

An fMRI Study of Semantic Priming: Modulation of Brain Activity by Varying Semantic Distances

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Objective: Our purpose was to study the effect of semantic priming at varying semantic distances on brain activation during a lexical decision experiment, using functional magnetic resonance imaging (fMRI).

Background: Neuroimaging studies have demonstrated decreased brain activation for primed versus unprimed stimuli in language areas due to semantic priming, suggesting facilitated semantic retrieval. However, the effect of varying semantic distances on brain activation has not been studied. Therefore we examined direct and indirect priming effects on cerebral activation to provide information regarding spread of activation in the semantic network.

Methods: Participants were presented with closely, distantly, and unrelated word pairs during fMRI, and asked to make a lexical decision on the second word.

Results: Behavioral measurements demonstrated significant priming effects for all semantic distances. Imaging results showed modulation of brain activation due to different semantic relationships in the left inferior frontal gyrus, bilateral middle frontal gyrus and anterior temporal lobe, and consisted of decreased magnitude of activation when primed stimuli were processed compared with unprimed stimuli, with the greatest effect observed for closely related words.

Conclusions: This study demonstrates graduated effects of semantic priming on fMRI in semantic but not attentional brain regions, contributing to explain how semantic knowledge is organized and retrieved. These findings support the network model for organization of the semantic lexicon.

Key Words: functional MRI, direct priming, indirect priming, lexical decision, semantic network

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Semantic priming is the facilitation of the response to a target word when it follows a semantically related prime and can be explained in terms of a network model of organization of the lexicon.^{1,2} This model assumes that activation of the prime will serve as a source of spreading activation in the network, lowering the threshold for neighboring nodes. Therefore, related targets (closer nodes) will be recognized faster because they are already activated to some degree. Support for such a model is provided by lexical decision experiments. Typically, a briefly presented prime word is followed by a target letter string which may be a real word or a nonword (NW), and participants are asked to make a decision about the target (is it a real word or not?). The real word target may be either related or unrelated to the prime, and priming effects are quantified by comparing the response times (RTs) to the target in different semantic relationship conditions.

Information regarding the spread and activation of the semantic network can be obtained by varying the semantic distance between the prime and the target word, as well as by manipulating the time between the presentation of the prime and target, also known as the stimulus onset asynchrony (SOA).^{2,3} Different levels of association between the prime and target word can yield differential semantic priming effects. The strongest effect is observed when the target word is closely related to the prime (direct priming). A weaker effect is observed for mediated (or indirect) priming, when the prime and target are not directly associated, but are both related to another word that establishes the link between them (eg, *lion-stripes*, mediating word is *tiger*). By varying the SOA, automatic versus controlled processing can also be examined. It has been suggested that processing is automatic at a short SOA (less than 250 ms), whereas longer SOAs allow additional mechanisms, such as expectancy and strategy, to be used, which result in more controlled processing.²⁻⁴

Behavioral studies of semantic priming have attempted to examine the spread and flexibility of the semantic network, both in normal and neurologically impaired individuals.^{3,5-9} In these studies, lexical decision experiments have been used to examine the effect of both SOA and of different semantic distances. In normal

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individuals, a direct priming effect seems to be independent of SOA although mediated priming is more evident at longer SOAs. The effect of L-Dopa on semantic priming has also been examined.^{3,5} In a study by Kischka et al.,³ healthy volunteers were tested in a lexical decision paradigm after administration of either L-Dopa or placebo. The main finding of this study was a reduction of the indirect semantic priming in the L-Dopa treatment group. Similar methodology by other researchers revealed significant direct and indirect priming at SOAs of 250 and 500 ms in the placebo group whereas in the L-Dopa group a significant priming effect was found only at an SOA of 250 ms.⁵ These studies suggest that dopamine has a role in modulating the spread of semantic processing, increasing the focus of activation in the semantic network, therefore restricting the access to distant nodes. This has been supported by semantic priming experiments in schizophrenic patients.^{8,9} However, semantic priming in patients with Parkinson disease has yielded mixed results.^{6,7}

Event-related potential studies have provided electrophysiologic evidence of the priming effect. The semantic priming effect is reflected in a decrease in amplitude of the N400 component when related prime-target pairs are processed compared with unrelated pairs, and may also begin to reveal the time course of the priming effects.¹⁰

