

Common Prefrontal Regions Coactivate with Dissociable Posterior Regions during Controlled Semantic and Phonological Tasks

Brian T. Gold^{1,3,4} and Randy L. Buckner^{1,2,3}

¹Department of Psychology

Washington University

One Brookings Drive

St. Louis, Missouri 63130

²Departments of Radiology and

Anatomy & Neurobiology

Washington University School of Medicine

St. Louis, Missouri 63110

³Howard Hughes Medical Institute

St. Louis, Missouri 63110

Summary

One of the most ubiquitous findings in functional neuroimaging research is activation of left inferior prefrontal cortex (LIPC) during tasks requiring controlled semantic retrieval. Here we show that LIPC participates in the controlled retrieval of nonsemantic representations as well as semantic representations. Results also demonstrate that LIPC coactivates with dissociable posterior regions depending on the information retrieved: activating with left temporal cortex during the controlled retrieval of semantics and with left posterior frontal and parietal cortex during the controlled retrieval of phonology. Correlation of performance to LIPC activation suggests a processing role associated with mapping relatively ambiguous stimulus-to-representation relationships during both semantic and phonological tasks. These findings suggest that LIPC participates in controlled processing across multiple information domains collaborating with dissociable posterior regions depending upon the kind of information retrieved.

Introduction

Prefrontal cortex is well established to play a prominent role in controlled aspects of language function and cognition more generally. Neuropsychological studies have noted that damage to prefrontal cortex impairs controlled access to and context-appropriate usage of stored knowledge (Stuss and Benson, 1984; Norman and Shallice, 1986). In particular, damage to *lateral* regions of the language-dominant prefrontal cortex can result in deficits associated with controlled components of language and cognition. For example, patients with lesions to lateral prefrontal cortex regions show marked difficulty in generating words beginning with a particular letter (Milner, 1964), monitoring verbal material maintained over a brief interval (Petrides and Milner, 1982), shifting from a learned concept to a novel one (Milner, 1963), and complex planning (Shallice, 1988), among other impairments.

Growing convergent evidence from human neuroimaging studies suggests that regions within language-

dominant, lateral prefrontal cortex are associated with various controlled components of language and cognition. Among these regions, left inferior prefrontal cortex (LIPC), encompassing Brodmann areas [BA] 45/47 and extending into BA 44, has been studied extensively. In particular, the anterior portion of LIPC (aLIPC; ~45/47) has repeatedly been associated with semantic (meaning-based) retrieval. Based on prominent aLIPC activation in semantic word generation and semantic monitoring tasks, Petersen et al. (1989) proposed that aLIPC's role in semantic processing is executive/strategic in nature. Evidence of aLIPC's role in controlled aspects of semantic processing includes demonstrations that the region decreases activity if generation of semantic associates is automated through practice (Raichle et al., 1994) and increases activity when associations are drawn between words with distant semantic relations (Roskies et al., 2001; Wagner et al., 2001). Importantly, Demb et al. (1995) showed that activation of aLIPC (as well as that of a region near BA 46) was not due to increased difficulty per se by demonstrating that the aLIPC remained activated when semantic and comparison tasks were matched for response time. On the basis of these and similar findings, it has been suggested that aLIPC, or regions just adjacent to it, are critical in the controlled retrieval of semantic information (Buckner, 1996; Gabrieli et al., 1996, 1998; Kapur et al., 1996; Fiez, 1997; Poldrack et al., 1999; Bokde et al., 2001; Roskies et al., 2001; Wagner et al., 2001).

Distinct regions within LIPC have also been activated during tasks involving phonological (speech sound) processing. For example, LIPC has been activated during monitoring of auditory nonwords for particular sequences of phonemes (Demonet et al., 1992) and auditory syllables for their final consonants (Zatorre et al., 1992), as well during active rehearsal of verbal material over brief intervals (Paulesu et al., 1993; Fiez et al., 1996). As noted by Fiez (1997), these studies have tended to report activation of regions within the LIPC posterior and dorsal to those activated in studies of controlled semantic processing.

Several recent functional neuroimaging studies employing both semantic and phonological tasks have reported a similar trend of LIPC recruitment patterns with dissociation between two regions along domain lines. An anterior ventral portion of LIPC (aLIPC; BA 45/47) has activated maximally during the performance of controlled semantic tasks. By contrast, a posterior dorsal portion of LIPC (pLIPC; near BA 44 and extending into precentral gyrus near BA 6) has activated maximally during the performance of phonologically related tasks (Buckner et al., 1995; Poldrack et al., 1999; Bokde et al., 2001). Such findings, coupled with earlier results of aLIPC activation during controlled semantic tasks, have led to suggestions of functional heterogeneity of LIPC based upon semantic-phonological domain lines. The model that has emerged is that aLIPC is relatively specialized for controlled use of semantic information and pLIPC is relatively specialized for controlled use of pho-

⁴Correspondence: bgold@artsci.wustl.edu

nological information (Poldrack et al., 1999; Bokde et al., 2001; Wagner et al., 2001).

Another line of studies of LIPC functioning has been conducted by Thompson-Schill and her colleagues (Thompson-Schill et al., 1997, 1998, 1999), who have suggested that a portion of pLIPC (near BA 44) is critical in selection of relevant semantic knowledge from a set of competing alternatives. Thompson-Schill et al. (1997) reported greater pLIPC activation under multiple task conditions in which the demand for selection from among competing alternatives was high (a stimulus associated with several potentially relevant response alternatives) than under conditions in which demands were low (a stimulus associated with one predominant response). Similar results were reported in a neuropsychological study comparing generation of verbs from nouns in patients with lesions of pLIPC near BA 44 to patients with lesions of the left prefrontal cortex outside the pLIPC and patients with right prefrontal lesions (Thompson-Schill et al., 1998). Relative to the other patient groups, the pLIPC lesion group showed significantly poorer performance on nouns with many highly associated verbs but not on nouns with few associated verbs. There are thus several theories on the functioning of LIPC regions in language.

Here we present an fMRI study that focuses on whether LIPC-mediated controlled processing is restricted to the semantic domain or participates across multiple linguistic domains. Networks of regions involved in controlled retrieval during semantic and phonological decision tasks were examined, including multiple regions in LIPC and posterior regions thought to be important in long-term storage of information. It is noteworthy that several studies examining neural correlates of phonological processing have utilized tasks that can be accomplished with limited emphasis on controlled retrieval processes. For example, tasks such as syllable counting place limited emphasis on controlled retrieval because the majority of syllable sounds are overlearned (Plaut et al., 1996). Here, a short/long vowel task was employed requiring decisions about sounds of visual words and pseudowords. Critically, whereas deriving sound codes of visual *words* can be accomplished through more automatic processing because the visual-to-sound mappings of items encountered frequently are relatively prepotent, deriving sound codes of visual *pseudowords* emphasizes controlled processes associated with novel visual-to-sound mappings. Two additional tasks were employed: an abstract/concrete task often used in studies of controlled semantic processing and a first letter/last letter alphabetic task shown elsewhere to match the abstract/concrete task for response time while minimizing controlled semantic retrieval (Demb et al., 1995).

Results suggest a view of LIPC functioning different from existing models. The aLIPC, and an anterior portion of the pLIPC (BA 44), participate in the controlled retrieval of semantic *and* nonsemantic information, suggesting domains not restricted to one form of verbal code. Relatively stronger specificity of linguistic domain was observed in more posterior regions.

