

Transient Disruption of Ventrolateral Prefrontal Cortex During Verbal Encoding Affects Subsequent Memory Performance

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Kahn, Itamar, Alvaro Pascual-Leone, Hugo Theoret, Felipe Fregni, Dav Clark, and Anthony D. Wagner. Transient disruption of ventrolateral prefrontal cortex during verbal encoding affects subsequent memory performance. *J Neurophysiol* 94: 688–698, 2005. First published March 9, 2005; doi:10.1152/jn.01335.2004. Episodic memory supports conscious remembrance of everyday experience. Prior functional neuroimaging data indicate that episodic encoding during phonological task performance is correlated with activation in bilateral posterior ventrolateral prefrontal cortex (pVLPFC), although uncertainty remains regarding whether these prefrontal regions make necessary contributions to episodic memory formation. Using functional MRI data to guide application of single-pulse transcranial magnetic stimulation (spTMS), this study examined the necessity of left and right pVLPFC for episodic encoding (as expressed through subsequent memory performance). To assess the timing of critical computations, pVLPFC function was transiently disrupted at different poststimulus onset times while subjects made syllable decisions about visually presented familiar and unfamiliar words; subsequent memory for these stimuli was measured. Results revealed that left pVLPFC disruption during encoding of familiar words impaired subsequent memory, expressed as a decline in recognition confidence, with disruption being maximal at 380 ms after stimulus onset. In contrast, right pVLPFC disruption facilitated subsequent memory for familiar words, expressed as an increase in medium confidence recognition, with this facilitation being maximal at 380 ms. Finally, phonological (syllable) decision accuracy was facilitated by right pVLPFC disruption, with this effect being maximal at 340 ms, but was unaffected by left pVLPFC disruption. These findings suggest that left pVLPFC mechanisms onset between 300 and 400 ms during phonological processing of words, with these mechanisms appearing necessary for effective episodic encoding. In contrast, disruption of correlated mechanisms in right pVLPFC facilitates encoding, perhaps by inducing a functional shift in the mechanisms engaged during learning.

INTRODUCTION

Episodic encoding entails the formation of long-term memory representations that support subsequent conscious remembrance of everyday experience (Tulving 1983). Prefrontal cortical (PFC) lesions result in modest impairments on episodic memory tasks indicating that PFC makes critical functional contributions to episodic memory (e.g., Milner 1982; Moscovitch and Winocur 1995; Schacter 1987; Shimamura 1996). However, it is unclear whether these deficits at least partially stem from dysfunction at encoding or whether they primarily reflect impaired cognition at retrieval. One hypothesis is that

PFC cognitive control processes modulate, and thus are necessary for, episodic learning (e.g., Buckner and Koutstaal 1998; Shimamura 1995; Wagner 1999). Correlational evidence supporting this perspective comes from functional imaging studies that have used the “subsequent memory” paradigm, wherein neural processes that are potentially important for successful memory formation are identified by sorting items processed at encoding according to whether they are later remembered or forgotten (Chapman et al. 1978; Paller et al. 1987; Sanquist et al. 1980; for review, see Paller and Wagner 2002; Rugg 1995; Wagner et al. 1999). Event-related functional MRI (fMRI) studies have identified subsequent memory effects during verbal encoding predominantly in left ventrolateral PFC (VLPFC; e.g., Baker et al. 2001; Buckner et al. 2001; Davachi et al. 2001; Henson et al. 1999; Kirchoff et al. 2000; Otten and Rugg 2001a; Wagner et al. 1998b), with such effects during phonological processing at encoding being particularly prevalent in left posterior VLPFC [Brodmann’s area (BA) 44/6] (e.g., Clark and Wagner 2003; Davachi et al. 2001; Otten et al. 2002). Importantly, although the subsequent memory approach has provided considerable leverage on identifying the neural correlates of episodic encoding, due to the correlational nature of functional imaging, uncertainty remains regarding the necessity of identified PFC regions for successful encoding and subsequent remembering.

One strategy for testing the necessity of PFC contributions to encoding is to combine information about localized neural populations wherein activation levels predict subsequent memory (identified by functional imaging) with neural disruption methods that transiently interfere with processing in these identified regions [using transcranial magnetic stimulation (TMS)]. This approach can reveal how stimulus processing and subsequent memory performance are affected by disrupted PFC function at encoding. For example, recent TMS studies have shown that left anterior VLPFC is necessary for intact semantic processing (Devlin et al. 2003; Kohler et al. 2004), that left posterior VLPFC is critical for phonological processing (Nixon et al. 2004), and that bilateral dorsolateral PFC (DLPFC) is necessary for verbal working memory (Grafman et al. 1994; Mottaghy et al. 2000; Mull and Seyal 2001; Pascual-Leone and Hallett 1994) and response selection (Hadland et al. 2001). Critically, subsequent memory for verbal material is impacted when TMS is applied to left anterior VLPFC during

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semantic encoding, with one study showing enhanced subsequent memory (Kohler et al. 2004) and another showing diminished subsequent memory (Floel et al. 2004). Other studies showed that 1) subsequent recognition of words is hindered when TMS is applied to left or right DLPFC at encoding (Sandrini et al. 2003), and 2) subsequent recognition of verbalizable pictures is hindered by disruption of left DLPFC (Rossi et al. 2001), whereas subsequent recognition of nonverbalizable pictures is hindered by disruption of right DLPFC (Epstein et al. 2002) or right anterior VLPFC (Floel et al. 2004). Collectively, these TMS studies suggest that PFC mechanisms make necessary contributions during semantic encoding of words and during encoding of visuo-object/visuo-spatial stimuli. In contrast, the necessary role of PFC, and in particular posterior VLPFC, to episodic encoding under phonological orienting conditions has not been directly assessed.

Extensive neuroimaging data indicate that left VLPFC is differentially active during the performance of verbal compared with nonverbal tasks (e.g., Kelley et al. 1998; Kirchoff et al. 2000; Smith et al. 1996; Wagner et al. 1998a), with the posterior portion of left VLPFC (pVLPFC; BA 44/6) being particularly sensitive to phonological processing demands (e.g., Fiez 1997; McDermott et al. 2003; Otten and Rugg 2001a; Otten et al. 2002; Poldrack and Wagner 2004; Poldrack et al. 1999; Roskies et al. 2001; Wagner et al. 2000; cf., Gold and Buckner 2002). Accordingly, efforts to understand PFC contributions to episodic encoding under phonological orienting conditions have focused on the potential contributions of left pVLPFC (e.g., Davachi et al. 2001; Otten et al. 2002; Wagner et al. 2001).

