

1 Running head: COMPUTER-MOUSE TRACKING TMS DISRUPTIONS OF MEMORY  
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14 **Computer-mouse tracking reveals TMS disruptions of prefrontal function during semantic**  
15 **retrieval**  
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18 Nicholas C. Hindy<sup>1,2</sup>,  
19 Roy Hamilton<sup>2,3</sup>,  
20 Andrea S. Houghtling<sup>1,2</sup>,  
21 H. Branch Coslett<sup>2,3</sup>,  
22 Sharon L. Thompson-Schill<sup>1,2,3</sup>  
23

24 <sup>1</sup>Department of Psychology, <sup>2</sup>Center for Cognitive Neuroscience,  
25 <sup>3</sup>Department of Neurology, University of Pennsylvania  
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38 Correspondence address:  
39 Nicholas Hindy  
40 Department of Psychology, University of Pennsylvania  
41 3720 Walnut Street, Room B51  
42 Philadelphia, PA 19104-6241  
43 E-mail: [hindy@psych.upenn.edu](mailto:hindy@psych.upenn.edu)  
44 Tel: (215) 573-3537  
45  
46

47 **Abstract**

48 Converging evidence from neuroimaging and neuropsychological studies is essential for  
49 understanding human frontal cortical function. We introduce a new method for studying the  
50 effects of transient disruptions of frontal activity during transcranial magnetic stimulation  
51 (TMS). Using a novel combination of TMS and computer-mouse tracking, two experiments  
52 tested process models of semantic competition in left ventrolateral prefrontal cortex (VLPFC).  
53 Upon TMS stimulation of left mid-VLPFC just after presentation of an ambiguous stimulus,  
54 participants' mouse-movement trajectories deviated more toward the incorrect target for weak-  
55 associate trials than for any other trial type. This effect was extinguished when participants were  
56 shown both target and cue stimuli simultaneously. Results suggest that left mid-VLPFC is  
57 necessary to resolve semantic competition when a response is underdetermined by the stimulus  
58 and the interpretive context of the stimulus is ambiguous. Computer-mouse movements reveal  
59 the dynamics of competitive interactions as they resolve, making this technique ideally suited for  
60 studying cognitive control processes and a more sensitive index of TMS disruption than reaction  
61 time and accuracy alone.

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70 **INTRODUCTION**

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

79 Arm movements are continually adjusted as a person reaches for an object (Goodale et al.  
80 1986). By measuring the time course of a participant's response during TMS, computer-mouse  
81 tracking exploits the non-ballistic nature of these arm movements. Just as saccadic eye  
82 movements have been used to assess parallel activation of competing representations during, for  
83 example, sentence comprehension (e.g., Tanenhaus et al. 1995), computer-mouse movements  
84 can provide a continuous, on-line measure of cognitive processing. Moreover, while inevitable  
85 facial muscle contractions make measures such as eye-tracking difficult during frontal  
86 stimulation, computer-mouse tracking is exceptionally well suited for TMS. Recent behavioral  
87 studies using computer-mouse tracking demonstrate that the graded manual output reflected in  
88 the computer-mouse trajectory reveals the temporal dynamics in cognitive processes of spoken  
89 word recognition (Spivey et al. 2005), semantic categorization (Dale et al. 2006), ambiguity  
90 resolution in interpreting garden-path sentences (Farmer et al. 2007), and task switching (Hindy  
91 & Spivey, 2008). In each of these studies, streaming x,y coordinates obtained from the mouse

92 movements reveal the graded spatial attraction of a participant's arm movements toward target  
93 and distractor stimuli.

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

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

115 top-down bias signal necessary when semantic representations are underdetermined by the  
116 stimulus. Henceforth, we will refer to these putative processes (i.e., controlled retrieval and  
117 post-retrieval selection) by the manipulations that Badre et al. (2005) developed to  
118 experimentally isolate them (i.e., “association strength” and “congruency,” respectively).

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

131 In trials that varied in congruency, participants were to click the target that matched the  
132 cue with respect to an individual specified feature (color, shape, size, or texture). For congruent  
133 trials, the correct target matched the cue along the specified dimension, *and* was a strong  
134 semantic associate of the cue. As with strong associate trials, bottom-up activation should be  
135 sufficient to correctly answer congruent trials. For incongruent trials, the correct target matched  
136 the cue along the specified feature, but was otherwise unrelated, while the distractor was a strong  
137 semantic associate of the cue. According to Badre et al. (2005), because task-irrelevant



160 In the fMRI studies reported in Badre et al. (2005), participants viewed all stimuli (cue,  
161 targets, and sorting dimension) at once during each trial. To adapt this paradigm to TMS, in  
162 which transient cortical stimulation must be time-locked with the process of interest, we  
163 performed two separate experiments that differed only in the timing of stimulus presentation  
164 within each trial. In each experiment, participants viewed three of the four stimuli before  
165 stimulation, and received TMS upon presentation of the critical fourth word. As shown in Figure  
166 1, Experiment 1 participants were shown the target stimuli (e.g., “hook” and “cards”) for each  
167 trial *before* seeing the cue stimulus for that trial (e.g., “queen”). Upon presentation of the cue  
168 stimulus, participants received brief-train TMS at left anterior VLPFC, left mid-VLPFC, or the  
169 control site. In Experiment 2, participants were shown both target and cue stimuli concurrently  
170 before TMS, and received brief-train TMS upon presentation of the sorting rule. As we  
171 demonstrate below, the order of stimulus presentation was decisive in determining the  
172 participant’s experience of each trial and the effect of brief-train TMS on their performance.

173

## 174 **EXPERIMENT 1**

### 175 **Materials & Methods**

176 **Participants.** Fifteen right-handed native English speakers (four males), aged 18-29 years,  
177 participated in a non-TMS version of Experiment 1. Twelve right-handed native English  
178 speakers (five males), aged 20-29 years, participated in a TMS version of Experiment 1. Non-  
179 TMS participants were paid \$10 for each of two sessions; TMS participants were paid \$40 for  
180 each of two sessions. TMS participants were recruited from fMRI studies at the Center for  
181 Cognitive Neuroscience, University of Pennsylvania. All participants gave informed consent as  
182 approved by the University of Pennsylvania Institutional Review Board.

183

184 **Dependent measures.** Streaming x,y mouse coordinates were recorded in 20 ms increments,  
185 starting with each participant's click of the trial initiation button and ending with the final click  
186 on one of the upper-corner targets. Accuracy was recorded for each trial. For correct trials, the  
187 primary dependent measure of interest was the maximum perpendicular pixel deviation toward  
188 the distractor, between the mouse-movement trajectory and an assumed straight line connecting  
189 start and end clicks. The maximum deviation measurements were derived directly from the raw  
190 time-stamped cursor coordinates. In addition to accuracy and maximum deviation, two separate  
191 time measurements were collected for each trial. Movement initiation time was computed as the  
192 number of milliseconds from display onset to when the participant moved the cursor more than  
193 10 pixels outside the 15<sup>2</sup>-pixel trial initiation button. Once the participant moved the mouse  
194 outside this trial-initiation window, movement time was calculated as the number of milliseconds  
195 between the end of movement initiation time and the final click of the target object. Figure 2  
196 shows a diagram of the dependent measures.

