Connectivity among semantic associates: An fMRI study of semantic priming

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Accepted 23 November 2005
Available online 18 January 2006

Abstract

Semantic priming refers to a reduction in the reaction time to identify or make a judgment about a stimulus that has been immediately preceded by a semantically related word or picture and is thought to result from a partial overlap in the semantic associates of the two words. A semantic priming lexical decision task using spoken words was presented in event-related fMRI and behavioral paradigms. Word pairs varied in terms of semantic relatedness and the connectivity between associates. Thirteen right-handed subjects underwent fMRI imaging and 10 additional subjects were tested in a behavioral version of the semantic priming task. It was hypothesized that priming would be greatest, reaction time fastest, and cortical activation reduced the most for related word pairs of high connectivity, followed by related word pairs of low connectivity, and then by unrelated word pairs. Behavioral and fMRI results confirmed these predictions. fMRI activity located primarily in bilateral posterior superior and middle temporal regions showed modulation by connectivity and relatedness. The results suggest that these regions are involved in semantic processing.

Keywords: Semantic priming; Temporal lobe; Connectivity

1. Introduction

The neural basis of semantic processing has been examined in numerous neuroimaging studies. However, a consensus on the role of individual regions in semantic processing has not been obtained. It has long been documented that the comprehension of word meaning can be dissociated from other linguistic functions (see Binder et al., 1997; Hart & Gordon, 1990; Caramazza & Zurif, 1976). Studies of neurologically impaired individuals such as patients with aphasia, semantic dementia, Alzheimer’s disease, and category specific semantic impairments have traditionally associated comprehension deficits with posterior or temporal/parietal damage (e.g., Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Grossman et al., 1997; Hart & Gordon, 1990; Hodges, Patterson, Oxbury, & Funnell, 1992).

In the study of semantic processing, many neuroimaging studies have focused on phonological versus semantic processing and have not found dissociations between these processes (e.g., Crosson et al., 1999; Fujimaki et al., 1999; Price, Wise, & Frackowiak, 1996; Pugh et al., 1996). Nor have they consistently confirmed the involvement of temporal/inferior parietal regions in lexical–semantic processing. Many studies have found either no activation or very small areas of activation in areas traditionally thought to subserve semantic processing (left temporal/parietal regions), and some find more robust activations in frontal than...
temporal regions (Crosson et al., 1999; Demonet et al., 1992; Fujimaki et al., 1999; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Price, Moore, Humphreys, & Wise, 1997; Pugh et al., 1996; Roskies, Fiez, Balota, Raichle, & Petersen, 2001). All of these neuroimaging studies of semantic processing used subtractive methodologies to isolate semantic processing from other stages of word processing such as phonemic or graphemic processing, and/or early auditory or visual processing. For example, a rhyming condition might be contrasted with a condition where semantic judgments are made on words. However, if semantic processing were assumed to proceed automatically and/or in an obligatory fashion when a word is perceived, then the activation of semantic representations would be present even in conditions where phonemic judgments are made on words. Subtraction of these two conditions would then result in (at least some of) the activation of semantic representations being subtracted out of the comparison (see Binder et al., 1997; Crosson et al., 1999; Friston et al., 1996; Fujimaki et al., 1999; Poeppel, 1996; Price et al., 1996; Pugh et al., 1996; Van Petten, Coulson, Rubin, Plante, & Parks, 1999 for discussions).

Priming paradigms take advantage of the automatic processing of words, and in fact, priming effects are predicated on the assumption that this processing does take place. In semantic priming, a word stimulus initiates activation of its network of neighboring semantic associates. Lexical decisions are faster for target words (doctor) that are preceded by semantically related associates (nurse), and slower for target words that are preceded by semantically unrelated associates (truck) (e.g., Meyer & Schvaneveldt, 1971; Neely & Besner, 1991; Schacter & Buckner, 1998a, 1998b). The precise mechanisms underlying priming have yet to be fully characterized, but it may reflect (at least in part) an automatic, involuntary spread of activation among lexical items, especially with short inter-stimulus intervals between word pairs (Collins & Loftus, 1975; Posner & Snyder, 1975a, 1975b).

