

Distractibility during Episodic Retrieval Is Exacerbated by Perturbation of Left Ventrolateral Prefrontal Cortex

Peter E. Wais^{1,2,3}, Olivia Y. Kim^{1,2,3} and Adam Gazzaley^{1,2,3}

¹Department of Neurology, ²Department of Physiology and ³Department of Psychiatry, W. M. Keck Center for Integrative Neurosciences, University of California, San Francisco, CA 94158, USA

Address correspondence to Peter E. Wais, UCSF—MC2512, 1600 16th Street, Room N474, San Francisco, CA 94158-2330, USA. Email: peter.wais@ucsf.edu.

The presence of irrelevant external stimuli during the retrieval of long-term memory (LTM) has a negative impact on the fidelity of recollected details. Top-down control processes that both guide the selection of internal information relevant to LTM goals and resolve interference on retrieval from irrelevant external information have been associated with the same region in left ventrolateral prefrontal cortex (VLPFC). The current study examined a causal role of the left VLPFC in memory performance when external distraction (i.e., visual stimuli irrelevant to the current task goals) was presented during retrieval of LTM. Immediately after functional perturbation of the left VLPFC with 1-Hz repetitive transcranial magnetic stimulation, participants' memory was tested when their eyes were closed and when their eyes were open and irrelevant visual stimuli were presented. The results showed that visual distraction diminished LTM performance based on an objective measure of recollection and that perturbation of left VLPFC exacerbated the disruptive effect. This is the first evidence of a direct role of the left VLPFC in diminishing the impact of distraction on recollection, elucidating neural mechanisms that are critically involved in how we reconstruct the past while navigating the external environment.

Keywords: distraction, LTM, rTMS, top-down control, VLPFC

Introduction

Episodic retrieval brings the context of a prior experience back into mind. This reconstruction of long-term memory (LTM) has been linked to processes that select a specific ensemble of mnemonic details among competing associations (Tulving 1985; Moscovitch 2000). When episodic retrieval occurs amidst the presence of irrelevant external stimulation, top-down control processes guide the selection of internal information relevant to our memory goals and inhibit interference from distracting information. Recent findings have revealed a negative impact of external distraction on retrieval of contextual details in recognition memory (Wais, Rubens, et al. 2010).

Recognition memory often involves recollection, which is the effortful retrieval of contextual details about a past episode (Atkinson and Juola 1973). Recollection is more specific than simple item recognition that is based on a general sense of knowing about an item when relevant details from past experience are not available (Mandler 1980). Neuropsychological studies have revealed that patients with lateral prefrontal cortex (PFC) lesions are impaired in recall of word lists (Janowsky et al. 1989) and retrieval of source memory (Duarte et al. 2005). Although lack of anatomical specificity in naturally occurring lesions has made it difficult to attribute behavioral

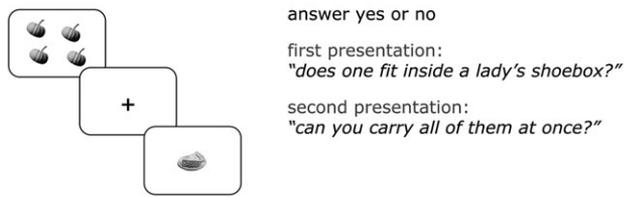
impairment to damage of a particular anatomical subregion within the lateral PFC, neural evidence from functional magnetic resonance imaging (fMRI) has begun to elucidate the roles of both the left ventrolateral PFC (VLPFC) (Badre and Wagner 2007) and the dorsolateral PFC (Blumenfeld and Ranganath 2006) in the cognitive control of memory.

Research using fMRI shows that objective recollection of goal-relevant details is accompanied by increased activity in the medial temporal lobe and regions of the PFC (Kahn et al. 2004; Habib and Nyberg 2007; Ranganath et al. 2007; Wais, Squire, et al. 2010; Wais 2011). Specifically, a region of the left inferior frontal gyrus (IFG) (ca. BA45, pars triangularis) referred to as mid-VLPFC (mVLPFC) has been associated with selection of contextual details during successful recollection (Dobbins and Wagner 2005; Law et al. 2005; Badre and Wagner 2007).

Notably, recent fMRI results show that the negative impact of visual distraction on LTM is accompanied by a disruption of the functional network between the left mVLPFC, hippocampus, and visual association cortex that supports successful recollection in the absence of external interference (Wais, Rubens, et al. 2010). Other studies have also implicated the left mVLPFC in top-down control processes involving domain-general mechanisms that resolve interference from perceptual representations on internal representations retrieved from memory (Nee and Jonides 2008, 2009; Nelson et al. 2009), as well as the inhibition of task-irrelevant actions (Chong et al. 2008). Although suggestive, fMRI evidence is correlational and only offers an indirect linkage between neural function and behavior. Thus, the causal role that the left mVLPFC serves during recollection of relevant details remains unclear.

The motivation for the current study was to assess the causal involvement of the left mVLPFC in episodic retrieval in the absence and presence of irrelevant environmental information (i.e., visual stimuli irrelevant to the memory task goals). The experiments probed performance on a cued-recall test when participants' eyes were closed and when eyes were open and irrelevant visual stimuli were presented (Fig. 1). The evaluation focused on task responses that indicated objective recollection of specific task-relevant details about a previously studied image (i.e., the number of objects in an image). Immediately prior to participants completing the memory retrieval tasks, repetitive transcranial magnetic stimulation (rTMS) was used to perturb function in an fMRI-guided region of interest (ROI), which was selected on the basis of the results of our recent study (Wais, Rubens, et al. 2010). Our approach incorporated 2 separate controls, such that the effects of actual rTMS perturbation could be compared with sham rTMS (i.e., perturbation control when the rTMS pulse is not directed at the brain) and the effects of rTMS to the mVLPFC could be

Study session— each image depicts 1, 2, 3 or 4 copies of a common object



Test session— hear “pumpkin,” then recall and respond 1, 2, 3, 4 or new

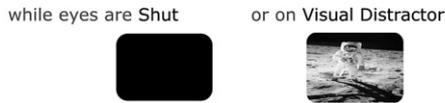


Figure 1. Experimental paradigm. A schematic of the procedure shows the study session, when participants answered 2 incidental questions about each of 168 images (3 s per presentation), and the test session when auditory cues described 168 targets and 72 lures in singular form (2.5 s per presentation). In each block of the test session, after 10 min of rTMS treatment, auditory cues probed participants’ recall while they wore earphones during trials presented in either the eyes shut (SHUT) or visual distractor (VD) conditions.

compared with a cortical region not associated with LTM function or higher order cognition (i.e., vertex control). Thus, each participant engaged in 2 separate experiments—rTMS and sham rTMS applied at the left mVLPFC and, on a different day, rTMS and sham rTMS applied at the vertex (Fig. 2).

