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TMS interferes with lexical-semantic retrieval in left inferior frontal gyrus and posterior middle temporal gyrus: Evidence from cyclical picture naming

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Abstract

We used TMS to investigate the contribution of left inferior frontal gyrus (LIFG) and posterior middle temporal gyrus (pMTG) to lexical/semantic selection and retrieval processes using a cyclical naming paradigm. Participants named pictures that were presented repeatedly across six cycles, either in semantically related or unrelated sets. Previous research has suggested that *selection* demands are higher for related sets, especially after repetition, since participants experience competition from the activation of semantic neighbours. In contrast, *retrieval* demands are greater for unrelated sets in the absence of semantic priming, particularly on the first cycle when the target names have not been previously activated. Therefore, this paradigm can reveal independent effects of (i) retrieval demands (i.e., the ease of accessing picture names from visual input) and (ii) selection/competition. We found that rTMS to LIFG and pMTG produced similar behavioural effects: stimulation of both sites disrupted picture naming performance on early cycles (when participants were less practised at producing the picture names) and for semantically-related sets (when there was the potential for increased competition and yet also facilitation from semantic neighbours). There were no effects of TMS when either retrieval or selection requirements were maximal on their own. The data therefore support the view that both LIFG and pMTG contribute to picture name retrieval, with both sites playing a critical role in mediating the semantic facilitation of naming when retrieval demands are high.

Keywords: semantic, selection, retrieval, TMS, naming

Introduction

The mechanisms that underpin the production of appropriate lexical and semantic information have been long been a focus of research within cognitive neuroscience and psycholinguistics. There is a consensus that activation spreads between semantically-related words and concepts (e.g., Chen & Mirman, 2012; Collins & Loftus, 1975; Foygel & Dell, 2000; Levelt et al., 1999), and this phenomenon is thought to underpin semantic priming effects in tasks such as picture naming. However, unchecked spreading activation could cause competition, since items that are semantically related to the target are also activated, raising the question of how words and concepts are selected for output. Researchers have proposed that lexical selection can be driven by processes intrinsic to the lexical/semantic system – i.e., when a potential output reaches a critical threshold for production, or via lateral inhibition of related representations (e.g., Foygel & Dell, 2000; Levelt et al., 1999). Additionally, when the system experiences strong competition and/or weak activation of any potential target, top-down cognitive control mechanisms may be triggered (Bedny et al., 2008; Jefferies et al., 2007; Schnur et al., 2009; Thompson-Schill et al., 1999). These processes could bias interactive-activation processes within the lexical-semantic system to dampen competition and promote the target response, and/or constrain ongoing processing so that it is appropriate to the current goal or task context.

The neurobiological underpinnings of these processes are not well-understood. Neuroimaging studies have reported stronger activity within left inferior frontal gyrus (LIFG) when competing lexical and semantic representations vie for selection (Badre et al., 2005; Moss et al., 2005; Thompson-Schill et al., 1997) and when top-down control processes guide lexical/semantic retrieval (Buckner et al., 1996; Demb et al., 1995; Fiez, 1997; Gabrieli et al., 1998; Kapur et al., 1994; Peterson et al., 1988; Wagner et al., 2000; 2001). These findings support the view that, at least under some circumstances, top-down control mediated by LIFG makes an important contribution to retrieving relevant aspects of lexical/semantic information and resolving competition (Bedny et al., 2008; Schnur et al., 2009; Thompson-Schill et al., 1997; 1999). Specifically, recent work suggests that LIFG is involved in *both* selection and retrieval (Badre et al., 2005; Bedny et al., 2008; Gold et al., 2006; Snyder et al., 2011; Wagner et al., 2001; Whitney et al., 2009) and these elements might interact since the lateral excitation of related concepts during retrieval would intensify selection demands (Martin & Cheng, 2006; Snyder et al., 2011).

Another site, posterior middle temporal gyrus (pMTG), is also strongly recruited during tasks involving lexical/semantic retrieval and selection, but the contribution of this region remains unclear. Numerous studies have specifically implicated pMTG in lexical/semantic retrieval, as opposed to selection (Badre et al., 2005; Bedny et al., 2008; Gold et al., 2006; Hickok & Poeppel, 2007; Noppeney et al., 2004). Nevertheless, like LIFG, pMTG is reliably recruited across lexical and semantic tasks that maximise executive demands in multiple ways (for review, see the activaton liklihood estimation meta-analysis of Noonan et al., 2013). pMTG can show co-activation with LIFG across diverse aspects of semantic control, including understanding ambiguous vs. non-ambiguous words, semantic retrieval in the presence of strong distracters and the retrieval of relatively weak semantic relationships (Bedny et al., 2008; Eviatar & Just, 2006; Gennari et al., 2007; Thompson-Schill et al., 1997; Whitney et al., 2011a; Zempleni et al., 2007). Furthermore, inhibitory TMS delivered to pMTG as well as LIFG disrupts tasks with high selection as well as retrieval demands (Whitney et al., 2011b, 2012). Since pMTG shows functional coupling with LIFG, one possibility is that controlled retrieval and selection depends on the interaction of these brain regions, with both sites showing increased recruitment when retrieval is relatively unconstrained by the context (i.e., retrieval demands are high), when competitors are highly active and/or when task requirements demand that unusual aspects of knowledge are brought to the fore.

