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Effects of Repetition and Competition on Activity in Left Prefrontal Cortex during Word Generation

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Summary

Neuroimaging studies have revealed an association between word generation and activity in the left inferior frontal gyrus (IFG) that is attentuated with item repetition. The experiment reported here examined the effects of repeated word generation, under conditions in which completion was either decreased or increased, on activity measured during whole-brain echoplanar functional magnetic resonance imaging. Activity in left IFG decreased during repetition conditions that reduced competition but increased during repetition conditions that increased competition; this pattern was contrasted to repetition effects observed in other cortical areas, specifically regions of left temporal cortex. The increase in left IFG activity, which is not predicted by a simple semantic retrieval account of prefrontal function, is consistent with the hypothesis that left IFG subserves the selection of semantic knowledge among competing alternatives.

Introduction

The cortical substrates of the human capacity to retrieve knowledge about objects, facts, concepts, and words and their meanings, also called semantic memory, have been the subjects of regular inquiry since the earliest reports of comprehension impairments in aphasia (Wernicke, 1968). Historically, the retrieval of semantic knowledge has been linked to the left temporal lobe based on evidence from behavioral studies of patients with semantic dementia (Hodges et al., 1992, 1994), focal lesions (Alexander et al., 1989), and Alzheimer's disease (Martin and Fedio, 1983; Hodges et al., 1990), and more recently from studies of evoked neural activity (Nobre et al., 1994; McCarthy et al., 1995; Nobre and McCarthy, 1995) and increased blood flow (e.g., Mummery et al., 1996) during semantic retrieval. However, the advent of modern neuroimaging techniques has also drawn attention to the possible role of left prefrontal cortex in semantic retrieval (Petersen et al., 1988; Démonet et al., 1992; Kapur et al., 1994; Demb et al., 1995; Martin et al., 1995; Gabrieli et al., 1996).

Increased blood flow in left prefrontal cortex, specifically the left inferior frontal gyrus (IFG), has been observed during a wide variety of tasks, including the generation of semantically similar words (Petersen et al., 1988; Martin et al., 1995), the classification of words according to a category (Kapur et al., 1994; Demb et al., 1995; Gabrieli et al., 1996), and semantic monitoring (Démonet et al., 1992). Increased activity in the left IFG has been attributed to the high semantic processing demands common to all of these disparate tasks. However, in a recent imaging study, an alternative account of activity in the left IFG was suggested: in tasks requiring the generation, classification, or comparison of semantic knowledge, activity in the left IFG was found to be related not to semantic retrieval per se but rather to demands for the selection of information among competing alternatives (Thompson-Schill et al., 1997). Furthermore, lesions to the left IFG were found to disrupt semantic processing only under conditions with high selection demands (Thompson-Schill et al., 1998). Based on these studies, we have suggested that left prefrontal cortex functions to bias or gate relevant information, when needed, from posterior (e.g., temporal lobe) semantic memory representations.

In the current study, we will test this hypothesis by examining the effects of manipulations of recent experience, specifically the effect of stimulus repetition, on activity in prefrontal cortex. Behaviorally, it has been widely reported that processing of a stimulus can be facilitated by recapitulation of mental processes with stimulus repetition (i.e., repetition priming; e.g., Srinivas and Roediger, 1990). Neural correlates of this repetition phenomenon have recently been reported in both humans and nonhuman primates. Stimulus repetition results in a reduced response of stimulus-selective inferotemporal neurons of nonhuman primates (Riches et al., 1991; Li et al., 1993; Miller et al., 1993; Miller and Desimone, 1994). This repetition suppression phenomenon may parallel stimulus repetition effects observed in extrastriate regions within the ventral processing stream in neuroimaging studies of humans performing picture recognition tasks (Buckner et al., 1998). Likewise, neuroimaging studies in humans have detected decreases in activity in both left prefrontal cortex and left temporal cortex during repeated semantic processing on verb generation (Raichle et al., 1994) and semantic classification tasks (Demb et al., 1995; Gabrieli et al., 1996).

How does the finding of decreased activity in prefrontal cortex during repeated semantic processing inform us about the functions of this area? One interpretation of these effects is that during repeated semantic retrieval, more efficient semantic processing results in less neural activity in areas involved in retrieval of semantic knowledge. This interpretation follows from the repetition suppression phenomenon noted above: the same neurons that initially fire in response to a stimulus are less active during repeated presentation of that stimulus. We offer a different interpretation of these same data, based on the selection framework described above: in prefrontal cortex, decreases in activity following repeated semantic processing may be the result of decreased *selection* demands. For example, in the verb generation task, one must select an action from all of the knowledge one has about an object. If the task is repeated, that action is

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Table 1. Experimental Conditions

Condition	Prior Task	Current Task	Latency	Accuracy
Baseline	—	read word (motive → "motive")	598	100
Unprimed	— —	generate action (tomato → "slice") generate color (milk → "white")	1062	94
Same	generate action (match → "strike") generate color (tar → "black")	generate action (match → "strike") generate color (tar → "black")	899	97
Different	generate action (dollar → "spend") generate color (moss → "green")	generate color (dollar → "green") generate action (moss → "grow")	1015	96

Definition and illustrative examples of the conditions used in the present study are listed, along with response latency (ms) and accuracy data (%) from a behavioral study of an independent group of 24 subjects. Patterns of both response times and error rates confirm that there is a reliable behavioral priming effect for both types of repetitions used in the current study.

more available so the competition from alternatives is decreased, resulting in decreased selection demands and decreased prefrontal activity. Although there is no way to distinguish these two interpretations of the neuroimaging data in prior studies, it is theoretically possible to distinguish between the effects of repetition and competition in prefrontal cortex.