Functional neuroimaging studies of priming have commonly shown a decrease in brain activation for primed versus unprimed stimuli.^{4,11-14} Although attempts to anatomically localize the processes involved in semantic priming have so far yielded inconsistent results, several common findings have been shown. During automatic processing, reduced brain activity for related versus unrelated word pairs has been observed in the left inferior frontal gyrus (LIFG),¹¹⁻¹³ a region identified in numerous neuroimaging studies as critical for retrieval, selection, and evaluation of semantic information.¹⁵⁻¹⁹ Neuroimaging studies have also found similar behavior in more posterior brain structures such as the superior and middle temporal gyri.^{4,11-14} It has been suggested that these regions play a role in semantic memory and storage of semantic representations.^{11,14} In addition, bilateral activation in the middle frontal gyrus (MFG) modulated by priming effects, has been demonstrated^{12,14} and is proposed to be the result of an extensive search of the semantic network, and retrieval effort.^{12,20}

It has been suggested that pure automatic processing should yield priming effects in "semantic" areas of the brain, whereas controlled processing should also implicate an additional "attentional" network.^{4,13} Activation in the anterior cingulate cortex (ACC),^{4,13} superior parietal lobe and right premotor cortex¹³ is believed to reflect the involvement of these areas in the attentional aspects of semantic priming.

In the light of these previous inconsistent findings we aimed to expand the current understanding of brain regions involved in semantic priming. Moreover, considering the results of the behavioral priming experiment described previously by Kischka et al.,³ showing signifi-

cant direct and indirect priming effects in normal volunteers under the placebo condition, we wished to establish the effect of semantic priming at 3 varying semantic distances on cerebral activation of the language areas. This effect of varying semantic distances for the lexical decision experiment has not been explored in functional neuroimaging studies before. We describe a functional magnetic resonance imaging (fMRI) experiment, using closely, distantly, and unrelated word pairs in a lexical decision paradigm. Because we used a relatively long SOA (700 ms), we predicted a complex pattern of brain activation due to the controlled semantic priming processing. We expected to find activation in semantic and attentional regions of the brain as described above. We hypothesized that activation in semantic areas would be modulated by priming, due to the effort necessary to access and retrieve information from semantic memory. Specifically, we anticipated an increase in brain activation during unrelated word pair processing, compared with related word pairs at 2 different levels of association, direct and indirect. We also expected a difference in activation for the intermediate semantic relationship, that is, processing closely related pairs would yield less activation than processing distantly related pairs.

MATERIALS AND METHODS

Research Participants

Twelve right-handed native English speakers (6 female; mean age 25.8y; range 19 to 32y; average school education 15y) participated. None of the participants had a history of psychiatric or neurologic problems, or of learning disabilities such as dyslexia. Participants reported normal or corrected-to-normal vision. Written consent was obtained from all participants in accordance with the regulations of the Institutional Review Board of The Ohio State University.

Priming Paradigm

A total of 140 prime-target word pairs were presented. The majority of the words were nouns but also included verbs, adjectives, and adverbs. All of the prime words were real English words. The target words included 100 real words and 40 pronounceable NW letter strings. The prime-target pairs were categorized according to an associative semantic relationship as defined by Kischka et al.³: for 25 of the real word pairs the target was closely (C) related to the prime (one associative step apart: eg, *farmer-field*), for another 25 pairs the target was distantly (D) related to the prime (two associative steps apart: eg, *summer-snow*; the connection between prime and target is obvious only through a mediating associated word, in this case *winter*) and for 50 word pairs the target was unrelated (U) to the prime (eg, *water-computer*). In this type of association the prime and the target can be from same semantic category (*doctor-nurse*) or can be associated with each other but from different semantic categories (*rake-leaf*, where the relationship is not that both words are from the same category but rather are

commonly coassociated: “*Rake the leaves*”). There was no significant difference in the distribution of the non-nouns (verbs, adjectives, and adverbs) among the different semantic conditions. Some of the word pairs were provided by Kischka et al, while the remaining words were constructed by the authors based on the norms from Kischka et al described above. The lists were tested on a small number of volunteers in a lexical decision experiment, and the differential RT to each category (shorter RT for the closely related, longer RT for distantly related and even longer for unrelated word pairs) confirmed the appropriate assignment of word pairs to each category.

