Semantic Processing in the Left Inferior Prefrontal Cortex: A Combined Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation Study

Joseph T. Devlin, Paul M. Matthews, and Matthew F. S. Rushworth

Abstract

■ The involvement of the left inferior prefrontal cortex (LIPC) in phonological processing is well established from both lesion-deficit studies with neurological patients and functional neuroimaging studies of normals. Its involvement in semantic processing, on the other hand, is less clear. Although many imaging studies have demonstrated LIPC activation during semantic tasks, this may be due to implicit phonological processing. This article presents two experiments investigating semantic functions in the LIPC. Results from a functional magnetic resonance imaging experiment demonstrated that both semantic and phonological processing activated a common set of areas within this region. In addition, there was a reliable increase in activation for semantic relative to phonological decisions in the anterior LIPC while the opposite comparison (phonological vs. semantic decisions) revealed an area of enhanced activation within the posterior LIPC. A second experiment used transcranial magnetic stimulation (TMS) to temporarily interfere with neural information processing in the anterior portion of the LIPC to determine whether this region was essential for normal semantic performance. Both repetitive and single pulse TMS significantly slowed subjects' reactions for the semantic but not for the perceptual control task. Our results clarify the functional anatomy of the LIPC by demonstrating that anterior and posterior regions contribute to both semantic and phonological processing, albeit to different extents. In addition, the findings go beyond simply establishing a correlation between semantic processing and activation in the LIPC and demonstrate that a transient disruption of processing selectively interfered with semantic processing. ■

INTRODUCTION

The posterior portion of the left inferior prefrontal cortex (LIPC), known as Broca's area, is associated with speech production (Broca, 1861). Clinical lesion studies have established that this region of the prefrontal cortex is essential for motor and phonological processes of expressive language and its role in phonological processing has been confirmed by functional neuroimaging (Turennout, Hagoort, & Brown, 1998; Fiez, 1997). Imaging studies have also implicated the LIPC in semantic processing despite the fact that lesions to this region are not thought to result in semantic deficits. Even so, functional neuroimaging studies have helped elucidate the contributions of the LIPC to both phonological and semantic processing and have led to the suggestion that the posterior regions of the LIPC are preferentially involved in phonological processing while anterior and ventral areas may be more involved in semantic processing (Fiez, 1997; Buckner, Raichle, & Petersen, 1995).

Relative to tasks which do not require any lexical analysis (i.e., low level baselines), phonological tasks activate posterior parts of the LIPC. For example, monitoring auditory syllables for particular phoneme sequences relative to simply listening passively to syllables or tones activates BA 44/6 and BA 44/45 (Demonet et al., 1992; Zatorre, Evans, Meyer, & Gjedde, 1992). Similarly, BA 45 is more active for phonemic relative to orthographic decisions in the visual domain (Fiez et al., 1995). By contrast, the anterior LIPC appears to be involved in semantic processing. Relative to orthographic decisions, Kapur et al. (1994) reported semantic-related activity in BA 45/47, while others found such activity in the mid-ventrolateral frontal cortex (BA 47, Petersen, Fox, Posner, Mintun, & Raichle, 1989). Additional evidence of BA 45/47 involvement in semantic processing comes from reductions in activation due to semantic priming (Wagner, Desmond, Demb, Glover, & Gabrieli, 1997; Demb et al., 1995). Taken together, these findings suggest that the LIPC is involved in both phonological and semantic processing (see also Gabrieli, Poldrack, & Desmond, 1998).

The precise location of semantic and phonological functions, however, has proven difficult to determine for several reasons. The three regions of the LIPC primarily associated with semantic and phonological processing are the pars opercularis (POp), the pars triangularis (PTr), and the pars orbitalis (POr; see

---

University of Oxford

© 2003 Massachusetts Institute of Technology

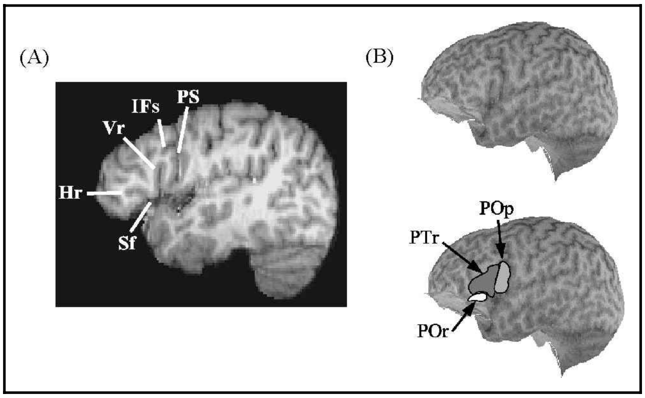


Figure 1. Anatomical landmarks within the LIPC. (A) In this sagittal plane, all three regions can be seen. The pars opercularis (POp) can be delimited rostrally, by the vertical (ascending) ramus of the Sylvian fissure (Vr); dorsally, by the inferior frontal sulcus (IFs); caudally, by the inferior segment of the precentral sulcus (PS); and ventrally, by the Sylvian fissure (Sf). Immediately anterior to this region is the pars triangularis (PTr), which is defined dorsally by the inferior frontal sulcus and ventrally by the horizontal ramus of the Sylvian fissure (Hr). Finally, the pars orbitalis (POr) is ventral to the PTr and extends to the lateral orbital sulcus and to the Sylvian fissure. (B) Two identical 3-D renderings of a left hemisphere illustrate these regions.

Figure 1) and correspond roughly to BA 44, 45, and 47 (but see Amunts et al., 1999). Of the three, PTr and POp have been associated with both semantic and phonological processing (Poldrack et al., 1999; Klein, Milner, Zatorre, Meyer, & Evans, 1995; Demonet et al., 1992) and POr has been associated with semantics (Fiez, 1997; Buckner et al., 1995). Thus, the relation between specific anatomic regions and types of linguistic processing is not yet clear. Is there a strong anterior–posterior division of labor or are all three regions involved in both semantic and phonological processing with relatively more involvement anteriorly for semantics and posteriorly for phonology? The latter is consistent with the fact that most studies which directly compared semantic and phonological conditions failed to find significant differences within the inferior prefrontal cortex (e.g., Demonet et al., 1992), although several have noted trends in agreement with previous findings (Mummery, Patterson, Hodges, & Price, 1998; Price, Moore, Humphreys, & Wise, 1997). Only one study has found reliably greater activation for semantic tasks in the POr (Poldrack et al., 1999). A lack of significant differences could occur for many reasons, of course, and therefore does not provide strong evidence for common areas of semantic and phonological processing.

The issue is particularly important in light of evidence for automatic, or implicit, semantic and phonological processing of meaningful stimuli such as words or pictures (Price, Wise, & Frackowiak, 1996; Van Orden, Johnson, & Hale, 1988). If semantic tasks automatically engage phonological processes, then activity throughout the LIPC may reflect phonological rather than semantic processing. Although functional neuroimaging can demonstrate a correlation between LIPC activation and semantic processing, it cannot establish a causal relation.

Transcranial magnetic stimulation (TMS) provides a complementary approach to determining whether the LIPC is involved in normal semantic processing. When TMS is applied over a brain area, normal functioning is transiently disrupted (Jahanshahi & Rothwell, 2000; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Walsh & Rushworth, 1999). If the stimulated area is involved in the cognitive task, then performance may be impaired or slowed (Ashbridge, Walsh, & Cowey, 1997; Amassian, 1989). If the area is not essential, then the TMS either has no effect or may even facilitate task performance (intersensory facilitation effect, Walsh & Rushworth, 1999). An important advantage of TMS relative to lesion studies is that there is insufficient time for functional reorganization to occur during single TMS events. Consequently, the results should not be substantially confounded by any recovery processes (Walsh & Cowey, 1998).