In the current study, predictions made from these two interpretations were tested in a word generation task that requires both the retrieval of semantic knowledge and the selection of some aspect of that knowledge among competing alternatives. For example, when asked to report an action word related to "apple," a subject must both retrieve semantic knowledge about an apple (e.g., round, red, fruit, good-to-eat, grows-on-trees, etc.) and select an appropriate action from that knowledge (e.g., eat). How might the repetition of semantic processing affect each of those processes? Repeated semantic processing of a word could facilitate the retrieval of semantic knowledge, perhaps, as described above, by decreasing neural computation requirements. In addition, if prior exposure to the word required the selection of the same type of semantic knowledge (e.g., an action), the subsequent increased availability of that knowledge would decrease competition from irrelevant information. Thus, repetition of relevant semantic information (as was the case in previous studies; Raichle et al., 1994) has the same effect on both selection demands and retrieval demands and thus can not distinguish between these two processes.

However, if prior exposure to the word required the selection of *competing* semantic knowledge (e.g., a color), the subsequent increased availability of the irrelevant information would increase competition and selection demands. What effect does priming irrelevant information have on retrieval demands? Priming irrelevant information also produces a repetition priming effect; on a semantic classification task, responses to repeated items were made more quickly and accurately than responses to novel items, even if the two presentations of the item required classification of competing types of information (Thompson-Schill and Gabrieli, 1999). This facilitation effect indicates that priming irrelevant information produces a decrease in semantic retrieval demands. Thus, by priming irrelevant information it is possible to decrease demands for semantic retrieval but increase demands for selection. The results of this manipulation in prefrontal activity can unambiguously discriminate between retrieval and selection interpretations of prefrontal function because opposite predictions are made by these two accounts.

Whole-brain echoplanar functional magnetic resonance imaging (fMRI) scans were acquired during three word generation conditions and a nonsemantic "baseline" condition (see Table 1). In the "same" repetition condition, priming with relevant information should result in a decrease in both retrieval demands and selection demands. Consequently, we predicted a decrease in left IFG activity relative to the "unprimed" condition, as observed in prior studies (Raichle et al., 1994). In the "different" repetition condition, priming with irrelevant information should result in a decrease in retrieval demands but an increase in selection demands. Thus, if activity in left IFG depends on retrieval demands, we should observe a decrease in left IFG activity relative to the "unprimed" condition. If, however, activity in left IFG depends on selection demands, we should observe an increase in left IFG activity relative to the "unprimed" condition. We also compared the effects of repetition and competition on activity in left IFG to those in other cortical areas that also demonstrated activity during word generation.

Results

Behavioral Results

An independent group of subjects performed the generation task outside of the scanner, to allow the acquisition of voice onset latencies during overt word generation, in order to verify the existence of a facilitation effect with this paradigm. The mean response latencies (and error rates) are reported for each condition in Table 1. Relative to the unprimed items, there was a significant reduction in both error rate and response time both for

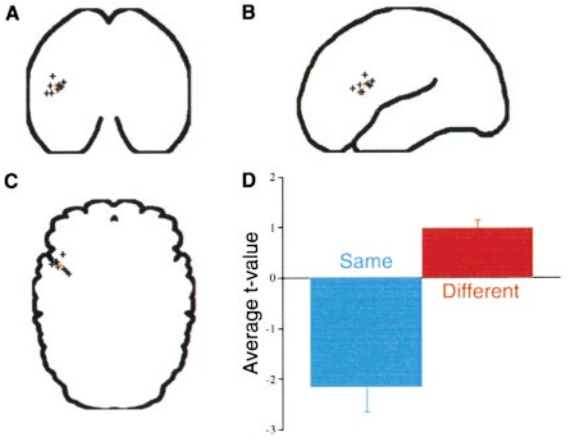

Figure 1. Priming Effects in the Inferior Frontal Gyrus

The local maximum of the ROI in left prefrontal cortex resulting from the comparison of word generation and word reading (“baseline”) is indicated for each subject (black) along with the median location across subjects (red). These maxima are projected onto (A) a coronal cross-section, (B) a lateral view of the left hemisphere, and (C) a horizontal cross-section. In left prefrontal cortex, the median location of the ROI fell in the posterior portion of the IFG ($x = -44$, $y = 15$, $z = 22$). There was very little variability in the location of the ROI across subjects (standard deviation = 5 mm along all three axes); in all eight subjects, the ROI was located either in the inferior frontal sulcus or in the IFG, in a posterior area corresponding roughly to Brodmann's area 44. In (D), for each subject two contrasts were examined within the subject's ROI: activity in the “same” condition compared to the “unprimed” condition (blue) and activity in the “different” condition compared to the “unprimed” condition (red). The average t value for each contrast across subjects is plotted in the figure. In the group analysis, there was significantly less activity in the ROIs in the “same” priming condition than in the “unprimed” condition ($t [7] = -4.81$, $p < 0.01$). However, there was significantly greater activity in the ROIs in the “different” priming condition than in the “unprimed” condition ($t [7] = 5.96$, $p < 0.01$). As would be expected from these patterns, the difference between the “same” and “different” priming conditions was significant ($t [7] = 8.46$, $p < 0.01$).

the “same” repetition condition (latency $t [23] = 8.85$, accuracy $t [23] = 3.78$, $p < 0.05$) and, critically, for the “different” repetition condition (latency $t [23] = 4.51$, accuracy $t [23] = 2.30$, $p < 0.05$). The findings on this task replicate previous studies (Thompson-Schill and Gabrieli, 1999) which found that priming irrelevant information produces a facilitation effect indicative of a decrease in semantic processing or retrieval demands.