Tasks that can at least partially separate retrieval and selection processes are crucial to understanding the role of LIFG and pMTG in semantic/linguistic control. The cyclical naming task – in which small sets of semantically related or unrelated items are presented repeatedly across several cycles – is one task which permits this type of separation, and can also reveal how these processes interact. On the first cycle in this task, when participants are producing the picture names for the first time, *retrieval* demands are relatively high because naming does not benefit from repetition priming. This explains why naming latencies fall sharply between cycles 1 and 2 (Belke et al., 2005; Navarrete et al., 2012; Schnur et al., 2009). Retrieval demands are also initially lower for semantically-related sets, since related items benefit from semantic priming, explaining why naming latencies are longer for unrelated than related sets on the first cycle in some studies (Navarrete et al., 2012). However, on later cycles, the initially beneficial effects of semantic priming are overtaken by negative “refractory” effects thought to result from increased competition. Previously-produced semantically-related items become strong competitors that interfere with the retrieval/production of target names, and therefore *selection* demands are increased on later cycles. This effect is thought to explain why naming latencies are higher for related than unrelated sets on later cycles (Belke et al., 2005; Gardner et al., 2012; Jefferies et al., 2007; Schnur et al., 2006; 2009). In summary, *retrieval* demands are highest for semantically-unrelated sets and on early cycles, while *selection* demands are highest for semantically-related sets and on later cycles.

Refractory effects in cyclical picture naming tasks have been suggested to reflect a build-up of competition at the lemma level in models of speech production (Schnur et al., 2006; 2009). However, similar effects can be found in comprehension tasks (Campanella & Shallice, 2011; Forde & Humphreys, 1997; Gardner et al., 2012; Jefferies et al., 2007), suggesting that this pattern is not specific to speech production. Instead, studies have linked the decline in performance across cycles (in both picture naming and comprehension) to failures of top-down executive control of competition across multiple tasks, mediated by LIFG (Gardner et al., 2012; Schnur et al., 2009). Both LIFG and pMTG show effects of 'semantic blocking' in fMRI studies examining the cyclical naming paradigm, with greater activation for semantically-related than unrelated sets (Schnur et al., 2009, see also Heim et al., 2009, for similar semantic blocking effects in LIFG). This stronger BOLD response might reflect the spread of activation to semantically-related concepts, and/or selection mechanisms that help to focus this increased activity on the target. Both of these sites also show increased activation when semantic competitors of target picture names are primed using a definitions task (De Zubicaray et al., 2006). However, neuroimaging studies of semantic blocking effects have not directly examined the influence of repetition across multiple cycles; moreover, since neuroimaging methods are correlational, such studies cannot confirm whether the increased activation at both sites has a *causal* role in controlling lexical/semantic activation.

Neuropsychological studies support the view that both LIFG and pMTG make a necessary contribution to the executive control of semantic activation (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010). Deficits of semantic control in patients with semantic aphasia (SA) result from lesions that have a peak overlap in either left IFG or pMTG. Moreover, on a wide variety of semantic tasks, cases with damage restricted to left temporoparietal cortex show a similar pattern of deficits to those with lesions in LIFG (although patients with frontal lesions can have less fluent speech production; Corbett et al., 2009a; Corbett et al., 2011; Jefferies & Lambon Ralph, 2006; Noonan et al., 2010): both sets of patients show poorer semantic retrieval in the absence of external constraints designed to reduce the need for internally-generated control over semantic activation (i.e., cueing effects; Corbett et al., 2011; Jefferies et al., 2008) and more impaired comprehension when there are strong distracters, a weak relationship between the probe and target, or when the subordinate meanings of ambiguous words must be retrieved (Noonan et al., 2010). Patients with SA demonstrate increasingly impaired performance for both naming and word-picture matching versions of cyclical tasks, perhaps reflecting some difficulty in dealing with the build-up of competition amongst related items across cycles, and they produce perseverative errors (e.g., Jefferies et al., 2007; Schnur et al., 2006). Nevertheless, cases with temporoparietal infarcts (who have damage to pMTG) show much weaker or non-existent effects of cycle on all versions of these tasks (Gardner et al., 2012; Jefferies et al., 2007; Schnur et al., 2009), despite being similar to the left frontal SA patients on other assessments of semantic and non-semantic control. Posterior SA patients do show poorer naming and comprehension for semantically-related sets , like those with LIFG lesions, but they tend to only show subtle effects of speed and cycle in response latencies (Jefferies et al., 2007), if at all. However, due to variable size and location of damage in patients with stroke aphasia, it is hard to make strong inferences about the contribution of specific parts of left frontal and temporoparietal cortex to different aspects of semantic control from such studies.

Finally, there is a growing literature on the effects of non-invasive brain stimulation on lexical-semantic retrieval and selection, which is broadly consistent with the dissociation between left prefrontal and temporoparietal cortex found in neuropsychological investigations. Anodal transcranial direct current stimulation (tDCS) to left prefrontal cortex has been shown to decrease effects of semantic interference in semantically-blocked picture naming, including dampening down increases in naming latencies that characterise the effects of repeating semantically-related sets of pictures (Pisoni et al., 2012; Wirth et al., 2011, although null results for LIFG were reported by Henseler et al., 2014). These effects might reflect a strengthening of top-down control following LIFG stimulation, since anodal tDCS is thought to enhance cortical excitability and thus facilitate processes within stimulated brain sites. In contrast, tDCS to the posterior superior temporal lobe was found to *increase* semantic interference effects (Pisoni et al., 2012), perhaps because greater excitability of this region led to more spreading activation between semantically-related items, and thus more competition. However, interpretation of these findings is not straightforward as tDCS is not a focal method, and not well-suited to drawing conclusions about the functions of specific brain regions. Neuroimaging studies have revealed multiple regions in both posterior temporal and prefrontal cortex with different roles (Badre et al., 2005; Bedny et al., 2008; Gold et al., 2006): for example, Bedny et al. (2008) found that while left posterior STG showed effects of semantic similarity, pMTG showed effects of ambiguity like LIFG. However, tDCS to the posterior temporal lobe would modulate the excitability of both pSTG and pMTG simultaneously.

