What Can Neuroimaging Tell Us About the Mind?

Insights From Prefrontal Cortex

Russell A. Poldrack[1] **and Anthony D. Wagner**[2]

[1]*Department of Psychology and Brain Research Institute, University of California, Los Angeles, and*
[2]*Department of Psychology and Neurosciences Program, Stanford University*

ABSTRACT—*Psychologists interested in the workings of the mind may wonder whether brain-imaging data can provide insight regarding cognitive mechanisms. Here we consider one means through which imaging can inform cognitive theory:* reverse inference, *wherein activations in well-characterized neural structures serve as markers for the engagement of particular cognitive processes. To illustrate this approach, we review brain-imaging evidence regarding the organization of cognitive and linguistic processes in the prefrontal cortex, which indicates that phonological (speech-sound-based) and semantic (meaning-based) processing are consistently associated with topographically distinct patterns of activity in the left inferior prefrontal cortex. We then illustrate how this finding of regional differentiation has provided useful guidance for understanding the cognitive processes supporting memory encoding and retrieval. We conclude with caveats that highlight some of the limitations of the reverse-inference approach.*

KEYWORDS—*cognitive control; semantic; phonological; neuroimaging*

Imaging of brain function has become an immensely popular technique over the past decade, yet many readers of this journal may harbor suspicions that it is nothing but a high-tech (and very expensive) revision of phrenology. A cursory glance at the neuroimaging literature readily reveals instances of “blob-ology,” wherein researchers, often in a post hoc manner, attempt to explain why a particular region was active during performance of a particular task. Yet, a broader consideration of the literature can reveal consistent patterns of activation that transcend the limitations of such ad hoc conclusions, appearing to reveal something more fundamental about the mapping between mind and brain. Such discoveries, which typically emerge from an extensive body of investigation, may nevertheless still leave open the question: What is the use of knowing which brain regions are active in association with a particular cognitive process?

Address correspondence to Russell A. Poldrack, UCLA Department of Psychology, Franz Hall, Los Angeles, CA 90095-1563; e-mail: poldrack@ucla.edu.

In this article, we aim to illustrate how knowledge of functional localization (i.e., the location of brain activations) can inform cognitive theories through the approach of *reverse inference*, wherein activation in a particular brain region (or regions) is taken as a marker of engagement of a particular cognitive process. We begin by describing a set of findings that suggest that meaning-based (*semantic*) and speech-sound-based (*phonological*) processes are consistently associated with topographically distinct patterns of activity in the left inferior prefrontal cortex (LIPC; see Fig. 1). We then illustrate how this discovery of localized processes can serve as a useful (though limited) guidepost, permitting neuroimaging data to inform cognitive models. We conclude by emphasizing some caveats regarding the reverse-inference approach.

EVIDENCE FOR FUNCTIONAL SEGREGATION IN LIPC

Functional neuroimaging measures local brain activity indirectly through the imaging of such parameters as blood flow or blood oxygenation. The effects of neurotransmitters released into the synapses between neurons result in increased blood flow and oxygenation in the region of those neurons, so that by comparing images acquired during the performance of tasks that differ in whether they engage a particular cognitive process, one can determine which regions exhibit activity that is putatively related to that cognitive process.

Some of the earliest neuroimaging studies of language revealed activity in LIPC on task comparisons meant to isolate semantic processing, phonological processing, or both, and an extensive body of subsequent research supported the conclusion that this area of the brain is activated during language production and comprehension. Tasks used to examine semantic processing have included generating semantic associates of cue words and classifying the meanings of words, such as deciding whether they are abstract (e.g., *love*) or concrete (e.g., *table*). Tasks used to examine phonological processing have included deciding whether words or pseudowords rhyme, counting syllables of words or pseudowords, and maintaining verbal materials in working memory (the immediately accessible form of memory in which information is held in mind and manipulated).