For example, a recent fMRI study from our laboratory sought to specify the contributions of the phonological (articulatory) control component of the phonological processing system to novel word learning (Clark and Wagner 2003). The study was motivated by prior behavioral and neuropsychological evidence suggesting that novel words require differential analysis and assembly by the phonological system and, in the process, differentially depend on the phonological system for encoding into long-term memory (Baddeley et al. 1998). Accordingly, in the fMRI experiment, subjects were scanned while familiar (English) and unfamiliar (pseudo-English) words were incidentally encoded (subjects made 2- or 3-syllable judgments), and subsequent recognition memory for the words was assessed 20 min later. The subsequent memory analyses of the encoding data revealed that regions in bilateral pVLPFC [MNI coordinates: left ($-36, 15, 27$)¹; right (48, 12, 30)] were differentially engaged for items later remembered relative to items later forgotten. Moreover, while the magnitude of the subsequent memory effect in left pVLPFC was larger for pseudo-English relative to English words, the magnitude of this effect in right pVLPFC was equivalent between the two word types even though there was an overall greater engagement of right pVLPFC during pseudo-English trials. These results suggest that left pVLPFC plays a central role in the encoding of unfamiliar (pseudo-English) words into long-term memory by mediating construction of novel phonological sequences. Conversely, engagement of right pVLPFC may reflect the recruitment of visuo-spatial attention, given imaging

data associating right VLPFC activation with visuo-spatial processing and encoding demands (e.g., Awh and Jonides 1998; D'Esposito et al. 1998; Haxby et al. 1995; Kelley et al. 1998; Kirchoff et al. 2000; Wagner 2002).

At present, it remains unclear whether left and right pVLPFC make necessary contributions to episodic encoding of unfamiliar (pseudo-English) and familiar (English) words or whether the fMRI-observed subsequent memory effects reflect correlated, but not necessary, processes. The objective of this TMS study was to directly assess the necessity of these two regions to encoding of novel and familiar words under phonological orienting conditions, using the fMRI data from Clark and Wagner (2003) to guide application of TMS in our subjects. Moreover, although most prior TMS studies have used repetitive TMS to interfere with PFC function at encoding, with one exception (Devlin et al. 2003), here we sought to use single-pulse TMS (spTMS) during learning so as to gain leverage on the temporal-specificity of encoding-related PFC computations.

Information about the putative optimal timing of spTMS application to PFC during phonological processing and episodic encoding comes from event-related potential (ERP) measurements [indexed using electrocorticography, electroencephalography (EEG), and magnetoencephalography (MEG)] that have documented the time-course of PFC computations during stimulus processing and episodic memory formation. Specifically, prior ERP studies, in combination with source modeling, suggest that phonological and/or semantic processes occur at around 400 ms after stimulus onset and are at least partially subserved by left VLPFC (e.g., Halgren et al. 1994a,b, 2002; Marinkovic et al. 2003; Rugg and Nieto-Vegas 1999). Moreover, anatomically constrained MEG data indicate that an N400-like MEG effect is localized to pVLPFC, among other regions (Halgren et al. 2002; Marinkovic et al. 2003). Finally, and perhaps most importantly, ERP subsequent memory effects have been observed to peak at around 400 ms (e.g., Friedman and Trott 2000; Paller et al. 1987; Van Petten and Senkfor 1996), although some data show such effects as early as 200 ms after stimulus onset (Otten and Rugg 2001b). Using current source density, subsequent memory effects during verbal encoding paradigms have been estimated to originate in left VLPFC (Friedman and Johnson 2000). Thus extant data suggest that left VLPFC processes—engaged before and peaking around 400 ms after stimulus onset—are potentially important for memory formation.

Motivated by these prior fMRI and ERP observations, this study used spTMS to examine whether pVLPFC computations during phonological encoding make necessary contributions to learning that supports subsequent memory. Specifically, we adopted a behavioral procedure similar to that in the fMRI study of Clark and Wagner (2003) and used their fMRI-identified pVLPFC foci to test the impact of spTMS to left and to right pVLPFC at encoding on later recognition of English and pseudo-English words. To shed light on the timing of critical PFC computations for encoding, pVLPFC function was transiently disrupted at various poststimulus onset times.

METHODS

Participants

Fourteen right-handed, native speakers of English (7 females; age 18–33 yr), with normal or corrected-to-normal vision, received \$45

¹Due to a typographical error, the coordinates of this focus were incorrectly reported as $-36, 15, 17$ in Clark and Wagner (2003).

for participation. One additional participant was enrolled but requested termination of the experiment before completion; the partial data collected from this participant were excluded from analysis. Informed consent was obtained in a manner approved by the Committee on the Use of Humans as Experimental Subjects at MIT and the Institutional Review Board of the Beth Israel Deaconess Medical Center.

Stimuli

The stimuli consisted of 240 items from each of four classes: two-syllable and three-syllable English and pseudo-English words. For a given subject, the English and pseudo-English words were drawn from the same pool of 960 English nouns. For each word in the pool, a pseudo-English word was generated by replacing one of the consonants in the base word with a randomly generated consonant, maintaining pronounceability. Across subjects, each base English word served as an English and a pseudo-English stimulus an equal number of times.

For counterbalancing purposes, each group of 240 words per class was divided into 24 subgroups of 10 items each, matched for mean word length (7.5 letters) and mean word frequency of the base English word (12.3 occurrences/million; Kucera and Francis 1967). Matching of word length across the two- and three-syllable items ensured that the syllable judgments were necessarily based on phonological, rather than visual, representations. For each subject, each of the 24 subgroups of items was pseudo-randomly assigned (without replacement) to 1 of the 24 stimulation conditions [stimulation onset timing (none, 250, 300, 320, 340, 350, 360, 370, 380, 390, 400, 600 ms) \times PFC hemisphere (left, right)], with the following constraints: 1) across subjects, each item subgroup was assigned to the left and right hemispheres an equal number of times, and 2) across subjects, each subgroup was assigned to a different stimulation onset timing within hemisphere.

Behavioral procedure

The experimental session began with three study phases, during which fMRI-guided spTMS was applied to left or right VLPFC during phonological processing of the four classes of words. Application of spTMS to left or right VLPFC was conducted in an intermixed manner within each study phase (i.e., stimulation was not blocked by hemisphere). Subsequently, following a 15-min retention interval, a recognition memory test was administered without spTMS. Brief practice on the phonological task was conducted immediately before initiation of the three study phases.

During each study trial, a single word was visually displayed and subjects indicated, as quickly and as accurately as possible, whether

the word consisted of two- or three-syllables by pressing one of two response keys under their left hand. Stimulus presentation was preceded by a 400-ms green fixation (+) preparing the subject for stimulus onset. The stimulus was presented for 250 ms, followed by a 750-ms backward mask (#####). The trial ended with an 1,100-ms fixation (+) presented after mask offset (participants had the entire 2,100 ms to respond; Fig. 1A). As described below, spTMS was applied to either right or left PFC at specific poststimulus onset times on subsets of trials, with application to the two foci being intermixed.