The current study used a brain stimulation method with much higher spatial resolution, namely transcranial magnetic stimulation (TMS), to modify performance on semantically-related and unrelated sets in a cyclical picture naming task. We used an inhibitory offline repetitive TMS protocol, allowing us to examine the effects of TMS to LIFG and pMTG without the disruptive effects of eye blinks and jaw contractions that are strongly elicited by stimulation at these sites. Our first aim was to clarify the role of each of these regions in picture naming, by manipulating selection and retrieval demands within a single task. For each site, we tested whether TMS-induced disruption was greatest (1) when selection demands were maximal (for related sets on later cycles), (2) when initial retrieval demands were maximal due to the absence of repetition or semantic priming (for early cycles and unrelated sets), or (3) when the spread of activity to semantically-related items could successfully overcome high retrieval demands in the absence of TMS (i.e., on early cycles for semantically-related sets). Given the previous neuroimaging literature indicating a role for LIFG (and potentially also pMTG) in *both* selection and retrieval, we might expect that TMS would interfere with naming of related sets on early cycles, since these trials are characterised by high retrieval demands which can be ameliorated by semantic priming, but only when spreading activation from semantic neighbours is at an optimal level. Secondly, we examined whether LIFG and pMTG showed a functional dissociation or parallel effects of TMS. Since LIFG and pMTG appear to form a distributed functional network for the executive control of lexical-semantic processing, with co-activation across a wide range of executive-semantic manipulations (e.g., Noonan et al., 2013), stimulation of these regions might elicit equivalent effects. However, other researchers have suggested that mid-LIFG (pars triangularis) contributes to both selection and controlled retrieval, while in contrast, pMTG is involved in lexical/semantic retrieval only (Badre et al., 2005). This functional dissociation would predict TMS effects for LIFG on late cycles/related sets (characterised by strong competition) and effects of pMTG stimulation on early cycles/unrelated sets (characterised by high retrieval demands).

Method

Design: A within subjects 2 x 2 x 2 x 6 factorial design was used, with TMS (no stimulation vs. stimulation), site (LIFG, pMTG), relatedness (related, unrelated), and cycle (1, 2, 3, 4, 5, 6) as factors. We used an offline TMS procedure: participants performed the task immediately after stimulation, allowing us to rule out the possibility that the loud clicks, jaw contractions, or eye blinks associated with each pulse disrupted performance on the behavioural task.

Participants: Eighteen participants were examined in the study (11 females; mean age = 20.78, SD = 2.37). All participants were right-handed, native British-English speakers recruited from the University of York student population, and were compensated £38 for their time. Participants were screened for TMS and MRI safety and were thus free from any history of neurological disease or mental illness and were not taking any prohibited medication. One participant who showed blanket facilitation across both sites for both conditions (related/unrelated) was excluded from the analysis, as well as one other participant who spoke Singaporean English.

Stimuli: These were colour pictures, which appeared on a white screen in succession, in either related blocks or unrelated blocks. The categories for the related sets were as follows: types of balls (x2), baked goods, birds, boats, cars, cartoon characters (x2), cereals, clothing, computer goods, dogs, drinks, evening wear, flowers, fruits, garden tools, hats, herbs/spices, musical instruments (x2), jewellery, kitchen goods (x3), pastries, pets, puddings, sea creatures, transport, tools, vegetables (x2), winter gear, zoo animals (x2). Items were named at the specific level and were highly semantically related, making the task more challenging than basic level naming.

Tasks: Picture probes were presented individually on a computer screen and participants named each picture as it appeared. The task alternated between related and unrelated sets. In each set, there were five items to be named in each cycle, and these were repeated across six cycles. The order of the items within blocks was random, with no item occurring twice in a row (i.e., radish, carrot, potato, onion, pepper, onion). No trials were repeated within or across sessions. Following six cycles of one set, the first cycle of a new set was presented. Therefore, this method eliminated the potential confound between cycle and time since stimulation. There were 72 cycles per condition.

A number naming control task was included to assess any non-specific effects of TMS. Participants produced the English names for strings of Arabic numerals presented on the screen. These numbers contained no commas (to increase difficulty), varied in length from tens of thousands to millions (e.g., 56395, 614592, 7246856), and shifted position slightly on the screen (reducing the availability of visual cues to number length/syntax).

Procedure: A PC running E-Prime software controlled stimulus presentation and recording of response times. Responses were given verbally into a microphone which was connected to a Serial Response (SR) Box (Psychology Software Tools). Each trial started with a fixation cross for 50ms followed by the presentation of the picture or number to be named. In picture naming blocks, the onset of the participant’s response triggered a blank screen (550ms) after which the next trial began. In number naming blocks, once the participant initiated their response, the text colour changed to grey but the number remained on screen to minimise working memory demands. Each block was preceded by a “ready?” screen to which participants gave a button response (see Figure 1).

Participants were familiarized with the stimuli and their correct names before the experiment. This helped to reduce naming errors so that we could examine the effects of cycle and relatedness on response latencies. In the familiarisation phase, each stimulus was presented twice, and this was self-paced. In addition, we reduced task practice effects by requiring participants to complete 12 related and 12 unrelated blocks of picture naming and 80 number trials prior to each TMS session. No practice items were used in the TMS experiment.

The TMS sessions began with further practice trials (6 related and 6 unrelated blocks, plus 80 number trials), followed by familiarisation of stimuli for the experiment. In the experiment, there were then 6 blocks per condition for picture naming (related/unrelated), and 20 number trials, assessed at three time points: before stimulation (baseline 1), immediately after stimulation (i.e., to capture performance under the influence of TMS), and 30 minutes after the end of the stimulation period (by which point, effects of TMS should have washed out; baseline 2). The two baseline measures were combined (as one baseline) for data analysis (an average of the two baselines was used for each participant). The related and unrelated sets alternated (e.g., related-unrelated-related etc.), and the number naming (one block) either preceded or followed semantic naming. The following variables were counterbalanced within and across participants: the order of sets (across both LIFG/pMTG sessions, and TMS/baseline periods), task order (whether the control task, related sets or unrelated sets were presented first), and order of LIFG/pMTG sessions.