Based on the literature, including our recent fMRI findings using the same paradigm (Wais, Rubens, et al. 2010), the study was designed to test the hypothesis that left mVLPFC mediates the interaction between representations of mnemonic details and representations of irrelevant perceptual information during retrieval of episodic memories. Explicitly, our study examined whether rTMS of left mVLPFC exacerbates the decline in recollection of relevant details that occurs in the presence of visual distraction, relative to retrieval when eyes are closed, and did not specifically address item recognition or roles of other PFC regions.

Materials and Methods

Participants

Twenty-seven adults between the ages of 18 and 30 years (12 males), who were native speakers of English, right-hand dominant, screened to be free from any neurological, psychiatric, or physiological complications for MRI and had completed 13 or more years of education, gave their informed consent to perform the experimental tasks in return for a small fee. Data from 5 participants were excluded from analysis because: in 2 cases, they experienced substantial drowsiness after rTMS treatment; in 2 other cases, participants failed to return for the third experimental session; and one participant failed to follow instructions in the use of the response box.

Experiment Overview

The experiment was separated into 3 sessions: an MRI structural scan, a behavioral session with actual rTMS or sham rTMS treatment at the left mVLPFC before each test block, and a behavioral session with actual rTMS or sham rTMS treatment at the vertex before each test block. Thus, the approach provided 2 controls in the comparison of effects from rTMS perturbation: target site (mVLPFC vs. vertex) and type of treatment (actual rTMS vs. sham rTMS). Importantly, the order of the 2 behavioral/rTMS sessions (i.e., mVLPFC target site and vertex target site) was counter-balanced across participants. Each of the behavioral/rTMS sessions had an encoding phase and, after an unfilled 1-h break, a test phase. Within a session, the order of treatment types (i.e., actual rTMS

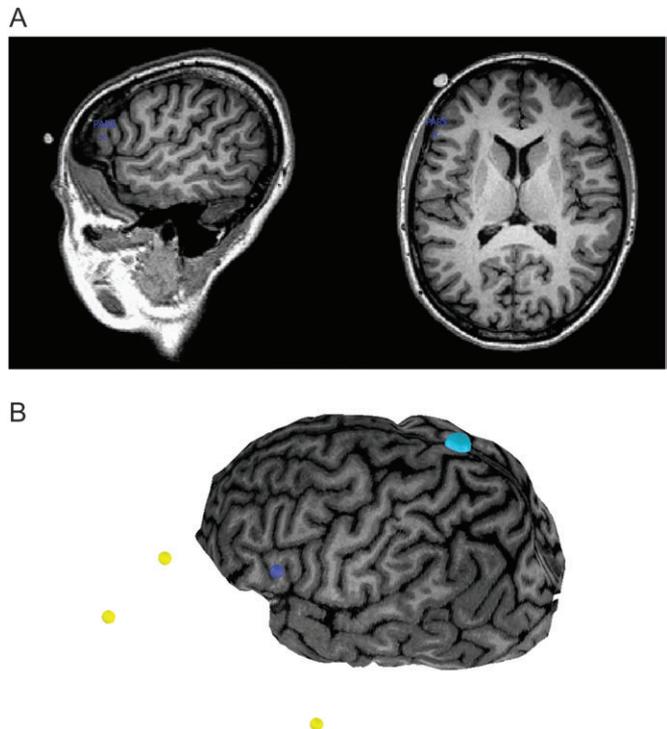


Figure 2. Rendering of ROIs for rTMS treatment. For each participant, the targeted ROIs for rTMS treatment were aligned onto their anatomical MRI in native space and rendered onto a virtual 3D cortical surface using Brainsight TMS software. (A) The functional ROI for the left mVLPFC from the group results in Wais, Rubens, et al. (2010) was inverse-warped to each participant’s anatomical MRI (i.e., blue x at the peak voxel, “PARS”). (B) A 3D cortical rendering was coregistered with the participant’s head position before rTMS treatment using reference points at the tip and bridge of the nose and the left and right preauricular spaces (yellow spheres). Targets on the virtual cortex were rendered for the left mVLPFC (blue sphere) and the Vertex (cyan sphere), which were aligned under the rTMS coil by the experimenter using Brainsight TMS software.

and sham rTMS) and test blocks (i.e., eyes closed, SHUT and eyes open with gaze fixed on presented visual distractors, VD) was counter-balanced across participants. At the end of the behavioral/rTMS session that included left mVLPFC treatment, participants completed a test that probed recognition of the distractor scenes. Written instructions were read out loud to each participant by the experimenter before each phase of each session, and the participant then completed a brief practice run for each phase with the experimenter.

MRI Structural Scan and rTMS Target Site Selection

A high-resolution T_1 -magnetization prepared rapid gradient echo scan was collected for each participant on a Siemens 3-T Magnetom Trio and compiled in SPM5. The functional ROI for the left mVLPFC was inverse-warped to each participant’s native brain space from the group results identified in Montreal Neurological Institute (MNI) space in Wais, Rubens, et al. (2010). The target voxel corresponded to $x = -54$, $y = 28$, $z = 6$ (axes in MNI space) and was situated on the IFG on pars triangularis (ca. BA45). The target voxel for the vertex site was mapped onto the anatomical images at the dorsomedial point where left and right central sulci were in closest proximity to each other, which corresponded to approximately $x = 0$, $y = -30$, $z = 76$ (axes in MNI space) (Rossi et al. 2010). A virtual 3D cortical surface was rendered for each participant using Brainsight TMS software (e.g., Fig. 2B), version 1.7.11, Rogue Research, Inc. The targeted ROIs will be referred to as mVLPFC and Vertex sites.

