



A procedure for identifying regions preferentially activated by attention to semantic and phonological relations using functional magnetic resonance imaging

Kathleen B. McDermott^{a,b,*}, Steven E. Petersen^{a,b,c,d},
Jason M. Watson^a, Jeffrey G. Ojemann^{a,c,e,f}

^a Department of Psychology, Washington University, Campus Box 1125, One Brookings Drive, St. Louis, MO 63130-4899, USA

^b Department of Radiology, Washington University School of Medicine, St. Louis, MO 63130-4899, USA

^c Department of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO 63130-4899, USA

^d Department of Neurology, Washington University School of Medicine, St. Louis, MO 63130-4899, USA

^e Department of Neurological Surgery, Washington University School of Medicine, St. Louis, MO 63130-4899, USA

^f Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63130-4899, USA

Abstract

A procedure is introduced for using functional magnetic resonance imaging (fMRI) techniques to identify neural regions associated with attention to semantic and phonological aspects of written words within a single group of subjects. Short lists (16 words/list), consisting of visually-presented semantically-related words (*bed, rest*) or rhyming words (*weep, beep*) were presented rapidly to subjects, who were asked to attend to the relations among the words. Regions preferentially involved in attention to semantic relations appeared within left anterior/ventral inferior frontal gyrus (IFG, approximate Brodmann Area, BA47), left posterior/dorsal IFG (BA44/45), left superior/middle temporal cortex (BA22/21), left fusiform gyrus (BA37), and right cerebellum. Regions preferentially involved in attention to phonological relations appeared within left inferior frontal cortex (near BA6/44, posterior to the semantic regions within IFG described above) and within bilateral inferior parietal cortex (BA40) and precuneus (BA7). This method is notable in that a comparison of the two tasks within some of the individual subjects revealed activation patterns similar to the group average, especially within left inferior frontal and left superior/middle parietal cortices. This fact combined with the efficiency with which the data can be obtained (here, in about an hour of functional scanning) and the adaptability of the task for many different subject populations suggests a wide range of possibilities for this technique: it could be used to track language development (e.g. in children), compare language organization across subject populations (e.g. for dyslexic or blind subjects), and identify language regions within individuals (e.g. potentially to aid in surgical planning).

© 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Neuroimaging; Reading; Encoding; Meaning; Rhyme; Phonetics; fMRI; Language

1. Introduction

Language is one of the primary abilities that distinguishes humans from other species. When the opportunity arose to complement lesion-deficit studies of human cognition with functional neuroimaging methods, one of the first such studies investigated language [28]. Since this initial report, there have been numerous attempts to identify language-related brain regions and to further characterize them as exhibiting preferential activity for various subcomponents of language processing (for reviews see [12,29,30]). Due to the complexity of linguistic processing, research has focused on the

reading of single words as a starting point for understanding the neural bases of language.

Two broad classes of processes in single word reading are semantic (or meaning-based) and phonological (or sound-based) processing. Regions active during semantic processing have been found consistently within left inferior frontal cortex [3,8,9,15,16,18,26,29,35]. Specifically, a region in the anterior and ventral aspect of the inferior frontal gyrus (IFG, approximate BA47/10) has been repeatedly identified as contributing to semantic processing. Other such regions have been identified in right cerebellum [10,33] and left middle temporal cortex [33,43].

Phonologically-related regions have been reported within left inferior parietal cortex (BA40) in or around the supra-marginal gyrus [17]. Other studies have focused on a region within the posterior aspect of the inferior frontal gyrus

* Corresponding author. Tel.: +1-314-935-8743; fax: +1-314-935-7588.
E-mail address: kmcd@npg.wustl.edu (K.B. McDermott).

corresponding roughly to Broca's area, [9,45]. Poldrack et al. [29] failed to find any frontal regions preferentially active for phonological processing and suggested that the reason may be that whenever semantic processing is performed on a word, phonological processing accompanies automatically, cf. [6]. Indeed, several other studies directly contrasting semantic and phonological processing have failed to find differences within IFG [19,31,32]. We attempted in the present report to diminish the tendency for recruitment of both semantic and phonological process during single word reading in order to more cleanly dissociate the two processes.

In an ostensibly unrelated literature, recent studies have demonstrated that false memories can be created by challenging semantic and phonological systems. When presented with many (e.g. 15) semantic associates, people often later recall and recognize having heard a word related to the presented associates but not itself presented. For example, after encountering *bed, rest, awake, tired* ... people recall and recognize having studied *sleep* [7,34]. Similarly, phonologically-related words can lead to false memories; after studying *sweep, steep, sleet, slop* people mistakenly recall and recognize *sleep* [23,38,46].

The goal in the present report was to apply the logic used in creating these false memory paradigms to study language; that is, we sought to use the lists of associated words to separately challenge the semantic and phonological systems in order to pull apart regions preferentially activated for semantic and phonological processing. The primary goal was to develop a tool with which to identify regions differentially activated by attention to semantics and to phonology.

2. Method

2.1. Subjects

Subjects ($N = 20$, 18 females, mean age 22.1, range 18–32 years) were recruited from the Washington University community in return for payment. All reported being right-handed native speakers of English with normal or corrected-to-normal vision and no history of significant neurological problems. Subjects provided informed consent in accordance with the guidelines set by the Washington University Human Studies Committee.

2.2. Materials

Seventy-two word lists served as stimuli. Lists consisted of 16 words related to one another semantically (e.g. *bed, rest, awake*) or phonologically (e.g. *weep, beep, heap*). The phonologically-related words all rhymed. Materials are available from the authors.

The median word length was 5 for both the semantic and phonological lists, and the median word frequency was 23 per million for the semantic lists and 13.5 per million for the phonological lists [20].

In six encoding runs, subjects studied 72 16-word lists (12 lists/run). A blocked design was used, such that each subject studied semantic and phonological lists (randomly-ordered) within each run. At the beginning of each block (i.e. list), a cue was displayed (“meaning” or “rhyme”) to inform subjects of the type of list they were about to see, and they were instructed to use the cue to help them focus on the relations among the upcoming words. Words were displayed quickly, such that each 16-word list was displayed in 10 s. Words were displayed one at a time for approximately 560 ms apiece with a 50 ms interstimulus interval. Following each block of words was a brief period (12.5 s), in which subjects were shown a crosshair and asked to fixate on it and await the next list.