For the (nonstimulated) subsequent memory test phase, participants performed a surprise old/new recognition task on all 960 studied words and 480 distractors. Items were presented in a self-paced fashion in 10 blocks of equal size, with a brief break permitted between blocks. For each item, subjects indicated whether the item was encountered during the study phase (OLD) or was unstudied (NEW); when responding OLD, an additional confidence rating was requested (high or moderate). For each word class, items from each of the three study phases were randomly distributed across each of the 10 blocks of the test phase.

fMRI-guided single-pulse TMS

Selection of stimulation targets was guided by prior fMRI measures of subsequent memory effects for English and pseudo-English words (Clark and Wagner 2003). In this prior fMRI experiment, an independent sample of subjects underwent fMRI scanning while performing the identical syllable decision task that was performed by the present sample of subjects who underwent spTMS. The fMRI subsequent memory analyses revealed that regions in bilateral VLPFC, including the posterior portion of inferior frontal cortex (BA 44/9; MNI coordinates of $-36, 15, 27$ and $48, 12, 30$), were differentially engaged during the encoding of items that were subsequently remembered relative to items subsequently forgotten (Fig. 1B). The present spTMS experiment sought to examine whether the mechanisms supported by these VLPFC regions are necessary for effective encoding, and if so, whether there is a differential necessity of the left and right subregions depending on word class (English/pseudo-English) and stimulation onset time (none, 250, 300, 320, 340, 350, 360, 370, 380, 390, 400, 600 ms).

Accordingly, for each subject in this spTMS experiment, high-resolution T1-weighted structural images were acquired and normalized to templates based on the MNI stereotaxic space. Guided by our fMRI data, the posterior portions of left and right ventrolateral PFC (pVLPFC) were targeted (Fig. 1C). Specifically, before stimulation, the PFC voxels corresponding to the two target locations were marked on the subject's normalized structural MRIs, thus identifying the two foci in relation to the underlying anatomy. Using frameless stereotaxy, these target locations were identified based on visual comparison of

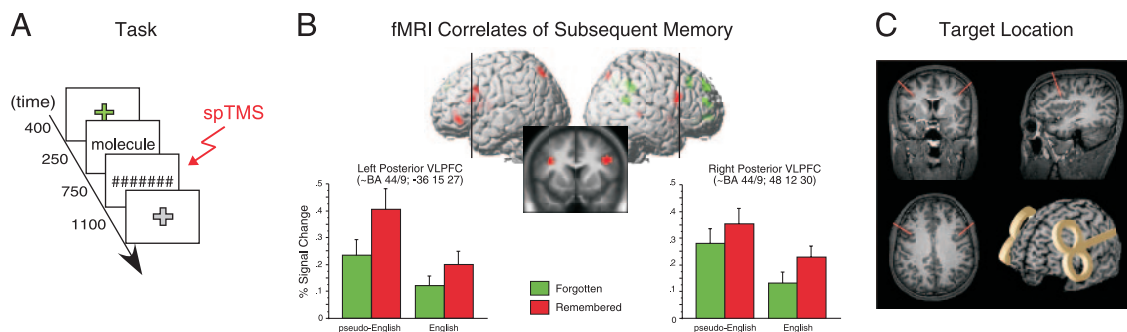


FIG. 1. Phonological encoding task procedure, functional MRI (fMRI) correlates of subsequent memory, and single-pulse transcranial magnetic stimulation (spTMS) target localization. *A*: schematic of encoding trials. Presentation of a pseudo-English (e.g., molecule) or an English (e.g., molecule) word was followed by a visual mask. At different poststimulus onset times, spTMS was applied. *B*: functional maps from Clark and Wagner (2003) depict regions that showed greater activation during words later remembered (collapsed across English and pseudo-English) relative to those later forgotten (red), as well as regions showing the reverse pattern (green). Bar graphs depict the peak percent signal change in left and right posterior ventrolateral prefrontal cortex (pVLPFC). *C*: target locations and placement of the bilateral TMS coils relative to the targets.

the subject's native (nonnormalized) space to the normalized MRIs. Subsequently, the orientations of the TMS coils on the scalp were determined (Paus et al. 1997).

During stereotaxy, a Polaris infrared tracking device (Northern Digital, Ontario, Canada) measured the position of the subject's head. Brainsight Software (Rogue Research, Montreal, Canada) coregistered the subject's native structural MRI with head position. The TMS coils were placed at the stimulation target sites according to the designation on the structural images and maximum field intensity of the coil (Fig. 1C). The coils were placed perpendicular to the central sulcus so that the long axis of the coil roughly paralleled the Sylvian fissure. Distance of target from the center of the figure-of-eight coil (junction of the wings) was 35.8 ± 2.90 and 28.9 ± 4.34 (SD) mm for the left and right targets, respectively, with these distances corresponding to the depths of the targets from the scalp. On first pass, this slight difference in distance from the coil may raise potential concerns that spTMS was less likely to effectively stimulate left pVLPFC. However, two factors suggest that such distance effects, if present, were likely to be minimal. First, for both targets, the maximal stimulation field overlapped with the region of interest as defined by the fMRI experiment (Fig. 1B). Second, in the study of Clark and Wagner (2003), the left pVLPFC region showing a subsequent memory effect extended laterally, such that it included the slightly medial focus ($-36, 15, 27$) explicitly targeted here with spTMS, as well as more lateral foci ($-45, 15, 36$ and $-54, 18, 21$). The present application of spTMS to left VLPFC likely also disrupted these more lateral foci.

On each encoding trial, a TMS pulse was applied to either the left or right pVLPFC (with baseline trials entailing no pulse delivery). As described above, two 70-mm figure-of-eight coils were positioned over bilateral pVLPFC, and stimulation was applied in an intermixed manner (i.e., stimulation was not blocked by onset time or hemisphere) using two Magstim Super-Rapid Transcranial Magnetic Stimulators (2.2-T maximum field strength; Magstim Company, Dyfed, UK). Because an analysis conducted by Robertson et al. (2003) suggested that motor threshold is uncorrelated with effects outside motor cortex, motor threshold was not used to gauge the biological effects in other cortical regions. Rather, a fixed stimulation intensity was adopted for all subjects, with this intensity initially being set to 70% of stimulator maximum output for both coils. Before the study phases, each subject was administered several TMS pulses to each target location. If the stimulation resulted in an uncomfortable sensation or elicited disruptive twitching of the facial muscles, the intensity was reduced in steps of 5% on both coils. Across subjects, stimulation intensities were $67 \pm 3.7\%$ of maximum output, with the lowest intensity set at 60%. Application of spTMS did not lead to overt eye blinking in any subject.