Few studies have applied TMS to linguistic tasks with most of the early ones focused on speech disruption because of its clinical relevance (Stewart, Walsh, Frith, & Rothwell, 2001; Epstein et al., 1996; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994; Pascual-Leone, Gates, & Dhuna, 1991). More recently, cognitive aspects of language have also been explored in two studies which investigated the effect of TMS on picture naming latencies (Stewart, Meyer, Frith, & Rothwell, 2001; Topper, Mottaghy, Brugmann, Noth, & Huber, 1998). These represent an important advance over speech arrest by providing a quantitative measure of subjects' responses (i.e., naming latencies), which could be statistically analyzed to demonstrate the reliability of the findings. There are, however, practical considerations with the use of TMS in language tasks. One concerns potential artifacts from oral–facial muscle movements induced by the TMS. The other relates to the difficulty in determining the precise site of stimulation as there is no obvious and immediate corollary of single pulse stimulation over the LIPC analogous to the muscle responses or phosphemes that are found after stimulating primary motor or visual regions. The current study was designed to address both of these issues. The use of a comprehension task avoided confounds between oral–facial muscle effects and central language effects that are inherent in speech production. The use of frameless stereotaxy enabled us to target a specific anatomical location in each of our subjects (Paus et al., 1997; Paus, 1999).

This article presents two experiments to investigate language functions in the LIPC. The first used functional magnetic resonance imaging (fMRI) to investigate semantic and phonological processes. Separate low-level baseline tasks were included to identify areas of activation common to both phonology and semantics. In addition, semantic and phonological tasks were directly contrasted to identify regional enhancements in activation. A second experiment used TMS to determine the extent to which semantic processing requires the LIPC.

RESULTS

Experiment 1: Phonological and Semantic Decisions with fMRI

We investigated the demands placed on the LIPC as subjects performed semantic and phonological tasks. The experiment was conducted in two consecutive scanning sessions (A and B). In Session A, participants made either a semantic or a phonological decision to a visually presented word (Figure 2). In Session B, participants made either a semantic or a perceptual decision to a visually presented word. Both sessions contained a resting baseline condition. Semantic decisions required subjects to make a choice based on the meaning of the word while phonological decisions forced participants to attend to its phonological form by judging the number of syllables in the word. Although perceptual decisions also used visually presented words, task performance was based on the size of the word rather than any lexical properties.

This design enabled us to identify three distinct patterns of activation in the LIPC. First, we used a conjunction analysis (Worsley & Friston, 2000; Friston, Holmes, Price, Buchel, & Worsley, 1999; Price & Friston, 1997) to identify common areas of phonological and semantic activity relative to rest. Because both semantic and phonological processes have been associated with "resting" baselines (Binder et al., 1999), a second analysis compared semantic decisions to a nonlinguistic baseline, namely, perceptual decisions, to determine whether the same LIPC areas were activated. Finally, the direct contrast of semantic and phonological decisions tested for regional specialization for the two types of processing. We expected that (i) both the semantic and phonological tasks would activate all three regions of the LIPC relative to low level baselines and (ii) semantic processes would show relatively greater activation in anterior regions while phonological processes would show relatively greater activation in posterior regions (Poldrack et al., 1999; Fiez, 1997; Buckner et al., 1995). Because voxel-based Gaussian random field corrections can be very conservative, a priori regions of interest (ROIs) were defined for the POp, PTr, and POr. These were used to both limit the number of statistical comparisons according to the above predictions and more precisely identify the anatomic locations of activations within LIPC (see Methods).

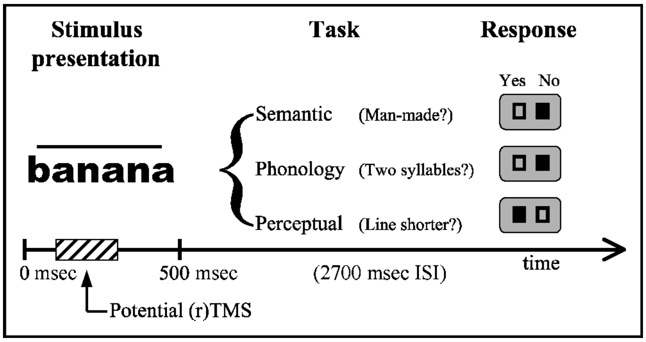


Figure 2. An illustration of the three behavioral tasks. In each, a trial began when a word and a horizontal line appeared on a blank screen. Participants made a button press response depending on the task they were performing. The semantic task involved deciding whether the word represented a man-made object. Phonological decisions were based on the number of syllables in the word and perceptual decisions compared the length of the word on the screen to the length of the line. In the TMS experiments, stimulation came between 100 and 300 msec poststimulus onset on 33% of the rTMS trials and 75% of the single pulse trials as indicated by the hatched block on the time line. After a 500-msec stimulus duration, the screen cleared and there was a 2700-msec interstimulus interval (ISI).

Table 1. Behavioral Results for Tasks in the fMRI Experiment

Task	*Accuracy [%]*	*Reactions Times (±SEM) [msec]*
Phonological decisions	95.7	901 (±56)
Semantic decisions	96.7	848 (±52)
Perceptual decisions	96.7	684 (±49)*

*$p < .05$.

Subjects' accuracy and reaction times (RTs) are reported in Table 1. The error rates were too low to analyze, indicating that the subjects were correctly performing the tasks. A one-way ANOVA with task as a factor and RTs as the dependent measure revealed a significant effect of task [$F_2(2) = 4.9, p < .05$]. Bonferroni corrected post hoc pairwise comparisons confirmed that perceptual decisions were faster than both the other tasks (both $p < .05$). There was no significant difference between RTs for the semantic and phonological decisions.

The areas commonly activated by the semantic and phonological tasks are shown in Table 2. These included a highly significant cluster of voxels spanning the anterior and posterior LIPC and including all three component regions, namely, the POp, PTr, and POr (see Figure 3A).

To investigate whether the resting baseline may have affected the activity in the LIPC, we next contrasted semantic decisions to the perceptual baseline task. As can be seen in Figure 3B, semantic decisions produced highly significant activation in all three regions of the LIPC with the two most significant peaks in anterior regions, namely, PTr ($x = -54$, $y = +34$, $z = +8$, $Z = 8.5$) and POr ($x = -38, y = +36, z = -16, Z = 9.0$). The main differences between the results of this analysis and the previous one was activity in the premotor,

Table 2. Brain Activity Common to Semantic and Phonological Decisions Relative to Separate Rest Conditions

Description	*x*	*y*	*z*	*SPM{Z}*	*Extent*
Frontal					
LIPC (POp)	−44	8	28	Inf	895
	−50	16	22	Inf	
LIPC (PTr)	−46	30	16	Inf	
	−42	24	0	5.3	
	−42	24	2	4.8	
LIPC (POr)	−36	26	−6	Inf	
	−42	48	−14	7.5	
	−46	20	−6	7.1	
L. SMA	−6	−2	62	Inf	23
Parietal					
L. posterior intraparietal sulcus	−28	−72	50	6.3	16
Temporal					
L. middle temporal gyrus	−52	−48	−2	7.3	89
L. fusiform extending into the cerebellum	−44	−54	−20	Inf	553
	−34	−42	−36	Inf	
	−36	−44	−28	Inf	
L. inferior temporal gyrus	−34	−6	−40	5.4	19
Occipital					
R. medial and extrastriate visual cortices	24	−98	−4	Inf	203
	18	−92	−10	Inf	
	34	−90	−14	6.9	
L. medial and extrastriate visual cortices	−24	−94	−6	Inf	143
	−36	−92	−10	6.4	
	−16	−92	−12	5.5	
Cerebellum					
R. Crus I	26	−50	−38	Inf	85
	34	−46	−40	Inf	
	42	−46	−38	Inf	
R. VIIB	12	−78	−44	6.6	49
R. V	10	−62	−14	6.1	18

The conjunction was inclusively masked by the comparison of semantic and perceptual decisions to remove nonlexical effects such as activations from button presses. SPM{*Z*} is the *Z*-score at the peak voxel where ‘‘Inf’’ indicates a $Z > 8.2$. The extents (in 2 mm^3 voxels) are shown for an uncorrected height threshold of $p < .001$.

