THE EFFECTS OF AGING AND COGNITIVE PERFORMANCE ON PATTERNS OF NEURAL ACTIVITY MEASURED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Jennifer Lee Johnson

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As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Jennifer Lee Johnson

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and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

Lee Ryan, Ph.D.	3/25/04 date
Elizabeth Glisky, Ph.D.	3/25/04 date
Theodore Trouard, Ph.D.	3/25/04 date
Cyma Van Petten, Ph.D.	03/25/04 date
Elena Plante, Ph.D.	3/25/04 date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director: Lee Ryan, Ph.D. 3/25/04 date

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SIGNED: 

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DEDICATION

This work is dedicated to my grandparents, Clarence and Mildred Johnson.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Previous functional magnetic resonance imaging (fMRI) research has shown that older adults activated bilateral frontal regions during tasks in which young adults had unilateral frontal activation (Cabeza, 2001). It has been suggested that older adults recruit bilateral frontal regions to compensate for declining brain function in other regions (Cabeza, Anderson, Locantore, and McIntosh, 2002). The primary aim of the current study was to determine how bilateral activation patterns observed in the frontal lobe during encoding and recognition were related to both cognitive performance of older adults and to function in other brain regions.

Thirty-five older adults and 9 young adults completed an encoding and recognition task during fMRI scanning. During the encoding scans participants determined whether presented words were "natural" or "man made" objects. During the recognition scans, participants made "old/new" judgments for each word presented. Four sets of bilateral regions of interest (ROI) were defined from an overlap image of all participants' fMRI data: 1) right and left frontal cortex 2) right and left medial temporal lobe, 3) right and left parietal lobe, and 4) right and left lateral temporal lobe.

On a separate day participants completed a neuropsychological testing session that included a series of tests that had been previously used to characterize older adults in two cognitive domains, frontal (FL) and medial temporal lobe (MTL) function (Glisky, Polster & Routhieaux, 1995; Glisky, Rubin & Davidson, 2001).

Consistent with the previous research, older adults showed greater bilateral fMRI activation in the frontal lobes during encoding than young adults. However, bilateral

activation in the frontal lobes during encoding was associated with two different activation patterns: 1) when MTL activation was present, bilateral frontal activation was observed in older adults with high FL factor scores; 2) when the MTL was not active, bilateral frontal activation was found in older adults with low MTL factor scores. Older adults with high FL factor scores but who did not activate MTL had left lateralized frontal activation. Importantly, older adults with and without MTL activation did not differ in recognition performance scores, or factor scores.

INTRODUCTION

Over the last decade the increasing availability of magnetic resonance imaging (MRI) has helped stimulate a dramatic increase in functional MRI (fMRI) research. fMRI is an exciting compliment to lesion studies because it provides a noninvasive and relatively quick method for investigating brain activity in normal brains as well as those affected by psychological or neurological disorders. In order for fMRI to be useful for studying different brain activation patterns associated with neurological disease or disorders that occur in latter life, it is imperative that we first have an understanding of how brain activation patterns revealed by fMRI change with normal aging. Although the number of fMRI experiments has steadily increased, relatively few experiments have investigated normal aging. The cognitive neuroscience of aging is a young field that strives to bridge the gap between neuroscience of aging and cognitive psychology of aging.

FMRI has been criticized for not providing new information beyond what is otherwise available through lesion or behavioral studies. However, the cognitive neuroscience of aging is one field in which fMRI is providing new insights to what we know about the aging brain. Although behavioral experiments emphasize age-related decline in cognitive resource (Craik & Simon, 1980) or generalized slowing (Salthouse, 1996), neuroimaging studies indicate that patterns of activation are shifting in complex ways over the adult life span. Understanding the functional significance of fMRI activation patterns associated with aging has proved difficult, particularly because results from early studies were mixed. In fact, inconsistent patterns have been reported to date:

A) younger and older adults have equivalent activation (Grady, Maisog, Horwitz, Ungerleider, Mentis, Salerno, *et al.,* 1994; Grady, McIntosh, Rajah & Craik, 1998; Grady, Bernstein, Beig & Siegenthaler, 2002), B) regions of activation remain the same, but older adults show less extent of activation (D'Esposito, Zarahn, Aguirre, & Rypma, 1999), or C) older adults have different patterns of activation, with activity in some regions that is not found at all in younger adults (for review, see Cabeza, 2002; Maguire and Frith, 2003).

Several factors may contribute to these inconsistent findings. Possible methodological differences that may contribute to inconsistent findings include: differences between the imaging methods used (Positron Emission Tomography (PET) or fMRI), experimental design (blocked design or event-related design), differences in the threshold level used to determine active voxels, and subtraction conditions. Differences in participants' physical condition could also affect results, such as whether or not participants with hypertension were included or excluded (Carusone, Srinivasan, Gitelman, Mesulam, & Parrish, 2002; D'Esposito, Deouell & Gazzaley, 2003). Finally, cognitive differences between participants could influence results (Cabeza, Anderson, Locantore & McIntosh, 2002; Rosen, Prull, O'Hara, Race, Desmond, Glover, et al., 2002).

The focus of this dissertation was to explore the relationship between cognitive differences among older adults and fMRI activation patterns during encoding and recognition. Surprisingly, of the imaging studies that have studied memory in older adults, only two have assessed general cognitive ability outside the scanner (Cabeza *et*

al., 2002; Rosen *et al.,* 2002), and both of these studies limited their analyses of fMRI effects to the frontal lobes.

It is well known that neuropsychological performance is increasingly variable with age (Light & LaVoie, 1991). The relationship between variable cognitive performance and age-related memory decline was examined in a study by Glisky, Polster, and Routhieaux (1995). A neuropsychological battery of tests was administered to older adults who also completed source and item memory tests. Factor analysis was used to determine a subset of tests thought to be related to frontal lobe (FL) and medial temporal lobe (MTL) function. Regression analyses were used to remove age effects from individual test scores. The correlation matrix of residual scores from the regression analyses was submitted to a factor analysis. Composite scores (referred to as factor scores) were calculated for each subject by transforming raw test scores into z-scores, which were then averaged across all tests contributing to the factor score. Glisky *et al.* (1995) reported a double dissociation in normal older adults between memory for items or source, and composite scores. Participants who performed well on FL tests but poorly on MTL tests had better memory for source than items. Participants with the reverse neuropsychological profile, low FL scores but high MTL scores, had source memory deficits yet preserved item memory. This study is important because it linked FL-type function can contribute to memory performance. The two factors derived from these tests were validated in a subsequent study in which 100 adults were studied in a similar fashion. A confirmatory factor analyses supported the initial distinction between FL and MTL tests (Glisky, Rubin, & Davidson, 2001).

One obvious question is whether individual differences in FL and MTL tests could contribute to explanations of differential fMRI activation patterns observed in older adults. The present experiment investigated individual differences among older adults by administering the same neuropsychological test battery used by Glisky et al. (1995) to older adults who also completed a semantic encoding task and recognition test during fMRI. Older adults were characterized based on high or low performance on tests of FL and MTL function. Thus, four groups were formed: 1) high FL and high MTL (HH); high FL and low MTL (HL); low FL and high MTL (LH); and low FL and low MTL (LL). The primary aim of the current study was to determine whether the variability of activation patterns that differentiate old from young could be explained by variable performance on neuropsychological tests.

Before further describing the present study, I will discuss the background and research issues of the cognitive neuroscience of aging. The literature review will primarily focus on memory-related aging effects in the frontal and medial temporal lobe, and will be divided into five sections: 1) brain changes in aging; 2) cognitive changes in aging; 3) age-related issues in fMRI; 4) an overview of existing findings from the cognitive neuroscience of aging and related theoretical explanations of the results from neuroimaging.

Literature Review

Brain changes with aging

Global changes in the brain are seen with normal, healthy aging (for review, see Raz, 2000). Autopsy and structural MRI data show that there is a decrease of brain

volume with age. In particular, age appears to affect the frontal lobes more than other brain regions (Raz, Gunning, Head, Dupuis, McQuain, Briggs, *et al.,* 1997). Although both gray matter and white matter are affected by aging, they decline at different rates over the life span (Scheibel, 1986; Sullivan, Marsh, Mathalon, Lim & Pfefferbaum, 1995). As the volume of brain tissue decreases, there are corresponding increases of cerebrospinal fluid (CSF), as evidenced by sulcal widening and ventricular enlargement. The common notion that we lose neurons with age accounts for less of the volume change than previously assumed. Rather, neurons appear to shrink with age. At the neuronal level, there is evidence of decreased dendritic branching, and decline in neurogenesis.

Aging is also associated with vascular changes. Cerbrovascular disease is among the leading causes of death in the United States. Including older adults with hypertension has been shown to exacerbate age effects (Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002). Vascular changes are also reflected in decreased cerebral perfusion and increased white matter damage (Gunning-Dixon & Raz, 2000; Raz, Rodriguez & Acker, 2003).

A common observation in the white matter of older adults is the presence of white matter hyperintensities (WMH), which are viewed as bright (hyperintense) areas on T2-weighted MRI images. WMH may vary in size, shape and location. WMH seem to have at least two forms, punctate lesions or patchy, diffuse lesions that are commonly found in the periventricular region. WMH are thought to be associated with hypertension, and transient ischemic attacks, though the exact cause is still debated (Raz, 2000; Gunning-

Dixon & Raz, 2000). Functionally, WMH may be related to the general slowing associated with aging.

Although there are global changes in the brain with aging, the frontal lobe is particularly vulnerable. There is a greater parenchymal decrease in the frontal lobe than in other regions with normal aging (Tisserand & Jolles, 2003; Tisserand, Pruessner, Arigita, van Boxtel, Evans, et al., 2002; Resnick, Pham, Kraut, Zonderman and Davatzikos, 2003; Raz, 2000). The change in the frontal lobe has been linked to cognitive changes in aging, including working memory deficits, personality changes, decline of source memory, and others (Gunning-Dixon and Raz, 2003; Raz, 2000). However, it is important to note that decreases in frontal gray matter volume are not always correlated with decreased performance (Van Petten, Plante, Davidson, Kuo, Bajuscak, & Glisky, in press). The temporal lobes are also affected by aging, although hippocampus has been shown to be less affected than other regions of the temporal lobe (Sullivan et al., 1995).

