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Computer-Mouse Tracking Reveals TMS Disruptions of Prefrontal Function During Semantic Retrieval

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Hindy NC, Hamilton R, Houghtling AS, Coslett HB, Thompson-Schill SL. Computer-mouse tracking reveals TMS disruptions of prefrontal function during semantic retrieval. *J Neurophysiol* 102: 3405–3413, 2009. First published October 7, 2009; doi:10.1152/jn.00516.2009. Converging evidence from neuroimaging and neuropsychological studies is essential for understanding human frontal cortical function. We introduce a new method for studying the effects of transient disruptions of frontal activity during transcranial magnetic stimulation (TMS). Using a novel combination of TMS and computer-mouse tracking, through two experiments we tested process models of semantic competition in left ventrolateral prefrontal cortex (VLPFC). On TMS stimulation of left mid-VLPFC just after presentation of an ambiguous stimulus, participants' mouse-movement trajectories deviated more toward the incorrect target for weak associate trials than for any other trial type. This effect was extinguished when participants were simultaneously shown both target and cue stimuli. Results suggest that left mid-VLPFC is necessary to resolve semantic competition when a response is underdetermined by the stimulus and the interpretive context of the stimulus is ambiguous. Computer-mouse movements reveal the dynamics of competitive interactions as they resolve, making this technique ideally suited for studying cognitive control processes and a more sensitive index of TMS disruption than reaction time and accuracy alone.

INTRODUCTION

Tracking computer-mouse movements is a precise measure of motor output that has recently emerged as a new window on cognitive processing. Most transcranial magnetic stimulation (TMS) studies to date have used reaction time and accuracy as dependent measures of stimulation effects and some have reported speed–accuracy interactions that can be difficult to interpret (cf. Cacioppo et al. 2007). Because computer-mouse tracking convolves reaction time and accuracy into a single index of cognitive function, while retaining precise temporal information about the decision process, this technique is particularly appropriate for investigating the speed–accuracy interactions often found with TMS.

Arm movements are continually adjusted as a person reaches for an object (Goodale et al. 1986). By measuring the time course of a participant's response during TMS, computer-mouse tracking exploits the nonballistic nature of these arm movements. Just as saccadic eye movements have been used to assess parallel activation of competing representations during, for example, sentence comprehension (e.g., Tanenhaus et al. 1995), computer-mouse movements can provide a continuous, on-line measure of cognitive processing. Moreover, whereas inevitable facial muscle contractions make measures such as eye-tracking difficult during frontal stimulation, computer-mouse tracking is exceptionally well suited for TMS. Recent behavioral studies using computer-mouse tracking demonstrate that the graded manual output reflected in the computer-mouse trajectory reveals the temporal dynamics in cognitive processes of spoken word recognition (Spivey et al. 2005), semantic categorization (Dale et al. 2006), ambiguity resolution in interpreting garden-path sentences (Farmer et al. 2007), and task switching (Hindy and Spivey 2008). In each of these studies, streaming x, y coordinates obtained from the mouse movements reveal the graded spatial attraction of a participant's arm movements toward target and distractor stimuli.

In the current study, we apply this technique to a recent debate regarding conceptual cognitive control processes in left prefrontal cortex. This debate began with a demonstration that activity in the left ventrolateral prefrontal cortex (VLPFC) during semantic retrieval is modulated by the cognitive control demands of the task (Thompson-Schill et al. 1997) and that this region is necessary for resolving semantic competition. Across three task manipulations, including verb generation, object classification, and object comparison, increases in competition were accompanied by an increase in left VLPFC activity compared with trials in which there was a single dominant response. Each manipulation contrast in study reported by Thompson-Schill et al. (1997) had a unique pattern of activation, but activation in all three contrasts overlapped in left mid-VLPFC. Wagner and colleagues (2001) showed that a fourth task manipulation, which involved varying the association strength among stimuli, also predicted neural activation in left VLPFC. [Note that although Wagner et al.'s interpretation of the association strength effect is sometimes seen as an alternative to a model that involves the resolution of conceptual competition, we have argued that both involve biased competition (Thompson-Schill and Botvinick 2006).]

Drawing on ideas developed by Thompson-Schill et al. (1997) and Wagner et al. (2001), Badre and colleagues (2005) proposed a two-process model of left VLPFC function (see also Badre and Wagner 2007). Badre and colleagues reported a double dissociation between *controlled retrieval* of semantic information in left anterior VLPFC (Brodmann area 47 [BA47]) and *postretrieval selection* among semantic alternatives in left mid-VLPFC (BA45). In their framework, postretrieval selection is a general-purpose control mechanism necessary when there are multiple active representations and task-irrelevant knowledge must be ignored. Controlled re-

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trieval is a top-down bias signal necessary when semantic representations are underdetermined by the stimulus. Henceforth, we will refer to these putative processes (i.e., controlled retrieval and postretrieval selection) by the manipulations that Badre et al. (2005) developed to experimentally isolate them (i.e., "association strength" and "congruency," respectively).

We evaluated predictions of this two-process model in the current investigation by attempting to independently disrupt each process with brief-train TMS, as measured by computer-mouse tracking. In two experiments, we separately manipulated association strength and congruency using the same stimuli that Badre et al. (2005) used to establish the left VLPFC two-process model with functional magnetic resonance imaging (fMRI). In trials that varied in association strength, the participant's task was to click the target most semantically related to the cue. According to the model of Badre et al. (2005), when the correct target is a strong associate of the cue, there should be very little demand for controlled retrieval of semantic knowledge. Bottom-up activation should quickly bias the participant's internal representation of the task and the correct target should become immediately obvious. When the correct target is a weak associate, there is no prepotent response, and thus controlled retrieval should be needed to bias the activation of relevant knowledge.