Fiez (1997) suggested that tasks requiring semantic or phonological processing engage anatomically distinct regions in LIPC. Activation

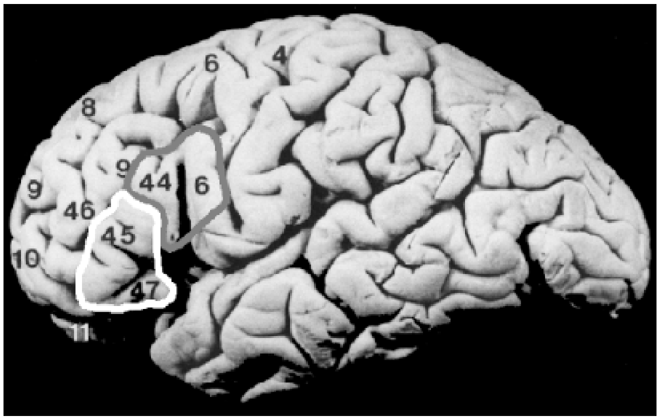

Fig. 1. Lateral view of the brain, with anterior left inferior prefrontal cortex outlined in white and posterior left inferior prefrontal cortex outlined in gray. Numbers represent approximate locations of Brodmann's areas (areas that differ in the arrangement and types of neurons). Adapted from ''Neuroanatomy of Frontal Lobe in Vivo: A Comment on Methodology,'' by H.C. Damasio, in *Frontal Lobe Function and Dysfunction* (p. 101), edited by H.S. Levin, H.M. Eisenberg, and A.L. Benton, 1991, New York: Oxford University Press. Copyright 1991 by Oxford University Press. Adapted with permission of H.C. Damasio and Oxford University Press.

during performance of semantic tasks was often observed in the more anterior (forward) and ventral (downward) section of LIPC, whereas activation during phonological tasks was often observed in the more posterior (rearward) and dorsal (upward) section of LIPC (Fig. 1). Subsequently, an extensive meta-analysis (i.e., an analysis combining the results from a number of studies) provided further support for this proposed functional segregation (Poldrack et al., 1999): Activation in anterior LIPC (aLIPC) was observed primarily during semantic tasks, whereas activation in posterior LIPC (pLIPC) was observed during tasks requiring phonological judgments, as well as during some semantic tasks. These findings led to the *semantic-phonological hypothesis* (SPH), according to which semantic and phonological processes differentially depend on the anterior and posterior subregions of LIPC.

Although early studies and meta-analyses motivated the SPH, direct evidence awaited within-subjects comparison of brain activation during semantic and phonological processing. A number of studies published since 1999 demonstrated differences between aLIPC and pLIPC activity when semantic and phonological tasks were compared directly (e.g., Devlin, Matthews, & Rushworth, 2003; Poldrack et al., 1999). For example, Otten and Rugg (2001) contrasted activation patterns when subjects made animacy judgments and syllable-counting judgments, observing greater aLIPC activation during the animacy task than during the syllable-counting task, but greater pLIPC activation during the syllable-counting task than during the animacy task (Fig. 2). Further evidence for the SPH comes from the observation that aLIPC and pLIPC exhibit different patterns of functional connectivity, or activity correlated with activity in other brain regions (Bokde, Tagamets, Friedman, & Horwitz, 2001). In particular, the connectivity patterns of pLIPC were modulated by the need for phonological processing, whereas the connectivity patterns of aLIPC were modulated by the need for semantic processing.

Though the results we have summarized tend to support the SPH, they are constrained by ambiguities inherent in the underlying task analyses, as these findings emerge from task comparisons that hinge on associating individual tasks with particular cognitive processes. However, because tasks may differ along multiple dimensions beyond those identified by the experimenter, it is rarely possible to uniquely assign a particular activation to a specific cognitive process. The consistency of findings across studies that used a variety of "semantic" and "phonological" tasks mitigates this concern to some extent. Moreover, as we describe in the next two sections, further evidence for the SPH comes from studies that examined the effects of separately manipulating either semantic or phonological processing demands within a given task.