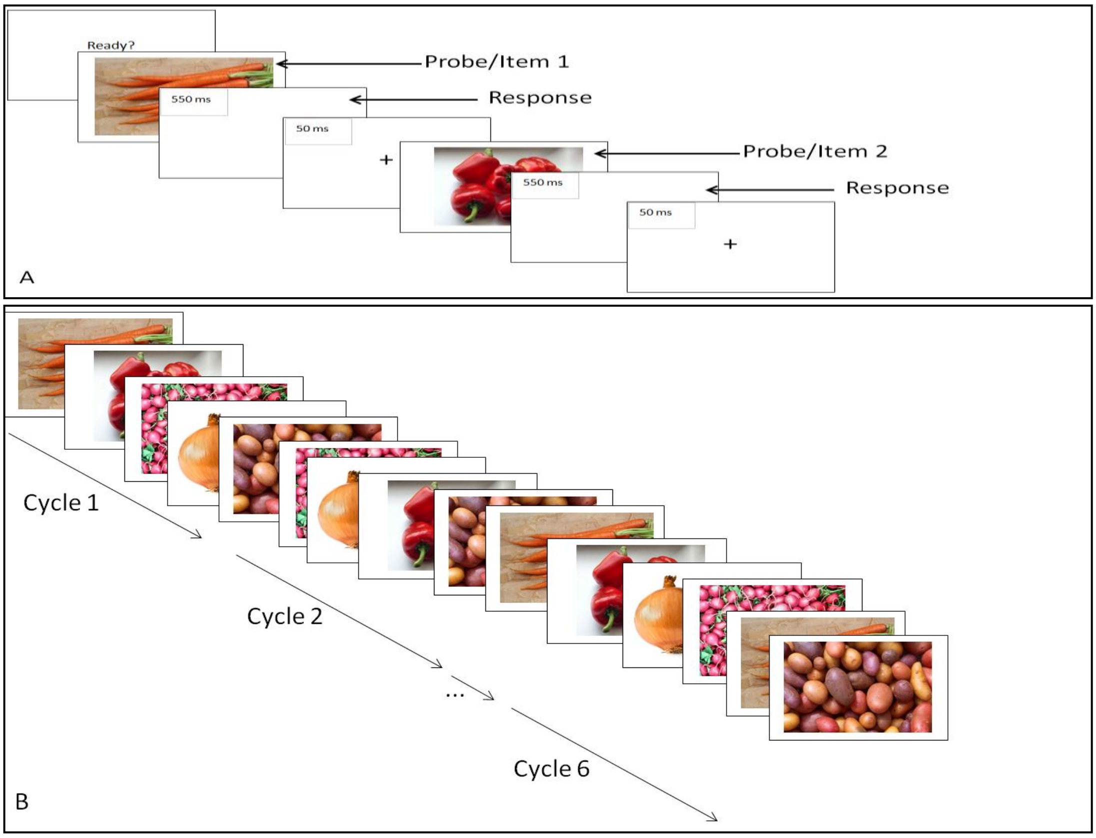

Figure 1: Experimental task procedure. Figure 1A provides a schematic of the trial structure; Figure 1B shows the repetition of cycles (related sets example).

Selection of TMS Site: Structural T1-weighted MRI scans were used to identify sites for stimulation in each participant's brain. Sites were identified from a recent neuroimaging meta-analysis examining manipulations of semantic control demands, in which the two strongest clusters were within LIFG (pars triangularis; -45, 19, 18; MNI coordinates), and pMTG (-54, -49, -2; Noonan et al., 2013). Brainsight 2 (Rogue Research, Montreal Canada, www.rogue-research.com/) was used to co-register participants' scalps to their MRI structural image and to identify these sites, which were transformed from standard to individual brain space. Four landmarks were used for co-registering each participant's head to their brain image (tip of the nose, bridge of the nose, left/right tragus).

Stimulation Parameters: Before TMS testing began (each session), individual motor threshold was determined by the lowest stimulation intensity required to elicit contraction of the first dorsal interosseous (FDI) muscle in the contralateral hand. Motor thresholds ranged between 39% and 65% (average: 51%) of maximum stimulator output. A 70 mm figure of eight coil, attached to a MagStim Rapid2 stimulator was used for repetitive magnetic pulses. Repetitive trains of TMS were delivered at 1Hz for 10 minutes, at 120% of each individual's motor threshold.

Data Analysis: TMS disruption was expected to manifest itself in slower response times (RT), rather than a decline in accuracy (Walsh & Cowey, 2000). Incorrect productions, missed trials and responses faster than 250ms were removed prior to analysis (5.2% of trials). We report an analysis based on median RT, since medians are not strongly influenced by outlying values which can be problematic in analyses of response latency. For completeness, the supplementary materials provide summary statistics (Table S1) and ANOVA results (Table S2) for response accuracy, although performance was close to ceiling (perhaps because of our familiarisation procedure which acquainted participants with the correct name for each picture before the experiment started). There were no significant effects of TMS or site on response accuracy. The majority of errors were response omissions: there were insufficient errors of commission to permit an analysis of different error types.

Results

Behavioural effects: As in other cyclical naming studies, there was a strong effect of relatedness overall ($F(1,15) = 68.8$, $p < .001$), with slower responses to items presented in related than unrelated sets (reflecting increased competition during picture naming when semantically-related items were named in the same block). There was also a strong effect of cycle ($F(5, 75) = 64.9$, $p < .001$), with a sharp decrease in RT between cycles one and two (due to repetition priming). As expected, there was a highly significant interaction between relatedness and cycle ($F(5,75) = 81.6$, p

< .001), which reflected (i) greater *retrieval* demands for *unrelated* sets particularly on *early* cycles and (ii) greater *selection* demands for *related* sets particularly on *later* cycles. This interaction was explored using Bonferroni t-tests, corrected for 6 comparisons (examining the effect of relatedness at each cycle). On cycle 1, there were faster responses for *related* than unrelated sets (t(13) = -7.1, p < .001), since semantic priming between related items helped to ameliorate the high retrieval demands during naming on cycle 1. The effect of semantic facilitation at cycle 1 was larger than that reported in several previous studies (e.g., Belke et al., 2005), perhaps because our familiarisation procedure ensured that participants knew the items within each set before the experiment commenced. Moreover, we used sets of highly related items that could be named at the specific level (i.e., types of shoes – clogs, trainers etc.), and previous work has shown stronger facilitation of picture naming by close semantic neighbours of the target (Mahon et al., 2007). In contrast, on cycles 2-6 following repetition of the related and unrelated sets, there were faster responses to *unrelated* items (Bonferroni t(13) > 5.9, p < .001). This advantage for unrelated over related sets became stronger across cycles, as competition between related items strengthened as they were repeated (t = 5.9 on cycle 2; t = 15.0 on cycle 6).