In trials that varied in congruency, participants were instructed to click the target that matched the cue with respect to an individual specified feature (color, shape, size, or texture). For congruent trials, the correct target matched the cue along the specified dimension *and* was a strong semantic associate of the cue. As with strong associate trials, bottom-up activation should be sufficient to correctly answer congruent trials. For incongruent trials, the correct target matched the cue along the specified feature, but was otherwise unrelated, whereas the distractor was a strong semantic associate of the cue. According to Badre et al. (2005), because task-irrelevant knowledge is automatically retrieved and must be ignored, incongruent trials should require postretrieval selection. Following from Badre et al. (2005), the stimuli that composed these trials were not the same as those that composed the association strength manipulation trials, a point that will be addressed at some length in the following text. Figure 1 shows representative trials of each condition.

If dissociable cognitive control processes subserved by distinct regions of left VLPFC are necessary to resolve competition created by each task, the mouse movements should reveal an interaction between trial condition and region of stimulation. Mouse-movement deviations toward the competitor during weak associate and incongruent trials should be exacerbated by stimulation of left VLPFC. For strong associate trials and congruent trials, stimulation of left VLFPC should have no effect on participants' motor responses because these trials do not demand cognitive control.

In *experiment* 1, participants received brief-train TMS at left anterior VLPFC, left mid-VLPFC, or a control site in right anterior VLPFC. In *experiment* 2, participants received brief-train TMS at left mid-VLPFC or the control site. We chose right anterior VLPFC as the control site for both experiments because stimulation of this region produces similar nonspecific TMS effects—particularly facial muscle contractions—as does TMS of the left VLPFC sites of interest. We will return to possible consequences of selecting right anterior VLPFC as a control stimulation site in the DISCUSSION.

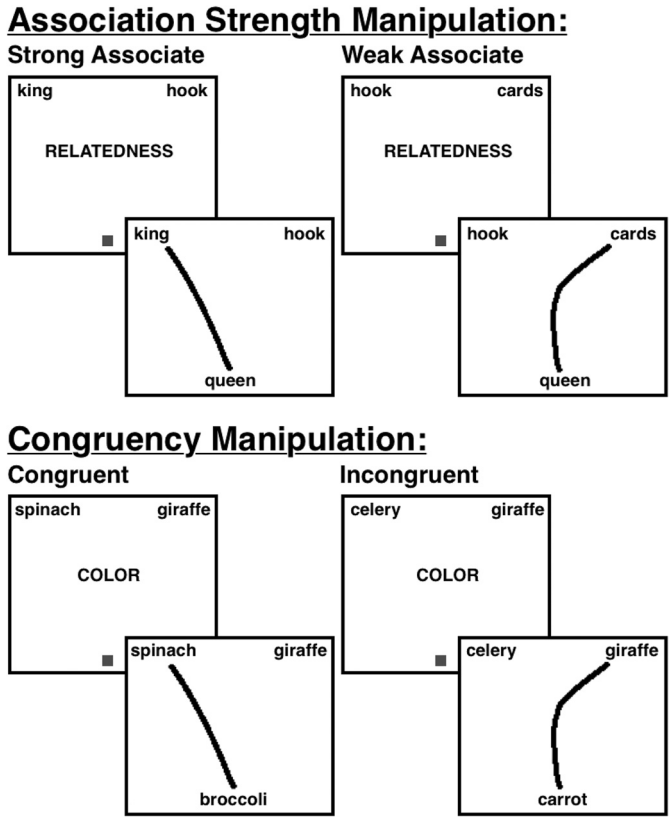

FIG. 1. Example trials of each experiment 1 condition, each with a hypothetical mouse trajectory to the correct target.

In the fMRI studies reported in Badre et al. (2005), participants viewed all stimuli (cue, targets, and sorting dimension) at once during each trial. To adapt this paradigm to TMS, in which transient cortical stimulation must be time-locked with the process of interest, we performed two separate experiments that differed only in the timing of stimulus presentation within each trial. In each experiment, participants viewed three of the four stimuli before stimulation and received TMS on presentation of the critical fourth word. As shown in Fig. 1, *experiment* 1 participants were shown the target stimuli (e.g., "hook" and "cards") for each trial *before* seeing the cue stimulus for that trial (e.g., "queen"). On presentation of the cue stimulus, participants received brief-train TMS at left anterior VLPFC, left mid-VLPFC, or the control site. In *experiment* 2, participants were shown both target and cue stimuli concurrently before TMS and received brief-train TMS on presentation of the sorting rule. As we subsequently demonstrate, the order of stimulus presentation was decisive in determining the participant's experience of each trial and the effect of brief-train TMS on their performance.

METHODS

Experiment 1

PARTICIPANTS. Fifteen right-handed native English speakers (four males, ages 18–29 yr) participated in a non-TMS version of *experiment* 1. Twelve right-handed native English speakers (five males, ages 20–29 yr) participated in a TMS version of *experiment* 1. Non-TMS

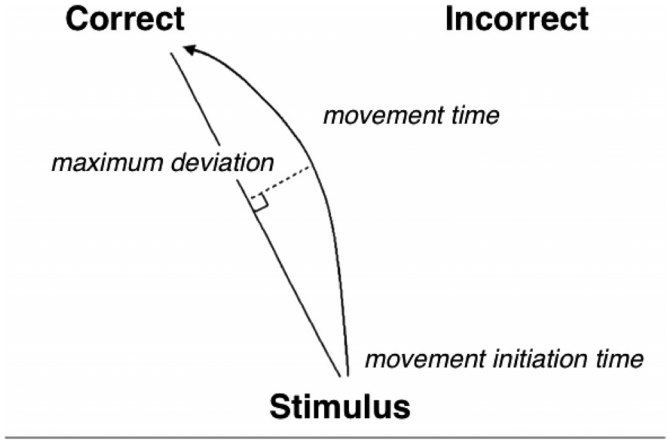

FIG. 2. Mouse-movement dependent measures, with a hypothetical mouse trajectory to the correct target.

participants were paid $10 for each of two sessions; TMS participants were paid $40 for each of two sessions. TMS participants were recruited from fMRI studies at the Center for Cognitive Neuroscience, University of Pennsylvania. All participants gave informed consent as approved by the University of Pennsylvania Institutional Review Board.