Subjects were instructed to attend closely to the relations among words within each list. In the semantic condition, they were told to think about how the words could be meaningfully connected (e.g. *tiger, circus, jungle*), and in the rhyme condition they were told to think about how the words sounded alike (e.g. *skill, fill, hill*) and to say the words silently to themselves while thinking about the similarity in the sounds. Subjects were informed that memory tests would occur after some runs but that they should simply focus on the task at hand while viewing the lists. The full set of instructions is available from the authors.

2.3. Scanning procedures

Scans were obtained on a 1.5 Tesla Siemens Vision System (Erlangen, Germany) with a standard circularly-polarized head coil. A Power Macintosh computer (Apple, Cupertino, CA) and Psyscope software [4] displayed the visual stimuli. An LCD projector shielded with copper wire displayed stimuli on a screen placed at the head of the bore. Subjects viewed the screen via a mirror fastened to the head coil. A pillow and surgical tape minimized head movement. Headphones dampened scanner noise and enabled communication with subjects.

Structural images were acquired using a high-resolution sagittal MPRAGE sequence (1.25 mm \times 1 mm \times 1 mm voxels). Functional images were collected with an asymmetric spin-echo-planar sequence sensitive to blood-oxygenation-level-dependent (BOLD) contrast [21,24]. In each functional run, 128 sets of 16 contiguous, 8 mm-thick axial images (TR = 2500 ms, 3.75 mm \times 3.75 mm in-plane resolution) were acquired parallel to the anterior–posterior commissure plane; this procedure offered whole-brain coverage at a high signal-to-noise ratio [5]. Approximately 3 min elapsed between runs, during which time instructions were given to subjects over their headphones. The first four images of each run were not included in the functional analyses but were used to facilitate alignment of the functional data to the structural images.

Each subject participated in six runs; after each of the first three runs, a recognition memory test was administered; the test data will be reported elsewhere.

A blocked design was used. Onset of lists coincided with onset of a TR (repetition time). Each task block spanned five TRs: the orienting word appeared for 2 s, followed by the 16 words in the list. Ordering of the blocks was unpredictable from the subjects' standpoint.

2.4. fMRI data analysis

Data for each subject were corrected for intensity differences across odd- and even-numbered slices, interpolated to $3\text{ mm} \times 3\text{ mm} \times 3\text{ mm}$ voxels, aligned to correct for slice-based within-trial differences in acquisition times, movement-corrected within and across runs, and transformed into standardized atlas space [39] via a linear warp [37]. Removal of the linear slope on a voxel-by-voxel basis corrected for frequency drift [2], whole brain normalization to a common mode of 1000 facilitated comparisons across subjects, and a Gaussian smoothing filter (6 mm full-width half-maximum) accommodated variations in activation loci across subjects.

Similarities between activation during semantic and phonological lists were demonstrated qualitatively by performing separate random effects *t*-tests for each 3 mm isotropic voxel on the activation magnitudes (% signal change) for the semantic lists relative to the control period and for the phonological lists relative to the control period. That is, we obtained activation magnitude estimates for each voxel for each subject for each condition (semantic list, phonological list, and control period); we then performed dependent-measures *t*-tests for each voxel for the semantic-control contrast and for the phonological-control contrast. Regions demonstrating preferential activation for one type of list over the other were of primary interest and were obtained using a similar *t*-test on the activation magnitudes for the semantic and phonological lists for each 3 mm isotropic voxel.

Previous Monte Carlo simulations on random noise patterns (using a method similar to that described in [14]) suggested that to achieve a whole-brain *P*-value of 0.05 we should accept only voxels exceeding $P < 0.0012$ that were also contiguous with at least 11 other voxels exceeding this threshold.

An automated peak-search algorithm was applied to the multiple-comparison corrected image resulting from the semantic-phonological *t*-test to identify the location (in atlas coordinates) of peak activations on the basis of level of statistical significance. Regions around the peak activations were identified interactively by choosing contiguous voxels surpassing the significance threshold.

The statistical activation maps in Talairach and Tournoux [39] atlas space were displayed using the Computerized Anatomical Reconstruction and Editing Toolkit (CARET) software [42], which is obtainable at <http://stp.wustl.edu>. This software was used to view cortical activations projected onto the surface of a high resolution structural brain image and to flatten the cortical data for display in two dimen-

sional “flatmaps” to enable views of the entire left and right hemispheres within one figure.

3. Results

3.1. Similarities between attending to semantic and phonological relations

Although the primary focus here is on the differences between two classes of verbal processing, one can see from the top two rows of Fig. 1 (left hemisphere) and Fig. 2 (right hemisphere) that relative to a low-level baseline (fixating on a crosshair) semantic and phonological lists elicited activation in many of the same regions. The similarities highlight the point that the differences we will focus on tend to represent differences in degree of activation within similar networks and not altogether different networks for semantic and phonological processing. Nonetheless, it is also evident from Figs. 1 and 2 that activation in some regions was statistically significant in one task but not the other task.

Relative to the baseline control condition, both tasks activated left inferior frontal cortex (BA45/46 and BA44/45/46 extending into premotor and motor areas), right inferior frontal cortex (BA44/45), bilateral occipital cortex (BA17/18/19), bilateral fusiform gyrus (BA37), and (not shown in the figures) medial frontal gyrus (BA6, pre-supplementary motor area, pre-SMA), bilateral precuneus (BA7), and bilateral cerebellum. Although inferior frontal activations were strongly left-lateralized ventrally they became bilateral more dorsally and extended into right middle frontal gyrus.

Some of the statistical differences highlighted in the following section can be intuited by examination of these images. To anticipate, in the top two rows of Fig. 1 it can be seen that relative to the low-level baseline condition, activation within left inferior frontal cortex was more extensive in the semantic condition than the phonological condition, especially in the anterior/ventral regions. Further, reliable left superior/middle temporal activation appears for the semantic condition but not the phonological condition.