Response latencies were also collected from the eight subjects during the functional imaging study. However, there are important differences in the method of obtaining these response latency measures between the imaging study and the behavioral study described above. In the behavioral study, response latencies were measured at the onset of the overt response. However, in the imaging study, no overt response was made. The response latency was measured at the time of a button press by the subject, which was to occur as soon as the subject thought of a word. Therefore, this is a latency to a different type of response and, conceivably, to a different point in the generation process. Second, because no accuracy data was available in the imaging study, all responses were included in the analysis. For these reasons, caution is needed in interpreting these data. Despite these caveats, the response latencies collected from subjects during functional imaging study showed the same pattern as those in the independent sample described above: response latencies in the both the “same” condition (mean = 1204, $t = 8.82$) and the “different” condition (mean = 1300, $t = 3.10$) were shorter than in the “unprimed” condition (mean = 1363).

fMRI Results

All eight subjects showed significant increases in fMRI activity during the generation conditions relative to the “baseline” condition in the posterior portion of the inferior frontal gyrus and the inferior frontal sulcus; the magnitude of the generation effect, in terms of percent signal change from the “baseline” condition, was 0.56% on average. (It should be noted that although these effects were evident in each subject, a mixed effects group analysis over the entire brain volume yielded no significant main effects due to the low power associated with that test with only 7 degrees of freedom when corrected for all mapwise comparisons.) In each subject, a functionally defined region of interest (ROI) in left IFG was created using voxels that demonstrated generation effects; these ROIs were used to test subsequent hypotheses regarding the effects of repetition and competition on fMRI signal. The location of these ROIs is illustrated in Figure 1. The extent of the activation in the thresholded map varied widely between subjects (from 4 to 84 contiguous voxels). In order to create ROIs of comparable extent, the 10 contiguous voxels with the highest values (around the point of maximal statistical difference) were selected to create an ROI of approximately 0.70 cm^3 for each subject. (If, instead, all of the activated voxels were included in the ROI, the pattern of results reported below was unchanged.) The time series from the ROI was spatially averaged, and priming effects within this region were assessed in each subject by examining the t value associated with each contrast (see Table 2). In all eight subjects, a decrease in activity (mean = −0.11%) was observed in the “same” condition relative to the “unprimed” condition. This decrease was reliable across subjects in a mixed effects analysis of the effect size ($t [7] = -4.81$, $p < 0.01$). In contrast, in all eight subjects, an *increase* in activity (mean = +0.05%) was observed in the “different” condition relative to the “unprimed” condition. This increase was reliable across subjects in a mixed effects analysis of the effect size ($t [7] = 5.96$, $p < 0.01$). The interaction between the “same” and “different” conditions, depicted in Figure 1, was significant ($t [7] = 8.46$, $p < 0.01$). Thus, the direction of the effects of semantic repetition on activity in left IFG depended on whether competition was either increased or decreased as a result of previous semantic processing.

In order to examine the specificity of this result to prefrontal cortex, we also examined other cortical areas that demonstrated generation effects. As noted above, these effects were examined within each subject, as there were no voxels that surpassed the threshold appropriate for a mapwise correction in a group mixed effects analysis. Aside from the region of prefrontal cortex noted above, the only other cortical area in which

Table 2. Individual and Group Priming Effects

Condition	S1	S2	S3	S4	S5	S6	S7	S8	Population
Left inferior frontal gyrus									
Same	−2.15	−4.40	−0.57	−2.17	−3.43	−0.36	−3.07	−2.46	−4.81
Different	1.41	0.65	1.80	1.14	0.60	0.96	0.43	0.77	5.96
Left temporal lobe									
Same	−2.26	−1.44	−0.55	−0.94	−0.83	−0.41	−0.79	−1.53	−5.06
Different	−1.00	−1.51	−0.69	−1.48	−0.68	−1.21	−1.12	−0.86	−9.37

For each subject, t values of contrasts of each condition versus the “unprimed” condition in ROIs in the left prefrontal cortex and left temporal lobe are listed. For the population, t values from a mixed effects test of differences from the “unprimed” condition are listed.

increased activity during word generation was identified in at least six of the eight subjects was in left temporal cortex. All eight subjects demonstrated activity in the left temporal lobe that was significantly associated with word generation. Effects of word generation were identified in an area of left temporal cortex that, across subjects, extended along the anterior collateral sulcus and into the medial portion of the left fusiform gyrus. In contrast to the ROIs identified in prefrontal cortex, there was considerable variability in the location of the functionally defined ROIs in temporal cortex (see Figure 2). Despite the functional similarity of these regions (i.e., all demonstrated word generation effects), the anatomical variability prevents us from drawing strong conclusions about the location of these effects in temporal cortex, beyond noting that the activation was primarily near the ventral surface of the left temporal lobe.