DEPENDENT MEASURES. Streaming x, y mouse coordinates were recorded in 20-ms increments, starting with each participant's click of the trial initiation button and ending with the final click on one of the upper-corner targets. Accuracy was recorded for each trial. For correct trials, the primary dependent measure of interest was the maximum perpendicular pixel deviation toward the distractor, between the mouse-movement trajectory and an assumed straight line connecting start and end clicks. The maximum deviation measurements were derived directly from the raw time-stamped cursor coordinates. In addition to accuracy and maximum deviation, two separate time measurements were collected for each trial. Movement initiation time was computed as the number of milliseconds from display onset to when the participant moved the cursor >10 pixels outside the 15^2-pixel trial initiation button. Once the participant moved the mouse outside this trial-initiation window, movement time was calculated as the number of milliseconds between the end of movement initiation time and the final click of the target object. Figure 2 shows a diagram of the dependent measures.

STIMULUS MATERIAL. Stimuli were selected from the stimulus sets used in Badre et al. (2005). This subset of stimuli was equated for word length across all conditions. As in Badre et al. separate stimulus sets were used for the association strength manipulation and congruency manipulation. Because of constraints on stimulus norming, there was a significant difference in frequency of use between these two stimulus sets, such that stimuli used for the association strength manipulation had, on average, a higher frequency index than did stimuli used for the congruency manipulation (Kučera and Francis 1967). Association strength and congruency stimulus sets also differed in their concreteness. Although all congruent and incongruent stimuli were concrete nouns, weak associate and strong associate stimuli contained some abstract words. (Note that this difference in concreteness was due to Badre et al.'s constraints in assembling the stimulus sets such that congruency stimuli could be matched according to their color, shape, size, or texture, whereas association strength stimuli had to have both a distinctly weak associate and a distinctly strong associate.)

Stimuli for the association strength manipulation included 96 cue words, each associated with both one strong associate target word and one weak associate target word. Based on single-response free-association norms (Moss and Older 1996; Postman and Keppel 1970), the mean normative probability that a strong associate word was generated in response to the cue (0.25) was about 25-fold higher than the mean probability that a weak associate was generated in response to the same cue (0.01). Stimuli for the congruency manipulation included 96 cue words, each with one associated and one unassociated target word. Based on the single-response free-association norms, the mean normative probability that an associated target word was generated for its respective cue (0.22) was approximately equal to the association strength of the strong associates in the association strength manipulation. Unassociated targets in the congruent and incongruent conditions were never generated as associates of the corresponding cue words (0.00).

The experiment was programmed using E-Prime (Psychology Software Tools, Pittsburgh, PA) and run on a laptop computer with a wireless optical mouse.

PROCEDURE. Each participant came into the lab for two sessions, spaced 3 to 7 days apart.[1] Participants sat upright in front of the computer screen, controlling the computer mouse with their right hand. As in Badre et al. 2005, association strength trials and congruency trials of each sorting dimension were blocked by trial type. Each TMS participant sat with his or her head in a chinrest to restrict movement and wore earplugs to reduce noise from coil stimulation. There were 96 trials in both sessions; participants were not stimulated on practice trials. In each session, TMS was delivered to either the left mid-VLPFC or left anterior VLPFC on 64 of the trials and the control site was stimulated on 32 trials. The order of site stimulation was fully counterbalanced, such that half of the participants were stimulated at left mid-VLPFC during session one and left anterior VLPFC during session two and half of the participants in the opposite order. Also, within each session, half of the participants were stimulated at the control site first and half of the participants at the left VLPFC site first. Figure 3 shows the two left VLPFC stimulation sites marked on a three-dimensional model of a participant's brain.

Association strength and congruency were separately manipulated (see Fig. 1). At the start of each trial, two target words appeared in the top corners of the screen. Whether a particular target word appeared on the left- or right-hand side of the screen was randomized. At the center of the screen, a sorting rule (related, color, shape, size, or

[1] Because of a technical complication with the E-Prime script during the second session of one participant, this participant came into the lab for a third session the following day to perform the task during control site stimulation. This complication did not affect counterbalancing in the order of site stimulation.

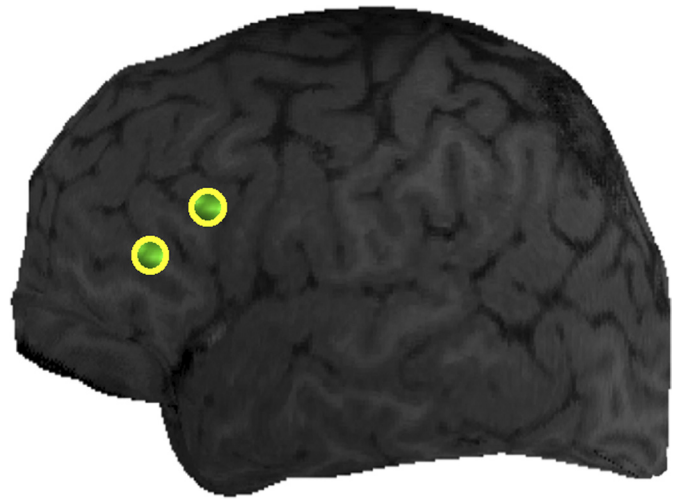

FIG. 3. Example 3-dimensional model of each participant's brain. The green and yellow spheres mark the 2 left ventrolateral prefrontal cortex (VLPFC) stimulation sites, left mid-VLPFC, and left anterior VLPFC.

texture) indicated the relevant sorting dimension. After 4 s, a 15^2-pixel button appeared at the bottom center of the screen. When participants clicked this button, a cue word appeared at the bottom center of the screen, in place of the trial initiation button. Thus the onset asynchrony between the appearance of the two targets and sorting rule and the subsequent appearance of the cue word was determined by the participant for each trial but was always ≥4 s.

