Yakov & Dudai, 2011) supports the idea that specific processes triggered by offsets contribute to memory formation.

One of the aims of this study was to compare the role of the left ventrolateral and dorsolateral prefrontal cortex in episodic memory formation. fMRI and non-invasive brain stimulation studies provide quite diverging results on the relative contribution of each area, with fMRI studies pointing to a greater involvement of the left VLPFC, and brain stimulation studies suggesting a predominant role of the left DLPFC (Blumenfeld et al., 2014). We found that rTMS interfered with encoding when delivered over the left VLFC, but not over the left DLPFC. Remarkably, this result was not dependent upon encoding depth, as we observed

the same disruptive effects of rTMS in both deep and shallow encoding. This should not lure the reader into assuming that the left DLPFC does not contribute to episodic memory formation. A scrutiny of individual participants' data in the DLPFC group reveals a great deal of variability, with some participants showing large detrimental effects, and other showing large enhancing effects. One hypothesis is that the left DPFC exerts its most robust influence on memory formation at an earlier stage of processing. This would be consistent with the observation that most high-frequency, online rTMS studies that targeted the left DLPFC disrupted a very early stage of memory encoding (within the first 600 ms from stimulus onset, Rossi et al., 2001, 2004, 2006; Sandrini et al., 2003; Turriziani et al., 2008; Innocenti et al., 2010). Our earliest onset of stimulation was 500 ms after the presentation of the word, thus any early DLPFC activity leading to successful encoding would not have been disrupted by rTMS in the current study. However, this interpretation is at odds with the data of Rossi et al. (2011) who found that rTMS over the left DLPFC decreased performance when administered between the last 500 ms of online processing and the first 400 of post-stimulus interval. It is unclear how to reconcile these conflicting findings. One reason may be the difference in stimulus material (visual images in Rossi et al., 2011 and visual words in the current investigation). Moreover, in Rossi et al. (2011) participants knew that their memory for the pictorial information would have been tested. It is thus very likely that at encoding they used maintenance and relational processes to stabilize the memory trace and keep it in mind for later remembering, which are associated with DLPFC activity (Cohen et al., 1997; Blumenfeld & Ranganath, 2007). Our task involving the incidental encoding of isolated words instead is more consistent with the engagement of the VLPFC shown by previous fMRI and TMS studies (Floel et al., 2004; Kohler et al., 2004; Khan et al., 2005; Blumenfeld & Ranganath, 2007; Machizawa et al., 2010; Blumenfeld et al., 2014; Vidal-Pinero et al.,2014).

It is worth noting that a recent TMS study that compared the effects of DLPFC and VLPFC TMS at encoding on subsequent retrieval (Blumenfeld et al., 2014) found very similar results to our study. In that study, VLPFC stimulation determined a significant decrease in

memory performance, whereas DLPFC stimulation generally increased performance, although this result was not statistically significant. Memory accuracy of individual participants in the two groups (Figure 3, p. 200) was also remarkably similar to our Figure 3 depicting individual effects in the post-stimulus interval. Blumenfeld et al. (2014) used an offline theta burst stimulation, therefore it is not possible to discern at what stage of processing the VLPFC exerts an effect on encoding. Our investigation is unique in showing that it is after the termination of the stimulus that the engagement of this brain region is necessary for memory formation.

One limitation of our study is that we used the International 10-20 EEG system to localize the two lateral prefrontal regions. The use of non-stereotaxically navigated brain areas is very common in TMS studies (Sparing et al., 2008; Beam et al., 2009). Although MRI-guided stereotaxic coil positioning is more accurate, studies have found that the International 10-20 EEG system is an acceptable and reliable method to localize brain regions, especially with large cortical areas such as the DLPFC or the VLPFC (Herwig, Satrap & Schönfeldt-Lecuona, 2003; Sparing et al., 2008; Beam et al., 2009). For instance, Herwig et al. (2003) investigated the underlying anatomy of F3 and found that in the vast majority of participants the location of F3 determined with the 10-20 system was within the DLPFC. Even though our localization method does not allow finer-grained distinctions within the DLPFC and VLPFC, this does not detract from the finding of a differential effect of rTMS along the dorsal-ventral axis of the lateral prefrontal cortex. In addition, the similarity between our findings and the study of Blumenfeld et al. (2014) provides reassurance on the specificity of the stimulation on the VLPFC and DLPFC, despite the use of scalp-based landmarks.