Cognitive changes with aging

Two well established facts in aging research are that memory declines with age and that variability increases with age. It is not surprising that there are variable age-effects on different types of memory. One general distinction is that over-learned, automatic, or bottom-up processes tend to be preserved in aging, while controlled or top-down processes are more likely to be affected by aging (Hasher & Zacks, 1977; Jennings & Jacoby, 1993; for recent reviews, see Anderson & Grady, 2001; Hedden & Gabrieli, 2004). For example, word naming tasks are considered bottom-up processes because

they involve a highly over learned and automatic skill. Working memory tasks such as mental arithmetic or digit span are examples of top-down processing.

The type of memory that older adults typically complain about involves episodic memory, which refers to the content of specific events and includes temporal-spatial relations among events (Tulving, 1972). An event or episode may be anything from a typical autobiographical event (i.e. a birthday), to a typical event utilized by research paradigms (i.e. studying a list of words).

Consistent with common complaints, research has shown that, indeed, episodic memory declines with age (for review, see Balota, Dolan & Duchek, 2000). Converging evidence from studies of episodic memory in amnesia (Schacter, Harbluck, & McLachlan, 1984; Shimamura and Squire, 1987), reality monitoring (Hashtroudi, Johnson & Chrosniak, 1989) and normal aging (Craik, Morris, Morris, and Loewen, 1990; Glisky *et al.,* 1995) have demonstrated that memory for source can be separated from memory for items. Older adults have shown greater difficulty for source than for item memory. However, performance variability has also been found in source memory among older adults. In a study of older adults with poor frontal function, a source memory deficit was observed, but improved when attention was directed to integrate contextual information during encoding. This suggests that the deficit was not exclusively a memory problem (Glisky *et al.,* 2001).

In fact, a long line of memory research has been concerned with examining the effects of different encoding strategies in both older and younger adults. Semantic or deep encoding tasks are known to improve memory performance over perceptual or

shallow encoding tasks (Craik & Lockhart, 1972). Several studies have found that in situations of incidental encoding (no mention of subsequent memory test or encoding strategy), older adults perform worse than young adults, but that older adults' memory improves when instructed to use a deep encoding strategy (Glisky *et al.,* 2001; Craik & Rabinowitz, 1985; Park, Smith, Morrell, Puglisi, & Dudley, 1990). Similarly, variable age-effects during encoding have been reported in neuroimaging studies (discussed below). Behavioral and neuroimaging studies have proposed that some older adults fail to initiate encoding strategies that would lead to successful subsequent memory (Glisky *et al.,* 2001; Logan *et al.,* 2002).

Functional MRI signal

The blood oxygen level dependent (BOLD) signal measured by fMRI is an indirect measure of neural activity. Active neurons require more oxygen, which is delivered via the capillary bed by an increase of blood flow, referred to as the hemodynamic response (HDR). Oxygen-rich blood flowing to the neurons is called oxygenated hemoglobin. When oxygen is taken from the blood it then becomes deoxygenated hemoglobin. Deoxygenated hemoglobin is paramagnetic, thus it perturbs the local magnetic field on a microscopic scale. The presence of a paramagnetic substance causes inhomogeneity in the local magnetic field. Nearby proton spins precess at different frequencies, which results in a faster decay of the MR signal. The change in the local magnetic field is measured by T2*-weighted MRI. The critical component of the BOLD signal is that more oxygenated hemoglobin is delivered in response to neuronal activity than can be used by the neurons. Thus, during an 'active state' there is

an increase in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin in the venous side of the capillary bed. The oxygen molecules act as insulators of the iron-rich hemoglobin, thereby reducing the paramagnetic effect they would normally have at rest, which increases the MR signal compared to baseline.

The time course of the blood flow increase is referred to as the hemodynamic response (HDR). A typical HDR in young people has been shown to have specific temporal and spatial properties (Bandettini, Jemenowitz, Wong & Hyde, 1993; Dale & Buckner, 1997). A typical HDR to a given stimulus will have a short delay of 1-2 seconds before rising for about 2 seconds. The peak of the HDR will occur over a 2-3 second range and then the signal will fall back to baseline over the course of 3-4 more seconds. Often there is an undershoot lasting a few seconds, in which blood flow dips below the pre-stimulus baseline level. A single HDR will return to baseline after 14-16 seconds. The shape of the HDR is variable across subjects (Aquirre, Zarahn, & D'Esposito, 1998; McGonigle, Howseman, Athwal, Friston, Frackowiak & Holmes, 2000; Cohen & DuBois, 1999).

Neuroimaging of aging

Age-related changes in HDR have also been studied (D'Esposito, Zarahn, Aguirre, Rypma, 1999; Huettel, Singermann, & McCarthy, 2001; D'Esposito, Deouell, & Gazzaley, 2003). D'Esposito et al. (1999) found fewer active voxels in the central sulcus region in older than younger adults during a simple reaction time task. In fact, 25% of the older adults (5/20) did not have any voxels that met study criteria for significance. Older adults also had a greater amount of noise within their signal than younger subjects.

One issue raised is whether decreased activation in older adults is evidence of decreased neural activity or rather reflects a change in neurovascular coupling. That is, either older adults actually have less activity, or that the vascular response to neuronal activity (increased blood flow) is different in older adults. Reuter-Lorenz (2002) suggested that evidence of increased neural activity in regions not activated by younger adults provides support that aging does not change the coupling of neural activity to the HDR. If only diminished or absent activation patterns were reported, the hypothesis of age-related reductions in the hemodynamic response would be supported. This raises the question of whether experiments that report diminished activation are measuring only the number of active voxels in particular regions, or if they assess the signal amplitude.

Cognitive neuroscience of aging

Over the last decade, PET and fMRI experiments have produced three common results when older adults are compared to younger adults. Compared to young adults, older adults show: 1) reduced activation, 2) reorganization of networks of activation, or 3) recruitment of contralateral regions.

First, the landmark paper by Grady et al. (1995) reported reduced right prefrontal cortex activation in older adults during recognition of faces and a lack of significant activation in left prefrontal cortex at encoding, compared to young adults. The lack of activation in older adults may reflect older adults' failure to initiate a specific strategy to aid memorization. In fact, when older adults were given a task that required semantic elaboration of words at encoding, activation in these regions was increased (Logan *et al.*, 2002). Reduced activation in older adults compared to younger adults is often interpreted

as simply reduced functioning for a given task or process. However, as reported by Stebbins *et al.* (2002), activity may appear to be reduced, but in fact, due to the subtraction method, it is truly reflecting increased activation during the control task. This finding underscores the importance of designing fMRI and PET experiments with appropriate baseline conditions.

Second, in a recent paper, Grady, McIntosh and Craik (2003) reported that during semantic encoding of pictures of objects and words, hippocampal activity was correlated with increased activity in dorsolateral prefrontal and parietal regions in older adults. In contrast, young adults' performance was correlated with a network of activation in hippocampus, ventral prefrontal and extrastriate cortex. Similarly, Grady *et al.* (2001) demonstrated that memory performance in young and older adults was related to two different networks of regions. Activation in frontal-temporal circuits was associated with memory success in young adults. For older adults, however, frontal activation significantly decreased, and memory success was related instead to activation in temporal-parietal circuits. The differences in activation patterns associated with memory success between young and older adults shows indirect support of the dedifferentiation view. This view holds that, as we age, neuronal networks (regions) become less specialized to govern a specific process (i.e. retrieval or encoding) and instead the same networks are more likely to be associated with multiple tasks (Li & Lindenberger, 1999). Direct support for the differentiation view would require finding the same region active in older adults during various tasks combined with finding that the temporal-parietal

network associated with memory success in older adults was used for a different process in young adults.

Third, older adults may show increased bilateral activation in homologous regions to those observed unilaterally in young adults. The pattern of increased bilateral activation in older adults has been described in a model developed by Cabeza as Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002). Broadly, Cabeza suggested that aging is accompanied by a shift from hemispheric asymmetry, or localization of function in a singular hemisphere, to bilateral activation. Supporting evidence for the HAROLD model comes from several experiments that have shown increases in bilateral activation in older adults across a variety of tasks in which younger adults show lateralized activity. For example, whereas right-lateralized prefrontal activation is observed in young adults during episodic retrieval tasks (Nyberg, Cabeza & Tulving, 1996), older adults show bilateral prefrontal activity during cued recall (Cabeza, Grady, Nyberg, McIntosh, Tulving, Kapur, et al., 1997), word recognition (Madden, Gottlob, Denny, Turkington, Provenzale, Hawk, *et al.,* 1999), and face recognition (Grady *et al.,* 2002).

Increased bilateral frontal activation has been reported in older adults who show normal levels of memory performance as compared to older adults with lower memory function and young adults (Cabeza, et al, 2002). The authors suggested that bilateral activation in older adults may reflect compensation for age-related declines in neurocognitive function. For example, when a region in one hemisphere no longer effectively performs a given process or task, the homologous region in the contralateral

hemisphere would be recruited to bolster performance. This view is supported by other studies that have shown that bilateral activation in frontal regions in older adults is associated with better performance in several domains, including working memory (Reuter-Lorenz *et al.,* 2001) and recognition accuracy (Rosen *et al.,* 2002).

Compensation vs. Dedifferentiation

Several reports in the cognitive neuroscience of aging have tried to set compensation and dedifferentiation views against one another. Cabeza *et al.* (2002) suggested that strong support for the compensation hypothesis comes from any study that finds increased bilateral frontal activation in high performing older adults compared to lower performing young adults. In contrast, according to Cabeza, finding bilateral activation in older adults with lower performance would be support for the dedifferentiation hypothesis, which implies that activation in the contralateral hemisphere is due to the damaging effects of aging (Cabeza, 2002). Compensatory activation of the non-dominant hemisphere has also been suggested to reflect the "deleterious influence of age upon dominant hemisphere neural systems (Rosen et al., 2002). Thus according to both compensation and dedifferentiation hypotheses an increase of bilateral activation with aging is ultimately suggestive of decline associated with aging. Whether that change has a neurological or cognitive basis is not yet known (Cabeza *et al.,* 2002).

Others have presented a different framework for the dedifferentiation hypothesis (Li & Lindenberger, 1999; Grady, 2002; Li et al., 2004). In fact, whereas Cabeza describes dedifferentiation as a rather negative outlook on aging, Li & Lindenberger (1999) suggest a more positive interpretation: that dedifferentiation is part of a natural

process of the aging brain. That is, developmentally, the brain starts out quite differentiated, then through neural pruning and experience regional specialization occurs throughout development and adulthood. In advanced age, as regions gain expertise and efficiency, other functions may be able to be performed by different regions.