LIPC = left inferior prefrontal cortex; POp = pars opercularis; PTr = pars triangularis; POr = pars orbitalis; SMA = supplementary motor area.

sensory–motor, SMA, and cerebellar regions presumably related to making a button press response in the perceptual condition but not during rest.

Finally, we directly contrasted semantic and perceptual decisions. Relative to phonological decisions, semantic decisions activated left hemisphere regions

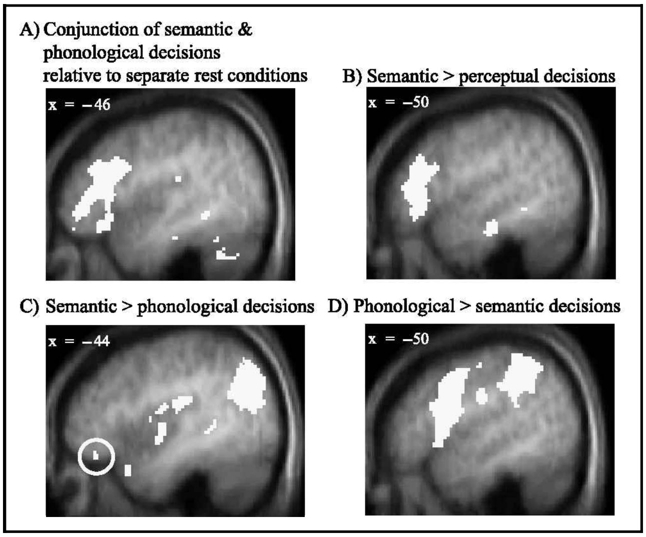


Figure 3. Parasagittal views of LIPC activations displayed on the mean structural MRI of the 12 subjects. (A) Activation was present for both semantic and phonological decisions relative to rest in the POp, PTr, and POr. (B) Semantic relative to perceptual decisions produced activation in all three regions of the LIPC at $Z > 3.1$ with the largest peaks in the PTr and POr (shown here at $Z > 4.7$). (C) Semantic decisions increased activation in a region of POr (circled) relative to phonological decisions (D) while the opposite comparison increased activation in a region of the POp.

within the frontal pole, the superior frontal sulcus, the inferior angular gyrus, and the precuneus (see Table 3). There was no significant activation for semantics relative to phonological decisions in the LIPC in the whole-brain analysis. When the sensitivity was increased by limiting the statistical comparisons to the area of expected differences, POr, and applying a small volume correction (Worsley et al., 1996), activation was identified at $x = -44$, $y = +38$, $z = -20$ (SPM$\{Z\}$ = 3.3, $p < .05$; Figure 3C). Even with an uncorrected $p < .05$ threshold ($Z > 1.65$), there was no activation present in either the PTr or the POp.

A larger network of brain regions showed significant activation for the opposite contrast, phonological relative to semantic decisions (see Figure 3D; Table 3). This included highly significant bilateral activations within the posterior LIPC (namely, the POp), the anterior insula, the dorsal surpramarginal gyrus, the posterior intraparietal sulcus, and the anterior fusiform gyrus. In addition, there was right lateralized activity in the paracingulate gyrus extending rostrally and ventrally from the pre-SMA, in the frontal pole near the fronto-marginal sulcus, and in the left cerebellum.

Experiment 2: TMS of the Anterior LIPC

The results of the fMRI experiment confirm that both semantic and phonological processing activate the whole of the LIPC but do not rule out the possibility that implicit phonological processing could produce the activation during the semantic task. Consequently, we conducted a second experiment using TMS to determine the extent to which the LIPC was necessary for normal performance of this semantic task.

TMS induces a local current in a target neuronal population that leads to a transient disruption of processing within a cortical area. Unlike a lesion, the effect is not a complete inactivation, but rather, an increase in noise, which lasts a limited period of time. For that reason, the effect is typically measured as increased RTs rather than in error rates (Jahanshahi & Rothwell, 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Walsh & Rushworth, 1999; Walsh & Cowey, 2000). In this experiment, we evaluated the contribution of the anterior LIPC to semantic decision making because this region showed relatively greater activation compared to both phonological and perceptual processing. Perceptual decisions were included as a control task. We anticipated that stimulation would interfere with the semantic but not perceptual task.

To observe a TMS effect, however, requires not only correct spatial localization but also delivery of the TMS pulse at an appropriate time relative to the stimulus. Repetitive TMS (rTMS) provides an excellent exploratory tool because the short train of pulses encompasses a larger temporal window and may produce a larger area of effect (due to intracortical spreading) than single pulses (Pascual-Leone et al., 1999). Consequently, the first part of this experiment used rTMS to determine whether stimulating an anterior region of the LIPC interfered with either task. In the second part of this experiment, single pulses of TMS were delivered at 100, 150, 200, 250, and 300 msec poststimulus onset to elucidate the time course of semantic processing in the LIPC. In both cases, the perceptual task was used as a control.

Frameless stereotaxy was used to identify the site of stimulation in each participant (Paus et al., 1997; Paus, 1999). Stimulation sites were mapped into a standard space by registering them to each participant's structural MRI and then to the Montreal Neurological Institute mean brain using an affine registration (Jenkinson & Smith, 2001). The mean stimulation site in the standard space was $x = -52$, $y = +24$, $z = -2$ (Figure 4). White circles indicate the position of the centers of stimulated brain areas for individual subjects. All stimulation sites were in front of the vertical ramus of the Sylvian fissure and on or above the horizontal ramus. They clustered near the apex of the PTr and on the PTr/POr border, both in the more anterior parts of the LIPC.

We compared the correspondence between the stimulation and activation sites in the three subjects who participated in both the fMRI and TMS experiments (see Figure 5 and Table 4). The stimulation sites ranged from 3 to 6 mm from the individual subject's nearest active voxel (where "active" was defined as

Table 3. A Comparison of Brain Activity in Semantic and Phonological Decisions

Description	*x*	*y*	*z*	*SPM{Z}*	*Extent*
Semantic > Phonological Decisions					
Frontal lobes					
L. frontal pole	−10	52	−8	6.8	64
	−14	44	−8	5.4	
L. superior frontal sulcus	−20	30	48	5.2	21
Parietal lobes					
Post. inferior angular gyrus	−42	−66	28	6.0	79
L. precuneus	−4	−56	28	5.7	74
Phonological > Semantic Decisions					
Frontal lobes					
LIPC (POp extending into the iFG)	−50	6	24	Inf	1117
	−42	0	28	Inf	
	−38	−2	44	6.6	
R. mFG/iFG	44	36	26	Inf	2184
	46	42	14	Inf	
	42	2	28	Inf	
RIPC (POr) extending into	46	28	−16	7.3	241
R. anterior insula	36	24	−8	6.0	
L. anterior insula	−30	20	−8	7.0	137
L. iFS/medial PTr	−42	34	12	5.6	72
	−38	34	20	5.5	
	−42	36	30	5.1	
R. paracingulate sulcus extending into the pre-SMA	6	36	42	7.8	604
	4	16	54	7.2	
	4	28	46	6.6	
R. frontal pole	24	52	−8	6.7	52
Parietal lobes					
R. dorsal supramarginal gyrus	46	−44	44	Inf	1335
	44	−56	52	Inf	
	52	−60	48	6.4	
L. dorsal supramarginal gyrus	−42	−40	46	Inf	1480
	−56	−44	46	7.5	
	−52	−48	54	7.4	
R. posterior intraparietal sulcus	28	−68	44	6.7	155
	34	−64	36	5.4	
L. posterior intraparietal sulcus	−20	−68	46	6.7	131
	−24	−72	36	5.5	

Table 3. (*continued*)

Description	*x*	*y*	*z*	*SPM{Z}*	*Extent*
Phonological > Semantic Decisions					
	−10	−70	50	5.4	
Temporal lobes					
L. fusiform	−48	−66	−20	7.1	393
	−50	−54	−20	6.9	
	−50	−66	−10	6.2	
R. fusiform	52	−56	−16	7.1	197
	52	−56	−26	6.0	
	42	−58	−10	5.4	
Cerebellum					
L. VIIIA	−30	−60	−44	6.4	81

The top portion of the table displays the regions of activation for semantic > phonological decisions. The bottom half shows the results of the opposite comparison. The extents (in 2 mm^3 voxels) are shown for a corrected height threshold of $p < .05$.