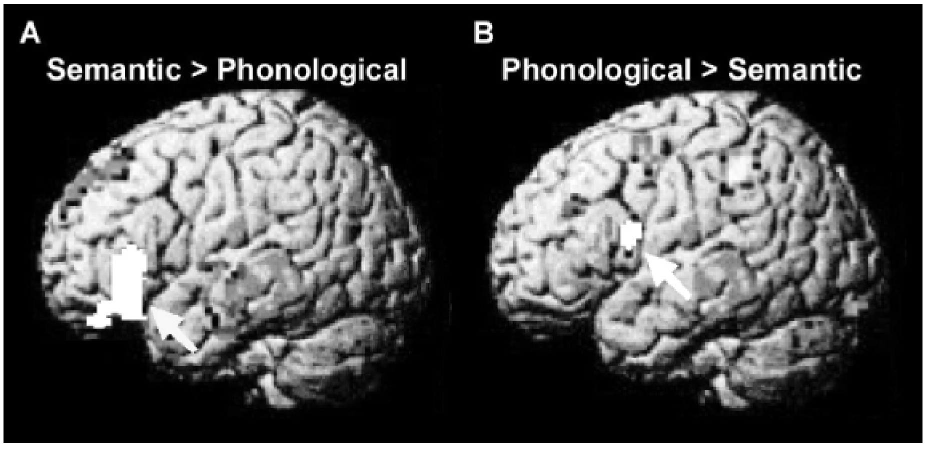

Fig. 2. Differential activation of anterior left inferior prefrontal cortex (aLIPC) and posterior left inferior prefrontal cortex (pLIPC) during semantic and phonological processing (data adapted from Otten & Rugg, 2001, with permission of L. Otten and Oxford University Press). As shown in (a), activation of aLIPC (highlighted in white) was greater when subjects made semantic (animate/inanimate) decisions about words than when they made phonological (syllable counting) decisions about words. In contrast, as shown in (b), activation of pLIPC (highlighted in white) was greater when subjects made phonological decisions than when they made semantic decisions about words.

RESPONSE TO SEMANTIC MANIPULATIONS

To the extent that aLIPC is differentially involved in semantic processing, it should be particularly responsive to manipulations that systematically vary demands on semantic processing. Experimental results have been consistent with this prediction, showing that aLIPC and pLIPC respond differently to manipulations that affect the need for *controlled retrieval* of semantic knowledge. Controlled retrieval is necessary in situations in which the relevant knowledge is less strongly available than other, irrelevant knowledge. For example, we (Wagner, Paré-Blagoev, Clark, & Poldrack, 2001) presented subjects with a similarity-judgment task, in which they were given a cue word and asked to choose the item most semantically similar to the cue from a set of possible target words. This study varied the strength of association between the cue and target in order to manipulate the level of control required to retrieve the relevant semantic knowledge. For example, for the cue "candle," the strongly associated target was "flame," whereas the weakly associated target was "halo." We also varied the number of possible target words, presenting either two or four words on each trial. Although both LIPC regions exhibited greater activity with an increasing number of targets, which could reflect either semantic or phonological demands inherent in processing additional words, aLIPC was more sensitive to the effects of semantic associative strength—and thus controlled retrieval demands—than was pLIPC.

Differences in aLIPC and pLIPC activity were also observed in the context of repetition priming (Wagner, Koutstaal, Maril, Schacter, & Buckner, 2000), which is the benefit that accrues due to having previously processed a stimulus (a benefit observed in terms of faster or more accurate performance). Neural correlates of priming are typically observed as reduced activation during the processing of repeated relative to novel stimuli. In this study, subjects initially made perceptual (uppercase/lowercase) judgments about some words and subsequently made semantic (abstract/concrete) judgments about those same words; for other words, subjects did not perform the perceptual task but rather performed the semantic task twice. Thus, every word was reencountered during the semantic task, but for some words this second encounter was in the context of a new task and for other words it was not. Decreased activity (priming) was observed in pLIPC during the second presentation of all words, regardless of whether the task had changed, whereas reduced activity (priming) occurred in aLIPC only when words were encountered twice within the semantic task. Given that priming effects are thought to reflect the nature of processing in a particular area, this finding suggests that aLIPC may differentially support semantic processing operations.

RESPONSE TO PHONOLOGICAL MANIPULATIONS

The SPH predicts that manipulations of phonological processing demands should have differential effects on activity in pLIPC. One variable that affects such demands in English is regularity, which is the degree to which a word's spelling and pronunciation follow the typical spelling-sound correspondences of the language; for example, *pint* or *yacht* are irregular, whereas *hint* and *batch* are regular. In a study consistent with the SPH, Fiez, Balota, Raichle, and Petersen (1999) observed that pLIPC, but not aLIPC, was sensitive to regularity, exhibiting greater activation for irregular than for regular words. Studies of phonological working memory provide additional evidence for differential phonological effects on pLIPC (for a review, see Smith & Jonides, 1999). Such studies have demonstrated that phonological rehearsal processes appear to selectively engage pLIPC, rarely impacting aLIPC activity.

