

## Aging Effects on Memory Encoding in the Frontal Lobes

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Functional magnetic resonance imaging (fMRI) was used to compare frontal-lobe activation in younger and older adults during encoding of words into memory. Participants made semantic or nonsemantic judgments about words. Younger adults exhibited greater activation for semantic relative to nonsemantic judgments in several regions, with the largest activation in the left inferior frontal gyrus. Older adults exhibited greater activation for semantic judgments in the same regions, but the extent of activation was reduced in left prefrontal regions. In older adults, there was a significant association between behavioral tests of declarative and working memory and extent of frontal activation. These results suggest that age-associated decreases in memory ability may be due to decreased frontal-lobe contributions to the initial encoding of experience.

Older adults typically remember recent experiences less well than younger adults ( Craik, 1977; Light, 1991). This age-associated decline in explicit or declarative memory is thought to be due to changes in the functioning of neural systems that support these memory processes. Memory comprises three temporal

phases of processing: (a) encoding or the acquisition of new information, (b) consolidation or the storage of information, and (c) retrieval or the recovering of already acquired information. Age-associated decline could result from changes in one or more of these stages (cf. Light, 1991). The experimental design of behavioral studies, however, limits the ability to assess mnemonic processes independently at each stage. Because behavior is assessed only at the time of retrieval, it is difficult to isolate the separate contribution of these three temporal phases of long-term memory. It is therefore uncertain as to whether age-associated declines in explicit memory begin during the encoding of new information, or whether they are instead the consequences of subsequent storage and retrieval phases of memory.

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Advances in functional neuroimaging have made possible the measurement of brain activity associated with different stages of memory function. Consequently, brain activity associated with encoding can be measured independently of subsequent consolidation or retrieval. In neuroimaging studies, encoding activation is often defined as greater activation for a study task that enhances subsequent declarative memory relative to another study task for the same kind of material (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). For example, semantic study yields greater subsequent declarative memory for words than nonsemantic study (Craik & Lockhart, 1972).

The most common site of such encoding-related activation, especially but not exclusively for verbal material, has been in left frontal-lobe regions. Specifically, the left inferior frontal regions show increased activation during encoding for meaning (deep encoding) compared with encoding for physical characteristics

(shallow encoding; e.g., Craik et al., 1999; Demb et al., 1995; Demonet et al., 1992; Desmond et al., 1995; Gabrieli et al., 1996; Kapur et al., 1996; Poldrack et al., 1999; Wagner, Desmond, Glover, & Gabrieli, 1998). The left inferior frontal region also shows activation for other encoding conditions that enhance later verbal memory, such as generating words relative to reading words (Frith, Friston, Liddle, & Frackowiak, 1991; Klein, Milner, Zatorre, Meyer, & Evans, 1995; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Raichle et al., 1994), generating the colors or uses relative to the names of objects (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995), or performing intentional relative to incidental encoding of words (Kapur et al., 1996; Kelley et al., 1998). Most of these studies were conducted using a block design in which participants perform a specific task (e.g., semantic decisions) for a block of trials, followed by performance of a different task (e.g., letter-case decisions). In functional magnetic resonance imaging (fMRI) studies, the blocks are repeated in alternating cycles for the length of the experiment. An event-related designed study, in which tasks are randomly mixed together (as typically occurs in behavioral studies), showed that greater left inferior prefrontal activation occurred for words that would later be remembered than for words that would later be forgotten (Wagner, Desmond et al., 1998). Together these studies indicate that the left inferior prefrontal cortex mediates processes that are important for successful encoding of verbal experience into long-term memory.

Positron emission tomography (PET) studies have compared frontal-lobe encoding activation between young and old participants. Grady and colleagues (Grady et al., 1995) studied age-related differences during the intentional encoding of faces compared with passive viewing of a visual noise pattern or perceptual matching of faces. Younger participants showed left frontal activation during the intentional encoding of faces compared with the passive viewing or perceptual matching encoding conditions, but older participants showed no encoding activation in this area. The older participants were worse at later recognizing the previously studied faces, and this may have resulted from impaired encoding as indexed by the absence of left frontal activation.

Cabeza and colleagues (Cabeza et al., 1997) studied age-related differences in frontal activation during intentional encoding of word pairs compared with reading word pairs. There was less left frontal activation during intentional encoding in older compared with younger participants. In addition, whereas the younger group showed asymmetrically greater left than right frontal activation during intentional encoding, the older participants showed symmetrical activation. Although the young and old did not differ significantly on behavioral testing of retrieval, the authors suggested that the lack of asymmetrical encoding activation reflected an alteration in the memory networks used during encoding in aged participants.

Anderson and colleagues (Anderson et al., 2000) studied age-related differences in activation during intentional elaborative encoding of word pairs and retrieval under conditions of full and divided attention. There were decreases of activation in prefrontal regions in older compared with younger participants for both encoding and retrieval. Dividing attention at encoding resulted in decreased left prefrontal activation, whereas dividing attention at retrieval had no such effect. Left prefrontal reduction in activation was similar for aging and for divided attention, suggesting both aging and divided attention interfere with elaborative encoding.

Together these results suggest that decreased left frontal activation indexes reduced encoding capabilities, which may contribute to decreased declarative memory performance in the elderly. There are, however, other possible explanations for the differences detected in these neuroimaging studies. First, these studies used intentional encoding paradigms: Participants were instructed to encode stimuli for a later memory test. Second, in these studies, no instructions were given to participants as to what encoding strategies to use. Older participants are known to perform worse at retrieval when required to develop their own encoding strategies as opposed to following externally provided strategies (Craik, 1990; Craik & Rabinowitz, 1985). Indeed, a comparison of intentional, nonintentional deep, and nonintentional shallow encoding of words and line drawings between younger and older participants revealed decreased left prefrontal activation during deep semantic compared with intentional encoding of words in the older group (Grady, McIntosh, Rajah, Beig, & Craik, 1999). Thus, the decrease in left frontal activation in aged participants during encoding may reflect a general decrease in encoding or a more limited decrease in intentional, strategic encoding abilities.

In the present study, we investigated differences in frontal-lobe activation during encoding of words using fMRI in younger and older persons. We used an incidental encoding manipulation by not informing the participants that they needed to study the words for a later memory test. We controlled the encoding strategy of the participants by using a levels-of-processing approach (Craik & Lockhart, 1972), in which encoding for meaning (deep encoding) was compared with encoding for physical characteristics (shallow encoding). Knowledge of word meaning is not strongly related to aging, and sometimes increases (Ackerman & Rolffhus, 1999). Thus, the encoding conditions were intended to provide a situation that would optimize the performance of older participants because the conditions were incidental, specified, and related to long-term knowledge of word meaning.