Table 1. Mean Response Times

Task	Condition	RT in ms (SD)
Semantic	Words	1108 (198)
Phonological	Words	1203 (254)
	Pseudowords	1359 (251)
Letter	Words	1066 (198)
	Pseudowords	1104 (215)

Results

Behavioral

Mean response times for the three tasks separated by stimulus type are shown in Table 1. Response times differed significantly across the three tasks performed with word stimuli [$F(2, 46) = 8.66, p < 0.001$]. Subjects took longer to respond in the phonological task than in either the letter [$t(23) = 4.21, p < 0.001$] or semantic [$t(23) = 2.25, p < 0.05$] tasks.

There was a significant task \times stimulus interaction in response times such that the increase in phonological latencies on pseudowords relative to words was significantly greater than the increase in letter latencies on pseudowords relative to words [$F(1, 23) = 19.87, p < 0.001$].

The two experimental tasks used in this study (abstract/concrete and short/long vowel) do not yield responses that can be classified as “correct” and “incorrect” in an absolute sense. Therefore, rather than reporting accuracy rates, performance is addressed via measures of response consensus (see below).

fMRI Regional Analyses

Activation patterns in six a priori regions of interest were first examined. These included regions within aLIPC (BA 45/47), the anterior extent of pLIPC (BA 44), the more posterior extent of pLIPC extending into BA 6, as well as distinct posterior regions previously implicated in semantic and phonological processing. Coordinate locations of peak activations defining the center of these six regions were taken from a related study (Logan et al., 2002), based on the prior literature discussed in the Introduction. For descriptive purposes, *regions* are labeled by their *approximate* Brodmann areas (similar to Logan et al., 2002). Table 2 presents a summary of the regions, Brodmann areas, and relevant reference papers.

Consistent with prior studies, BA 45/47 (aLIPC) showed significantly greater activation in semantic than other tasks when word stimuli were considered (Figure 1; words; top panel; [$F(2, 46) = 39.89, p < 0.0001$]). BA 45/47 activated significantly more during semantic than phonological [$t(23) = 6.66, p < 0.0001$] or letter [$t(23) = 7.57, p < 0.0001$] decisions on words. Of central importance, BA 45/47 was also activated significantly by the phonological task (compared to the letter task) when pseudowords were used as stimuli (Figure 1; pseudowords; top panel; [$t(23) = 4.60, p < 0.0001$]). BA 45/47 activated significantly more during phonological decisions on pseudowords than words [$t(23) = 4.44, p < 0.001$] but not letter decisions on pseudowords compared to words ($p = .89$).

Table 2. Regions of Interest

Region ^a	Approximate Gyral Location	Atlas Coordinates			Reference Papers ^b
		x	y	z	
BA 45/47 ^c	Left (anterior) inferior frontal gyrus	-45	35	-4	1, 2, 3, 4, 5
BA 44 ^c	Left (posterior) inferior frontal gyrus	-47	17	24	4, 5
BA 21 ^c	Left middle temporal gyrus	-51	-55	2	2, 6, 7
Crus 1 ^c	Right posterior cerebellum	23	-85	-36	1, 8
BA 6	Left precentral gyrus	-55	-1	28	4, 9, 10
BA 40	Left supramarginal gyrus	-41	-43	34	9, 10, 11

^aRegions are named based on their approximate Brodmann Area (BA) in the Talairach and Tournoux (1988) atlas for cortical regions and Schmahmann et al. (2000) atlas for the cerebellar region. Region labels should be considered approximate.

^bSelected reference papers that motivate interest in the regions: (1) Petersen et al., 1989; (2) Raichle et al., 1994; (3) Buckner et al., 1995; (4) Poldrack et al., 1999; (5) Wagner et al., 2001; (6) Vandenberghe et al., 1996; (7) Thompson-Schill et al., 1997; (8) Buckner et al., 2000; (9) Jonides et al., 1998; (10) Paulesu et al., 1993; (11) Awh et al., 1996. See text for further discussion and additional references.

^cRegions predicted to be involved in controlled semantic processing.

Further between-region analyses suggested that dissociable posterior regions are involved in the controlled retrieval of semantic and phonological information. During the semantic word task, BA 21, which includes a posterior portion of the left middle temporal gyrus, was activated relative to other tasks using words (Figure 1; words; middle panel; [$F(2, 46) = 11.02, p < 0.0001$]). Left BA 21 was more active for semantic than either phonological [$t(23) = 4.34, p < 0.0005$] or letter [$t(23) = 3.06, p < 0.01$] decisions on words. During the phonological pseudoword condition, BA 40, which included the supramarginal gyrus in left parietal cortex, was activated significantly more than in other conditions (Figure 1; pseudowords; lower panel). BA 40 was more active during phonological decisions on pseudowords than either phonological decisions on words [$t(23) = 4.53, p < 0.0001$], letter decisions on words [$t(23) = 4.66, p < 0.0001$], or letter decisions on pseudowords [$t(23) = 3.16, p < 0.005$].

Formal analyses based on ANOVA confirmed that posterior regions BA 21 and BA 40 activated differently during controlled retrieval of semantic and phonological information. Separate analyses were conducted on tasks performed with words and those performed with pseudowords (a fully crossed analysis was not possible because semantic processing cannot be performed with pseudowords). A significant region \times task interaction [$F(2, 46) = 28.24, p < 0.0001$] indicated that BA 21 and BA 40 showed different patterns of activation on the tasks performed with words. Whereas BA 21 was activated most strongly by the semantic-word task, BA 40, if anything, showed reduced activation in the semantic task relative to other tasks performed with words. A significant region \times task interaction [$F(1, 23) = 11.00, p < 0.005$] indicated that these two regions also showed different patterns of activation on the tasks performed with pseudowords. Whereas BA 40 was activated most strongly by the phonology-pseudoword task, BA 21 showed minimal response to both tasks performed with pseudowords. Thus, patterns of activation of BA 21 and BA 40 dissociated for semantic and phonological information domains, respectively.

Two regions within the posterior portion of the left frontal cortex along the dorsal extent of inferior frontal gyrus (BA 44 and BA 6) showed patterns of activation

that were functionally heterogeneous (Figure 2). There was a significant region \times task interaction between activation patterns in BA 44 and a more posterior region, corresponding to the precentral gyrus (BA 6) on tasks performed with words [$F(2, 46) = 44.41, p < 0.0001$]. Whereas BA 44 showed significantly greater activation in the semantic than the phonological task for words [$t(23) = 3.37, p < 0.005$], BA 6 showed significantly greater activation in the phonological task than the semantic task for words [$t(23) = 4.29, p < 0.0005$]. By contrast, a significant region \times task interaction on tasks performed with pseudowords [$F(1, 23) = 7.02, p < 0.05$] indicated that BA 44 showed a greater increase in response to phonological (relative to letter) processing of pseudowords than did BA 6. The strength of response of BA 44 during semantic processing of words and phonological processing of pseudowords align the region's activation patterns with those of BA 45/47 and dissociate it from BA 6 which, similarly to BA 40, shows activation more specific to phonology.