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Insert Figure 2 about here

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200 **Stimulus Material.** Stimuli were selected from the stimulus sets used in Badre et al. (2005).  
201 This subset of stimuli was equated for word length across all conditions. As in Badre et al.,  
202 separate stimulus sets were used for the association strength manipulation and congruency  
203 manipulation. Because of constraints on stimulus norming, there was a significant difference in  
204 frequency of use between these two stimulus sets, such that stimuli used for the association  
205 strength manipulation had, on average, a higher frequency index than did stimuli used for the

206 congruency manipulation (Kucera & Francis, 1967). Association strength and congruency  
207 stimulus sets also differed in their concreteness. While all congruent and incongruent stimuli  
208 were concrete nouns, weak associate and strong associate stimuli contained some abstract words.  
209 (Note that this difference in concreteness was due to Badre et al.'s constraints in assembling the  
210 stimulus sets such that congruency stimuli could be matched according to their color, shape, size,  
211 or texture, while association strength stimuli had to have both a distinctly weak associate and a  
212 distinctly strong associate.)

213         Stimuli for the association strength manipulation included 96 cue words, each associated  
214 with both one strong associate target word and one weak associate target word. Based on single-  
215 response free-association norms (Moss & Older, 1996; Postman & Keppel, 1970), the mean  
216 normative probability that a strong associate word was generated in response to the cue (.25) was  
217 approximately 25 times higher than the mean probability that a weak associate was generated in  
218 response to the same cue (.01). Stimuli for the congruency manipulation included 96 cue words,  
219 each with one associated and one unassociated target word. Based on the single-response free-  
220 association norms, the mean normative probability that an associated target word was generated  
221 for its respective cue (.22) was approximately equal to the association strength of the strong  
222 associates in the association strength manipulation. Unassociated targets in the congruent and  
223 incongruent conditions were never generated as associates of the corresponding cue words (.00).

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

226

227 **Procedure.** Each participant came into the lab for two sessions, spaced three to seven days  
228 apart.<sup>1</sup> Participants sat upright in front of the computer screen, controlling the computer mouse

229 with their right hand. As in Badre et al. 2005, association strength trials and congruency trials of  
230 each sorting dimension were blocked by trial type. Each TMS participant sat with his or her  
231 head in a chinrest in order to restrict movement and wore earplugs to reduce noise from coil  
232 stimulation. There were 96 trials in both sessions; participants were not stimulated on practice  
233 trials. In each session, TMS was delivered to either the left mid-VLPFC or left anterior VLPFC  
234 on 64 of the trials, and the control site was stimulated on 32 trials. The order of site stimulation  
235 was fully counterbalanced, such that half of the participants were stimulated at left mid-VLPFC  
236 during session one and left anterior VLPFC during session two, and half of the participants in the  
237 opposite order. Also, within each session, half of the participants were stimulated at the control  
238 site first, and half the participants at the left VLPFC site first. Figure 3 shows the two left  
239 VLPFC stimulation sites marked on a 3D model of a participant's brain.

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Insert Figure 3 about here

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243 Association strength and congruency were separately manipulated (see Figure 1). At the  
244 start of each trial, two target words appeared in the upper corners of the screen. Whether a  
245 particular target word appeared on the left- or right-hand side of the screen was randomized. At  
246 the center of the screen, a sorting rule (related, color, shape, size, or texture) indicated the  
247 relevant sorting dimension. After four seconds, a 15<sup>2</sup>-pixel button appeared at the bottom center  
248 of the screen. When participants clicked this button, a cue word appeared at the bottom center of  
249 the screen, in place of the trial initiation button. Thus, the onset asynchrony between the  
250 appearance of the two targets and sorting rule, and the subsequent appearance of the cue word,  
251 was determined by the participant for each trial but was always at least four seconds.

252 Online repetitive TMS was separately administered to each of the three stimulation sites,  
253 using a Magstim Rapid magnetic stimulator, fitted with a 70-mm figure-eight air-cooled coil  
254 (Magstim, Whitland, UK). The resting motor threshold (MT), the minimum intensity required to  
255 produce a motor-evoked potential, was determined for each participant by stimulating over the  
256 hand area of motor cortex and adjusting the machine output until a visible response of the  
257 participant's hand was identified on less than 50% of trials (mean = 57.08% of maximum  
258 stimulator output, SD = 4.80, uncorrected for scalp-cortex distance). Across participants, the  
259 average scalp-cortex distance was 12.83 mm (SD = 2.32) for left mid-VLPFC, 12.50 mm (SD =  
260 2.67) for left anterior VLPFC, and 12.66 mm (SD = 1.81) for the control site (right anterior  
261 VLPFC). There were no reliable differences among the target sites in scalp-cortex distance (all  
262  $p$ 's > .1).

263 Previously obtained structural MRI scans, along with anatomical landmarks and  
264 Talaraich coordinates specified in Badre et al. (2005), were used to localize each region of  
265 stimulation. Each participant's structural MRI was co-registered with the location of the  
266 participant's head using a Polaris infrared tracking system (Northern Digital, Waterloo, Canada)  
267 and Brainsight Software (Rogue Research, Montreal, Canada). Anatomical landmarks used for  
268 locating left mid-VLPFC, pars triangularis, included the inferior frontal sulcus and insular  
269 sulcus. Anatomical landmarks used for locating left and right anterior VLPFC, pars orbitalis,  
270 included the horizontal ramus of the lateral fissure and the orbital gyrus. Across participants, the  
271 average distance between left mid-VLPFC and left anterior VLPFC targets was 27.81 mm (SD =  
272 8.43). Each stimulation site was marked and saved on the structural MRI prior to the initial TMS  
273 session, thus ensuring that the coil's position was identical across sessions. The coil was held  
274 tangentially to the scalp, such that the coil wings intersected directly above the cortical target,

275 and was secured in place with a mechanical arm, connected to a metal frame. One hundred  
276 milliseconds after stimulus onset for each trial, participants received three pulses at a frequency  
277 of 10 Hz at 100% MT.

278

## 279 **Results**

280 **Non-TMS Behavioral.** Mouse movements were recorded from the click of the trial initiation  
281 button at the bottom of the screen to the final click of one of the target words at the top of the  
282 screen. Trials on which participants initially clicked outside of either of the target words were  
283 excluded from analysis. This accounted for approximately 2% of all trials across both  
284 experiments. Participants erred on 3.45% of all trials. Accuracy was submitted to a two-way  
285 repeated measures analysis of variance (ANOVA) for the within-subjects factors of task  
286 (association strength vs. congruency) and cognitive control demand (high vs. low). This  
287 revealed a significant main effect for cognitive control demand ( $F(1, 14) = 51.85, p < .001$ ), but  
288 no main effect for task ( $p = .50$ ) and no interaction ( $p = .11$ ).