3.2. Differences between attending to semantic and phonological relations

Differences in activity for the two list types can be seen in the bottom rows of Fig. 1 (left hemisphere) and Fig. 2 (right hemisphere) and in Tables 1 and 2. Whereas the blue activity at the top of the figures represents de-activation (of the active task state relative to the control state), it represents regions preferentially active for the phonological task (relative to the semantic task) in the bottom row, and the red–yellow represents regions preferentially active for the semantic task (relative to the phonological task). The activation magnitudes (% signal change) underlying these

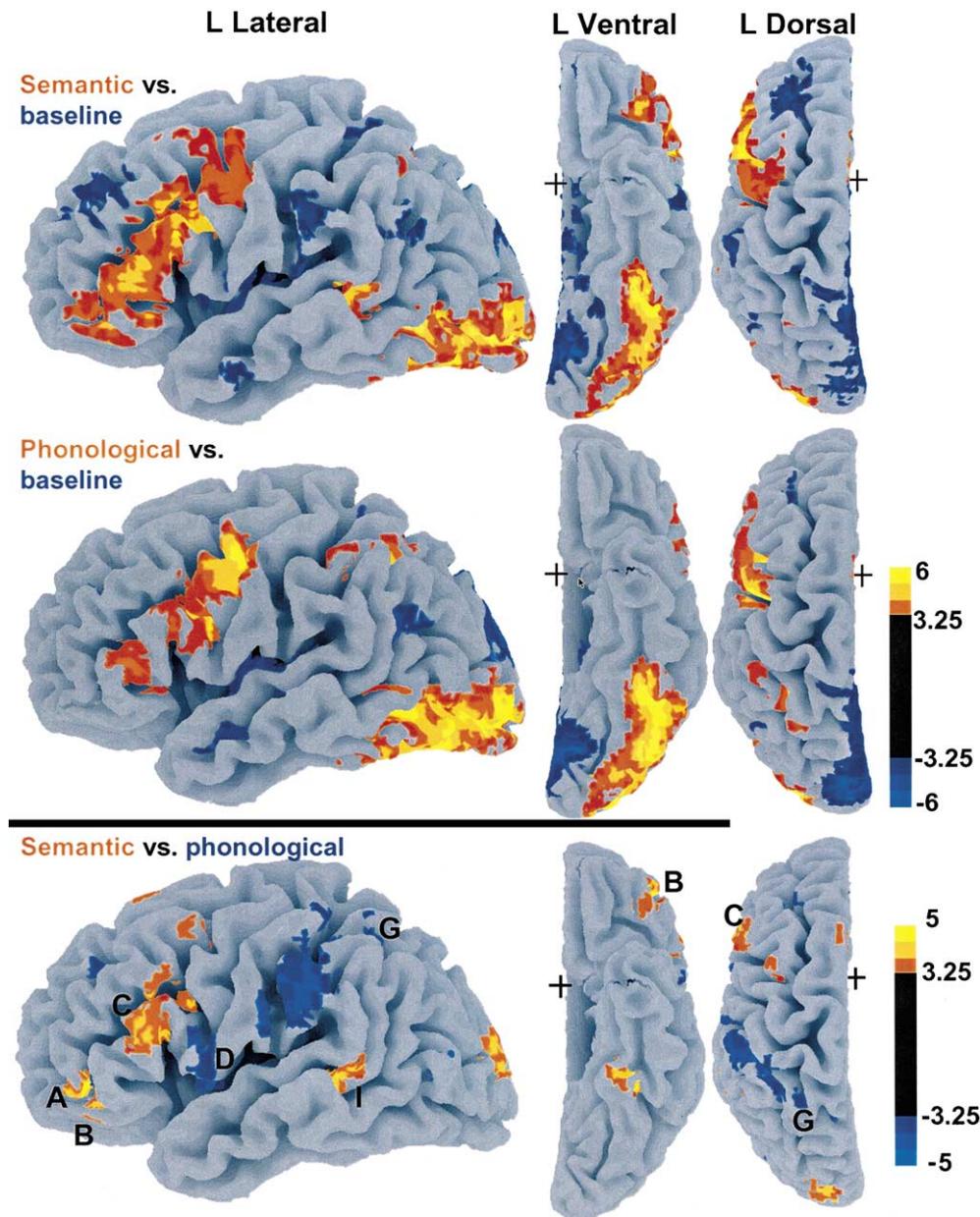


Fig. 1. Left hemisphere cortical regions more active for semantically-related lists (top row) and phonologically-related lists (middle row) relative to the baseline activation state as determined by multiple-comparison corrected random-effects *t*-tests. For the top two rows, regions shown in orange–yellow are those showing greater activation for the task state than the baseline control state; those shown in blue demonstrated greater activation during the baseline control period than during the task state. The bottom row exhibits regions more active for semantically-related lists than phonologically-related lists (shown in orange-to-yellow) and regions showing the opposite pattern (phonological > semantic, shown in blue). Regions of particular interest are labeled with letters, and the corresponding peak coordinates can be seen in the tables. Cases in which regions do not appear indicate regions occluded by more lateral cortical tissue. Labels in the color bar correspond to *z*-statistics (or level of statistical significance).

differences and the peak activation coordinates for the regions can be seen in Table 1 (semantic > phonological) and Table 2 (phonological > semantic).

As can be seen by examining the orange–yellow regions in Fig. 1, preferential activation for semantic processing was observed in the LIFG both anteriorly/ventrally (BA47) and posteriorly/dorsally (BA44/45). In addition, regions within left superior/middle temporal gyrus (BA22/21), left occipital cortex (BA18/17), left fusiform gyrus (BA37), and right

frontal cortex (BA9/46, shown in Fig. 2) showed this pattern of greater activation for semantic than phonological processing.

Preferential activation for phonological processing (shown in blue) occurred in left premotor cortex along the posterior border of the inferior frontal gyrus (BA6/44). In addition, regions within bilateral inferior parietal cortex (BA40) and precuneus (BA7) showed similar patterns. Below we consider in more detail the patterns shown in

