

Age-related Changes in Brain Activity across the Adult Lifespan

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Abstract

■ A number of theories have emerged to explain the well-studied changes in memory that occur with age. Many of these theories invoke mechanisms that have the potential to affect multiple cognitive domains, in addition to memory. Such mechanisms include alterations in attentional or inhibitory function, or dysfunction of specific brain areas, such as the frontal lobes. To gain insight into these mechanisms, we used functional magnetic resonance imaging to examine brain activity during encoding and recognition tasks in young, middle-aged, and older adults to identify correlations between age and brain activity across the various tasks. The goal was to see whether these correlations were task-specific or common across tasks, and to determine whether age differences emerged in a linear

fashion over the adult years. Across all memory tasks, at both encoding and recognition, linear increases of activity with age were found in areas normally decreased during task performance (e.g., medial frontal and parietal regions), whereas activity in regions with task-related activation (e.g., dorsolateral prefrontal cortex) decreased with age. These results suggest that there is a gradual, age-related reduction in the ability to suspend non-task-related or “default-mode” activity and engage areas for carrying out memory tasks. Such an alteration in the balance between default-mode and task-related activity could account for increased vulnerability to distraction from irrelevant information, and thereby affect multiple cognitive domains. ■

INTRODUCTION

It is well known that older age is associated with reductions in memory, particularly in recollecting personally experienced events (episodic memory; Tulving, 1983). In the laboratory, these age differences in episodic memory are seen in a reduced ability to learn and retrieve lists of stimuli (for a review, see Craik & Bosman, 1992). Reductions in recall of real-life, autobiographical memories also have been reported (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; Piolino, Desgranges, Benali, & Eustache, 2002), consisting mainly of a reduction in retrieval of event details. Retrieval of personal semantics is not reduced with age. A number of ideas have been proposed to account for age differences in memory, including impairments in attentional resources (Craik & Bosman, 1992; Craik, 1983) and information processing (Salthouse, 1996). Another hypothesis is that older adults have a heightened susceptibility to interference due to a reduced ability to inhibit irrelevant information (Hasher & Zacks, 1988; Winocur & Moscovitch, 1983). Other theories have focused on age-related changes in brain function, rather than on cognitive processes. The most prominent theory in this group is the frontal lobe theory of aging,

which suggests that many age-related changes in cognition are due to the particular vulnerability of the frontal lobes to the structural and neurochemical changes that occur with age (Buckner, 2004; Raz, 2000; Raz et al., 1997; West, 1996).

Recently, functional neuroimaging has been used to examine the neural substrates of these age-related reductions in memory. Some of these experiments found reduced activation in older compared to young adults in brain areas supporting memory function, such as the prefrontal cortex and the medial-temporal lobes (Logan, Sanders, Snyder, Morris, & Buckner, 2002; Stebbins et al., 2002; Grady et al., 1995). On the other hand, the opposite result, more prefrontal activity during memory tasks in older adults than in younger adults, also has been reported (Gutchess et al., 2005; Morcom, Good, Frackowiak, & Rugg, 2003; Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady, Bernstein, Siegenthaler, & Beig, 2002; Logan et al., 2002; Rosen et al., 2002; Madden et al., 1999; Backman et al., 1997), particularly during memory retrieval. In addition, functional interactions or correlations among brain regions involved in memory tasks differ between young and old adults (Grady, McIntosh, & Craik, 2003; Scarmeas et al., 2003; Della-Maggiore et al., 2000; Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997). The evidence to date suggests that these age-related

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alterations in brain activity may be compensatory and aid memory performance in older adults, but the exact relationship between brain activity and memory ability in the elderly is unclear.

One aspect of age-related differences in brain activity during memory tasks that has not yet been addressed is when in the lifespan do these changes begin. Behavioral studies have shown that the rate of change in memory and other cognitive functions across the lifespan can be variable. Some have reported a linear rate of change in memory scores from early adulthood into the 80s (Park et al., 2002), whereas others have found nonlinear changes (Salthouse, Atkinson, & Berish, 2003). Nonlinear change usually takes the form of acceleration with increasing age, such that middle-aged adults perform more like younger adults, and those over the age of 60 or 65 are characterized by lower scores. Some of this discrepancy could be due to differences in test sensitivity across experiments, or to sampling differences, but also could be an accurate reflection of the variable nature of cognitive change in the middle years. With functional neuroimaging, it is possible to address the neural correlates of cognitive change across the lifespan. The study of middle-aged, as well as young and old adults, can provide information about when in the lifespan the functional brain changes that are evident in older adults begin to occur. Such experiments can help determine whether there is a gradual transition between youth and old age, or whether differences in brain activity accelerate with increasing age (i.e., are nonlinear).

In addition, examining changes in brain activity across a wide range of ages may be instrumental in providing support for one, or more, of the current theories of cognitive aging. For example, a number of studies mentioned above reported more frontal lobe activity in older adults compared to younger adults. This type of result would be consistent with the frontal lobe theory of aging, at least to the extent that it indicates a critical role for the frontal cortex in cognitive aging. Support for the frontal lobe theory of aging also has been found in several studies that reported age differences in common frontal areas across memory, attention, and perceptual tasks (Cabeza et al., 2004; Grady, 2002). Additional evidence for the frontal lobe theory would be found if changes in brain activity over the lifespan were primarily in the frontal cortex. Specificity of frontal lobe changes with age, such as a progressive loss of activity in frontal regions thought to play a role in inhibiting the influence of irrelevant material or responses (e.g., Garavan, Ross, & Stein, 1999; Jonides, Smith, Marshuetz, Koeppel, & Reuter-Lorenz, 1998), would provide support for the idea that susceptibility to interference occurs with increasing age. Similarly, an increase with age in regions thought to index “default-mode” activity, that is, activity seen when people are in a quiescent state and attending to an internal rather than an external task-based focus

(Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001), also could signal a reduction in inhibitory processes or the ability to engage attention appropriately. This idea has particular appeal as activity in these default-mode regions is consistently increased during rest periods or periods of low-level sensorimotor tasks compared to visual (Shulman et al., 1997; Haxby et al., 1994) or auditory tasks (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Alain, Arnott, Hevenor, Graham, & Grady, 2001). Indeed, several studies have found that activity in default-mode regions during task performance is not reduced in healthy older adults to the same degree as in young adults (Lustig et al., 2003) or in patients with dementia compared to healthy elderly individuals (Greicius, Srivastava, Reiss, & Menon, 2004; Lustig et al., 2003). However, the generality of this effect, or when in the lifespan it might occur, is unknown. All of these potential age-related changes could affect cognitive function in a general way, representing a “common factor” underlying changes across multiple cognitive domains. Such a common factor has been advocated by Salthouse et al. (2003) and Salthouse and Ferrer-Caja (2003), although recent work has suggested that age also may impact on memory directly (Salthouse & Ferrer-Caja, 2003).