Repetition priming is the most frequently examined type of priming in single unit neurophysiology and neuroimaging studies. Stimulus repetition often produces a reduction in neural activity (for exceptions see Henson, Shallice, & Dolan, 2000a, 2000b, 2000c; Miller & Desimone, 1994; Ojemann, Schoenfield-McNeill, & Corina, 2002a, Ojemann, Ojemann, & Lettich, 2002b; Schnyer, Ryan, Trouard, & Forster, 2002). This “repetition suppression” may be an automatic intrinsic response of cortical neurons in that it can be found regardless of the behavioral relevance of the stimulus; it also mirrors many of the characteristics of behavioral repetition priming (see Brown & Xiang, 1998; Wiggs & Martin, 1998 for reviews). Repetition suppression has been documented in temporal and frontal regions in single unit recording studies (Baylis & Rolls, 1987; Brown, Wilson, & Riches, 1987; Desimone, 1996; Li, Miller, & Desimone, 1993; Miller & Desimone, 1994; Rainer & Miller, 2000; Riches, Wilson, & Brown, 1991; Ringo, 1996; Suzuki, Miller, & Desimone, 1997). Functional imaging studies of repetition priming using words have often shown reduced activation with the repeated exposure of familiar stimuli in most of those regions originally used to process the stimuli (Badgaiyan, Schacter, & Alpert, 1999; Blaxton et al., 1996; Buckner & Koutstaal, 1998; Buckner, Koutstaal, Schacter, & Rosen, 2000; Buckner et al., 1995; James, Humphrey, Gati, Menon, & Goodale, 1999; Naccache & Dehaene, 2001a, 2001b; Squire et al., 1992).

In repetition priming, the orthographic, phonological, and semantic aspects of the words are identical, and therefore priming related changes would be expected in all of these stages of word processing. In semantic priming, the orthographic and phonological aspects of the pairs of words are different, but the words share semantic attributes, hence the priming related changes would be expected mainly in the semantic processing stage(s) and in those regions subserving semantic processing. The current study used a semantic priming paradigm in conjunction with an event-related fMRI design using auditory words. We hypothesized that semantic priming would result in decreases in activity in those regions that were involved in semantic processing and that these regions would be located predominately in temporal/inferior parietal regions. The experiment also manipulated levels of semantic priming in different groups of word pairs to identify regions whose activation levels varied with priming. Lexical activation is thought to vary as a function of the connectivity between associates of the word (Nelson, Bennett, Gee, Schreiber, & McKinney, 1993). Nelson and colleagues have developed a large pool of words from extensive normative studies, each with, among other variables, quantitative values representative of the connectivity between semantic associates (see Fig. 1). The mean connectivity of the word dinner would be computed by summing the number of connections between each associate (17) and dividing by the number of associates (5) resulting in a connectivity score of 3.4. The word dog has only 1 connection between its associates, resulting in a connectivity score of 1/5 or 0.20. Memory studies of words drawn from this large pool have consistently demonstrated the
2. Materials and methods

2.1. Subjects

Thirteen right-handed healthy controls (9 males, 4 females) between the ages of 21 and 28 (mean = 24 years) participated in the study. All were right handed, native speakers of English with no reported hearing abnormalities. Subjects were fully informed of the procedures and signed written consent forms before the study began. An additional 4 male subjects (average age = 30) were also run using two counterbalanced versions of the word list (see below for details).

2.2. Stimuli

Words were selected from the University of South Florida word association, rhyme, and word fragment norms (http://www.usf.edu/Freassocation) developed by Nelson, McEvoy, and Schreiber (1998). For the connectivity measures reported in the database, first the associates of each word were tabulated. An associate word would be counted as such if it were given as a response to a particular target word by (at least two) subjects during performance of the free association task. So if the word “cat” was given as a free association response to “dog,” then the word cat would be counted as one associate. Another couple of subjects might produce the word animal in response to dog and then animal would be added to the list of associates of dog and so on. Then the associates of each word were then normed in terms of interconnections between them using a different group of respondents or subjects. For example, if a few subjects produced the word animal in response to cat, then a connection would be assumed to exist between these two associates of the word dog. High and low connectivity words for this study were chosen according to the methodology described in Nelson et al. (1993). Stimuli consisted of 48 pairs of unrelated words, 48 pairs of related words (24 high connectivity, 24 low connectivity), and 12 pairs of a word followed by a pronounceable non-word. All words were spoken by a female and recorded using a sound editor (Sound Forge XP, Sonic Foundry, Madison, Wisconsin), and stored as wave files on a personal computer. Stimulus word pairs within each related condition were matched in terms of the strength of forward association between the cue and target (mean forward strength = .53 for high and low pairs; t(46) = -.047; p = .168). Words in all conditions were matched in terms of frequency, number of syllables, and length or number of letters, and familiarity as found in the MRC Psycholinguistic Database (http://www.psy.uwa.edu.au). An additional set of 4 subjects (ages 22–43, average 33) were run using a modified word list where either the prime or target words in the high and low connectivity condition were paired in the new list to make unrelated word pairs. The two resulting counterbalanced word lists were used as an additional control for any differences in words between conditions. This manipulation resulted in an AB word list used for 2 subjects and a CD word list used for 2 subjects.

