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The effects of lateral prefrontal transcranial magnetic stimulation on item memory encoding

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ABSTRACT

Previous neuroimaging research has established that the left ventrolateral prefrontal cortex (VLPFC) is involved in long-term memory (LTM) encoding for individual items. Dorsolateral prefrontal cortex (DLPFC) is implicated less frequently, and one theory that has gained support to explain this discrepancy is that DLPFC is involved in forming item-item relational but not item LTM. Given that neuroimaging results are correlational, complimentary methods such as repetitive transcranial magnetic stimulation (TMS) have been used to test causal hypotheses generated from imaging data. Most TMS studies of LTM encoding have found that disruption of lateral PFC activity impairs subsequent memory. However these studies have lacked methods to precisely localize and directly compare TMS effects from frontal subregions implicated by the neuroimaging literature. Here, we target specific subregions of lateral PFC with TMS to test the prediction from the item/relational framework that temporary disruption of VLPFC during encoding will impair subsequent memory whereas TMS to DLPFC during item encoding will not. Frontal TMS was administered prior to a LTM encoding task in which participants were presented with a list of individual nouns and asked to judge whether each noun was concrete or abstract. After a 40 min delay period, item recognition memory was tested. Results indicate that VLPFC and DLPFC TMS have differential effects on subsequent item memory. VLPFC TMS reliably disrupted subsequent item memory whereas DLPFC TMS led to numerical enhancement in item memory, relative to TMS to a control region.

1. Introduction

A wealth of neuropsychological and neuroimaging data suggest that prefrontal cortex (PFC) implements control processes that are critical to long-term memory (LTM) function (Shimamura, 1995; and Blumenfeld & Ranganath, 2007 for review). Most neuroimaging studies examining LTM encoding find that ventrolateral regions of PFC (VLPFC) demonstrate enhanced activity during subsequently remembered compared to forgotten trials (for reviews see: Paller & Wagner, 2002; Blumenfeld & Ranganath, 2007). However, activity in more dorsolateral regions of PFC (DLPFC) rarely predicts subsequent LTM, and in some studies DLPFC activity was enhanced during subsequently forgotten compared to remembered trials (Blumenfeld & Ranganath, 2006; Staresina & Davachi, 2006; Summerfield et al., 2006; Murray & Ranganath, 2007; Jenkins & Ranganath, 2010; Blumenfeld, Parks, Yonelinas, & Ranganath, 2011 see Fig. 1).

Blumenfeld and Ranganath (2006, 2007) hypothesized that this pattern of findings can be explained by the fact that most encoding studies examine subsequent memory for item information, and specific DLPFC regions are critically involved in LTM encoding of inter-item relational information and not item information. In contrast, specific regions of VLPFC are hypothesized to contribute to encoding of item information. This hypothesis has received support from several neuroimaging studies (e.g. Blumenfeld & Ranganath, 2006; Staresina & Davachi, 2006; Summerfield et al., 2006; Murray & Ranganath, 2007; Blumenfeld et al., 2011).

Given that neuroimaging results, such as the subsequent memory effect, are correlational, complimentary methods are needed to establish causal links between functional brain activation and behavior. Repetitive transcranial magnetic stimulation (TMS), a non-invasive technique that temporarily alters neural excitability over a focal cortical region, offers neuroscientists such a method. There is a growing literature using TMS to probe the causal role of PFC in LTM encoding where frontal cortex function is disrupted prior to encoding and the effect on subsequent LTM performance is assessed (Floel & Cohen, 2007 for review). The majority of these studies do indeed find that TMS disrupts subsequent memory. However most previous studies did not use stereotaxic methods that can precisely and reliably target specific frontal subregions, and no study, to the best of our knowledge, has directly compared TMS effects between PFC regions within the same hemisphere. Thus, it is unclear from this literature whether different PFC regions support different LTM encoding functions. Here, we targeted dorsal and ventral

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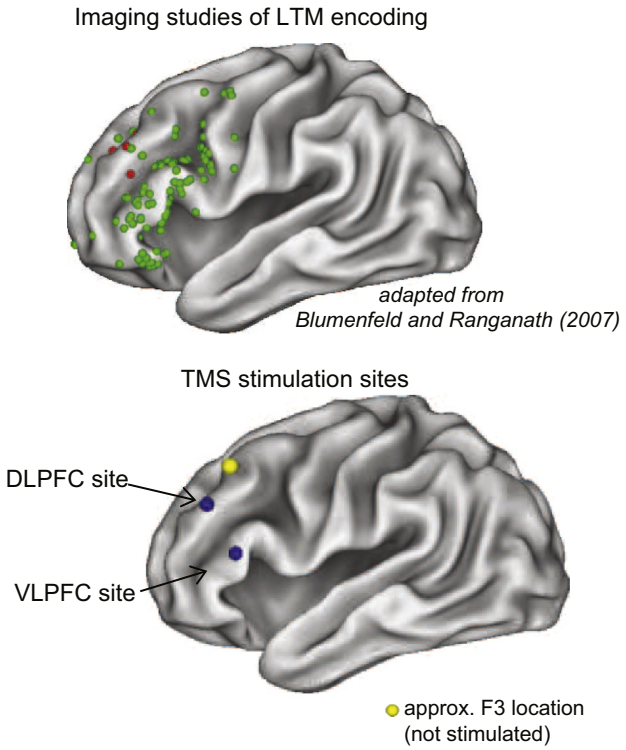

Fig. 1. Top: Plot of the local maxima implicated in the fMRI LTM encoding literature. Shown in green are regions implicated in successful subsequent memory. In red are maxima implicated in subsequent forgetting. Bottom: Shown in blue are the DLPFC and VLPFC TMS locations in standardized space. The yellow sphere depicts the approximate stimulation location when F3 electrode is used for TMS localization. Notice that this region is far caudal and dorsal to the DLPFC implicated in the fMRI literature as well as the region stimulated in this study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subregions of lateral PFC with TMS to test a prediction of the item/relational framework (Blumenfeld & Ranganath, 2007). Specifically, we hypothesize that VLPFC TMS (~BA 45: Petrides & Pandya, 1994) will impair item encoding whereas DLPFC TMS (~BA 9/46 or 46: Petrides & Pandya, 1994) will not. TMS was applied before LTM encoding and a subsequent memory paradigm was used that required deep encoding of single items, but placed minimal demands on encoding relations amongst items (Wagner et al., 1998).