In the current experiment, functional magnetic resonance imaging (fMRI) was used to measure brain activity in young, middle-aged, and older adults (from 20 to 87 years). Participants were scanned during two different tasks of encoding lists of words and pictures of objects, recognition for these stimuli, and during a fixation baseline. The goal was to determine whether the effects of age on memory-related brain activity were task or stimulus specific, or more general in nature, and when in the lifespan these effects might first be found. Our expectation was that brain activity in the middle-aged adults would fall in between that of young and old adults, thus representing a gradual transition in the expression of age-related differences. We also addressed whether differences in brain activity in middle-aged adults would be apparent even if behaviorally this group was not different from the younger adults. Such brain differences have been found between young and old adults in the absence of behavioral differences (Cabeza et al., 2002; McIntosh, Sekuler, et al., 1999; Grady et al., 1994), so we thought it likely that brain measures would be more sensitive in the middle years as well. Our approach was to use a multivariate analytic technique to determine modulations of brain activity across the tasks in the young, middle-aged, and older adults, and to correlate brain activity with age. Of particular interest was whether we could identify a pattern of correlation that would describe most or all of the tasks, and thus, provide support for a common cause of age effects in cognition. That is, a common pattern of correlation across both encoding and recognition tasks, as well as for both kinds of visual stimuli, would support the idea

of a generalized age effect that could potentially affect multiple cognitive domains.

RESULTS

Behavioral Results

Participants were administered a brief battery of neuropsychological tests to assess general intellectual function and memory (Table 1). Scores from these tests were analyzed with ANOVAs and Bonferroni-corrected post hoc *t* tests for assessing group differences. There were no group differences in verbal fluency. In contrast, age differences were found for immediate verbal recall, $F(2,37) = 9.8, p < .001$, delayed verbal recall, $F(2,37) = 13.6, p < .001$, and verbal recognition, $F(2,37) = 11.9, p < .001$. There also was a significant effect of age on the digit-symbol task (a measure of working memory), $F(2,37) = 9.8, p < .001$. For all of these tests, the older group scored lower than either the young or middle-aged groups ($p < .01$), and there were no differences in performance between the young and middle-aged adults. The remaining test, vocabulary, also showed an effect of age, $F(2,37) = 3.7, p < .05$, but in this case the older adults scored higher than the young adults ($p < .05$).

During the fMRI scans, participants carried out a series of encoding tasks on common nouns and pictures of objects, using both semantic (animacy) and perceptual (size) judgments. Following the encoding scans, recognition scans assessing memory for semantically and perceptually encoded words and pictures were conducted (the “picture” recognition task was done using the corresponding words, rather than the pictures themselves, to reduce the picture superiority effect; Paivio, 1971). There were no significant age differences on the fMRI encoding tests (Table 1). However, there were significant effects of stimulus type, $F(1,36) = 11.6, p < .01$, task, $F(1,36) = 116.0, p < .001$, and a significant interaction of stimulus and task, $F(1,36) = 53.4, p < .001$. Pictures were encoded overall more accurately than words, and the semantic task was more difficult than the perceptual task. The interaction of stimulus and task was due to a bigger difference between the semantic and perceptual tasks when processing words.

In contrast to the encoding tasks, there was a significant main effect of age on recognition accuracy (proportion of hits minus proportion of false alarms), $F(2,36) = 4.7, p < .02$. Post hoc tests showed that there was a significant difference between the young and old groups ($p < .02$), with a trend for a difference between the old and middle-aged groups ($p = .10$), but no difference between young and middle-aged participants. In addition, the main effect of prior encoding task on recognition accuracy was significant, $F(1,36) = 53.1, p < .001$, as was the Stimulus \times Task interaction, $F(1,36) = 4.7,$

Table 1. Demographic and Behavioral Data

Task	Young	Middle-Aged	Old
<i>Demographic Data</i>			
Age	23.2 (2.3)	46.5 (5.5)	74.4 (6.6)
Education (years)	14.8 (3.2)	14.9 (3.1)	14.9 (4.5)
Mental status	28.6 (1.5)	28.9 (1.4)	29.0 (1.2)
<i>Neuropsychological Tests</i>			
Verbal fluency	44.0 (9.3)	52.6 (13.7)	49.6 (9.7)
Immediate verbal recall	9.1 (1.3)	8.4 (1.6)	6.7 (1.4) ^{a,b}
Delayed verbal recall	9.3 (1.8)	9.4 (1.4)	6.4 (2.0) ^{a,b}
Verbal recognition	11.1 (1.3)	11.9 (0.3)	9.2 (2.1) ^{a,b}
Vocabulary	39.2 (13.3)	49.2 (11.6)	51.1 (10.8) ^c
Digit symbol	85.6 (14.3)	78.4 (17.7)	59.4 (16.5) ^{a,b}
<i>fMRI Tasks</i>			
Words			
Semantic task	0.76 (0.10)	0.81 (0.07)	0.80 (0.06)
Perceptual Task	0.99 (0.02)	0.97 (0.03)	0.99 (0.02)
Recognition—Semantic	0.73 (0.16)	0.73 (0.22)	0.48 (0.28) ^c
Recognition—Perceptual	0.35 (0.26)	0.36 (0.26)	0.23 (0.22) ^c
Pictures			
Semantic Task	0.91 (0.06)	0.91 (0.09)	0.86 (0.09)
Perceptual Task	0.92 (0.06)	0.95 (0.10)	0.95 (0.06)
Recognition—Semantic	0.60 (0.17)	0.55 (0.22)	0.45 (0.27) ^c
Recognition—Perceptual	0.42 (0.16)	0.34 (0.16)	0.32 (0.32) ^c

Values are mean (*SD*).

Mental status scores are from the MMSE (Folstein et al., 1975). The verbal recall and verbal recognition scores are mean number of words retrieved. Accuracy on the fMRI encoding tasks is proportion correct. Accuracy on the fMRI recognition tasks is proportion hits minus proportion false alarms. Note: $n = 11$ in the middle-aged group for fMRI tasks due to loss of behavioral data from one participant.

^aDiffers from young, $p < .01$.

^bDiffers from middle aged, $p < .01$.

^cDiffers from young, $p < .05$.

$p < .05$. Both words and pictures were recognized better after semantic encoding, compared to perceptual encoding, but there was a larger effect of prior encoding task on word memory, compared to picture memory. None of the interactions involving age were significant for either the encoding or recognition tasks. Thus, a

similar pattern of age-related differences was seen across all of these behavioral tests, indicating no difference between the young and middle-aged groups, and a significant reduction in memory performance in the older group.

fMRI Results

The multivariate approach used here for the fMRI analysis identifies patterns of activity across the brain that covary with some aspect of the experimental design (McIntosh, Bookstein, Haxby, & Grady, 1996). This approach does not prespecify the task contrasts, but rather reveals the contrasts that account for the most covariance between the tasks and brain activity. This analysis was carried out on the imaging data from all three age groups to assess changes in activity across the nine task conditions (i.e., four encoding conditions, four recognition conditions, and fixation). Because the primary analysis of interest here is the correlation between brain activity and age (see below), we report only the first pattern of brain activity that resulted from the analysis of all the memory task conditions and the fixation baseline. This pattern ($p < .002$) identified a common set of brain regions with increased or decreased activity in all of the encoding and recognition tasks compared to fixation (Figure 1A). In addition, this overall pattern of changes in brain activity differentiated the fixation condition from the tasks in all three age groups (Figure 1B), although this differentiation appeared to be somewhat better in the young and old adults than in the middle-aged group. Increased activity during all of the memory tasks, regardless of type of task or stimulus, was seen in the left inferior frontal gyrus, and in the bilateral regions of the dorsolateral prefrontal cortex, the lateral parietal cortex, and the fusiform gyrus (Table 2). Brain areas with reduced activity during the tasks, compared to fixation, included the medial frontal cortex, anterior cingulate, posterior cingulate extending into the precuneus, and bilateral peri-sylvian and temporal regions.