As with the prefrontal ROIs, signal in the temporal ROI of each subject was spatially averaged, and priming effects within the region were examined within each subject. The patterns of activity in response to repeated semantic processing of words that were primed with either relevant (“same”) or irrelevant (“different”) semantic knowledge look quite different in left temporal cortex than in left prefrontal cortex. In left temporal cortex ROIs, decreases in activity (mean $= -0.05\%$), relative to unprimed words, were observed for both priming conditions, regardless of the type of knowledge that had previously been retrieved (Figure 2). Significant reductions in activity were observed across subjects for both the “same” condition ($t [7] = -5.06$, $p < 0.01$), and the “different” condition ($t [7] = -9.37$, $p < 0.01$). The interaction between these conditions did not approach statistical significance ($t < 0.5$). The differential effects of an irrelevant prime on activity in left temporal cortex and left prefrontal cortex were evident in the direct comparison of the effects in these two areas across subjects ($t [7] = 11.73$, $p < 0.01$).

Discussion

In this study, we examined the behavioral and physiological effects of priming word generation with either relevant or irrelevant semantic information. When relevant information was used to prime word generation, we observed a behavioral facilitation effect and a decrease in activity in left prefrontal cortex. These findings replicate previous work showing the effects of repetition on word generation (Raichle et al., 1994). The novel finding in this report concerns the effects of priming word generation with irrelevant semantic information. As with relevant primes, we observed a behavioral facilitation effect; however, irrelevant primes produced an *increase* in activity in left prefrontal cortex, despite the fact that performance under these conditions was both faster and more accurate. We have used the repetition of irrelevant semantic information to dissociate semantic retrieval from selection and found that activity in prefrontal cortex

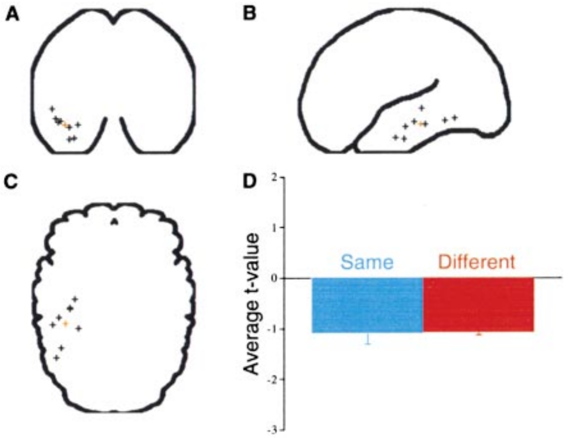

Figure 2. Priming Effects in Temporal Cortex

The local maximum of the ROI in left temporal cortex resulting from the comparison of word generation and word reading (“baseline”) is indicated for each subject (black) along with the median location across subjects (red). These maxima are projected onto (A) a coronal cross-section, (B) a lateral view of the left hemisphere, and (C) a horizontal cross-section. In left temporal cortex, the median location of the ROI fell along the anterior extent of the collateral sulcus ($x = -40$, $y = -28$, $z = -12$). The location of the ROI within the temporal lobe varied to the greatest extent along the anterior–posterior (y) axis (standard deviation = 17 mm) and to a lesser extent along the medial–lateral (x) axis (standard deviation = 8 mm) and the dorsal–ventral (z) axis (standard deviation = 8 mm). In seven of the eight subjects, the ROI fell either in the medial fusiform gyrus or in the collateral sulcus (the remaining subject’s ROI was in the middle temporal gyrus). In (D), for each subject two contrasts were examined within the subject’s ROI: activity in the “same” condition compared to the “unprimed” condition (blue) and activity in the “different” condition compared to the “unprimed” condition (red). The average t value for each contrast across subjects is plotted in the figure. In the group analysis, there was significantly less activity in these ROIs in the “same” condition ($t [7] = -5.06$, $p < 0.01$) and in the “different” condition ($t [7] = -9.37$, $p < 0.01$) than in the “unprimed” condition. The difference between the “same” and “different” priming conditions did not approach statistical significance ($t [7] = 0.11$).

is related to selection, and not retrieval, of semantic knowledge. Further, this pattern was not observed in the left temporal lobe, where repetition was associated with decreased activity for both relevant and irrelevant primes. The dissociation between activity in prefrontal and temporal cortex in response to stimuli primed with irrelevant information may reflect the different roles that these two cortical areas play in the selection and retrieval of semantic memory, respectively. These possible functions of prefrontal and temporal cortex will be discussed in turn.

Left Prefrontal Cortex

Until the advent of neuroimaging, relatively little was known about the neural basis of semantic memory, and virtually nothing was known about the role that prefrontal cortex might play in semantic processing. The link between prefrontal cortex and semantic memory is based almost entirely on recent neuroimaging studies that paint a convincing yet puzzling story about the role of prefrontal cortex in semantic memory. The challenge has been to reconcile the recent neuroimaging results with the literature on cognitive impairments following focal brain injury, which reveals no particular association between semantic memory and left prefrontal cortex (Goodglass and Kaplan, 1983). One frequently cited convergence of neuroimaging and neuropsychological findings is the involvement of prefrontal cortex in word retrieval, or fluency, tests (Milner, 1964). Although lesions to prefrontal cortex do impair the ability to generate semantically related words on a category fluency task, they also impair performance on nonsemantic fluency tasks (i.e., letter fluency; Baldo and Shimamura, 1998). Furthermore, dissociations between category fluency and letter fluency have been reported in studies of patients with either frontal or posterior pathology (Newcombe, 1969; Coslett et al., 1991; Rosser and Hodges, 1994), in normal subjects when concurrently performing additional tasks (Moscovitch, 1992; Martin et al., 1994), and in patterns of activity from neuroimaging (Mummery et al., 1996). These studies converge on the conclusion that letter fluency is more dependent on frontal cortex, whereas category fluency is more dependent on temporal cortex. Specifically, the neuroimaging study found that in a direct comparison of activity during letter fluency and category fluency tasks, activity in left prefrontal cortex (specifically, inferior frontal sulcus) was greater for letter fluency while activity in left temporal cortex (specifically, anterior fusiform gyrus) was greater for category fluency. Furthermore, dissociations within category and letter fluency tasks have been described between clustering and switching components of these tasks, which are hypothesized to be related to temporal and frontal cortices, respectively (Troyer et al., 1997; see also Chertkow and Bub, 1990). The dissociation between these components mirrors the distinction we have made in the present study between retrieval and selection.