In addition, we investigated the relationship between frontal-lobe activation during encoding of words and performance scores on behavioral tests of declarative memory (immediate and delayed recall memory), working memory, word knowledge, processing speed, and reasoning in both the younger and older samples. The psychological processes measured by a number of these tests may be related to frontal-lobe contributions to word encoding, and age-associated decrements in performance have been demonstrated for recall memory (Craik, 1977), processing speed, working memory, and reasoning (Salthouse, 1982; Salthouse & Babcock, 1991). We predicted in particular that frontal-lobe activation during word encoding into long-term memory would be related to behavioral measures of verbal declarative and working memory abilities.

## Method

### *Participants*

The participants were 30 volunteers from the Chicago area, 15 younger adults (3 women, 12 men; age range = 22–32 years, mean age = 25.33 years) and 15 older adults (2 men, 13 women; age range = 65–87 years, mean age = 76.53 years). All participants were right-handed and had no history of neurological illness. Younger participants were recruited through advertisements at Rush–Presbyterian–St. Luke's Medical Center and at the University of Illinois at Chicago campus. The older persons in this study

were participants in the Religious Orders Study, a longitudinal clinical-pathologic study of aging and Alzheimer's disease. The study performs annual, detailed clinical evaluations on more than 900 older nuns, priests, and brothers without dementia who agree to brain donation at the time of death (see the author note). Details of the clinical evaluation and cognitive function testing have been reported previously (Chu, Cochran, Bennett, Mufson, & Kordower, 2001; Gilmore et al., 1999; Kordower et al., 2001; Mitchell et al., 2000; Mufson et al., 1999, 2000; Wilson et al., in press). Briefly, the evaluation included a medical history, neurologic examination, neuropsychological performance testing, and review of a structural brain scan when available. Cognitive performance tests were reviewed by a board-certified neuropsychologist.

All participants were evaluated in person by a neurologist with expertise in the evaluation of older persons with dementia. On the basis of this evaluation, participants were classified with respect to Alzheimer's disease, mild cognitive impairment, and other common neurologic disorders. Cognitive function tests were selected to assess a broad range of cognitive abilities that are commonly impaired in older persons. Each participant provided a written consent approved by the Institutional Review Board at Rush-Presbyterian-St. Luke's Medical Center. Data on participant demographics and selected cognitive performance measures are presented in Table 1.

### Materials

The stimuli were taken from a list of 264 3- to 12-letter words with a mean frequency of 32.4 per million (Kučera & Francis, 1967), half of which were abstract and half of which were concrete. Two word lists containing 12 blocks of 11 words each were divided randomly with the constraint that across all lists, half the words were abstract and half were concrete. Across all lists, half the abstract words and half the concrete words were randomly selected to appear in uppercase; the remaining words appeared in lowercase. Thus, each set contained two or three abstract words in uppercase (e.g., *TECHNOLOGY*), three or two abstract words in lowercase (e.g., *vocal*), two or three concrete words in uppercase (e.g., *SALOON*), and three or two concrete words in lowercase (e.g., *bicycle*). Words in each list were placed into a pseudorandom order with the constraint that no more than three abstract or concrete and no more than three uppercase or lowercase words appeared consecutively.

### Behavioral Procedure

Participants performed a semantic encoding test, in which they had to decide whether words were abstract or concrete in meaning (abstract-

concrete task), with an alternating, nonsemantic encoding task, in which they had to decide whether words were printed in uppercase or lowercase letters (uppercase-lowercase).

Participants saw 12 sets of 11 words presented consecutively. One encoding task was performed on odd blocks (i.e., the first, third, fifth, etc.), and the other task was performed on the even blocks (i.e., the second, fourth, sixth, etc.). Each pair of tasks constituted a cycle, so that six cycles were performed by each participant in each experiment. An instruction card at the beginning of each set of 11 words (e.g., *Task-Abstract*) indicated the target for that set (e.g., abstract words). Participants were asked to respond by pressing a pneumatic bulb in response to either concrete or abstract words during the abstract-concrete task and to either upper- or lowercase words during the uppercase-lowercase task; they were instructed not to respond to nontarget words. Words appeared centrally on a computer monitor for a duration of 1 s, followed by a 1-s interval before the next word appeared. Word orders were kept constant across participants, but the order of alternating encoding tasks was counterbalanced across participants. Thus, encoding tasks were counterbalanced across words.

Accuracy of semantic and nonsemantic judgments was recorded. Memory for encoded words was not tested for two reasons. First, participants were examined with multiple tests of verbal abilities (e.g., vocabulary knowledge, word list memory) prior to scanning that could have contaminated retrieval performance. Second, some of the participants participated in a second series of fMRI scanning protocols that required verbal memory (a verbal working memory task), and assessing memory for the encoded words could have interfered with performance on the second series of experiments in the same participants.

### Cognitive Performance Measures

Participants were tested on cognitive performance measures assessing general mental status, vocabulary knowledge, immediate and delay recall memory, processing speed, working memory, and reasoning. The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used as a measure of general mental status. The Extended Range Vocabulary Test (Ekstrom, French, Harman, & Kermen, 1976) was used as a measure of vocabulary knowledge. In this test, participants select the best definition for target words from five alternative choices. The measure of immediate and delay recall memory was the East Boston Story immediate and delayed recall (Albert et al., 1991). In this test, participants are presented with a short story and asked to recall the elements of the story immediately and after a short delay. The measure of processing speed was the Symbol Digit Modalities Test (Smith, 1968). In this test, participants are presented with a key of symbol digit pairings. They then produce the correct symbol for presented digits as quickly as possible. The measure of working memory was the Listening Span Test (Salthouse & Babcock, 1991). In this test, participants must process verbally presented sentences to answer questions about the sentence while remembering the last word of the sentence. The measure of reasoning was the Raven Progressive Matrices test (Raven, Court, & Raven, 1976). In this test, participants are presented with a series of designs that follow a logical progression with the final design missing. The task is to choose the correct design to complete the series using the logic presented in the series. Some of these measures were obtained at the time of screening for participation. The remaining tests were administered at the time of participation.