Support for the compensation view was sought by two recent studies in which older adults were divided into high- and low-performing groups based on neuropsychological testing obtained outside the scanning environment (Cabeza *et al.*, 2002; Rosen *et al.*, 2002). Cabeza *et al.* (2002) determined group assignment based on participants' performance on a series of tests (described above) that were previously developed and validated to characterize memory and executive function in older adults (Glisky *et al.*, 1995, Glisky *et al.*, 2001). Adults were selected who had high executive function (frontal function) but who had either high memory function (old-high group) or low memory function (old-low group). Cabeza collected PET scans during paired-associates recall and during source memory retrieval. In both experiments the control condition was simple visual fixation. Behavioral results were consistent with neuropsychological testing; the old-low group had worse memory performance than both old-high and young participants. When PET data from the recall task was contrasted with PET data from the source task, the HAROLD pattern of greater bilateral activation was seen in the old-high group during the source memory task. Older adults with low memory performance had left-lateralized activation similar to that of young participants in the study. Results from the reverse contrast (recall > source) were not consistent with the HAROLD model; young participants had greater activation in left dorsolateral

prefrontal cortex than both older adult groups, and the old-high group had less activation than young and old-low groups in the left ventrolateral region. Cabeza concluded that older adults with low memory function were using the same network as young adults, but ineffectively, whereas older adults with high memory ability were able to succeed at the memory task because they were able to recruit the contralateral hemisphere during the more difficult source memory task.

A second study that combined information from neuropsychological testing with neuroimaging was reported by Rosen *et al.* (2002). Whereas Cabeza's study used PET scanning during retrieval, Rosen *et al,* (2002) collected fMRI scans during a deep encoding task (natural or manmade judgment) and a shallow encoding task (upper or lower case judgment). Another distinction between the two studies is that Cabeza selected older adults with equal executive function performance based on five neuropsychological tests, and the Rosen study equated Mini-Mental Status Exam and National Adult Reading Test (NART) scores across older adult groups. Older adults were divided into high and low memory groups based on average percent correct from four memory tests. Two of the tests – Weschler Memory Scale Logical Memory I and Paired Associates I – were the same as the memory factor tests (Glisky *et al.,* 1995), which were used by Cabeza *et al.* (2002). The Benton Visual Retention Test - Revised and a locally developed memory recall test were also used. Recognition memory performance was best in the young participant group, followed by older adults with high memory, and older adults with low memory had the lowest recognition performance. When fMRI signal intensity data (corrected for spatial extent) from shallow encoding was

subtracted from deep encoding, Rosen *et al.* (2002) found that older adults with high memory function had greater activation than young adults in the right prefrontal cortex. Older adults with low memory performance had lower activation amounts than older adults with high memory performance in all regions of interest. It was concluded that finding greater right frontal activation in older adults with high memory performance was evidence for functional compensation for reduced function of the dominant (left) hemisphere. Findings from this study were consistent with the HAROLD model.

Similar to the experiments reported by Cabeza et al. (2002) and Rosen et al. (2002), a recent fMRI study reported activation differences between groups of older adults (Daselaar, Veltman, Rombouts, Raaijmakers & Jonker, 2003). Older adults were divided into high and low memory groups based on recognition performance during fMRI. Daselaar et al. (2003) used an event-related fMRI design to scan during incidental encoding (pleasantness judgment for words) as well as during recognition. Successful encoding was associated with fMRI activation in the left anterior MTL in young adults and older adults with normal memory. Older adults with reduced memory performance had lower levels of percent signal change in left anterior MTL compared to older adults with normal memory and young adults. During recognition performance, older adults with low memory performance also showed increased activation in multiple brain regions compared to the other two groups. Daselaar et al. (2003) suggested that lower recognition performance in older adults resulted from an encoding deficit, evidenced by reduced MTL activation, and further, that increased activation during recognition in the same group could reflect attempted compensation for poor encoding. In contrast to the

HAROLD model, older adults whose memory performance equaled young adults showed left-lateralized activation during recognition, whereas young adults and older adults with reduced memory had similar left and right activation. Daselaar suggested that differences in experimental design could have contributed to the failure to replicate the HAROLD pattern. In particular, only correct items were compared to baseline in the self-paced event-related design utilized by Daselaar, whereas Cabeza's PET study used blocked design.

Cognitive neuroscience of aging: current issues

Although older adults have been grouped based on memory performance, no existing functional neuroimaging experiment has divided older adults according to assessment of executive function. The observation of reduced asymmetry in the frontal lobes, coupled with known deleterious age-related changes in FL parenchyma, begs the question: what is the relationship between neuropsychological measures of frontal lobe function and the HAROLD pattern of activation during encoding and recognition?

The functional significance of the HAROLD pattern is unknown. A common interpretation is that increased activity in the non-dominant hemisphere reflects a need for compensation for failings of the dominant hemisphere (Rosen *et al.,* 2002; Cabeza *et al.,* 2002). Cabeza also suggested that reduced asymmetry in prefrontal cortex is evidence of compensation for declining memory function associated with the changes in memory networks. However, he does not specify which neural regions would be included in that network (Cabeza *et al.,* 2002). More research is needed to determine whether the HAROLD pattern reflects a change in the FL alone, or if there is a broader network

involving regions beyond the frontal lobe that may be changing. Results reported by Daselaar et al. (2003) suggest that older adults may show more than one activation pattern when medial temporal lobe is also examined.

As mentioned above, a few researchers have considered multiple regions simultaneously. Notably, work from Grady and colleagues have used partial least squares (PLS) analyses to determine activation networks related to participant performance (i.e., Grady et al., 2001; 2002; 2003). Additionally, a recent study of response inhibition, which is typically mediated by the right prefrontal – parietal network, found increased left PFC and increases in bilateral parietal regions in older adults with poor inhibition performance (Nielson, Langenecker, & Garavan, 2002).

Present Study

The primary aim of this study was to determine the relationship between executive and memory function and functional activation patterns in older adults during encoding and recognition. The present study was based on the three experiments described above that grouped older adults by memory performance. As pointed out by Daselaar et al. (2003), comparing older adults with high and low memory performance allows "normal" age-related changes to be distinguished from age-related changes that influence memory performance. Differences between young adults and older adults with normal memory would reflect "natural" brain changes across the lifespan, whereas differences between older adults with poor memory ability and young adults may indicate brain regions/processes associated with poor memory performance.

The same neuropsychological assessment that was developed by Glisky *et al.* (1995) and used by Cabeza et al. (2002) was used to determine high and low memory function in older adults. Additionally, the current study used FL factor scores to characterize high and low executive function in older adults (described in detail below). Similar to Rosen et al. (2002) and Daselaar et al. (2003), fMRI scans were collected during intentional semantic encoding of visually presented words while subjects made natural or manmade judgments, and during old/new recognition judgments. In contrast, Cabeza *et al.* (2002) collected PET data during retrieval of paired associates and source memory.

The inclusion of both FL and MTL factors allowed further investigation of the interaction between FL and MTL activation patterns during semantic encoding and recognition. Although the HAROLD model only makes predictions regarding activation in the frontal lobes, evidence presented by Daselaar et al. (2003) suggested that frontal activation interacts with MTL activation. This study examined whether the HAROLD pattern would be found in four ROIs including frontal lobe (FL), medial temporal lobe (MTL), parietal lobe (PL), and lateral temporal lobe (LTL). The frontal lobe and medial temporal lobe regions were specifically selected because it would be important to examine these regions since frontal lobe and medial temporal lobe function was assessed. Parietal lobe regions have been identified as part of a network involved in memory for faces (Grady et al., 2002). The lateral temporal lobe region has been observed during semantic categorization tasks (Saykin, Flashman, Frutiger, Johnson, Mamourian, et al., 1999) and with semantic encoding in older adults (Daselaar, et al., 2003). Since a

semantic encoding task was used in this study, lateral temporal lobe activation was expected.

Hypotheses were based on existing literature to predict behavioral performance and fMRI results during encoding and recognition. First, regarding behavioral performance, it was expected that all participants would perform well on the encoding task, and that young adults would perform better than older adults on the recognition task completed during scanning. Among older adults, it was expected that recognition performance in the scanner would correspond to neuropsychological assessment. Older adults with high MTL factor scores were predicted to perform better than their counterparts with lower MTL factor scores. Even though a deep encoding task and short recall interval were used specifically to encourage retrieval success, results from similar studies suggest that recognition performance would differ across groups. This pattern of behavioral results was found in the study by Rosen et al. (2002), who used the same semantic encoding task, and who also presented each item once. The experiment reported by Cabeza et al. (2002) repeated stimuli during encoding and found that only older adults in the low memory group performed worse than young adults. Daselaar et al. (2003) also repeated stimuli during encoding and found a similar pattern of behavioral performance as Cabeza et al. (2002).

Comparison of frontal lobe activation across age groups was predicted to show the HAROLD pattern, i.e., greater bilateral frontal activation in older adults, during both encoding and recognition. Among older adults, those with high MTL scores were predicted to have more bilateral activation during both encoding and recognition. In

agreement with previous findings (Rosen et al., 2002; Daselaar et al., 2003), it was expected that, during encoding, adults with low MTL factor scores would have reduced activation compared to other groups, but activation would be greater in left frontal lobe during encoding. In contrast, during recognition, older adults with low memory function were predicted to have greater bilateral activation in comparison to other groups. It was also expected that the HAROLD pattern would be observed in other ROIs examined in this study.

The present study examined whether bilateral frontal activation would be observed when older adults are grouped according to executive function performance, and whether posterior regions would show bilateral activation patterns similar to what has been observed in the frontal lobes. Although no previous fMRI or PET studies have compared older adults with high or low executive function, Cabeza et al. (2002) only included older adults with high executive function, and observed laterality differences among adults who differed only on memory performance. Activation patterns similar to those shown by Cabeza et al. (2002) in high and low memory performance groups were predicted in the high and low executive function groups matched for memory performance.

The relationship between recognition performance and fMRI activation during encoding and recognition was expected to be similar to predictions based on MTL factor scores. Older adults with low MTL factor scores were predicted to have lower recognition performance, and to show reduced activation during encoding and increased activation during recognition.