2.3. General procedures for an fMRI session

Subjects were placed in the magnet with the head held within an air-filled VAC-FIX (S&S X-Ray Products, Brooklyn, NY) cushion that inflates to conform to head shape to secure against movement. Tape was then placed across the forehead and the chin. A signal indicating the application of RF pulses by the functional pulse sequence was used to trigger the stimulus presentation program and response collection program (Neurobehavioral System’s Presentation software http://www.neurobiologysystems.com). Words were presented through sound-insulated earphones (Silent Scan, Avotec, Jensen Beach, FL) at a DB level of 80 db. The PC collected responses via a fiber optic button box that is held by the subject while in the magnet. The button box was connected to an interface for the PC that allows for the collection of response time and frequency data (Current Designs, Philadelphia, PA).

2.4. fMRI imaging methodology

2.4.1. Image acquisition

All images were acquired at the Brigham and Women’s Hospital using a GE 1.5 Tesla Signa System with a HORIZON hardware/software package (GE Medical Systems, Milwaukee, WI). Anatomical images were acquired following initial sagittal localizer scans. The coronal (oblique) spoiled-gradient-recalled (SPGR) images were taken using the same slice thickness and in the same location and plane as the functional images using the following parameters: TE = 5 ms, TR = 35 ms, one repetition, nutation angle = 45°, FOV = 24 cm, matrix = 256 x 192, slice thickness = 6 mm. The images are acquired perpendicular to the line of the superior temporal sulcus. The 24 slices covered the majority of the brain for most subjects. The images were prescribed to include all of the frontal lobe so that if any
According to Forman et al. (1995), to investigate further, characterized in terms of spatial extent and peak height for each voxel (SPM_t). The maps were thresholded to produce statistical parametric maps of the brain areas producing significant effects that might be induced by blocking the stimuli into related and unrelated blocks. Stimulus trial types were randomly intermixed with the constraint that each run contained 24 related (12 high connectivity, 12 low connectivity), 24 unrelated word pairs, 6 non-word-pairs, and 12 null events or trials in which no stimulus pairs were presented.

2.4.2. fMRI priming study

Before entering the magnet, subjects correctly responded to six practice trials, (two unrelated, two related, and two word-non-word pairs). Subjects were required only to respond to non-words (instead of pushing one button for non-words and one for words) to eliminate any response related effects from the activation to related and unrelated word pairs (in an attempt to better isolate processes only related to semantic activation). Two continuous fMRI runs were used. For each run, stimuli were presented in an event-related paradigm with an inter-trial interval of 8 s between the start of each word pair. For each word pair, the time between the start of the first word and the start of the second word of the pair or stimulus onset asynchrony (SOA) was 750 ms. The words are presented aurally, so that the average time between the end of the first word and the beginning of the second word of the pair was 214 ms. The event-related fMRI design protected against strategic effects that might be induced by blocking the stimuli into related and unrelated blocks. Stimulus trial types were randomly intermixed with the constraint that each run contained 24 related (12 high connectivity, 12 low connectivity), 24 unrelated word pairs, 6 non-word-pairs, and 12 null events or trials in which no stimulus pairs were presented.

2.4.3. Data analyses

The event-related fMRI data were analyzed using the SPM99 software package (Wellcome Department of Cognitive Neurology, London, UK). fMRI images were realigned to the first functional image (after initial five scans are deleted) to correct for head movement between scans. All images were then spatially normalized into a standard space (Talairach & Tournoux, 1988) using nonlinear three-dimensional transformations. Each image was then smoothed using an isotropic Gaussian kernel of 6-mm FWHM to accommodate inter-subject differences in anatomy. Condition effects were estimated according to the general linear model at each voxel in brain space with global intensity normalization. Linear contrasts tested the hypotheses that produced statistical parametric maps of the _t_ statistic for each voxel (SPM_t). The maps were thresholded to _p_ < .0001 for the group analyses, and the resulting foci were characterized in terms of spatial extent and peak height according to Forman et al. (1995). To investigate further regions showing variations with regard to the differences in word pair connectivity of the related trials, simple regression or correlation analyses (with the relative connectivity of the word pair trials: high = 1, low = 2, and unrelated = 3 entered as covariates) were performed for each subject. The resulting SPM_t contrast maps tested which brain areas showed significant variance correlating with these priming conditions (see Buchel, Wise, Mummery, Poline, & Friston, 1996). For each subject, contrast maps were analyzed in 2nd level analyses to characterize the group effects.