289 For each correctly answered trial, we calculated the maximum deviation between the  
290 mouse trajectory and a straight line connecting its start and stop points. Because error trials  
291 involved the participant directing the mouse all the way to the incorrect target, the value for each  
292 error trial was operationalized as the largest calculable pixel deviation from a straight line  
293 connecting the start point and correct target.<sup>2</sup> From these measurements, a median maximum  
294 deviation for each participant for each condition was determined, and submitted to a two-way  
295 repeated measures ANOVA. This revealed a main effect for cognitive control demand ( $F(1, 14)$   
296  $= 10.45, p < .01$ ), but no main effect for task ( $p = .77$ ), and no interaction of task and cognitive  
297 control demand ( $p = .57$ ). The difference in maximum deviation was significant between weak

298 associate and strong associate trials ( $t(1, 14) = 3.59, p < .01$ ), and between incongruent and  
299 congruent trials ( $t(1,14) = 2.63, p < .05$ ). Figure 4 shows the maximum deviation means and  
300 standard errors for each non-TMS condition in Experiment 1.

301 -----  
302 Insert Figure 4 about here

303 -----  
304 In addition to maximum deviation, medians were calculated for initiation time and  
305 movement time. In a two-way repeated measures ANOVA, initiation time showed a main effect  
306 for cognitive control demand,  $F(1, 14) = 16.03, p < .01$ , but no main effect for task ( $p = .80$ ), and  
307 no interaction ( $p = .95$ ). Similarly, movement time showed a main effect for cognitive control  
308 demand ( $F(1, 14) = 61.14, p < .001$ ), but no main effect for task ( $p = .53$ ), and no interaction ( $p =$   
309 1.00).

310  
311 **Brief-train TMS.** Participants clicked the incorrect target on approximately 3.1% of all trials.  
312 An omnibus ANOVA on the accuracy revealed a significant main effect for cognitive control  
313 demand ( $F(1, 11) = 28.12, p < .001$ ), but there were no stimulation site main effects or  
314 interactions in the accuracy data (all other  $p$ 's  $> .1$ ).

315 An initial omnibus ANOVA on the maximum deviation data from all three stimulation  
316 sites revealed a reliable main effect for cognitive control demand ( $F(1, 11) = 16.82, p < .01$ ), as  
317 well as a main effect for stimulation site ( $F(2, 22) = 3.34, p = .05$ ), and a marginal stimulation  
318 site by task interaction ( $F(2, 22) = 2.82, p = .08$ ). To further characterize this interaction,  
319 separate two-way repeated measures ANOVAs compared performance during stimulation of  
320 each left VLPFC site to performance of the same task during stimulation of the control site.



344

345 **EXPERIMENT 2**

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

354

355 **Materials & Methods**

356 Stimulus materials and dependent measures used in Experiment 2 were identical to those used in  
357 Experiment 1. Experiment 2 included a separate group of participants and varied from  
358 Experiment 1 in its procedure as detailed below.

359

360 **Participants.** Ten right-handed native English speakers (five males), aged 20-31 years,  
361 participated in Experiment 2.

362

363 **Procedure.** Each participant came into the lab for two sessions, spaced three to seven days  
364 apart. Participants received TMS on 96 trials in each experimental session. Left mid-VLPFC  
365 was stimulated on 48 of the trials, and the control site was stimulated on 48 trials. (Because  
366 there were no effects of left anterior VLPFC stimulation in Experiment 1, we restricted our

367 procedure to left mid-VLPFC in Experiment 2, which allowed us to increase the number of trials  
368 in each condition given the limitation on the number of stimulation trials permitted daily.) For  
369 each trial, participants received three pulses of 10 Hz TMS at 100% of MT (mean = 55.00% of  
370 maximum stimulator output,  $SD = 7.54$ , uncorrected for scalp-cortex distance). Across  
371 participants in Experiment 2, the average scalp-cortex distance was 12.87 mm ( $SD = 1.95$ ) for  
372 left mid-VLPFC, and 12.82 mm ( $SD = 2.17$ ) for the control site (right anterior VLPFC). The  
373 difference between the target sites in scalp-cortex distance did not approach significance ( $p =$   
374  $.95$ ). The order of site stimulation was counterbalanced, such that five participants were  
375 stimulated at left mid-VLPFC first and the control site second for session one, and then the  
376 control site first and left mid-VLPFC second for session two. The remaining participants had the  
377 opposite order of stimulation. TMS parameters were the same as in Experiment 1.

378

379 Experiment 2 differed from Experiment 1 in two important respects. 1.) In Experiment 1,  
380 the sorting rule appeared along with the two target words, and the participant clicked the  
381 initiation button to see the cue word; in Experiment 2 the cue word appeared on the screen with  
382 the two target words, and the participant clicked the initiation button to see the sorting rule. The  
383 onset asynchrony between the appearance of the two targets and the cue word, and the  
384 subsequent appearance of the sorting rule, was determined by the participant for each trial but  
385 was always at least four seconds. 2.) In Experiment 1, association strength trials and congruency  
386 trials of each sorting dimension were separately blocked. To ensure that participants would not  
387 be able to anticipate each trial's sorting rule before clicking the initiation button, association  
388 strength and congruency trials for all sorting dimensions were randomly intermixed in  
389 Experiment 2. Figure 6 shows a sample trial from Experiment 2.

390 -----

391 Insert Figure 6 about here

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### 393 **Results**

394 Participants clicked the incorrect target on approximately 3.37% of all trials. An omnibus  
395 ANOVA on the accuracy revealed a significant main effect for cognitive control demand ( $F(1,9)$   
396  $= 11.04$ ,  $p < .01$ ), but there were no stimulation site main effects or interactions in the accuracy  
397 data (all other  $p$ 's  $> .1$ ). Similarly, an omnibus ANOVA on the maximum deviations revealed a  
398 significant main effect for cognitive control demand ( $F(1,9) = 12.78$ ,  $p < .01$ ), but no other main  
399 effects or interactions. There were no significant differences in maximum deviation between the  
400 stimulation sites for any trial type (all  $p$ 's  $> .1$ ). Figure 7 shows maximum deviation means and  
401 standard errors across participants for weak and strong associate trials and incongruent and  
402 congruent trials for the two stimulation sites.

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404 Insert Figure 7 about here

405 -----

406 Medians were also calculated for movement time and initiation time for correctly  
407 answered trials. Two-way repeated measures ANOVAs compared performance during  
408 stimulation of left mid-VLPFC site to performance of the same task during stimulation of the  
409 control site. For both initiation time and movement time, there were no reliable interactions  
410 between stimulation site and association strength, and there were no reliable interactions between  
411 stimulation site and congruency (all  $p$ 's  $> .1$ ).