Analysis procedures

TMS-induced changes in accuracy and reaction time (RT) on the syllable judgment task were computed (change = spTMS condition

–no stimulation baseline). Only correct trials were included when computing syllable judgment RTs and when analyzing subsequent memory performance. Response latency analyses were performed on median RTs.

On the subsequent memory test, *probability Hits* (pHits) and *probability False Alarms* (pFAs) were computed 1) collapsed across high and moderate confidence responses and 2) separately by confidence. Because a single index of pFAs was derived for a given word class (English or pseudo-English), the critical subsequent memory measure was change in pHits. Accordingly analyses were performed on the observed changes in pHits and RTs to hits after spTMS.

To determine the effects of stimulation, the change data (collapsed across onset time) were entered into mixed-effect ANOVAs, treating hemisphere (left and right pVLPFC), word class (English and pseudo-English), and confidence rating (medium and high) as repeated measures and subjects as a random effect. To examine possible effects of spTMS relative to the no stimulation baseline, one-sample Student's *t*-tests with hypothesized mean of zero were performed on the change scores, correcting for multiple comparisons (Bonferroni's procedure). To examine possible differential effects of hemisphere according to spTMS onset time, paired Student's *t*-tests were performed (left vs. right) on pHits change scores at each onset time (250, 300, 320, 340, 350, 360, 370, 380, 390, 400, and 600 ms), correcting for multiple comparisons (Bonferroni's procedure). Finally, the change score at each onset time was contrasted with a hypothesized mean of zero.

RESULTS

Baseline subsequent memory performance

Subsequent memory performance for the baseline (no stimulation) condition is displayed in Table 1. Collapsing across confidence, pHits was greater than pFAs for English [$F(1,13) = 13.00, P < 0.005$] and pseudo-English words [$F(1,13) = 7.13, P < 0.05$], showing that subjects discriminated between studied and unstudied items for both word classes. Consideration of confidence levels separately revealed that high confidence pHits were greater than pFAs for both English and pseudo-English words [$F_s(1,13) > 18.24, P_s < 0.001$]. Similarly, medium confidence pHits were moderately but reliably greater than medium confidence pFAs [$F_s(1,13) > 12.30, P_s < 0.005$], when correcting for the opportunity to make such a response (Kahn et al. 2004; Yonelinas and Jacoby 1995). Focusing on pHits, recognition was superior for English than pseudo-English words [overall: $F(1,13) = 5.16, P < 0.05$; high confidence: $F(1,13) = 6.55, P < 0.05$]. Corrected recognition (pHits –pFAs), when computed collapsed across confidence, did not differ across word class ($F < 1$), but was superior for English than for pseudo-English words when

TABLE 1. Baseline (no stimulation) performance on the syllable decision task and on the subsequent memory test

Condition	Syllable Judgments		Subsequent Memory			
	Accuracy	RT	"HC-Old"		"MC-Old"	
			Proportion	RT	Proportion*	RT
English						
Studied	0.85 ± 0.03	784 ± 57.8	0.19 ± 0.05	1546 ± 306.2	0.30 ± 0.03	1253 ± 78.0
Unstudied			0.04 ± 0.02	1451 ± 147.8	0.25 ± 0.04	1371 ± 105.7
Pseudo-English						
Studied	0.82 ± 0.03	828 ± 59.9	0.07 ± 0.03	1795 ± 213.3	0.27 ± 0.03	1390 ± 96.6
Unstudied			0.01 ± 0.01	2390 ± 448.4	0.21 ± 0.05	1500 ± 132.6

Values are means \pm SE. "HC-Old", "High confidence-old"; "MC-Old", "Moderate confidence-old"; RT, reaction time. *Corrected for the opportunity to make such a response.

restricting attention to high confidence responses [$F(1,13) = 8.64, P < 0.05$].

Consideration of RTs at recognition revealed no reliable difference between hits and FAs when collapsing across confidence for both English [$F(1,13) = 1.70, P > 0.1$] and pseudo-English words ($F < 1$). When considering medium and high confidence responses separately, medium confidence responses to hits were reliably faster relative to those to FAs for English words [$F(1,13) = 5.46, P < 0.05$]; a trend to this effect was also observed for pseudo-English words [$F(1,13) = 3.21, P < 0.1$]. High confidence responses, while showing a qualitatively similar pattern, did not reliably differ between hits and FAs [English: $F(1,10) = 2.90, P = 0.12$; pseudo-English: $F(1,7) = 2.72, P = 0.14$]². Focusing on hits, RTs were reliably faster to English relative to pseudo-English words when collapsing across confidence and when focusing on medium confidence responses [overall: $F(1,13) = 6.48, P < 0.05$; medium confidence: $F(1,13) = 9.36, P < 0.01$]; RTs did not differ for high confidence hits to English and pseudo-English words ($F < 1$).

TMS changes in subsequent memory accuracy

Consideration of the impact of spTMS at encoding on subsequent pHits was conducted through analyses on recognition change scores (spTMS – no stimulation baseline). ANOVA on the change scores, collapsed across confidence and spTMS onset time, revealed a reliable main effect of hemisphere [$F(1,13) = 18.57, P < 0.001$]: while modest, subsequent memory was consistently facilitated when spTMS was applied to the right (0.02 ± 0.016 SE) relative to the left (0.00 ± 0.015) pVLPFC during encoding. Although the effect of word class was not reliable ($F < 1$), there was a reliable word class \times hemisphere interaction [$F(1,13) = 6.40, P < 0.05$; Fig. 2A]. Relative to stimulation of left pVLPFC, spTMS to right pVLPFC differentially facilitated encoding of English words [$F(1,13) = 23.45, P < 0.0005$]. The same pattern was obtained when pHits change scores were scored proportionally [(spTMS – baseline)/baseline: right (0.14 ± 0.033), left (0.00 ± 0.032)]. In contrast, there was no differential effect of left versus right stimulation on subsequent memory for pseudo-English words [$F(1,13) = 1.60, P > 0.1$; Fig. 2A]. Again, the same pattern was obtained using proportional scoring: right (0.09 ± 0.045) and left (0.06 ± 0.046). A one-sample one-tailed t -test showed that spTMS to right pVLPFC for English words reliably facilitated subsequent memory relative to the no stimulation baseline [$t(13) = 1.96, P < 0.05$; corrected for multiple comparisons]. Collectively, these results indicate that spTMS to right pVLPFC reliably facilitated encoding for English words relative to both baseline and left pVLPFC stimulation.

Further consideration of the recognition data, sorted by confidence, revealed two interactions with word class (Fig. 2B). First, the confidence \times word class interaction was significant [$F(1,13) = 7.22, P < 0.05$]: spTMS tended to increase the probability of recognizing studied English words with

²The degrees of freedom are lower for the RT analyses separated by confidence because some subjects failed to respond high confidence to studied words (hits) in the baseline condition (no stimulation) and/or to unstudied foils (FAs). Specifically, for pseudo-English words, four subjects had no high confidence hits and three subjects had no high confidence FAs; for English words, three subjects had no high confidence FAs.