A region in right lateral cerebellum (Crus 1) also exhibited a pattern similar to that of BA 45/47 and BA 44 (Figure 3). As with these prefrontal regions, activation in Crus 1 was higher during semantic decisions on words and phonological decisions on pseudowords than during other conditions. Activation in Crus 1 was significantly greater in semantic than other tasks when word stimuli were considered [$F(2, 46) = 4.64, p < 0.05$]. Crus 1 was more active for semantic than either phonological [$t(23) = 2.67, p < 0.05$] or letter [$t(23) = 2.44, p < 0.05$] decisions on words. There were slight trends toward greater activation during phonological processing of pseudowords than letter processing of words [$t(23) = 1.49, p = .15$] and than letter processing of pseudowords [$t(23) = 1.38, p = .18$].

Taken collectively, these results suggest BA 45/47 (aLIPC), BA 44 (the anterior portion of pLIPC), and Crus 1 (a right cerebellar region) form a network that activates during controlled processing of both semantic and non-semantic information.

The surprising finding that BA 45/47 generalized its response to certain nonsemantic conditions raises the central question of what its role may be in these conditions; that is, what do those tasks activating this region share in common? One possibility is that subjects spon-

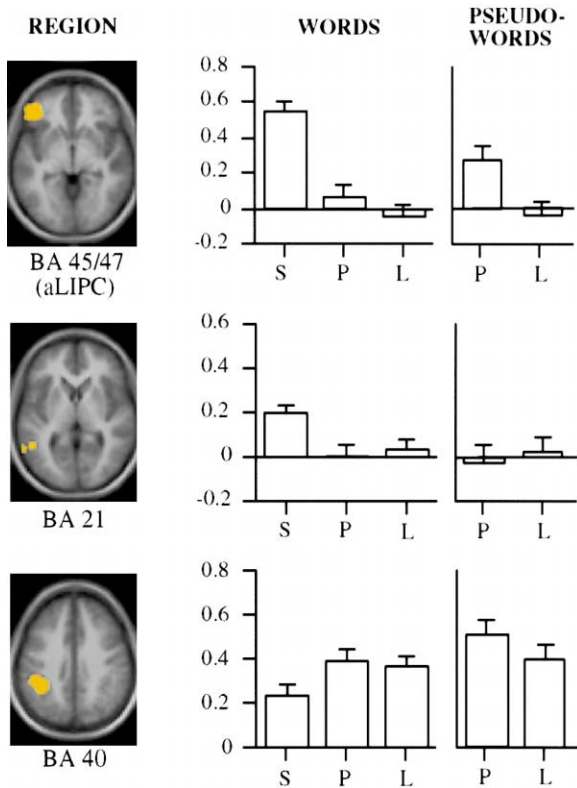


Figure 1. BA 45/47 (aLIPC) Coactivates with Domain-Preferential Posterior Regions during Controlled Semantic and Phonological Decision Tasks

Left panels (region) plot representations of a priori defined regions of interest in yellow overlaid on top of averaged anatomic images. The two adjacent columns display changes in signal amplitude (in percent) across conditions compared to fixation. Middle panels (words) plot signal change for semantic (S), phonological (P), and letter (L) decisions on words. Right panels (pseudowords) plot signal change for phonological (P) and letter (L) decisions on pseudowords. Error bars show standard error of the mean. BA 45/47 ($-45\ 35\ -4$) activates during both semantic decisions on words and phonological decisions on pseudowords. Moreover, dissociable posterior regions activate depending on the domain of information being processed. BA 45/47 and a left temporal region (BA 21; $-51\ -55\ 2$) were both activated strongly during semantic decisions on words, while BA 45/47 and a left parietal region (BA 40; $-41\ -43\ 34$) were both activated strongly during phonological decisions on pseudowords.

taneously adopt a strategy for pseudowords based on similarities to words and their associated meanings (Gabrieli et al., 1998). While possible, such a strategy seems unlikely to involve retrieval of *word meaning* in that activation of left temporal cortex near BA 21 is noticeably absent, unlike the semantic task where it is prominent. Two other hypotheses seem more likely. One theory regarding processing contributions of lateral prefrontal cortex suggests it increases participation when a stimulus does not constrain fully the necessary representation for a given task context (Petrides and Milner, 1982; Goldman-Rakic, 1987; Shallice, 1988; Frith et al., 1991; Thompson-Schill et al., 1997; Fletcher et al., 2000). Under such conditions, BA 45/47 could serve to constrain further the representation *de novo* in collaboration with posterior cortex. Alternatively, BA 45/47 may be acti-

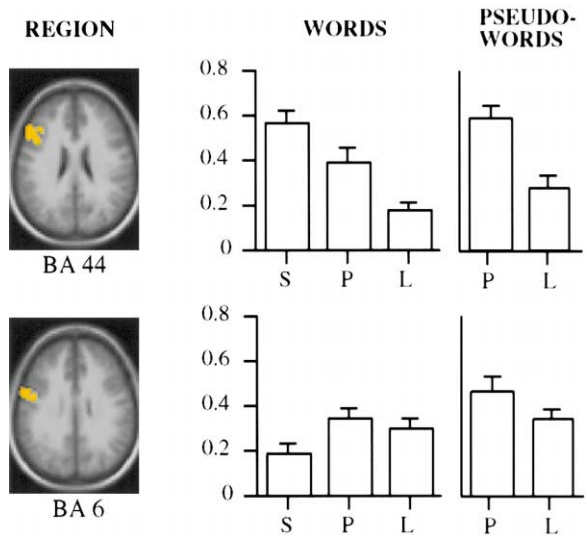


Figure 2. pLIPC Is Functionally Heterogeneous

Graphs plot regional activation similar to Figure 1. An anterior portion of pLIPC (BA 44; $-47\ 17\ 24$) was activated significantly during semantic decisions on words and phonological decisions on pseudowords, paralleling the behavior of BA 45/47 (see Figure 1), while a more posterior portion region of the frontal cortex near the precentral gyrus (BA 6; $-55\ -1\ 28$) showed a pattern that parallels that of a parietal region near the supramarginal gyrus (BA 40) (see Figure 1).

vated when operations are extended in time, as is the case with tasks having long response times.

Two aspects of the behavioral data were explored to assess whether either of these variables tracked with BA 45/47 activation. First, the correlation between mean response time and BA 45/47 activation was examined. Second, as a rough proxy measure of how directly the stimulus constrained the necessary task representation, the mean consistency of response (response consensus) was computed across subjects and similarly correlated with BA 45/47 activation. The degree of response consensus was associated strongly with BA 45/47 activation, accounting for 87% of the variance (Figure 4). As consensus decreased, reflecting more ambiguous stimulus-to-representation mappings, BA 45/47 activa-

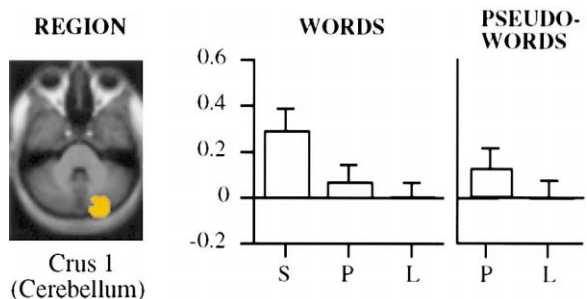


Figure 3. Right Cerebellum Participates in Semantic and Nonsemantic Controlled Processing

Graphs plot regional activation similar to Figure 1. Like BA 45/47, activation in right cerebellar cortex (Crus 1; $23\ -85\ -36$) was most strong during semantic decisions on words and phonological decisions on pseudowords.