Other recent studies, however, have suggested the aLIPC may be sensitive to manipulations thought to preferentially affect phonological processing. For example, Gold and Buckner (2002) observed aLIPC and pLIPC activation during both semantic (abstract/concrete) judgments on words and phonological (short/long vowel) judgments on pseudowords. Having observed aLIPC activation during a putatively phonological task, they hypothesized that aLIPC mediates controlled processing regardless of stimulus domain, rather than specifically within the semantic domain. The magnitude of activity in aLIPC was consistent with this hypothesis, as aLIPC activation was lower the more subjects agreed in their responses (e.g., the larger the proportion of people who agreed that *love* is abstract). The extent to which subjects' responses on this task agree may reflect the degree of competition between different meanings or sounds, so this correlation raises the possibility that aLIPC mechanisms select or otherwise constrain the stimulus interpretation in a given task irrespective of the relevant domain. However, this interpretation is difficult to reconcile with Gold and Buckner's finding that aLIPC activity was more than twice as great during semantic processing of words as during phonological processing of pseudowords, despite a difference of less than 1% in response consensus between semantic and phonological conditions.

IMPLICATIONS FOR COGNITIVE THEORY

This brief review illustrates that a considerable body of evidence in favor of the SPH has been amassed. Accordingly, we return to the question raised at the outset: Why should a psychologist care that semantic and phonological processes are associated with activation in different areas of the brain? Although brain imaging may inform and constrain cognitive theory in multiple ways, here we focus on the implications of the reverse-inference approach. In particular, the discovery of systematic localization offers the possibility that researchers may be able to extend the SPH to drive hypotheses in different cognitive domains. That is, when aLIPC and pLIPC are found to be activated in other cognitive domains, these results can be interpreted in terms of engagement of semantic versus phonological computations, providing evidence that can adjudicate between competing cognitive models and also suggesting further hypotheses for subsequent testing.

An example of such an application comes from the memory literature. Cognitive theories of encoding in episodic memory (i.e., conscious memory for prior events) suggest that it involves multiple control processes, including both semantic and phonological processes. For example, strategies for episodic encoding can rely on either rote rehearsal (e.g., repeating a set of words in working memory) or elaborative rehearsal (e.g., elaborating semantic relations between words), with elaborative rehearsal generally resulting in better subsequent memory. One subject of significant debate over the past 30 years has been whether phonological rehearsal, absent semantic elaboration, is sufficient to create new episodic memories. This question was addressed in a set of neuroimaging studies motivated by the SPH. Wagner, Maril, Bjork, and Schacter (2001) compared rote and elaborative rehearsal, and found that pLIPC was extensively engaged during rote and elaborative encoding, whereas aLIPC was robustly active only during elaborative rehearsal.

To more directly test whether phonological rehearsal contributes to the creation of episodic memories, Davachi, Maril, and Wagner (2001) further examined the divergent roles of pLIPC and aLIPC in memory encoding. Results revealed that pLIPC activity during rote rehearsal predicted how well individual items were subsequently remembered, but pLIPC activity during elaborative rehearsal did not. The fact that pLIPC activity was modulated by rote rehearsal (Wagner, Maril, Bjork, & Schacter, 2001) and has been consistently associated with phonological processing supports the reverse inference that the observed correlation between pLIPC activation during rote rehearsal and subsequent episodic memory demonstrates that phonological processes contribute to the creation of new memories. In this manner, a localized pattern of neural activation, in combination with the SPH, provides important new evidence regarding a fundamental cognitive debate. Similar application of reverse inference based on the SPH has provided a framework through which to interpret differential activity of pLIPC and aLIPC in studies of retrieval from episodic memory, during which pLIPC supports maintenance of retrieval cues in phonological working memory, whereas aLIPC subserves elaboration on the meaning of these cues so as to assist in triggering remembering (Dobbins, Foley, Schacter, & Wagner, 2002). We see this kind of cross-domain application as the most valuable contribution of the SPH and the reverse-inference approach.

CONCLUSIONS

Although there is significant evidence in favor of a segregation of phonological and semantic processing in the LIPC, a number of important questions regarding this distinction remain.

First, there is mixed evidence regarding whether aLIPC and pLIPC are necessary for semantic and phonological processing, respectively. Neuroimaging can demonstrate that brain activity is correlated with a cognitive task or process, but cannot demonstrate that the region is necessary for that task or process: This requires showing that disruption of the region results in impairment of the function. Lesion studies have provided mixed evidence for the necessity of aLIPC for semantic processing; although most patients with aLIPC lesions can make accurate semantic judgments, their performance is significantly slowed (Swick & Knight, 1996). In addition, Devlin et al. (2003) disrupted LIPC function using transcranial magnetic stimulation, a method that causes a temporary “virtual lesion” by inducing electrical activity in the brain using magnetic fields. They observed that disruption of LIPC did not affect accuracy of semantic judgments but did slow them, whereas the same stimulation did not disrupt nonsemantic processing. Thus, the data currently available suggest that aLIPC may not be absolutely necessary for semantic analysis of stimuli, but is necessary for normal access to semantic knowledge. Regarding phonology, the evidence is less substantial but does suggest that lesions to pLIPC result in impaired phonological processing.