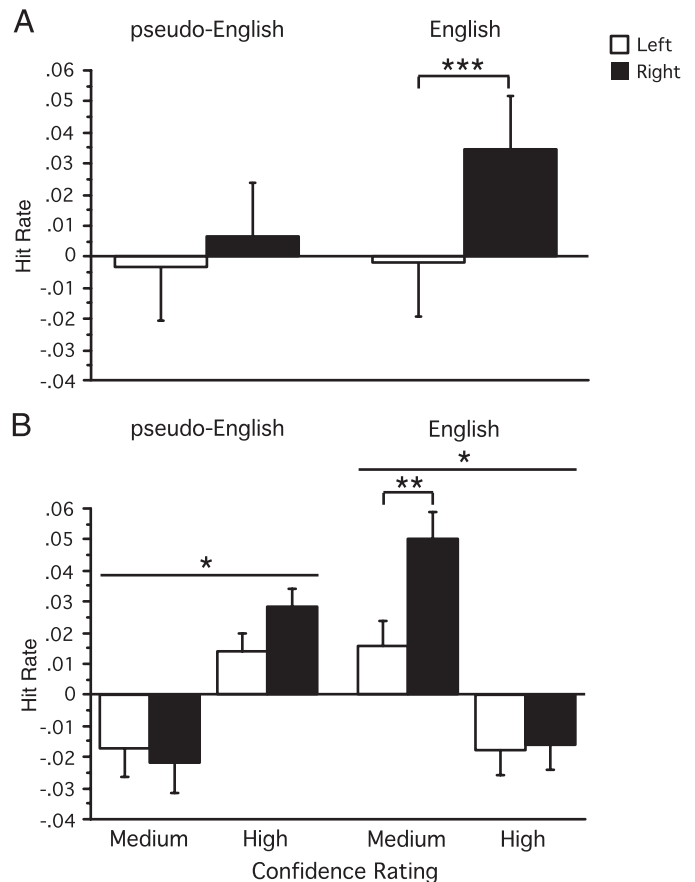


FIG. 2. Consequences of spTMS on subsequent memory performance. Changes in hit rate (spTMS – no stimulation) for pseudo-English and English words following left and right spTMS are displayed. A: collapsed across recognition confidence. B: separately for medium and high confidence responses. In all figures, * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$; error bars in all figures are within-subject SE.

medium (0.03 ± 0.011) relative to high (-0.02 ± 0.013) confidence [$F(1,13) = 4.38, P < 0.1$], whereas the opposite pattern was observed for pseudo-English words [medium: -0.02 ± 0.016 ; high: 0.02 ± 0.009 ; $F(1,13) = 2.92, P > 0.1$]. Second, confidence \times word class \times hemisphere interacted [$F(1,13) = 5.43, P < 0.05$]. Planned contrasts revealed that, for English words, stimulation of right pVLPFC increased medium confidence recognition to a greater extent than did stimulation of left pVLPFC [$F(1,13) = 9.53, P < 0.01$], whereas change in high confidence recognition was unaffected by hemisphere ($F < 1$). Importantly, the increase in subsequent medium confidence recognition differed from the decline in high confidence recognition of English words after both left and right stimulation [$F(1,13) > 8.41, P < 0.05$]. Moreover, the increase in subsequent medium confidence recognition for English words, relative to the no stimulation baseline, was reliable when spTMS was applied to right pVLPFC [$t(13) = 3.38, P < 0.05$; corrected for multiple comparisons]. This pattern has two critical implications: 1) while overall subsequent memory for English words (i.e., pHits) was unaffected by spTMS to left pVLPFC, such stimulation nevertheless had a negative impact on subsequent memory, expressed as a decline in subsequent recognition confidence; and 2) the facilitative effect on subsequent memory for English words after spTMS to right pVLPFC reflected an increase in medium

confidence hits above and beyond the decrease in high confidence hits.

Further unpacking the confidence \times word class \times hemisphere interaction, additional planned contrasts revealed that, for pseudo-English words, neither medium nor high confidence recognition was differentially impacted by stimulation hemisphere [$F_s(1,13) < 1.64$, $P_s > 0.22$]. However, both left and right stimulation yielded a reliable increase in high compared with medium confidence responses [$F_s(1,13) > 7.34$, $P_s < 0.05$]. The increase in high confidence recognition after right stimulation also tended to differ from the no stimulation baseline [$t(13) = 2.02$, $P = 0.03$; uncorrected]. Thus, although overall subsequent memory (i.e., pHits) was unaffected by spTMS, such stimulation facilitated subsequent recognition of pseudo-English words as revealed by an increase in recognition confidence.

The effect of spTMS onset time \times hemisphere was considered separately for English and pseudo-English words, using paired- t contrasts (left vs. right) at each onset time (Fig. 3). For English words, an effect of hemisphere was reliable at 380 ms [$t(13) = 4.83$; $P < 0.005$; corrected for multiple comparisons], with the facilitation effect after right spTMS reliably differing from the inhibitory effect after left spTMS. Supplementary analyses using one-sample one-tailed t -tests revealed that, relative to the no stimulation baseline, spTMS to left pVLPFC at 380 ms resulted in a significant decline in high confidence recognition [$t(13) = 2.54$, $P < 0.05$; corrected for multiple comparisons], whereas such stimulation of right pVLPFC resulted in a significant increase in medium confidence recognition [$t(13) = 2.95$, $P < 0.05$; corrected for multiple comparisons; Fig. 3C]. No other effects of hemisphere were obtained at any of the remaining onset times for English words or for any of the onset times for pseudo-English words, when correcting for multiple comparisons.

TMS-induced changes in subsequent memory RT

Consideration of the impact of spTMS on RTs during recognition revealed that memory decisions for English words ($1,243 \pm 18.9$ ms) were reliably faster relative to those for pseudo-English words [$1,425 \pm 25.2$ ms; $F(1,10) = 22.62$, $P < 0.001$], paralleling the pattern obtained for the baseline conditions. No other main effects or interactions were observed ($P_s > 0.15$). Furthermore, consideration of RT change scores (spTMS – baseline) revealed no reliable main effects or interactions ($P_s > 0.15$). Taken together, these data suggest that spTMS did not have an effect on subsequent memory RT, indicating that the above changes in subsequent memory accuracy did not arise due to a speed-accuracy tradeoff.