2.4.4. Behavioral priming study

Six additional subjects, 2 male and 4 female (average age 32 years) were studied in a separate behavioral version of the semantic priming task using the same paradigm and words as in the current study. Because stimulus repetition within a subject would produce repetition priming, the subjects were not those used in the fMRI study. Stimulus pairs were presented aurally and subjects made a speeded lexical decision to the second stimulus by pressing a “yes” button for a word, and a “no” button for a non-word (the yes response was not required for the fMRI experiment, these subjects were only required to press the button for non-words). Subjects were instructed to respond as quickly and accurately as possible.

3. Results

3.1. Behavioral priming study

Subjects obtained an overall accuracy of 92% correct on the lexical decision task. As expected, all subjects showed significant priming effects with the related word pairs that were modulated by levels of connectivity and relatedness such that high connectivity pairs showed the most priming, low connectivity pairs showed moderate levels of priming, and unrelated word pairs showed no priming (see Fig. 2). The mean difference in response latencies between related and unrelated word pairs was highly significant (mean difference = 198 ms; _t_ = 10.55; _df_ = 5; _p_ < .0001). Within the related condition, mean response latencies for high connectivity word pairs were shorter than response latencies for low connectivity and unrelated word pairs.

![Fig. 2. A graph of average behavioral reaction time measures (plus the standard error of the mean + SEM) during the lexical decision task for high connectivity, low connectivity, and unrelated word pairs.](image-url)
low connectivity word pairs (average difference = 165 ms) that were in turn shorter than response latencies for unrelated words (mean difference = 116 ms) as indicated through a repeated measures linear contrast test ($F = 67.86; \text{df} = 1; p < .0001$).

3.2. fMRI study

For the fMRI study, subjects were only required to push a button for the 12 non-word pairs. Subjects correctly responded to the non-words with an accuracy of 83% and correctly omitted a response to the word–word pairs on 98% of the trials. fMRI analyses also showed significant differences as a function of the relatedness of word pairs. Contrasts of unrelated versus related conditions (collapsed over high and low connectivity) revealed relative reductions in fMRI activity to related word pairs in left inferior frontal, bilateral anterior cingulate/supplementary motor areas (the peak of the cluster was in the right hemisphere, but it extended bilaterally), and temporal regions, including clusters in posterior superior and middle, and more anterior temporal regions. As predicted, no temporal lobe regions showed greater activity in the related than unrelated condition; the only region showing greater activity in the related condition was the precuneus region ($x = -4, y = -34, z = 46$). Fig. 3 shows the activation for all subjects in the 3 priming conditions versus the baseline or null condition, the fMRI/semantic priming pattern revealed relatively increased activity to unrelated word pairs, less activity to the related, low connectivity word pairs, and even less activity to the related, high connectivity word pairs. In addition, a correlation analysis was performed using SPM99 to test for modulation of activity due to priming level (e.g., high connectivity < low connectivity < unrelated). The results of this analysis showed that bilateral lateral temporal lobe activity (mostly in the posterior superior and middle temporal regions) was significantly modulated by the level of connectivity/priming as shown in Fig. 4 and Table 1. A contrast showing regions whose activity was modulated by word-pair type (null events < high connectivity < low connectivity < unrelated word pairs) also confirmed the involvement of the posterior superior/middle temporal region (bilaterally). Fig. 5 shows that the two counterbalanced word lists (AB and CD) showed similar results to those shown in Fig. 3.

4. Discussion

In the behavioral priming experiment, reaction time was fastest for word pairs of high connectivity, intermediate for those with low connectivity, and slowest for unrelated word pairs. This result was predicted by the hypothesis that levels of semantic priming would vary as a function of connectivity with the highest levels of semantic priming occurring for pairs of high connectivity and no semantic priming for unrelated word pairs. The idea of interconnectivity between concepts has been used to explain many phenomena in memory research and is a fundamental feature of most cognitive memory models (see Nelson et al., 1993 for a discussion). For example, connectivity between the associates of a word has been shown to affect recall, even when semantic relatedness is held constant (Nelson et al., 1993).