TMS effects on cyclical naming: Figure 2 shows naming latencies for each site, cycle and related/unrelated sets, with and without an influence of TMS, while Figure 3 shows the TMS effect (i.e., a difference score) for each condition. Omnibus ANOVA examining the effects of site by TMS by relatedness by cycle (2 x 2 x 2 x 6) revealed a significant 3-way interaction between TMS, relatedness and cycle, indicating that TMS had a differential effect for the related/unrelated sets across the six cycles (see Table 1). There was also a site by relatedness interaction: the relatedness effect (i.e., slower naming of related than unrelated sets, which characterised cycles 2-6) was somewhat larger for pMTG (Bonferroni t(15) = 8.38, *p* < .001) than for LIFG (Bonferroni t(15) = 6.09, *p* < .001). We focus the remainder of the analysis on the way in which TMS effects varied as a function of relatedness and cycle (at each site separately), and return to the question of whether there could be subtle differences across sites in the Discussion.

	Df	F	*p*
Site	1, 15	<1	0.34
TMS	1, 15	<1	0.93
Site x TMS	1, 15	<1	0.56
Site x Relatedness	1, 15	**5.72**	**0.03**
TMS x Relatedness	1, 15	<1	0.57
Site x TMS x Relatedness	1, 15	1.49	0.24
Site x Cycle	5, 75	<1	0.78
TMS x Cycle	5, 75	<1	0.84
Site x TMS x Cycle	5, 75	<1	0.98
Site x Relatedness x Cycle	5, 75	1.58	0.18
TMS x Relatedness x Cycle	5, 75	**3.44**	**0.01**
Site x TMS x Relatedness x Cycle	5, 75	<1	0.67

Table 1. Omnibus ANOVA investigating interactions of TMS with site and task. Site = LIFG vs. pMTG. TMS = baseline performance vs. post-TMS session. Relatedness = related vs. unrelated picture naming sets. Cycle = Cycle 1, 2, 3, 4, 5, 6.

To unpack the complex three-way interaction between TMS, relatedness and cycle, we computed ANOVAs at each site for each cycle to establish *when* and *where* TMS was having a differential effect on the naming of related and unrelated sets (see Table 2). For LIFG, there was a TMS by relatedness interaction at cycle 1. There were no main effects or interactions involving TMS for any other cycle at this site. The TMS by relatedness interaction on the first cycle was further examined using two-tailed Bonferroni-corrected t tests that computed the difference between related and unrelated sets in the presence or absence of TMS to LIFG. The *p* values were corrected across 2 comparisons (examining the effect of relatedness at baseline and following TMS). These t tests confirmed that there was a highly significant advantage for related over unrelated sets in the baseline data (Bonferroni t(15) = 7.98, *p* < .001). Following TMS to LIFG, semantic facilitation was weaker but still reached significance (Bonferroni t(15) = 3.05, *p* = .016).

There was also an interaction (TMS by relatedness) at cycle one for the pMTG site (Table 2). Again, Bonferroni-corrected t-tests were used to investigate this interaction, as above. There was a strong advantage for related over unrelated sets at baseline (Bonferroni t(15) = 6.18, *p* < .001) and a smaller yet still significant effect of relatedness following the application of TMS (Bonferroni t(15) = 2.11, *p* = .03). Thus, TMS to both sites reduced the semantic facilitation effect.

<u>TMS effects on number naming control task</u>: TMS did not increase number naming latencies, at either LIFG (baseline: 972ms, SE=52; post-TMS: 946ms, SE = 54) or pMTG (baseline: 966ms, SE = 69; post-TMS: 924ms, SE=61). In fact, there was near-significant facilitation of number naming

following TMS (F(1, 15) = 3.99, *p* = .064). TMS-induced facilitation of control tasks has also been reported in other studies (e.g., Hoffman et al., 2011). This pattern confirms that the disruptive effect of TMS on cycle 1 for related sets was specific to lexical/semantic retrieval, and did not extend to speech production in general.

		LIFG		pMTG	
		TMS	TMS x Relatedness	TMS	TMS x Relatedness
Cycle	*df*	1, 15	1, 15	1, 15	1, 15
1	F	<1	**4.64**	<1	**5.27**
	p	*0.78*	***0.04***	*.88*	***0.04***
2	F	<1	1.82	<1	<1
	p	*0.99*	*0.20*	*0.67*	*0.76*
3	F	<1	2.16	<1	<1
	p	*0.97*	*0.16*	*0.45*	*0.86*
4	F	<1	1.07	<1	<1
	p	*0.77*	*0.32*	*0.43*	*0.99*
5	F	<1	3.45	<1	<1
	p	*0.80*	*0.08*	*0.88*	*0.64*
6	F	1.08	<1	<1	2.42
	p	*0.31*	*0.48*	*0.41*	*0.14*

Table 2. ANOVAs investigating TMS effects for each cycle, following stimulation of LIFG and pMTG. Relatedness = related vs. unrelated picture naming sets.