When word generation is primed with irrelevant information, we observed an increase in prefrontal activity that we hypothesize to result from an increase in selection demands. One might expect conditions that require an increase in processing demands to result in an increase in response latencies; that is, instead of a behavioral facilitation effect, irrelevant primes could be expected to produce a behavioral inhibition effect. Yet in the current study, as well as in previous research on the behavioral effects of irrelevant primes (Thompson-Schill and Gabrieli, 1999), a facilitation effect has been consistently observed. Where then is the “cost” for the putative increase selection demands? We suggest that this cost can be measured by the difference between response latencies in the “same” and “different” conditions. Both of these conditions are expected to result in a decrease in semantic retrieval demands, which should produce a decrease in response latencies. In the “same” condition, the decrease in selection demands should further decrease response latencies, whereas in the “different” condition, the increase in selection demands should increase response latencies, although perhaps not back to the level of unprimed performance. Thus, the opposite effects on selection demands in the “same” and “different” conditions could drive the response latencies apart, resulting in the difference between the two conditions. This logic highlights the fact the response latency measure is influenced by both selection and retrieval processes, and cannot be used as an index of either process in isolation.

The results presented here support our hypothesis that prefrontal cortex subserves the selection of knowledge among competing information. A number of other studies, in addition to those reviewed earlier (e.g., Thompson-Schill et al., 1997, 1998), are consistent with this hypothesis as well. For example, lesions to prefrontal cortex have been shown to impair sentence completion and word association (Robinson et al., 1998), as well as category fluency (Randolph et al., 1993), when there are many possible responses but not when there are few possible responses. Also, prefrontal lesions affect the ability of patients to select the appropriate meaning of ambiguous words (Swaab et al., 1998). Selection effects in prefrontal cortex have also been shown in paradigms that are not best described as semantic retrieval tasks: increased prefrontal activity was observed during word stem completion for stems that had many as opposed to few possible completions (Desmond et al., 1998), although that activation was more superior and anterior to that observed in the present experiment. While all of these studies support the role of prefrontal cortex in selection processes, they do not address whether this is a unique function of prefrontal cortex. In this study, we can begin to consider the unique role that prefrontal cortex plays in the selection of competing information, in contrast to posterior cortical areas that may have quite different functions, through our comparison of the effects we observed in prefrontal cortex with those we observed in left temporal cortex.

Left Temporal Cortex

The left temporal lobe has long been associated with semantic memory on the basis of neuropsychological evidence. Reports of selective impairments of semantic memory typically are the result of herpes simplex encephalitis (e.g., De Renzi et al., 1987), posterior cerebral artery infarctions (e.g., Alexander et al., 1989), and Pick’s disease atrophy (e.g., Hodges et al., 1992), which have in common damage to left temporal cortex. A somewhat more refined locus of this pathology is suggested by the finding that lesions of basal portions of the left temporal lobe are most resistant to recovery of aphasia, especially comprehension, after stroke than are other posterior lesions (Goldenberg and Spatt, 1994); basal temporal areas involved in comprehension have also been identified with presurgical stimulation mapping in epileptic subjects (e.g., Burnstine et al., 1990). Field potentials recorded from intracranial electrodes have indicated that a language-sensitive potential (termed the N400) is generated in the neocortex near the collateral sulcus and anterior fusiform gyrus (McCarthy et al., 1995; Nobre and McCarthy, 1995). It has been suggested that this area of the temporal lobe, which is sensitive to semantic content, may play a role in the storage or retrieval of word concepts (Nobre et al., 1994). This conjecture is consistent with our finding that activity in this area is greater during word generation than word reading, presumably due to increased demands on retrieval of semantic knowledge required by the generation task. Similar areas have been identified in other neuroimaging studies of semantic retrieval (Démonet et al., 1992; Klein et al., 1995; Mummery et al., 1996). Additionally, our finding of decreased activity in this basal temporal area during semantic retrieval of primed items (see also Raichle et al., 1994) may be related both to the phenomenon of repetition suppression observed in neurons in anterior–ventral inferotemporal cortex of nonhuman primates (Riches et al., 1991; Li et al., 1993; Miller et al., 1993; Miller and Desimone, 1994) and to the effects of semantic priming on intracranial field potentials recorded from this area in humans (McCarthy et al., 1995; Nobre and McCarthy, 1995).

Thus, evidence from a number of diverse sources is consistent with the hypothesis that basal portions of the left temporal lobe subserve the storage and retrieval of semantic information. In the present study, we used repetition to manipulate semantic retrieval demands; repeated semantic retrieval about a concept should facilitate subsequent semantic retrieval attempts. Further, we argued that semantic retrieval demands should be unaffected by the relevance of previous retrieval tasks for subsequent retrieval. For both relevant (“same”) and irrelevant (“different”) prime conditions, repeated semantic retrieval should be facilitated; behavioral evidence from this and previous studies (Thompson-Schill and Gabrieli, 1999) supports this claim. In regions near the basal surface of the left temporal lobe, we observed decreases in activity in both prime conditions that parallel the putative decreases in retrieval demands. This finding is consistent with the hypothesized role of temporal cortex in the retrieval of semantic knowledge.