### fMRI Procedure

Imaging was performed with a 1.5 T whole-body MRI scanner (General Electric Medical Systems Signa, Revision 5.4) at Rush-Presbyterian-St. Luke's Medical Center. Head movement was minimized by using a bite bar formed with each participant's dental impression. A T2\*-sensitive gradient, echo spiral sequence (Glover & Lai, 1998), with TR equal to 300 ms, TE equal to 40 ms, and flip angle equal to 45°, was used for functional

Table 1  
Means and Standard Deviations of Participants'  
Demographic Information

Variable	Older ( <i>n</i> = 15)	Younger ( <i>n</i> = 15)	<i>t</i>
Age	76.53 (5.11)	25.33 (3.06)	33.28**
Education	17.80 (3.34)	16.70 (2.78)	< 1
MMSE	29.00 (1.71)	29.60 (0.69)	< 1
Extended Range Vocabulary Test	12.14 (2.63)	9.60 (2.46)	2.40*
East Boston Story			
Immediate	9.77 (1.69)	10.73 (0.79)	1.97
Delayed	8.46 (3.69)	10.47 (0.98)	2.04
Listening Span	2.31 (1.89)	2.85 (1.14)	< 1
Raven Progressive Matrices test	11.31 (3.15)	15.13 (1.25)	4.34**
SDMT	45.07 (11.68)	61.92 (12.45)	3.69**

Note. MMSE = Mini-Mental State Examination; SDMT = Symbol Digit Modalities Test.

\*  $p < .05$ . \*\*  $p < .01$ .

images. Bilaterally placed local receiver coils 5 in. (12.7 cm) in diameter were positioned to encompass the frontal lobes on either side of the participant's head. Eight interleaves were obtained for each image, with a total acquisition time of 1.5 s per image. Four contiguous 7-mm-thick slices (in plane resolution of  $2.4 \times 2.4$  mm) were acquired in the coronal plane of Talairach & Tournoux (1988) at 10 mm anterior to the anterior commissure (AC).

T1-weighted, flow-compensated, spin-warp anatomy images (TR = 500, TE = minimum) were acquired for all sections that received functional scans. These images were used to correlate functional activation with anatomical structures; that is, voxels that are found to be significantly activated during the functional scan are overlaid on these structural images.

Visual stimuli were presented to participants using a magnet-compatible projector (Resonance Technology, Inc., Van Nuys, CA) that back-projects visual images onto a screen mounted on a modified TMJ head holder (General Electric Medical Systems). Participants viewed the projected image via a mirror mounted on the TMJ head holder. A Macintosh Powerbook 5300c (Cupertino, CA) computer was used to generate visual stimuli and to control experimental parameters written in PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993).

### *fMRI Signal Analysis*

Image reconstruction was performed off-line by transferring the data to a Sun SparcStation. A gridding algorithm was used to resample the raw data into a Cartesian matrix. Once individual images were reconstructed, time series of each voxel were correlated with a reference waveform, creating a map of Z scores of each voxel (SPM{Z} map; Friston, Jezzard, & Turner, 1994). The reference waveform was calculated by convolving a square wave representing the time course of the alternating conditions (semantic and nonsemantic encoding), with an estimated hemodynamic response function template derived using the method described by Friston, Jezzard, & Turner (1994). The SPM{Z} maps were processed with a median filter having a spatial width of 2 voxels to emphasize spatially coherent patterns of activation. The filter was used with the assumption that spuriously correlated voxels (i.e., false positives due to Type I errors) are less likely to occur in clusters than genuinely correlated voxels, and thus clusters of correlated voxels are more likely to reflect an active region. The resulting maps were overlaid on T1-weighted structural images for each participant. For the present experiment, the SPM{Z} maps reflected voxel values that increased during the semantic encoding task and decreased during the nonsemantic encoding task. In addition, the difference of signal intensity between semantic and nonsemantic encoding was calculated for each voxel and expressed as a percentage of signal change value.

The analyses of the activation differences between younger and older participants entailed two sets of comparisons. The first comparison, used for characterizing activation maps within each group, involved creating a composite image of activation for each group by transforming the individual SPM{Z} maps to a common anatomical space and combining the transformed images. The second comparison, used for analyzing between-group differences, involved tracing gyral regions of interest (ROIs) on the individual participants' structural images, applying these ROIs to the SPM{Z} maps, and comparing group differences in various fMRI measures of activation. The latter analysis was used in addressing between-groups differences, to reduce the possibility of structural differences between the groups contaminating the assessment of functional differences. So that we could minimize such contamination, gyri for each participant were manually traced to preclude inclusion of widened sulci among the voxels of interest. Both types of comparisons were random-effects types of analyses, in that degrees of freedom for statistical tests reflected the number of subjects scanned rather than the number of scans within sessions (Friston, Holmes, Price, Buchel, & Worsley, 1999).

*Composite analysis.* So that we could obtain composite maps of activation over all participants, averaged functional activation maps were

created by transforming the coronal sections 10 mm anterior to the AC from every participant to a common standardized brain volume (Talairach & Tournoux, 1988). So that we could accomplish this, y coordinates were obtained using the millimeter distance from the AC measured at the time of slice acquisition (coronal slices were prescribed perpendicular to the AC-PC line). The x and z coordinates were obtained by transforming each coronal section into the two-dimensional region of a standardized coronal section, obtained from the Talairach and Tournoux (1988) atlas. This procedure consisted of manually tracing each participant's coronal sections and midline. From these measurements, scaling, rotation, and translation values were computed. So that we could obtain a more precise anatomical matching with the atlas, the scaled, translated, and rotated sections were warped to fit the perimeter of the atlas-derived coronal sections using the following steps: (a) For each coronal section, a set of points was defined around the perimeter of that section as well as the perimeter of the Talairach section. These points were found by casting rays in all directions from the centroid of the image in  $0.5^\circ$  increments of a circle. For each ray, the intersection of the ray with the outer boundary of the image (formed by the manually traced lines) could be found, resulting in an equal number of boundary points for the coronal and Talairach sections. (b) From these boundary points, a grid of points was formed across the functional map, and a corresponding grid was formed for the standardized section, such that a one-to-one mapping existed for the grid points of each set. (c) By mapping values from the grid points of the coronal and Talairach sections, both functional and anatomical data could be transformed into the confines of the Talairach section. This procedure was performed using customized software written in Interactive Data Language (IDL, Boulder, CO). For each participant, a contrast volume was created for voxels that increased during semantic encoding and decreased during the nonsemantic encoding. These contrast volumes were entered into a second-level analysis (random effects model) for group comparisons. This approach takes into account between-subjects variability and allows generalization of inferences beyond the specific sample participants.