All words and NWs consisted of between 3 and 7 letters, with an average word length of 5.06 letters. There were no significant differences between the 3 conditions (C, D, U) for common variables such as written word frequency, concreteness, and imageability (MRC Psycholinguistic Database, http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). The words were presented one at a time on the center of a screen using SuperLab experiment generator software (Version 2.0, Cedrus Corp, San Pedro, CA). Participants were able to see the screen through a mirror mounted on the head coil. During the presentation of the targets, participants were instructed to indicate whether each was a real word or not (yes for C, D, and U pairs; no for NW pairs) as quickly as possible, by pressing the appropriate button on an fMRI-compatible response system (Lumina LP 400, Cedrus Corp, San Pedro, CA). RTs and accuracy were recorded using SuperLab.

Although a randomized presentation of the 4 types of word pair stimuli would be ideal for this type of experiment, we wished to maximize the magnetic resonance signal by using a block design. Nevertheless, a pseudo-randomization was achieved by the random incorporation of NWs within blocks and by alternating the blocks containing different semantic conditions. For this experiment, 10 task blocks were interleaved with 11 rest blocks. Each rest block (a fixation point in the center of the screen) was 15 seconds long, whereas each task block was 21 seconds long and consisted of 5 word pairs of either closely, distantly, or unrelated word pairs and 2 randomly placed NW pairs. The presentation of each word pair was as follows: the prime word was presented for 400 ms followed by a plus sign (+) for 300 ms, and then the target word (either a real word or a NW) for 1.3 seconds. A blank screen (1 s) separated each of the word pairs.

Two fMRI runs were performed: one consisting of alternating epochs of closely related word pairs and unrelated word pairs and the other of distantly related and unrelated word pairs. To avoid order effects, task epochs were counterbalanced both within runs and between runs as follows: one quarter of the participants saw the blocks of stimuli in a CUCUCU...DUDUDU... order, one quarter saw UCUCUC...UDUDUD..., one quarter DUDUDU...CUCUCU..., and one quarter UDUDUD...UCUCUC.... A practice trial was performed inside the scanner, before data acquisition, until

participants were comfortable with the task and the scanner conditions. These word pairs were not reused during the actual experiment.

Imaging Data Acquisition

Images were collected with a 1.5T General Electric (Milwaukee, WI) Signa scanner equipped with a quadrature head coil. Structural T1-weighted images were acquired for anatomic localization and coregistration, using the 3D FAST SPGR pulse sequence (256 × 128 matrix; 240 mm FOV; 60 axial slices; 2.5 mm slice thickness). GE's EPIBOLD/EPIRECON tools were used to collect and reconstruct off-line the BOLD contrast functional data (gradient echo EPI sequence; TR = 3 s; TE = 40 ms; 90-degree flip angle; in-plane resolution 3.75 × 3.75 mm; matrix 64 × 64, 28 axial slices for whole brain coverage; 5 mm slice thickness). Total time for the functional scans was 6 minutes 24 seconds. The first 3 image volumes were acquired to allow stabilization of longitudinal magnetization, and were discarded before data analysis.

Imaging Data Analysis

The imaging data were analyzed using FSL,²¹ and AFNI²² software. Prestatistics processing was performed using FSL and consisted of motion correction,²³ nonbrain signal removal,²⁴ Gaussian spatial smoothing (full-width half maximum = 5 mm), intensity normalization of all volumes by the same factor, and high-pass temporal filtering.

Average Group Activation Maps

To identify the areas of the brain activated by the lexical decision paradigm individual and group analyses were performed. Statistical analysis was carried out by first using FILM (FMRIB's Improved Linear Model, part of the FSL package) to create individual activation maps. For these, Z statistic images were obtained using cluster analysis with clusters determined by $Z > 3$ and a cluster significance threshold of $P = 0.05$.²⁵⁻²⁷ Registration to the Montreal Neurological Institute standard brain was then carried out.^{23,28} These registered Z-score maps were then used as input into a higher level analysis using FLAME (FMRIB's Local Analysis of Mixed Effects, part of the FSL package)²⁹ to generate average group maps of the brain regions activated by each of the tasks (C, D, and U word pairs), when compared with resting baseline. For the average group maps, Z statistic images were similarly created using cluster analysis with clusters determined by $Z > 3$ and a cluster significance threshold of $P = 0.05$.²⁵⁻²⁷

MR Signal Time Courses

Different regions of interest, commonly activated by the 3 types of stimuli, were identified from the group activation maps and further analysis was performed in order to better characterize the difference in activation between unrelated and related word pairs. Specifically, as a more sensitive measure, individual MR signal time

courses were examined. The preprocessed data sets were analyzed via cross-correlation with a boxcar function using AFNI.²² For each participant the different activated regions of the brain, either previously determined from the group maps or as reported in the literature were determined and labeled using specific anatomic landmarks. Then, the voxels with the highest correlation coefficients (> 0.3) in these regions were identified. The MR signal time courses for these voxels were extracted. The percent signal changes associated with the 3 different tasks (C, D, and U), normalized to the baseline rest condition, for each region of interest and for each participant, were examined via an analysis of variance (ANOVA), and post hoc Bonferroni comparisons were conducted in order to detect the priming effects.