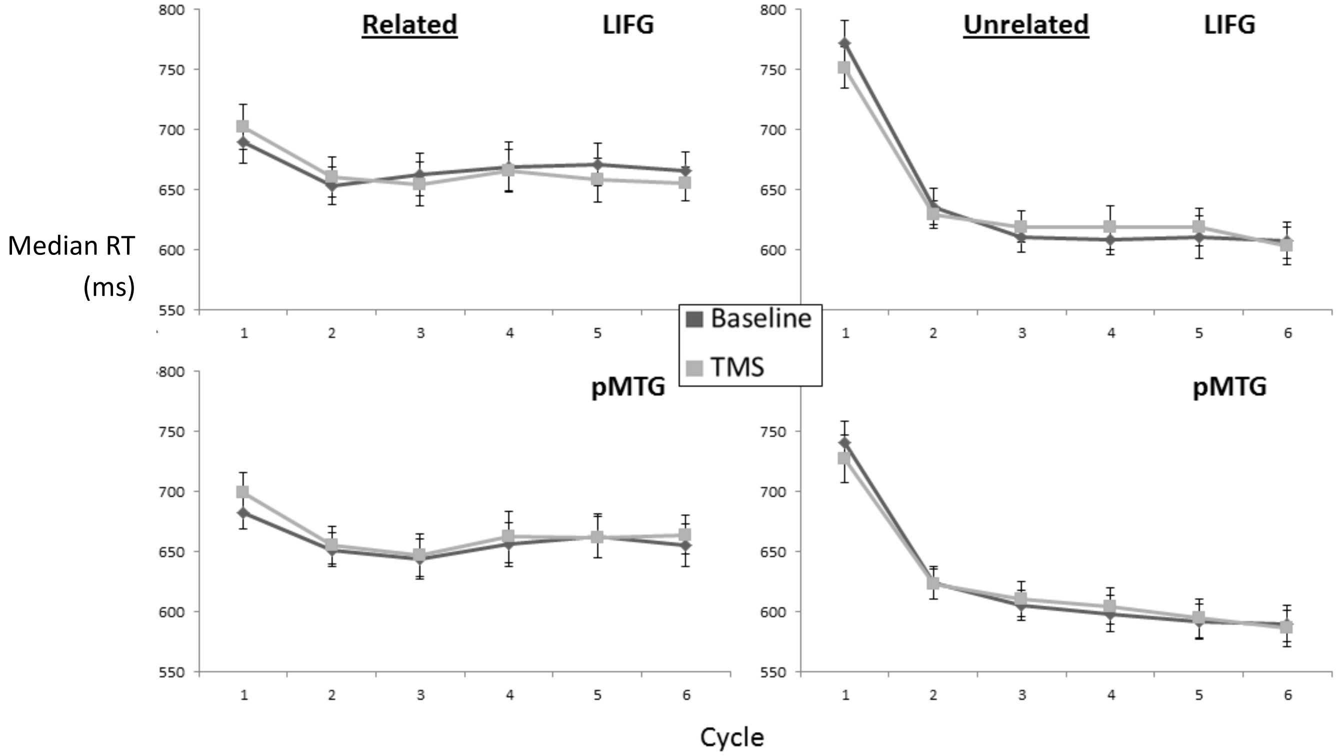

Figure 2. Median picture naming latencies for semantically related and unrelated sets, with and without an influence of TMS (baseline = no TMS) at each site (LIFG, pMTG). Error bars indicate standard error of the mean.

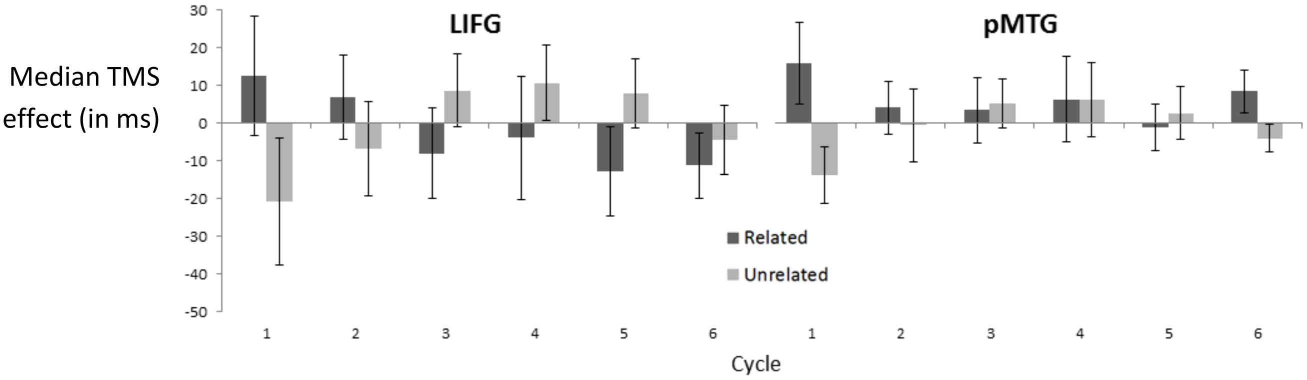

Figure 3. TMS effects (TMS – baseline) at each cycle (1-6). Error bars indicate standard error of the mean.

Discussion

This study investigated the contributions of LIFG and pMTG to retrieval and selection processes within a cyclical naming task, using inhibitory offline TMS. The findings revealed a highly similar involvement of these two sites, converging with recent neuroimaging and TMS studies suggesting that LIFG and pMTG work together to support lexical and semantic retrieval, particularly in executively-demanding contexts (e.g., Noonan et al., 2013; Noppeney et al., 2004; Whitney et al., 2011a; 2011b; Wright et al., 2011). TMS to both sites produced selective slowing for *semantically related* items on the *first cycle* – i.e., when high retrieval demands could be overcome by drawing on the activation of neighbouring concepts. Specifically, the size of the semantic facilitation effect was reduced by the application of TMS to both LIFG and pMTG.