MATERIALS AND METHODS

Participants

Nine young adults (18-32 years old) and thirty-five older adults (65-85 years old) were recruited from the University of Arizona campus and greater Tucson community to participate in the study. All participants were screened to rule out any current or past psychological or physical condition that would interfere with cognitive functioning, such as head injury, loss of consciousness with sequelae, drug or alcohol addiction, or psychiatric disorder. The study was limited to right-handed native English speakers, who passed a metal screening questionnaire to ensure eligibility for fMRI. Informed consent was obtained in accordance with the University of Arizona Human Subjects Committee guidelines. Participants received payment of $6 per hour upon completion of the study.

Each participant completed two experimental appointments: a neuropsychological testing session and fMRI session. The neuropsychological testing session was completed within 2-3 hours and the fMRI session duration was 1.5-2 hours. Unless otherwise requested, the two experimental sessions were scheduled on separate days to avoid fatigue.

Three older adults were excluded from the study. One participant was excluded because he had a severe stutter, which invalidated results from any timed neuropsychological tests. Another participant was excluded because of a signal drop off and warping artifact in functional scans caused by the presence of a permanent dental bridge made from porcelain and gold. A final participant was not included because of an

inability to complete the fMRI session due to concerns about the noise level during the procedure.

Neuropsychology protocol

Testing was completed in a small quiet room free from distraction. Neuropsychological tests were selected to assess memory, executive function and general cognitive performance. Executive function and memory performance were measured by a series of neuropsychological tests that have been previously used to dissociate older adults into four groups based on their level of performance on tests of frontal lobe (FL), and medial temporal lobe (MTL) function (Glisky, Polster, & Routhieaux, 1995; Glisky, Rubin, & Davidson, 2001).

Tests contributing to the FL factor include: number of categories achieved on the modified Wisconsin Cart Sorting Test (Hart, Kwentus, Wade, & Taylor, 1988), the total number of words generated in a word fluency test, using initial letters *F*, *A*, and *S* (Spreen and Benton, 1977), Mental Arithmetic from the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler, 1981), Mental Control and Backward Digit Span from the Wechsler Memory Scale–III (WMS-III; Wechsler, YEAR). The tests contributing to the MTL factor include: Logical Memory I (WMS-III), Verbal Paired Associates I, and Visual Paired Associates II (WMS-R), Faces 1, first recall total (WMS III) and the Long-Delay Cued Recall measure from the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987).

FMRI Protocol

The fMRI sessions were completed using a General Electric 1.5T Signa LX Echospeed scanner at the University Medical Center at the University of Arizona. FMRI scans were collected during semantic encoding and a recognition memory task. DMDX computer presentation software (Forster and Forster, 2003) was used to present stimuli and obtain response times. Words and control items were presented in uppercase white 80-point Times New Roman font centered on a black background. During the fMRI session, participants viewed the stimuli through MR Vision 2000 goggles manufactured by Resonance Technology Inc., California. Response times were collected using two computer mice modified for use in the MRI scanner. Participants also wore headphones with an attached microphone in the scanner to enable the experimenter and participant to easily communicate between scans. To minimize head movement during scanning, foam cushions were placed between the participants' head and the head coil.

The fMRI recognition memory task was divided into two encoding and recognition sets, which were separated by a short break (2-3 minutes). Each run used a block design in which six experimental blocks (encoding or recognition) were alternated with seven control blocks, such that the scan began and ended with a control block. Each encoding and recognition block consisted of a list of 8 words displayed for 3 seconds each. Participants viewed words one at a time and were asked to make a decision about each word. The decision to be made varied with the phase of the experiment. Run 1 contained a series of 13 alternating blocks of encoding and control conditions. During the encoding phase participants were asked to press a button with the index finger of one hand if the word represented a natural object, and to press a button with the index finger

of the opposite hand if the word represented a nonliving (manmade) object. During the control condition, participants were asked to press the left mouse button when a string of "L's" appeared, and to press the mouse button in their right hand when a string of "R's" appeared. The control condition allowed activity related to visual processing and motor response to be subtracted from the two conditions of interest (encoding and recognition). Run 2 used the same blocked design as Run 1, however, during the recognition phase participants were asked to determine which words were previously presented during the encoding phase (old) and which are new words. Five of the eight words presented in each recognition block were seen in the preceding encoding phase, such that 30 words from the encoding phase were randomly distributed across the recognition blocks. After 2-3 minutes, a second set of encoding and recognition runs was collected (Run 3 and Run 4).

Prior to the experiment, participants were instructed to remember the words that they were to make natural/manmade judgments about because their memory for those words would be tested later. Participants were told that if they thought a word could be either natural or manmade, that they should respond with their first impression. Instructions for the upcoming run were reviewed prior to each scan. Prior to the scanning session, participants completed a short encoding and recognition practice session on a computer outside the scan room and were given an opportunity to ask questions. The only words that were repeated during the experiment were words from the encoding blocks that become "old" words during recognition blocks.

Stimulus selection

Lexical stimuli were selected by using the MRC Psycholinguistic Database (Wilson, 1987). Nouns were selected that fit the following parameters: number of letters = 4-7, Kucera-Francis (1967) written frequency was greater than 60 (min=60, max=591, average=157), and concreteness score greater than 350 (scale is 100-700, higher numbers indicate more concrete words, min=386, max=642, mean=561). Words retrieved from the list were divided into words that represent natural items and words that represent man-made items. Division was determined by the experimenter. Microsoft Excel was used to sort each natural and manmade word list by an assigned random number. The first 66 words from each list were selected to be used in the study. Forty-eight words were randomly chosen from each word list to be used for encoding trials, and the remaining 18 words were used as foils for the recognition test. Thirty words were randomly selected from each encoding list to be presented as targets for the recognition test. Natural and manmade word lists were combined within encoding and retrieval conditions, and then randomly ordered. The randomized list was then divided into 12 blocks of 8 words. The only constraint was that each block had to contain at least 3 words from each category. The blocks were divided into two runs of 6 blocks each (2 blocks 4 natural/4manmade; 2 blocks 3 natural/5manmade; 2 blocks 5 natural/3manmade). Seven blocks of control items were made using the same randomizing procedure described for word stimuli. Seven control blocks were used such that the scan began and ended with a control block.

Neuroimaging protocol

A three-plane GRE scout image was collected to be used to plan subsequent scans (matrix=256x128, TE=1.6 and TR, FOV=24cm, slice thickness=5mm, interslice skip=1.5mm). Next, a T1 weighted spin echo sequence was collected with the same slice selection as the functional scans (matrix=256x256, TE=9, TR=450, FOV=22cm, slice thickness=5mm, interslice skip=0, 20 images collected parallel to the AC-PC plane and planned such that one image passes through the AC-PC plane). Functional data was collected using a single-shot spiral sequence (Glover and Lee, 1995; TE=40, TR=1500, Flip=90, FOV=22cm, in plane resolution= 3.75 x 3.75, 246 repetitions). Collection of functional imaging data began nine seconds (6 TRs) after the start of the scan in order to exclude scanner signal noise (inhomogeneity) that occurs at the start of every scan. High resolution SPGR images (matrix=256x256, Flip=30, TE=9, TR=22, FOV=25cm, slice thickness=1.5mm) were collected to provide anatomical reference images for functional scans and to transform image sets into standard Talairach space.

Analyses

Neuropsychological testing

Each participant was assigned two scores, one representing relative performance on the group of executive tests associated with FL function and the other representing relative performance on the group of memory tests thought to represent MTL function. These tests were grouped previously according to the results of factor analyses: a) an exploratory principle factor analysis of data from 48 older adults (Glisky *et al.,* 1995), b) a confirmatory factor analysis of data from a separate group of 100 older adults (Glisky *et al.,* 2001), and c) a principal components analysis of updated versions of the

neuropsychological tests (which also added Faces I to the MTL factor) from a new group of 98 older adults (Glisky, unpublished).

Since participants in the present study were recruited from the same regional population as participants in the Glisky studies (Glisky et al., 1995; Glisky et al., 2001), composite scores were generated for each individual relative to Glisky's normative sample of 98 older adults. Additionally, the Wescheler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999) and the Mini Mental Status Exam (MMSE; Folstein, Folstein & McHugh, 1975) to further characterize general cognitive performance. Factor scores were included in fMRI analyses to determine how cognitive function relates to neural activation patterns during encoding and recognition.

fMRI behavioral data

A percent correct score was calculated separately for each encoding run. During the encoding task participants were asked to decide whether presented words were "natural" or "manmade." A few items were ambiguous, such as "spring," which could either mean the season, a water source, or a coil – as in a bed spring. Participants were instructed that if they encountered a word for which they could think of ways it could be either natural or manmade, they were to simply respond to the first meaning that came to mind. The percent correct score generated for the encoding condition was used to check that participants were correctly completing the task. Percent correct, hits, misses, correct rejections, and false alarms (FA) were calculated for each participant combined across both recognition task runs. Average scores for each group (young/old) were calculated. Differences between young and older adult recognition performance were assessed by t-

test. Recognition performance (hits-FA) of older adults was further assessed using a 2 x 2 ANOVA with FL (high, low) and MTL (high, low) groups as the two between-subjects factors.

Neuroimaging data analyses

Preprocessing. Images analyses were completed using Analysis of Functional Neuroimages software (AFNI, version 2.52g; Cox, 1996). First, raw GE spiral image files were reconstructed and converted to AFNI format. Image data from both encoding runs were concatenated together to produce one encoding file. Likewise, data from the two recognition runs were concatenated together to make one recognition file. Linear drift was removed from functional images. Minor head movement was corrected using a 3D-volume registration algorithm (AFNI 3dvolreg), in which all images were registered to one image from the first run. Active voxels for each condition were determined by using a voxel by voxel correlation of signal intensity from the imaging data and a model hemodynamic waveform. Since the hemodynamic response may be variable, both across older and younger adults and across brain regions within each subject, a set of 15 hemodynamic waveform models were submitted to the correlation analysis. Each waveform was tested on a voxel by voxel basis, and the waveform with the best-fit to the data was used. Analyses included voxels with correlation values significant at the $p < .001$ level. Since older adults may have less activation than younger adults, single voxels were kept in the analyses to maximize the number of voxels included in the analyses.