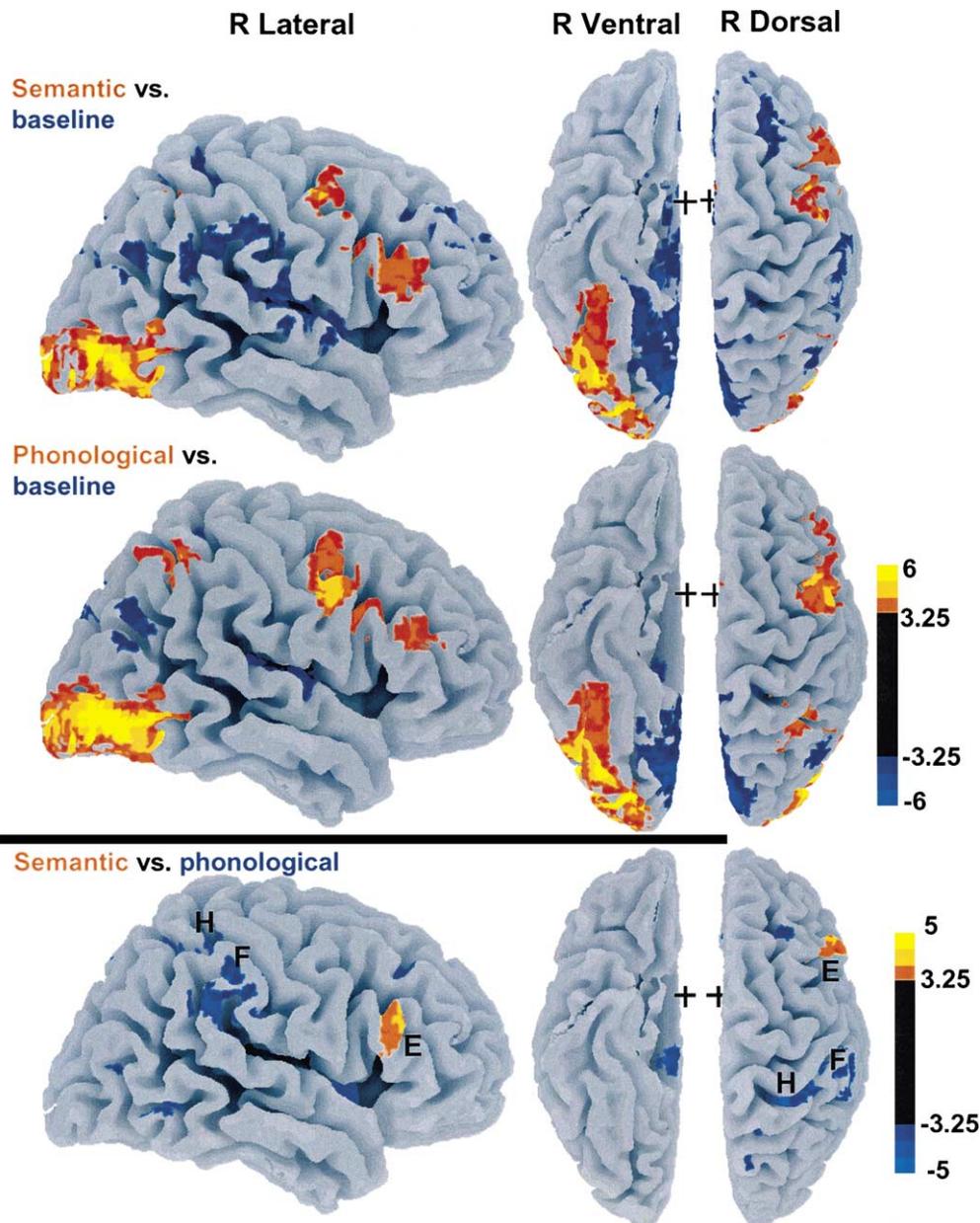


Fig. 2. Right hemisphere cortical regions more active for semantically-related lists (top row) and phonologically-related lists (middle row) relative to the baseline activation state as determined by multiple-comparison corrected random-effects *t*-tests. For the top two rows, regions shown in orange–yellow are those showing greater activation for the task state than the baseline control state; those shown in blue demonstrated greater activation during the baseline control period than during the task state. The bottom row exhibits regions more active for semantically-related lists than phonologically-related lists (shown in orange-to-yellow) and regions showing the opposite pattern (phonological > semantic, in blue). Regions of particular interest are labeled with letters, and the corresponding peak coordinates can be seen in the tables. Cases in which regions do not appear indicate regions occluded by more lateral cortical tissue. Labels in the color bar correspond to *z*-statistics (or level of statistical significance).

selected regions emerging in frontal, parietal, temporal, and occipital cortices.

3.3. Frontal cortex

Within frontal cortex, greater activation for semantic than phonological lists was observed within left anterior/ventral inferior frontal cortex (BA47; peak $-43, 39, 0$, labeled A

in Fig. 1). A similarly left-lateralized activation pattern was seen in a region even further ventral (BA47/11; peak $-37, 36, -12$, labeled B in Fig. 1, best seen in the ventral view). In both cases there was reliable activation (relative to baseline) for the semantic lists but little (BA47) or not significant (BA47/11) activation for the phonological lists.

As can be seen in the region labeled C in Fig. 1, a separate region within left inferior frontal cortex, which

Table 1

Regions demonstrating greater activation for lists of semantically-related words than lists of phonologically-related words

	Coordinates (x, y, z)	% Change		Approximate location	Label in Figs. 1 and 2
		Semantic	Phonological		
Frontal	-43, 39, 0	0.32*	0.08*	Left inferior/middle frontal gyri (BA47)	A
	-37, 36, -12	0.32*	0.07	Left middle/inferior frontal gyrus (BA47/11)	B
	-37, 18, 18	0.52*	0.24*	Left inferior frontal gyrus (BA44/45)	C
	-31, 3, 27	0.58*	0.29*	Left inferior frontal gyrus (BA44)	C
	-34, 3, 51	0.28*	0.06	Left middle frontal gyrus (BA6)	
	52, 27, 24	0.60*	0.34*	Right middle/inferior frontal gyri (BA46/44/9)	E
	-7, 9, 54	0.30*	0.08	Medial frontal gyrus (pre-SMA, BA6)	
Temporal	-58, -45, 0	0.28*	0.08	Left middle/superior temporal gyrus (BA22/21)	I
Occipital	-16, -96, -3	0.30*	0.19*	Left cuneus (BA17)	
	-19, -99, 12	-0.11	-0.36*	Left cuneus (BA18)	
Cerebellum	19, -81, -33	0.15*	-0.02	Right cerebellum	
	31, -75, -36	0.06	-0.09*	Right cerebellum	
	-10, -78, -33	0.16*	0.04	Left cerebellum	
Fusiform	-34, -45, -18	0.33*	0.19*	Left fusiform gyrus (BA37)	

Coordinates correspond to peak activations, magnitudes correspond to percent signal change relative to baseline, and asterisks (*) indicate activation magnitudes greater than baseline (fixation) levels ($P < 0.05$). Regions shown in bold font are those demonstrating activation in the positive direction for the semantic condition relative to baseline.

is found dorsal and posterior to those just described, also showed preferential activation for semantic lists. For region definition we separated this activation into separate components (around the two peaks found by the search algorithm, -37, 18, 18; -31, 3, 27), although this was a large area of activation and may represent one large func-

tional area. The activation spread along the IFG (BA44, along the border with BA45) and into middle frontal gyrus. Although greater activation was found for semantic lists, these regions showed robust activation for both semantic and phonological lists (all magnitudes reliably exceeded baseline magnitudes).