*ROI analyses.* ROIs were drawn from the T1-weighted structural scans for each participant using software written in IDL. ROIs were drawn for each slice obtained (four per participant) for left and right superior, middle, inferior frontal, and cingulate gyri. These ROIs were determined with reference to an MRI atlas of the human brain (Schnitzlein & Murtagh, 1990). Reductions in gray matter could reduce fMRI signals by reducing the substrate of the fMRI signal. So that we could control for these possible differences in brain volume that were due to atrophy, the number of voxels in each analysis was corrected for the total number of voxels in the ROI.

Differences in fMRI ROI activation between the younger and older participants during the semantic and nonsemantic encoding tasks were analyzed using a random-effects, repeated measures analysis of variance (ANOVA) model (Friston et al., 1999). The main analysis compared the spatial extent of activation as indexed by the number of voxels exceeding the significance criterion of  $p < .01$ . These data provided an estimate of the size of activated neural tissue during the semantic encoding task relative to the nonsemantic encoding task, while controlling for differences in brain volume.

Two additional analyses probed possible differences in the hemodynamic response and neural processing of older subjects that could confound the intended measure of neural systems mediating encoding processes. One analysis examined the percentage of signal change values between the two encoding tasks for the significantly activated voxels identified from the SPM{Z} data set. These data provided an estimate of the intensity (magnitude or amplitude) of fMRI activation during semantic encoding compared with nonsemantic encoding. A second analysis examined the average positive Z value of those voxels exceeding the significance criterion between younger and older participants. The Z value was determined by both the magnitude and the variability of signal changes between encoding conditions.

So that we could examine the relationships between extent of fMRI activation during semantic encoding compared with nonsemantic encoding and cognitive performance, separate multiple regressions were used to identify the contribution of previously obtained cognitive performance measures to fMRI parameters. Thus, cognitive performance measures were regressed on each ROI in both younger and older samples.

## Results

### Behavioral Performance

Correct classification of words during semantic and nonsemantic encoding was calculated for each participant (hits plus correct rejections). These scores were analyzed in a  $2 \times 2$  (Group  $\times$  Encoding Condition) repeated measures ANOVA. Correct classification during nonsemantic encoding was superior to that during semantic encoding: main effect for encoding condition,  $F(1, 28) = 25.47, p < .01$ . This difference primarily reflected that some words had multiple interpretations of meaning. There were no significant differences between younger and older participants for correct classifications (main effect of group,  $F < 1.0$ ). The interaction between encoding condition and group was not reliable ( $F < 1.0$ ; younger semantic:  $M = 58.47, SD = 1.31$ ; older semantic:  $M = 58.33, SD = 1.48$ ; maximum semantic score = 66, younger nonsemantic:  $M = 65.40, SD = 5.01$ ; older nonsemantic:  $M = 63.75, SD = 6.73$ ; maximum nonsemantic score = 66).

### Imaging: Composite Analysis

Significant increases in activation for semantic encoding compared with nonsemantic encoding were detected with an individual voxel threshold of  $p < .01$ , two-tailed. A spatial extent threshold of  $p < .05$  was used to control for multiple comparisons (Friston, Worsley, et al., 1994). Both groups showed greater activation for semantic relative to nonsemantic encoding in a number of frontal and cingulate regions (Table 2; Figure 1). The largest activation occurred in the left inferior frontal gyrus (Brodmann's areas

[BAs] 44, 45/47) for both younger and older participants. Major activations were also observed in the right inferior frontal gyrus, left and right cingulate gyrus (BA 32), right middle frontal gyrus (BA 46), and left superior frontal gyrus (BA 8).

### Imaging: ROI Analyses

The number of voxels in the ROIs of younger and older participants was not significantly different,  $F(1, 28) = 2.80, MSE = 22,532.40, p = .11$ . Overall, the percentage of voxels that exceeded the significance criterion ( $p < .01$ , two-tailed) did not differ significantly between younger participants ( $M = 3.7\%, SD = 4.3\%$ ) and older participants ( $M = 2.3\%, SD = 3.5\%$ ): main effect of group,  $F(1, 28) = 1.93, MSE = 0.006, p = .18$ . The extent of left hemisphere activation was significantly greater than right hemisphere activation: main effect of hemisphere,  $F(1, 28) = 8.53, MSE = 0.001, p < .01$ , in the younger but not older participants; Hemisphere  $\times$  Group interaction,  $F(1, 28) = 4.33, MSE = 0.001, p < .05$ . Extent of left hemisphere activation was nearly twice as large as right hemisphere activation in younger participants (left hemisphere activation:  $M = 4.8\%, SD = 3.7\%$ ; right hemisphere activation:  $M = 2.7\%, SD = 2.4\%$ ),  $t(14) = 2.65, p < .02$ , whereas laterality of activation was nearly equivalent in older participants (left hemisphere activation:  $M = 2.5\%, SD = 2.9\%$ ; right hemisphere activation:  $M = 2.2\%, SD = 2.9\%$ ),  $t(14) = 1.26, p = .23$  (see Figure 2). The extent of left hemisphere activation in eight of the older participants fell within one standard deviation of the younger participants' group mean activation, but activation in the remaining 7 older participants fell below one standard deviation of the younger participants. Extent of activation in the inferior gyrus was significantly greater than middle, superior, or cingulate gyral activation: main effect of gyrus,  $F(3, 84) = 8.07, MSE = 0.001, p < .01$ . Examination of separate hemisphere by gyrus group differences revealed no significant group differences in right hemisphere gyri (all  $t_s < 1.33$ ; all  $p_s >$

Table 2  
Stereotactic Locations and Brodmann's Areas (BAs) of Clusters of Significant fMRI Activation During Semantic Encoding Versus Perceptual Encoding

Locations	Younger				Older			
	x	y	z	Z max	x	y	z	Z max
Left superior frontal gyrus (BA 6)	-8	10	49	3.89				
Left middle frontal gyrus (BA 8)	-3	17	44	4.34				
Left inferior frontal gyrus (BA 44/45)	-51	24	-6	3.58	-52	24	9	4.56
	-38	17	24	4.39	-43	31	2	4.12
	-44	24	1	4.27				
	-46	17	15	4.21				
Left insula	-34	17	1	4.83				
Right middle frontal gyrus (BA 8)	42	10	30	3.32				
Right inferior frontal gyrus (BA 44/45)	32	24	-7	3.80	46	10	26	4.29
	36	10	11	3.93				
	47	17	26	3.18				
Right insula	31	17	-2	3.88	35	17	13	3.48
Cingulate (BA 32)	-4	24	37	3.91	-5	10	33	4.45
	5	10	41	3.97				

Note. Location x, y, and z coordinates are based on the atlas of Talairach and Tournoux (1988). Z scores are expressed as the maximum within each area (Z max). Voxel dimensions are 2.40 mm  $\times$  2.40 mm  $\times$  7 mm. Local maxima are separated by a minimum of 10 mm. fMRI = functional magnetic resonance imaging.