rTMS Threshold and Alignment

Magnetic stimulation was applied at the scalp (1 Hz pulse) with a Magstim Standard Rapid TMS Unit that generates pulses using

a 70-mm figure-of-8 induction coil. For each participant, the effective rTMS intensity for perturbation at the mVLPFC was calibrated after determination of their left motor cortex excitability threshold (i.e., motor threshold [MT]) according to the procedure of Stokes et al. (2005). Based on this approach, the mean MT intensity of the study population was $71\% \pm 4$ and the mean mVLPFC stimulation intensity was $59\% \pm 4$. The same stimulation intensity was used at the vertex. All participants reported that their respective levels of rTMS intensity were tolerable at both target sites. During the test sessions, the position of the participant's head and a 3D rendering of their cortical surface were coregistered usingBrainsight frameless stereotaxic software so that the rTMS target sites (mVLPFC and Vertex) could be precisely targeted. During rTMS treatment, the coil was handheld by the experimenter with the handle approximately parallel to the Sylvian fissure and touching the participant's scalp, such that the targeting software showed the smallest variance from the coordinates of the fMRI-guided ROI (i.e., total deviation on x , y , and z axes was typically 0.7 mm). During the sham treatment blocks, the rTMS coil was rotated 90° to be perpendicular to the scalp, mimicking the auditory artifacts and sensation of weight that accompany actual treatment without the magnetic discharge stimulating the cortex.

Stimuli

Three hundred and thirty-six target images, 240 images of neutral environmental scenes and 480 recordings of singular nouns that described the target images or lures, were organized into 2 sets, 1 for each of the 2 behavioral/rTMS sessions. Stimuli were not repeated over the behavioral/rTMS sessions.

The target images were used in the Study phase of the experiment as the memoranda. All images were presented on a computer screen (1024×768 pixel resolution) foveally, subtending 4° of visual angle from fixation. Each target image displayed 1–4 copies of a common object from a 3D perspective, in color, on a plain white background. There were an equivalent number of target images with each of the 4 object counts (1, 2, 3, or 4 copies). The objects were selected from a stimulus set of common items developed by Bakker et al. (2008) that were controlled for concreteness and ease in namability. The displacement in the viewable area from the objects was held as constant as possible, whereas the actual objects varied in size (i.e., wishbones vs. sofas).

The auditory stimuli were used during the Test phase of the experiment to cue recall of the number of objects in the target images. The recordings of singular nouns (i.e., auditory cues) were performed in the same, flat female voice, and they were equated and normalized for power spectral density in Audacity 1.3.5d digital audio editor.

The neutral environmental scenes were used as distractor stimuli in the Test phase of the experiment. These stimuli were compiled from the International Picture Affective Survey (IAPS) library, as well as edited stock photos with normative neutral ratings from a previous study (Anderson et al. 2006). Stimuli were presented using E-prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA).

Procedure for Behavioral/rTMS Sessions

Each of these sessions had a Study phase and a Test phase, duplicating the protocol used in Wais, Rubens, et al. (2010). During the Study phase, each of 168 target images was presented for 3000 ms, in random order, over 2 runs. When participants viewed each target image during the first run, they entered a yes or no answer into the computer keyboard to indicate their judgment about whether one of the objects from the image could fit inside a lady's shoebox and during the second run, to indicate whether they believed they could carry all of the objects from the image across the room using only their hands and arms. The incidental encoding tasks promoted in-depth visualization of the targets without specifically referencing numerosity or the need to remember the objects. Two runs were used in order to enhance participants' learning of the details of the target images. Each of the 336 trials was preceded by a 2000 ms fixation cross, and 12-s rest periods occurred after each block of 60 trials.

Approximately 30 min after the study session was completed, participants were positioned using the frameless stereotaxic software

for rTMS treatment and instructed about the memory test (for the first experiment session, this constituted a surprise memory test, but repetition of the protocol was obvious to participants during the second experiment session). Actual or sham rTMS treatment was applied for 10 min (i.e., 600 pulses) to a target site immediately preceding each test block, based on our estimate that 10 min of treatment would cause 7–10 min of perturbation effects (Hoffman et al. 2010; Zanto et al. 2011). Participants were fitted with earphones and the audio system volume output was adjusted to a comfortable level so that they could hear the auditory cues clearly, as well as have protection from noise associated with the rTMS procedure. During each test block, participants gave recollection responses to auditory cues during 2 different conditions (2 blocks for each condition): when visual stimulation was nil (no scene displayed and eyes closed: SHUT) and when neutral visual environmental stimuli were presented (looking at pictures of scenes: visual distraction or VD) (Fig. 1). The visual stimulus appeared simultaneously with the presentation of the auditory cue and remained on screen for 2500 ms. Participants were instructed to fix their gaze at the center of the computer screen during stimulus presentation in VD trials and "not to blink or look away when the screen changes from the fixation cross." Previous research from our laboratory suggests that fixating on a uniform gray screen does not produce a significantly distracting influence during memory retrieval (Wais, Rubens, et al. 2010). During SHUT blocks, an observer monitored the participant's compliance with instructions to keep eyes shut for the entire block.

Four blocks with 60 trials each were presented during the test phase (42 targets presented in a random order with 18 lures). Actual rTMS was applied preceding one SHUT and one VD block and sham rTMS was applied preceding one SHUT and one VD block. Each trial began with a fixation cross on a white background for 2500 ms, followed by an auditory cue that described an object encoded in the previous session or a novel (i.e., unstudied) object, in singular form. Participants were instructed to recall the count for the object described by the cue from a study image and give their answer by pressing 1, 2, 3, 4, or "new" (pressing all 4 buttons simultaneously) on a response pad, as rapidly as possible without sacrificing accuracy. The 2500-ms test period was followed by a 5500-ms intertrial interval, the last 500 ms of which included a visual (enlarged fixation cross) or auditory cue (2 beeps) to indicate the next trial was about to begin.

At the conclusion of the 3 sessions, participants completed a verbal exit interview in which the experimenter inquired about the strategy adopted to solve the recall question and whether they noticed an effect of rTMS treatment during either of the sessions. Eighteen of 22 participants reported using mental imagery of the studied object images during most or all of their responses to the recall test auditory cues. Participants' reports were mixed about whether they thought actual rTMS had any effect on the accuracy of their recall performance.