Table 2

Regions demonstrating greater activation for lists of phonologically-related words than lists of semantically-related words

	Coordinates (x, y, z)	% Change		Approximate location	Label in Figs. 1 and 2
		Semantic	Phonological		
Frontal	-55, 3, 15	-0.06	0.14*	Left inferior frontal/precentral gyri (BA6/44)	D
	40, 3, 0	-0.15*	-0.04	Right insula	
	31, 24, 45	-0.22*	-0.10*	Right middle frontal gyrus (BA8)	
Parietal	-43, -39, 36	-0.21*	0.07	Left inferior parietal gyrus (BA40)	
	-55, -36, 30	-0.10*	0.04	Left inferior parietal/supramarginal gyrus(BA40)	
	-58, -33, 39	-0.16*	0.07	Left inferior parietal lobule (BA40)	
	-40, -42, 57	-0.21*	0.09	Left inferior parietal lobule (BA40)	
	43, -39, 45	-0.05	0.10*	Right inferior parietal lobule (BA40)	F
	52, -30, 27	-0.19*	-0.10*	Right inferior parietal lobule (BA40)	
	55, -33, 36	-0.28*	-0.13*	Right inferior parietal lobule (BA40)	
	52, -45, 30	-0.20*	-0.06	Right supramarginal gyrus (BA40)	
	-13, -69, 39	-0.28*	-0.13*	Left precuneus (BA7)	
	13, -60, 48	-0.14*	0.03	Right precuneus (BA7)	
	19, -69, 33	-0.23*	-0.07	Right precuneus (BA7)	
	-31, -57, 48	0.06	0.26*	Left superior/inferior parietal lobule (BA7/40)	G
	31, -48, 51	0.03	0.21*	Right superior/inferior parietal lobule (BA7/40)	H
Occipital/temporal	-40, -81, 6	0.00	0.10	Left middle occipital gyrus (BA19)	
	43, -60, -6	0.35*	0.49*	Right middle occipital gyrus (BA19)	
	10, -69, 30	-0.76*	-0.58*	Right cuneus/precuneus	
Cingulate	4, -30, 39	-0.28*	-0.12*	Right posterior cingulate (BA31)	

Coordinates correspond to peak activations, magnitudes correspond to percent signal change relative to baseline, and asterisks (*) indicate activation magnitudes greater than baseline (fixation) levels ($P < 0.05$). Regions shown in bold font are those demonstrating activation in the positive direction for the phonological condition relative to baseline.

Posterior to this region within posterior/dorsal IFG was a functionally distinct region (labeled D), which demonstrated the opposite pattern: greater activation for the phonologically-related lists. This pattern was found along the border of the left precentral and inferior frontal gyri (peak $-55, 3, 15$, BA6/44) and extended ventrally into left insular cortex. This region demonstrated reliable activation (relative to baseline) for the phonological lists but not the semantic lists (see Table 2).

A single region in right frontal cortex showed greater activation for semantic than phonological processing (peak $52, 27, 24$, labeled E in Fig. 2). Two right frontal regions demonstrated the opposite pattern (i.e. phonological > semantic); however, they demonstrated decreases in activity relative to baseline in the semantic condition but less negative activations (or nonsignificant activity) in the phonological conditions. It is unclear how to interpret regions that show decreases in activation during an active task (e.g. is a region that shows more pronounced de-activation for semantic than phonological attention a semantic region or a phonological region?) Therefore, no strong conclusions will be drawn for these regions (or any regions showing similar patterns). The details of these activations can be gleaned from the tables.

3.4. Parietal cortex

Whereas most of the left IFG differences involved a semantic preference, multiple regions in parietal cortex demonstrated a phonological preference. These included regions within bilateral inferior (BA40) parietal cortex in the vicinity of the supramarginal gyrus and bilateral precuneus (BA7).

Unlike the patterns seen throughout most of frontal cortex but similar to those frontal regions most recently discussed, many of the parietal regions demonstrated decreases in activity relative to baseline in the semantic condition but non-

significant activations (or less negative activations) in the phonological conditions. As argued above, it is ambiguous how regions showing such patterns should be interpreted. Further complicating the issue is that some of these parietal regions demonstrating decreases relative to the control state appear similar to those that tend to de-activate across a wide variety of tasks [36]. Multiple regions within left inferior parietal cortex (BA40) demonstrated the same pattern: robust deactivation (relative to the baseline measure) in the semantic condition and no reliable activation (albeit consistently in the positive direction) in the phonological condition.

There were three parietal regions in Table 2, though, that demonstrated strong positive activation for the phonological task (peaks $43, -39, 45; -31, -57, 48; 31, -48, 51$ for regions labeled F, G, and H, respectively). Note that these regions (like those in precuneus) are fairly medial and therefore are not well-viewed with the lateral surfaces shown in Figs. 1 and 2.

3.5. Temporal cortex

A single peak within temporal cortex was obtained in the semantic-phonological *t*-test; specifically, a region in or near the superior temporal sulcus (BA22/21; I in Fig. 1) demonstrated preferential activation for the semantic lists (peak $-58, -45, 0$). Relative to baseline, this region exhibited reliable activation for the semantic lists but not the phonological lists.

3.6. Occipital cortex

Two regions in early visual areas demonstrated greater activation for semantically-related than phonologically-related lists (see Table 1). This was unexpected and might represent a manifestation of perceptual priming in unusually early visual regions. That is, the phonologically-related lists

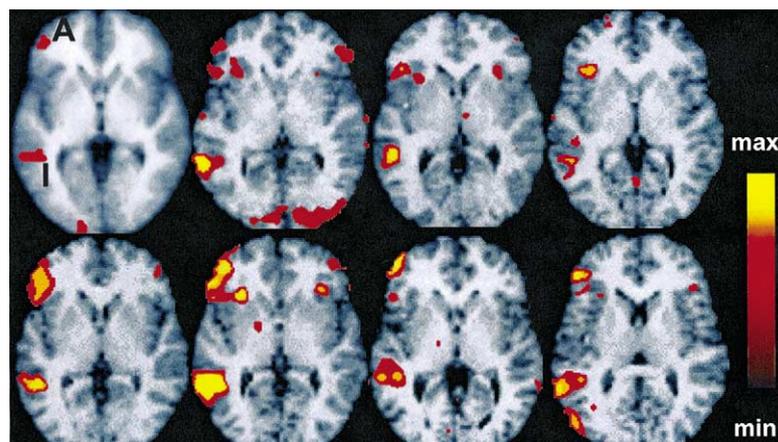


Fig. 3. Contrasts between attention to semantics and to phonology at the individual subject level often revealed a similar region in left superior/middle temporal gyrus (BA22/21) as being more active for semantically-related lists than phonologically-related lists. In addition, a region in left inferior/middle frontal gyrus (BA47) can be seen. The upper left image shows the region revealed by the multiple-comparison-corrected whole-brain random effects analysis (*t*-test) across all 20 subjects; A and I refer to region labels given in Fig. 1. For the seven individual subject images, increasing color intensity reflects increasing level of statistical significance.