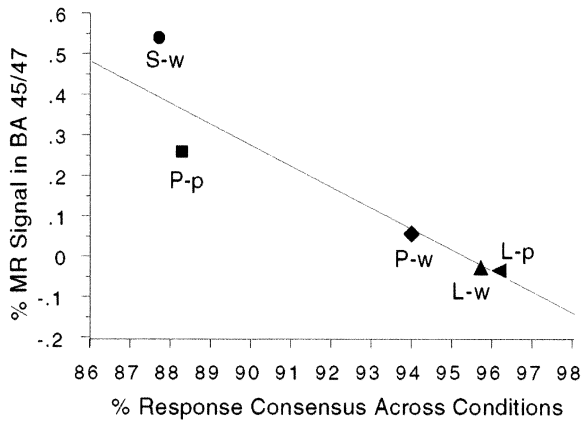


Figure 4. BA 45/47 Activation Tracks Response Consensus across Conditions

Regression of subject response consensus (see text) against percent MR signal change in BA 45/47 indicates that degree of subject response consensus accounted for 87% of the variance. Semantic decisions on words (S-w) and phonological decisions on pseudowords (P-p) were associated with the lowest degrees of subject response consensus and the highest levels of signal change. Conditions with higher degrees of subject response consensus such as phonological decisions on words (P-w) and letter decisions on words (L-w) and pseudowords (L-p) showed lower signal changes.

tion increased. By contrast, response time accounted for only 5% of the variance in BA 45/47 activation (see also Demb et al., 1995).

Generally, similar patterns were observed for BA 44 and Crus 1, again suggesting their coordinated participation with BA 45/47 in a network supporting controlled processing that generalizes across domains (consensus accounted for 89% and 79% of variance in BA 44 and Crus 1, respectively, with response time accounting for 44% and 19% of the variance). In the present study, activation patterns of BA 44 were largely parallel to patterns of BA 45/47, with each region recruited significantly during both semantic decisions on words and phonological decisions on pseudowords, and showing activation patterns that tracked inversely with response consensus.

However, for two reasons, results involving BA 44 were less unequivocal than those of BA 45/47. First, anatomically, the region defined as BA 44, which includes the anterior portion of pLIPC, borders the precentral gyrus (near BA 6) which showed an activation pattern relatively biased toward phonological processing, and the spatial resolution of fMRI makes it difficult to distinguish between these regions with confidence. The spatial proximity is also a likely contributing factor to why past studies (using both PET and fMRI) have often grouped BA 44 and BA 6 within the same functional unit. Second, unlike BA 45/47, BA 44 activation tracked with response time, perhaps reflecting spatial blurring with BA 6. Thus, although results suggest that BA 44 processing, like that of BA 45/47, generalizes across linguistic domains, evidence for the role of BA 45/47 was stronger.

Whole-brain analyses confirmed the importance of the aLIPC (~BA 45/47) and the anterior portion of pLIPC (~BA 44) in the controlled processing of semantic and

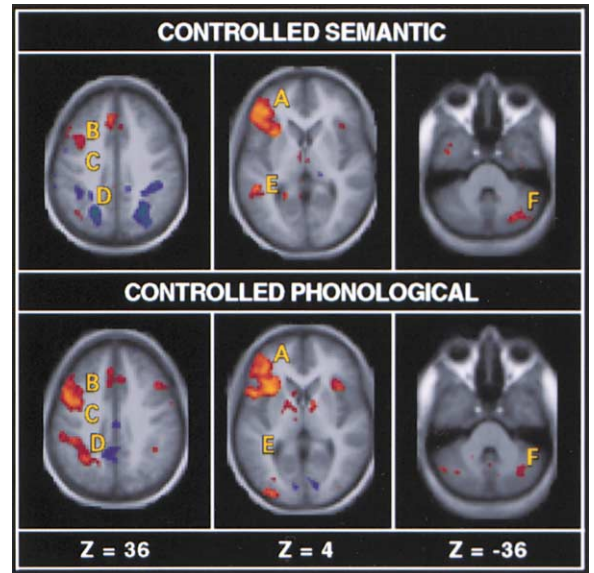


Figure 5. Whole-Brain Activation Maps Show Regions Involved in the Controlled Semantic and Controlled Phonological Decision Tasks, Corroborating Regional Analyses in Figures 1 to 3

The top panel (controlled semantic) displays activation patterns in selected transverse planes resulting from the direct comparison of the semantic task on words and letter task on words. The bottom panel (controlled phonology) displays activation patterns in the same slices resulting from the phonological task on pseudowords compared to the letter task on words. Activation maps plot z values from a voxel-based random effects analysis. Positive (red) and negative (blue) signal changes are displayed overlaid on top of an averaged anatomic image warped to the space of Talairach and Tournoux (1988) atlas. Z coordinates indicate the plane within the atlas. Activation that generalizes across semantic and phonological decision tasks is present in both comparisons including (A) aLIPC (BA 45/47), (B) anterior portion of pLIPC (BA 44), and (F) right lateral cerebellum. Activation of (C) posterior frontal cortex near the precentral gyrus (BA 6) and (D) parietal cortex near the supramarginal gyrus (BA 40) were related to the controlled phonological decision task, while activation of (E) left temporal cortex near the middle temporal gyrus (BA 21) was related to the controlled semantic decision task.

nonsemantic information, as well as the dissociability of BA 21, involved in controlled semantics, from BA 6 and BA 40, involved in controlled phonology (Figure 5).

Discussion

Results from recent functional neuroimaging studies have led to several prominent models of LIPC functioning. A domain-oriented model suggests functional heterogeneity based upon semantic-phonological lines, with an anterior ventral portion of the LIPC (aLIPC; near BA 45/47) relatively specialized for controlled use of semantic information and a posterior dorsal portion (pLIPC; near BA 44/6) relatively specialized for controlled use of phonological information (Poldrack et al., 1999; Bokde et al., 2001; Wagner et al., 2001). A process-oriented model (focusing particularly on a region near BA 44) holds that LIPC is critical in selection of relevant semantic knowledge from a set of competing alternatives (Thompson-Schill et al., 1997, 1998, 1999). *The present results dem-*

onstrate that aLIPC (BA 45/47) and an anterior portion of pLIPC (near BA 44) are involved in processes related to the controlled retrieval of information from both semantic and nonsemantic domains.

Regions within the LIPC were activated significantly during controlled phonological decisions on pseudowords in addition to even stronger activation during controlled semantic decisions on words. Importantly, while multiple LIPC regions were involved in controlled retrieval across domains, more posterior regions showed patterns of response that were dissociable along semantic and phonological domain lines. As predicted, aLIPC (BA 45/47) coactivated with a posterior portion of the left middle temporal gyrus (BA 21) during the retrieval of word meaning (Raichle et al., 1994; Vandenberghe et al., 1996; Binder et al., 1997; Thompson-Schill et al., 1997; Price et al., 1999). By contrast, aLIPC coactivated with posterior frontal cortex near the precentral gyrus (BA 6) and a region of the supramarginal gyrus of the parietal lobe (BA 40) during retrieval of phonology. These regions are often activated by tasks requiring verbal working memory and are believed to be part of a phonological loop that supports rehearsal and short-term maintenance of phonological material (Paulesu et al., 1993; Awh et al., 1996; Jonides et al., 1998; but see Fiez et al., 1996). Both BA 6 and BA 40 showed reduced activation in the semantic task relative to other conditions, but were activated during all tasks relative to fixation. The most probable explanation is that these regions are relatively specialized for phonology and that their involvement in semantic processing relates to phonological processes associated with meaning-based retrieval involving words. Left BA 21, by contrast, showed a more absolute response pattern, activating only during controlled semantic decisions. Thus, while it is unlikely that any one region is specialized entirely for a single language process, overall patterns of activation found in the present research provide strong evidence for relative degrees of specialization in posterior cortex.