Manipulating the levels of semantic priming allowed us to identify regions whose activity also varied with priming. Also as predicted, lateral temporal lobe fMRI activation systematically declined as the semantic priming of the word pairs increased: related, high connectivity word pairs showed the least amount of activation, related low connectivity words showed slightly more, and unrelated word pairs showed the most activity. Thus, semantic priming, as reflected in faster, more efficient processing of related word pairs, corresponded to decreased temporal lobe activity.

Activation in the lateral middle and posterior superior temporal regions showed modulation with levels of priming, providing converging evidence for the involvement of these regions in lexical–semantic processing. This is a supposition that is generally well supported in studies of neurologically impaired individuals and in those using brain stimulation as we will discuss below. The large body of neuroimaging studies of semantic processing whose results do not support temporal lobe involvement tend to use designs that emphasize the metalinguistic aspects of
language processing and that require subjects to attend and respond to specific features of words (e.g., rhyme judgement versus semantic judgement). Under these conditions, the automatic semantic activation to words may be largely subtracted out of critical contrasts.

In general, priming studies (that are predicated on the assumption that semantic activation is automatic) and other neuroimaging studies where the metalinguistic demands of the task are kept to a minimum do converge with lesion and stimulation studies in finding a role for the temporal lobe in semantic processing (e.g., Copland et al., 2003; Crinion, Lambon-Ralph, Warburton, Howard, & Wise, 2003; Giesbrecht, Camblin, & Swaab, 2004; Kotz, Cappa, von Cramon, & Friederici, 2002; Matsumoto, Idaka, Haneda, Okada, & Sadato, 2005; Rissman, Eliassen, & Blumstein, 2003; Rossell, Price, & Nobre, 2003; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). For example, Rissman et al. (2003) used a semantic priming task in conjunction with event-related fMRI. Priming related decreases in activation were found in the left superior temporal region and in bilateral middle temporal gyri; results that are very similar to our findings.

In the following section we will discuss general frameworks for auditory speech perception and semantic processing and the evidence for the involvement of posterior superior and lateral temporal regions in these functions. Although there is much convergence in the literature, there are key points of disagreement between researchers that effect the interpretation of our results.

Research with neurologically impaired individuals shows that impairments in semantic processing can, to some extent, be dissociated from other stages of linguistic processing. However, psychological theories of language differ in terms of the number of stages, the type of information represented in each stage, and the interactivity of the stages (see Caramazza, Papagno, & Ruml, 2000 for a critical review). In many models, the speech signal is thought to concurrently activate candidate auditory word forms that compete for recognition, subsequently activating corresponding semantic representations (see Cutler & Clifton, 1999). These same phonological and lexical–semantic representations used in perception are also thought to be activated in speech production, but in a reverse order (see Indefrey & Levelt, 2004). Semantic representations themselves may also concurrently activate all of the phonological lexical items that share a conceptual feature (Caramazza & Miozzo, 1997). So semantic priming could theoretically produce priming related decreases in regions housing both phonological word forms and lexical–semantic representations as was proposed in (Matsumoto et al., 2005). If these suppositions are true, then the results from the

### Table 1

<table>
<thead>
<tr>
<th>Stereotaxic coordinates</th>
<th>Anatomical region approximate Brodmann’s areas</th>
<th>Peak Z score (number of voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Y Z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated &gt; Related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>–48 –22 10</td>
<td>Left lateral temporal (superior/posterior) 21/22</td>
<td>4.26 (80)</td>
</tr>
<tr>
<td>–64 –24 0</td>
<td>Left lateral temporal 21/22</td>
<td>4.37 (126)</td>
</tr>
<tr>
<td>–56 –2 14</td>
<td>Left lateral temporal (anterior)</td>
<td>4.27 (51)</td>
</tr>
<tr>
<td>6 20 46</td>
<td>Anterior cingulate/SMA</td>
<td>4.86 (857)</td>
</tr>
<tr>
<td>–46 24 2</td>
<td>Left inferior frontal</td>
<td>4.62 (492)</td>
</tr>
<tr>
<td>Related &gt; unrelated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>–4 –34 48</td>
<td>Superior parietal/precuneus 7</td>
<td>4.69 (65)</td>
</tr>
<tr>
<td>Correlation analysis: High connectivity &lt; low connectivity &lt; unrelated word pairs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62 –20 –8</td>
<td>Right lateral temporal regions (BA 39, 42, 22/21)</td>
<td>5.84 (956)</td>
</tr>
<tr>
<td>–38 –32 6</td>
<td>Left lateral temporal regions (BA 39, 42, 22/21)</td>
<td>5.34 (657)</td>
</tr>
<tr>
<td>0 10 48</td>
<td>Supplementary motor area (BA 6)</td>
<td>5.06 (139)</td>
</tr>
</tbody>
</table>