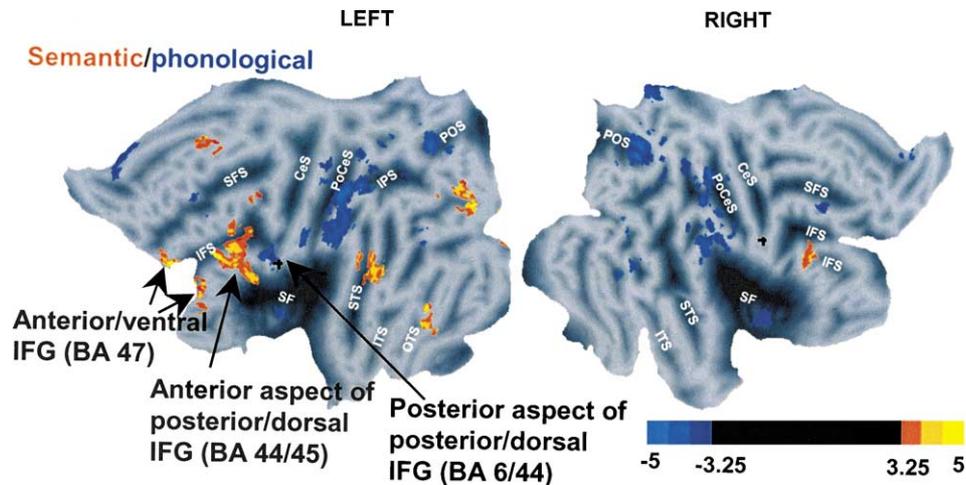


Fig. 4. Two-dimensional, flattened representations of the cortical regions emerging from the semantic/phonological contrasts. This method of display highlights the need for distinguishing multiple regions within inferior frontal cortex as contributing differentially to verbal processing. An anterior/ventral region (BA47; labeled **A** in Fig. 1) showed preferential activation for semantic lists. Within more posterior frontal regions, there were further functional distinctions. A region in the more anterior aspect of posterior LIFG (BA44/45) showed preferential activation for semantic processing, whereas a more posterior region (BA6/44) demonstrated the opposite pattern. Major sulcal landmarks are labeled; abbreviations are superior frontal sulcus (SFS), inferior frontal sulcus (IFS), Sylvian Fissure (SF), central sulcus (CeS), postcentral sulcus (PoCeS), intraparietal sulcus (IPS), parieto-occipital sulcus (POS), superior temporal sulcus (STS), inferior temporal sulcus (ITS), and occipital-temporal sulcus (TOS).

contained words that were orthographically similar (in addition to being phonologically similar). It may have been that reading words such as *weep*, *beep*, *heap* led to low-level priming of the visual system (relative to reading semantically-related words, which would be expected to show semantic priming but little or no low-level visual priming).

3.7. Individual subject data

The strength of the manipulation performed in this experiment can be seen by examining the data of individual subjects. For many (but not all) of our subjects, a simple contrast between activation levels for semantic and phonological lists revealed differences qualitatively similar to those seen at the group level. Most robust among these differences were the regions near the superior temporal sulcus (BA22/21) and left anterior/ventral IFG (BA47), which are highlighted with seven subjects' data in Fig. 3.

Phonological superiority within regions in inferior and superior parietal cortices was sometimes observed at the level of individual subjects, as well, although the regions were not as cleanly obtained as those mentioned above and were seen less consistently.

3.8. Flatmaps

Fig. 4 displays the semantic-phonological *t*-test data (displayed at the bottom of Figs. 1 and 2) in flattened space [41,42]. One of the benefits of such a display is that the entire left and right hemisphere cortical activations can be viewed in a single glance. For current purposes, these projections are used primarily to highlight the distinctions being made among frontal regions. Fig. 4 strengthens the conclusions

made previously: attention to semantics and to phonology activate functionally separable regions within inferior frontal cortex. Regions within ventral/anterior IFG show greater activation to semantic than phonological lists. In addition, there are functionally distinct regions within posterior/dorsal IFG; the anterior aspect (BA44/45) shows preferential activation for semantic processing, whereas a more posterior region close (but not contiguous) to this region shows the opposite pattern: preferential activation to phonology (BA6/44).

In addition, the preferential activation in left superior/middle temporal cortex can be seen in this view as can the single right hemisphere region showing preferential activation for attention to semantics (relative to phonology).

4. Discussion

The results obtained here are consistent with a large body of neuroimaging of reading/language studies that demonstrate differential activation patterns for semantic and phonological processing within left inferior frontal cortex, left superior/middle temporal cortex, bilateral inferior parietal cortex, precuneus, left fusiform gyrus, and right cerebellum. We view the current dataset as making two primary contributions.

4.1. Primary contributions

4.1.1. Further specification of the functional distinction between anterior/ventral and posterior/dorsal regions within IFG

There has been considerable recent interest in elucidating the potentially different contributions made by anterior/

ventral and posterior/dorsal IFG in language processing [11,16,22,27,44,45]. For example, Fiez [11] noted that “activations attributed to semantic processing have been most often located anteriorly within the ventral inferior prefrontal cortex (BA47/10), whereas activations attributed to phonological processing have been more frequently located posteriorly within the triangular and opercular portions of the inferior frontal gyrus (BAs 44 and 45)” (pp. 81–82).

The present study contributes to this understanding. Although both attention to semantic and to phonological processing activate a large swath of cortex along the IFG that (relative to a low-level baseline measure) appears somewhat similar, contrasts between the tasks reveal the importance of the emerging distinction between anterior/ventral (BA47) and posterior/dorsal (BA44/45) IFG. However, this dataset goes beyond that distinction in that it demonstrates that although there indeed appears to be an alignment of the anterior/ventral portion of IFG with semantic processing, there is an important subdivision to be made within the posterior/dorsal portion of IFG. That is, *within* dorsal/posterior IFG there appears to be an anterior/posterior distinction such that the anterior component (BA44/45) aligns with semantic processing and the posterior portion (BA6/44) aligns with phonological processing.