Taken together, these results suggest a revision of prior models of the functional role of LIPC and its relation to posterior cortical regions (Buckner, 1996; Gabrieli et al., 1996, 1998; Kapur et al., 1996; Fiez, 1997; Poldrack et al., 1999; Bokde et al., 2001; Roskies et al., 2001; Wagner et al., 2001). *aLIPC (BA 45/47) and an anterior portion of the pLIPC (BA 44) are involved in controlled processing that generalizes across domains and coactivate with dissociable posterior regions depending on the kind of information being retrieved.*

The observation that aLIPC showed minimal activation in the phonology-word condition suggests that it does not always participate in phonological processing, but is recruited when phonological task conditions involve stimulus-to-representation mappings that are relatively ambiguous, as is the case in our vowel sound task when stimuli are pseudowords. Visual words are associated with a dominant sound code because repeated exposure to pronounceable visual forms strengthens links to corresponding sound codes (Coltheart et al., 1993; Plaut et al., 1996). Thus, the visual-to-sound code mappings of words are overlearned, whereas the visual-to-sound code mappings of pseudowords are less constrained, with a greater number of possible pronunciations (Plaut et al., 1996). Semantic tasks such as the

abstract/concrete task used here also have multiple potential task-relevant mappings because many words have multiple corresponding representations and associations that are likely derived differently depending on task context. For example, the word *couple* can correspond to a representation of two people (concrete), or two ideas (abstract). In support of the notion that aLIPC's role in semantic processing of words and phonological processing of pseudowords relates to mapping relatively ambiguous stimulus-to-representation relationships, Figure 4 shows that aLIPC activation tracks overall levels of response consensus for semantic, phonological and letter tasks. Task conditions eliciting relatively variable responses show increased aLIPC activity. pLIPC near BA 44 showed a similar pattern.

In many respects, aLIPC's role in phonological information processing thus parallels its role in semantic processing, which is also limited to controlled retrieval contexts. For example, single word reading, which is thought to result in automatic activation of semantic associations (Neely, 1977; MacLeod, 1991), has been shown to recruit a distributed network of areas associated with language processing, but not typically the aLIPC (Petersen et al., 1989; Howard et al., 1992; Rumsey et al., 1997). In addition, practicing semantic-based word generation results in stereotyped responding and also does not prominently activate aLIPC (Raichle et al., 1994; Domb et al., 1995; Buckner et al., 2000; Wagner et al., 2000). A role for aLIPC in deriving stimulus-to-representation mappings that are relatively ambiguous is not entirely inconsistent with results from previous studies of phonology. For example, aLIPC has sometimes been activated during reading of pseudowords (Herbster et al., 1997; Hagoort et al., 1999) and rhyming involving pseudowords (Pugh et al., 1996; Poldrack et al., 2001), both of which involve under-constrained stimulus-to-representation mappings.

Many existing theories of LIPC function suggest that aLIPC is specialized for the controlled retrieval of semantic information (Buckner, 1996; Gabrieli et al., 1996, 1998; Kapur et al., 1996; Fiez, 1997; Poldrack et al., 1999; Bokde et al., 2001; Roskies et al., 2001; Wagner et al., 2001). The present results demonstrate that aLIPC's role in controlled processing generalizes beyond the semantic domain, contributing to retrieval and manipulation of nonsemantic representations. These results are broadly in-line with recent findings from primate neurophysiology (Petrides, 1994; Assad et al., 1998) and human neuroimaging studies of working memory (Owen et al., 1998; D'Esposito et al., 1998; Barde and Thompson-Schill, 2002), which demonstrate the capacity for certain lateral prefrontal regions to perform controlled processing operations on information from multiple domains. For instance, Barde and Thompson-Schill (2002) found greater activation in dorsolateral prefrontal regions (~BA 46/9) than ventrolateral regions (~BA 44, 45/47) during manipulation than maintenance of information in working memory. However, no differences were found between aLIPC (~BA 45/47) and pLIPC (~BA 44) related to the kind of information (semantic or phonological) manipulated in working memory. More generally, the present findings support the view that certain prefrontal regions are capable of dynamic selection and interaction with

domain-specific posterior regions (Miller, 2000; Duncan, 2001).

An open question involves aLIPC's precise role in controlled phonology task conditions such as the present short/long vowel task performed with pseudowords. One possibility is that aLIPC's involvement in establishing sounds of visual pseudowords relates to processes associated with grapheme-to-phoneme conversion. Such a role could explain the observed increase in aLIPC response during phonological processing of pseudowords relative to words in that reading novel items is known to place increased emphasis on grapheme-to-phoneme conversion. However, it is difficult to reconcile this explanation with aLIPC's more established role in controlled semantic tasks (including its strong activation in the present abstract/concrete task). Such an explanation would require assigning a dual function to the aLIPC, with one set of functions associated with grapheme-to-phoneme conversion and a separate set of functions associated with retrieval of word meaning.

Another possibility, which we believe is more likely, is that aLIPC activation relates to a common set of controlled retrieval processes required to perform many semantic tasks but also appropriate to certain nonsemantic tasks. For example, it is possible that reading pseudowords occurs through analog to real words. Analog models suggest that pseudowords are read by retrieving real words from the pseudoword's orthographic neighborhood in the lexicon, choosing the best candidate, and then determining the pronunciation by analogy (Glushko, 1979; Friedman et al., 1992). On this account, aLIPC activation would be associated with selecting the appropriate lexical representation and then mapping a pseudoword's related sound code. Such a set of controlled retrieval processes involving increased selection demands from outside the semantic domain would parallel aLIPC's assumed role in controlled selection from within the semantic domain (Thompson-Schill et al., 1997). Within this view, it may also be possible to reconcile why controlled semantic tasks so often recruit aLIPC and the present finding of significant, but more modest, activation during a nonsemantic task. Semantic tasks, by way of their reliance on conceptual representations in novel task contexts, seem to invariably place high demands on mapping stimuli to multiple possible representations. Nonetheless, similar underlying controlled retrieval processes may be called upon when task demands require novel stimulus-to-representation mappings outside of the semantic domain, such as during the present phonology task performed with pseudowords.