RESULTS

Behavioral Data

Mean RTs and error rates were calculated for each participant and across subjects for each of the 3 semantic conditions. All response errors were removed and RTs below 200 ms and above 1000 ms were considered outliers and excluded from analysis. This resulted in the exclusion of less than 3% of the data. NW pairs were included in the design only to avoid a response bias during the task blocks. An analysis of the RTs for these pairs revealed that there was no significant difference among the NW trials between blocks, therefore their contribution cancelled when blocks were compared with each other. No further analysis was performed on these trials. To test for general effects of semantic priming on RTs, an ANOVA was performed with RT as the dependent variable. This analysis revealed a significant main effect for type (C, D, U) of semantic relationship [$F(2, 1158) = 26.735, P < 0.0005$]. Post hoc analyses using Bonferroni comparisons revealed significantly faster RTs for the closely related compared with unrelated targets, for distantly related compared with unrelated targets, and for closely compared with distantly related ones. These results are presented in Table 1. After the completion of the study, when they were told about the hypothesis, all subjects reported that they had not thought about any relationship between the words in the pairs.

Imaging Data

Average Group Activation Maps

Group activation maps obtained using FSL's cluster analysis for each of the 3 semantic conditions (C, D, U) compared with the resting baseline condition revealed

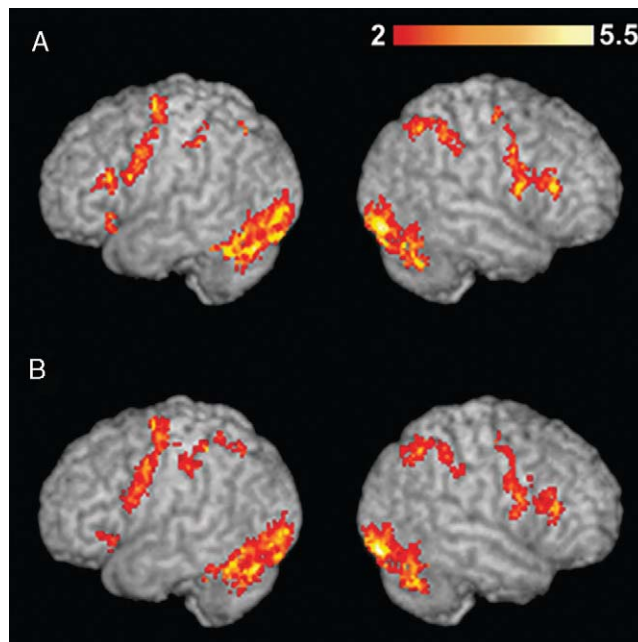


FIGURE 1. Group activation during CU/UC runs: A, Brain activation during unrelated (U) word pairs blocks compared with resting baseline; B, Brain activation during closely (C) related word pairs blocks compared with resting baseline.

brain activation in the anterior LIFG (BA44/45/47), bilaterally in the MFG (BA46/9), dorsal to and including the inferior frontal sulcus, insula, parietal cortex (BA7), and the anterior ACC (BA32/24). Visual, somatosensory, motor and premotor cortices were also activated due to visual presentation of stimuli and required motor response. The pattern of brain activation associated with the processing of closely related, distantly related, and unrelated word pairs is shown in Figures 1 and 2. The Montreal Neurological Institute coordinates for the peak activity in the regions showing a semantic priming effect are presented in Table 2.

MR Signal Time Courses

The ANOVA analysis of individual MR signal time courses for the voxels with the highest correlation coefficients in the above mentioned regions of the brain revealed a difference in activation during processing of the different word pairs (C, D, and U) in the LIFG and bilateral MFG. In addition, when individual MR signal time course analysis was carried out for other areas of the brain previously reported in literature as activated by

TABLE 1. Mean Response Times in Milliseconds and the Mean Priming Effects as Revealed by Bonferroni Multiple Comparisons

Semantic Relationship Between Prime and Target	RT (SD)		Mean Difference in RT (SD)	
C (closely related)	517 (61)	U vs. C	46.80 (7.8)	$P < 0.00005$
D (distantly related)	560 (66)	U vs. D	24.98 (6.8)	$P < 0.001$
U (unrelated)	586 (71)	D vs. C	21.81 (7.8)	$P < 0.01$

RT indicates response time; SD, standard deviations.