On a more speculative note, an examination of Fig. 1 suggests there may be yet another functional region within left IFG, which is active equivalently for attention to semantics and phonology; this region (peak $-50, 30, 8$; in or near BA45) can be seen as the most anterior region active in the phonological versus baseline comparison and is also revealed in the semantic versus baseline comparison. However, it did not emerge from the contrast between the two lists types (but would lie between regions A and C in Fig. 1). This null effect is suggestive of a region that could be active for verbal tasks in general but not showing preferential activation for attention to semantic or phonological relations among words; such a region might play a role in more general lexical processing.

4.1.2. An efficient method for identification of cortical language sites

The second (and perhaps primary) contribution of this study is that it demonstrates a method for efficiently and cleanly identifying language regions within a single group of subjects and within a subset of individual subjects. Attending to relations among associated words is a fairly natural task, one which can be performed by a wide variety of subject populations (including people with incompletely-developed language, e.g. children). Hence, this task could be readily adapted for the study of cross-population differences in reading (e.g. tracking the development of language in children, examining differences between dyslexic and normal readers). It also appears to be a viable option for subject groups who cannot tolerate long scanning sessions.

The potential to obtain interpretable data within individual people in about an hour of functional scanning sug-

gests that this may be a useful task to explore with respect to pre-operative scanning. Neurosurgical procedures for patients (e.g. with intractable seizures or brain tumors) in left frontal and temporal cortices often require localization of language function [25]. Intraoperative cortical stimulation mapping identifies regions responsible for language function, but such procedures require substantial effort on the part of patients, require patients to be awake for a portion of the procedure, are time consuming, and (most critically) cannot divulge before surgery whether a region is inoperable due to its recruitment in language function [40]. However, correlating fMRI activation with cortical stimulation and with surgical outcome has thus far been difficult [13,47], at least in part because gaining interpretable data within subjects is challenging. We are currently exploring the extent to which the contrasts available from this procedure might identify language regions similar to those pinpointed by intraoperative cortical mapping. That is, we are examining the semantic-phonological comparison and the semantic and phonological lists together relative to baseline to see which contrasts (if any) predict localization of function within the operating room.

We consider here features of this method that may contribute to its power in detecting language differences. First, the lists themselves were designed to selectively (although admittedly not exclusively) challenge semantic and phonological systems, and this feature of the lists is one that is thought to give rise to false recall [23]. Second, we enhanced this naturally-occurring selective activation by instructing people to attend to the relations among words within lists. Further, we presented subjects with a cue (“meaning” or “rhyme”) so that they would not need to figure out which dimension to attend to during presentation of the first several words. In addition, we presented the words rapidly in an attempt to challenge the systems of interest and to leave few cognitive resources for processing alternate dimensions of the words. That is, when presented with *bed, rest, awake*, etc. rapidly and told to attend to the semantic relations among the words people cannot readily ponder the phonological characteristics of the words; likewise, when presented with *beep, weep, peep*, etc. and asked to attend to the rhyming aspects of the words, people have little time to attend to the words’ meanings. This feature is in contrast to tasks such as semantic generation and semantic decisions, which have led to substantial understanding of the neural bases of language but also are likely less process pure in that their slow nature leaves time and resources for multiple confounding processes to intrude; in addition, these methods make metalinguistic response demands that are not present in the current procedure, in which no overt responding is required. Finally, we employed a rapidly-alternating blocked design sequence, which has been shown to be one of the most efficient, robust means of acquiring fMRI data [1]. It is worth noting that future studies that wish to capitalize upon the possibility of obtaining interpretable data within a subset of individual subjects may benefit from an expansion of

materials and the number of functional runs (perhaps doubling both).

We believe that a critical component of the task is that it is challenging. Hence, although it may be important to increase the presentation duration (or simplify the words) for use by some subject groups, we feel that it is optimal to have the presentation rate be challenging to the subject; further, although there is nothing critically important about having exactly 16 words, we propose that it is also desirable that people be presented with many related words (and be asked to attend to the relations among them). It may also be that associates that converge in multiple directions upon a critical “missing” word (such as those used here) present an additional challenge to the subject who is trying to integrate the words in a way that (say) lists of categorical words might not.

4.2. Additional considerations

Throughout the paper, we have referred to the processes under investigation as being phonological or semantic in nature. There are several caveats that should be applied here. First, we have examined controlled attention to semantic relations or phonological relations among words. We do not yet know the extent to which these differential neural responses reflect that attention or whether they would emerge from more automatic processing, too. It is also not known whether these differences are modality-specific or whether they will generalize to the auditory domain. Further, there are multiple types of semantic and phonological processing, and we are unable to map specific subprocesses onto neural regions with this dataset.

In addition, the phonologically-related lists have significant orthographic overlap. Although we cannot rule out some influence of orthographic overlap, we believe that the semantic-phonological terminology provides a reasonable description of the contrast in this experiment. First, the words within phonological lists all rhymed, and subjects were specifically asked to attend to that feature. They were told to say the words in their heads and to think about how each word sounded like the other words within the list. Second, the activation patterns achieved are similar to those seen in other studies of phonological processing. Thus, we believe that the semantic-phonological description provides a reasonable heuristic (albeit at a somewhat general level) for the processes contrasted here.

5. Conclusion

In conclusion, we have described a method for cleanly identifying neural substrates of processes underlying attention to semantic and phonological relations among written words. We have demonstrated that the distinction between anterior/ventral IFG and posterior/dorsal IFG as being involved in semantic and phonological processing (respectively) may benefit from further precision. That is, *within poste-*

rior/dorsal IFG, there appears to be an anterior-semantic component (BA44/45) and a posterior-phonological component (BA6/44). More generally, we believe we have identified a tool with potentially wide-ranging utility in the study of the neural bases of language.

Acknowledgements

This work was supported by grants from the McDonnell-Pew Program in Cognitive Neuroscience (99-29 CN-QUA.05), the National Science Foundation (SES-0074848), and the National Institutes of Health (MH62514) to KM. JW is supported by a postdoctoral fellowship from the McDonnell Center for Higher Brain Function. We thank Laura Lodewyck and Eileen McAllister for help with programming and data collection, Jeff Bloch and April Clift for assistance in data analysis, and Donna Hanlon, John Harwell, and David van Essen for assistance with CARET.