It is unclear whether aLIPC processing is truly domain general, with the capacity for controlled retrieval from nonlinguistic domains. A recent review of the functional neuroimaging literature suggests that regions at or near aLIPC have been activated by cognitive tasks related broadly to the processing of response conflict and to the processing of task novelty, including conditions involving motor learning (Duncan and Owen, 2000). We do, however, expect aLIPC to be involved in processes related to assembling and/or selecting between representations relevant for a specific task context, as opposed to more response-based forms of conflict resolution (Milham et al., 2001). Future research varying the

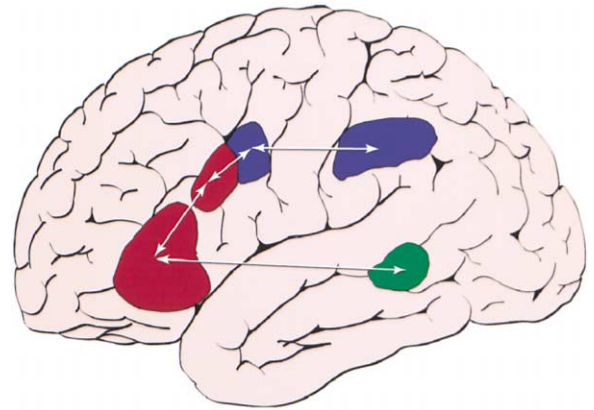


Figure 6. One Possible Schematic of the Present Results (Red) The aLIPC (BA 45/47) and an anterior portion of the pLIPC (BA 44) form a network with right cerebellar cortex (not shown) that is involved in controlled processing that generalizes across semantic and nonsemantic information. These regions that generalize across domains coactivate with dissociable posterior regions depending upon the domain of information being retrieved. (Blue) A posterior portion of frontal cortex near the precentral gyrus (BA 6) and left parietal cortex near the supramarginal gyrus (BA 40) are involved in domain-preferential controlled phonological processing, while (green) left temporal cortex near the middle temporal gyrus (BA 21) is involved in domain-preferential controlled semantic processing.

specific kinds of controlled processing tasks, stimulus forms, and input and output modalities will enable a more fine-grained characterization of the controlled processing routines available to aLIPC, as well as its relation to anatomically distinct, but functionally similar regions such as pLIPC near BA 44.

Figure 6 presents one possible schematic of the present results. Within the left frontal cortex, aLIPC (BA 45/47) and an anterior portion of pLIPC (BA 44) are involved in controlled processing that extends across multiple linguistic domains, along with right posterior-lateral cerebellum (Crus 1; not shown). These regions are functionally distinct from a posterior region of the left frontal cortex near the precentral gyrus (BA 6), which contributes most strongly to controlled phonology. The network involving aLIPC coactivates with domain-preferential posterior regions dependent upon the domain of code being processed, collaborating with a region of the left middle temporal gyrus (BA 21) during controlled use of semantic information, and with left precentral gyrus (BA 6) and left parietal cortex near the supramarginal gyrus (BA 40) during controlled use of phonological information.

Experimental Procedures

Subjects

Twenty-four volunteers (13 females) participated in the study (age 20 to 34; $M = 24.6$ years, $SD = 3.3$). All were native English speaking, right-handed, and reported no significant neurological history. Informed consent was obtained using procedures approved by the Washington University School of Medicine Human Studies Committee.

Tasks and Stimuli

In a *semantic decision task*, subjects decided whether words represented concepts that were abstract or concrete (Demb et al., 1995).

In a *phonological decision task*, subjects decided whether words/pseudowords were short or long vowel items. An item is long vowel when any of the full vowel sounds “a,” “e,” “i,” “o,” or “u” are present anywhere in the item, no matter which letter(s) form the sound (Fiez et al., 1995). For example, the word “weight” would usually be classified as “long vowel” because it contains the sound “a.” In a *letter decision task*, subjects decided whether the first or last letter in each word/pseudoword came earlier in the alphabet (Demb et al., 1995). For example, the correct response to the item “teacher” would be “last letter” because “r” precedes “t” in alphabetic order.

For stimuli, 216 high-frequency nouns (above 100 per million) of 3–7 letters and 1–2 syllables were selected from the norms of Kucera and Francis (1967). Matching groups of pseudowords were created by changing one or two of the letters of a word. Six matched stimulus-specific lists of 36 items were then created. Words were assigned to their lists such that half were abstract, half were short vowel, and half had first letters preceding last letters in alphabetic ordering. Pseudowords were divided similarly for their relevant dimensions. Word lists were matched for frequency and length, and pseudoword lists were matched for length. Order of task presentation and stimulus lists were counterbalanced across subjects.

Experimental Paradigm

A blocked-task paradigm was employed with conditions manipulated between runs. Each run alternated between four reference blocks of 22.5 s of fixation (during which subjects fixated a cross-hair [+]) and three 30 s task blocks of 12 stimuli each. In addition, runs began with the presentation of 10 s of fixation (while steady-state magnetization was reached). Each condition was presented in two sequential runs, for a total of ten relevant runs per subject. Trials during task blocks were time-locked to the onset of successive whole-brain image acquisitions. Stimuli were projected centrally (24 pt geneva font, white on black background) for a duration of 2000 ms, followed by presentation of a fixation cross-hair for the remainder of the trial (500 ms). Stimuli were projected onto a screen at the back of the magnet bore, viewed through a mirror. Subjects indicated responses via a custom built, fiber-optic button press connected to a Psyscope button box (Carnegie Mellon University, Pittsburgh, PA). Stimulus presentation and recording of responses were implemented with Psyscope software (Cohen et al., 1993) run on an Power Macintosh computer (Apple, Cupertino, CA).

Response Consensus

As one proxy measure of the relative strength of stimulus-to-representation mappings, response consensus (consistency) was computed for each condition. Conditions tending toward single, dominant stimulus-to-representation mappings will tend to have high consensus ratings. This relation is imperfect and may not be fully comparable between tasks, but nonetheless serves as one measure that estimates stimulus-to-representation mappings, much as naming agreement can estimate the consistency of word labels in picture naming (Snodgrass and Vanderwart, 1980). Response consensus ratings for each condition were determined by first computing the degree of subject agreement for each of the 8,640 stimuli (36 stimuli per condition \times 5 conditions \times 2 runs \times 24 subjects). Thus, for each stimulus, the percentage of each of two possible responses was computed (i.e., percentage of subjects responding “abstract” and percentage responding “concrete” to each item in the semantic task). The higher of the two percentages associated with each item was then entered into an average percentage consensus rating for each condition.

Imaging

Scanning was performed at 1.5 Tesla on a Siemens Vision System (Erlangen, Germany). Structural images were acquired using a sagittal MP-RAGE T1-weighted sequence (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, TI = 20 ms, voxel size = 1 \times 1 \times 1.25 mm). Functional images were acquired using an asymmetric spin-echo echo-planar sequence (T.E. Conturo et al., 1996, Soc. Neurosci., abstract). For functional runs, 72 sequential whole-brain acquisitions were acquired with each including 16 contiguous 8 mm thick axial slices (TR = 2.5 s, TE = 37 ms, 3.75 mm² in-plane resolution; acquired parallel to the anterior-posterior commissure plane). Functional runs

began with 4 “dummy” image acquisitions to allow stabilization of longitudinal magnetization.

MR Data Analysis

Functional images were preprocessed prior to analysis to correct for motion artifact using rigid-body rotation and translation (Snyder, 1996). Sync interpolation was used to account for between-slice timing differences, and linear slope was removed on a voxel-by-voxel basis (Bandettini et al., 1993). The data were normalized to a whole-run mean magnitude of 1,000 to allow for comparisons across subjects. Each subject’s structural and functional data were then resampled into 2 mm isotropic voxels, warped to a standard stereotaxic atlas space (Talairach and Tournoux, 1988), and smoothed with a gaussian filter (6 mm FWHM).