TMS-induced changes in encoding task performance

The impact of spTMS on performance accuracy in the syllable decision encoding task was assessed through analyses on proportion-correct change scores (spTMS – baseline; Fig. 4A). ANOVA on these change scores, collapsed across spTMS onset time, revealed a main effect of hemisphere [$F(1,13) = 5.06$, $P < 0.05$], with there being a small, but consistent improvement in performance when spTMS was applied to right (0.01 ± 0.01) relative to left (0.00 ± 0.01) pVLPFC. The main effect of word class and the hemisphere \times word class interaction was not significant [$F_s(1,13) < 1.24$, $P_s > 0.29$].

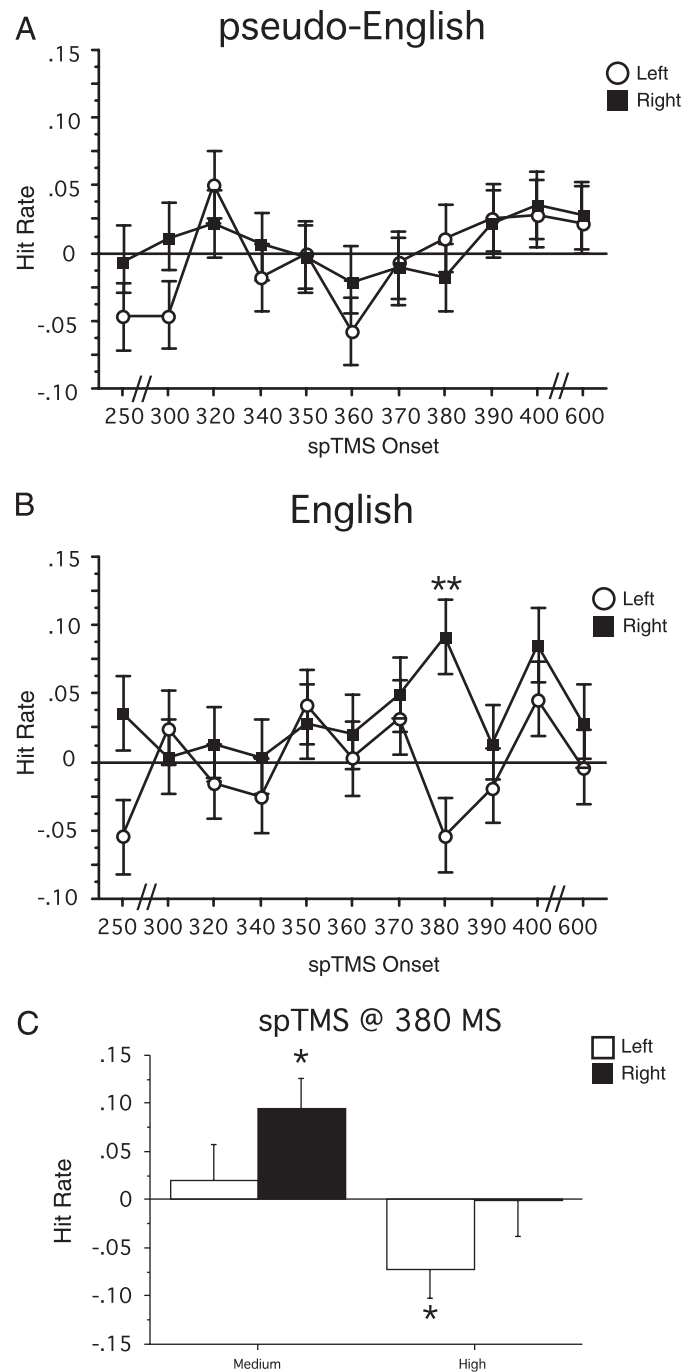


FIG. 3. Time-specific influence of spTMS on subsequent memory performance. Changes in hit rate as a function of poststimulus onset of spTMS to left or right pVLPFC are displayed for (A) pseudo-English and (B) English words. C: changes in medium and high confidence hits after spTMS at 380 ms after stimulus onset are shown for English words.

The effect of spTMS onset time \times hemisphere was considered separately for each word class, using paired- t contrasts at each onset time (Fig. 4B). For English words, an effect of hemisphere was reliable at 340 ms [$t(13) = 3.47$, $P < 0.05$; corrected for multiple comparisons] with a facilitation effect after right spTMS reliably differing from a null effect after left spTMS. For pseudo-English words, a similar pattern was observed at 340 ms [$t(13) = 3.48$, $P < 0.05$]. Supplementary analyses revealed that both English and pseudo-English words

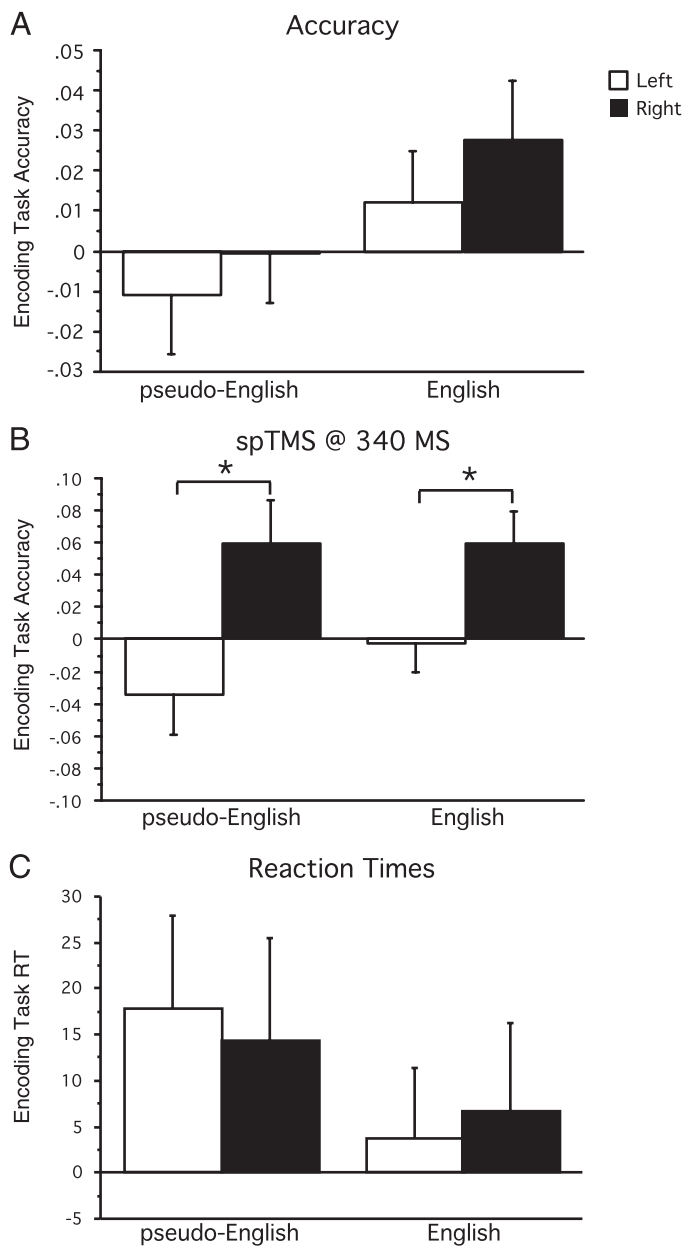


FIG. 4. Consequences of spTMS on phonological task performance. *A*: collapsed across poststimulus onset times, change in overall accuracy when phonological task performance was accompanied by left or right stimulation is depicted. *B*: change in task accuracy is depicted when spTMS was applied at 340 ms after stimulus onset. *C*: collapsed across spTMS onset times, change in reaction time (RT) to make accurate phonological (syllable) decisions is displayed.

were reliably facilitated relative to the no stimulation baseline when spTMS was applied to right pVLPFC at 340 ms [$t(13) > 2.17$, $P_s < 0.05$; corrected for multiple comparisons]. No other effects of hemisphere were obtained at any of the remaining onset times for English or pseudo-English words when correcting for multiple comparisons.