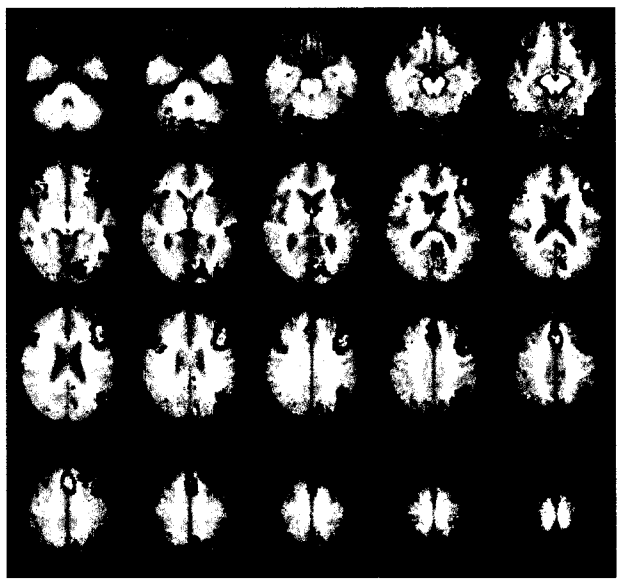
Each analysis described below was performed separately for imaging data collected during encoding and recognition phases of the experiment. For each functional

scan, experimental epochs (encoding or recognition) were contrasted with the control condition. Furthermore, each analysis was completed using two different fMRI measures: voxel counts, and fit coefficients. Although fit coefficient measures have been shown to be more reliable than voxel count measures (Cohen, 1997; Cohen & DuBois, 1999), voxel count was included here to allow for comparison to other imaging studies.

Regions of Interest. Regions of interest (ROIs) to be used in analyses of fMRI data were identified by examining regions of common activation across participants. This was achieved by generating group overlap maps of group activation. Overlap maps were generated by first transforming individual data to standard Talairach-space (Talairach and Tournoux, 1988). Functional data from each participant was then transformed into binary values such that every active voxel was assigned a value of 1, and all other voxels were assigned a value of zero. Binary values were summed at each voxel across participants to create a group image indicating the number of participants who had activation above the threshold. Group overlap maps were generated for both young and all older adult groups for fMRI data from encoding and recognition (see Figures 1 and 2).

ENCODING

A. Older Adults



B. Young Adults

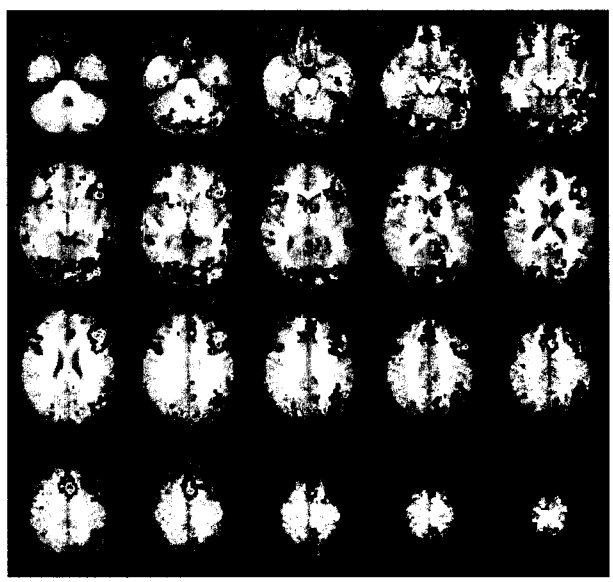
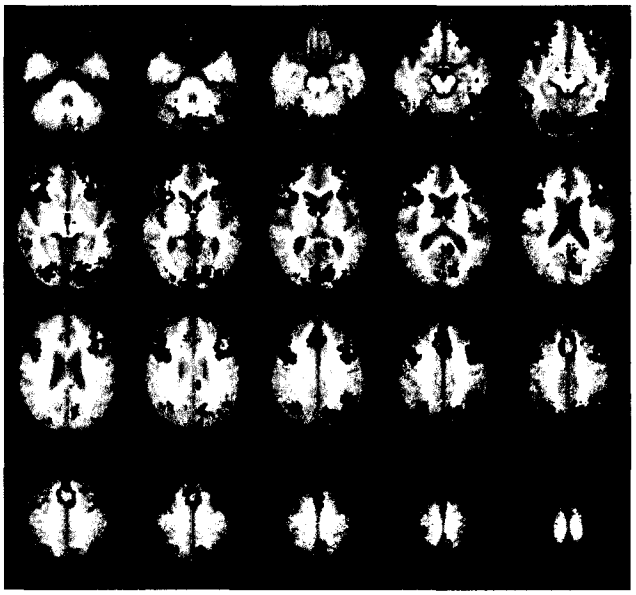


Figure 1. Common areas of activation during encoding in older adults (A) and young adults (B). Color intensity indicates number of subjects with suprathreshold activation ($p<.001$). Older adults: blue = 6, red = 24. Young adults: blue = 3, red = 9.

RECOGNITION

A. Older Adults



B. Young Adults

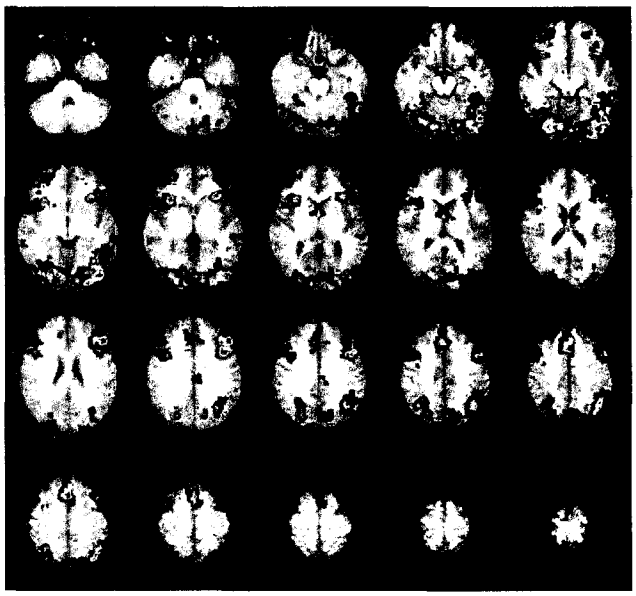


Figure 2. Common areas of activation during recognition in older adults (A) and young adults (B). Color intensity indicates number of subjects with suprathreshold activation ($p<.001$). Older adults: blue = 6, red = 23. Young adults: blue = 3, red = 9.

A grand overlap map of all participant data was generated to aid in defining ROI boundaries that included the maximum amount of data. Four sets of bilateral regions of interest (ROI) were generated from an overlap image of all participants' data: 1) right and left frontal cortex 2) right and left medial temporal lobe, 3) right and left parietal lobe, and 4) right and left lateral temporal lobe (Figure 3). Additionally, overlap maps revealed common activation in right and left superior medial frontal gyrus. Since the activation area spanned the midline, it would have required an artificial divide in the ROI to separate it into the left and right frontal lobe ROI. Because of this limitation, medial frontal activation was excluded from lateral and anterior (BA 10) frontal regions.

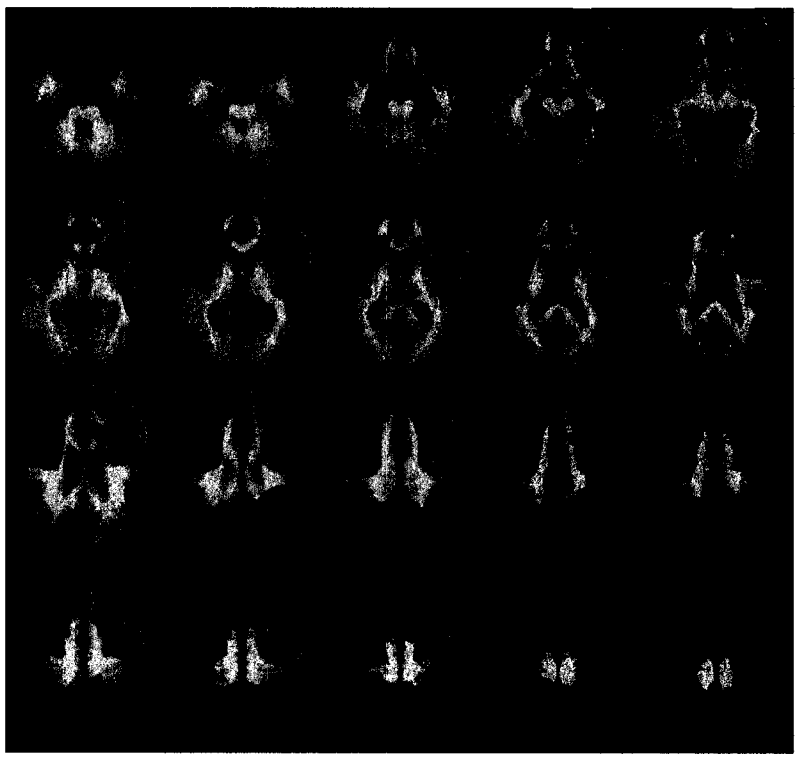


Figure 3. Regions of interest. Blue=right frontal lobe, aqua=left frontal lobe, pink= right lateral temporal lobe, purple=left lateral temporal lobe, orange=right medial temporal lobe, red=left medial temporal lobe, dark green=right parietal lobe, light green=left parietal lobe.

Lateralization Indices. The number of voxels above the activation threshold ($p<.001$) within each ROI, and the average fit coefficient for active voxels within right and left ROIs were used to create separate "lateralization indices." A threshold cut-off was used instead of applying a fixed mask to every subject in order to maximize the number of voxels included. Since the focus of this study was to broadly identify differences between young and older adults, applying a single mask to each subject would have risked missing individual differences in functional fields.