Behavioral Analysis

The impact of visual distraction on retrieval of LTM and the direct role of the left mVLPFC during retrieval were analyzed through comparison of results in several categories of responses to the auditory cues. Correct: responses that gave the correct object count corresponding with a previously studied image (i.e., targets) were interpreted as being based on an objective measure of recollection. Incorrect: responses that gave an incorrect object count for a target indicated that the participant recognized the object when recollection of the relevant details was weak or unavailable and thus were interpreted as being based on item recognition (Mandler 1980). It is also possible that some incorrect responses were based on recollection of noncriterial details, and so the data analysis focused primarily on Correct responses, when objective evidence of recollection was obtained. False Alarms: cues for unstudied objects (i.e., lures) that were erroneously given an object count were classified as false alarms. Forgotten: the trials in which the cue for a target was given a new response were classified as forgotten. Cues for lures that were given a new response were classified as correct rejections.

Results

Behavioral performance was evaluated in each of the 2 experiments on the basis of the following memory subtypes:

Correct responses (i.e., objective recollection indicated by the correct count of objects), Incorrect responses (i.e., item recognition indicated by an incorrect count of objects), Forgotten targets, and false alarms. A summary of the mean performance of the study population in each category of response to the targets and the lures is provided in Table 1, and the bases for the memory subtypes are described in the Materials and Methods: Behavioral Analysis.

We examined the effects of visual distraction and rTMS treatment on retrieval of LTM by comparing results for each memory subtype in separate 3-way repeated-measures analysis of variance (ANOVA) of Site (mVLPFC, Vertex) \times rTMS (sham, actual) \times Condition (SHUT, VD). There was no main effect of Site for measures of Correct responses, Incorrect responses, Forgotten targets, or false alarms (all comparisons, $F_{1,21} < 1.95$, $P > 0.18$); nor was there a main effect of rTMS (Correct responses, $F_{1,21} = 2.95$, $P = 0.10$; and comparisons of Incorrect responses, Forgotten targets, or false alarms, all $F_{1,21} < 1.70$, $P > 0.21$). Condition showed a main effect for Correct (Fig. 3; $F_{1,21} = 33.25$, $P < 0.001$) and Incorrect responses ($F_{1,21} = 10.50$, $P < 0.004$), as well as Forgotten targets ($F_{1,21} = 9.91$, $P < 0.006$), but no effect for false alarms ($F_{1,21} = 0.30$). These results revealed the disruptive impact of visual distraction on recollection of goal-relevant details across both experiments (i.e., in the eyes open condition, Correct responses declined and retained availability of item memory led to increased Incorrect responses), replicating findings from our previous behavioral and fMRI study (Wais, Rubens, et al. 2010) (Supplementary Fig. S1). These results also revealed that Forgotten responses were greater in the VD condition, indicating that overall memory for the targets (i.e., the sum of Correct and Incorrect responses) was diminished by distraction.

Importantly, the Correct response ANOVA further showed a significant interaction of Site \times Condition ($F_{1,21} = 5.80$, $P < 0.03$) such that Correct responses decreased during VD, relative to SHUT, to a greater degree in the mVLPFC experiment than the Vertex experiment (Fig. 4A). The difference in Correct responses between conditions can be presented as a distractibility index of recollection performance (i.e., SHUT Correct - VD Correct), and a comparison of this index between Sites shows that the effect of distraction was exacerbated in the mVLPFC experiment (pairwise test, $t_{21} = 2.46$, $P < 0.02$; Fig. 4B). The ANOVA also revealed a strong trend for an interaction of rTMS \times Condition ($F_{1,21} = 3.80$, $P = 0.07$) such that Correct responses were reduced during VD, relative to SHUT, to a greater degree after actual rTMS than

sham (Fig. 4C). Thus, the comparison of the distractibility index after actual rTMS, relative to that index after sham, further suggests that distraction was exacerbated by rTMS (Fig. 4D).

The 3-way ANOVA comparing false alarms also revealed an interaction of Site \times Condition ($F_{1,21} = 9.50$, $P < 0.01$), such that there were more of these errors during VD, relative to SHUT, in the mVLPFC experiment compared with the Vertex experiment. There were no other 2-way or 3-way interactions for any of the other measures.

Planned pairwise tests were performed to directly compare the effects of rTMS and Condition on Correct responses during the mVLPFC experiment. This analysis showed that Correct responses decreased in VD after actual rTMS relative to sham treatment ($t_{21} = 2.60$, $P < 0.02$), but there was no difference in SHUT after actual or sham treatment ($t_{21} = 0.40$). The results thus revealed that the effects on recollection of rTMS perturbation of left mVLPFC function were selective for the condition with visual distraction and exacerbated the disruptive impact of visual distraction on recollection.

Table 1
Behavioral results

	Targets			Lures	
	Correct	Incorrect	Forgotten	False alarms	Correct rejections
mVLPFC					
Total	57.1% (2.2)	31.5% (1.6)	11.4% (2.0)	15.0% (1.6)	85.0% (1.6)
SHUT	62.2% (2.1)	29.5% (1.4)	8.3% (2.0)	13.3% (2.0)	86.7% (2.0)
VD	52.0% (2.5)	33.5% (1.6)	14.5% (2.0)	16.7% (1.4)	83.3% (1.4)
Vertex					
Total	56.7% (2.4)	29.6% (1.8)	13.7% (2.1)	17.7% (2.3)	82.3% (2.3)
SHUT	59.1% (2.3)	28.8% (1.6)	12.1% (2.0)	18.0% (2.3)	82.0% (2.3)
VD	54.3% (2.8)	30.5% (2.0)	15.3% (2.3)	17.3% (2.1)	82.7% (2.1)

Note: A summary shows statistics for the responses to sets of 168 targets and 72 lures that were presented during the test sessions that followed rTMS treatment targeted at the left mVLPFC and at the vertex. The mean performance for 22 participants is given in each of the conditions (standard error of the mean).