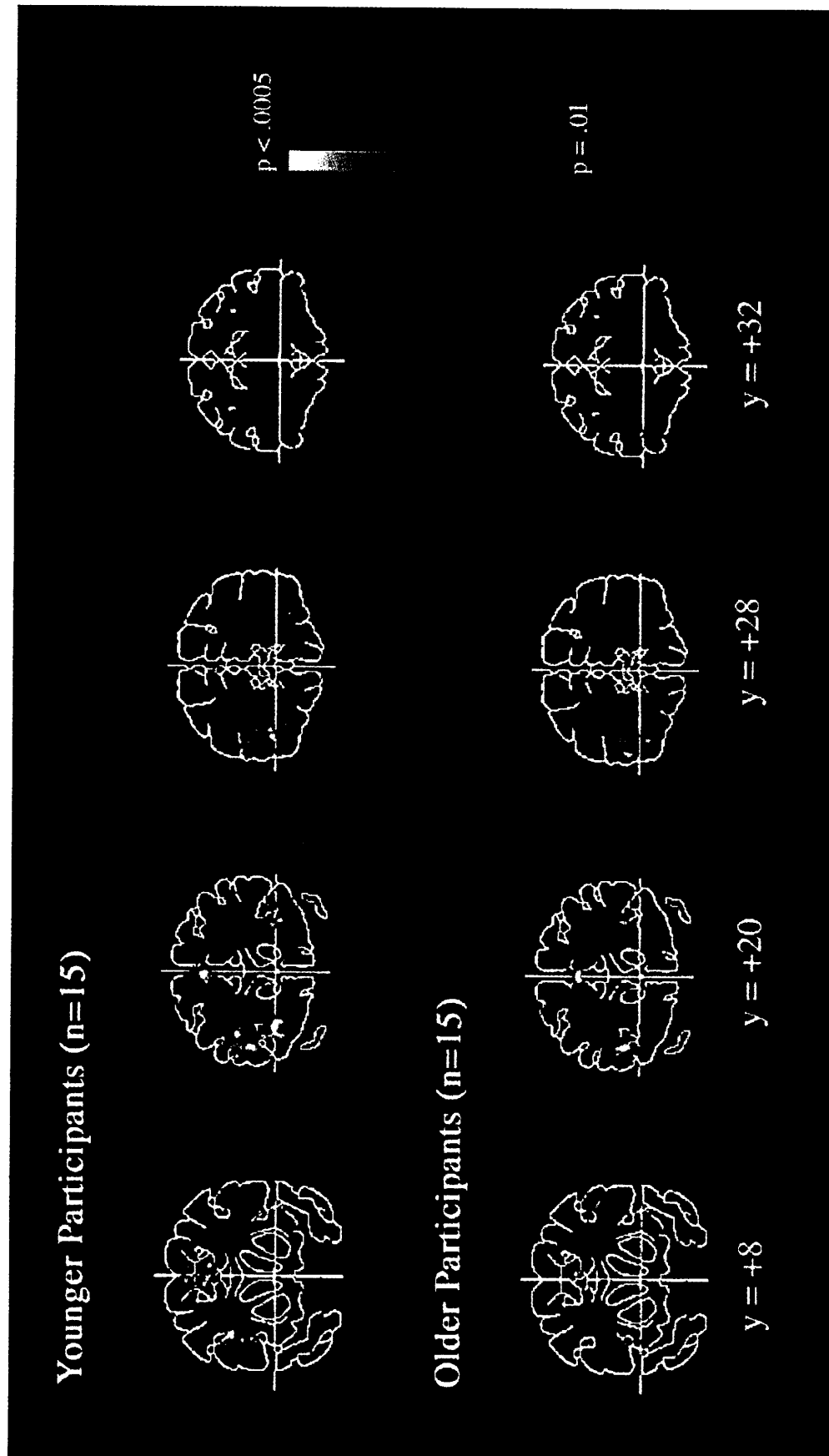


Figure 1. Regions of significant activation for younger (top row) and older (bottom row) participants during semantic versus nonsemantic encoding. Three-dimensional volumes were created from contiguous individual slices and normalized to a common standardized brain volume (Talairach & Tournoux, 1988). These composite images are displayed on coronal sections ( $y = +8$ ,  $+20$ ,  $+28$ , and  $+32$ ) from the stereotaxic atlas of Talairach and Tournoux (1988), corresponding to the nearest coordinates of the individually acquired slices. The color scale indicates significance of correlation magnitudes with lowest appearing in dark red ( $p < .01$ ) and the highest in bright yellow or white. The left side of the images represents the left side of the brain.

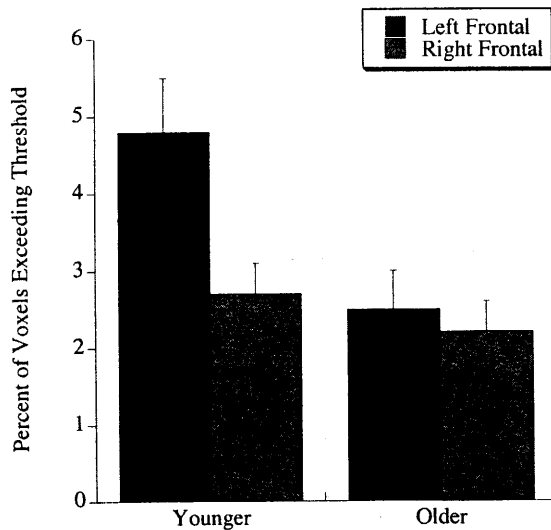


Figure 2. Mean percentages (with standard error bars) of all voxels in the left and right frontal lobes exceeding a significance criterion of  $p < .01$  for greater activation during semantic versus nonsemantic encoding in younger and older participants.