LIPC = left inferior prefrontal cortex; RIPC = right inferior prefrontal cortex; POp = pars opercularis; iFG = inferior frontal gyrus; mFG = middle frontal gyrus; POr = pars orbitalis; iFS = inferior frontal sulcus; SMA = supplementary motor area.

$Z > 3.1$) or from 7 to 13 mm from their most active voxel. In general, activation in the semantic versus perceptual decisions contrast was anterior to the site of stimulation (cross-hairs).

As anticipated, TMS did not significantly influence participants' accuracy in either the repetitive [$t(7) = 0.35$, *ns*] or single pulse trials [$F_2(1,6) = 0.28$, *ns*; see Table 5]. There were, however, reliable RT differences with stimulation (see Figure 6). Relative to no stimulation (solid bars), rTMS (hatched bars) produced a significant increase in RTs for the semantic decision task [one sample $t(7) = 2.07$, $p < .05$ one-tailed; see Figure 6A) with a mean slowing of 72 msec, or 12% relative to the non-TMS baseline. The effect was present in seven of eight subjects and ranged from a 5% decrease in RTs to a 47% increase. In contrast, stimulation did not significantly increase RTs in the perceptual task [one sample $t(7) = 1.34$, *ns*; Figure 6C]. There was, however, only a nonsignificant trend for the TMS-induced disruption to be greater in the semantic task than the perceptual task [paired $t(7) = 1.14$, $p > .1$, one-tailed].

The data from the single pulse experiment are shown in Figure 6. It can be seen that when single TMS pulses were applied 250 msec after the presentation of the stimulus, they slowed subjects' responses in the semantic task by an average of 11% (range: 4–48%; Figure 6B). Single TMS pulses in the perceptual task, on the other hand, had relatively little effect (Figure 6D). The large range in the data made them difficult to analyze because one subject showed an effect approximately five times larger than any other subject, although this subject's RTs were consistent with the pattern seen in the group as a whole. In order to avoid the data from this subject having a disproportionate effect on the results, we used two different analysis strategies. First, we used a nonparametric test based on score ranks rather than raw scores. We found there was a significant effect of TMS pulses applied at different times during semantic task performance [Friedman's ANOVA $\chi^2(5) = 12.3$, $p < .05$] but not during perceptual task performance [Friedman's ANOVA $\chi^2(5) = 8.6$, *ns*]. In order to test whether TMS affected the tasks differently, we also calculated a difference score representing the change in performance between the tasks at each time point per subject. These data were also analyzed with a nonparametric Friedman's ANOVA, which revealed a trend towards a larger effect of TMS in the semantic than in the perceptual task [$\chi^2(5) = 10.1$, $p < .1$]. Second, we used a standard parametric approach to compute linear within-subject contrasts using the general linear model but excluded the data from the outlying subject. One-way ANOVAs confirmed an effect of TMS in the semantic task [$F_2(1,5) = 6.36, p < .05$] but not in the perceptual task [$F_2(1,5) = .06$, *ns*]. In addition, a 2 × 5 ANOVA with task (semantic and perceptual decisions) and TMS (100, 150, 200, 250, and 300 msec) as independent factors confirmed a significant interaction [$F(4,20) = 6.93, p < .05$]. Thus, both statistical approaches revealed virtually equivalent results: namely, a significant effect of stimulation in the

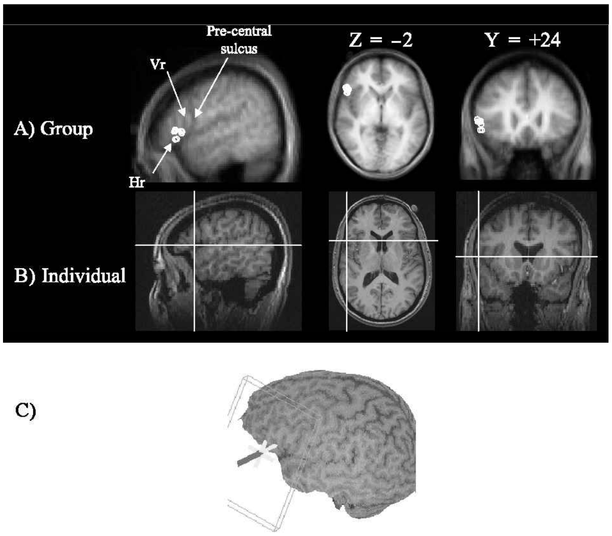


Figure 4. TMS sites. (A) White circles indicate the position of the center of the stimulated brain area in individual subjects shown on the mean MRI scan of the nine TMS subjects, after registration into standard space. The sections are taken at the mean stimulation site ($x = -52$, $y = +24$, $z = -2$). All sites are within the anterior LIPC with most clustered within the PTr although two are on the border with the POr. (B) The frameless stereotaxy recording of the stimulation site in a single individual. The cross-hairs indicate the location of the maximum field intensity as it intersects the underlying cortex. (C) A rendering of a single subject's brain showing the position and plane of the stimulation coil as well as a projection of the maximum field intensity into an anterior and inferior region of the PTr.

semantic task but not in the perceptual task, with a significant interaction between the two tasks.

DISCUSSION

The work presented here confirms a role for the LIPC in semantic processing. The fMRI results provide strong evidence that the anterior and posterior regions are involved in both semantic and phonological processing and therefore constrain theories of a strong spatial division between these two types of linguistic processes. Gold and Buckner (2002) have recently reported similar results. They found that the anterior and the posterior LIPC were significantly activated by semantic and phonological decisions on single words although the two regions interacted with partially dissociable networks, depending on the specific task. In addition, Barde and Thompson-Schill (2002) found no difference between activity in the anterior and posterior LIPC—semantic and phonological tasks activated both areas. Like previous authors (Price et al., 1997; Demonet et al., 1992), these authors concluded that the LIPC is involved in both semantic and phonological processing. Our results extended this claim by directly demonstrating that these processes activate common areas of the LIPC including the POp, PTr, and POr.

In addition to this large area of common activation, we also observed relative enhancements in activation demonstrated by a double dissociation. Phonological decisions enhanced activation in the posterior LIPC, in area POp, relative to semantic decisions while the opposite comparison, semantic versus phonological decisions, revealed an area of enhanced activation within the anterior LIPC, in area POr. Although inferences concerning relative neuronal activation on the basis of fMRI signal intensity change must be done with caution, these results suggest that the POr contributed more to semantic processing while the POp contributed more to phonological processing.

Our findings go beyond simply establishing a correlation between semantic processing and activation in the LIPC. We have demonstrated that a transient disruption of processing within the anterior LIPC selectively interfered with semantic but not perceptual processing. In direct cortical stimulation studies, Ojemann (1979) found that stimulation of the posterior LIPC consistently disrupted speech. Interestingly, the same was true for a native deaf signer in whom stimulation of posterior Broca's area disrupted phonetic processing (Corina et al., 1999). Thus, the same

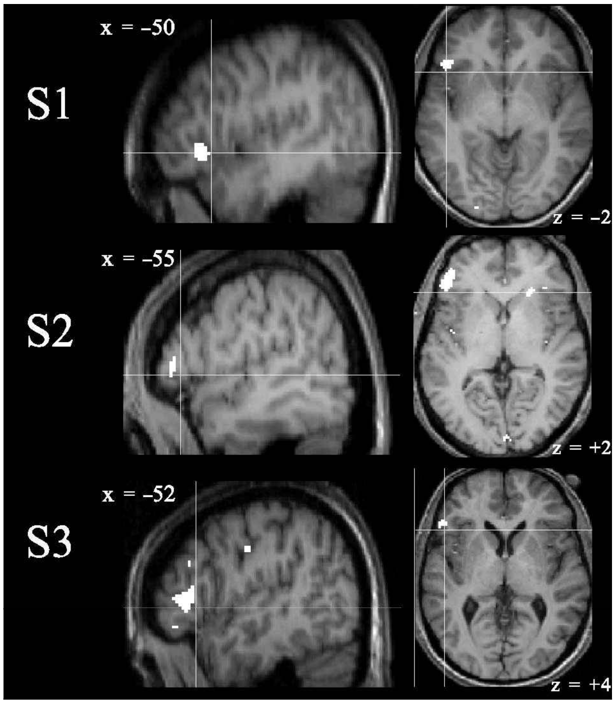


Figure 5. Stimulation and activation sites in three participants. Activations are rendered onto the individual's structural image after registration into standard space. In addition, the cross-hairs indicate the participant's site of stimulation. In all three subjects, the stimulation site was between 3 and 6 mm posterior to activation in the LIPC.