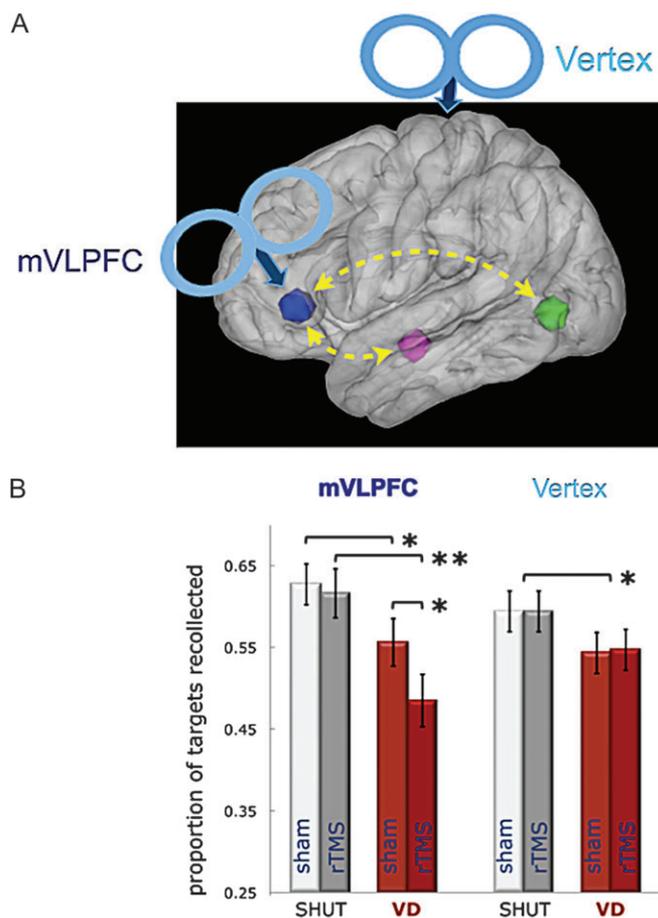


Figure 3. Role of the left mVLPFC in retrieval of Correct responses during visual distraction. A schematic illustration (A) shows the rTMS targets located on a sagittal rendering of the MNI template brain, including the mVLPFC ROI (blue) functionally connected in a recollection network with the left hippocampus (magenta) and lateral occipital cortex (green), as represented in Wais, Rubens, et al. (2010). (B) Objective recollection performance is shown in each experiment by condition (SHUT, VD) after sham or actual rTMS treatment. Recollection of episodic details was disrupted by visual distraction, and there was an interaction of actual rTMS on recollection during visual distraction after mVLPFC treatment but not after Vertex rTMS treatment. Error bars represent the standard error of the mean; ** indicates a difference between means, $P < 0.005$; and * indicates a difference between means, $P < 0.05$.

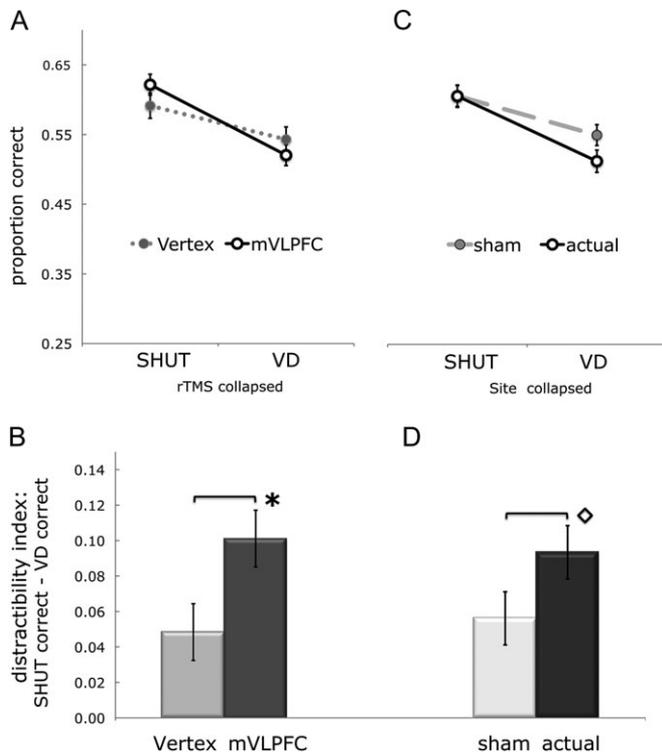


Figure 4. Comparison of the effects of Site and rTMS on episodic retrieval. Pairwise comparisons collapsed across blocks after actual and sham rTMS treatment showed that (A) the difference in Correct responses (i.e., based on recollection) between the SHUT and VD conditions increased in the mVLPFC experiment relative to the Vertex experiment and (B) an index of distractibility (i.e., SHUT Correct – VD Correct) was greater in the mVLPFC experiment. Pairwise comparisons collapsed across the Vertex and left mVLPFC sites suggested that (C) disruption of recollection during VD was exacerbated after actual relative to sham rTMS and (D) an index of distractibility increased after actual relative to sham rTMS. Error bars represent the standard error of the mean difference; * indicates a difference between means, $P < 0.023$; and \diamond indicates a difference between means, $P < 0.058$.

In order to confirm that visual distraction specifically disrupted recollection (i.e., visual distraction disrupted Correct responses to a greater degree than Incorrect responses, relative to performance in SHUT), we compared source accuracy scores for each participant. Source accuracy scores were calculated as the proportion of responses that correctly indicated the count, given that an item was not forgotten (i.e., percent Correct/(percent Correct + percent Incorrect). A 3-way repeated-measures ANOVA of Site (mVLPFC, Vertex) \times rTMS (sham, actual) \times Condition (SHUT, VD) for the source accuracy scores showed there was no main effect of Site ($F_{1,21} < 1.00$), a trend for an effect of rTMS ($F_{1,21} = 3.74$, $P = 0.07$), and a main effect of Condition ($F_{1,21} = 27.99$, $P < 0.001$) such that performance was diminished in VD. There was an interaction of Site \times Condition ($F_{1,21} = 4.57$, $P < 0.05$) such that source accuracy declined during VD, relative to SHUT, to a greater degree in the mVLPFC experiment than the Vertex experiment. There was a trend for the interaction of rTMS \times Condition ($F_{1,21} = 3.08$, $P = 0.09$), suggesting that source accuracy declined during VD, relative to SHUT, to a greater degree after actual rTMS than sham. Therefore, this follow-up analysis confirmed the same pattern of results revealed in the direct comparison of Correct responses.