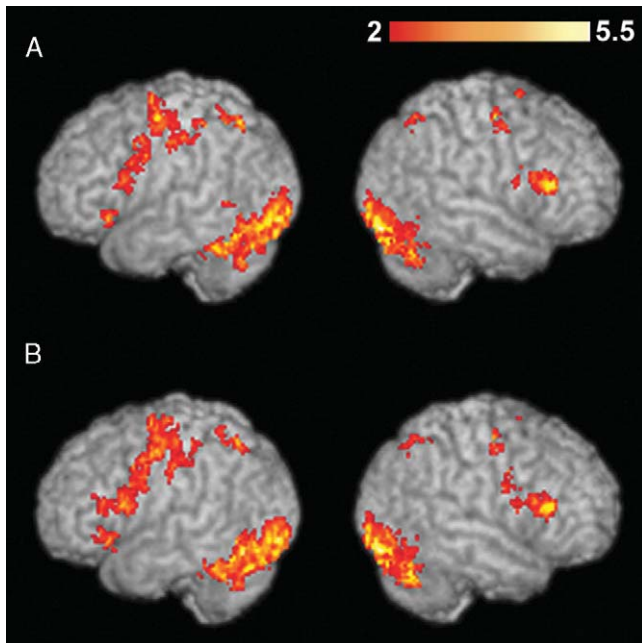


FIGURE 2. Group activation during DU/UD runs: A, Brain activation during unrelated (U) word pairs blocks compared with resting baseline; B, Brain activation during distantly (D) related word pairs blocks compared with resting baseline.

semantic priming paradigms,^{4,12,13} differential activation in the anterior temporal lobes (ATL) (BA 38) in both hemispheres was also detected.

Post hoc analyses were performed using Bonferroni comparisons and significant differences in the percent signal changes for direct and indirect priming were found. A decrease in BOLD signal change was observed when closely related word pairs were processed as compared with unrelated word pairs in the LIFG and bilaterally in the MFG and ATL. With the exception of the left ATL, an effect of the intermediate semantic relation (distantly vs. closely related) was also observed in these areas. In the left anterior ATL, the BOLD signal change for the unrelated word pairs was significantly larger than the signal during distantly related word pair processing (see Table 3).

DISCUSSION

The present study aimed to determine the neuroanatomic substrate of semantic priming, and the effect of varying semantic distances on this substrate, using fMRI during a lexical decision task.

Behavioral measurements demonstrated a significant priming effect for all semantic distances. Imaging results showed that semantic priming activates a complex brain system, which includes semantic areas and a proposed attentional network. Similar brain areas seem to be activated during all conditions, with differences between conditions observed in the magnitude of activation.

The use of a block design to increase the magnetic resonance signal could be considered a possible confounding factor for this experiment. However, we believe that strategic and expectation effects have been minimized by the random incorporation of NWs within blocks and by alternating the blocks containing different semantic conditions. This has been supported by the findings from our pilot studies and the behavioral results of this study, which demonstrated a significant priming effect with this paradigm design. It is also possible that the participants might have tried to evaluate the semantic distance between words in the pair, thus resulting in different RTs, faster when the relationship was immediately noticeable (closely related words). However, we suspect that this was not the case. Participants were told to only attend to the target, and decide if it is a word or not, and were not told anything about relationships between prime and target. After the completion of the study, when they were told about the hypothesis all subjects reported that they had not thought about any relationship between the words in the pairs, suggesting, at least, that there was no conscious evaluation of this type.