On-line repetitive TMS was separately administered to each of the three stimulation sites, using a Magstim Rapid magnetic stimulator, fitted with a 70-mm figure-eight air-cooled coil (Magstim, Whitland, UK). The resting motor threshold (MT)—the minimum intensity required to produce a motor-evoked potential—was determined for each participant by stimulating over the hand area of motor cortex and adjusting the machine output until a visible response of the participant's hand was identified on <50% of trials (mean = 57.08% of maximum stimulator output, SD = 4.80, uncorrected for scalp–cortex distance). Across participants, the average scalp–cortex distance was 12.83 mm (SD = 2.32) for left mid-VLPFC, 12.50 mm (SD = 2.67) for left anterior VLPFC, and 12.66 mm (SD = 1.81) for the control site (right anterior VLPFC). There were no reliable differences among the target sites in scalp–cortex distance (all P values >0.1).

Previously obtained structural MRI scans, along with anatomical landmarks and Talaraich coordinates specified in Badre et al. (2005), were used to localize each region of stimulation. Each participant's structural MRI was coregistered with the location of the participant's head using a Polaris infrared tracking system (Northern Digital, Waterloo, Canada) and Brainsight Software (Rogue Research, Montreal, Canada). Anatomical landmarks used for locating left mid-VLPFC, pars triangularis, included the inferior frontal sulcus and insular sulcus. Anatomical landmarks used for locating left and right anterior VLPFC, pars orbitalis, included the horizontal ramus of the lateral fissure and the orbital gyrus. Across participants, the average distance between left mid-VLPFC and left anterior VLPFC targets was 27.81 mm (SD = 8.43). Each stimulation site was marked and saved on the structural MRI prior to the initial TMS session, thus ensuring that the coil's position was identical across sessions. The coil was held tangentially to the scalp, such that the coil wings intersected directly above the cortical target, and was secured in place with a mechanical arm, connected to a metal frame. By 100 ms after stimulus onset for each trial, participants received three pulses at a frequency of 10 Hz at 100% MT.

Experiment 2

Stimulus materials and dependent measures used in *experiment* 2 were identical to those used in *experiment* 1. *Experiment* 2 included a separate group of participants and varied from *experiment* 1 in its procedure as detailed in the following text.

PARTICIPANTS. Ten right-handed native English speakers (five males, ages 20–31 yr) participated in *experiment* 2.

PROCEDURE. Each participant came into the lab for two sessions, spaced 3 to 7 days apart. Participants received TMS on 96 trials in each experimental session. Left mid-VLPFC was stimulated on 48 of the trials and the control site was stimulated on 48 trials. (Because there were no effects of left anterior VLPFC stimulation in *experiment* 1, we restricted our procedure to left mid-VLPFC in *experiment* 2, which allowed us to increase the number of trials in each condition given the limitation on the number of stimulation trials permitted daily.) For each trial, participants received three pulses of 10-Hz TMS at 100% of MT (mean = 55.00% of maximum stimulator output, SD = 7.54, uncorrected for scalp–cortex distance). Across participants in *experiment* 2, the average scalp–cortex distance was 12.87 mm (SD = 1.95) for left mid-VLPFC and 12.82 mm (SD = 2.17) for the control site (right anterior VLPFC). The difference between the target sites in scalp–cortex distance did not approach significance (P = 0.95). The order of site stimulation was counterbalanced, such that five participants were stimulated at left mid-VLPFC first and the control site second for session one, and then the control site first and left mid-VLPFC second for session two. The remaining participants had the opposite order of stimulation. TMS parameters were the same as those in *experiment* 1.

Experiment 2 differed from *experiment* 1 in two important respects. *1*) In *experiment* 1, the sorting rule appeared along with the two target words, and the participant clicked the initiation button to see the cue word; in *experiment* 2 the cue word appeared on the screen with the two target words and the participant clicked the initiation button to see the sorting rule. The onset asynchrony between the appearance of the two targets and the cue word—and the subsequent appearance of the sorting rule—was determined by the participant for each trial but was always ≥4 s. *2*) In *experiment* 1, association strength trials and congruency trials of each sorting dimension were separately blocked. To ensure that participants would not be able to anticipate each trial's sorting rule before clicking the initiation button, association strength and congruency trials for all sorting dimensions were randomly intermixed in *experiment* 2. Figure 6 shows a sample trial from *experiment* 2.

RESULTS

Experiment 1

NON-TMS BEHAVIOR. Mouse movements were recorded from the click of the trial initiation button at the bottom of the screen to the final click of one of the target words at the top of the screen. Trials on which participants initially clicked outside of either of the target words were excluded from analysis. This accounted for roughly 2% of all trials across both experiments. Participants erred on 3.45% of all trials. Accuracy was submitted to a two-way repeated-measures ANOVA for the within-subjects factors of task (association strength vs. congruency) and cognitive control demand (high vs. low). This revealed a significant main effect for cognitive control demand [$F(1,14) = 51.85$, $P < 0.001$], but no main effect for task (P = 0.50) and no interaction (P = 0.11).