2. Methods

2.1. Participants

Twenty nine participants were enrolled (14 female, mean age 33.5 ± 3.7). Data from one participant was excluded for not complying with instructions and data from two participants were excluded because their memory performance could not be estimated due to ceiling performance (0 false-alarms). Participants gave informed consent and were paid for their participation.

2.2. Study design

A mixed design was used. Participants were randomly assigned to 1 of 2 groups. Both groups participated in 2 TMS sessions on two separate days. Participants in the VLPFC group received TMS stimulation to VLPFC in one session, and in a separate control session, they received TMS to vertex. Participants in the DLPFC group received TMS to DLPFC in one session and received TMS to vertex in a separate control session. The order of stimulation session (PFC site vs. vertex) was counterbalanced between groups. Age, years of education and gender was matched between groups.

2.3. Materials

Stimuli consisted of a list of concrete (200 and mean concreteness 585.4) and abstract nouns (200 and mean concreteness 319) taken from the MRC Psycholinguistic database (Coltheart, 1981). From this master list, two smaller lists of 200 words (100 concrete, 100 abstract words) were constructed. These two lists contained different words and were used on separate sessions per participant. Within these session lists, 100 words (50 concrete, 50 abstract) served as the study list during encoding and 100 (50 concrete, 50 abstract) words served as novel foils during item recognition. The assignments to the study and foil lists were counterbalanced between participant and mean concreteness, frequency, imageability and number of phonemes was matched between all lists. In addition, we categorized each item according to semantic category and distributed the items equally across studied and foil lists. The assignment to session was counterbalanced.

2.4. Behavioral procedures

2.4.1. Item encoding task

During study, items were presented individually for 1 s. Participants were instructed to read the word and decide whether it was concrete or abstract. Participants were told that concrete nouns can be visualized as a whole. Participants were told that abstract nouns do not refer to the whole of an entity and cannot easily be visualized on their own. After initial presentation, a probe was additionally presented for 0.5 s at the bottom of the screen containing words: "concrete or abstract". Participants were instructed to make a response at the probe but not before. This was to ensure that participants spent equal time encoding each item. There was a 1 s inter-trial interval. Participants received instructions and a brief training run before TMS administration.

2.4.2. Item recognition

Nouns were presented individually in the center of the computer screen. Under the noun, the numbers 1 through 6 appeared. Participants were instructed to rate their confidence using a 1–6 scale about whether each word was studied or novel. Participants were told that "1" represented high confidence that the item is a novel foil and "6" indicates high confidence that the item was studied. Participants were further instructed to use the entire scale of responses. At the beginning of each session, participants received a brief training on the recognition test after the encoding training. They were told explicitly that their item recognition memory will be tested, but they should focus only on performing the task and not perform any additional mnemonic.

2.5. Definition of stimulation sites in standard space

The VLPFC stimulation site was based on standardized coordinates published by Wagner et al. (1998). This study used a nearly identical behavioral task in an fMRI encoding paradigm and found that activity in a VLPFC region (centered on −51, 25, 12 in MNI space (Montreal Neurologic Institute, Montreal, Quebec, Canada)) was enhanced for subsequently recognized item encoding trials compared to item encoding trials that were subsequently forgotten. We used a similar coordinate that was situated more clearly on the cortical surface of pars triangularis (−53, 28, 12). This location was a more reliable landmark for stereotaxy. The coordinate for the DLPFC stimulation site was based on a local maximum in a fMRI study by Blumenfeld et al. (2011). This study found that a region of DLPFC (−44, 35, 26) correlated with subsequent LTM for inter-item relational information but not detailed item information. The present study used a similar coordinate (−43, 35, 30). It should be noted that although the VLPFC and DLPFC stimulation sites are on adjoining gyri, care was taken to ensure that the coordinates chosen were at least 20 mm apart in every direction. Although there is no consensus on the minimum distance needed between sites to prevent stimulation overlap, it has been shown that motor-evoked potentials are not induced in motor areas situated more than 10 mm away from the center of coil during stimulation (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992). We therefore considered 10 mm the minimum distance between stimulation sites and ensured that the sites chosen exceeded 10 mm. It should be further noted that the two stimulation sites were at similar rostro-caudal positions. A 10 mm spherical masks were constructed at the VLPFC and DLPFC stimulation sites (see Fig. 1) in MNI-space.

2.6. Procedure for defining stimulation site for each subject

The standard-space DLPFC and VLPFC masks were reversed normalized into individual subject space for each participant using their high-resolution structural image. The DLFC and VLPFC subject-space masks for each subject were visually reviewed to ensure that there was no overlap between them. Depending on group assignment, either the subject-space DLPFC or VLPFC mask was selected as the stimulation site and this mask overlaid on top of the structural image was used for frameless stereotaxy.