Behaviourally, we observed both semantic facilitation and interference effects in this study. (i) Facilitation occurred on the first cycle, when retrieval demands were maximal (i.e., naming was faster for related than unrelated items). Our use of specific-level picture naming and highly related sets of concepts (i.e., different types of shoe, with largely-overlapping features) may have increased levels of facilitation in our paradigm, given that in previous studies, strong semantic neighbours elicited improved performance (Mahon et al., 2007; Navarrete et al., 2012). (ii) On later cycles, we saw semantic interference instead of facilitation (better performance for unrelated than related sets). Computational models based on interactive-activation and competitive settling show that weak activation of non-target neighbours produces facilitation, while strong activation elicits interference (Chen & Mirman, 2012): this provides a parsimonious account of why semantic effects switched from facilitation to interference in this experiment (see also Rahman & Melinger, 2009 for a related account).

TMS to both LIFG and pMTG selectively interfered with semantic facilitation effects on cycle 1 and did not modulate the magnitude of semantic interference effects on later cycles. This pattern of results might reflect TMS-induced disturbance to the ability to maintain weak activation within a set of semantically-related items and/or a failure to benefit normally from this semantic set, due to difficulty 'settling' on the target response when levels of activation were low. There was no disruptive effect of TMS at either site when retrieval demands were maximal yet semantic processing and selection demands were minimised (i.e., on the first cycle for *unrelated* sets) – instead, these trials tended to show *facilitation* following TMS. There was also no clear disruptive TMS effect when competition between highly activated semantically-related items was maximal (i.e., on later cycles for related sets), even though the behavioural effects of competition were apparent (namely, there was a strong advantage for unrelated over related sets from cycle 2). Finally, there were no inhibitory TMS effects on a demanding number naming control task that tapped language production yet minimised lexical/semantic selection and retrieval – if anything, TMS again facilitated performance on this task. The TMS results therefore show that both LIFG and pMTG make a necessary contribution to semantically-driven word production, especially when retrieval demands are maximal, yet the role of these sites cannot be characterised simply in terms of lexical/semantic 'retrieval' or 'selection'.

We propose that TMS to LIFG and pMTG modulates spreading activation within the *conceptual* system, as opposed to effects within the speech production system per se. Although some researchers have proposed a special role for LIFG in resolving competition within the speech production architecture, and have characterised the semantic blocking effects seen in cyclical picture naming tasks as arising from the 'lemma' level of psycholinguistic models (Belke et al., 2005; Maess et al., 2002; Schnur et al., 2006), patients with lesions to mid-LIFG and pMTG show parallel deficits on comprehension tasks employing verbal and non-verbal stimuli (Corbett et al., 2009a; 2009b; 2011), suggesting that this site contributes to the selection and retrieval of internally-stored conceptual representations across modalities. This hypothesis is supported by the finding that, unlike semantic blocking, *phonological* blocking manipulations (where phonologically-similar items are presented repeatedly in sets for naming) are not associated with increased activation in LIFG or pMTG (Schnur et al., 2009). Moreover, although early research focussed on the issue of whether LIFG has a particular role in lexical/semantic selection or controlled aspects of retrieval (Badre et al., 2005; Thompson-Schill et al., 1997; Wagner et al., 2001), more recent studies suggest that these components of semantic cognition interact and are supported by the same control mechanisms (e.g., Snyder et al., 2011). This viewpoint is compatible with our finding of maximal TMS disruption when there were high retrieval demands, plus semantically-related sets (i.e., when the spread of activity through the semantic system was relevant to naming performance).

A key question motivating this study concerned the *relative* contribution of pMTG and LIFG to the selection and retrieval of lexical/semantic representations. Some researchers have argued that although pMTG and LIFG show coupled activation, they nevertheless have functionally dissociable roles, with pMTG supporting semantic retrieval and LIFG playing a more unique role in selection (Badre et al., 2005; Bedny et al., 2008; Gold et al., 2006). This framework might predict a double dissociation, such that TMS to pMTG should slow naming on the first cycle of unrelated sets (when retrieval demands are high), while stimulation of LIFG should leave the first cycle of naming unaffected, with disruption at later cycles (i.e., when selection peaks). We found no such dissociation: both sites showed the same pattern on a task designed to separate selection and retrieval requirements. This fits well with the idea that these two sites become functionally coupled in tasks in which lexical/semantic activation must be controlled (Jefferies, 2013; Noonan et al., 2013; Turken & Dronkers, 2011) and with TMS studies showing that stimulation of both pMTG and LIFG produces equivalent disruption of tasks designed to maximise either semantic selection requirements or controlled retrieval demands (Whitney et al., 2011b, 2012).

Given our data and these previous findings, it seems unlikely that lexical/semantic selection and controlled retrieval can occur only on the basis of processes intrinsic to the lexical/semantic system. Instead, top-down cognitive control mechanisms appear to play an important role in biasing interactive-activation processes to promote the target response, and constraining processing to suit the context (Bedny et al., 2008; Jefferies et al., 2007; Schnur et al., 2009; Thompson-Schill et al., 1999). This top-down control of lexical/semantic activation appears to recruit a distributed functional system drawing on *both* LIFG and pMTG. We and others have previously proposed that interactions between LIFG and pMTG are necessary for the identification and maintenance of aspects of semantic knowledge that are currently relevant – a crucial function for the executive control of semantic activation (Jefferies, 2013; Noonan et al., 2013; Turken & Dronkers, 2011). This hypothesis fits well with the data from this study, since Rahman and Melinger (2009) have suggested that on the first presentation of sets in cyclical naming tasks (in the absence of TMS), participants might establish an 'ad-hoc category' (cf. Barsalou, 1991) that encompasses the concepts that are likely to be relevant in the current task context. If TMS to LIFG and pMTG disrupted the ability to identify and maintain concepts that are currently relevant, semantic facilitation would be reduced on cycle 1, and the process of efficiently ‘settling’ on the target response in the face of high retrieval demands would be impaired. However, competition within the semantically related sets might also be reduced on later cycles by this failure to maintain currently-relevant aspects of knowledge, and this might explain the absence of a TMS effect at either site when selection demands were maximal.