Additionally, because the perturbation effect of 1-Hz rTMS is expected to dissipate rapidly (Hoffman et al. 2010), we

hypothesized that the effect of actual rTMS treatment at the mVLPFC would weaken between the first and second halves of each test block. Correct responses in the mVLPFC experiment were compared using repeated-measures ANOVA with factors of Period (first half, second half) and Condition (SHUT, VD). The analysis revealed a main effect of Period ($F_{1,21} = 6.71$, $P < 0.02$), such that fewer targets were recollected during the first half than the second half of the test blocks and a main effect of Condition ($F_{1,21} = 27.98$, $P < 0.001$), such that Correct responses declined in VD compared with SHUT. There was no significant interaction of Period \times Condition ($F_{1,21} = 0.85$). Pairwise comparisons showed that the number of Correct responses increased in the second half of VD blocks relative to first half ($t_{21} = 2.15$, $P < 0.05$) but did not differ between halves of the SHUT blocks ($t_{21} = 1.11$, $P = 0.28$). Importantly, the same analysis by period for the Vertex experiment showed no difference between first-half and second-half performance in the blocks after rTMS at Vertex (SHUT: $t_{21} = 0.80$, $P = 0.43$ and VD: $t_{21} = 0.96$, $P = 0.35$), thus providing additional evidence that perturbation of the vertex had no effect on the impact of visual distraction on recollection.

Subgroup Analysis

In a previous study, we showed that the effect of visual distraction on recollection varied across individuals (Wais, Rubens, et al. 2010). In order to assess if individual differences in susceptibility to distraction influences the impact of mVLPFC rTMS on distractibility during recollection, we separated the participants' data from the mVLPFC session into 2 subgroups using the distractibility index obtained with sham rTMS data (i.e., proportion of SHUT Correct – proportion of VD Correct). Seven participants were Non-Distractible (i.e., index was 0 or negative, mean = -0.08 ± 0.02 , indicating that Correct responses in VD were not reduced relative to SHUT), and 15 participants were Distractible (i.e., index was positive, mean = 0.13 ± 0.02 , indicating that Correct responses in VD declined relative to SHUT).

A comparison of indices after actual rTMS revealed that the distractibility index was no longer different between the subgroups (Fig. 5A). This resulted from the robust impact of mVLPFC rTMS on the Non-Distractible participants (actual vs. sham, $t_6 = 4.65$, $P < 0.003$) but not on the Distractible participants as a subgroup (actual vs. sham, $t_{14} = 0.05$). However, within the Distractible subgroup, the effect of rTMS was inversely correlated with their distractibility index, such that the less distractible they were, the more they were impacted by mVLPFC rTMS ($r = -0.61$, $P < 0.003$; Fig. 5B). These subgroup analyses converge to suggest that rTMS exacerbated distractibility in those individuals who were not already susceptible to distraction effects.

Discussion

The current study explored the causal role of the left mVLPFC in mediating the distracting impact of irrelevant external information on the episodic retrieval of visual details. Results revealed that visual distraction diminished correct responses for the number of objects appearing in previously studied images—an indication of objective recollection. These results replicated a previous finding that even when external information is outside the focus of our goals, the presence of environmental visual stimuli interferes with the reconstruction

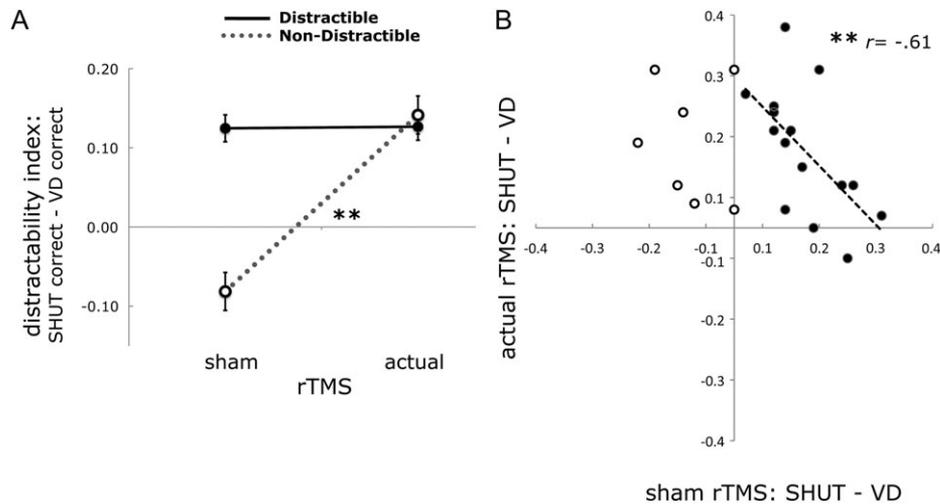


Figure 5. Individual differences in the impact of visual distraction on episodic retrieval. The separation of participants into subgroups based on a distractibility index (i.e., disruption to recollection measured by SHUT Correct – VD Correct) is shown with the effect of mVLPFC rTMS treatment. (A) Seven participants were not distracted before treatment (Non-Distractible), yet suffered disruption to recollection from external interference after mVLPFC rTMS. Fifteen participants who were Distractible before treatment did not show increased distractibility after mVLPFC rTMS. (B) A scatter plot shows, for the Distractible participants (solid dots), increased distractibility after mVLPFC rTMS was inversely correlated with their index of disruption before treatment. These results suggest a direct role of left mVLPFC interacting with external interference during recollection. Error bars represent the standard error of the mean difference; ** indicates a difference between means or a correlation between variables, $P < 0.005$.

of detailed memories (Wais, Rubens, et al. 2010). The novel finding of the current study is that perturbation of left mVLPFC function by rTMS resulted in increased susceptibility to the disruptive impact of visual distractors on recollection of relevant details.

The exacerbation of distractibility when left mVLPFC function was compromised by rTMS suggests a causal role of this region in diminishing the impact of interference during episodic retrieval. Nee and colleagues have proposed a similar interpretation of the left mVLPFC role based on fMRI results that show activity in this region increases in association with proactive interference resolution during short-term memory retrieval (Nee and Jonides 2008; Nelson et al. 2009). According to the interpretation from Nee and colleagues, increased activity in left mVLPFC is an indication of increased recruitment of top-down resources to resolve proactive interference from perceptual information that is irrelevant to task goals of memorial selection (Nee and Jonides 2009). In contrast to the results from the current study, this prior work did not compare between retrieval conditions with and without external distraction nor provide evidence for a causal role of the left mVLPFC in preserving the fidelity of recollection in the presence of external distraction.