To examine the relation between brain activity and age, we used the same multivariate approach. In this case, we calculated the covariance between the fMRI signal in each brain voxel and age within each task and then contrasted this covariance across tasks (e.g., McIntosh, 1999). This analysis identified a single significant pattern of correlations ($p < .002$) where activity was strongly and linearly correlated with age (Figure 2A). The correlations with age were similar for all of the tasks but differed between the tasks and fixation (Figure 3). During all of the encoding and recognition tasks, increased activity with increasing age was seen in the medial prefrontal cortex and the dorsal portion of the anterior cingulate (Table 3). Increased activity with age also was found in a medial and posterior area of the brain that included the posterior cingulate gyrus and

precuneus. In contrast, activity in the bilateral prefrontal cortex, caudate nuclei, left putamen, and left fusiform gyrus decreased with age during the tasks (Table 3 and Figure 2A). Thus, older adults had more activity during the tasks in medial regions of the brain, and less activity in frontal regions and caudate, compared to younger adults, with the middle-aged adults showing intermediate activity levels. This pattern was reversed during fixation.

Visual inspection of the regions where activity was correlated with age suggested that these areas overlapped to some extent with those areas where there were activity changes in the task analysis. To test this quantitatively, we determined whether each of the regions showing a correlation with age also made a reliable contribution to the pattern of task-related changes seen in Figure 1. The contributions of these areas to the pattern of activity distinguishing the tasks from fixation are shown in Table 3 (i.e., the bootstrap ratios for each of these regions from the task analysis; see Methods). Most of the regions where activity during the tasks increased with age showed activity *reductions* during the memory tasks relative to fixation, and all but one of these reductions were significant. That is, the medial frontal, precuneus, and cingulate regions (both posterior and dorsal anterior areas) had lower activity during the tasks compared to fixation. To illustrate this, Figure 2B shows the mean activity for the precuneus in each of the three groups averaged over all the task blocks for each time point (expressed as percent change relative to the last time point in the preceding fixation block). It can be seen from this figure that both the young and middle-aged groups showed a marked reduction in precuneus activity during the tasks. In contrast, the older adults showed little change of activity in this region. To examine activity in this region in more detail, we carried out a repeated-measures ANOVA on the time course data. There was a significant main effect of group, $F(2,42) = 3.3$, $p < .05$, as well as a significant Group \times Time interaction, $F(14,259) = 6.7$, $p < .001$. Subsequent analyses at each time point indicated that the percent change in the older adults differed significantly from that of the young group beginning at 10 sec and for all subsequent time points ($p < .05$, corrected). The old group also differed from the middle-aged group between 12 and 18 sec (time points 5 through 7, $p < .05$, corrected). There were no significant differences between young and middle-aged adults.

Unlike the areas with age-related increases of activity, the brain areas where activity during the tasks decreased with age were generally regions that showed activity *increases* during the memory tasks (Table 3). This effect is shown in Figure 2C for the right middle frontal gyrus. All three groups showed increased activity in this frontal area above baseline, and there was no significant main effect of age group. There was, however, a significant Group \times Time interaction, $F(14,259) = 2.2$, $p < .05$.