.21). Extent of left hemisphere activation was greater in younger compared with older participants in the superior gyrus (younger:  $M = 4.8\%$ ,  $SD = 5.0\%$ ; older:  $M = 1.8\%$ ,  $SD = 2.6\%$ ),  $t(28) = 2.09$ ,  $p < .05$ , and middle gyrus (younger:  $M = 3.8\%$ ,  $SD = 3.0\%$ ; older:  $M = 1.7\%$ ,  $SD = 1.7\%$ ),  $t(28) = 2.28$ ,  $p < .05$ , but not the cingulate gyrus (younger:  $M = 2.7\%$ ,  $SD = 2.9\%$ ; older:  $M = 2.8\%$ ,  $SD = 5.5\%$ ),  $t(28) < 1$ . There was a nonsignificant trend toward greater extent of left inferior gyrus activation in younger participants compared with older participants (younger:  $M = 7.9\%$ ,  $SD = 7.1\%$ ; older:  $M = 3.8\%$ ,  $SD = 4.1\%$ ),  $t(28) = 1.93$ ,  $p = .06$ . Those voxels that exceeded the significance criterion did not differ between groups in either mean percentage of signal change,  $F(1, 28) = 2.47$ ,  $p = .13$ , or mean Z value,  $F(1, 28) = 3.03$ ,  $p = .09$  (see Figure 3).

Separate stepwise multiple regressions were used to assess the relationship between behavioral measures of cognitive function and the measure of extent of activation during semantic encoding relative to nonsemantic encoding in each ROI. Included were measures that are typically affected by normal aging: general mental status (MMSE; Folstein et al., 1975), immediate and delayed recall memory (East Boston Story; Albert et al., 1991), processing speed (Symbol Digit Modalities Test; Smith, 1968), working memory (Listening Span; Salthouse & Babcock, 1991), and reasoning (Raven Progressive Matrices test; Raven et al., 1976); and measures relatively unaffected by aging: years of education and word knowledge (Extended Range Vocabulary Test; Ekstrom et al., 1976).

In the younger participants, only one behavioral measure was significantly associated with the spatial extent of fMRI activation. Working memory performance was significantly associated with the extent of fMRI activation in the left cingulate ROI ( $R = .58$ ,  $p < .05$ ). In the older participants, only two behavioral measures were significantly associated with the spatial extent of fMRI activation. Working memory performance was positively associ-

ated with spatial extent of fMRI activation in the left inferior gyrus ROI ( $R = .76$ ,  $p < .01$ ) and left middle gyrus ROI ( $R = .66$ ,  $p < .01$ ). Immediate recall memory (East Boston immediate recall) performance was positively associated with spatial extent of fMRI activation in the right inferior gyrus ROI ( $R = .58$ ,  $p < .05$ ) and left middle gyrus ROI ( $R = .59$ ,  $p < .05$ ). None of the behavioral measures showed a significant relationship with the extent of activation in the right or left superior gyrus, right middle gyrus, or right or left cingulate in the older participants.

## Discussion

Younger and older participants made semantic and nonsemantic judgments with high and equal accuracy. Both younger and older groups demonstrated increased frontal-lobe activation during semantic relative to nonsemantic judgments. The largest region of activation for both groups was in the left inferior frontal gyrus, a result consistent with prior fMRI studies with this task in young adults (Demb et al., 1995; Gabrieli, Desmond, Demb, & Wagner, 1996; Poldrack et al., 1999; Wagner, Poldrack, et al., 1998). Activation was also evident in the right inferior frontal gyrus, left and right middle and superior frontal gyri, and the cingulate. The major difference between younger and older adults was not in the locations of activations, but rather in the reduced spatial extent of activation in the left superior, middle, and inferior frontal gyri. The age-associated reduction in left prefrontal activation eliminated the left hemisphere asymmetry evident in the younger participants, who exhibited twice as much activation in left relative to right prefrontal activation.

These results suggest that frontal-lobe-mediated processes important for encoding new verbal experience into long-term memory are altered in healthy aging. These findings are consistent with prior PET studies reporting reduced left prefrontal activity during encoding in older relative to younger adults for nonverbal (Grady et al., 1995) and verbal (Cabeza et al., 1997) materials. The present study extends the prior findings in three important ways. First, the

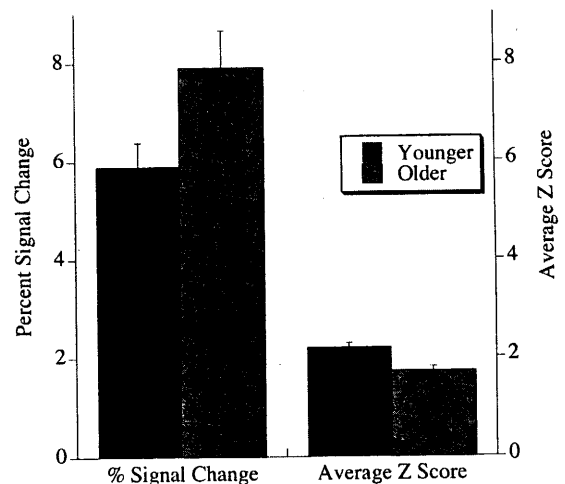


Figure 3. Mean percentages (with standard error bars) of signal change (right columns) and average Z scores (left columns) for frontal-lobe voxels exceeding a significance criterion of  $p < .01$  for greater activation during semantic versus nonsemantic encoding in younger and older participants.

age-associated reduction occurred under circumstances that were most conducive for encoding for older adults. The encoding task was one of knowledge of word meaning, an area of knowledge that is minimally affected by healthy aging. Indeed, the older participants outscored the younger participants on a standardized vocabulary test (Table 1). The encoding task was specified and incidental; these two conditions typically minimize age-associated changes in encoding efficiency. These circumstances, which were selected to minimize the effects of aging, nevertheless resulted in significantly reduced extent of left frontal activation in the older adults.

Second, the analysis of individually defined ROIs addresses concerns about the possible influence of greater variability of activation and atrophy in older adults. When PET (Cabeza et al., 1997; Grady et al., 1995, 1999) or fMRI results (Table 2) are analyzed for a group, an activation focus emerges to the extent that each member of the group exhibits greater activation for one condition relative to another in a particular brain region. In principle, a group of older participants could have as great a spatial extent of activation as younger participants, but if the older participants were more variable from one to another in the locations of activation, activation in far fewer voxels would surpass a statistical threshold. In such a case, the group activation would be misleading, because greater variability across participants in activation loci would simply appear as reduced activation. In the present study, we not only analyzed activation at the group level, but we were also able to analyze activation at the single-participant level, using individually determined ROIs in which group consistency is irrelevant to the analysis. This analysis also showed that older participants had a substantially reduced extent of left frontal activation relative to younger participants, and this reduction could not be the consequence of greater variability in older than in younger participants. Because these analyses were performed on the percentages of voxels present in ROIs, the results are unlikely to be secondary to age-associated atrophy or reduced volumes.