Table 4. The Stimulation and Activation Sites of Three Participants

Subject	*TMS Site*	*Nearest Suprathreshold Voxel*	*Distance (mm)*	*Nearest Peak Voxel*	*Distance (mm)*
S1	−50 +19 −4	−50 +22 −4	3.0	−50 +26 −2	7.3
S2	−55 +27 +2	−50 +30 +2	5.8	−54 +34 +10	10.7
S3	−52 +21 +2	−54 +24 +4	4.1	−54 +32 +8	12.7

Activations are from comparing the semantic relative to the perceptual decisions in each individual subject. All coordinates are in standard space (Talairach & Tournoux, 1988).

anterior–posterior pattern seen in imaging has now been demonstrated with two different cortical stimulation techniques. Before considering the implications of these findings, it is worth briefly discussing the striking spatial correspondence between the fMRI and TMS results.

We found that the group peak fMRI activation was approximately 14 mm from the mean TMS stimulation site. Two other studies have reported similar findings in motor tasks. Wassermann et al. (1996) compared the peak activation for finger movements (using PET) and the TMS site, which produced the strongest EMG responses in the corresponding muscle. The two sites ranged from 5 to 22 mm apart. Terao et al. (1998) reported even better spatial agreement between fMRI and TMS results using essentially the same task (3.3 ± 0.8 mm). It is worth being cautious regarding these figures, however, as many factors affect their accuracy. In TMS, there is uncertainty about the precise position, with respect to the coil, at which the TMS effect will be maximal. In fMRI, there are nonlinearities in the image and there is the problem of choosing the appropriate measure of ''activation,'' namely, does one choose the nearest ''active'' voxel based on an arbitrary threshold or the most active voxel whose position can be strongly influenced by the proximity of draining veins? In addition, both TMS and fMRI are limited by their intrinsic spatial resolutions and the accuracy of the image registration processes (i.e., during frameless stereotaxy, measurements of the subject's head position are registered to his or her MRI scan and in fMRI analyses the subject's MRI scan is registered into standard space). These methodological considerations limit our ability to draw conclusions from this finding other than to note the high spatial reliability between the functional imaging and TMS results in both the motor and cognitive domains.

The Role of the Inferior Prefrontal Cortex in Semantic Processing

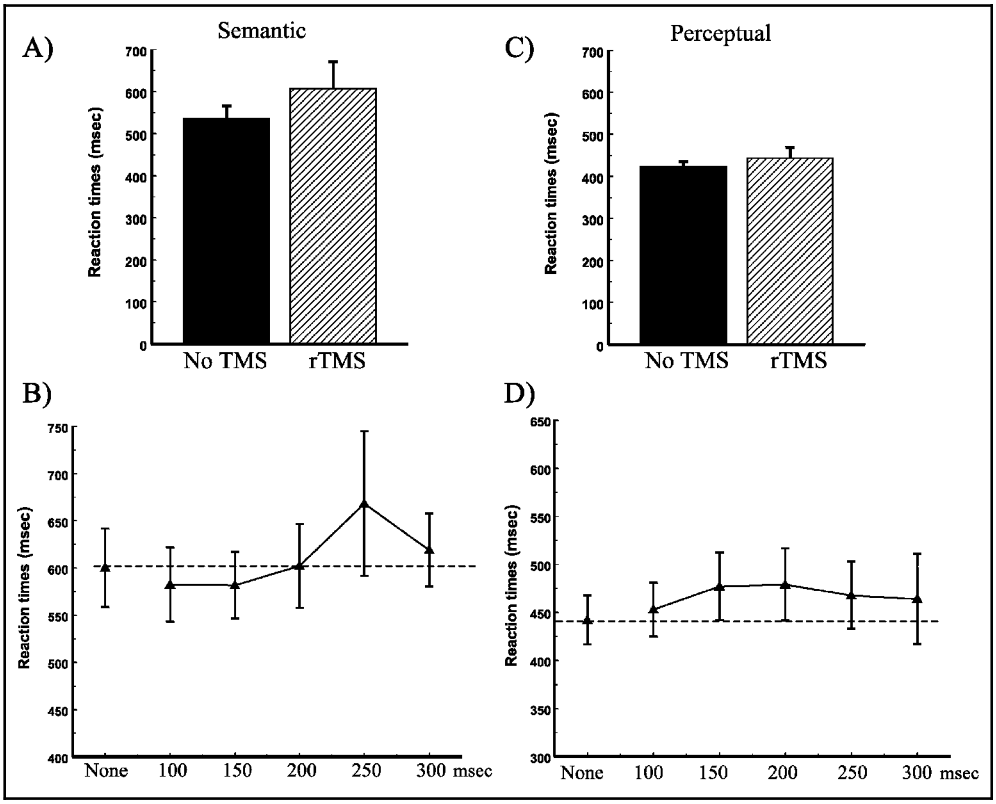
Our TMS results establish that an anterior region of the LIPC was involved in normal performance of this semantic task. In other words, although TMS did not increase subjects' error rates, it significantly increased their RTs. This result indicates that the LIPC is involved in normal semantic processing even though it may not be necessary for correct performance of the task. Furthermore, our results suggest this involvement may be most critical approximately 250 msec poststimulus onset, a finding consistent with both ERP and MEG studies of single-word reading (Samelin, Schnitzler, Schmitz, & Freund, 2000; Breier, Simos, Zouridakis, & Papanicolaou, 1999; Khateb et al., 1999).

Patients with lesions to the LIPC, on the other hand, do not typically present with semantic deficits. In fact, Price, Mummery, Moore, Frackowiak, and Friston (1999) have shown that the left inferior frontal cortex is not necessary to correctly perform even demanding semantic tasks. They investigated SW, a global aphasic with a large left fronto-parietal lesion including most of the POp and PTr. Despite extensive damage to the region, SW was able to perform a version of the Pyramids and Palm Trees task of semantic associations (Howard & Patterson, 1992) as accurately as normal controls (SW, 81%; normal range, 78–94%). Furthermore, SW's PET scan revealed normal brain activation except for a lack of activity in the LIPC. Despite reducing the statistical threshold, the authors observed no activity in the LIPC, even in the undamaged and presumably viable peri-infarct tissue. From these

Table 5. Accuracy (in % Correct) of Participants in TMS Experiments

	rTMS Stimulation		*Single Pulse Stimulation*					
	None	*rTMS*	*None*	*100 msec*	*150 msec*	*200 msec*	*250 msec*	*300 msec*
Semantic	95	96	85	94	91	93	90	89
Perceptual	95	93	91	92	92	89	95	90

Figure 6. Results of the TMS experiment. (A) rTMS produced a reliable 72-msec increase in RTs when subjects made semantic decisions relative to no stimulation. (B) Single pulse stimulation also produced a significant slow-down relative to the baseline of no stimulation (shown as a dashed line) when the pulse came at 250 msec post-stimulus onset in the semantic task. In contrast, neither the (C) rTMS nor the (D) single pulse stimulation produced a significant increase in RTs at any time point when subjects made perceptual decisions.



findings, they concluded that although the LIPC was normally activated for the task, it was not "necessary" for adequate performance.