Region-Wise Analysis

Specific regions of interest were defined a priori as “semantic” or “phonological” based on the literature and locations of peak activations taken from a related study conducted in our laboratory (Logan et al., 2002). This study involved a contrast between the semantic and letter tasks for word stimuli, as described above. Six target regions were selected a priori including four hypothesized to be involved in controlled semantic processing and two involved in phonological processing (see Table 2). For each location, a three-dimensional region was defined to include all activated voxels within 12 mm of the peak. These a priori regions were then explored in the present data set.

Magnitude estimates were obtained for each region for the present study using an implementation of the general linear model (McDermott et al., 1999) first on a voxel-by-voxel basis. A delayed boxcar convolved with a γ function (Boynton et al., 1996) was used as the model basis excluding effects of slope and run mean (similar to Friston et al., 1995). Magnitude estimates for each condition were referenced to fixation, for each subject, and scaled to percent signal change. The average signal change within the region was then submitted as a single value to a series of statistical tests based on a mixed-effects model including subjects as a random effect.

Whole-Brain Analysis

To confirm and explore further the data set, a whole-brain analysis was also employed using a random-effect statistical model *t* test at each voxel. Resulting *t* statistics were converted to *z* statistics and plotted over the whole brain. This was accomplished by mapping the *p* value associated with the *t* statistic onto an equivalent *p* value on the normal distribution, yielding the *z* statistic. All results obtained in the targeted a priori analyses above were confirmed in the whole-brain analysis (*p* < 0.001).

Acknowledgments

We thank Kate O’Brien for assistance with data collection, and Avi Snyder, Luigi Maccotta, Mark Wheeler, Mark McAvoy, Jes Logan, Steve Petersen, and David Balota for discussion and support. In addition, we thank Cathy Price and three anonymous reviewers for helpful comments on an earlier version of this manuscript. The Howard Hughes Medical Institute, the James S. McDonnell Foundation Program in Cognitive Neuroscience (99-63/9900003), the Alzheimer’s Association, and the National Institute of Mental Health (MH57506) provided support.

Received: January 24, 2002

Revised: May 15, 2002

References

- Assad, W.F., Rainer, G., and Miller, E.K. (1998). Neural activity in the primate prefrontal cortex during associative learning. *Neuron* 21, 1399–1407.
- Awh, E., Jonides, J., Smith, E.E., Schumacher, E.H., Koeppel, R.A., and Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: evidence from PET. *Psychol. Sci.* 7, 25–31.
- Bandettini, P.A., Jesmanowicz, A., Wong, E.C., and Hyde, J.S.

- (1993). Processing strategies for time-course data sets in functional MRI of the human brain. *Magn. Reson. Med.* 30, 161–173.
- Barde, L.H.F., and Thompson-Schill, S. (2002). Models of functional organization of lateral prefrontal cortex in verbal working memory: Evidence in favor of the process model. *J. Cogn. Neurosci.*, in press.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Cox, R.W., Rao, S.M., and Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *J. Neurosci.* 17, 353–362.
- Bokde, A.L.W., Tagamets, M.A., Friedman, R.B., and Horwitz, B. (2001). Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. *Neuron* 30, 609–617.
- Boynton, G.M., Engel, S.A., Glover, G.H., and Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci.* 16, 4207–4221.
- Buckner, R.L. (1996). Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychon. Bull. Rev.* 3, 149–158.
- Buckner, R.L., Raichle, M.E., and Petersen, S.E. (1995). Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. *J. Neurophysiol.* 74, 2163–2173.
- Buckner, R.L., Koutstaal, W., Schacter, D.L., and Rosen, B.R. (2000). Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. *Brain* 123, 620–640.
- Cohen, J.D., MacWhinney, R.C., Flatt, M., and Provost, J. (1993). Psycoscope: An interactive graphic system for designing and controlling experiments in the psychology laboratory using Macintosh computers. *Behav. Res. Methods Instrum. Comput.* 25, 257–271.
- Coltheart, M., Curtis, B., Atkins, P., and Haller, M. (1993). Models of reading aloud: dual-route and parallel-distributed-processing approaches. *Psych. Rev.* 100, 589–608.
- Demb, J.B., Desmond, J.E., Wagner, A.D., Vaidya, C.J., Glover, G.H., and Gabrieli, J.D.E. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *J. Neurosci.* 15, 5870–5878.
- Demonet, J.F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J.L., Wise, R., Rascol, A., and Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain* 115, 1753–1768.
- D'Esposito, M., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K., and Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Brain Res. Cogn. Brain Res.* 7, 1–13.
- Duncan, J. (2001). An adaptive coding model of neural functioning in prefrontal cortex. *Nat. Rev. Neurosci.* 2, 820–829.
- Duncan, J., and Owen, A.M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* 23, 475–483.
- Fiez, J.A. (1997). Phonology, semantics, and the role of the left inferior prefrontal cortex. *Hum. Brain Mapp.* 5, 79–83.
- Fiez, J.A., Tallal, P., Raichle, M.E., Miezin, F.M., Katz, W.F., and Petersen, S.E. (1995). PET studies of auditory and phonological processing: Effects of stimulus characteristics and task demands. *J. Cogn. Neurosci.* 7, 357–375.
- Fiez, J.A., Raife, E.A., Balota, D.A., Schwarz, J.P., Raichle, M.E., and Petersen, S.E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *J. Neurosci.* 16, 808–822.
- Fletcher, P.C., Shallice, T., and Dolan, R. (2000). Sculpting the response space—an account of left prefrontal activation at encoding. *Neuroimage* 12, 404–417.
- Friedman, R.B., Ferguson, S., Robinson, S., and Sunderland, T. (1992). Dissociation of mechanisms of reading in Alzheimer's disease. *Brain Lang.* 43, 400–413.
- Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., and Turner, R. (1995). Analysis of fMRI time-series revisited. *Neuroimage* 2, 45–53.
- Frith, C.D., Friston, K.J., Liddle, P.F., and Frackowiak, R.S.J. (1991). A PET study of word finding. *Neuropsychologia* 29, 1137–1148.
- Gabrieli, J.D.E., Desmond, J.E., Demb, J.B., Wagner, A.D., Stone, M.V., Vaidya, C.J., and Glover, G.H. (1996). Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. *Psychol. Sci.* 7, 278–283.
- Gabrieli, J.D.E., Poldrack, R.A., and Desmond, J.E. (1998). The role of the left prefrontal cortex in language and memory. *Proc. Natl. Acad. Sci. USA* 95, 906–913.
- Glushko, R.J. (1979). The organization and activation of orthographic knowledge in reading aloud. *J. Exp. Psychol. Hum. Percept. Perform.* 5, 674–691.
- Goldman-Rakic, P.S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In *Handbook of Physiology: The Nervous System Vol. 5*, F. Plum and V. Mountcastle, eds. (Baltimore, MD: Williams & Wilkins), pp. 373–417.
- Hagoort, P., Indefrey, P., Brown, C., Herzog, H., Steinmetz, H., and Seitz, R.J. (1999). The neural circuitry involved in the reading of German words and pseudowords: A PET study. *J. Cogn. Neurosci.* 11, 383–398.
- Herbster, A.N., Mintun, M.A., Nebes, R.D., and Becker, J.T. (1997). Regional cerebral blood flow during word and nonword reading. *Hum. Brain Mapp.* 5, 84–92.
- Howard, D., Patterson, K., Wise, R., Brown, W.D., Friston, K., Weiller, C., and Frackowiak, R. (1992). The cortical localization of the lexicons: Positron emission tomography evidence. *Brain* 115, 1769–1782.
- Jonides, J., Schumacher, E.H., Smith, E.E., Koeppel, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., and Willis, C.R. (1998). The role of parietal cortex in verbal working memory. *J. Neurosci.* 18, 5026–5034.
- Kapur, S., Tulving, E., Cabeza, R., McIntosh, A.R., Houle, S., and Craik, F.I. (1996). The neural correlates of intentional learning of verbal materials: a PET study in humans. *Brain Res. Cogn. Brain Res.* 4, 243–249.
- Kucera, H., and Francis, W.N. (1967). *The Computational Analysis of Present-Day American English* (Providence, RI: Brown University Press).
- Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., and Buckner, R.L. (2002). Under-recruitment and non-selective recruitment: dissociable neural mechanisms associated with aging. *Neuron* 33, 827–840.
- MacLeod, C.M. (1991). Half a century of research on the Stroop effect: an integrative review. *Psychol. Bull.* 109, 163–203.
- McDermott, K.B., Buckner, R.L., Petersen, S.E., Kelley, W.M., and Sanders, A.L. (1999). Set- and code-specific activation in the frontal cortex: an fMRI study of encoding and retrieval of faces and words. *J. Cogn. Neurosci.* 11, 631–640.
- Milham, M.P., Banich, M.T., Webb, A., Barad, V., Cohen, N.J., Wszalek, T., and Kramer, A.F. (2001). The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Brain Res. Cogn. Brain Res.* 12, 467–473.
- Miller, E.K. (2000). The prefrontal cortex and cognitive control. *Nat. Rev. Neurosci.* 1, 59–65.
- Milner, B. (1963). Effects of different brain lesions on card sorting. *Arch. Neurol.* 9, 90–100.
- Milner, B. (1964). Some effects of frontal lobectomy in man. In *The Frontal Granular Cortex and Behavior*, J.M. Warren, and K. Akert, eds. (New York: McGraw-Hill), pp. 313–334.
- Neely, J.H. (1977). Semantic priming and retrieval from lexical memory: Roles of inhibitionless spreading activation and limited-capacity attention. *J. Exp. Psychol. Gen.* 106, 226–254.
- Norman, D.A., and Shallice, T. (1986). Attention to action: willed and automatic control of behavior. In *Consciousness and Self-Regulation*, R.J. Davidson, G.E. Schwartz, and D. Shapiro, eds. (New York: Plenum), pp. 1–18.
- Owen, A.M., Stern, C.E., Look, R.B., Tracey, I., Rosen, B.R., and Petrides, M. (1998). Functional organisation of spatial and non-spatial working memory processes within the human lateral frontal cortex. *Proc. Natl. Acad. Sci. USA* 95, 7721–7726.
- Paulesu, E., Frith, C.D., and Frackowiak, R.S.J. (1993). The neural