Fig. 5. Single subject data showing that the two counterbalanced word lists resulted in activation patterns that were consistent with the group data reported (T values range from 5 (dark red) to 14 (white); p < .05 corrected).
semantic priming task cannot distinguish between changes in the activation of phonological representations and changes in the activation of semantic representations due to semantic priming.

In the following section we will turn to evidence for the relationship between semantic and phonological language functions and brain regions. We will focus on the evidence concerning the functional roles of the posterior superior temporal and middle temporal regions. Individual studies as well as recently completed meta-analyses or reviews of lesion and stimulation studies (as well as some functional imaging studies) of speech comprehension and production show a remarkable convergence in terms of the identification of the regions involved in lexical–semantic processing. Hickok and Poeppel (2000) propose that sound based speech representations are processed in bilateral posterior superior temporal regions. These sound representations then make contact with an auditory-conceptual interface in the temporal-occipital-parietal junction of the left hemisphere that acts to connect the sound based speech representations with widely distributed conceptual representations (see also Alexander, Benson, & Stuss, 1989; Binder & Price, 2001; Hart & Gordon, 1990). However, some researchers question the existence of the phonological word form area and there is also disagreement regarding the brain regions involved (see Price, Winterburn, Giraud, Moore, & Noppeney, 2003 for a discussion).

The middle temporal gyrus has been shown in three recently published comprehensive studies to be involved in lexical–semantic representation. An extensive meta-analysis of language production and comprehension studies concluded that the middle temporal region was involved in conceptually driven lexical selection (see Indefrey & Levelt, 2004). A study of 101 patients with left hemisphere damage found that comprehension was most affected by lesions of the middle temporal gyrus (Bates et al., 2003; see also Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). A comprehensive review of results from cortical stimulation and hemispheric anesthetization studies concluded that auditory comprehension was disrupted from stimulation of the posterior superior temporal region as well as the middle and inferior temporal gyri, among other areas (Boatman, 2004).

Although there is a convergence of evidence for the role of the posterior superior temporal and left middle temporal regions in phonological and lexical–semantic representation from these studies, the exact nature of the processing or type of representations involved and a clear delineation or dissociation of the roles for these regions has not been forthcoming. To quote Dronkers et al. (2004) “These findings all provide evidence that the posterior temporal lobe is needed for word level comprehension. Whether it is specifically the conceptual-semantic side, the phonological form side, or the actual linking between form and concept is unclear.”

The nature of the interface between phonological and semantic representations and the organization of semantic information have both been a subject of some controversy, adding to the difficulty in understanding the role of the middle temporal gyrus. Does the middle temporal activation seen in the present study reflect the activation of semantic representations per se? Indefrey and Levelt (2004) claim that this region is involved in conceptually driven lexical selection, but not in conceptual representation. Damasio et al. (1996) claimed that the middle temporal region (along with more inferior temporal regions) contained categorically organized amodal representations or mediators between modality specific word forms and semantic information. However, the idea of an amodal mediating representation is controversial (Caramazza, 1996, 1997, 2000), especially with regard to formulations where the amodal or lemma representation also contains information about grammatical category (e.g., Indefrey & Levelt, 2004).

In summary, there is some debate about whether the posterior superior temporal region represents phonological word forms or some type of link between word forms and semantic representations. In addition, although there is a consensus that the middle temporal region is involved in semantic processing, there is debate as to the exact nature of the representations, with many researchers claiming that the semantic representations are not stored there.