One assumption we have made in our interpretation of these data is that the decrease in generation latencies, which is mirrored in all conditions by a decrease in activity in left temporal cortex, reflects a decrease in semantic retrieval demands. However, behavioral facilitation can result from a number of nonsemantic factors as well; for example, repetition of the perceptual form of a stimulus, in the absence of any semantic processing, can result in facilitation on certain tasks (e.g., Scarborough et al., 1979; Weldon, 1991). Two possible alternative sources for the facilitation in the present experiment are perceptual repetition (repetition of the exact form of the stimulus) and lexical repetition (repetition of the same lexical entry); if either or both of these sources can explain the behavioral facilitation effect, then they could also explain the decrease in activity in left temporal cortex, which would suggest a different interpretation of the function of that area. In the current study, we cannot rule out these two alternatives. However, we contend that the interpretation that we have presented is not only more consistent with the neuropsychological and electrophysiological literature concerning the function of temporal cortex, but it is also more plausible in light of recent studies demonstrating that facilitation on the word generation task is indeed the result of semantic repetition. Repetition of perceptual and lexical processing in the absence of semantic processing does not produce a facilitation effect on the word generation task (S. L. T.-S. and I. P. K., unpublished data), whereas repetition of semantic processing with no perceptual or lexical repetition does result in a generation priming effect (e.g., priming of the same concept across different languages; Seger et al., 1999). These results suggest that it is unlikely, albeit not impossible, that our results can be explained as nonsemantic effects, and future work may clarify this issue further.

Thus far, our discussion of the differences we observed in left prefrontal and left temporal cortex has focused on the hypothesized dissociation between these two areas in the effects of competition on brain activity. Another striking difference we observed, which is quite apparent in a comparison of Figures 1 and 2, is in the degree of variability of the ROIs across subjects. In left prefrontal cortex we observed a tight clustering of ROIs within a few millimeters of each other in the posterior portion of the inferior frontal gyrus. In contrast, in left temporal cortex the variability in the location of ROIs was quite large, particularly in the rostral–caudal dimension, in which the range was 48 mm. In our analysis of the priming effects within these ROIs, we are in effect treating voxels that are nearly 5 cm apart as though they derive from the same functional area of cortex. By analogy, such a range within frontal cortex would be comparable to considering the frontal pole and the posterior extent of the inferior frontal gyrus as a single functional area. Although this analogy to frontal cortex helps to illustrate the problem, perhaps its shortcoming is that the temporal lobe and the frontal lobe are different cortical areas; what one expects as reasonable variation in functional organization of one structure need not apply to another structure. Certainly, not all parts of the brain share the same principles of functional–anatomical organization and variability. Thus, our observation of variability of responses in temporal cortex, in contrast to the tight clustering of responses in prefrontal cortex, may be an important and unique property of the functional organization of the temporal lobe.

Although this outcome was unanticipated in the present study, there are a number of examples in the literature of similar variability in temporal cortex which suggest that such a result is not without precedent. After mapping language areas in over 100 patients, Ojemann and colleagues (1989) concluded that although there were often highly localized language areas within the temporal lobe in a given patient, these sites had exceedingly diverse anatomic locations across subjects. This sort of variability has been noted specifically within basal temporal cortex as well. Early electrical stimulation studies of basal temporal cortex identified across subjects an area of approximately 2 cm × 2 cm in the left fusiform gyrus that was related to language processing (Lüders et al., 1986). Subsequent studies using a larger array of electrode sites have revised this initial estimate to describe a language-related area of the fusiform and parahippocampal gyri that extends at least 63 mm in the rostral-caudal dimension (Burnstine et al., 1990). That is not to say that every patient had 6 cm of basal temporal cortex devoted to language; in some patients, a language area was identified in the anterior extent of this region, whereas other patients had a language area in the posterior extent of the region. That is, basal temporal cortex exhibited quite extensive functional variability across subjects. Other studies linking basal temporal cortex to semantic processing have found similar variability. McCarthy and colleagues reported that the N400, an event-related potential (ERP) component related to semantic processing, originated from this basal temporal area (McCarthy et al., 1995). They observed N400s at sites along the collateral sulcus as far anterior as the amygdala and as far posterior, in some patients, as the posterior fusiform gyrus (posterior to the hippocampus). In other words, several previous studies have reported considerable variability between subjects in the functional organization of the basal temporal cortex that is consistent with the variability that we observed in the present study.

In addition to this evidence suggesting that the variability that we observed might reflect true variability in the functional organization of the basal temporal lobe, we also propose another possible explanation for the variability in the location of the ROIs in our findings. In this study, we have, for the purposes of initial simplification, regarded all types of semantic knowledge about all categories of objects as forming a single memory system. In fact, there is mounting evidence to the contrary, suggesting, for example, that there may be anatomically distinct representations of visual and functional semantic knowledge (Martin et al., 1995; Thompson-Schill et al., 1999). A recent neuroimaging study concluded that the temporal lobe may be organized to reflect similarity in features, with the lateral–medial dimension of basal temporal cortex coding similarity in object form and the inferior–superior dimension of lateral temporal cortex coding similarity in object motion (Martin et al., 1999). Any number of factors in the current study (e.g., what type of actions a subject retrieved during the action generation task, what information a subject spontaneously retrieved during the read task, etc.) could have influenced which portions of this distributed semantic representation were the most active in the comparison of word generation and word reading in a given subject. In other words, there may be important functional differences between the ROIs we have identified in temporal cortex that we have, for the purposes of the current investigation, treated as homogeneous. Whether this can explain the variance we observed in the ROIs in the present study, and, further, whether it could explain the variance in the previous electrical stimulation and recording research, should be the subject of future consideration.