For each correctly answered trial, we calculated the maximum deviation between the mouse trajectory and a straight line connecting its start and stop points. Because error trials involved the participant directing the mouse all the way to the incorrect target, the value for each error trial was operationalized as the largest calculable pixel deviation from a straight line connecting the start point and correct target.[2] From these measurements, a median maximum deviation for each participant for each condition was determined and submitted to a two-way repeated-measures ANOVA. This revealed a main effect for cognitive control demand [$F(1,14) = 10.45$, $P < 0.01$], but no main effect for task (P = 0.77) and no interaction of task and cognitive control demand (P = 0.57). The difference in maximum deviation was significant between weak associate and strong associate trials [$t(1,14) = 3.59$, $P < 0.01$] and between incongruent and congruent trials [$t(1,14) = 2.63$, $P < 0.05$]. Figure 4 shows the maximum deviation means and SEs for each non-TMS condition in *experiment* 1.

In addition to maximum deviation, medians were calculated for initiation time and movement time. In a two-way repeated-

[2] Error trials did not significantly influence the results for two reasons: *1*) they constituted a small percentage of trials (ranging from 3.1 to 3.5% of all data samples); and *2*) because median values were used for analysis rather than mean values, the fact that error trials were assigned the largest possible deviation value did not skew the computed median value in a meaningful way.

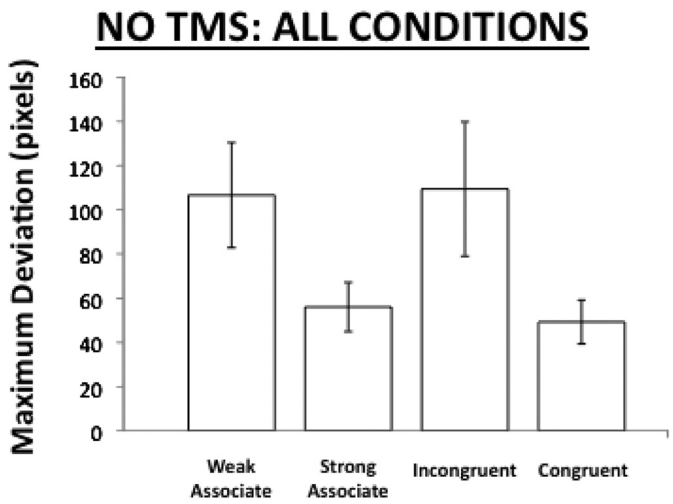

FIG. 4. Means and SEs across participants, based on the median maximum deviation for each condition for each participant, in a non–transcranial magnetic stimulation (TMS) version of *experiment* 1.

measures ANOVA, initiation time showed a main effect for cognitive control demand [$F(1,14) = 16.03$, $P < 0.01$], but no main effect for task ($P = 0.80$) and no interaction ($P = 0.95$). Similarly, movement time showed a main effect for cognitive control demand [$F(1,14) = 61.14$, $P < 0.001$], but no main effect for task ($P = 0.53$) and no interaction ($P = 1.00$).

BRIEF-TRAIN TMS. Participants clicked the incorrect target on roughly 3.1% of all trials. An omnibus ANOVA on the accuracy revealed a significant main effect for cognitive control demand [$F(1,11) = 28.12$, $P < 0.001$], but there were no stimulation site main effects or interactions in the accuracy data (all other P values >0.1).

An initial omnibus ANOVA on the maximum deviation data from all three stimulation sites revealed a reliable main effect for cognitive control demand [$F(1,11) = 16.82$, $P < 0.01$], as well as a main effect for stimulation site [$F(2,22) = 3.34$, $P = 0.05$], and a marginal stimulation site × task interaction [$F(2,22) = 2.82$, $P = 0.08$]. To further characterize this interaction, separate two-way repeated-measures ANOVAs compared performance during stimulation of each left VLPFC site to performance of the same task during stimulation of the control site. There was reliable association strength × stimulation site interaction for left mid-VLPFC compared with the control site [$F(1,11) = 8.81$, $P = 0.01$], but no such interaction for left anterior VLPFC compared with the control site [$F(1,11) = 2.11$, $P = 0.18$]. However, the association strength interaction between left mid-VLPFC and left anterior VLPFC did not approach significance ($P = 0.37$). There were no significant differences in maximum deviation between any of the stimulation sites for either congruent or incongruent trials (all P values >0.1).

Across the two manipulations during left mid-VLPFC stimulation, there was a reliable stimulation site (mid-VLPFC, control) × task (association strength, congruency) × cognitive control demand (high, low) interaction [$F(1,11) = 5.04$, $P < 0.05$]. This three-way interaction was driven by the large effect of left mid-VLPFC stimulation on weak associate trials, contrasted with the null effect of left mid-VLPFC stimulation on incongruent trials. Figure 5 shows means and SEs across participants for weak and strong associate trials and incongruent and congruent trials for each of the three stimulation sites.

Medians were also calculated for movement time and initiation time for correctly answered trials. Two-way repeated-measures ANOVAs compared performance during stimulation of each left VLPFC site to performance of the same task during stimulation of the control site. For both initiation time and movement time, there were no reliable interactions between stimulation site and association strength and there were no reliable interactions between stimulation site and congruency (all P values >0.1). Thus the computer-mouse trajectory deviations were uniquely sensitive to the selective effects of brief-train TMS on these tasks.

Experiment 2

The effect of left VLPFC stimulation on computer-mouse movements under a condition of high cognitive control demands provides new evidence about the necessity of this region of cortex in these circumstances. However, the results were not as predicted by the framework developed by Badre et al. (2005). Although we used the same materials as Badre et al. (2005), we did modify their procedure to adapt the paradigm to the TMS methodology. In *experiment* 2, we examined the consequences of alterations of the trial structure because these variations may influence the extent and timing of cognitive control demands in these tasks. In particular, the changes in the trial structure were designed to increase the potency of the congruency manipulation.