Consideration of the impact of spTMS on RTs during correct syllable decision responses at encoding was conducted on RT change scores (spTMS – baseline; Fig. 4*C*). ANOVA on the RT change scores, collapsed across spTMS onset time, revealed no reliable main effects or interactions ($F_s < 1$). Moreover, consideration of the effect of hemisphere at each

onset time revealed no reliable differences for English and for pseudo-English words. Thus spTMS did not reliably affect RTs at encoding arguing against a speed-accuracy tradeoff interpretation of the changes in encoding task accuracy and against a time-on-task interpretation of the effects of spTMS at encoding on subsequent memory performance.

DISCUSSION

This study assessed the contribution of left and right pVLPFC to the formation of episodic memory for phonologically processed stimuli. Transient disruption of pVLPFC during phonological encoding revealed four important outcomes. First, subsequent memory for familiar (English) words was impaired by disruption of left pVLPFC, expressed as a decline in subsequent recognition confidence (Fig. 2*B*). As noted below, these effects of left pVLPFC stimulation on subsequent memory for familiar words depended on stimulation onset time (Fig. 3*B*). Second, disruption of right pVLPFC facilitated overall memory performance for familiar words, predominantly by boosting medium confidence responses, and also facilitated subsequent recognition of unfamiliar (pseudo-English) words, expressed as an increase in recognition confidence. Third, differential contributions of left and right pVLPFC to encoding of familiar words were strongest at 380 ms, as revealed by a decline in subsequent high confidence recognition when left pVLPFC was disrupted and an increase in subsequent medium confidence recognition when right pVLPFC processing was disrupted. Finally, encoding task accuracy was facilitated by disruption of right pVLPFC, with the effect being strongest at 340 ms for both familiar and unfamiliar words. Collectively, these data indicate that pVLPFC computations during phonological processing of familiar and, to a more limited extent, of novel words influence episodic encoding, as evidenced by a change in subsequent memory performance when these regions are disrupted during learning.

Left posterior VLPFC contributions to episodic encoding

Extensive evidence regarding the role of left VLPFC in stimulus processing suggests that there is a functional dissociation between aVLPFC and pVLPFC, with one characterization of this dissociation emphasizing distinctions between semantic and phonological computations (e.g., Fiez 1997; Poldrack and Wagner 2004). Previously reported correlations between activity levels in these regions and subsequent memory performance suggest that both regions make important contributions to episodic encoding (e.g., Baker et al. 2001; Clark and Wagner 2003; Davachi et al. 2001; Kirchoff et al. 2000; Otten et al. 2001; Wagner et al. 1998b). Recent TMS studies that have targeted disruption of aVLPFC further indicate that this region is necessary for intact semantic processing of stimuli and for the effective creation of episodic memory traces, as evidenced by changes in subsequent memory behavior (Devlin et al. 2003; Floel et al. 2004; Kohler et al. 2004).

This study provides new evidence that, as with left aVLPFC engagement during semantic processing, left pVLPFC appears to make necessary contributions to episodic encoding during phonological processing. First, spTMS to left pVLPFC resulted in an overall decline in subsequent recognition confidence for familiar words. That is, although overall recognition rates

remained unchanged, disruption of this region resulted in impoverished or weaker memory traces. Second, spTMS applied at 380 ms after stimulus onset resulted in a decline in overall subsequent recognition of familiar words (including a decline in high confidence recognition), suggesting that the left pVLPFC-mediated processes that impact memory formation appear to be brought on-line at approximately this time. The observed timing of these disruptive effects during memory encoding corresponds with evidence from electrophysiological studies suggesting that left VLPFC is engaged at around 400 ms during tasks eliciting phonological and/or semantic processing (e.g., Halgren et al. 1994a,b, 2002; Marinkovic et al. 2003; Rugg and Nieto-Vegas 1999) and episodic encoding (e.g., Friedman and Trott 2000; Otten and Rugg 2001b; Paller et al. 1987).

It is worth noting that the observed disruption of subsequent memory performance for familiar words was not accompanied by changes in performance on the incidental-encoding task, suggesting that encoding-related consequences of PFC function are more susceptible to disruption or are dissociated in time from language-related (phonological) processes. One possibility is that the negative consequence of left pVLPFC stimulation for encoding reflects an indirect disruption of other regions within the network—e.g., medial temporal structures—although because only a single pulse of TMS was applied, such *trans*-synaptic disruption is not likely to best account for this pattern (Chouinard et al. 2003; Paus 1999). Alternatively, the asymmetry in the consequence of left pVLPFC disruption for encoding, relative to the absence of an effect on phonological task performance, may reflect a disruption of functional coupling between PFC and other regions. For example, disruption of PFC coupling with posterior brain structures could impair the nature of the inputs to the medial temporal memory system, including disrupting cortical-medial temporal synchronization that is known to correlate with effective encoding (e.g., Fell et al. 2001; Kirk and Mackay 2003). While speculative, such a mechanistic account would be consistent with the observed differential negative consequence of left pVLPFC disruption for encoding.

Left posterior VLPFC and the encoding of novel words

Functional neuroimaging studies using visually presented unfamiliar (pseudo-English) relative to familiar (English) words support a putative role of left pVLPFC in subserving phonological control processes that may activate stored orthographic-to-phonological mappings (e.g., Clark and Wagner 2003; Poldrack et al. 1999; Tagamets et al. 2000) and may guide the assembly of novel phonological word units from these activated representations (e.g., Clark and Wagner 2003; see also, Coltheart et al. 1985). Based on neuropsychological and behavioral evidence, Baddeley et al. (1998) hypothesized that the phonological working memory system—which partially depends on left pVLPFC—is differentially more important for episodic encoding of novel than familiar word forms. For example, neural insult that disrupts phonological working memory leads to impaired word-nonword associative learning but leaves word-word learning relatively intact (Baddeley 1993; Baddeley et al. 1988). Seemingly consistent with this perspective, Clark

and Wagner (2003) observed that fMRI measures of encoding activation in left pVLPFC were differentially predictive of subsequent memory for pseudo-English than for English words. Accordingly, it was anticipated that spTMS to left pVLPFC would differentially disrupt subsequent memory for unfamiliar relative to familiar words.