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

418

### 419 **AMBIGUITY ANALYSIS**

420           Previous studies suggest that contextual ambiguity may drive neural activity in left  
421 VLPFC, and may account for linguistic deficits in patients with damage to this area (Bedny et al.  
422 2007; Snyder & Munakata, 2008). In this section, we explore the possibility that unintentional  
423 variations in contextual ambiguity might also account for the effect of stimulation of left mid-  
424 VLPFC on trials with weak associates. Recall that stimuli for the association strength  
425 manipulation were taken from free-response norms in which subjects generated a single associate  
426 for each cue word (Postman & Kappell, 1970). Strong associate targets were generated by the  
427 majority of subjects, while weak associate targets were generated by a very small fraction of  
428 subjects. As it happens, the stimuli seem to have a property such that weak and strong associate  
429 targets vary not only in their association strength to the cue word, but also in the contextual  
430 ambiguity of the association. This is especially pronounced when a target word is homonymous  
431 (multiple unrelated meanings) or polysemous (multiple related meanings), and the target-cue  
432 association reflects a subordinate meaning of the target. For instance, the target “cards” is a  
433 weak associate of “queen” only in the context of playing cards, not in the context of greeting  
434 cards and postcards. To examine this potential confound between contextual ambiguity and

435 association strength, two raters independently coded each strong and weak associate target item  
 436 as either “contextually ambiguous” or “contextually unambiguous” with respect to its cue word.  
 437 Because they were often homonyms or polysemes, more weak associate targets than strong  
 438 associate targets were coded as contextually ambiguous ( $X^2 = 20.02$ ,  $p < .001$ ). Table 1 shows  
 439 the contextual ambiguity ratings of strong and weak associate trials, and Table 2 (in  
 440 Supplemental Material) provides the ambiguity classification of each item.

441 -----

442 Insert Table 1 about here

443 -----

444 In the association strength stimulus set, adopted from Badre et al. (2005) and Wagner et  
 445 al. (2001), association strength seems to be partially confounded with contextual ambiguity.  
 446 Why is this relevant to the current experiments? In Experiment 1, the targets were presented  
 447 (along with the task instruction) prior to the cue word; if one retrieved the subsequently  
 448 irrelevant meaning of an ambiguous target, the application of TMS would occur simultaneously  
 449 with the cue that disambiguates the meaning of the target word. In Experiment 2, the targets and  
 450 cues were presented together, in advance of TMS, so any need for ambiguity resolution could  
 451 have been completed before disruption of VLPFC.

452 To see whether ambiguity of the correct target predicted movement deviation during  
 453 TMS of left mid-VLPFC, association strength trials for both experiments were recoded in terms  
 454 of contextual ambiguity. In Experiment 1, participants deviated more toward the distractor for  
 455 ambiguous trials when left-mid VLPFC was stimulated than when the control site was  
 456 stimulated. Comparing TMS of left mid-VLPFC to TMS of the control site, an ANOVA of  
 457 ambiguity by stimulation site revealed a trend toward an interaction ( $F(1,11) = 3.18$ ,  $p = .10$ ).

458 This trend was weaker comparing left anterior VLPFC to the control site in Experiment 1  
459 ( $F(1,11) = 1.58, p = .24$ ). There was no indication of an ambiguity by stimulation site interaction  
460 in Experiment 2, in which the difference in maximum deviation between ambiguous and  
461 unambiguous trials was the same during mid-VLPFC stimulation as during control site  
462 stimulation ( $F(1, 9) = 0.17, p = .69$ ). Figure 8 shows the maximum deviations for ambiguous  
463 and unambiguous target trials in the TMS versions of Experiments 1 and 2.

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Insert Figure 8 about here

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467 Both high contextual ambiguity and low association strength predicted deviation toward  
468 the incorrect target in Experiment 1, and neither predicted deviation toward the incorrect target  
469 in Experiment 2. To disentangle the effects of ambiguity from those of association strength in  
470 Experiment 1, an ambiguity by association strength ANOVA suggested that target association  
471 strength predicted movement deviation during TMS stimulation of left mid-VLPFC only for  
472 trials with ambiguous targets ( $F(1,11) = 3.14, p = .10$ ). This was not the case for trials with  
473 unambiguous targets ( $F(1,11) = 0.37, p = .55$ ).

474

## 475 GENERAL DISCUSSION

476 The purpose of this investigation was two-fold. First, we aimed to introduce a new  
477 technique for assessing subtle behavioral effects during online TMS. Continuous tracking of  
478 computer-mouse movements is a newly validated measure of dynamic cognitive processing that  
479 is ideally suited to the constraints of the TMS apparatus. In Experiment 1, spatial elements of  
480 participants' computer-mouse movements proved to be a more sensitive index of the effects of

481 TMS than were either accuracy or reaction time measurements alone.<sup>3</sup> Second, we aimed to use  
482 this method to evaluate a two-process model of cognitive control during semantic memory  
483 retrieval. Towards this end, we reported two unexpected findings: (1) stimulation of left VLPFC  
484 did not affect performance on incongruent trials; and, (2) stimulation of left mid-VLPFC, but not  
485 left anterior VLPFC, affected performance on weak-associate trials, but only in Experiment 1.  
486 We discuss each of these findings in turn.

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

501         Questions about the role of right VLPFC in these tasks also bear on our choice of the  
502 anterior-most region of right VLPFC as our control site in both experiments. Ideally, stimulation  
503 of a control site should have no effect on the specific processes of interest while producing the

504 same non-specific effects on behavior as does stimulation of the experimental site(s). In  
505 stimulation studies of VLPFC, the choice of a control site is complicated by one particular non-  
506 specific side effect of stimulation, namely the perceptible and potentially distracting contraction  
507 of the facial muscles (i.e., a brief facial twitch). In order to ensure that any observed effects of  
508 left VLPFC stimulation on behavior were not simply the result of this non-specific effect, we  
509 were limited in our choice of control sites to areas of VLPFC. Although right anterior VLPFC  
510 appears to have relatively limited involvement during conceptual retrieval (cf. Badre & Wagner,  
511 2007), using this region as a control site may have led the present investigation to underestimate  
512 TMS effects upon left VLPFC stimulation.

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

524         Given the confound between target ambiguity and association strength, results may be  
525 best interpreted within a contextual ambiguity framework for semantic retrieval (cf. Bedny et al.  
526 2007; Snyder & Munakata, 2008). In Experiment 1, TMS occurred simultaneously with the

527 appearance of the cue word, which provided a disambiguating context for homonymous and  
528 polysemous targets. TMS may have disrupted the process of using the context created by the cue  
529 word to resolve the ambiguity of the target word. When the target was a strong associate, its  
530 ambiguity did not matter, but when the target was a weak associate, contextual disambiguation  
531 was important. In Experiment 2, the cue and target words were all presented before TMS  
532 stimulation, so no effect of ambiguity under this account would be predicted. Our post-hoc  
533 analysis of the effect of TMS on trials with ambiguous targets provides preliminary support for  
534 this interpretation, which warrants further attention in an experiment designed to unconfound  
535 association strength and ambiguity.

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

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

561

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613

614 **ACKNOWLEDGEMENTS**

615 We thank Olufunsho Faseyitan for technical assistance.

616

617 **GRANTS**

618 This research was funded by the National Institutes of Health (ROI DC009209) and a National  
619 Science Foundation Graduate Research Fellowship to NCH.