Our data are compatible with the findings of many neuropsychological studies, as noted above; however, on the cyclical naming paradigm specifically, patients with lesions encompassing our two stimulation sites show important differences: cases who have damage to LIFG show increasing errors across cycles for semantically-related sets, while patients with damage restricted to temporoparietal regions show only very subtle or no effect of cycle (Campanella et al., 2009; Gardner et al., 2012; Jefferies et al., 2007; Schnur et al., 2009). Some researchers have suggested that this difference reflects a greater involvement of LIFG in the resolution of competition (Schnur et al., 2006; Schnur et al., 2009) and, at first glance, these data do not relate very easily to the TMS findings we report here. However, it is difficult to draw direct comparisons between patients and healthy individuals on the cyclical naming task because the behavioural effects, even without any effect of TMS, show a different profile. In healthy individuals, the blocking profile (i.e., faster naming of unrelated sets) starts on cycle 2 and is stable across subsequent cycles – whereas in patients with LIFG lesions, the blocking effect builds-up cumulatively across cycles (Belke & Stielow, 2013). One possibility, suggested by the current TMS data and other tasks in the neuropsychological literature, is that LIFG and pMTG do jointly support semantic control, and their engagement is maximised in situations in which both selection and retrieval demands are high (since these processes interact), but that patients with LIFG lesions show more dramatic effects of cycle, and a growth of perseverations across cycles, because they have additional deficits (following their more extensive lesions or white matter damage) – for example, in resetting top-down goals for semantic retrieval as the target shifts, or in overcoming interference from previously-selected responses and re-activating representations which were previously inhibited.

Finally, even though stimulation of LIFG and pMTG had broadly equivalent effects, we briefly consider the possibility of subtle differences between these sites. In the omnibus ANOVA, there was a site by relatedness interaction: this reflected virtually identical naming latencies for the related sets across the two sites, yet slightly slower responses to the unrelated items for LIFG. The unrelated sets may have had longer RTs because there was a near-significant TMS by relatedness interaction on cycle 5 at this site (see Table 2), characterised by greater interference for unrelated sets. By the later cycles, the unrelated items might have started to generate substantial competition (since all of the items in the set had been named repeatedly), and yet they may still have posed greater retrieval demands than the related items: in other words, this near-significant interaction between TMS and relatedness might once again reflect TMS-induced disruption when both retrieval and selection demands were relatively high. Further empirical work is need to confirm whether these possible effects are genuine. However, if TMS to LIFG does prove to increase naming latencies for unrelated sets at later cycles more than stimulation of pMTG, LIFG might play a greater role in establishing and maintaining an ad-hoc category of possible responses when this is not based on semantic relationships.

In conclusion, the cyclical naming task provides a unique opportunity to separate retrieval processes (which are maximal on cycle one for unrelated sets) and selection demands (which are high on later cycles for related sets). We show that TMS to pMTG and LIFG disrupted performance on the first cycle for related sets, i.e., when high retrieval demands could be ameliorated through the activation of semantically-related items from the set. This corroborates previous TMS studies demonstrating a similar involvement of the two sites in the control of lexical/semantic retrieval (Whitney et al., 2011b, 2012). This pattern could reflect disturbance to the ability to identify and maintain concepts that are currently relevant, impairing the process of efficiently ‘settling’ on the target response in the face of high retrieval demands.

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Supplementary materials

		LIFG		pMTG	
		Mean	SD	Mean	SD
Baseline, related	Cycle 1	0.94	.065	0.94	.045
	Cycle 2	0.94	.043	0.96	.031
	Cycle 3	0.94	.054	0.95	.035
	Cycle 4	0.93	.066	0.94	.065
	Cycle 5	0.94	.058	0.95	.048
	Cycle 6	0.94	.063	0.95	.059
Post-TMS, related	Cycle 1	0.93	.070	0.94	.061
	Cycle 2	0.95	.082	0.94	.064
	Cycle 3	0.92	.092	0.94	.063
	Cycle 4	0.95	.069	0.94	.068
	Cycle 5	0.93	.074	0.94	.060
	Cycle 6	0.94	.064	0.93	.069
Baseline, unrelated	Cycle 1	0.94	.055	0.94	.031
	Cycle 2	0.95	.054	0.97	.037
	Cycle 3	0.96	.070	0.97	.028
	Cycle 4	0.95	.060	0.98	.017
	Cycle 5	0.95	.076	0.96	.050
	Cycle 6	0.95	.104	0.97	.031
Post-TMS, unrelated	Cycle 1	0.91	.115	0.94	.055
	Cycle 2	0.93	.138	0.94	.042
	Cycle 3	0.94	.107	0.96	.050
	Cycle 4	0.95	.087	0.98	.021
	Cycle 5	0.95	.075	0.97	.034
	Cycle 6	0.97	.058	0.96	.037

Supplementary Table S1. Descriptive statistics for naming accuracy. Table shows mean proportion of trials correct in each condition across 16 participants. SD = standard deviation.

	df	F	*p*
Relatedness	1, 15	5.97	**.03**
Cycle	1, 15	3.42	**.01**
Relatedness x Cycle	5, 75	2.83	**.02**
Site	1, 15	<1	.46
TMS	1, 15	1.69	.21
Site x TMS	1, 15	<1	.79
Site x Relatedness	1, 15	2.67	.12
TMS x Relatedness	1, 15	<1	.98
Site x TMS x Relatedness	1, 15	<1	.42
Site x Cycle	5, 75	<1	.78
TMS x Cycle	5, 75	<1	.54
Site x TMS x Cycle	5, 75	<1	.59
Site x Relatedness x Cycle	5, 75	<1	.45
TMS x Relatedness x Cycle	5, 75	<1	.73
Site x TMS x Relatedness x Cycle	5, 75	<1	.66

Supplementary Table S1. Omnibus ANOVA for naming accuracy. There were no significant main effects or interactions involving site or TMS.