Behavioral Results

Response latency data were in agreement with previous findings.^{3,5,8,11} Namely, RTs for primed stimuli were shorter than for unprimed stimuli. Moreover, participants showed faster responses when the targets were closely related to the prime, compared with targets distantly related to the prime. Thus, we were able to demonstrate support for the network model for the

TABLE 2. Activated Brain Regions Showing the Semantic Priming Effect During the Two Functional Runs

Location		CU/UC Runs				DU/UD Runs				
		Z Score	x	y	z	Z Score	x	y	z	
Left IFG (BA 44/45)	U	3.86	-46	26	-12	U	3.43	-48	28	-6
	C	3.82	-44	24	-6	D	4.19	-42	24	-8
Left MFG (BA 46/9)	U	4.63	-48	26	22	U	3.87	-50	16	18
	C	4.78	-48	18	22	D	4.5	-44	12	18
Right MFG (BA 46/9)	U	4.83	46	32	16	U	4.9	46	32	16
	C	4.43	46	32	16	D	4.8	44	32	14

BA, Brodmann area; C, closely related word pairs; D, distantly related word pairs; U, unrelated word pairs.

TABLE 3. Priming Effects as Revealed by Bonferroni Multiple Comparisons Performed on BOLD Signal Changes

Brain Area	Task Comparison	Mean Difference (SD)	P
Left inferior frontal gyrus (BA 44/45)	U vs. C	0.29 (0.07)	0.00005
	D vs. C	0.30 (0.08)	0.002
	U vs. D	-0.01 (0.07)	1.0
Left middle frontal gyrus (BA 46/9)	U vs. C	0.42 (0.07)	0.00005
	D vs. C	0.27 (0.08)	0.006
	U vs. D	0.15 (0.07)	0.134
Right middle frontal gyrus (46/9)	U vs. C	0.27 (0.06)	0.00005
	D vs. C	0.31 (0.07)	0.00005
	U vs. D	-0.04 (0.07)	1.0
Left anterior temporal lobe (BA 38)	U vs. C	0.41 (0.07)	0.00005
	D vs. C	0.17 (0.08)	0.116
	U vs. D	0.24 (0.07)	0.002
Right anterior temporal lobe (BA 38)	U vs. C	0.30 (0.07)	0.00005
	D vs. C	0.25 (0.08)	0.012
	U vs. D	0.05 (0.07)	1.0

C indicates closely related word pairs; D, distantly related word pairs; SD, standard deviations; U, unrelated word pairs.

Note: The mean difference is significant at the 0.05 level (significant results are in bold).

organization of the semantic lexicon, where words are represented as nodes in the network and the distances between those nodes represent the semantic relationship between those words.^{2,3}

Imaging Results

During the lexical decision task, activation was observed in a cerebral network known to be involved in language processing and attention to the task. This network included the LIFG (BA44/45/47), bilateral MFG (BA46/9), parietal cortex (BA7), premotor cortex (BA6), and ACC (BA32/24), consistent with those described in previous studies.^{4,11-14} Signal time course analyses revealed differences in the magnitude of the BOLD signal for varying semantic distances in both hemispheres in the ATL and MFG, and also in the LIFG. The pattern for these differences was a decrease in BOLD signal change during processing of closely related target words when compared with brain activation during the presentation of unrelated word pairs and distantly related pairs. In addition, reduced signal change was observed in distantly related pairs compared with unrelated pairs in the left anterior temporal lobe. These reductions in BOLD signal suggest a decreased neural activity possibly because the recognition threshold for the related targets is lowered by the spreading of activation from the prime.^{2,11,30}

The critical role of the LIFG in language processing has been widely studied and demonstrated through both lesion and neuroimaging studies. Findings suggest involvement of the LIFG in executive mechanisms such as retrieval, selection, and evaluation.¹⁵⁻¹⁹ However, its exact role in semantic processing is still controversial. The competing hypotheses are that the role of the IFG is either retrieval of semantic information^{16,19} or selection among alternatives.^{12,18} In the present study, because selection demands were kept constant (participants had to

decide whether the target was a word or not, regardless of other associative parameters), the results seem to support the semantic retrieval hypothesis. The stronger activation observed for unrelated and distantly related word pair processing compared with activation during closely related word pair presentation suggests that access to these words is more demanding. The closely related target processing is facilitated by the spreading of activation from the prime, whereas the unrelated or distantly related targets require a more extensive effort in order to be retrieved from semantic memory.^{11,12,14} This interpretation is also supported by behavioral data, as the responses to unrelated and distantly related targets are typically slower than the responses for closely related targets.

The pattern of activation in the MFG is also similar to previous findings^{12,14} and could be interpreted in a similar manner, namely, as the result of a search of the semantic network. The activation in the right MFG could be interpreted as a result of retrieval effort²⁰ which is higher for unprimed words, compared with primed words.