Third, the present study shows not only that older people had reduced activation relative to younger people during the encoding of memories (as shown also by Cabeza et al., 1997; Grady et al., 1995), but also that the extent of activation among older people was significantly associated with performance on standardized tests of working and declarative memory. These findings suggest that the degree of age-associated reduction in frontal-lobe activation is related to variability in age-associated reductions in declarative memory. There was considerable specificity in these relationships by location (left and right inferior frontal gyri, left middle frontal gyrus) and by psychological domain. Extent of frontal-lobe activation was significantly associated with scores on tests of immediate declarative memory and verbal working memory, but not significantly associated with tests of delayed declarative memory, nonverbal reasoning, processing speed, vocabulary knowledge, or years of education. These findings support the idea that the age-associated reductions in frontal-lobe activation are important for memory ability, with lesser activation being associated with worse memory ability.

### *Methodological Interpretation of Findings*

An important issue in interpreting fMRI differences between younger and older groups is that fMRI signals reflect neural

activity (and the psychological processes mediated by that neural activity) indirectly through a blood oxygenation level-dependent (BOLD) hemodynamic response function (HRF). Age-associated changes in vascular functions potentially unrelated to neural activity may alter the relation between the measured BOLD HRF and the associated neural activity. One approach toward investigating the status of the BOLD HRF in old age has been to measure it in visual or motor areas unrelated to higher cognitive functions (D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Ross et al., 1997; Taoka et al., 1998). These studies report age-related reduction in signal changes in the visual cortex to visual stimulation (Ross et al., 1997) or to an increase in noise, but not in signal components of the BOLD HRF in motor cortex, in response to a buttonpress (D'Esposito et al., 1999). It is difficult to know whether these age-related changes reflect BOLD HRF changes that are separable from psychological functions. For example, high correlations have been reported between performance on simple visual and motor tasks and on higher cognitive tasks in older people (Lindenberger & Baltes, 1997). Those correlations raise the possibility that there are psychological interactions between cognitive and perceptual-motor processes, and age-related changes in BOLD HRF of visual and motor cortex may reflect real neuropsychological changes in aging. At present, therefore, there is no certain way to dissociate age-related changes in BOLD HRF from age-related changes in brain-behavior relations.

Nevertheless, possible influences of the age-related changes in BOLD HRF may be considered in the present results. The block design of the present study (in contrast to an event-related design) minimizes the influences of subtle BOLD HRF differences, because it compares two active conditions over relatively long periods. The worst confound would be a global reduction in BOLD HRF signal change, because that alone could result in the reduced spatial extent of activation seen in the older adults (to the extent that such a global reduction diminishes measurement differences between the semantic and nonsemantic conditions because of floor or ceiling effects). Such a global reduction, however, is inconsistent with the present results. Although the younger group evidenced greater activation in superior, middle, and inferior frontal gyri, the extent of activation in the cingulate was numerically greater in the older group. Furthermore, there was equal activation in the right prefrontal regions despite the reduced left prefrontal activation in the older group.

The regional specificity of the age-related reductions argue against a global reduction in BOLD HRF signal change in aging. Additionally, a global reduction in signal change in aging is inconsistent with the fact that signal change in voxels that surpassed the significance threshold did not differ significantly between younger and older groups (indeed, the signal change tended to be greater in the older adults). Another confound would be greater variability in signal changes, but the Z scores, which are influenced by variability, did not differ significantly between younger and older groups for voxels that surpassed the significance threshold. The fact that the percentages of signal change and the average Z scores for voxels that surpassed the significance threshold did not differ between younger and older participants shows that the BOLD HRF differences were limited to the extent of frontal-lobe activation. Finally, the fact that there was a relation between extent of activation and standardized test scores among the older participants indicates that the fMRI measure, rather than

being an artifact of age-associated changes in the BOLD HRF, reflects the frontal-lobe basis of important mnemonic processes.

Another issue relevant to interpretation of age-associated changes in fMRI is age-associated changes in brain structure, especially reductions in volume due to atrophy. This is especially relevant for the present study of prefrontal function because of evidence that prefrontal regions show disproportionately large atrophy in normal aging (Raz et al., 1997). The relation between structural atrophy and fMRI in aging remains to be determined, but several observations may be made. First, because fMRI measures differences between conditions within an individual, it is uncertain whether a reduction in volume would lead to a reduction in differential activation. Second, if atrophy and fMRI signal were related, this would not be a confound but rather a structure-function relation in aging. Third, there is evidence that a great deal of age-related atrophy is related to reductions in white matter rather than in gray matter (Double et al., 1996; Guttmann et al., 1998; Tang, Nyengaard, Pakkenberg, & Gundersen, 1997). The fMRI signal is thought to arise from gray matter activity, and therefore white-matter atrophy may have minimal direct consequences for fMRI. Fourth, reduced extent of activity was present statistically, even though the numbers of activated voxels were calculated as a percentage of the voxels per gyrus per subject (i.e., those values were corrected for any gross volume differences even though those differences were not significant).

In the present study, reduced left prefrontal activation in the older adults is interpreted as disadvantageous. Smaller activations are not necessarily fMRI signatures of inferior processing. For example, reduced activation has been reported in response to increased facility of performance, including acquisition of motor skills (Karni et al., 1995) or repetition of semantic processing in priming experiments (Gabrieli et al., 1996; Raichle et al., 1994). One could posit that in the present study, for example, older adults had reduced activation because their superior vocabulary knowledge facilitated their semantic judgments. The fact that all the observed regressions between standardized test scores and frontal activations were positive correlations, however, favors the view that reduced activation in aging reflected worse frontal-lobe functioning. This same relation between decreased frontal-lobe activation and inferior performance has been observed in an fMRI study of working memory in older adults (Rypma & D'Esposito, 2000; younger adults in that study showed the opposite relation between activation and performance). Also, reduced left frontal activation was associated with inferior subsequent recognition (Grady et al., 1995) in older relative to younger participants. In the present study, therefore, the age-related reductions of activation in left prefrontal cortex likely indexed disadvantageous changes in prefrontal contributions to memory processes.

### *Neuropsychological Interpretation of Findings*

Much of the foregoing discussion has considered issues in the interpretation of age-associated changes in fMRI activations. These issues are important to consider, and future research may provide more direct and revealing insights into age-related changes in the BOLD HRF and in structure-function relations. Nevertheless, functional neuroimaging offers novel insights into the brain bases of age-related changes in cognition and memory that pre-

sumably occur because of age-related changes in the functioning of the brain.