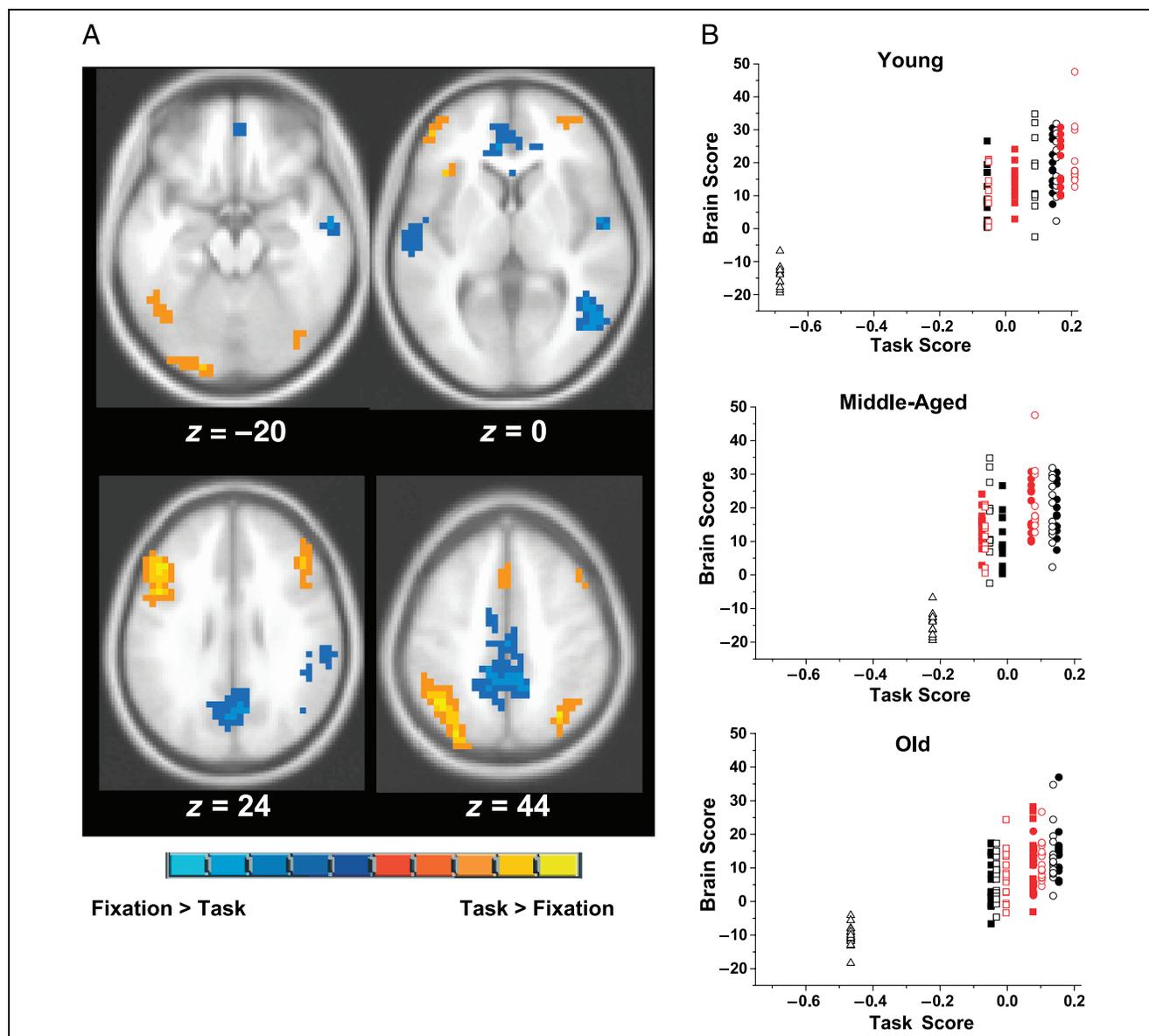


Figure 1. Brain areas identified by the analysis examining task-related brain activity across all three age groups ($p < .002$) are shown on the MNI average brain in A (the right hemisphere is on the right side of the images). Axial slices at four different z levels relative to the AC–PC line are shown. Orange and yellow areas are those with increased activity during the encoding and recognition tasks, relative to fixation, and blue areas had decreased activity relative to fixation. B shows plots of brain scores against task scores to show how brain activity seen in A varied across the conditions in the three age groups. Brain scores are summary scores of activity across the entire brain. Task scores are derived such that more positive scores are associated with increased activity in the orange/yellow brain areas and more negative scores are associated with increased activity in the blue areas. In these graphs, data from the picture conditions are shown in black and data from the word conditions are shown in red. In addition, the encoding tasks are represented by squares (filled = semantic task, open = perceptual task), the recognition tasks by circles (filled = recognition of items encoded with the semantic task, open = recognition of items encoded with the perceptual task), and the fixation condition by black triangles.

Subsequent analyses revealed no significant differences between age groups at any point (at $p < .05$, corrected), but there were trends for a difference between the young and old groups at time points 3, 5, and 7 ($p < .08$, corrected).

Finally, it should be noted that there was not a complete overlap between those areas with task-related changes and those whose activity was correlated with age. For example, a ventral inferior frontal region, the left

caudate nucleus, and the fusiform gyrus showed a decrease in activity with age, but did not show significant modulations of activity due to the tasks. In addition, many of the regions with task-related changes in activity did not show a correlation with age. These include the bilateral anterior and left dorsolateral prefrontal cortex and lateral parietal regions, which showed increased activity during the tasks. Similarly, there were regions of the temporal lobes where activity during the memory

Table 2. Brain Areas with Task-related Modulation of Activity

<i>Brain Region</i>	<i>Hem</i>	<i>BA</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Ratio</i>
<i>Task > Fixation</i>						
Inferior frontal gyrus	L	47	-40	24	-4	7.8
	L	10	-48	40	12	8.3
Middle frontal gyrus	R	9	44	20	32	9.6
	R	10	32	52	8	7.8
	L	46	-48	28	24	11.7
Fusiform gyrus	R	18	36	-76	-20	7.2
	L	37	-48	-52	-24	8.3
Inferior parietal	L	40	-44	-56	44	11.9
Superior parietal	R	7	32	-68	40	10.5
<i>Task < Fixation</i>						
Medial frontal gyrus	L	10	12	44	-12	-12.3
Dorsal anterior cingulate	L	24	-12	-8	40	-7.8
Posterior cingulate gyrus	R	23	8	-60	16	-9.2
	R	31	8	-40	36	-10.5
Superior temporal gyrus	R	22	44	-36	16	-8.8
Middle temporal gyrus	R	21	56	-8	-24	-9.0
	R	37	48	-60	4	-10.6
	L	21	-48	-44	8	-7.1
	L	37	-44	-64	8	-7.6
Inferior temporal gyrus	L	21	-60	-16	-4	-7.3

Coordinates are in MNI space. *x* (right/left): Negative values are in the left hemisphere; *y* (anterior/posterior): Negative values are posterior to the zero point (located at the anterior commissure); *z* (superior/inferior): Negative values are inferior to the plane defined by the anterior and posterior commissures.

Hem = hemisphere; R = right; L = left; BA = Brodmann's area; Ratio = salience/*SE* ratio from the bootstrap analysis, which is a measure of the reliability of each voxel's contribution to the pattern of activity (ratio ≥ 4.0 , $p < .001$).

tasks was reduced, but no correlation with age was found. Thus, although most of the areas where activity correlated with age also showed task-related modulations in activity, these areas were only a subset of those areas showing task-related changes.

DISCUSSION

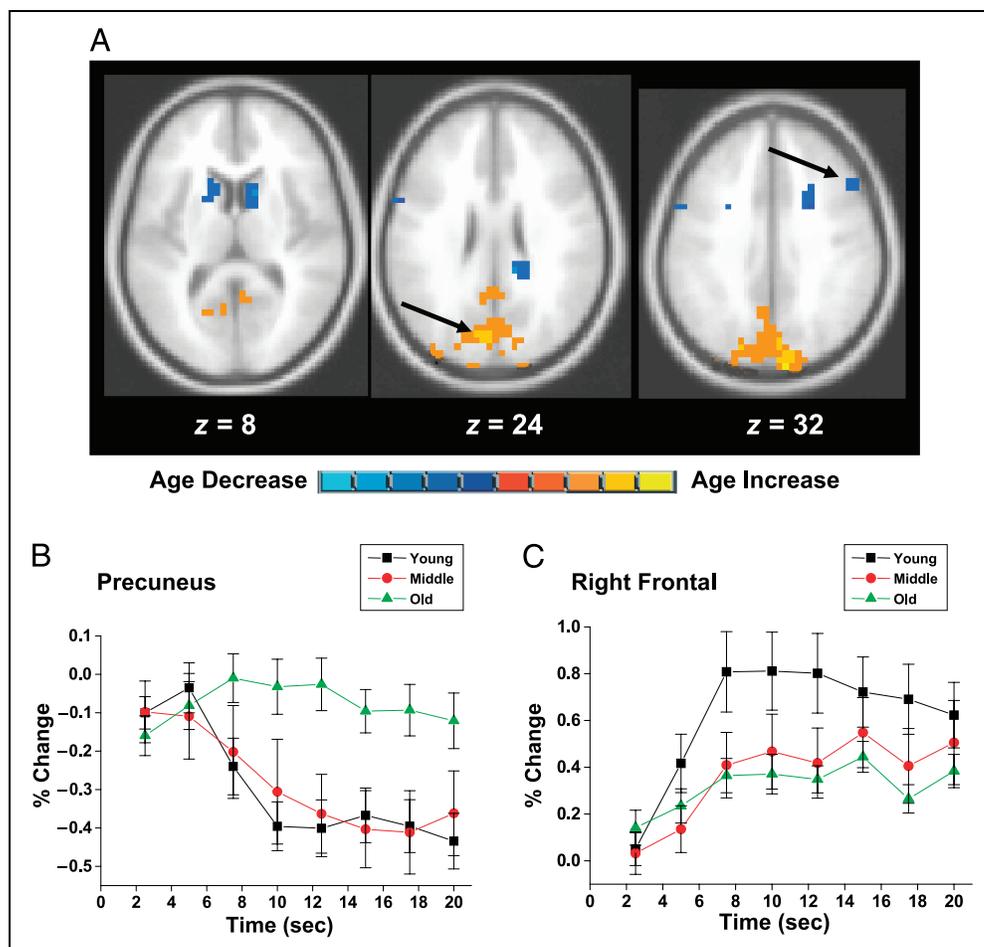
There are two novel findings from this experiment. The first is that significant linear correlations were found in a number of regions between activity and age, and these correlations characterized all of the encoding and recognition tasks, relative to fixation. The observed pattern of correlations suggests a generalized mechanism that is

not specific to either task demands or to the type of visual stimulus that is processed. The second main finding of this experiment is that some areas of the brain with increased activity during the tasks showed a linear reduction with age in this increase, whereas other areas with task-related decreases of activity showed an increase with age. This indicates that the degree of modulation of brain activity that occurs in response to carrying out these memory tasks, both in terms of increases and decreases in activity, is reduced over the adult lifespan. We conclude that this pattern of results reflects a progressive inability to recruit some of the areas engaged by younger adults for task performance and/or reduce activity in areas typically less active during cognitive tasks.