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621 **SUPPLEMENTAL MATERIAL**

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Insert Table 2 here

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640 **FOOTNOTES**

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

645

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

651

652 3. An alternative spatial measure of mouse-movement deviation is the “accumulated deviation”  
653 of the mouse-movement trajectory. This can be calculated as the (signed) area between the  
654 assumed baseline trajectory and the participant’s actual movement trajectory. The Pearson’s  
655 correlations between accumulated deviation and maximum deviation ranged from .86 to .90 for  
656 all of the data samples reported here. For all analyses, results for the accumulated deviation  
657 measurements resembled the maximum deviation results.

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663 **FIGURE LEGENDS**

664 *Figure 1.* Example trials of each condition, each with a hypothetical mouse trajectory to the  
665 correct target.

666

667 *Figure 2.* Mouse-movement dependent measures, with a hypothetical mouse trajectory to the  
668 correct target.

669

670 *Figure 3.* Example 3D model of each participant's brain. The green and yellow spheres mark the  
671 two left VLPFC stimulation sites, left mid-VLPFC and left anterior VLPFC.

672

673 *Figure 4.* Means and standard errors across participants, based on the median maximum  
674 deviation for each condition for each participant, in a non-TMS version of Experiment 1.

675

676 *Figure 5.* Maximum deviation means and standard errors for the (A) association strength and (B)  
677 congruency manipulations in Experiment 1. (BA45 = left mid-VLPFC; BA47 = left anterior  
678 VLPFC; Control = right anterior VLPFC)

679

680 *Figure 6.* Example trial with a hypothetical mouse trajectory to the correct target.

681

682 *Figure 7.* Maximum deviation means and standard errors for the (A) association strength and (B)  
683 congruency manipulations in the TMS version of Experiment 2. No reliable stimulation site  
684 effects for either manipulation. (BA45 = left mid-VLPFC; Control = right anterior VLPFC)

685

686 *Figure 8.* Ambiguity analysis of association strength effect. (A) Association strength trials from  
687 Experiment 1; (B) association strength trials from Experiment 2. (BA45 = left mid-VLPFC;  
688 BA47 = left anterior VLPFC; Control = right anterior VLPFC)

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709 **TABLE LEGENDS**

710 *Table 1.* Trials with ambiguous targets.

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712 *Table 2.* Strong and weak associate targets, and their recoding as either “ambiguous” or

713 “unambiguous.”

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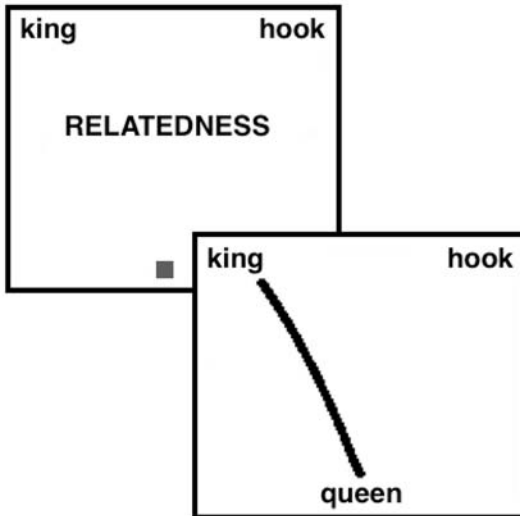
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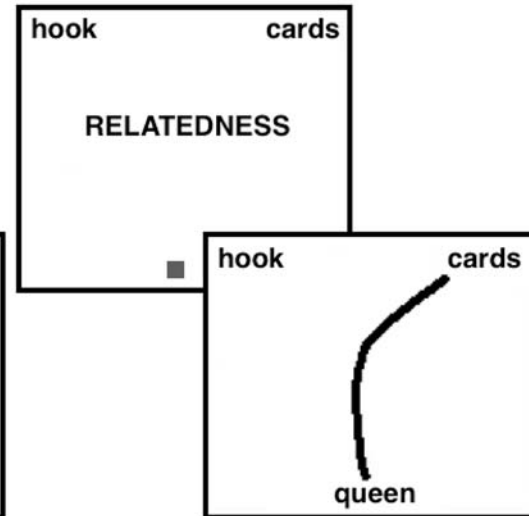
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## Association Strength Manipulation:

Strong Associate

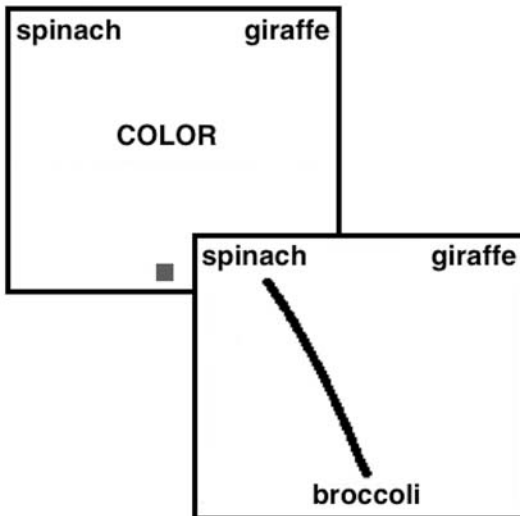


Weak Associate

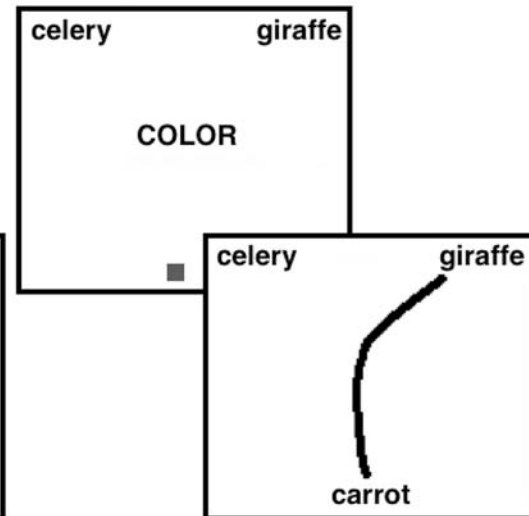


## Congruency Manipulation:

Congruent

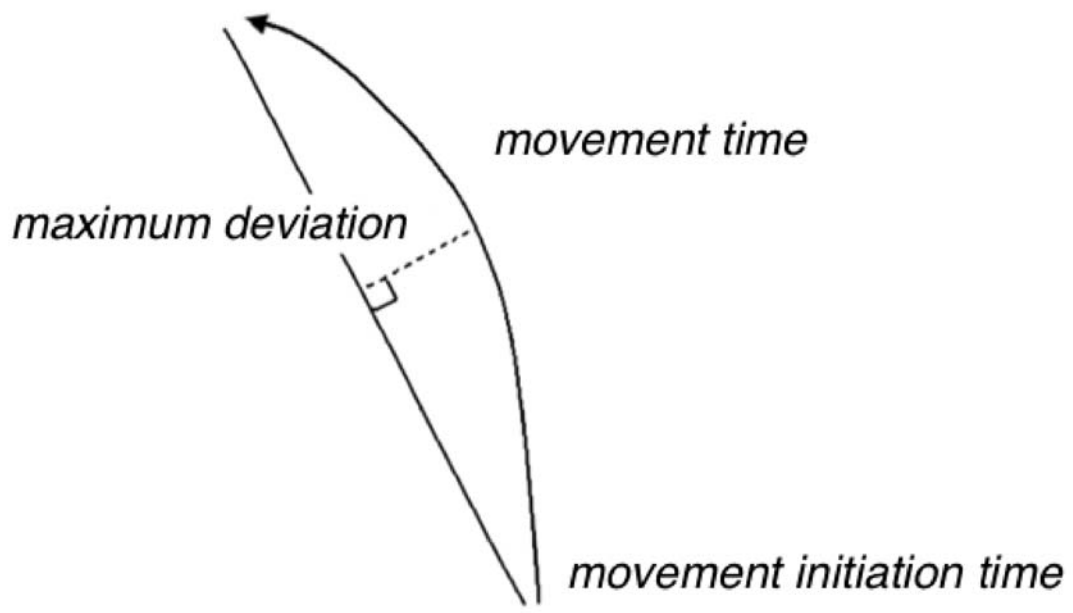


Incongruent



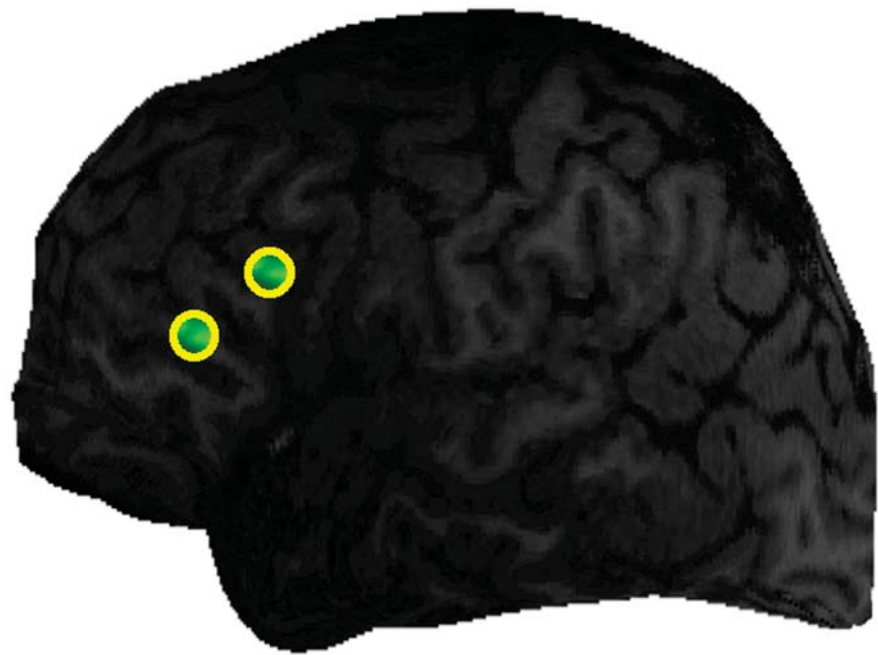
**Correct**

**Incorrect**

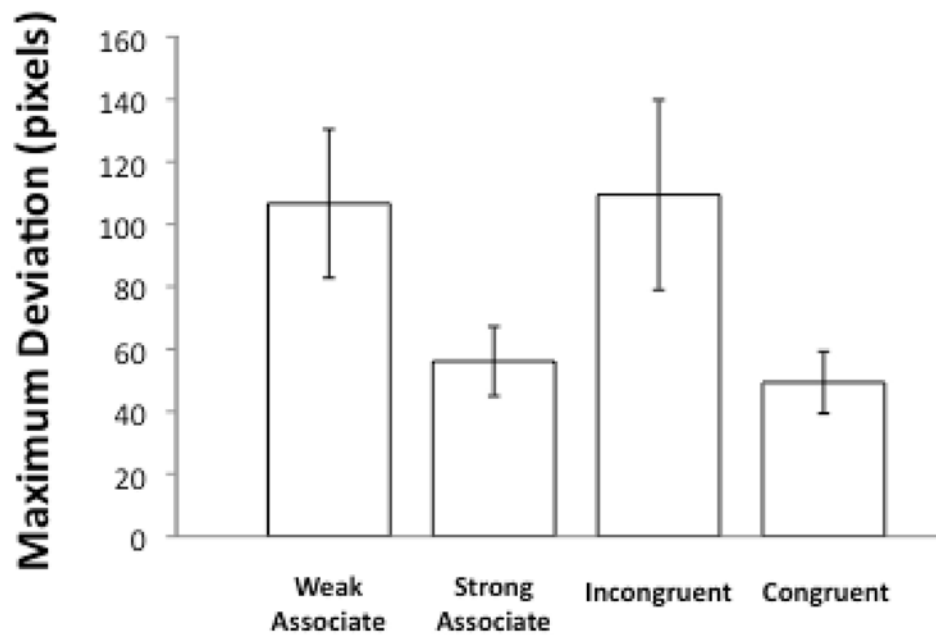


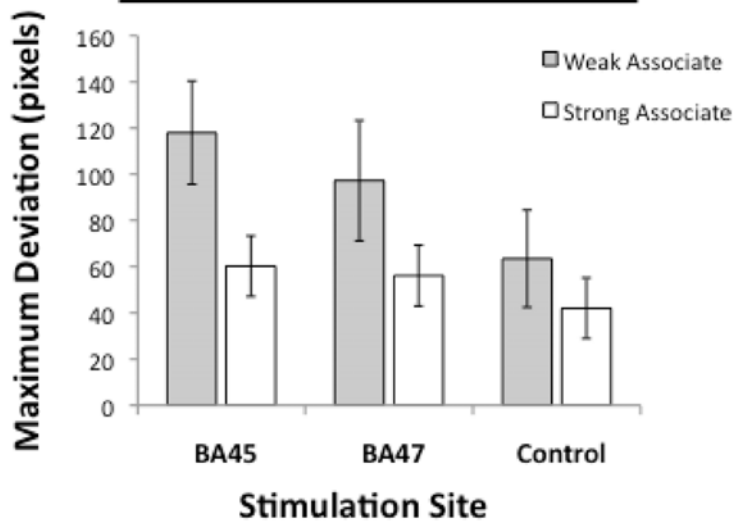
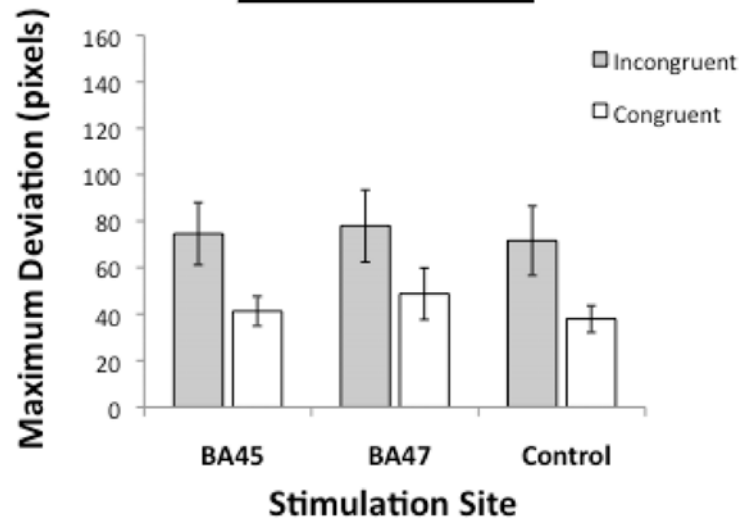
**Stimulus**