PARTICIPANTS AND PROCEDURES. Participants clicked the incorrect target on about 3.37% of all trials. An omnibus ANOVA on the accuracy revealed a significant main effect for cognitive control demand [$F(1,9) = 11.04$, $P < 0.01$], but there were no stimulation site main effects or interactions in the accuracy

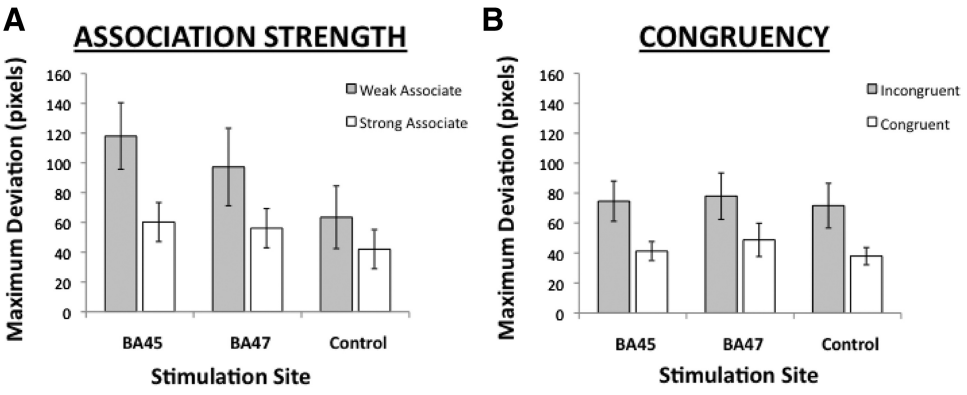

FIG. 5. Maximum deviation means and SEs for the (*A*) association strength and (*B*) congruency manipulations in *experiment* 1 (Brodmann area 45 [BA45] = left mid-VLPFC; BA47 = left anterior VLPFC; Control = right anterior VLPFC).

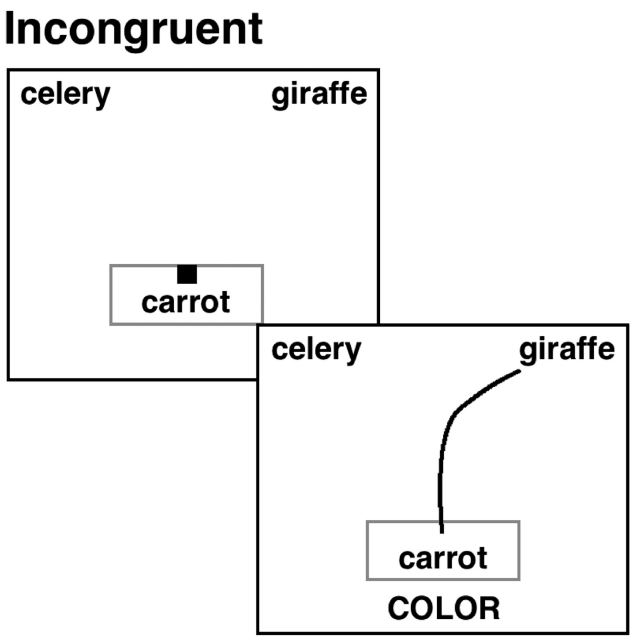

FIG. 6. Example trial from experiment 2 with a hypothetical mouse trajectory to the correct target.

data (all other P values >0.1). Similarly, an omnibus ANOVA on the maximum deviations revealed a significant main effect for cognitive control demand [$F(1,9) = 12.78$, $P < 0.01$], but no other main effects or interactions. There were no significant differences in maximum deviation between the stimulation sites for any trial type (all P values >0.1). Figure 7 shows maximum deviation means and SEs across participants for weak and strong associate trials and incongruent and congruent trials for the two stimulation sites.

Medians were also calculated for movement time and initiation time for correctly answered trials. Two-way repeated-measures ANOVAs compared performance during stimulation of left mid-VLPFC site to performance of the same task during stimulation of the control site. For both initiation time and movement time, there were no reliable interactions between stimulation site and association strength and there were no reliable interactions between stimulation site and congruency (all P values 0.1).

The procedural alterations to *experiment* 2 were designed to increase the likelihood of finding a congruency effect; instead, these data indicated that the changes eliminated the once reliable association strength effect. What follows is a post hoc explanation of the association strength effect, which is consistent with its appearance and disappearance under different timing procedures and which also serves to link the effect to the prior literature on the function of the left mid-VLPFC.

Ambiguity analysis

Previous studies suggest that contextual ambiguity may drive neural activity in left VLPFC and may account for linguistic deficits in patients with damage to this area (Bedny et al. 2007; Snyder and Munakata 2008). In this section, we explore the possibility that unintentional variations in contextual ambiguity might also account for the effect of stimulation of left mid-VLPFC on trials with weak associates. Recall that stimuli for the association strength manipulation were taken from free-response norms in which subjects generated a single associate for each cue word (Postman and Kappell 1970). Strong associate targets were generated by the majority of subjects, whereas weak associate targets were generated by a very small fraction of subjects. As it happens, the stimuli seem to have a property such that weak and strong associate targets vary not only in their association strength to the cue word, but also in the contextual ambiguity of the association. This is especially pronounced when a target word is homonomous (multiple unrelated meanings) or polysemous (multiple related meanings) and the target–cue association reflects a subordinate meaning of the target. For instance, the target "cards" is a weak associate of "queen" only in the context of playing cards, not in the context of greeting cards and postcards. To examine this potential confound between contextual ambiguity and association strength, two raters independently coded each strong and weak associate target item as either "contextually ambiguous" or "contextually unambiguous" with respect to its cue word. Because they were often homonyms or polysemes, more weak associate targets than strong associate targets were coded as contextually ambiguous ($\chi^2 = 20.02$, $P < 0.001$). Table S1 shows the contextual ambiguity ratings of strong and weak associate trials and Table S2 provides the ambiguity classification of each item (see Supplemental Material).[3]

In the association strength stimulus set, adopted from Badre et al. (2005) and Wagner et al. (2001), association strength seems to be partially confounded with contextual ambiguity. Why is this relevant to the current experiments? In *experiment* 1, the targets were presented (along with the task instruction) prior to the cue word; if one retrieved the subsequently irrel-

[3] The online version of this article contains supplemental data.