Many researchers do agree that semantic representations themselves are organized categorically and stored in widely distributed posterior (temporal and possibly parietal) regions (e.g., Tranel, Damasio, & Damasio, 1997), but they disagree about the structure of the semantic system (see Caramazza, 1996; Caramazza and Shelton, 1998; Safran and Scholl, 1999; Thompson-Schill, D’Esposito, and Kan, 1999; Shelton and Caramazza, 1999). If the semantic representations are widely distributed and organized by category, then it is possible that fMRI technology would not detect the activation of individual semantic representations. If each word creates a different constellation of distributed activated regions, then summing the activation over words would only show activity in regions where the representations converge, but not in those regions representing the distributed semantic information itself. In other words, over trials there may not be enough activity in any one group of distributed regions to contribute to significant activation. As discussed previously, studies examining single unit responses to linguistic stimuli in the human lateral temporal lobes (of both hemispheres) show much more extensive responsiveness to stimuli than is usually reported in functional imaging studies, lending credence to this argument (see Ojemann et al., 2002a, 2002b).

In summary, converging evidence from a broad literature shows that the posterior superior temporal and middle temporal regions act in concert to mediate phonological lexical–semantic processing at the single word level. However, the interpretation of neuroimaging results regarding semantic processing are hampered by a lack of agreement regarding the processing stages, the type of representations involved in lexical–semantic processing, and regarding the organizational structure of semantic representations.
We identified a lateral temporal region whose activity was modulated by levels of semantic priming, and in addition, found that unrelated word pairs produced greater activity than related word pairs in left inferior frontal, and anterior cingulate/supplementary motor areas, and lateral temporal regions. Table 2 summarizes the overlap of results from event-related priming studies for these regions for the unrelated minus related contrast and shows that the priming related reductions in activity found in our study have been replicated in a number of the semantic priming neuro-imaging studies. However, none of the individual studies showed priming related decreases in all of these regions (Copland et al., 2003; Kotz et al., 2002; Matsumoto et al., 2005; Rissman et al., 2003; Giesbrecht et al., 2004; Rossell et al., 2003) and some studies have shown priming related increases in activity (e.g., Kotz et al., 2002; Rossell et al., 2003). Studies using block designs (Mummery, Shallice, & Price, 1999; Rossell, Bullmore, Williams, & David, 2001) or repeated stimuli within subjects (Rossell et al., 2001), although valuable for examining lexical decision, preclude the examination of priming related decreases to specific word pairs. However, our findings did show considerable overlap with these studies in terms of regions activated in the lexical decision task, especially with the Mummery et al. (1999) paper.

As discussed above, the inferior frontal cortex and anterior cingulate showed decreased activity to related word pairs relative to unrelated word pairs, findings replicated in other event-related semantic priming studies and other studies manipulating semantic relationships among words (e.g., Matsumoto et al., 2005; Mummery et al., 1999; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997). These activations were somewhat surprising to us given that these regions are usually implicated in strategic or effortful processing and that our task should not require these processes. Neither the cingulate nor the inferior frontal cortex are thought to store semantic representations (Grodzinsky, Pinango, Zurif, & Drai, 1999; Mohr et al., 1978; Sylvester & Shimamura, 2002) with the possible exception of verbs for the frontal lobe (Hillis, Wityk, Barker, & Caramazza, 2003; Tranel, 2001). However, in addition to differing in terms of semantic activation, the unrelated and related semantic priming conditions may have differed in terms of the difficulty of the lexical decision judgment, the attentional demands, the level of response conflict, or the type of strategies used to make the lexical decision such as the degree of subvocal repetition of the words. These factors could account for the cingulate/frontal activations. Both regions are involved in and sometimes co-activated during language tasks (Alexander, 2002; Boatman, 2004; Bates et al., 2003; Indefrey & Levelt, 2004; Paus, Petrides, Evans, & Meyer, 1993; and see also MacLean & Newman, 1988; Jurgens & von Cramon, 1982).

The cingulate has also been thought to be involved in attention, orienting, error monitoring, and conflict resolution (e.g., Carter et al., 2000; Kiehl, Liddle, & Hopfinger, 2000; Mesulam, 1981; Posner, Petersen, Fox, & Raichle, 1988; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005). Inferior frontal regions have been hypothesized to be involved in the selection among competing alternatives (e.g., Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; Thompson-Schill et al., 1999, 1998), the executive control of retrieval from semantic memory (e.g., Demb et al., 1995; Gabrieli, Poldrack, & Desmond, 1998; Wagner, Koutstaal, Maril, Schacter, & Buckner, 2000; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001), the active maintenance and organization of information (e.g., D’Esposito & Postle, 2002), and the controlled retrieval and maintenance of information stored in posterior regions (Gold & Buckner, 2002, Gold, Balota, Kirchhoff, & Buckner, 2005; Shivde & Thompson-Schill, 2004).