Linear correlations between brain activity and age were observed for both encoding and recognition tasks, indicating that the age differences in brain activity occur gradually, with middle age representing a transition between the pattern observed in youth to that found with old age. In addition, these correlations were found despite the fact that there were no significant age differences in encoding performance, and no difference between young and middle-aged adults on any of the fMRI tasks or standard memory tests. It has been noted previously that differences in brain activity between young and old adults can be found even when there are no observable differences in behavioral performance (Grady et al., 2003; Cabeza et al., 2002; McIntosh, Sekuler, et al., 1999). Our results show that brain measures also can be more sensitive to the effects of age than behavioral measures in middle-aged adults. One factor that could lead to this differential sensitivity in middle-aged and older adults is education, as a number of groups have shown that higher education in patients with dementia is associated with less severe behavioral deficits than would be expected on the basis of their brain abnormalities (Alexander et al., 1997; Stern, Alexander, Prohovnik, & Mayeux, 1992). This type of "protective effect" on behavior could also characterize our sample, most of whom were fairly well educated. That is, higher-education levels in the middle-aged and older adults may allow for some redundancy of brain function or compensation that leads to preserved performance, at least on some tests, despite altered brain activity. On the other hand, it is possible that other cognitive functions, not assessed in this study, would show a difference between young and middle-aged adults. For example, we did not assess attentional function or inhibition directly, and it may be that behavior on tests tapping these functions would show a pattern of difference more in line with that seen in brain activity. Clearly, the age differences in brain function that we found here need to be examined in relation to a broader spectrum of cognitive abilities.

Any mechanism of aging that has the potential to affect multiple types of processing should be seen across

Figure 2. Areas where activity was correlated with age are shown on the MNI average brain ($p < .002$) in A. Orange and yellow areas are those where there was increased activity with age during the encoding and recognition tasks, and blue areas are those with decreased activity with age during the tasks (see also Figure 3). B shows the time course of activity in the task blocks (averaged over all the tasks for each time point or TR) for the three groups in the precuneus (see Table 3). C shows the mean time courses for a right frontal voxel (see Table 3). Data in these time courses are expressed as the percent change relative to the preceding fixation time point. The two regions for which the time course data were extracted are indicated by black arrows. Error bars indicate the standard error.



a variety of stimuli, tasks, and cognitive domains. The pattern of activity that was seen here satisfies the first two criteria, that of generality across stimuli and tasks. Although our data speak only to differences seen in the memory domain, the fact that there was no hint of any task specificity suggests that this pattern may hold for other cognitive domains as well. Across all of our tasks, increasing age was associated with more activity (i.e., less “deactivation”) in the medial frontal, cingulate, and the precuneus. These medial brain areas have been recently described as part of a “default-mode” network (Raichle et al., 2001). Default-mode activity is thought to accompany the monitoring and evaluating of one’s environment and internal milieu, and thus, is greater when participants are not engaged in a specific task. Medial regions, such as the cingulate gyrus, are particularly suited for such a function, given the convergence of inputs to the anterior portion of the cingulate from the amygdala and limbic regions and to the posterior cingulate from the occipital and parietal cortex (Van Hoesen, Morecraft, & Vogt, 1993; Vogt, Finch, & Olson, 1992; Vogt & Pandya, 1987). There also is evidence from functional neuroimaging experiments of anterior medial frontal activity during self-reference tasks (Fossati et al., 2003; Craik et al., 1999) and posterior cingulate activity

during visuospatial attention tasks (Small et al., 2003), suggesting a role for these regions in monitoring the internal and external environments, respectively. If these areas do indeed function as a default-mode network, our results suggest that there is a progressive reduction with increasing age in the ability to suspend this default-mode activity during task performance. If this monitoring is not suspended, it might make it difficult to filter out extraneous and irrelevant information in the internal or external environment. Our finding of reduced default-mode activity with age is consistent with a recent report by Lustig et al. (2003), and extends their work to show that age changes in default-mode activity begin in middle age and occur in the context of multiple tasks. Another recent article (Chee & Choo, 2004) found reduced “deactivation” in default-mode regions after sleep deprivation, suggesting that this effect may be a general response to less efficient brain function under a number of conditions, in addition to aging.

What might cause a reduction in the ability to suspend activity in these default-mode regions? One possibility is that there is reduced activity in one or more brain regions that act to inhibit this network. We found decreased activity with age in dorsolateral prefrontal regions, similar in location to frontal areas implicated

in inhibition of conflicting or interfering information (Garavan et al., 1999; Jonides et al., 1998), allocating attention (Luks, Simpson, Feiwell, & Miller, 2002), and monitoring information retrieved from memory (Henson, Shallice, & Dolan, 1999). Also of interest is a recent study that found increased dorsolateral prefrontal activity during a condition in which there was inter-

ference between conflicting auditory and visual cues (Weissman, Warner, & Woldorff, 2004). Thus, activity in the prefrontal cortex during the memory tasks used here, particularly in the right middle frontal gyrus, might be an indication of either heightened attention or suppression of distracting sounds needed to carry out the visual memory tasks in the noisy MRI environment. Greater activity in these frontal areas could, in turn, lead to greater reductions in brain activity in default-mode areas. It is not possible to determine from our data whether this frontal activity represents increased attentional focus or inhibition, but regardless, the end result of less activity in the prefrontal cortex, and more activity in default-mode regions, could be a reduced ability to ignore distracting or irrelevant information from the environment.