The present study revealed an age-associated reduction of the asymmetrical, left-lateralized, prefrontal activation exhibited by the younger group. A number of functional neuroimaging studies have reported that older adults exhibit reduced asymmetry of prefrontal activations, with decreased activation in the hemisphere that is most activated in young adults and increased activation in the contralateral prefrontal region (e.g., Bäckman et al., 1997; Cabeza et al., 1997; Grady et al., 1999; Madden et al., 1999; Reuter-Lorenz et al., 2000). Compensatory mechanisms in older adults have been postulated as the cause for increased contralateral activation (Bäckman et al., 1997; Reuter-Lorenz et al., 2000). That interpretation, however, does not seem to apply to the present study, because the symmetrical activation in the older group was the consequence of a reduction in left hemisphere activation without a concomitant increase in the contralateral hemisphere. In support of the current finding, other studies that have examined encoding per se (as opposed to retrieval or working memory) have not reported increased contralateral activation together with the observed age-related reduction of activation in the dominant hemisphere (Cabeza et al., 1997; Grady et al., 1995).

The present findings indicate that left hemisphere prefrontal contributions to the encoding of new verbal memories, as measured by fMRI, are reduced by 50% in normal aging. This finding relates specifically to differences in brain activation during semantic encoding relative to nonsemantic encoding, because we did not use a baseline condition (e.g., fixation, rest). Thus, the decrease in left prefrontal activation during semantic encoding in the older group could be due to increased activation in this region during nonsemantic encoding.

Prior imaging studies in young adults have consistently reported left prefrontal activations for encoding conditions that enhance later memory for verbal, and sometimes nonverbal, materials. The reduction in healthy older adults suggests that psychological processes that enhance memory in young adults are attenuated in older adults. Such an attenuation could have a profound affect on memory, because impoverished encoding would diminish later memory for any experience (even if the subsequent storage and retrieval mechanisms were unaffected by aging; e.g., Anderson et al., 2000). The large age-associated reduction of left prefrontal activation during encoding, therefore, suggests that diminished later memory for experiences in older age begins by poor encoding occurring during each new experience.

Specifying the prefrontally supported psychological processes that are reduced in older participants depends on how those processes are characterized in younger adults. The presence of extensive left-prefrontal activations during semantic processing that enhances subsequent memory was initially unexpected on the basis of lesion evidence. Left prefrontal lesions are not associated with profound deficits in either semantic knowledge or long-term memory (amnesia). Consistent with this point, older participants in the present study exhibited reduced left prefrontal activation despite superior semantic knowledge for words and despite age-equivalent performance on both the semantic and nonsemantic tasks. It has been proposed that left prefrontal activations observed during semantic tasks signify working memory processes recruited for performance of semantic judgments (Desmond, Gabrieli, & Glover, 1998; Gabrieli et al., 1996; Thompson-Schill, D'Esposito,

Aguirre, & Farah, 1997; Thompson-Schill et al., 1998). This interpretation is consistent with considerable evidence that prefrontal regions mediate working memory processes (e.g., Goldman-Rakic, 1987), and that left prefrontal activations are increased as working memory demands, such as selection and competition from alternative responses, are increased on semantic or other verbal tasks (e.g., Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2000; Desmond et al., 1998; Smith & Jonides, 1998; Thompson-Schill et al., 1997).

The finding that the older participants evidenced significantly less left prefrontal activation during semantic than nonsemantic judgments may, therefore, represent age-related decreases in working memory ability related to semantic processing. This interpretation is consistent with considerable evidence that aging is characterized by disproportionate decreases in working memory performance across the lifespan (Gabrieli, 1996; Prull, Gabrieli, & Bunge, 2000; Salthouse, 1982; Salthouse, Hambrick, & McGuthry, 1998). In the present study, the extent of left prefrontal activation among older participants was positively correlated with verbal working memory capacity. This finding directly links working memory and semantic encoding processes. Also, the relationship between frontal activation and long-term memory test performance was significant for immediate, but not delayed story recall. Immediate, but not delayed story recall has been associated with performance on executive tasks assessing frontal-lobe functioning (Baddeley, in press). Thus, immediate story recall may reflect a frontal-lobe interaction between working memory capacity and long-term memory encoding, whereas delayed recall may depend more on storage processes associated with medial temporal-lobe structures. Thus, the pattern of associations between frontal activation and these measures in the older participants may represent aging effects on common psychological processes involved in working memory and long-term declarative memory encoding.

The associations between left prefrontal activations and performance on tests of reasoning and processing speed were not significant. Both reasoning and processing speed performance measures are highly correlated with measures of working memory (Salthouse & Babcock, 1991; Salthouse et al., 1998), and the measures we used required the selection of appropriate responses from competing alternative responses for successful performance. However, the working memory measure used verbal material, but the reasoning measure used difficult-to-verbalize patterns, and the processing speed measure used nonsense symbols paired with digits. This suggests a specificity of the relationship between left prefrontal activation and working memory for verbal material.

The left prefrontal decline, however, was not uniform across the older group. About half of the older group had activation levels within one standard deviation of the younger group's mean. Thus, fMRI could not only measure differences between the younger and older groups but also substantial variation among the older participants. That variation was meaningful because it correlated with standardized tests of verbal working memory and verbal long-term memory. These findings therefore suggest not only that age-related changes in left prefrontal cortical processing contribute importantly to cognitive aging, but that the degree of such changes may help to determine whether an individual has more versus less severe age-related decline in verbal memory. fMRI, therefore, may be useful in determining the brain basis of more versus less successful pathways of cognitive aging.

It is common in behavioral studies of aging to use different tests to measure different age-associated changes (or the lack thereof) in different psychological domains such as semantic memory, working memory, or declarative memory. In reality, however, a specific psychological process may be invoked by multiple tests in each of these domains. The left prefrontal cortex appears to mediate a family of processes that are relevant for all three sorts of memory performance, and thus this region may serve as a crossroad between other processes, mediated by other neural systems, involved in semantic, working, and declarative memory (Gabrieli, Poldrack, & Desmond, 1998). The present findings depict an age-associated decline in prefrontal activation that may reflect reduced working memory resources for making semantic judgments that, in turn, may diminish declarative memory for those judgments. Such an age-associated decline may prevent knowledge of the meaning of an experience to enhance later memory for that experience. The magnitude of this decline, however, appears to vary considerably among older adults.

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