It is possible that SW may have recovered his ability to accurately perform the task after his stroke as a result of functional reorganization. Price, Mummery, et al. (1999) provided indications that SW's performance may not have been entirely normal. For instance, his RTs were significantly slower than the healthy controls. In addition, relative to the control group, SW activated three "novel" brain regions. The authors noted, however, that each of these areas was also active in one to four healthy subjects although the activations were not significant for the group. Plastic changes within the remaining areas may have enabled correct, but slowed, task performance. If this is true, the LIPC cannot be said to be "necessary" for semantic performance because other regions sufficed to perform the task (Price & Friston, in press).

Other studies have found patients with LIPC damage with deficits on some semantic tasks such as poor word fluency on semantic category tests and difficulty providing an appropriate word with which to complete a sentence (Robinson, Blair, & Cipolotti, 1998; Costello & Warrington, 1989). In addition, "Broca's aphasics" demonstrate a variety of abnormal semantic priming effects (Utman, Blumstein, & Sullivan, 2001). In both cases, these deficits have been interpreted as evidence for dysfunctional executive processes such as semantic retrieval, selection, and inhibition (see also Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner et al., 1997; Petersen et al., 1989). Consistent with this hypothesis, it was clear from the reports of subjects in our experiments that they had to both focus on the meaning of the presented word and inhibit unwanted semantic associations. For instance, when deciding whether "kennel" was man-made or not, several subjects mentioned that they experienced momentary confusion because "kennel" so readily evoked the idea of an animate "dog." The current study, however, does not permit us to differentiate between the competing claims regarding the LIPC's role in semantic retrieval or selection (but see Wagner, Pare-Blasgoev, Clark, & Poldrack, 2001; Thompson-Schill, D'Esposito, & Kan, 1999).

In conclusion, our study provides new evidence that neural activity in the LIPC is not only correlated with making semantic decisions, but that it is involved in normal performance. This work illustrates the value of combining fMRI and TMS to investigate cognitive functions such as language. fMRI can be used to demonstrate a correlation between behavior and neural activity, which can then be used to select the site(s) of stimulation. TMS can be used to determine whether (and when) a particular cortical region contributes to the performance of the task, thus allowing one to differentiate between areas necessary for normal performance and those which are activated by, but not essential, for the task.

METHODS

Subjects

Twelve adults (6 women, 6 men) aged 21–33, participated in the fMRI experiment while nine (5 women, 4 men, age range 22–38) participated in the TMS experiments. Four of these (2 women, 2 men) participated in both. All subjects were right-handed, native English speakers with no personal or family history of epilepsy or any other neurological condition. Each gave informed consent after the experimental methodology was explained. The experiments were approved by the Local Research Ethics Committee.

Scanning Procedure

Subjects participated in two consecutive scanning sessions separated by approximately 1 min where the trials were blocked in an ACBC design. In one, they made semantic (A1) and phonological (B1) decisions separated by blocks of rest (C1). In the other, they made semantic (A2) and perceptual (B2) decisions separated by rest (C2). The order of the sessions was counterbalanced across participants. Within a session, each stimulus was seen twice, once in each task. By keeping the stimuli identical and varying only the task, differences in activation could be ascribed to semantic or phonological processing rather than stimuli differences. Each scanning session lasted 7.5 min and stimuli were presented in 32-sec blocks which contained 10 trials. All decision tasks were separated by 13 sec of rest (i.e., a blank screen). Stimuli were presented out of phase with data acquisition to ensure an unbiased sampling of the hemodynamic response (cf. Price, Veltman, Ashburner, Josephs, & Friston, 1999). During the session, 150 T2* images were collected. An additional four dummy volumes were collected at the start of the session to allow for T1 equilibrium before the test trials began.

In each of the tasks, a word was presented in the center of the screen below a horizontal line (see Figure 2). In the semantic task, participants decided whether the word represented a man-made (e.g., RADIO) or natural item (e.g., CLOUD). In the phonological task, they decided whether the stimulus was a two-syllable word and in the perceptual task, they decided whether the horizontal line above the word was shorter than the word. Stimuli were presented for 500 msec with 2700 msec of blank screen between trials for an intertrial interval of 3.2 sec. Subjects pressed a button to indicate their response: The index finger indicated YES (man-made, two syllable, or shorter line), while the middle finger indicated NO (natural, one or three syllables, or longer line). Accuracy and RTs were measured. The same presentation parameters were used in both the fMRI and TMS experiments.

Stimuli were concrete nouns taken from the MRC Psycholinguistic database (Coltheart, 1981) and half represented man-made items and the other half were natural kinds. These were matched for familiarity [man-made = 525 vs. 530 for natural, $t(94) = 0.5$], written word frequencies [22 vs. 28, $t(88) = 0.75$], letter [5.4 vs. 5.4, $t(98) = 0.15$], and syllable lengths [1.6 vs. 1.7, $t(98) = 0.92$, all t value, *ns*].

Scans were carried out using the Varian-Siemens 3 Tesla MRI scanner at the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre in Oxford. A Magnex head-dedicated gradient insert coil was used in conjunction with a birdcage head radio-frequency coil tuned to 127.4 MHz. A gradient-echo EPI sequence was used for image collection (TR 3 sec, TE 30 msec, 64 by 64 resolution, 256 by 256 mm FOV). Twenty-five slices were employed to cover the brain with 5 mm slice thickness and in-plane resolution of 4 mm. An automated shimming algorithm was used to reduce magnetic field inhomogeneities (Wilson & Jezzard, 2001) and a TE of 30 msec jointly optimized BOLD contrast-to-noise and image signal-to-noise while minimizing intravoxel dephasing.

Functional images were realigned (Friston, Ashburner, et al., 1995) to correct for small head movements using the Statistical Parametric Mapping software (SPM99, Wellcome Institute of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm99). Translation and rotation corrections did not exceed 2.3 mm and 2.5°, respectively, for any of the participants. The mean image created by the realignment procedure was used to determine the parameters for transforming the images onto the MNI mean brain. The normalization parameters were then applied to the functional images (Ashburner & Friston, 1997; Ashburner, Neelin, Collins, Evans, & Friston, 1997). Finally, each image was smoothed with a 5-mm at full-width half-maximum (FWHM) gaussian filter. The SPM software was used to compute a fixed-effects analysis using the general linear model (Friston, Holmes, et al., 1995). Trials were modeled as events and temporal derivatives were included to better fit regional deviations in timing from the canonical HRF. Voxel-based statistical values survived correction for multiple comparisons at $p < .05$ (Worsley et al., 1996).

Conjunction analyses are the only statistical method for identifying ''common areas'' of activation across contrasts but they require that the contrasts be orthogonal (Worsley & Friston, 2000; Friston et al., 1999; Price & Friston, 1997). Consequently, the contrasts used in our first analysis were phonological decisions > rest (from Session A) and semantic decisions > rest (from Session B). The second analysis contrasted semantic and perceptual decisions from Session B. The third analysis contrasted semantic and phonological decisions in Session A.

Regions of Interest

To identify the location of activations within the LIPC, we created three ROI masks corresponding to the POp, PTr, and POr. Ideally, these would be based upon probability mapping of each region (cf. Tomaiuolo et al., 1999), however, in the absence of such maps for the PTr and the POr, we instead defined the regions based on sulcal anatomy (see Figure 1). Boundaries between regions were drawn at the fundus of the sulci even though cytoarchitectonic borders in individual subjects may occur in either sulcal wall (Amunts et al., 1999). Even so, the convexities are consistent with BA 44 and 45 (Amunts et al., 1999). The Duvernoy (1991) atlas was used to identify the anatomical landmarks in Figure 1 on two participants' high-resolution structural MRIs (1 × 1 × 1.2 mm), registered into standard space. The other participants had lower resolution structural scans (1 × 1 × 3 mm), which made these landmarks less clear. Consequently, one mask was created per region based on the two high-resolution images. These masks were then applied to the group results to identify regional activations with the LIPC and to test the hypothesis that semantic decisions would activate the anterior LIPC region POr relative to phonological decisions.