In conclusion, we found that the VLPFC plays a critical role in the formation of new episodic memories at a late stage of encoding. There is reason to believe that rTMS disrupted processes that develop only after the stimulus is gone and are specifically linked to its termination. This finding invites us to amend the common assumption that all memories are formed at an early, online stage of processing. It will be important for future studies to

gain better understanding on the nature of these processes, and to clarify their relationship with the temporal properties of the stimulus.

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Figure Captions:

Figure 1. Stimulation conditions. The 500 ms trains of rTMS stimulation started 500 ms after the onset of the word, at the offset of the word, and 100, 200, 300 and 400 ms after the offset of the word. The vertex stimulation started at the offset of the word and was used a as control condition for the unspecific effects of TMS. A no-TMS condition was also included.

Figure 2: Retrieval accuracy as a function of the onset of the stimulation, separately for participants who received DLPFC and VLPFC stimulation. A decrease in accuracy is evident in the VLPFC group when rTMS was administered at word offset and 100 ms after word offset, thus when the stimulation interfered with the first 600 milliseconds of the post-stimulus interval. The baseline (far right column) is based on the collapsed vertex and no-TMS conditions, separately in each group. ** denotes $p < 0.01$.

Figure 3: Effects of post-stimulus rTMS for individual participants. The graph depicts for every participant the difference in memory accuracy between the baseline and the collapsed first two post-stimulus intervals (rTMS delivered at word offset and 100 ms after word offset) where statistically significant differences emerged. Negative values indicate a disruption (left) and positive values an enhancement (right). The disruption following VLPFC stimulation was evident in all but three subjects. DLPFC effects instead involved a decrease in retrieval accuracy in half subjects, and an increase in the other half.

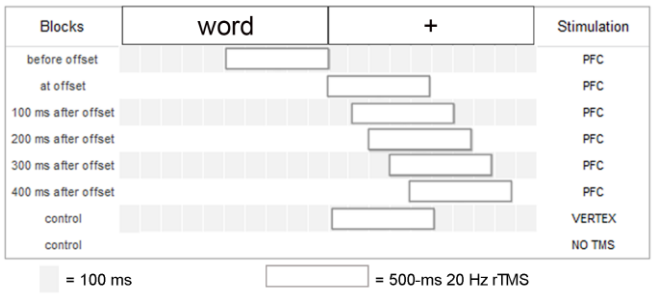

Fig 1

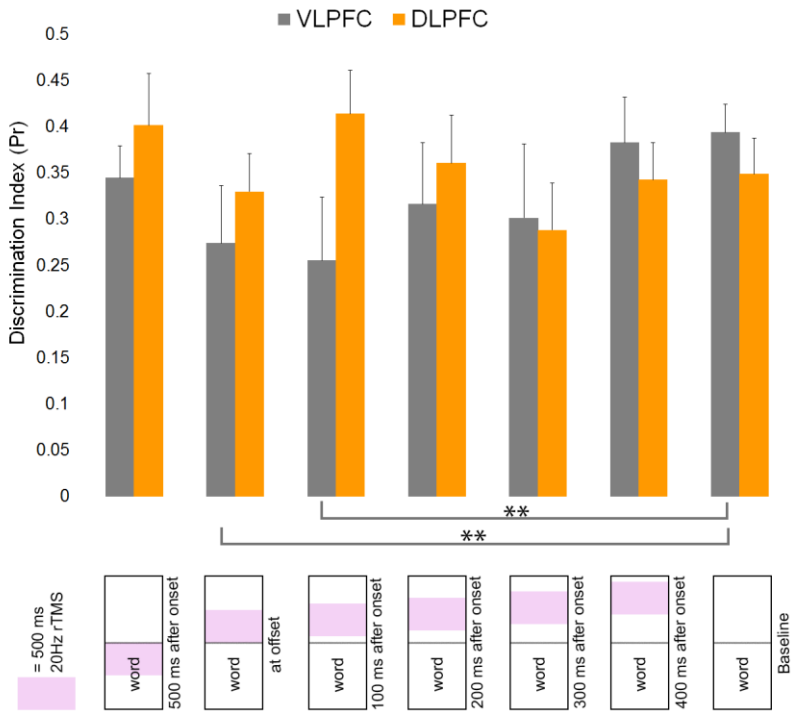

Fig 2

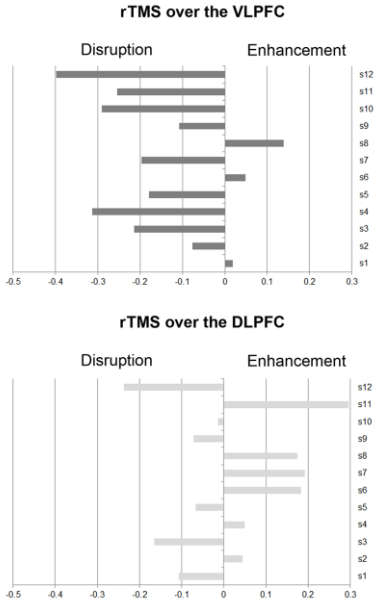

Fig 3

TABLES

Table 1. Percentage of correct judgments and response times at the encoding task (SD is displayed in parentheses).

