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Dynamic changes in prefrontal cortex involvement during verbal episodic memory formation

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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 encoding-related VLPFC engagement starts at a relatively late processing stage, and may reflect brain processes related to the offset of the stimulus.

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, Rohrbaugh, Syndulko, & Lindsley, 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 (Blumenfeld, Lee, & D'Esposito, 2014; Javadi & Walsh, 2012; Köhler, Paus, Buckner, & Milner, 2004; Machizawa, Kalla, Walsh, & Otten, 2010; Rossi et al., 2001, 2004, 2006, 2011).

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,

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Thangavel, Whitfield-Gabrieli, Knutson, & Gabriel, 2006; Galli, Wolpe, & Otten, 2011; Otten, Quayle, Akram, Ditewig, & Rugg, 2006; Park & Rugg, 2010). 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 et al., 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 (Blumenfeld & Ranganath, 2007; Fletcher, Shallice, & Dolan, 1998; Galli, 2014), whereas only few studies reported DLPFC activations (Blumenfeld & Ranganath, 2006; Savage et al., 2001). On the contrary, most TMS and tDCS studies of episodic memory found an effect of left DLPFC stimulation on subsequent retrieval (Elmer, Burkard, Renz, Meyer, & Jancke, 2009; Epstein, Sekino, Yamaguchi, Kamiya, & Ueno, 2002; Gagnon, Schneider, Grondin, & Blanchet, 2011; Innocenti et al., 2010; Javadi & Walsh 2012; Javadi & Cheng, 2013; Javadi, Cheng, & Walsh, 2012; Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013; Rossi et al., 2001, 2004, 2006, 2011; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003; Skrdlantová et al., 2005; Turriziani et al., 2008; Turriziani, Smirni, Oliveri, Semenza, & Cipolotti, 2010) whereas only a few targeted the left VLPFC (Blumenfeld et al., 2014; Floel et al., 2004; Kahn et al., 2005; Köhler et al., 2004; Machizawa et al., 2010; Vidal-Piñeiro 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.