Although it is difficult to draw strong conclusions about the locus of the semantic retrieval effects in the temporal lobe in light of this variability, the region that was identified in all subjects was clearly inferior to classical temporal lobe language areas (i.e., Wernicke's area). Although the precise extent and location of "Wernicke's area" has been the subject of both historical (reviewed by Bogen and Bogen, 1976) and contemporary debate (for a review of lesion analyses of aphasia syndromes, see Dronkers and Ludy, 1998), by none of these accounts is Wernicke's aphasia suggested to result from lesions to basal temporal cortex. Notably, lesions to basal temporal cortex are associated instead with the syndrome of transcortical sensory aphasia, which has been described as fundamentally a disorder of semantic processing (reviewed by Alexander, 1997), as well as other impairments of global (i.e., verbal and nonverbal) semantic knowledge, including semantic dementia (Hodges et al., 1992, 1994), category-specific knowledge deficits (e.g., Warrington and Shallice, 1984), and associative agnosia (reviewed by Farah, 1990). Thus, lesions to this basal area of temporal cortex will produce a general semantic memory impairment as opposed to a Wernicke's-type aphasia; this area may be part of a system that subserves the storage and retrieval of semantic concepts, distinct from their specific linguistic forms (e.g., phonological information).

Conclusions

In this report, we have proposed the that generation of semantically related words requires two processes—retrieval and selection—and we have demonstrated a difference in the roles of frontal and temporal cortex that may be related to these two processes. Knowledge about the word or concept must be retrieved from semantic memory. Repeated retrieval of knowledge about a specific concept results in decreased response latencies (i.e., repetition priming) and, in the current study, resulted in decreased activity in left basal temporal cortex, around the anterior collateral sulcus and fusiform gyrus, that may be related to the neural mechanisms that result in repetition suppression in inferotemporal neurons of nonhuman primates. Additionally, specific information required for the task must be selected from this knowledge. Selection demands will depend on, among other things, what information has been recently selected and made available about that concept. When recently selected information is irrelevant, selection demands will be higher than when recently selected information is relevant. In this study, we found that activity in left prefrontal cortex, in the IFG, was dependent on the demands for selection; this result is consistent with earlier work linking left IFG to selection of semantic knowledge (Thompson-Schill et al., 1997, 1998). Thus, the roles that temporal and frontal cortex play in semantic processing appear to be quite distinct, with temporal cortex subserving the retrieval of semantic information and prefrontal cortex functioning in perhaps a nonsemantic role, enabling the selection of relevant information from competing semantic knowledge.

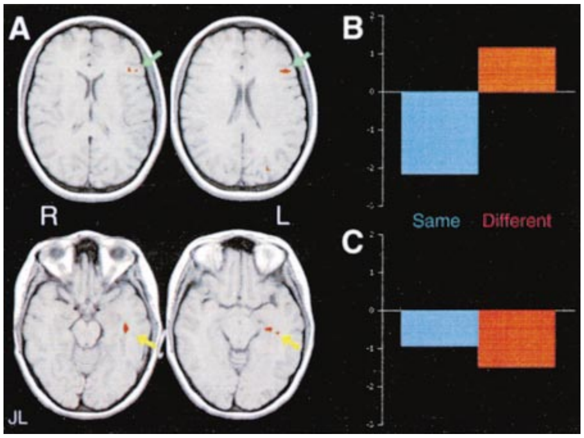

Figure 3. Priming Effects in a Representative Subject

In each subject, functional ROIs were identified that showed increased activity during verb generation compared to word reading.

(A) ROIs identified in one representative subject are shown on axial slices, in the left IFG (green arrow, $z = +15, +19$) and in or near the left collateral sulcus in the temporal lobe (yellow arrow, $z = -15, -11$). Time series within each ROI were averaged across voxels, and contrasts orthogonal to the main effect used to define the ROI were examined.

(B) In the left IFG, relative to the "unprimed" condition, there was less activity during the "same" condition ($t = -2.17$) but more activity during the "different" condition ($t = +1.14$).

(C) In left temporal cortex, relative to the "unprimed" condition, there was less activity during both the "same" condition ($t = -0.94$) and the "different" condition ($t = -1.48$).

In an identical fashion, ROIs were computed for all eight subject and contrasts were examined within each ROI, as summarized in Table 2.

Experimental Procedures

Subjects

Subjects were four males and four females, aged 19–30 years (mean age = 25 years). All subjects met the following inclusion criteria: they were (1) high-school educated, (2) native English speakers, and (3) right handed. General exclusionary criteria were (1) a history of neurological or psychiatric illness or (2) current use of medication affecting the central nervous system (e.g., psychotropic drugs). Two additional subjects were excluded because of excessively poor performance. Informed consent was obtained from all subjects. Verification of the behavioral facilitation effect was tested in an independent group of 24 subjects who met all of the criteria above.

Image Acquisition

Following the acquisition of saggital and axial T1-weighted localizer images, gradient echo, echoplanar fMRI was performed in 21 contiguous 5 mm axial slices (TR = 2000, TE = 50, 64 × 64 pixels in a 24 cm field of view) using a 1.5-T GE Signa system equipped with a fast gradient system and the standard quadrature head coil. Head motion was minimized by using foam padding. Twenty seconds of "dummy" gradient and rf pulses preceded the actual data acquisition to approach steady-state magnetization.