In previously published semantic priming studies, the relative increases in activation in the unrelated condition was attributed to a greater level of response conflict for the cingulate activation (Matsumoto et al., 2005) and to increased selection demands for the frontal activation (Kotz et al., 2002; Matsumoto et al., 2005). A relative increase in frontal activation in the unrelated condition was also attributed to the retrieval of semantic information when the information cannot be accessed through strong preexisting associations (Copland et al., 2003). We believe that any of these theories could also explain our findings of increased cingulate and inferior frontal activation for unrelated word pairs and unfortunately, our data cannot help us to distinguish between alternative theories.

The right temporal lobe was also activated in our experiment and it is clear that it has some role in semantic processing. Neuronal recordings in human subjects during reading, naming and other tasks generally show equal numbers of cells active in right and left temporal regions (see Ojemann, 2003 for a review). There has been mixed

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Event-related neuroimaging studies of semantic priming: Regions showing semantic priming related decreases</th>
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<tbody>
<tr>
<td></td>
<td>Lateral, middle, inferior or anterior temporal lobe</td>
</tr>
<tr>
<td>Copland et al. (2003)</td>
<td>X (left MTG)</td>
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<tr>
<td>Giesbrecht et al. (2004)</td>
<td>X (left MTG)</td>
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<td>Kotz et al. (2002)</td>
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<td>Matsumoto et al. (2005)</td>
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<tr>
<td>Rissman et al. (2003)</td>
<td>X (bilateral MTG)</td>
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<tr>
<td>Rossell et al. (2003)</td>
<td>X (anterior medial temporal cortex)</td>
</tr>
</tbody>
</table>
evidence for the right hemisphere being more involved in metaphorical meaning, connotative meaning, or the processing of abstract semantic concepts (e.g., Bottini et al., 1994; Brownell, Simpson, Bihrlr, Potter, & Gardner, 1990; see Gagnon, Goulet, Giroux, & Joanette, 2003; Larsen, Baynes, & Swick, 2004 for discussions). There are also reports that certain categories of semantic information are bilaterally represented in the temporal lobes (e.g., Tranel et al., 1997).

In summary, there is much evidence that right temporal regions participate in semantic processing and our finding of right temporal involvement is broadly consistent with this body of literature. The Hickok and Poeppel (2000) model of language processing posits a special role for the left hemisphere in the interface between auditory word forms and conceptual representations. There are several remaining lexico-semantic functions that could be localized in right and/or bilateral temporal regions.

In a final note, it is important to address issues regarding some important limitations of the sensitivity of neuroimaging techniques used here in the study of semantic processing. First, because the time course of fMRI activation is relatively coarse with respect to the time course of neural activity, there may be changes other than decreases related to semantic priming that we simply cannot detect, such as transient increases or decreases in activity in response to priming (e.g., Dhond, Buckner, Dale, Marinkovic, & Halgren, 2001). It is also important to note that fMRI images also have artifacts in some ventral temporal and frontal regions that may be active during semantic priming but would not have been detected in the present experiment. Most notably, the entorhinal/perirhinal regions may be central to semantic processing and may not show activation in many fMRI experiments because of susceptibility artifact in and around those regions (see Devlin et al., 2000 for a discussion).

In summary, the present study parametrically manipulated semantic priming has identified a lateral/middle temporal region whose activity was modulated by levels of semantic priming. Our findings demonstrate that when the automatic nature of semantic processing is taken into account, neuroimaging studies can produce data that are in agreement with conclusions based on lesion analysis and stimulation studies. These results also add to converging evidence showing that semantic priming, like repetition priming, can result in relative decreases in activity. The results also have important implications for any studies using semantically related words in their experimental conditions. If the inter-stimulus interval is short enough, related words may produce un-hypothesized decreases in activation that are due to semantic priming, especially in temporal lobe regions.

Acknowledgments

This study was supported by an NIMH Grant: 1 R01 MH067080-01A1. The study was also supported in part by a Department of Veterans Affairs REAP Award (R.W.M.) a Veterans Affairs Merit Award (P.N. and M.H.N.), a grant from the National Institute of Health R01 MH 40799 (R.W.M.), and the MIND institute (Albuquerque, NM—R.W.M.).

Appendix A. Supplementary data


References