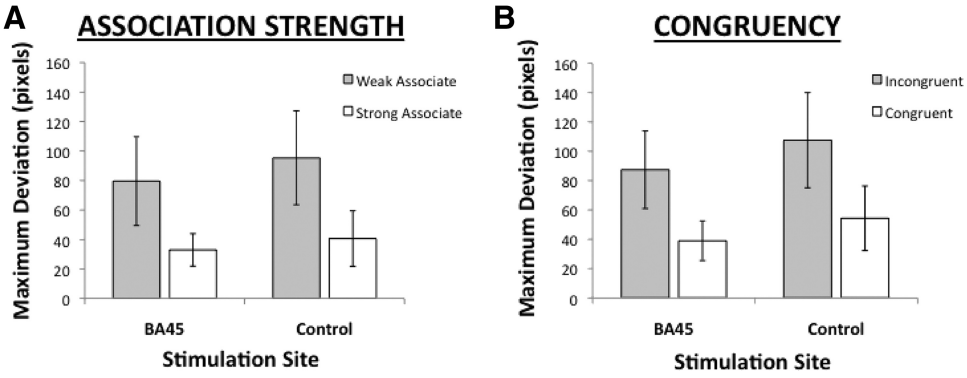

FIG. 7. Maximum deviation means and SEs for the (*A*) association strength and (*B*) congruency manipulations in the TMS version of *experiment* 2. No reliable stimulation site effects for either manipulation (BA45 = left mid-VLPFC; Control = right anterior VLPFC).

evant meaning of an ambiguous target, the application of TMS would occur simultaneously with the cue that disambiguates the meaning of the target word. In *experiment* 2, the targets and cues were presented together, in advance of TMS, so any need for ambiguity resolution could have been completed before disruption of VLPFC.

To see whether ambiguity of the correct target predicted movement deviation during TMS of left mid-VLPFC, association strength trials for both experiments were recoded in terms of contextual ambiguity. In *experiment* 1, participants deviated more toward the distractor for ambiguous trials when left-mid VLPFC was stimulated than when the control site was stimulated. Comparing TMS of left mid-VLPFC to TMS of the control site, an ANOVA of ambiguity × stimulation site revealed a trend toward an interaction [$F(1,11) = 3.18$, $P = 0.10$]. This trend was weaker in comparing left anterior VLPFC to the control site in *experiment* 1 [$F(1,11) = 1.58$, $P = 0.24$]. There was no indication of an ambiguity × stimulation site interaction in *experiment* 2, in which the difference in maximum deviation between ambiguous and unambiguous trials was the same during mid-VLPFC stimulation as that during control site stimulation [$F(1,9) = 0.17$, $P = 0.69$]. Figure 8 shows the maximum deviations for ambiguous and unambiguous target trials in the TMS versions of *experiments* 1 and 2.

Both high contextual ambiguity and low association strength predicted deviation toward the incorrect target in *experiment* 1 and neither predicted deviation toward the incorrect target in *experiment* 2. To disentangle the effects of ambiguity from those of association strength in *experiment* 1, an ambiguity × association strength ANOVA suggested that target association strength predicted movement deviation during TMS stimulation of left mid-VLPFC only for trials with ambiguous targets [$F(1,11) = 3.14$, $P = 0.10$]. This was not the case for trials with unambiguous targets [$F(1,11) = 0.37$, $P = 0.55$].

DISCUSSION

The purpose of this investigation was twofold. First, we aimed to introduce a new technique for assessing subtle behavioral effects during on-line TMS. Continuous tracking of computer-mouse movements is a newly validated measure of dynamic cognitive processing that is ideally suited to the constraints of the TMS apparatus. In *experiment* 1, spatial elements of participants' computer-mouse movements proved to be a more sensitive index of the effects of TMS than were either accuracy or reaction time measurements alone.[4] Second, we aimed to use this method to evaluate a two-process model of cognitive control during semantic memory retrieval. Toward this end, we reported two unexpected findings: *1*) stimulation of left VLPFC did not affect performance on incongruent trials; and *2*) stimulation of left mid-VLPFC, but not left anterior VLPFC, affected performance on weak associate trials, but only in *experiment* 1. We discuss each of these findings in turn.

We found no effect of TMS to either anterior or mid-VLPFC on response time, accuracy, or mouse movements during incongruent trials, during which cognitive control processes associated with this region were hypothesized to guide the selection of the task-relevant response. Although there are many possible reasons why one might obtain a null result, we highlight one here: The lack of an effect of TMS on performance on incongruent trials in both experiments may be attributable to bilateral involvement of prefrontal cortex for these trials. In a comparison of feature judgments versus global relatedness judgments, Badre et al. (2005) reported activity differences not only in left VLPFC, but also in right premotor, right mid-VLPFC, right dorsolateral PFC, and right frontopolar cortex. Additionally, Thompson-Schill et al. (1997) reported considerably greater bilateral activation for a feature-comparison task (similar to the one used here) than that for other cognitive control tasks that recruit left VLPFC, including verb generation and object classification. Because we cannot simultaneously stimulate left and right VLPFC, it is possible that right VLPFC regions are effectively recruited during left VLPFC stimulation, leading to unimpaired performance on incongruent trials.