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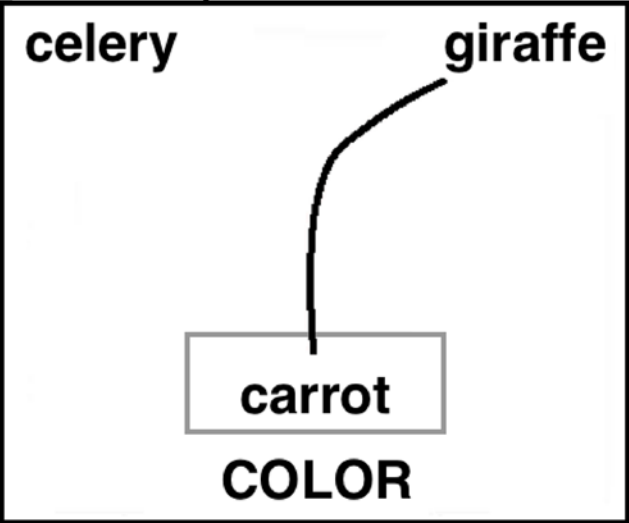
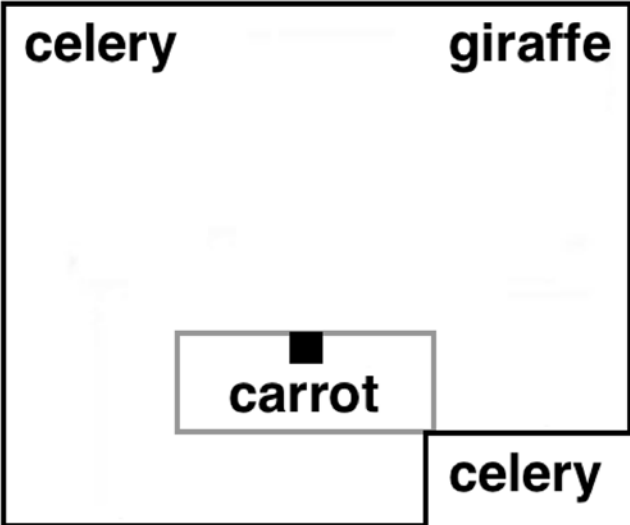


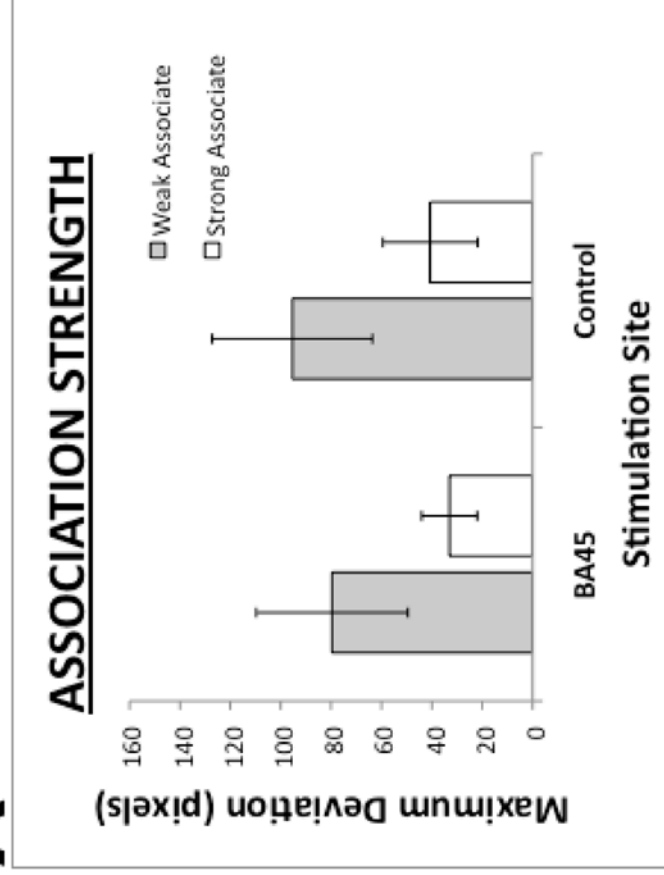
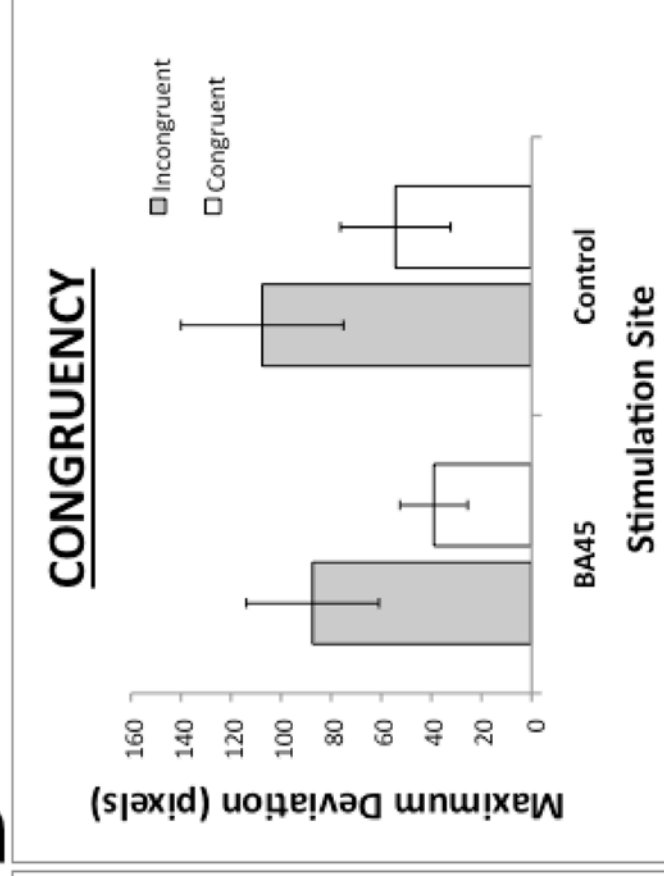
## NO TMS: ALL CONDITIONS