Analysis of the time course data in the precuneus and right frontal cortex suggested that the age differences in areas with less activity during the tasks might take a slightly different form from that seen in the regions with task-related increases, at least in these two regions. That is, the age difference in the precuneus was sustained throughout the task block, whereas that in the right frontal region was less reliable, with a trend for an age difference only in the middle portion of the task block. This result could have been influenced by the greater degree of variability in the right frontal signal and could indicate that age differences in deactivation are more robust than differences in activation. This conclusion is reasonable if the activity in medial frontal and parietal regions is truly the “default” mode of the brain, and reflects activity that characterizes the brain when it is not carrying out any specific task. If so, then this activity should be less variable within and across groups than task-related activity, which by its very nature would be different from one task to another. Our results also highlight the importance of examining deactivations in the brain, in addition to activations, to determine differences due to age, dementia, or other factors. The vast majority of functional neuroimaging studies have focused solely on activations (e.g., Cabeza & Nyberg, 2000), but our results, and those of others who have

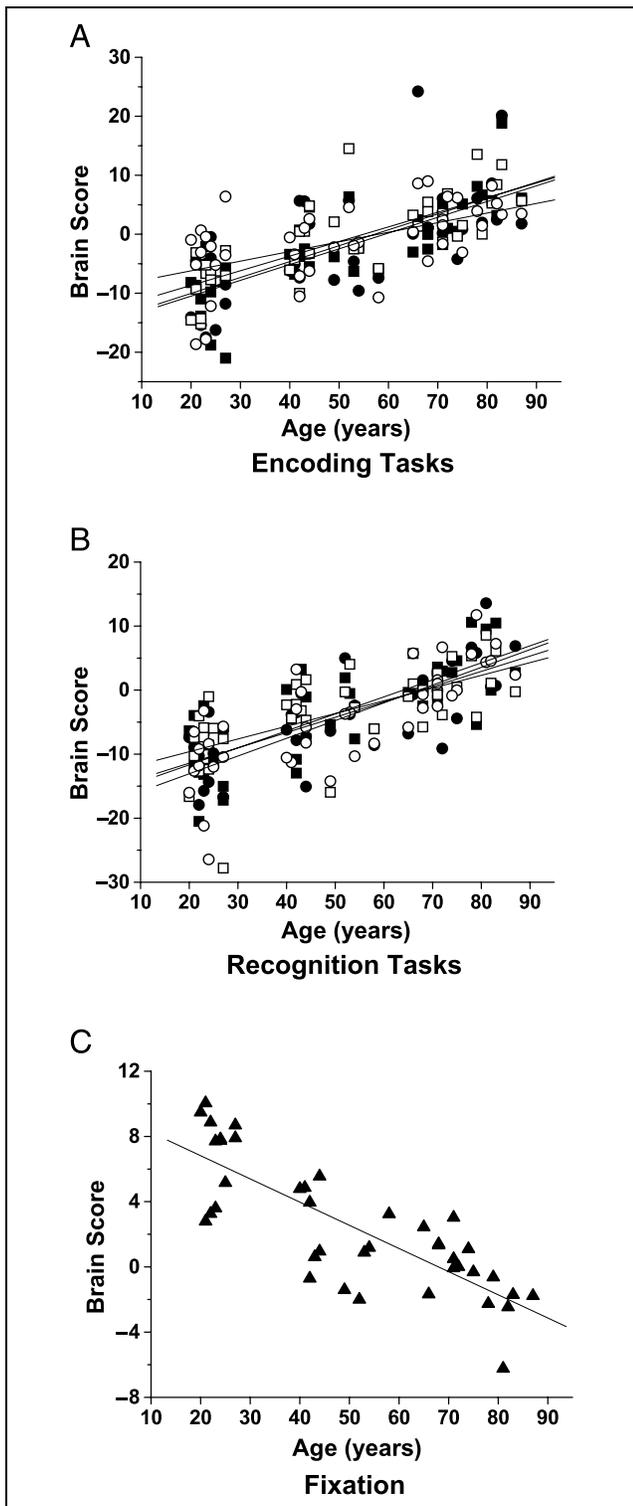


Figure 3. Scatterplots of brain scores versus age for the memory tasks and fixation are shown. During the memory tasks, the correlations are positive, whereas the correlation is negative during fixation. That is, during the encoding and recognition tasks, older adults show greater activity in the yellow and orange areas seen in Figure 2 (resulting in more positive brain scores), whereas younger adults show more activity in the blue regions (resulting in more negative brain scores). During fixation this pattern was reversed. All of the correlations between brain scores and age are reliable (99% confidence interval). Data from the picture conditions are shown as squares and data from the word conditions are shown as circles. Filled symbols indicate the semantic conditions, and open symbols the perceptual conditions. The fixation condition is shown by triangles.

Table 3. Brain Areas where Activity is Correlated with Age during the Tasks

<i>Gyrus or Region</i>	<i>Hem</i>	<i>BA</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Age</i>	<i>Task</i>
<i>Increase with Age</i>							
Medial frontal gyrus	L	10	8	52	-8	4.4	-5.8
Cingulate/medial frontal	M	24/6	0	-8	48	5.0	-4.0
Middle occipital gyrus	L	19	-40	-88	20	4.3	-2.1
Cuneus	R	19	12	-92	36	8.9	0.1
Precuneus	L	18	-8	-76	24	6.8	-5.5
Precuneus	L	7	4	-40	48	5.3	-8.9
Posterior cingulate	R	31	-4	-52	28	4.8	-6.0
<i>Decrease with Age</i>							
Middle frontal gyrus	R	9	48	20	32	-5.2	8.1
Inferior frontal gyrus	R	47	24	28	-12	-4.4	1.2
	L	44	-56	8	36	-4.9	5.4
Caudate nucleus	R		12	12	8	-5.5	3.9
Caudate nucleus	L		-12	16	8	-4.9	-1.6
Putamen	L		-24	4	0	-6.1	4.1
Fusiform gyrus	L	37	-40	-52	-16	-5.4	0.5

Coordinates are in MNI space. *x* (right/left): Negative values are in the left hemisphere; *y* (anterior/posterior): Negative values are posterior to the zero point (located at the anterior commissure); *z* (superior/inferior): Negative values are inferior to the plane defined by the anterior and posterior commissures.

Hem = hemisphere; R = right; L = left; M = midline; BA = Brodmann's area; Age = salience/*SE* ratio of each region (measure of the reliability of each voxel's contribution to the pattern) from the correlation analysis of age and brain activity ($p < .001$); Task = salience/*SE* ratio for each set of coordinates taken from the analysis of brain activity across the task conditions (to indicate whether each of the regions also showed a reliable change in activity between task and fixation, ratio ≥ 4.0 , $p < .001$). Time courses for the regions in italics are shown in Figure 2B and C.

studied the default mode (Greicius et al., 2004; Lustig et al., 2003), indicate that this approach overlooks some valuable information about brain function.

Other areas with age differences besides the right prefrontal cortex and the default-mode regions also deserve some comment. Our finding of reduced occipital (fusiform) activity with age during memory tasks is consistent with that noted by others during a variety of tasks (for a review, see Anderson & Grady, 2001), and with the suggestion that reduced sensory processing might be a common cause of age differences in cognition (Cabeza et al., 2004). Our results would suggest, however, that areas involved in visual processing are part of a larger network of task-relevant regions that is recruited to a lesser degree in older adults. In this view,

reduced sensory processing would be only a part of the common mechanism. The decrease in caudate activity with age also is interesting given the proposed role of this area in habit learning and probabilistic learning (Beauchamp, Dagher, Aston, & Doyon, 2003; Poldrack et al., 2001). In addition, the increased activity in the dorsal anterior cingulate seen with age is in a region of the cingulate involved in motor tasks (Paus, 2001; Petit, Courtney, Ungerleider, & Haxby, 1998). This decrease with age in caudate activity, coupled with an increase in motor cingulate activity, may indicate that there is a decrease with age in learning the procedural aspects of cognitive tasks, and thus, more demand on the regions involved in motor activity or motor planning. Increased activity in the motor cingulate could also be related to the increase in response times that is routinely seen with age.