Our findings related to the pattern of activation in the anterior temporal lobe in both hemispheres also correlate with previous results^{4,13} and suggest an important role of these regions in lexical-semantic processing. This is also supported by ERP studies of semantic priming in patients with temporal lobe lesions.³¹ These studies have found reduced and delayed semantic priming effects in patients with either right or left ATL lesions, and concluded that the right temporal lobe might be involved in aspects of semantic categoric priming, whereas the left ATL monitors the functional associative priming. Based on their PET findings of a complex pattern of activation in the left ATL, which was modulated by varying the proportion of related word pairs used, Mummery et al¹³ suggested that this area plays a role in the strategic processes associated with

controlled semantic processing. Our study, as well as the study of Rossell et al,⁴ supports this interpretation, because both used a long SOA and this is believed to result in controlled semantic processing.^{2,4} This may also relate to our finding that this was the only region showing a significant difference between activation during distantly related words and unrelated words. If strategic searching of the network is involved then this can be used to reach the distantly related words through the mediating path, therefore allowing them to be retrieved more easily than the unrelated words. However, the lack of a BOLD signal difference between the distantly related and unrelated word pairs elsewhere has to be interpreted with caution. Whereas the behavioral data have shown a difference in response latencies between these conditions, this was not reflected in the imaging data (except for the left ATL). It is possible that these differences were not detectable in the other regions with the methods employed in this study, and they may become apparent if an event-related paradigm, higher magnetic field strength or a larger number of participants are employed.

Other possible interpretations must also be considered, which may not be specific to semantic priming. For example, the LIFG activation may be involved in examining lexical properties of the stimuli, and the modulatory effect of semantic distance on the LIFG and more dorsal frontal areas may reflect decision-making about close or distant lexical associates through the interaction of these regions.

Three regions, the ACC, parietal cortex (BA7), and right premotor cortex (BA6), were activated during the lexical decision experiment, but not modulated by the semantic priming effect. This might reflect the involvement of attentional demands associated with controlled processing at the long SOA as suggested by previous studies.^{4,13} Among the variety of functions attributed to ACC, it has been shown that this area of the brain is also engaged in events that require response selection during semantic processing (for a review, see Devinsky et al³²). Previous neuroimaging studies have demonstrated activation of the caudal ACC during a long SOA semantic priming experiment, similar to our results.^{4,13} In support of the hypothesis that activation of the ACC is due to the involvement of strategic effects, the PET study conducted by Mummery and colleagues mentioned above found a decrease in ACC activation with increase in the proportion of related word pairs.¹³ It was proposed that, as the proportion of related pairs increases, the more routine the task is,^{2,13} requiring less attention, therefore leading to less activity in the ACC.

The superior parietal lobe and right premotor cortex showed similar activation, not influenced by the semantic conditions. These regions have also been associated with attentional mechanisms.^{13,33} Considering that the prime was not masked and was presented for a relatively long time, these findings could reflect a conscious evaluation of the prime target relationship.³⁴ They could also reflect the selection and execution of the motor response.

On a critical note, the lack of activation in the middle and superior temporal gyrus might be surprising given the published literature.¹¹⁻¹⁴ One possible explanation could be the methodology employed. The high proportion of related targets (50%) could have resulted in obscuring the automatic spreading of activation in these areas.^{4,13}

Nevertheless, this study has demonstrated that graduated effects of semantic priming, can be detected with fMRI. Two different categories of brain regions activated during a lexical decision semantic priming task have been identified. Areas known to be involved in lexical-semantic processing showed activation that was modulated by the semantic relationship between the prime and the target word. Areas in the attentional network were activated due to the controlled processes associated with the use of a long SOA, but were not affected by the different semantic conditions. Our study specifically examined the effect of varying semantic distances on brain activation during priming, yielding robust effects with direct priming, and limited effects from indirect priming. Studies using alternative methodologies are necessary to further clarify brain behavior in this semantic condition. This research may serve as a tool for examining semantic networks in patient populations or pharmacologic modulation of semantic networks.