Each lateralization index is the difference between the number of active voxels in each hemisphere (from a given region) to the total number of active voxels in the entire frontal lobe. The following calculation was used: ((right ROI – left ROI)/ (right ROI + left ROI)) x 100 (after Blanchet *et al.,* 2001; Cabeza, 2002). The score range is −100 to +100, where −100 signifies completely left lateralized activation; +100 indicates completely right lateralized activation; and symmetrical or perfectly bilateral activation is given a score of 0. The frontal lobe regions of interest that were used to calculate the Frontal Lateralization Index (FLI) were defined as all right and left neocortex anterior to the central sulcus, and excluded the medial frontal gyrus activation. For the Medial Temporal Lateralization Index (MTLI), right and left temporal lobe were defined as parahippocampus (including entorhinal & perirhinal) and hippocampus. Parietal Lateralization Index (PLI), contrasted right and left parietal lobe, defined as superior and inferior parietal lobule, supramarginal gyrus, angular gyrus and precuneus. A total of 16 lateralization indices were calculated: 2 measurements (fit coefficient, voxel count) x 4 ROIs (frontal, parietal, medial temporal and lateral temporal) x 2 experimental conditions

(encoding, recognition). Lateralization indices are abbreviated to reflect condition (Enc = encoding, Rec = recognition), region (FL = frontal, MTL = medial temporal, PL = parietal, LTL = lateral temporal), and measurement (fit = fit coefficient, vox = voxel count). For example "Enc-FLfit" is the lateralization index of fit coefficient in the frontal lobe during encoding. For reference, Table 1 lists the name and abbreviation for each ROI.

Table 1
List of Abbreviations and Number of Participants for each Region of Interest (ROI).

		ENCODING			RECOGNITION		
Region	Measurement	Abbreviation	Young (N)	Elderly (N)	Abbreviation	Young (N)	Elderly (N)
Frontal Lobe	fit coefficient	Enc-FLfit	9	32	Rec-FLfit	9	30
	voxel count	Enc-FLvox			Rec-FLvox		
Medial Temporal Lobe	fit coefficient	Enc-MTLfit	7	22	Rec-MTLfit	7	23
	voxel count	Enc-MTLvox			Rec-MTLvox		
Parietal Lobe	fit coefficient	Enc-PLfit	9	32	Rec-PLfit	9	30
	voxel count	Enc-PLvox			Rec-PLvox		
Lateral Temporal Lobe	fit coefficient	Enc-LTLfit	9	32	Rec-LTLfit	9	30
	voxel count	Enc-LTLvox			Rec-LTLvox		

Lateralization indices are useful for describing the ratio of activation or intensity across the hemispheres, however, lateralization indices do not reflect the absolute amount of activation in a region (e.g. the lateralization index will indicate if there more activation on the right or on the left—regardless of the total number of voxels activated). For example, participants A and B could both have a frontal lateralization index score of –50, where person A had 6 active voxels on the left, and 2 voxels on the right; and person B had 180 active voxels on the left and 60 voxels on the right. Given the variability of the amount of activation seen in older adults, using a lateralization score provides a degree of normalization when comparing groups or individuals. Importantly, activation patterns

can be described as more or less left lateralized, but this does not mean that there is an absence of activation on the right. Only the extreme scores of –100 and +100 are indicators of lack of activation in one hemisphere. Finally, comparison of lateralization indices can show whether the proportion of right to left activation differs between groups, but the lateralization score itself does not indicate whether a difference between groups is driven by an increase on the left, or decrease on the right.

Another issue relevant to the analyses of the lateralization indices is that the number of participants included in a given regression analysis was variable depending on the ROIs included in the model. Not every participant had activation in the medial temporal lobe or lateral temporal ROI. Table 1 (above) lists the ROIs and the corresponding number of cases with data for each ROI.

Primary Analyses Questions

Analyses comparing functional activation across ROIs, and groups will aim to answer four primary questions.

1. Is there hemispheric asymmetry reduction (laterality shift) within the frontal lobe of older adults compared to younger adults, and if so, do frontal lobe activation patterns differ among older adult groups as a function of neuropsychological factor score?
2. What is the relationship between laterality patterns in all four regions of interest and neuropsychological performance?
3. Is recognition performance better predicted by fMRI activation at encoding, retrieval, or a combination of both?

4. Does the present study provide evidence of frontal lobe compensation either for the contralateral region in the non-dominant hemisphere, or in relationship to other regions of interest?

RESULTS

Behavioral Results

Demographics. Behavioral data is reported in Table 2a and 2b. Young and older adults differed by less than one point on the Mini Mental Status Exam, yet this difference was significant ($t(40) = 2.05$, $p < .05$). There was not a difference between young and older adults on the Vocabulary subtest of the Weschler Abbreviated Scale of Intelligence ($t(40) = -1.49$, $p = .15$), or in the number of years of education ($t(21.72) = -1.67$, $p = .11$; equal variances not assumed).

Table 2a
Participant Characteristics. Mean (SD).

Group	Number of Cases	Age	Years of Education
Young	9	21.7 (3.0)	14.6 (1.6)
All Elderly	35	72.2 (5.7)	15.7 (2.7)
Factor Group HH	8	74.3 (7.5)	17.5 (2.3)
Factor Group HL	10	69.1 (3.2)	17.1 (2.5)
Factor Group LH	7	73.7 (5.8)	15 (2.5)
Factor Group LL	10	71.1 (4.6)	13.6 (1.3)

Table 2b
Cognitive measures. Mean (sd).

Group	Vocabulary[a]	MMSE	Frontal Factor Score	Memory Factor Score
Young	57.9 (6.3)	29.6 (.73)	n/a	n/a
All Elderly	61.4 (6.3)	28.8 (1.1)	-0.08 (.64)	-0.02 (.66)
Factor Group HH	65.9 (5.9)	29.1 (.99)	0.59 (.26)	0.42 (.25)
Factor Group HL	63.4 (6.2)	29.1 (.90)	0.41 (.19)	-0.65 (.59)
Factor Group LH	61.2 (3.9)	28.7 (1.2)	-0.40 (.29)	0.50 (.40)
Factor Group LL	56.6 (4.9)	28.3 (1.0)	-0.80 (.456)	-0.58 (.30)

a. Weschler Abbreviated Scale of Intelligence, T-Score mean = 50, sd = 10.

Neuropsychological Testing. Although both young and elderly participants completed the same neuropsychological test battery, factor scores were not calculated for young adults because the normative database is based solely on older adults. Figure 4 shows the distribution of FL and MTL factor scores among older adults in the sample.

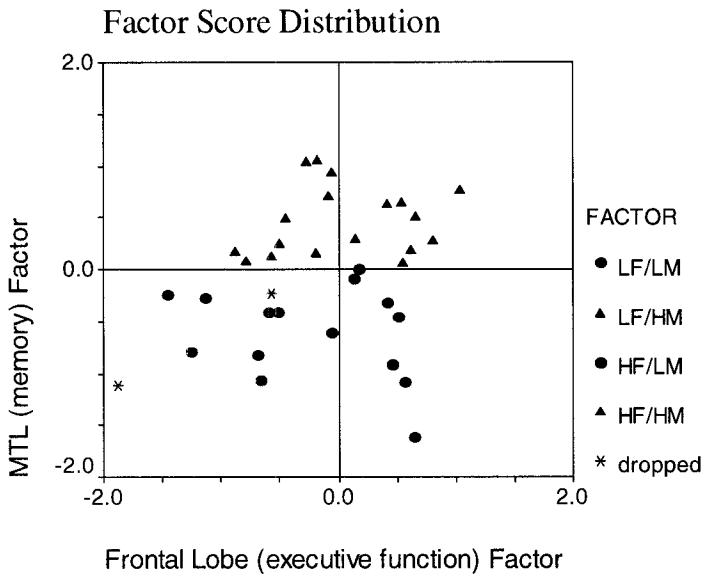


Figure 4
Distribution of frontal lobe (FL) factor score and memory (MTL) factor scores. Blue indicates high frontal individuals, purple indicates low frontal. Triangle shaped markers indicate high MTL factor scores, circles indicate low MTL factor scores. The two purple asterisks show the two individuals who were excluded from further analyses because of low recognition performance.

Encoding and Recognition Performance during fMRI.

Elderly participants performed as well as young on the semantic encoding task (elderly mean percent correct = 97.05, sd=4.36; young mean percent correct = 97.57, sd=2.56). Older adults did not perform as well as young on the recognition task (see Table 3). Two older adults were removed from further analyses because they performed near chance level on the recognition test during fMRI scanning (outliers: percent correct

= 50.53, and 48.86; remaining elderly percent correct: mean = 80.4, SD = 6.8). Independent t-tests confirmed that younger adults had consistently better scores on each recognition performance measure (Table 3).

Table 3
Recogntion Performance during fMRI by age group.

	Young		Old		Statistic		
	Mean	sd	Mean	sd	t	df	p
Hit Rate (H)	0.96	0.03	0.82	0.11	5.93a	36	< .001
False Alarm Rate (FA)	0.13	0.06	0.22	0.11	-2.15	36	< .05
H - FA	0.82	0.07	0.60	0.13	4.95	36	< .001
Percent Correct	92.22	2.92	80.41	6.80	5.03	36	< .001

Independent Samples T-test comparison between young and older adults for each measure of recognition performance. a. Equal variances not assumed.

Figure 5 shows mean Hit Rate and False Alarm Rate across older adults as a function of high or low executive function (FL factor score), and high or low memory function (MTL factor score). An ANOVA comparing two measures of recognition performance (hit rate, false alarm rate) by FL factor and MTL factor groups, did not find any significant main effects or interactions. Two participants who were excluded due to exceptionally low recognition performance were not included in this analysis were low on both FL and MTL factor scores.

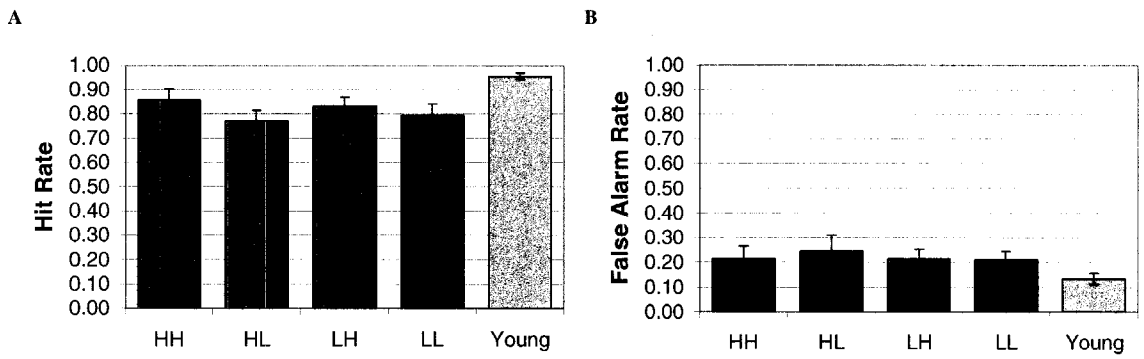


Figure 5. A. Mean Hit Rate and B. Mean False Alarm Rate, on recognition for each factor score group and young adults. HH=high FL, high MTL factor; HL=high FL, low MTL factor; LH=low FL, high MTL factor; LL = low FL, low MTL factor. Error bars represent mean square error.

fMRI Results

Lateralization Indices. Lateralization indices were calculated from fit coefficient and voxel count measures for each region of interest. It was found that the two measures were strongly correlated with each other within each ROI (Table 4). Although often the two measures produced similar results (i.e. correlation values to FL and MTL factors), there were also cases in which lateralization indices based on fit coefficient were correlated more strongly to cognitive factors that would have been overlooked if only voxel counts data were used. Despite its limitations, voxel count data was reported here in addition to measures based on fit coefficient values, because hypotheses were based on existing literature that reported voxel count data.