References

- [1] Aguirre GK, D'Esposito M, Experimental design for brain fMRI. In: Moonen CTW, Bandettini PA, editors. *Functional MRI*. Berlin: Springer; 2000. p. 369–80.
- [2] Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. *Magnetic Resonance in Medicine* 1993;30:161–73.
- [3] Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. *Journal of Neuroscience* 1997;17:353–62.
- [4] Cohen JD, MacWhinney B, Flatt M, Provost J. PsyScope: a new graphic interactive environment for designing psychology experiments. *Behavior Research Methods, Instruments, & Computers* 1993;25:257–71.
- [5] Conturo TE, McKinsty RC, Akbudak E, Snyder AZ, Yang TZ, Raichle ME. Sensitivity optimization and experimental design in functional magnetic resonance imaging. *Society for Neuroscience Abstracts* 1996;22:7.
- [6] Craik FIM, Lockhart RS. Levels of processing: a framework for memory research. *Journal of Verbal Learning & Verbal Behavior* 1972;11:671–84.
- [7] Deese J. On the prediction of occurrence of particular verbal intrusions in the immediate recall. *Journal of Experimental Psychology* 1959;58:17–22.
- [8] Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *Journal of Neuroscience* 1995;15:5870–8.
- [9] Demonet JF, Chollet F, Ramsay S, Cardebat D, Nespoulous JL, Wise R, et al. The anatomy of phonological and semantic processing in normal subjects. *Brain* 1992;115:1753–68.
- [10] Fiez JA. Cerebellar contributions to cognition. *Neuron* 1996;16:13–5.
- [11] Fiez JA. Phonology, semantics, and the role of the left inferior prefrontal cortex. *Human Brain Mapping* 1997;5:79–83.
- [12] Fiez JA, Petersen SE. Neuroimaging studies of word reading. *Proceedings of the National Academy of Sciences USA* 1998;95:914–21.
- [13] FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, et al. Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *American Journal of Neuroradiology* 1997;18:1529–39.

- [14] Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine* 1995;33:636–47.
- [15] Gabrieli JD, Desmond JE, Demb JB, Wagner AD, Stone MV, Vaidya CJ, et al. Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. *Psychological Science* 1996;7:278–83.
- [16] Gold BT, Buckner RL. Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron* 2002;35:803–12.
- [17] Jonides J, Schumacher EH, Smith EE, Koeppel RA, Awh E, Reuter-Lorenz PA, et al. The role of parietal cortex in verbal working memory. *Journal of Neuroscience* 1998;18:5026–34.
- [18] Kapur S, Rose R, Liddle PF, Zipursky RB, Brown GM, Stuss D, et al. The role of the left prefrontal cortex in verbal processing: semantic processing or willed action? *NeuroReport* 1994;5:2193–6.
- [19] Klein D, Milner B, Zatorre RJ, Meyer E, Evans AC. The neural substrates underlying word generation: a bilingual functional-imaging study. *Proceedings of the National Academy of Sciences USA* 1995;92:2899–903.
- [20] Kucera H, Francis WN. *Computational analysis of present-day American English*. Providence, RI: Brown University Press; 1967.
- [21] Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences USA* 1992;89:5675–9.
- [22] Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron* 2002;33:827–40.
- [23] McDermott KB, Watson JM. The rise and fall of false recall: the impact of presentation duration. *Journal of Memory and Language* 2001;45:160–76.
- [24] Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences USA* 1992;89:5951–5.
- [25] Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. an electrical stimulation mapping investigation in 117 patients. *Journal of Neurosurgery* 1989;71:316–26.
- [26] Ojemann JG, Buckner RL, Akbudak E, Snyder AZ, Ollinger JM, McKinstry RC, et al. Functional MRI studies of word-stem completion: reliability across laboratories and comparison to blood flow imaging with PET. *Human Brain Mapping* 1998;6:203–15.
- [27] Otten LJ, Rugg MD. Task-dependency of the neural correlates of episodic encoding as measured by fMRI. *Cerebral Cortex* 2001;11:1150–60.
- [28] Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 1988;331:585–9.
- [29] Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JD. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *NeuroImage* 1999;10:15–35.
- [30] Price CJ. The anatomy of language: contributions from functional neuroimaging. *Journal of Anatomy* 2000;197:335–59.
- [31] Price CJ, Moore CJ, Humphreys GW, Wise RJS. Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience* 1997;9:727–33.
- [32] Pugh KR, Shaywitz BA, Shaywitz SE, Constable RT, Skudlarski P, Fulbright RK, et al. Cerebral organization of component processes in reading. *Brain* 1996;119:1221–38.
- [33] Raichle ME, Fiez JA, Videen TO, MacLeod AM, Pardo JV, Fox PT, et al. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex* 1994;4:8–26.
- [34] Roediger HL, McDermott KB. Creating false memories: remembering words not presented in lists. *Journal of Experimental Psychology: Learning, Memory, and Cognition* 1995;21:803–14.
- [35] Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE. Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. *Journal of Cognitive Neuroscience* 2001;13:829–43.
- [36] Shulman GL, Corbetta M, Fiez JA, Buckner RL, Miezin FM, Raichle ME, et al. Searching for activations that generalize over tasks. *Human Brain Mapping* 1997;5:317–22.
- [37] Snyder AZ. Difference image versus ratio image error function forms in PET-PET realignment. In: Bailey D, Jones T, editor. *Qualifications of brain function using PET*. San Diego, CA: Academic Press; 1996, p. 131–7.
- [38] Sommers MS, Lewis BP. Who really lives next door: creating false memories with phonological neighbors. *Journal of Memory & Language* 1999;40:83–108.
- [39] Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain*. NY: Thieme; 1988.
- [40] Toga AW, Ojemann G, Ojemann JG, Cannestra AF. Intraoperative brain mapping. In: Maziotta JC, Toga AW, Frackowiak RSJ, editor. *Brain mapping: the disorders*. San Diego, CA: Academic Press; 2000, p. 77–105.
- [41] Van Essen DC, Drury HA, Anderson CH. An automated method for accurately reconstructing the cortical surface. *NeuroImage* 1999;9:173.
- [42] Van Essen DC, Drury HA, Dickson J, Harwell J, Hanlon D, Anderson CH. An integrated software suite for surface-based analyses of cerebral cortex. *Journal of the American Medical Informatics Association* 2001;8:443–59.
- [43] Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. *Nature* 1996;383:254–6.
- [44] Wagner AD, Koutstaal W, Maril A, Schacter DL, Buckner RL. Task-specific repetition priming in left inferior prefrontal cortex. *Cerebral Cortex* 2000;10:1176–84.
- [45] Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron* 2001;31:329–38.
- [46] Wallace WP. Incidental learning: the influence of associative similarity and formal similarity in producing false recognition. *Journal of Verbal Learning & Verbal Behavior* 1968;7:50–4.
- [47] Yetkin FZ, Mueller WM, Morris GL, McAuliffe TL, Ulmer JL, Cox RW, et al. Functional MR activation correlated with intraoperative cortical mapping. *American Journal of Neuroradiology* 1997;18:1311–5.