- correlates of the verbal component of working memory. *Nature* 362, 342–345.
- Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M., and Raichle, M.E. (1989). Positron emission tomographic studies of the processing of single words. *J. Cogn. Neurosci.* 1, 153–170.
- Petrides, M. (1994). Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in non-human primates. In *Handbook of Neuropsychology* Vol. 9, F. Boller and J. Grafman, eds. (Amsterdam: Elsevier), pp. 59–82.
- Petrides, M., and Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* 20, 249–262.
- Plaut, D.C., McClelland, J.L., Seidenberg, M.S., and Patterson, K. (1996). Understanding normal and impaired word reading: Computational principles in quasi-regular domains. *Psychol. Rev.* 103, 56–115.
- Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., and Gabrieli, J.D.E. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10, 15–35.
- Poldrack, R.A., Temple, E., Protopapas, A., Nagarajan, S., Tallal, P., Merzenich, M., and Gabrieli, J.D.E. (2001). Relations between the neural bases of dynamic auditory processing and phonological processing: Evidence from fMRI. *J. Cogn. Neurosci.* 13, 687–697.
- Price, C.J., Mummery, C.J., Moore, C.J., Frackowiak, R.S.J., and Friston, K.J. (1999). Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *J. Cogn. Neurosci.* 11, 371–382.
- Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Constable, R.T., Skudlarski, P., Fullbright, R.K., Bronen, R.A., Shankweiler, D.P., Katz, L., Fletcher, J.M., and Gore, J.C. (1996). Cerebral organization of component processes in reading. *Brain* 119, 1221–1238.
- Raichle, M.E., Fiez, J.A., Videen, T.O., Macleod, A.M.K., Pardo, J.V., Fox, P.T., and Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb. Cortex* 4, 8–26.
- Roskies, A.L., Fiez, J.A., Balota, D.A., Raichle, M.E., and Petersen, S.E. (2001). Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. *J. Cogn. Neurosci.* 13, 829–843.
- Rumsey, J.M., Horwitz, B., Donohue, B.C., Nace, K., Maisog, J.M., and Andreason, P. (1997). Phonologic and orthographic components of word recognition: a PET-rCBF study. *Brain* 119, 739–759.
- Schmahmann, J.D., Doyon, J., Toga, A.W., Petrides, M., and Evans, A.C. (2000). *MRI Atlas of the Human Cerebellum* (San Diego, CA: Academic Press).
- Shallice, T. (1988). *From Neuropsychology to Mental Structure* (Cambridge: Cambridge University Press).
- Snodgrass, J.G., and Vanderwart, M.J. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J. Exp. Psychol. [Hum. Learn.]* 6, 174–215.
- Snyder, A.Z. (1996). Difference image vs. ratio image error function forms in PET-PET realignment. In *Quantification of brain function using PET*, D. Bailey and T. Jones, eds. (San Diego, CA: Academic Press), pp. 131–137.
- Stuss, D.T., and Benson, D.F. (1984). Neuropsychological studies of the frontal lobes. *Psychol. Bull.* 95, 3–28.
- Talairach, J., and Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain* (Stuttgart: Thieme).
- Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K., and Farah, M.J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proc. Natl. Acad. Sci. USA* 94, 14792–14797.
- Thompson-Schill, S.L., Swick, D., Farah, M.J., D'Esposito, M., Kan, I.P., and Knight, R.T. (1998). Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proc. Natl. Acad. Sci. USA* 95, 15855–15860.
- Thompson-Schill, S.L., D'Esposito, M., and Kan, I.P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron* 23, 513–522.
- Vandenberghe, R., Price, C., Wise, R., Josephs, O., and Frackowiak, R.S.J. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature* 383, 254–256.
- Wagner, A.D., Koutstaal, W., Maril, A., Schacter, D.L., and Buckner, R.L. (2000). Task-specific repetition priming in left inferior prefrontal cortex. *Cereb. Cortex* 10, 1176–1184.
- Wagner, A.D., Paré-Blagoev, E.J., Clark, J., and Poldrack, R.A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron* 31, 329–338.
- Zatorre, R.J., Evans, A.C., Meyer, E., and Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. *Science* 256, 846–849.