Behavioral Task

Stimuli were presented in blocks of eight words; each block began with an 800 ms instruction ("read," "color," or "action"), followed by a series of eight words, each presented for 2 s, followed by a 400 ms intertrial interval, totaling 20 s per block. Each block comprised items from one of four experimental conditions (see Table 1): for four blocks, subjects saw novel abstract words and covertly read the words ("baseline"); for eight blocks, subjects saw novel concrete words and covertly generated related action (four blocks) or color (four blocks) words ("unprimed"); for four blocks, subjects saw repeated concrete words (from previous blocks of the same scan) and covertly generated the same type of response as during the initial presentation ("same"); and, for four blocks, subjects saw repeated concrete words (from previous blocks of the same scan) and covertly generated a different type of response as during the initial presentation ("different"). The presentation order of these blocks was in an alternating pattern, counterbalanced across subjects; to allow for proper counterbalancing, immediately prior to each scan, during the "dummy" acquisition period, a block of unprimed items was presented so that the first block during the scan could be either a novel or a repeated block. The lag between the initial and repeated presentations of an item ranged from three to eight blocks, with an average of five blocks, or 100 s, between stimulus repetitions. Subjects indicated their successful completion of the task in all conditions with a bilateral button press. A total of four 400 s scans were conducted for each subject, resulting in 800 observations per voxel per subject.

Image Processing

Offline data processing was performed on Sun Sparc workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO). After image reconstruction, the data were sinc interpolated in time to correct for the fMRI acquisition sequence. A slicewise motion compensation method was utilized that removed spatially coherent signal changes by the application of a partial correlation method to each slice in time (Zarahn et al., 1997). Additional motion detection and correction was undertaken using a six-parameter, rigid-body transformation provided by Statistical Parametric Mapping (SPM96) software. None of the subjects had translational motion that exceeded 2 mm in any plane or angular motion that resulted in more than a 2 mm displacement. No spatial smoothing or normalization was performed.

Voxelwise analysis was performed by using a general linear model for serially correlated error terms (Worsley and Friston, 1995); included within the model was an estimate of intrinsic temporal autocorrelation (Aguirre et al., 1997) and sine and cosine regressors for frequencies below that of the task (0.0093 Hz). Global signal covariates were not included in the analyses because of the potential difficulty that their inclusion creates in the interpretation of negative correlations as decreases in activity (Aguirre et al., 1998). Temporal data were smoothed with an empirically derived estimate of the hemodynamic response of the fMRI system; this analysis has been empirically demonstrated to hold the mapwise false positive rate at or below tabular values (Zarahn et al., 1997). Given 233 effective degrees of freedom, the critical t value of 4.5 was used to maintain a mapwise $\alpha = 0.05$.

In order to identify functionally defined ROIs in which to test our hypotheses, activity in the three generation conditions ("unprimed," "same," "different") was compared to the "baseline" condition. Anatomical landmarks were identified in each subject to define the following cortical areas: left prefrontal cortex, left temporal cortex, and cingulate cortex; in addition, other cortical areas (e.g., right prefrontal cortex) were examined for unexpected effects. After thresholding the statistical parametric map at the critical t level for each subject, significant activity in at least one voxel within a given cortical area was considered a positive main effect for that subject in that area. For purposes of reporting the location of this ROI in standardized space, the local maximum within each ROI was identified, and the approximate coordinates in the Talairach and Tournoux brain atlas (Talairach and Tournoux, 1988) were computed with a landmark-guided, nine-parameter differential scaling algorithm. Throughout this report, x, y, and z coordinates are expressed in millimeters along the medial–lateral axis (negative, left), the anterior–posterior axis (negative, posterior), and the dorsal–ventral axis (negative, ventral), respectively.

In order to compute an effect size in each subject for the two hypotheses of interest, we averaged the time series for all of the voxels in the ROI together. Thus, for each subject, we had one spatially averaged time series for each ROI. Two planned contrasts, each orthogonal to the contrast used to define the ROIs, were calculated for each time series: the first contrast compared the "same" condition to the "unprimed" condition and the second contrast compared the "different" condition to the "unprimed" condition. The t value for the parameter describing each of these contrasts was computed as an index of effect size in each subject (Figure 3). The t value was used as an index of the effect size because it provides information about the magnitude of the signal change relative to the variability, or noise, in the data; this is preferable over a measure such as percent signal change, because of the variability between subjects in the overall scaling of the BOLD signal, which affects both the signal and the noise of fMRI data. (When a percent signal change measure was used instead, the pattern of effects we reported here was unchanged, although the variability of the effects was slightly increased.)

For each subject, four t values were calculated: the "same" priming effect in the prefrontal ROI, the "same" priming effect in the temporal ROI, the "different" priming effect in the prefrontal ROI, and the "different" priming effect in the temporal ROI. The t values across all eight subjects were then used as the dependent variable in a group analysis; we used a mixed effects analysis with subjects treated as a random variable in order to determine whether a significant effect was present in the population from which our sample was drawn (for discussion of random effects models of fMRI data, see Holmes and Friston, 1998, Neuroimage, abstract). In order to test for a dissociation between frontal and temporal areas, t values from both contrasts were compared between ROIs using a paired t test; this is equivalent to testing an interaction between the priming effect and the region of interest. In order to examine the effects observed under each condition in each cortical area, a t test was used to ascertain whether the t values from each of the above contrasts were reliably different than 0 (see Table 2).

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