Second, there are now several studies showing that aLIPC is sometimes engaged during putatively phonological tasks (cf. Gold & Buckner, 2002), suggesting that the semantic-phonological dimension may not be the proper way to distinguish aLIPC and pLIPC functions. These findings highlight the difficulty of equating tasks with cognitive processes: Without convergent results from behavioral studies, there is no way to confirm that a “phonological” task does not also recruit semantic processes, and vice versa. Future work should examine which aspects of phonological processing may modulate the engagement of aLIPC. Studies that employ multiple manipulations of semantic processing and multiple manipulations of phonological processing will be most useful in answering this question.

Finally, it is important to note that the reverse-inference approach requires a strong caveat, because it is not a logically valid form of deductive reasoning. For example, in the present case, reverse inference would hold true logically only if activity in aLIPC or pLIPC occurred only because of semantic or phonological processing, respectively (i.e., it requires an “if and only if” statement to be logically true), and few researchers would support such a claim. Accordingly, the reverse-inference approach is strongest when it is used not as an ad hoc means to explain the occurrence of particular activations in a single study, but rather as a tool to drive hypotheses that are then tested in subsequent experiments. Indeed, well-designed neuroimaging studies intended to adjudicate between competing psychological hypotheses that, themselves, have been formally described are precisely the kind of studies in which the reverse-inference approach may be justified. Through such an approach, neural markers of cognition hold promise for advancing understanding of the mechanisms of mind.

Recommended Reading

Badre, D., & Wagner, A.D. (2002). Semantic retrieval, mnemonic control, and the prefrontal cortex. *Behavioral and Cognitive Neuroscience Reviews*, *1*, 206–218.

Bookheimer, S. (2002). Functional MRI of language. *Annual Review of Neuroscience*, *25*, 151–188.

Fiez, J., & Petersen, S.E. (1998). Neuroimaging studies of word reading. *Proceedings of the National Academy of Sciences, USA*, *95*, 914–921.

REFERENCES

Bokde, A.L., Tagamets, M., Friedman, R.B., & Horwitz, B. (2001). Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. *Neuron*, *30*, 609–617.

Damasio, H.C. (1991). Neuroanatomy of frontal lobe in vivo: A comment on methodology. In H.S. Levin, H.M. Eisenberg, & A.L. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 92–129). New York: Oxford University Press.

Davachi, L., Maril, A., & Wagner, A.D. (2001). When keeping in mind supports later bringing to mind: Neural markers of phonological rehearsal predict subsequent remembering. *Journal of Cognitive Neuroscience*, *13*, 1059–1070.

Devlin, J.T., Matthews, P.M., & Rushworth, M.F. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience*, *15*, 71–84.

Dobbins, I.G., Foley, H., Schacter, D.L., & Wagner, A.D. (2002). Executive control during episodic retrieval: Multiple prefrontal processes subserve source memory. *Neuron*, *35*, 989–996.

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

Fiez, J.A., Balota, D.A., Raichle, M.E., & Petersen, S.E. (1999). Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron*, *24*, 205–218.

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.

Otten, L.J., & Rugg, M.D. (2001). Task-dependency of the neural correlates of episodic encoding as measured by fMRI. *Cerebral Cortex*, *11*, 1150–1160.

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

Smith, E.E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science*, *283*, 1657–1661.

Swick, D., & Knight, R.T. (1996). Is prefrontal cortex involved in cued recall? A neuropsychological test of PET findings. *Neuropsychologia*, *34*, 1019–1028.

Wagner, A.D., Koutstaal, W., Maril, A., Schacter, D.L., & Buckner, R.L. (2000). Task-specific repetition priming in left inferior prefrontal cortex. *Cerebral Cortex*, *10*, 1176–1184.

Wagner, A.D., Maril, A., Bjork, R.A., & Schacter, D.L. (2001). Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *NeuroImage*, *14*, 1337–1347.

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