Table 4
Correlation of Voxel Count and Fit Coefficient Lateralization Indices by Condition and Region.

	Encoding			Recognition		
	r	p	N	r	p	N
Frontal Lobe	0.331	0.064	32	0.613	< .001	30
Parietal Lobe	0.400	0.023	32	0.586	< .001	30
Medial Temporal Lobe	0.860	< .001	22	0.865	< .001	23
Lateral Temporal Lobe	0.651	< .001	32	0.850	< .001	30

Analyses. All correlation analyses reported here used Pearson product-moment correlation analyses. Regression analyses were also completed, but because of relatively low number of cases, Pearson r values did not reach significance for many variables, thus very few significant models were found. Instead, where appropriate, independent r's were compared using Fisher's z' transformation tests and dependent r's were compared using a formula described in Cohen & Cohen (1983; developed by Steiger, 1980).

Question 1

Is there hemispheric asymmetry reduction within the frontal lobe of older adults compared to younger adults, and if so, do frontal lobe activation patterns differ among older adult groups as a function of factor score?

Before predictors of unilateral or bilateral activation patterns in older adults can be examined, it must first be determined whether a laterality difference between young and older adults was observed in the present sample. It was hypothesized that, as predicted by the HAROLD model, young adults would show greater laterality than older adults during both encoding and retrieval. Young adults would show fMRI activation patterns consistent with the HERA model: greater left frontal activation (FLI closer to –

100) during encoding, and greater right frontal activation (FLI closer to +100) during retrieval. The average FLI score for the older adult group would be closer to 0 than 100, during both encoding and retrieval. An independent samples t-test comparing young and older adults' FLI scores was completed separately for data from encoding and recognition scans.

Further, it will be necessary to determine whether fMRI activation patterns were variable among older adults in the present study. The hypothesis was that older adults would show variable fMRI frontal lateralization patterns related to FL and MTL factor score profiles. Supporting Cabeza *et al.*2002, older adults with low MTL factor scores would show unilateral frontal lobe activation, similar to the young; and older adults with high factor scores (frontal and MTL) would show bilateral activation. A 2 x 2 between-subjects ANOVA, comparing FLI score of MTL factor groups (high, low) and FL factor groups (high, low) was completed.

Question 1 – Results

Frontal lobe lateralization indices of activation amount (voxel count) and intensity (fit coefficient) showed that during semantic encoding both young and older adults had more active voxels in the left frontal lobe than in the right frontal lobe. Suprathreshold voxels also had greater intensity on average in the left than right frontal lobe. At encoding, young and elderly had significantly different lateralization index scores as measured by both fit coefficient and voxel count ($t(33.8) = -3.61$, $p < .001$, equal variances not assumed; $t(41) = -2.43$, $p < .05$, respectively; Figure 3A). Although both groups had more left-lateralized activation, the difference between left and right frontal

lobes was greater in the young group. During recognition, young and older adults had bilateral activation patterns in the frontal lobe. No significant differences were found between young and older adults' frontal lateralization indices at recognition (Rec-FLfit: $t(39) = -.12$, $p = .91$; Rec-FLvox: $t(39) = -.64$, $p = 53$; Figure 3B).

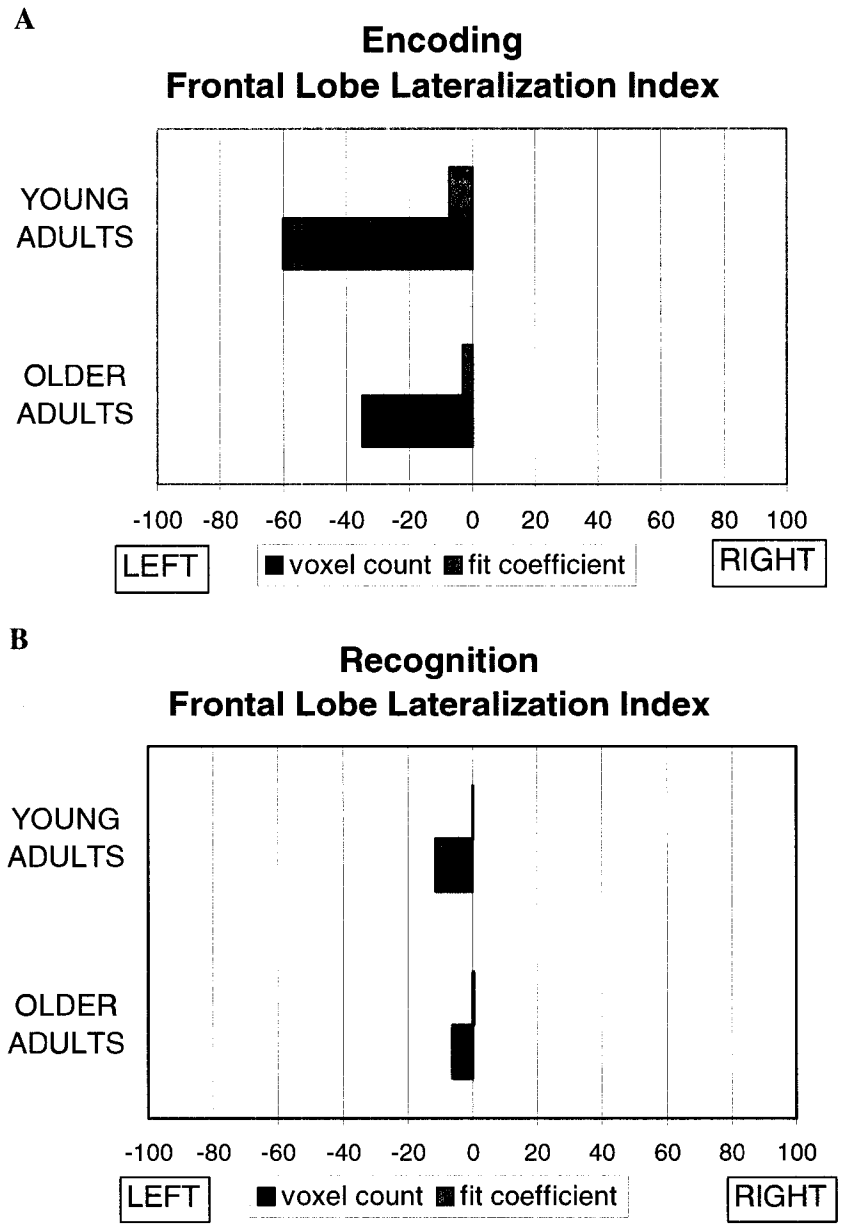


Figure 6. Mean Frontal Lateralization Indices by fit coefficient (blue) and voxel count (purple) for A. Encoding and B. Recognition in young and older adults.

Consistent with the analyses of frontal lateralization indices (FLI), the lateralization difference between age groups at encoding was also reflected in an

ANOVA in which the number of voxels in each frontal lobe hemisphere (within-subjects factor; left, right) was compared across age groups (between-subjects factor; young, old). A significant main effect of hemisphere was found ($F(1, 39) = 79.11$, $MSE = 1204.4$, $p<.0001$), and the interaction was marginally significant ($F(1,39) = 3.28$, $p = .08$). Numerically, older adults have fewer voxels active in the left FL, and more voxels active in the right FL than young adults (Figure 7). Although the total number of voxels active was not statistically different between age groups, FLI analyses showed that the ratio of voxels active in left and right hemispheres is a more sensitive measure.

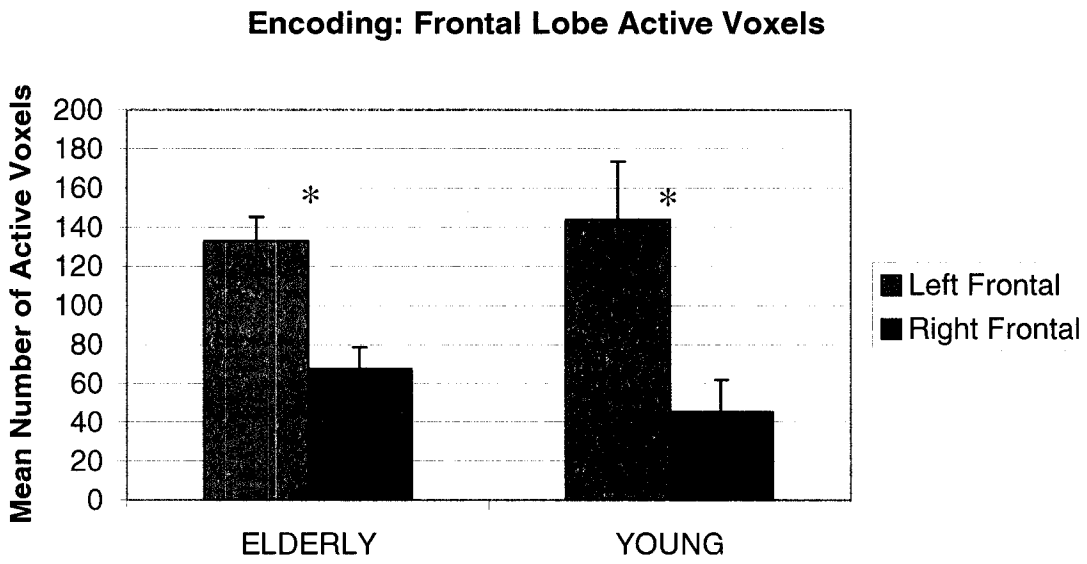


Figure 7. Mean number of suprathreshold voxels active during encoding in the left and right frontal lobes of young and older adults. Error bars are standard error of the mean. * $p<.05$, significant main effect of hemipshere.