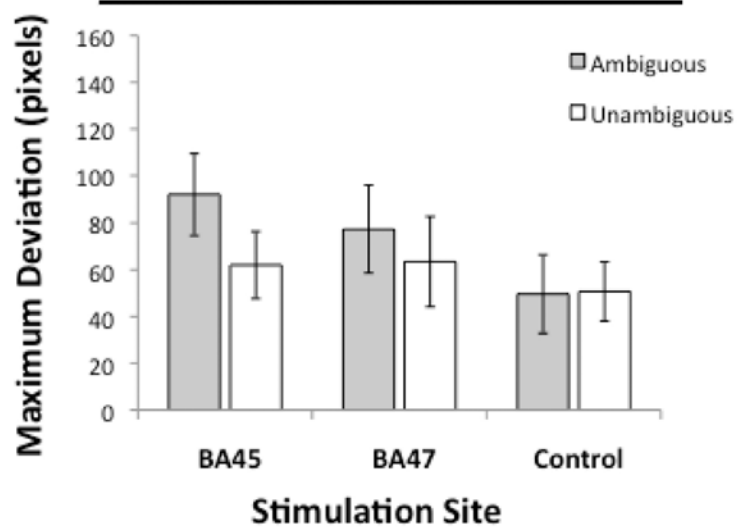
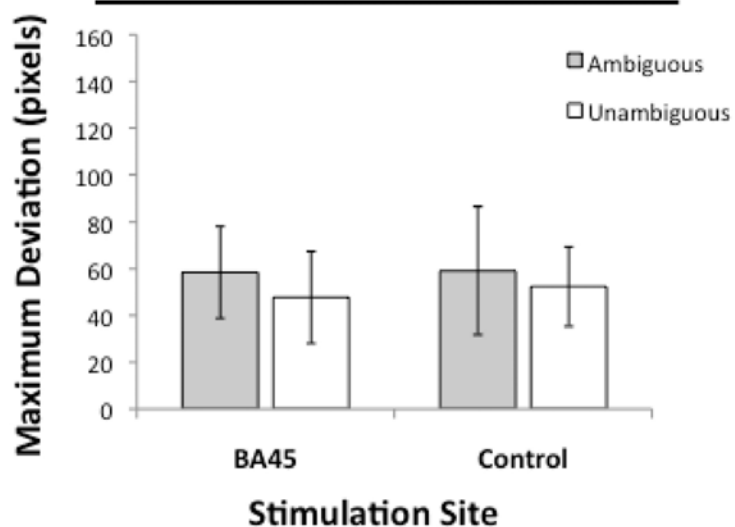
**A****ASSOCIATION STRENGTH****B****CONGRUENCY**

# Incongruent



**A****B**

	<b>STRONG ASSOCIATE</b>	<b>WEAK ASSOCIATE</b>
<b>AMBIGUOUS</b>	<b>32</b>	<b>63</b>
<b>UNAMBIGUOUS</b>	<b>64</b>	<b>33</b>

**A****EXPERIMENT 1: AMBIGUITY****B****EXPERIMENT 2: AMBIGUITY**

**Bold Italics** = Ambiguous Target

<b>STRONG</b>	<b>WEAK</b>	<b>PROBE</b>	<b>STRONG</b>	<b>WEAK</b>	<b>PROBE</b>
<b>ASSOCIATE</b>	<b>ASSOCIATE</b>		<b>ASSOCIATE</b>	<b>ASSOCIATE</b>	
metal	<i>material</i>	aluminum	tiger	jaw	lion
deer	<i>stag</i>	antelope	<i>wind</i>	climate	monsoon
writer	critic	author	<i>stars</i>	rocket	moon
cry	pink	baby	<i>thread</i>	<i>pain</i>	needle
<i>peel</i>	<i>slip</i>	banana	cereal	slop	oatmeal
soup	<i>kidney</i>	bean	cake	<i>steamy</i>	oven
ugly	<i>painting</i>	beautiful	fail	<i>skip</i>	pass
<i>dam</i>	<i>den</i>	beaver	Hawaii	sticky	pineapple
<i>sting</i>	<i>hum</i>	bee	<i>grow</i>	worm	plant
money	beak	bill	<i>pipes</i>	<i>mess</i>	plumber
<i>sweet</i>	<i>acid</i>	bitter	movie	cinema	preview
<i>eggs</i>	bake	boil	juice	<i>wither</i>	prune
read	<i>rack</i>	book	king	<i>cards</i>	queen
girl	toys	boy	leaves	<i>fork</i>	rake
butter	<i>rise</i>	bread	stop	cease	refrain
statue	<i>tan</i>	bronze	faith	sect	religion
moth	<i>spots</i>	butterfly	<i>baron</i>	jewels	robber
cow	<i>farm</i>	calf	pepper	<i>grains</i>	salt
flame	<i>halo</i>	candle	neck	<i>wrap</i>	scarf
kittens	<i>sleek</i>	cats	<i>tall</i>	<i>thin</i>	short
crackers	tangy	cheese	disease	<i>sore</i>	sickness
<i>smoke</i>	<i>case</i>	cigarette	<i>fast</i>	lazy	slow
<i>spice</i>	cider	cinnamon	silk	<i>level</i>	smooth
clowns	<i>dust</i>	circus	shoes	<i>smell</i>	socks
hat	<i>tail</i>	coat	<i>army</i>	<i>field</i>	soldier
<i>mob</i>	<i>wild</i>	crowd	grapes	vinegar	sour
<i>late</i>	cops	curfew	<i>web</i>	eight	spider
flower	<i>frail</i>	daffodil	speak	wheel	spoke
appear	fog	disappear	paint	air	spray
<i>bark</i>	<i>domestic</i>	dog	summer	<i>hatch</i>	spring
gown	<i>wrinkle</i>	dress	cooking	<i>gas</i>	stove
wet	cracked	dry	hair	<i>island</i>	strand
bird	<i>noble</i>	eagle	avenue	gutter	street
food	<i>satisfy</i>	eating	clothes	<i>press</i>	suit
<i>exit</i>	<i>front</i>	entrance	mud	<i>mush</i>	swamp
walk	<i>tired</i>	feet	<i>quick</i>	sudden	swift
toilet	<i>flat</i>	flush	maple	<i>thick</i>	syrup
tree	grove	forest	<i>orange</i>	<i>refresh</i>	tangerine
<i>box</i>	<i>bond</i>	fuse	<i>steal</i>	<i>silver</i>	thief
dead	<i>hole</i>	grave	beer	<i>filled</i>	thirsty
boat	<i>inlet</i>	harbor	turtle	snail	tortoise
sweat	<i>energy</i>	heat	<i>tracks</i>	<i>horn</i>	train
<i>load</i>	<i>trunk</i>	heavy	pants	<i>pair</i>	trousers
rope	flax	hemp	<i>belt</i>	<i>middle</i>	waist
<i>climb</i>	<i>rolling</i>	hill	drink	ice	whiskey
<i>tight</i>	<i>release</i>	hold	<i>blow</i>	tone	whistle
love	perfume	intimate	<i>instrument</i>	<i>hollow</i>	xylophone
steel	ring	iron	<i>sun</i>	<i>straw</i>	yellow