The current findings may also be explained by a direct role of the left mVLPFC in the active suppression of posterior cortical representations of visual distractors. If the left mVLPFC modulates visual association cortex activity according to task goals (i.e., suppression of distractors), then perturbation of this region by rTMS would increase bottom-up influences from irrelevant information that can interfere with processes supporting recollection, such as those involved in visual imagery. This interpretation is consistent with other studies that have found optimal performance on working memory (WM) and perception tasks depend upon filtering interference from bottom-up influences associated with external information irrelevant to task goals (Rainer et al. 1998; Lavie et al. 2004; Zanto and Gazzaley 2009). Additionally, behavioral results have suggested that active suppression of irrelevant information

facilitates recognition (Glenberg et al. 1998; Healey et al. 2010). However, direct evidence of the active suppression of visual cortical activity by PFC regions during LTM retrieval in the setting of distraction has yet to be revealed, as has been recently shown for WM encoding (Zanto et al. 2011). Also, this explanation that left mVLPFC actively mediates suppression of bottom-up processing would invoke a secondary role of this region concurrent with its role in mnemonic networks that support episodic retrieval.

Recent fMRI results have revealed that left mVLPFC functional connectivity with the left hippocampus and visual association cortex increases in association with successful recollection of task-relevant details in the absence of distraction (i.e., with eyes closed) (Wais, Rubens, et al. 2010). Critically in guiding the current study, these results also showed that memory performance and connectivity in this network were diminished in the presence of visual distraction. These findings provided evidence that irrelevant external information interferes with the reconstruction of ensembles of mnemonic details that occurs during reinstatement of encoding activations (Johnson et al. 2009) and/or visual imagery associated with the memoranda (Kahn et al. 2004; Mechelli et al. 2004; Ranganath et al. 2004) and further suggest that the left mVLPFC may be a locus of interference.

Taking these findings into account with others that reveal the left mVLPFC subserves mnemonic selection processes (Badre and Wagner 2007) raises the question of how this region might be involved in both recollection and, as suggested by the current results, diminishing the impact of visual distraction on episodic retrieval? A parsimonious explanation is that the left mVLPFC is involved in one process of selection that evaluates information active during effortful memory retrieval (Badre and D'Esposito 2009), whether this information represents task-relevant associations stored in memory or external stimuli. In the current study, the influence of external information during retrieval would be driven solely by the bottom-up salience of the irrelevant scenes, since there were no task goals to attend to the distractor stimuli. This

explanation suggests that the ability to maintain the goals of the task (i.e., episodic retrieval) and resist the negative impact of distraction requires weighting the allocation of left mVLPFC resources toward selection of mnemonic information and away from representations of external information. If this region does become engaged in evaluation of distracting external stimuli, the limited capacity of top-down resources is exceeded and accuracy in mnemonic selection declines. Evidence for this explanation was suggested by our previous study using the same paradigm, which showed that functional connectivity between left mVLPFC and a region of the visual association cortex that represented distracting stimuli was greater in association with Incorrect than Correct responses (Wais, Rubens, et al. 2010).

Therefore, if left mVLPFC subserves one process that evaluates information active during retrieval, the influence of external distractors may usurp resources during the selection of retrieved task-relevant details. Such a diversion of left mVLPFC resources may explain the diminished connectivity of this region with the hippocampus and visual association cortex representing the memoranda in the setting of distraction (Wais, Rubens, et al. 2010) and would suggest that the mVLPFC serves as a control region to mediate the competition between representations of external information and those generated during the retrieval of mnemonic details. Therefore, in the setting of functional perturbation of left mVLPFC by rTMS, the limited resources available for mnemonic selection were further depleted and resulted in diminished recollection accuracy.

Conclusions from the current study do not preclude the possibility that this region may also be involved in resolving competition on a broader scale, for example, between competing representations of external information, including sensory modalities other than vision. The role of this region in resolving competition in a more extensive manner is an important focus of future research.

Notably, the current results did not show that rTMS perturbation of the left mVLPFC resulted in diminished episodic retrieval when there was no influence of external distraction (i.e., eyes shut condition). This result does not support the interpretation that a function of the left mVLPFC is to guide mnemonic selection, as a number of studies have concluded based on fMRI evidence of increased activity and functional connectivity with this region in association with successful episodic retrieval (Kahn et al. 2004; Badre et al. 2005; Dobbins and Wagner 2005; Law et al. 2005; Wais, Rubens, et al. 2010). Considering limitations of the rTMS procedure, however, the null results here do not preclude a role of this region in retrieval. One possibility is that in the absence of external interference (i.e., eyes closed), left mVLPFC is solely engaged in memory selection goals and, relative to increased demands during the distractor condition, is not substantially compromised by rTMS perturbation. Another possibility is that the rTMS perturbation did not disrupt the complete subsystem of regions within the left IFG that has been proposed to interact on the basis of the complexity of task demands during effortful retrieval of mnemonic details (Badre and D'Esposito 2009). This view is based on evidence from fMRI showing engagement of an anterior IFG region (BA47), pars orbitalis, during retrieval of associative information from conceptual domains and engagement of mid-IFG (BA45), pars triangularis (the primary rTMS target for our experiment), during more

generalized selection processes that resolve interference among semantic competitors (Badre et al. 2005).

The data also revealed that rTMS of the left mVLPFC diminished episodic retrieval in the presence of visual distractors more in the Non-Distractible subgroup, as well as the least distractible participants in the Distractible subgroup. Thus, distractible participants (i.e., those who were most susceptible to interference by external distraction in the sham condition) were least susceptible to the negative impact of mVLPFC rTMS. This finding suggests that for a subset of participants the influence of visual distraction results in insensitivity of this region to further disruptive effects by rTMS. An explanation for this finding is that those individuals who are most distractible have already exhausted their left mVLPFC resources by processing irrelevant external information and thus are not further susceptible to a negative effect on memory performance by rTMS.

In summary, the results reveal that the left mVLPFC has a direct role in resolving competition during retrieval of LTM between irrelevant external information and relevant mnemonic details. Limitations in processing capacity of prefrontal regions are a fundamental aspect in understanding the framework of cognitive control (Braver et al. 2009). The evidence here revealed a critical role of the left mVLPFC in the ability to reconstruct memories while interacting with our external environment.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

Funding

National Institutes of Health Grant R01-AG30395; Ellison Foundation.