Stimulation Procedure

Subjects participated in two TMS experiments, one with repetitive stimulation and one with single pulses. The presentation parameters and stimuli were identical to those used in Session B of the fMRI experiment (semantic and perceptual decisions). The anterior LIPC was chosen as the target site of stimulation and stimulation was directed at the apex of the PTr because the branching of the vertical and horizontal rami of the Sylvian fissure was easily identified on each subject's structural MRI. To identify the corresponding location and orientation for the TMS coil on the scalp, frameless stereotaxy was used (Paus et al., 1997). A Polaris infrared tracking device (Northern Digital, Ontario, Canada) measured the position of the subject's head. BrainSight software (Rogue Research, Montreal, Canada) co-registered the subject's head with that person's structural MRI. The TMS coil was placed at the approximate site of stimulation and was adjusted until the estimated direction of maximum field intensity intersected the target stimulation site on the MRI scan. The coil was placed tangential to the head at the point of contact and held such that its handle pointed down and forward at approximately a 30° angle. This orientation meant that the long axis of the coil roughly followed the vertical ramus of the Sylvian fissure.

To determine whether stimulation at this site interfered with semantic judgements, subjects performed a short semantic decision task. Thirty trials were presented. On 10 of these, a 300-msec, 10-Hz train of stimulation was produced 100 msec after the stimulus appeared on the screen. In all TMS experiments, a 40-mm diameter figure-of-eight coil was used with a MagStim RAPID stimulator (MagStim, Whitland, Carmarthenshire, UK). The small coil together with very short TMS trains (3 pulses, 100 msec apart) minimized discomfort from oral–facial muscle movement. The rTMS train frequency, intensity, and duration were well within safety limits (Wassermann, 1998). Stimulation was at 10% above the subject's motor threshold. If TMS did not produce slower RTs than no stimulation, a new site was chosen approximately 1 cm away on the scalp. One subject did not show an effect of rTMS after trying eight sites so testing stopped for this individual. Note that she was one of the four people to participate in both the fMRI and the TMS experiments. Thus, in 8 out of 9 subjects, rTMS produced slower RTs than no stimulation. In each, the site of the effect was within 1 cm of the original stimulation location. When the ultimate site of stimulation was different than the initial estimate, then the new location was marked on the subject's MRI using BrainSight.

Using this site, subjects participated in an rTMS and a single-pulse testing session. In the rTMS session, subjects performed 90 sec of semantic and 90 sec of perceptual decisions on novel stimuli with stimulation parameters identical to those above (300 msec, 10 Hz, 10/30 trials). In the single pulse condition, subjects performed blocks of semantic and perceptual decisions (5 blocks of each). Each block had 20 stimuli with a single TMS pulse presented randomly on 15 trials. Pulses arrived 100, 150, 200, 250, or 300 msec poststimulus onset. Blocks alternated between semantic and perceptual decisions with a self-paced pause between blocks. As in the fMRI experiment, the stimuli in the semantic and perceptual decision conditions were held constant and only the task changed across blocks.

Subjects' median RTs per condition per experiment were normalized to reflect relative changes due to stimulation [% change = (RT with TMS − RT without TMS)/(RT without TMS) × 100] and analyzed. This type of analysis is commonly used with TMS to take into account individual differences in baseline RTs (Stewart, Meyer, et al., 2001; Schluter, Rushworth, Mills, & Passingham, 1999). The data from the repetitive stimulation experiment were analyzed with t tests for comparing stimulation versus no stimulation and semantic versus perceptual decisions. The data from the single pulse experiment were entered into a two way ANOVA with TMS (100, 150, 200, 250, and 300 msec poststimulus onset) and task (semantic, perceptual) as independent factors and normalized RTs as the dependent measure. All statistics are reported for one-tailed distributions as the fMRI results provide strong evidence that stimulation in this region would increase, rather than decrease, RTs for semantic decisions.

Acknowledgments

We thank Cathy Price and two anonymous reviewers for helpful suggestions; Peter Hobden, Patricia Figueiredo, Heidi

Johansen-Berg, Donna Lloyd, and Mark Walton for their assistance collecting data; and all of our subjects for participating. This work was supported by the Medical Research Council (J. T. D., P. M. M., M. F. S. R.) and the Royal Society (MFSR).

Reprint requests should be sent to Joseph T. Devlin, FMRIB Centre, Department of Clinical Neurology, Oxford University, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK, or via e-mail: devlin@fmrib.ox.ac.uk.

The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2002-11354.

REFERENCES

Amassian, V. E. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalography and Clinical Neurophysiology, 74,* 458–462.

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B. M., & Zilles, K. (1999). Broca's region revisited: Cytoarchitecture and intersubject variability. *Journal of Comparative Neurology, 412,* 319–341.

Ashbridge, E., Walsh, V., & Cowey, A. (1997). Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia, 35,* 1121–1131.

Ashburner, J., & Friston, K. (1997). Multimodal image coregistration and partitioning—a unified framework. *Neuroimage, 6,* 209–217.

Ashburner, J., Neelin, P., Collins, D. L., Evans, A. C., & Friston, K. J. (1997). Incorporating prior knowledge into image registration. *Neuroimage, 6,* 344–352.

Barde, L. H. F., & Thompson-Schill, S. L. (2002). Models of functional organization of lateral prefrontal cortex in verbal working memory: Evidence in favor of the process model. *Journal of Cognitive Neuroscience, 14,* 1054–1063.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious resting state: A functional MRI study. *Journal of Cognitive Neuroscience, 11,* 80–95.

Breier, J. I., Simos, P. G., Zouridakis, G., & Papanicolaou, A. C. (1999). Temporal course of regional brain activation associated with phonological decoding. *Journal of Clinical and Experimental Neuropsychology, 21,* 465–476.

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé; suivies d'une observation d'aphemie. *Bulletin de la Société Anatomique de Paris, 6,* 330–357.

Buckner, R. L., Raichle, M. E., & Petersen, S. E. (1995). Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. *Journal of Neurophysiology, 74,* 2163–2173.

Coltheart, M. (1981). The MRC Psycholinguistics database. *Quarterly Journal of Experimental Psychology, 33A,* 497–505.

Corina, D. P., McBurney, S. L., Dodrill, C., Hinshaw, K., Brinkley, J., & Ojemann, G. (1999). Functional roles of Broca's area and SMG: Evidence from cortical stimulation mapping in a deaf signer. *Neuroimage, 10,* 570–581.

Costello, A. L., & Warrington, E. K. (1989). Dynamic aphasia. The selective impairment of verbal planning. *Cortex, 25,* 103–114.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. E. (1995). Semantic encoding an retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience, 15,* 5870–5878.

Demonet, J.-F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J.-L., Wise, R., Rascol, A., & Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain, 115,* 1753–1768.

Duvernoy, H. (1991). *The human brain: Surface, three dimensional sectional anatomy and MRI.* New York: Spring-Verlag.

Epstein, C. M., Lah, J. K., Meador, K., Weissman, J. D., Gaitan, L. E., & Dihenia, B. (1996). Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. *Neurology, 47,* 1590–1593.

Fiez, J. A. (1997). Phonology, semantics, and the role of the left inferior prefrontal cortex. *Human Brain Mapping, 5,* 79–83.

Fiez, J. A., Raichle, M. E., Miezin, F. M., Petersen, S. E., Tallal, P., & Katz, W. F. (1995). PET studies of auditory and phonological processing: Effects of stimulus characteristics and task demands. *Journal of Cognitive Neuroscience, 7,* 357–375.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. *Human Brain Mapping, 2,* 165–189.

Friston, K. J., Holmes, A. P., Price, C. J., Buchel, C., & Worsley, K. J. (1999). Multisubject fMRI studies and conjunction analyses. *Neuroimage, 10,* 385–396.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-B., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2,* 189–210.