Our finding of reduced activity in some brain regions and increased activity in other areas is unlikely to be due to structural changes in the brain that are common with age (e.g., Raz et al., 1997; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995; Murphy, DeCarli, Schapiro, Rapoport, & Horwitz, 1992), due to the fact that the correlation pattern differentiated the memory tasks from fixation. If the functional changes were simply the result of structural alterations, the pattern would have been the same across all conditions, including fixation. It also might be argued that the older adults exhibit a more "flattened" brain response, compared to the younger adults (i.e., less of a decrease or an increase depending on the direction of change seen in the younger group), due to age differences in the hemodynamic response and in signal-to-noise (Huettel, Singerman, & McCarthy, 2001; Buckner, Snyder, Sanders, Raichle, & Morris, 2000; D'Esposito, Zarahn, Aguirre, & Rypma, 1999). However, our finding that only some, and not all, of the brain regions with task-induced modulation of activity also showed correlations with age argues against the idea that our results are due solely to age differences in the hemodynamic response. That is, a simple "flattening" of the brain's response to cognitive challenge in older adults would be expected to affect most, if not all, of the areas showing this response, rather than just a subset of them. Instead, the effect of age appears to be somewhat selective, affecting mainly default-mode regions and the dorsolateral prefrontal cortex. A role for age-related vascular changes cannot be ruled out completely, but it appears unlikely that vascular changes alone could account for our results.

Another question to consider is whether the age-related changes seen here between task conditions and the fixation baseline could be the result of age differences in the baseline condition itself. This question cannot be answered from fMRI data, as absolute measures of function are not obtained with the blood oxygen level dependent (BOLD) technique used here. However, data from studies of resting glucose metabolism using

positron emission tomography are relevant to this issue. Reductions with age in cerebral glucose metabolic rates have not always been found and, when present, are not found in all regions of the brain (e.g., Ibanez et al., 2004; Leenders et al., 1990; Duara et al., 1984; Kuhl, Metter, Riege, & Phelps, 1982). Recent evidence suggests that the most consistent areas with age-related reductions are the anterior temporal lobes, frontal opercula, medial frontal, and lateral frontal regions, with relative sparing of occipito-parietal and posterior cingulate regions (Willis et al., 2002; Petit-Taboué, Landeau, Desson, Desgranges, & Baron, 1998; Moeller et al., 1996). This pattern of reductions in baseline metabolic function does not readily explain our findings. For example, both medial and lateral frontal regions show age reductions in metabolism, but different correlations with age in our experiment (positive and negative correlations, respectively). In addition, it is not clear why relatively preserved resting activity in medial posterior brain regions, such as the precuneus and posterior cingulate, would result in the failure of these regions to modulate their activity between baseline and task states to the same degree as in younger adults. In fact, one might even argue that preservation of function in this region should make it *more* likely that the response would be similar to that found in younger individuals, but clearly it is not.

Finally, it should be noted that our finding of altered default-mode activity in older adults is similar to that seen in patients with Alzheimer's disease, or AD (Lustig et al., 2003). It is not possible to know with certainty that one has excluded older individuals who have a dementing illness, but as yet show no symptoms, even if the mental status scores are in the normal range. Therefore, despite the fact that all of our older participants had normal mental status, the pattern of age differences in brain activity seen here could be influenced by inclusion of some older adults with incipient AD. However, there are two aspects to the results that argue against the conclusion that our results are influenced significantly by this problem. First, we found that middle-aged adults showed intermediate brain activity between young and older adults, and the incidence of dementia only rises rapidly after age 60 (e.g., Brookmeyer, Gray, & Kawas, 1998). The second finding arguing against an influence of incipient AD in our sample is that the variability of the fMRI signal in the older group was no larger than that seen in either of the other two age groups (see Figure 2B and C). In addition, there were no outliers in the older group in terms of brain activity in our analyses (see Figures 1B and 3). If this older group contained some individuals with undiagnosed AD, as well as healthy individuals, one would expect the variance to be larger, or for there to be outliers, or both.

In conclusion, we have shown that there are alterations of brain function with age that can affect a number of cognitive processes. The increase of activity in brain areas not typically engaged during memory

tasks, along with reductions of activity in task-relevant areas, is consistent with the theory of cognitive aging that older adults are more susceptible to the distracting effects of task-irrelevant information (Hasher & Zacks, 1988). The efficiency with which one can reduce activity in areas engaged when resting or in a baseline state, and redirect attention elsewhere, would be fundamental to cognitive function in general. Reductions in this efficiency could underlie many of the cognitive changes that are seen with advanced age. In addition, our results would be broadly consistent with the frontal lobe theory of aging, in that the frontal cortex is one of the main regions involved in the age differences seen here and may play a critical role in producing these differences. However, the pattern of changes in its entirety is complex and extends beyond the frontal cortex. Cognitive aging thus may be the result of an alteration in the balance between default-mode activity and task-related activity that depends on a number of age-related changes in the brain, as well as on the complex interplay of biological and nonbiological factors that may have to be taken into account to understand this brain modulation effect.

METHODS

A total of 21 young (20–30 years of age), 19 middle-aged (40–60 years), and 29 old adults (65–87 years) participated in the study. Data from some of the participants could not be used due to excessive motion during scanning or other technical problems. In addition, as the young and old groups were initially recruited to examine the effects of education on brain activity (Springer, McIntosh, Winocur, & Grady, 2005), a few of them had somewhat low mental status scores on the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975), consistent with their lower educational level (Crum, Anthony, Bassett, & Folstein, 1993). Exclusion of these individuals resulted in a final sample of 12 young (5 men), 12 middle-aged (4 men), and 16 old adults (8 men). All were right-handed. Structural MRIs were obtained at the same time as the functional scans to screen out participants who had overt brain abnormalities, more atrophy than would be expected for their age, or severe white matter changes. Exclusion criteria included history of stroke, heart attacks, and psychiatric diseases. As is typical for older adults, some were on medications for hypertension (5 participants), high cholesterol (3 participants), and arthritis (4 participants). There were no differences among groups in mean years of education (Table 1). There also were no group differences in mental status scores and all participants scored in the normal range (≥ 26). The Ethics Committee of Baycrest Centre for Geriatric Care approved this experiment and each participant gave informed consent.

Participants were administered a brief battery of neuropsychological tests to assess various aspects of cogni-

tive function. These included the vocabulary and digit-symbol subtests from the Wechsler Adult Intelligence Scale (Wechsler, 1955), the Controlled Oral Word Association Test (Spreen & Strauss, 1998) to assess verbal fluency, and the Hopkins Verbal Learning Test (Brandt, 1991). Scores on these tests, which were at or above the 50th percentile for the age- and education-matched norms on these tests (Benedict, Schretlen, Groninger, & Brandt, 1998; Spreen & Strauss, 1998; Wechsler, 1997), are shown in Table 1.

The stimuli used for fMRI were black line drawings of nameable objects and words corresponding to the names of objects (Snodgrass & Vanderwart, 1980) presented on a white background. Two lists of objects and two lists of words were assigned to the encoding tasks in a counterbalanced fashion. The object lists were matched in terms of item familiarity and complexity of the line drawings. The word lists were equated for the frequency of the words in the English language (Kucera & Francis, 1967) and word length.