Notes

We thank Shawn Wen for her valuable contribution in the collection and analysis of the data. *Conflict of Interest:* None declared.

References

- Anderson AK, Wais PE, Gabrieli JD. 2006. Emotion enhances remembrance of neutral events past. *Proc Natl Acad Sci U S A*. 103:1599-1604.
- Atkinson R, Juola J. 1973. Factors influencing the speed and accuracy of word recognition. In: Kornblum S, editor. *Attention and performance*. New York: Academic Press. p. 583-612.
- Badre D, D'Esposito M. 2009. Is the rostro-caudal axis of the frontal lobe hierarchical? *Nat Rev Neurosci*. 10:659-669.
- Badre D, Poldrack R, Paré-Blagoiev E, Insler R, Wagner A. 2005. Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron*. 47:907-918.
- Badre D, Wagner A. 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*. 45:2883-2901.
- Bakker A, Kirwan CB, Miller M, Stark C. 2008. Pattern separation in the human hippocampus CA3 and dentate gyrus. *Science*. 319:1640-1642.
- Blumenfeld R, Ranganath C. 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J Neurosci*. 26:916-925.
- Braver T, Paxton J, Locke H, Barch D. 2009. Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proc Natl Acad Sci U S A*. 106:7351-7356.
- Chong T, Williams M, Cunnington R, Mattingly J. 2008. Selective attention modulates inferior frontal gyrus activity during activity observation. *Neuroimage*. 40:298-307.

- Dobbins I, Wagner A. 2005. Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cereb Cortex*. 15:1768-1778.
- Duarte A, Ranganath C, Knight RT. 2005. Effects of unilateral prefrontal lesions on familiarity, recollection, and source memory. *J Neurosci*. 25:8333-8337.
- Glenberg A, Schroeder J, Robertson D. 1998. Averting the gaze disengages the environment and facilitates remembering. *Mem Cognit*. 26:651-658.
- Habib R, Nyberg L. 2007. Neural correlates of availability and accessibility in memory. *Cereb Cortex*. 18:1720-1726.
- Healey M, Campbell K, Hasher L, Oshers L. 2010. Direct evidence for the role of inhibition in resolving interference in memory. *Psychol Sci*. 10:1464-1470.
- Hoffman P, Jefferies E, Lambon Ralph M. 2010. Ventrolateral prefrontal cortex plays an executive regulation role in comprehension of abstract words: convergent neuropsychological and repetitive TMS evidence. *J Neurosci*. 30:15450-15456.
- Janowsky J, Shimamura A, Kritchevsky M, Squire L. 1989. Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behav Neurosci*. 103:548-560.
- Johnson JD, McDuff SG, Rugg MD, Norman KA. 2009. Recollection, familiarity, and cortical reinstatement: a multivoxel pattern analysis. *Neuron*. 63:697-708.
- Kahn I, Davachi L, Wagner A. 2004. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *J Neurosci*. 24:4172-4180.
- Lavie N, Hirst A, De Fockert J, Viding E. 2004. Load theory of selective attention and cognitive control. *J Exp Psychol Gen*. 133:339-354.
- Law JR, Flanery MA, Wirth S, Yanike M, Smith AC, Frank LM, Suzuki WA, Brown EN, Stark CE. 2005. Functional magnetic resonance imaging activity during the gradual acquisition and expression of paired-associate memory. *J Neurosci*. 25:5720-5729.
- Mandler G. 1980. Recognizing: the judgment of previous occurrence. *Psychol Rev*. 87:252-271.
- Mechelli A, Price C, Friston K, Ishai A. 2004. Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cereb Cortex*. 14:1256-1265.
- Moscovitch M. 2000. Theories of memory and consciousness. In: Tulving E, Craik F, editors. *The oxford handbook of memory*. New York: Oxford University Press. p. 609-626.
- Nee DE, Jonides J. 2008. Neural correlates of access to short-term memory. *Proc Natl Acad Sci U S A*. 105:14228-14233.
- Nee DE, Jonides J. 2009. Common and distinct neural correlates of perceptual and memorial selection. *Neuroimage*. 25:963-975.
- Nelson J, Reuter-Lorenz P, Persson J, Sylvester C, Jonides J. 2009. Mapping interference resolution across task domains: a shared control process in left inferior frontal gyrus. *Brain Res*. 1256:92-100.
- Rainer G, Asaad WF, Miller EK. 1998. Selective representation of relevant information by neurons in the primate prefrontal cortex. *Nature*. 393:577-579.
- Ranganath C, Cohen M, Dam C, D'Esposito M. 2004. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *J Neurosci*. 24:3917-3925.
- Ranganath C, Heller A, Wilding E. 2007. Dissociable correlates of two classes of retrieval processing in prefrontal cortex. *Neuroimage*. 35:1663-1673.
- Rossi S, Innocenti I, Polizzotto N, Feurra M, De Capua A, Olivelli M, Bartalini S, Cappa S. 2010. Temporal dynamics of memory trace formation in the human prefrontal cortex. *Cereb Cortex*. 21:368-373.
- Stokes M, Chambers C, Gould I, Henderson T, Janko N, Allen N, Mattingley J. 2005. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *J Neurophysiol*. 94:4520-4527.
- Tulving E. 1985. Memory and consciousness. *Can J Psychol*. 26:1-12.
- Wais PE. 2011. Hippocampal signals for strong memory when associative memory is available and when it is not. *Hippocampus*. 21:9-21.
- Wais PE, Rubens MT, Bocciafuso J, Gazzaley A. 2010. Neural mechanisms underlying the impact of visual distraction on retrieval of long-term memory. *J Neurosci*. 30:8541-8550.
- Wais PE, Squire LR, Wixted JT. 2010. In search of recollection and familiarity signals in the hippocampus. *J Cogn Neurosci*. 22:109-123.
- Zanto T, Gazzaley A. 2009. Neural suppression of irrelevant information underlies optimal working memory performance. *J Neurosci*. 29:3059-3066.
- Zanto T, Rubens M, Thangavel A, Gazzaley A. 2011. Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nat Neurosci*. 14:656-661.