Gabrieli, J. D. E., Poldrack, R. A., & Desmond, J. E. (1998). The role of the left inferior frontal cortex in language and memory. *Proceedings of the National Academy of Sciences, U.S.A., 95,* 906–913.

Gold, B. T., & Buckner, R. L. (2002). Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron, 35,* 803–812.

Howard, D., & Patterson, K. (1992). *Pyramids and palm trees: A test of semantic access from pictures and words.* Bury St. Edmunds: Thames Valley.

Jahanshahi, M., & Rothwell, J. (2000). Transcranial magnetic stimulation studies of cognition: An emerging field. *Experimental Brain Research, 131,* 1–9.

Jenkinson, M., & Smith, S. M. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5,* 143–156.

Jennum, P., Friberg, L., Fuglsang-Frederiksen, A., & Dam, M. (1994). Speech localization using repetitive transcranial magnetic stimulation. *Neurology, 44,* 269–273.

Kapur, S., Craik, F. I. M., Tulving, E., Wilson, A. A., Houle, S., & Brown, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proceedings of the National Academy of Sciences, U.S.A., 91,* 2008–2011.

Khateb, A., Annoni, J.-M., Landis, T., Pegna, A. J., Custodi, M.-C., Fonteneau, E., Morand, S. M., & Michel, C. F. (1999). Spatio-temporal analysis of electric brain activity during semantic and phonological word processing. *International Journal of Psychophysiology, 32,* 215–231.

Klein, D., Milner, B., Zatorre, R. J., Meyer, E., & Evans, A. C. (1995). The neural substrates underlying word generation: A bilingual functional-imaging study. *Proceedings of the National Academy of Sciences, U.S.A., 92,* 2899–2903.

Mummery, C. J., Patterson, K., Hodges, J. R., & Price, C. J. (1998). Functional neuroanatomy of the semantic system: Divisible by what? *Journal of Cognitive Neuroscience, 10,* 766–777.

Ojemann, G. A. (1979). Individual variability in cortical localization of language. *Journal of Neurosurgery, 50,* 164–169.

Pascual-Leone, A., Bartres-Faz, D., & Keenan, J. P. (1999). Transcranial magnetic stimulation: Studying the brain–behaviour relationship by induction of "virtual lesions". *Philosophical Transactions of the Royal Society London B, 354,* 1229–1238.

Pascual-Leone, A., Gates, J. R., & Dhuna, A. (1991). Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology, 41,* 697–702.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. *Current Opinions in Neurobiology, 10,* 232–237.

Paus, T. (1999). Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia, 37,* 219–224.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. *Journal of Neuroscience, 17,* 3178–3184.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1989). Positron emission tomographic studies of the processing of single words. *Journal of Cognitive Neuroscience, 1,* 153–170.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage, 10,* 15–35.

Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: A new approach to brain activation experiments. *Neuroimage, 5,* 261–270.

Price, C. J., & Friston, K. J. (in press). Functional imaging studies of neuropsychological patients: Applications and limitations. *Neurocase.*

Price, C. J., Moore, C. J., Humphreys, G. W., & Wise, R. J. (1997). Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience, 9,* 727–733.

Price, C. J., Mummery, C. J., Moore, C. J., Frackowiak, R. S. J., & Friston, K. J. (1999). Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *Journal of Cognitive Neuroscience, 11,* 371–382.

Price, C. J., Veltman, D. J., Ashburner, J., Josephs, O., & Friston, K. J. (1999). The critical relationship between the timing of stimulus presentation and data acquisition in blocked designs with fMRI. *Neuroimage, 10,* 36–44.

Price, C. J., Wise, R. J. S., & Frackowiak, R. S. J. (1996). Demonstrating the implicit processing of visually presented words and pseudowords. *Cerebral Cortex, 6,* 62–70.

Robinson, G., Blair, J., & Cipolotti, L. (1998). Dynamic aphasia: An inability to select between competing verbal responses? *Brain, 121,* 77–89.

Samelin, R., Schnitzler, A., Schmitz, F., & Freund, H.-J. (2000). Single word reading in developmental stutterers and fluent speakers. *Brain, 123,* 1184–1202.

Schluter, N. D., Rushworth, M. F. S., Mills, K. R., & Passingham, R. E. (1999). Signal-, set-, and movement-related activity in the human premotor cortex. *Neuropsychologia, 37,* 233–243.

Stewart, L., Meyer, B. U., Frith, U., & Rothwell, J. (2001). Left posterior BA37 is involved in object recognition: A TMS study. *Neuropsychologia, 39,* 1–6.

Stewart, L., Walsh, V., Frith, U., & Rothwell, J. C. (2001). TMS produces two dissociable types of speech disruption. *Neuroimage, 13,* 472–478.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* Stuttgart: Thieme.

Terao, Y., Ugawa, Y., Sakai, K., Miyauchi, S., Fukuda, H., Sasaki, Y., Takino, R., Hanajima, R., Furubayashi, T., Putz, B., & Kanazawa, I. (1998). Localizing the site of magnetic brain stimulation by functional MRI. *Experimental Brain Research, 121,* 145–152.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A re-evaluation. *Proceedings of the National Academy of Sciences, U.S.A., 94,* 14792–14797.

Thompson-Schill, S. L., D'Esposito, M., & Kan, I. P. (1999). Effects of repetition and competition on activity in the left prefrontal cortex during word generation. *Neuron, 23,* 5113–5522.

Tomaiuolo, F., MacDonald, J. D., Caramanos, Z., Posner, G., Chiavaras, M., Evans, A. C., & Petrides, M. (1999). Morphology, morphometry and probability mapping of the pars opercularis of the frontal gyrus: An in vivo MRI analysis. *European Journal of Neuroscience, 11,* 3033–3046.

Topper, R., Mottaghy, F. M., Brugmann, M., Noth, J., & Huber, W. (1998). Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Experimental Brain Research, 121,* 371–378.

Turennout, M., Hagoort, P., & Brown, C. M. (1998). Brain activity during speaking: From syntax to phonology in 40 milliseconds. *Science, 280,* 572–574.

Utman, J. A., Blumstein, S. E., & Sullivan, K. (2001). Mapping from sound to meaning: Reduced lexical activation in Broca's aphasics. *Brain and Language, 79,* 444–472.

Van Orden, G. C., Johnson, J. C., & Hale, B. L. (1988). Word identification in reading proceeds from spelling to sound to meaning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 14,* 371–386.

Wagner, A. D., Desmond, J. E., Demb, J. B., Glover, G. H., & Gabrieli, J. D. E. (1997). Semantic repetition priming for verbal and pictorial knowledge: A functional MRI study of the left inferior prefrontax cortex. *Journal of Cognitive Neuroscience, 9,* 714–726.

Wagner, A. D., Pare-Blasgoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31,* 329–338.

Walsh, V., & Cowey, A. (1998). Magnetic stimulation studies of visual cognition. *Trends in Cognitive Science, 2,* 103–110.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1,* 73–79.

Walsh, V., & Rushworth, M. F. S. (1999). The use of transcranial magnetic stimulation in neuropsychological testing. *Neuropsychologia, 37,* 125–135.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology, 108,* 1–16.

Wassermann, E. M., Wang, B., Zeffiro, T. A., Sadato, N., Pascual-Leone, A., Toro, C., & Hallett, M. (1996). Locating the motor cortex on the MRI with transcranial magnetic stimulation and PET. *Neuroimage, 3,* 1–9.

Wilson, J., & Jezzard, P. (2001). *Fast, fully automated global and local shimming of the human brain.* Paper presented at the 10th Annual Meeting of the ISMRM, Glasgow.

Worsley, K. J., & Friston, K. J. (2000). A test for conjunction. *Statistics and Probability Letters, 47,* 135–140.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4,* 58–83.

Zatorre, R. J., Evans, A. C., Meyer, E., & Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. *Science, 256,* 846–849.

Copyright of Journal of Cognitive Neuroscience is the property of MIT Press and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.