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REFERENCES

1. Dehaene S, Jonides J, Smith EE, et al. Thinking and problem solving. In: Zigmund MJ, Bloom FE, Landis SC, et al. ed. *Fundamental Neuroscience*. 1st ed. San Diego: Academic Press; 1999:1543-1564.
2. Neely JH. Semantic priming effects in visual word recognition: a selective review of current findings and theories. In: Besner D, Humphreys GW, eds. *Basic Processes in Reading: Visual Word Recognition*. New Jersey: Lawrence Erlbaum Associates Inc; 1991:264-336.
3. Kischka U, Kammer T, Maier S, et al. Dopaminergic modulation of semantic network activation. *Neuropsychologia*. 1996;34:1107-1113.
4. Rossell SL, Bullmore ET, Williams SC, et al. Brain activation during automatic and controlled processing of semantic relations: a priming experiment using lexical-decision. *Neuropsychologia*. 2001;39:1167-1176.
5. Angwin AJ, Chenery HJ, Copland DA, et al. Dopamine and semantic activation: an investigation of masked direct and indirect priming. *J Int Neuropsychol Soc*. 2004;10:15-25.
6. Arnott WL, Chenery HJ, Murdoch BE, et al. Semantic priming in Parkinson's disease: evidence for delayed spreading activation. *J Clin Exp Neuropsychol*. 2001;3:502-519.
7. Filoteo JV, Friedrich FJ, Rilling LM, et al. Semantic and cross-case identity priming in patients with Parkinson's disease. *J Clin Exp Neuropsychol*. 2003;25:441-456.
8. Spitzer M, Braun U, Maier S, et al. Indirect semantic priming in schizophrenic patients. *Schizophr Res*. 1993;11:71-80.
9. Spitzer M, Weisker I, Winter M, et al. Semantic and phonological priming in schizophrenia. *J Abnorm Psychol*. 1994;103:485-494.
10. Anderson JE, Holcomb PJ. Auditory and visual semantic priming using different stimulus onset asynchronies: an event-related brain potential study. *Psychophysiology*. 1995;32:177-190.
11. Copland DA, de Zubicaray GI, McMahon K, et al. Brain activity during automatic semantic priming revealed by event-related

- functional magnetic resonance imaging. *Neuroimage*. 2003;20:302–310.
12. Kotz SA, Cappa SF, von Cramon DY, et al. Modulation of the lexical-semantic network by auditory semantic priming: an event-related functional MRI study. *Neuroimage*. 2002;17:1761–1772.
 13. Mummery CJ, Shallice T, Price CJ. Dual-process model in semantic priming: a functional imaging perspective. *Neuroimage*. 1999;9:516–525.
 14. Rissman J, Eliassen JC, Blumstein SE. An event-related fMRI investigation of implicit semantic priming. *J Cogn Neurosci*. 2003;15:1160–1175.
 15. Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci*. 2002;25:151–188.
 16. Demb JB, Desmond JE, Wagner AD, et al. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci*. 1995;15:5870–5878.
 17. Poldrack RA, Wagner AD, Prull MW, et al. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage*. 1999;10:15–35.
 18. Thompson-Schill SL, D'Esposito M, Aguirre GK, et al. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc Natl Acad Sci U S A*. 1997;94:14792–14797.
 19. Wagner AD, Pare-Blagoev EJ, Clark J, et al. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron*. 2001;31:329–338.
 20. Rugg MD, Wilding EL. Retrieval processing and episodic memory. *Trends Cogn Sci*. 2000;4:108–115.
 21. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23:208–219.
 22. Cox RW, Hyde JS. Software tools for analysis and visualization of fMRI data. *NMR Biomed*. 1997;10:171–178.
 23. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17:825–841.
 24. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002;17:143–155.
 25. Friston KJ, Worsley KJ, Frakowiak RSJ, et al. Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp*. 1994;1:214–220.
 26. Froman SD, Cohen JD, Fitzgerald M, et al. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med*. 1995;33:636–647.
 27. Worsley KJ, Evans AC, Marrett S, et al. A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab*. 1992;12:900–918.
 28. Jenkinson M, Smith SA. global optimization method for robust affine registration of brain images. *Med Image Anal*. 2001;5:143–156.
 29. Behrens TE, Woolrich MW, Smith S. Multi-subject null hypothesis testing using a fully Bayesian framework: theory. Hum Brain Mapp meeting, June 2003, New York.
 30. Schacter DL, Buckner RL. On the relations among priming, conscious recollection, and intentional retrieval: evidence from neuroimaging research. *Neurobiol Learn Mem*. 1998;70:284–303.
 31. Kotz SA, Friederici AD. Auditory word list priming in left and right temporal lobe lesions patients. *Brain Lang*. 1999;69:294–296.
 32. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behavior. *Brain*. 1995;118:279–306.
 33. Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol*. 1990;28:597–613.
 34. Henson RN. Neuroimaging studies of priming. *Prog Neurobiol*. 2003;70:53–81.