Questions about the role of right VLPFC in these tasks also bear on our choice of the anterior-most region of right VLPFC as our control site in both experiments. Ideally, stimulation of a control site should have no effect on the specific processes of interest while producing the same nonspecific effects on behavior as does stimulation of the experimental site(s). In stimulation studies of VLPFC, the choice of a control site is complicated by one particular nonspecific side effect of stimulation: the perceptible and potentially distracting contraction of the facial muscles (i.e., a brief facial twitch). To ensure that

[4] An alternative spatial measure of mouse-movement deviation is the "accumulated deviation" of the mouse-movement trajectory. This can be calculated as the (signed) area between the assumed baseline trajectory and the participant's actual movement trajectory. The Pearson's correlations between accumulated deviation and maximum deviation ranged from 0.86 to 0.90 for all of the data samples reported here. For all analyses, results for the accumulated deviation measurements resembled the maximum deviation results.

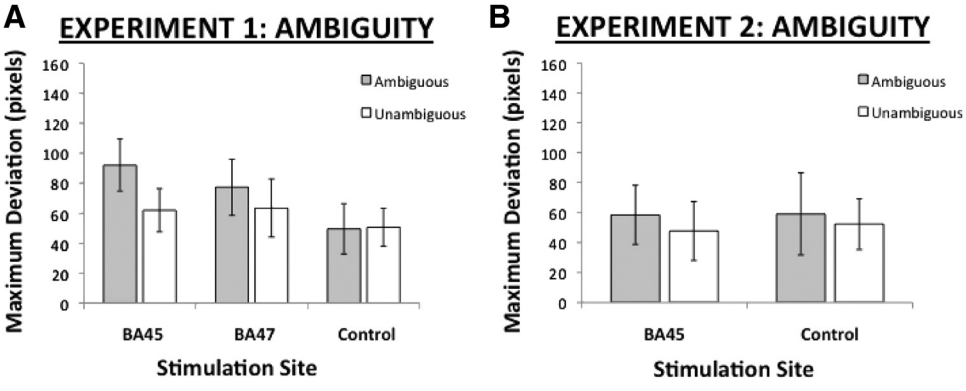

FIG. 8. Ambiguity analysis of association strength effect. *A*: association strength trials from *experiment* 1. *B*: association strength trials from *experiment* 2 (BA45 = left mid-VLPFC; BA47 = left anterior VLPFC; Control = right anterior VLPFC).

any observed effects of left VLPFC stimulation on behavior were not simply the result of this nonspecific effect, we were limited in our choice of control sites to areas of VLPFC. Although right anterior VLPFC appears to have relatively limited involvement during conceptual retrieval (cf. Badre and Wagner 2007), using this region as a control site may have led the present investigation to underestimate TMS effects on left VLPFC stimulation.

Turning to the association strength manipulation, we observed an effect of stimulation of left mid-VLPFC specifically during weak associate trials. The effect of increased deviation toward the incorrect target on these trials was absent in *experiment* 2. The primary difference between *experiments* 1 and 2 was the sequence of events prior to stimulation during each trial. In *experiment* 1, participants were shown the cue stimulus (and received TMS) for each trial only after evaluating the target stimuli for that trial. In *experiment* 2, participants viewed cue and target stimuli together before receiving TMS; therefore this null effect for the association strength manipulation may be attributed to participants forming contextually appropriate associations between cue and target stimuli before clicking the trial initiation button. Under this account, before receiving TMS, participants had already resolved the contextual ambiguity of the weak associate trial.

Given the confound between target ambiguity and association strength, results may be best interpreted within a contextual ambiguity framework for semantic retrieval (cf. Bedny et al. 2007; Snyder and Munakata 2008). In *experiment* 1, TMS occurred simultaneously with the appearance of the cue word, which provided a disambiguating context for homonymous and polysemous targets. TMS may have disrupted the process of using the context created by the cue word to resolve the ambiguity of the target word. When the target was a strong associate, its ambiguity did not matter, but when the target was a weak associate, contextual disambiguation was important. In *experiment* 2, the cue and target words were all presented before TMS stimulation, so no effect of ambiguity under this account would be predicted. Our post hoc analysis of the effect of TMS on trials with ambiguous targets provides preliminary support for this interpretation, which warrants further attention in an experiment designed to unconfound association strength and ambiguity.

A biased competition model of semantic retrieval, with bilateral activation for incongruent trials, fits the present data very easily (Kan and Thompson-Schill 2004; see also Desimone and Duncan 1995). In such a model, top-down projections resulting from competitive interactions in lateral prefrontal cortex bias mutually inhibitory long-term conceptual representations (ensembles of interconnected neurons) distributed across the left temporal lobe. For strong associate and congruent trials, automatic bottom-up spreading activation is all the participant needs to determine the correct target. For these trials, the top-down bias from the VLPFC is not needed for semantic retrieval, and so disrupting the VLPFC with TMS does not disrupt the participant's performance on the task. For weak associate trials with ambiguous contexts, top-down projections from the lateral prefrontal cortex are necessary to bias conceptual representations. Thus when the top-down bias signal is disrupted by TMS to the mid-VLPFC during contextually ambiguous weak associate trials, the participant falters and shows increased movement deviation toward the distractor target.

Applying the real-time measure of computer-mouse movements is shown to be a useful tool for testing between these cognitive frameworks in the present paradigm. Long-standing "cascade models" of human cognition suggest that the continuous evolution of motor plans during visually guided reaching reflect the underlying competition of conceptual representations (McClelland 1979). More recent primate neurophysiology studies demonstrate that motor representations continuously develop and compete with one another in premotor cortex as a primate reaches toward a target (Bastian et al. 2003; Cisek and Kalaska 2005). At the same time that conceptual representations compete with one another in prefrontal cortex, complementary motor representations compete with one another as the participant moves the computer mouse and cursor to a target object. Measuring mouse movements captures these competitive interactions as they unfold and, when combined with TMS, provides a window into the neural basis of cognitive control.

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