Participants lay supine on the MRI scanner bed with their head stabilized by an air-filled vacuum cushion. The stimuli were projected from a computer located outside of the scanner room onto a mirror inside the head coil, or, for participants needing correctional lenses, through Silent Vision Goggles (Avotec, Stuart, FL) placed over the participant's eyes. Participants were scanned while engaged in four encoding and two recognition tasks. Two different encoding tasks were performed on words and pictures in order to facilitate comparison with other studies of aging and episodic memory (e.g., Grady et al., 2002; Stebbins et al., 2002; Grady, McIntosh, Rajah, Beig, & Craik, 1999; Schacter, Alpert, Savage, Rauch, & Albert, 1996). In a perceptual encoding condition, participants determined whether the pictures presented were large or small and whether the words were printed in capital letters or in lower case. In a semantic encoding condition, participants judged whether the pictures or words corresponded to living or nonliving entities. The participants pushed one of two buttons to indicate their response. The stimulus lists for each encoding condition were divided into blocks of six words or pictures; each presented for 3 sec with 1 sec between stimuli. Following each 24-sec stimulus block was a baseline block of equal duration in which participants pushed a button each time a fixation cross appeared on the screen. Thus, each study list consisted of a total of 24 words or pictures, broken up into four stimulus blocks alternating with the same number of fixation blocks. The order of the encoding conditions was counterbalanced across the participants.

After completion of the encoding tasks, participants were administered two scanned recognition tests, one for the studied words and the other for the studied pictures. The order in which the tests were given was counterbalanced across participants. Both recognition tests were made up of words written in lowercase

letters, including the one for the encoded pictures. This was done so that picture memory would be more similar to that for the studied words, reducing the picture superiority effect (Paivio, 1971). Each recognition list consisted of 48 words, 32 of which had been studied in one of the previous encoding conditions (as either a word or picture) and the remaining 16 consisting of new stimuli that the participant had not encountered during the encoding phase. Participants indicated via button press whether each stimulus was old or new. The test lists were divided into blocks of six stimuli (4 old and 2 new), each presented for a duration of 3 sec with a 1 sec interstimulus interval. Blocks containing old items that had been semantically encoded alternated with blocks containing perceptually processed stimuli. Intervening between these task blocks was the same fixation cross monitoring task that was used as the control task for the encoding scans.

Imaging was performed with a 1.5-T MRI scanner with a standard head coil (CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). The functional BOLD MRI signal was measured from 26 slices (5 mm thick). The imaging sequence was a single shot T2*-weighted pulse sequence with spiral readout (TR = 2500 msec, TE = 40 msec, flip angle 80°). A structural scan was obtained prior to the functional runs by using a 3-D T1-weighted pulse sequence (TR = 12.4 msec, TE = 5.4 msec, flip angle 35°, 22 × 16.5 field of view, 124 axial slices 1.4 mm thick). Six functional runs were obtained in total, four for encoding and two for recognition.

Motion correction of the images was performed using the Analysis of Functional Neuroimages software package (Cox, 1996). Each of the six functional runs for each participant was registered to the run that reduced the amount of movement to less than 1 mm (typically the first functional run of the encoding tasks). The realigned images were spatially normalized to a template in the brain space of the Montreal Neurological Institute (MNI), which approximates the space of a standard brain atlas (Talairach & Tournoux, 1988), and smoothed with an 8-mm filter using SPM99 (Frackowiak & Friston, 1994).

Partial least squares (PLS; McIntosh, Bookstein, et al., 1996) was used for two analyses on the brain images, one to examine brain activity across the task conditions and one to assess correlations of brain activity with age. The fMRI signal within each block of images (task and fixation) was normalized to the first image in the block and averaged across blocks for each task. This resulted in nine conditions in each of the PLS analyses: semantic encoding of words and pictures, perceptual encoding of words and pictures, recognition of semantically encoded words and pictures, recognition of perceptually encoded words and pictures, and fixation. In the first analysis that examined task-related activity, the images for all conditions for all three groups were entered into a single analysis. PLS was used to determine the

covariance between brain voxels and the experimental design, thus identifying a new set of variables (so-called latent variables or LVs) that optimally relate the two sets of measurements. Each LV identifies a pattern of differences in brain activity across the tasks and the brain voxels showing this effect. Thus, this type of analysis identifies a group of brain regions that together covary with some aspect of the experimental design. Each brain voxel has a weight on each LV, known as a salience, which indicates how that voxel is related to the LV. A salience can be positive or negative, depending on whether the voxel shows a positive or negative relation with the pattern of task differences identified by the LV. Multiplying the signal intensity in each brain voxel for each subject by the salience for that voxel, and summing across all voxels, gives a “brain” score for each subject for each task on a given LV that indicates the degree to which each subject expresses the pattern of brain activity seen on the LV. Each task condition also has a corresponding “task” score that is an index of how the identified pattern of activity is expressed in each condition (these can also be either positive or negative). Plotting brain scores against task scores (see Figure 1B) gives an indication of how brain activity varies across tasks. To assess the effect of age, we carried out a second PLS analysis that calculated the covariance between the fMRI signal in each brain voxel and age within each task and then contrasted this covariance across tasks (e.g., McIntosh, 1999).

Two independent statistical measures were obtained for each PLS analysis. The reliability of each voxel’s contribution to each LV was determined through bootstrap resampling (Sampson, Streissguth, Barr, & Bookstein, 1989; Efron & Tibshirani, 1986). A reliable contribution for a given voxel was defined as a ratio of its salience to the standard error of the salience greater than or equal to 4.0, which approximates a p value of .001 (Sampson et al., 1989). Locations of the maxima for each reliable region are reported in terms of MNI coordinates as well as the estimated gyrus or Brodmann’s area (BA) as defined in the atlas. The bootstrap for the analysis of age effects also provided confidence intervals for each correlation between age and the brain scores from each LV, allowing assessment of how strongly the pattern of activity seen on the LV was correlated with age in each condition. The 99% confidence interval was used as the threshold for reliability for these correlations. In addition to these bootstrap measures, we assessed the statistical significance of each LV by means of a permutation test (McIntosh, Bookstein, et al., 1996; Edgington, 1980). In both the permutation and bootstrap procedures, all saliences are calculated in a single analytical step, hence, there is no need for correction for multiple comparisons (McIntosh, Bookstein, et al., 1996).

The time courses shown in Figure 2 were obtained by extracting the signal across all runs for all participants in a right frontal region ($x = 48, y = 20, z = 32$) and the

precuneus ($x = -8, y = -76, z = 24$). The signal for each time point in each task block was expressed as the percent difference from the last time point in the preceding fixation block and then averaged across all tasks for each participant to create a single “task” time course across the first eight TRs of the block (20 sec). These time courses were then averaged for the three age groups and analyzed using repeated-measures ANOVAs. Post hoc comparisons were made with t tests and Bonferroni corrections for multiple comparisons.

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The data reported in this experiment have been deposited in the fMRI Data Center (www.fmridc.org). The accession number is 2-2005-119CE.

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