Although the present findings point to reliable negative consequences of left pVLPFC disruption for the encoding of familiar words, this effect was not accompanied by a comparable or greater effect for unfamiliar (pseudo-English) words. Thus our data cannot be interpreted to provide support for the perspective that this component of the phonological processing system is differentially critical for the encoding of unfamiliar words. In fact, the consequences of left pVLPFC disruption for pseudo-English word processing and subsequent memory were limited in nature, and, if anything, were counter to this prediction. Specifically, while overall recognition accuracy was unaffected, left pVLPFC stimulation facilitated subsequent recognition of pseudo-English words, as revealed by a modest increase in recognition confidence. Moreover, the absence of an effect of left pVLPFC disruption on overall recognition rates for pseudo-English words differed from the overall decline in recognition of English words when left pVLPFC was disrupted at 380 ms. Interpretive caution is warranted, however, as this failure to observe a reliable change in overall subsequent memory for unfamiliar words may stem from the lower level of memory performance for the pseudo-English relative to the English stimuli in the baseline condition, thus perhaps making it difficult to detect downward changes in performance. Accordingly, future studies are needed to further clarify whether there is a differential role of left pVLPFC in encoding novel words.

Right posterior VLPFC contributions to episodic encoding

Functional neuroimaging studies of episodic encoding have observed a consistent pattern, wherein verbal stimuli tend to preferentially engage left pVLPFC and nonverbal stimuli tend to engage right pVLPFC (e.g., Brewer et al. 1998; Kelley et al. 1998; Kirchoff et al. 2000; Wagner et al. 1998a). Such studies are consistent with the suggestion that VLPFC regions contribute to the maintenance of representations in working memory in the course of goal-directed action (e.g., Owen et al. 1996; Petrides 1994), and have led to the hypothesis that left and right pVLPFC differentially mediate control processes that support access to and maintenance of phonological and visuo-object/visuo-spatial representations, respectively (e.g., Awh and Jonides 1998; Wagner 1999). Within this context, Clark and Wagner (2003) observed that the magnitude of the subsequent memory effect in right pVLPFC was equivalent for unfamiliar and familiar words, raising the possibility that phonological task performance elicits engagement of visuo-spatial attention that impacts encoding.

On their surface, these data support the suggestion derived from neuroimaging results that right pVLPFC mechanisms influence episodic encoding, as the largest mnemonic effects of spTMS followed disruption of this region. First, spTMS to right pVLPFC reliably facilitated encoding of both pseudo-English and English words. Second, this

facilitative effect on subsequent memory for English words was revealed as an increase in medium confidence hits above and beyond a decrease in high confidence hits. Third, at 380 ms after stimulus onset, spTMS to right pVLPFC facilitated subsequent memory as expressed through an increase in medium confidence hits. Collectively, these results suggest that, in contrast to disruption of left pVLPFC, the transient disengagement of right pVLPFC facilitates the encoding of verbal material.

Recently, in a study of semantic processing and subsequent memory, Kohler et al. (2004) observed facilitated subsequent memory after repetitive TMS to left aVLPFC relative to stimulation of control sites in right aVLPFC and left superior parietal cortex. Interestingly, RTs to make correct semantic decisions during encoding were reliably slower under left aVLPFC stimulation than in the two control conditions, and there was a similar trend for improved encoding task accuracy with left aVLPFC disruption. Kohler et al. (2004) argued that left aVLPFC disruption during semantic processing led to enhanced item distinctiveness as a result of the transient processing interruptions produced by the TMS pulse trains. According to this perspective, interruption of left aVLPFC processes necessitated partial reanalyses and further stimulus elaboration, with the consequence being increments in subsequent memory performance. Importantly, these results highlight that TMS disruption of PFC function may, at times, facilitate episodic encoding.

How might we understand the beneficial consequences of disrupting right pVLPFC for encoding? One possibility is that these beneficial effects reflect a generalized processing facilitation that accompanies stimulation of any region that is not required for effective encoding. From this perspective, the consequences of right pVLPFC stimulation are not specific to this region, but rather may have been obtained if an additional control site (other than left pVLPFC) were disrupted during encoding. Although possible, it is worth noting that the disruption of right pVLPFC resulted in facilitation relative to both disruption of left pVLPFC and the no stimulation baseline, with these consequences being temporally focused. Moreover, prior studies applying repetitive TMS to control sites beyond PFC (e.g., parietal cortex) during encoding have failed to obtain evidence for such a generalized facilitation of encoding (e.g., Kohler et al. 2004).

Alternatively, building on prior arguments regarding the putative role of right VLPFC in visuo-spatial attention, the facilitative effect of right pVLPFC disruption may reveal that there is sometimes an encoding benefit of diminished allocation of visuo-spatial attention to stimulus form (in the present case, orthographic features). Although speculative, disengagement of these mechanisms may shift processing demands such that greater emphasis is placed on left pVLPFC mechanisms that activate and assemble phonological representations. Consistent with this possibility, in contrast to the absence of an effect of left pVLPFC stimulation on phonological task performance, disruption of right pVLPFC at 340 ms facilitated the accuracy of phonological decisions about familiar and unfamiliar words. In this manner, disruption of right pVLPFC—which may support correlated (but not necessary) processes that are engaged during phonological processing—facilitates the encoding of the target phonological information in episodic

memory by triggering a processing shift to reliance on more effective verbal learning mechanisms.

In summary, these findings constitute the first demonstration that transient disruption to neural processes localized to pVLPFC impacts the formation of episodic memory. The current results converge with extant evidence from fMRI and EEG/MEG, suggesting that the processes subserved by left pVLPFC are brought on-line at around 300–400 ms in the service of phonological processing and that such processes influence the likelihood or extent to which the event will be effectively encoded in episodic memory. These data also highlight the use of integrated TMS-fMRI approaches, because they show that right pVLPFC regions that show correlated activation during phonological processing that predicts subsequent memory may not be necessary for the encoding of such memories. Rather, disengagement of these correlated processes may elicit a functional shift that has facilitative consequences for memory. These data add to a growing literature highlighting the relation between cognitive control processes and episodic memory formation and the putative interaction between multiple forms of memory (e.g., Braver et al. 2001; Davachi et al. 2001; Wagner et al. 2001). As such, the present data show that, while PFC lesions do not result in dense amnesia, nevertheless PFC cognitive control mechanisms make necessary contributions that modulate the effective building of memories such that experience can be subsequently remembered.

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