	DLPFC		VLPFC	
Stimulation	**Deep**	**Shallow**	**Deep**	**Shallow**
During word presentation	94.0 (5.1)	91.1 (9.7)	92.9 (8.6)	91.1 (10.2)
	770 (181)	723 (135)	714 (108)	708 (92)
At word offset	96.4 (3.7)	94.0 (7.4)	95.8 (3.7)	93.5 (6.4)
	773 (132)	730 (100)	760 (126)	772 (152)
100 ms after word offset	95.2 (5.6)	94.6 (5.4)	92.2 (7.5)	91.1 (9.2)
	829 (230)	788 (233)	752 (183)	764 (173)
200 ms after word offset	94.6 (8.7)	96.6 (5.7)	94.6 (8.7)	94 (7.4)
	815 (155)	777 (200)	734 (156)	794 (194)
300 ms after word offset	93.5 (4.8)	96.4 (4.8)	94 (8.0)	95.8 (5.7)
	804 (155)	735 (143)	744 (149)	770 (164)
400 ms after word offset	97.6 (3.5)	95.8 (5.7)	94.6 (6.2)	95.2 (4.7)
	798 (184)	760 (184)	773 (139)	776 (154)
Vertex	96.4 (5.7)	98.8 (2.8)	95.2 (9.8)	94 (7.4)
	843 (226)	751 (148)	710 (94)	755 (168)
No TMS	95.2 (5.6)	97 (3.7)	92.9 (8.6)	95 (5.6)
	788 (131)	704 (96)	767 (184)	755 (168)

Table 2. Retrieval accuracy and response times across different experimental conditions (SD is displayed in parentheses).

	DLPFC				VLPFC		
	Hits		False Alarms		Hits		False Alarms
Stimulation	**Deep**	**Shallow**			**Deep**	**Shallow**	
During word presentation	78.6 (14.6)	60.1 (19.0)	29.2 (12.3)		74.4 (17.6)	56.5 (13.8)	29.2 (13.7)
	1374 (271)	1467 (279)	1523 (386)		1347 (367)	1524 (628)	1552 (715)
At word offset	78.0 (14.1)	58.9 (12.4)	35.4 (10.0)		72.0 (16.6)	54.8 (16.1)	38.5 (23.1)
	1359 (312)	1402 (305)	1513 (502)		1438 (392)	1519 (454)	1532 (580)
100 ms after word offset	82.7 (9.0)	63.7 (13.5)	31.8 (11.8)		69.6 (22)	54.8 (20.7)	38.5 (18.4)
	1408 (493)	1515 (395)	1712 (574)		1449 (483)	1423 (504)	1538 (493)
200 ms after word offset	83.9 (9.7)	64.3 (14.0)	38.0 (18.1)		67.3 (14.7)	53 (19.4)	31.3 (21.5)
	1368 (278)	1413 (279)	1531 (432)		1513 (526)	1318 (378)	1558 (538)
300 ms after word offset	79.2 (11.8)	61.9 (16.9)	41.7 (19.8)		70.2 (20.4)	57.7 (13.8)	38.0 (20.2)
	1504 (453)	1467 (348)	1586 (468)		1313 (367)	1329 (385)	1535 (575)
400 ms after word offset	71.4 (15.2)	60.7 (12.9)	31.8 (13.8)		74.4 (15.8)	51.8 (21.3)	27.6 (16.5)
	1515 (466)	1370 (255)	1520 (549)		1329 (342)	1431 (430)	1359 (386)
Vertex	73.8 (12.1)	59.5 (20.1)	27.6 (12.9)		72.6 (15.9)	54.8 (15)	23.4 (11.0)
	1407 (371)	1455 (322)	1589 (438)		1406 (457)	1441 (514)	1415 (521)
No TMS	78.6 (15.6)	56.0 (15.4)	36.5 (13.0)		78.6 (16.9)	53.9 (13.7)	27.3 (10.2)
	1467 (279)	1462 (333)	1601 (499)		1524 (628)	1579 (400)	1639 (508)