Frontal Lobe: Differences Among Factor Groups in Elderly. To determine whether frontal activation patterns differed within the older adult group as a function of FL and MTL factor score group, a series of four 2 x 2 between-subjects ANOVAs were completed. Frontal factor score groups (low, high) and MTL factor score groups (low, high) were compared for each FLI (fit coefficient, voxel count) and experimental condition (encoding, recognition). No significant main effects or interactions were found (all F's > 1). However, given the distribution of FL and MTL factor scores (see Figure 4), it may be more appropriate in this case to use statistical analyses in which factor scores can be treated as continuous variables rather than create high and low subgroups. This possibility was explored in subsequent correlational analyses, which also included other regions of interest.

Question 2

What is the relationship between laterality patterns in all four regions of interest and neuropsychological performance?

The second question addresses a critical issue in the literature: whether differences in fMRI activation patterns among older adults, as well as in comparison to young adults, reflect a more general change in cognitive performance. Several imaging studies have shown support for the HAROLD model, which states that older adults show greater bilateral prefrontal cortex activation during encoding and retrieval, whereas young adults show unilateral activation (right PFC during retrieval; left PFC during encoding). The present study contributes to existing literature because neuropsychological profiles were collected from each participant who completed the

fMRI scan. Neuropsychological information was used to categorize older adults' as high or low memory function and high or low, executive function. Two recent studies, which also divided older adults according to cognitive performance, reported opposite findings. Cabeza *et al.* (2002) found bilateral frontal activation related to better memory performance (during source memory; based on the same memory factor score tests used in the present study). Daselaar *et al.* (2003) found bilateral activation in older adults with reduced memory performance (for correct rejection items; groups based on recognition performance during fMRI).

Two predictions were made in regard to the current study. First, older adults with higher scores on all of the neuropsychological tests would show bilateral activation across all ROIs. Second, older adults with lower performance on frontal tests would have unilateral activation in each ROI.

Question 2 - Results

Figure 8 shows lateralization indices for young and older adults in each region of interest at encoding and recognition. Figure 8A and 8B are repeated from Figure 7 above. As described above, the HAROLD pattern (greater bilateral activation in older adults compared to young adults) was found in the frontal lobes at encoding. Older adults also had greater bilateral activation than young adults in the medial temporal lobe (Enc-MTLvox: $t(27) = -3.32$, $p < .01$) and lateral temporal lobe (Enc-LTLvox: $t(39) = -2.94$, $p < .01$) during encoding. Young and older adults showed similar lateralization patterns in the parietal lobe (Enc-PLvox: $p = .51$). The HAROLD pattern was not observed in any region during recognition.

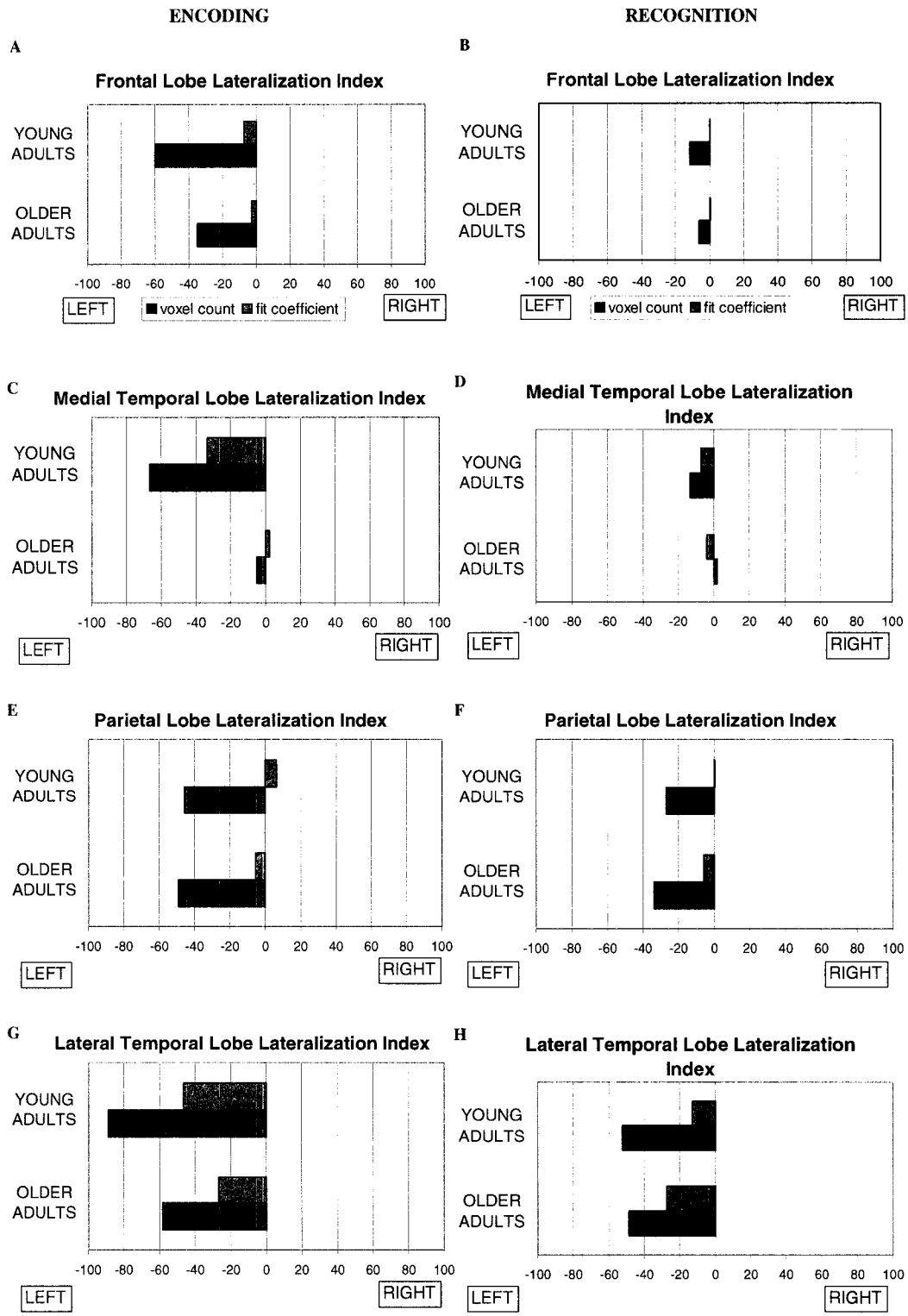


Figure 8. Regional lateralization indicies by fit coeffiecient (blue bars) and voxel count (purple bars) for young and older adults during encoding and recognition. Laterailization score of -100 = left lateralized activation, +100 = right lateralized activation, 0 = bilateral activation.

Pearson Product Moment correlation analyses were completed to examine the relationship between factor scores and lateralization indices. Table 5 lists the Pearson r values of the correlation between lateralization indices (calculated by voxel count and fit coefficient measures) for each ROI with FL and MTL factor scores.

Table 5.
Pearson R Correlation Between Factor Scores and Lateralization Indices in Older Adults.

ENCODING		Frontal Factor		MTL Factor	
	N	voxel r	fit r	voxel r	fit r
Frontal Lobe	32	0.10	0.03	-0.06	-0.08
Parietal Lobe	32	0.15	0.04	0.25	0.05
Medial Temporal Lobe	22	0.16	0.26	-0.09	-0.04
Lateral Temporal Lobe	32	0.12	0.19	0.15	0.36*
RECOGNITION		FL Factor		MTL Factor	
	N	voxel r	fit r	voxel r	fit r
Frontal Lobe	30	0.20	0.14	-0.05	-0.25
Parietal Lobe	30	-0.33	-0.34	0.23	-0.18
Medial Temporal Lobe	23	-0.08	-0.14	-0.13	-0.25
Lateral Temporal Lobe	30	0.10	0.20	0.08	0.00

* $p < .05$

Correlation between Factor Scores and Lateralization Indices

FL and MTL factor scores were moderately correlated with a few of the lateralization indices. A positive correlation between factor scores and lateralization indices indicates that lower factors scores were associated with greater left-lateralized activity, and the reverse, higher factor scores are associated with greater right-lateralized activity. MTL factor was positively correlated with lateralization of intensity in the lateral temporal lobe (Enc-LTLfit: $r = .36$, $p < .05$), and with the laterality of activation amount in the parietal lobes (Enc-PLvox: $r = .25$, $p = .17$) during encoding. MTL factor

scores were also positively correlated with amount of parietal lobe activation at recognition (Rec-PLvox r = .23, p = .22), and negatively correlated with frontal intensity lateralization index (Rec-FLfit: r = -.25, p = .18), and medial temporal lobe intensity (Rec-MTLfit: r = -.25, p = .26). In contrast, FL factor scores were negatively correlated with the parietal lobe measures at recognition (Rec-PLvox: r = -.33, p = .07, Rec-PLfit: r = -.34, p = .07) and positively correlated with the frontal lobe lateralization index (Rec-FLvox: r = .20, p = .29; Rec-LTLfit: r = .20, p = .30).

A significance test between correlation coefficients was completed to answer the following question. Is variable X more highly correlated with variable Y to a significantly different degree than variable V does (Cohen & Cohen, 1983)? In this case, comparison between encoding and recognition showed that the parietal lobe lateralization index (by voxels) at recognition is significantly more correlated with frontal factor scores than the parietal lobe lateralization index at encoding ($t(29) = 3.23$, $p < .01$). There was no significant difference between Pearson correlation coefficients for memory factor scores and lateral temporal lobe lateralization indices at encoding and recognition.

In addition to laterality indices, raw mean fit coefficient and mean number of voxels values from each ROI were also submitted to Pearson's correlation analyses to examine the relationship to factor scores (see Figures 9 and 10). Mean fit coefficient and mean number of suprathreshold voxels for each region of interest were correlated with frontal and memory factor scores (Table 10). Frontal factor scores were positively correlated with the right lateral temporal lobe during encoding, and negatively correlated with the mean number of active voxels in the right and left frontal lobe and right parietal

lobe during recognition. However, the correlations with the frontal lobe ROIs during recognition were driven by a single subject who had more voxels active in the frontal lobe than any other older adult in the sample.

The memory factor score was positively correlated with mean fit coefficient in frontal, parietal and lateral temporal lobe ROIs during encoding, and left parietal lobe during recognition. The mean number of voxels active in the right parietal lobe during recognition also showed a positive correlation with the memory factor scores.

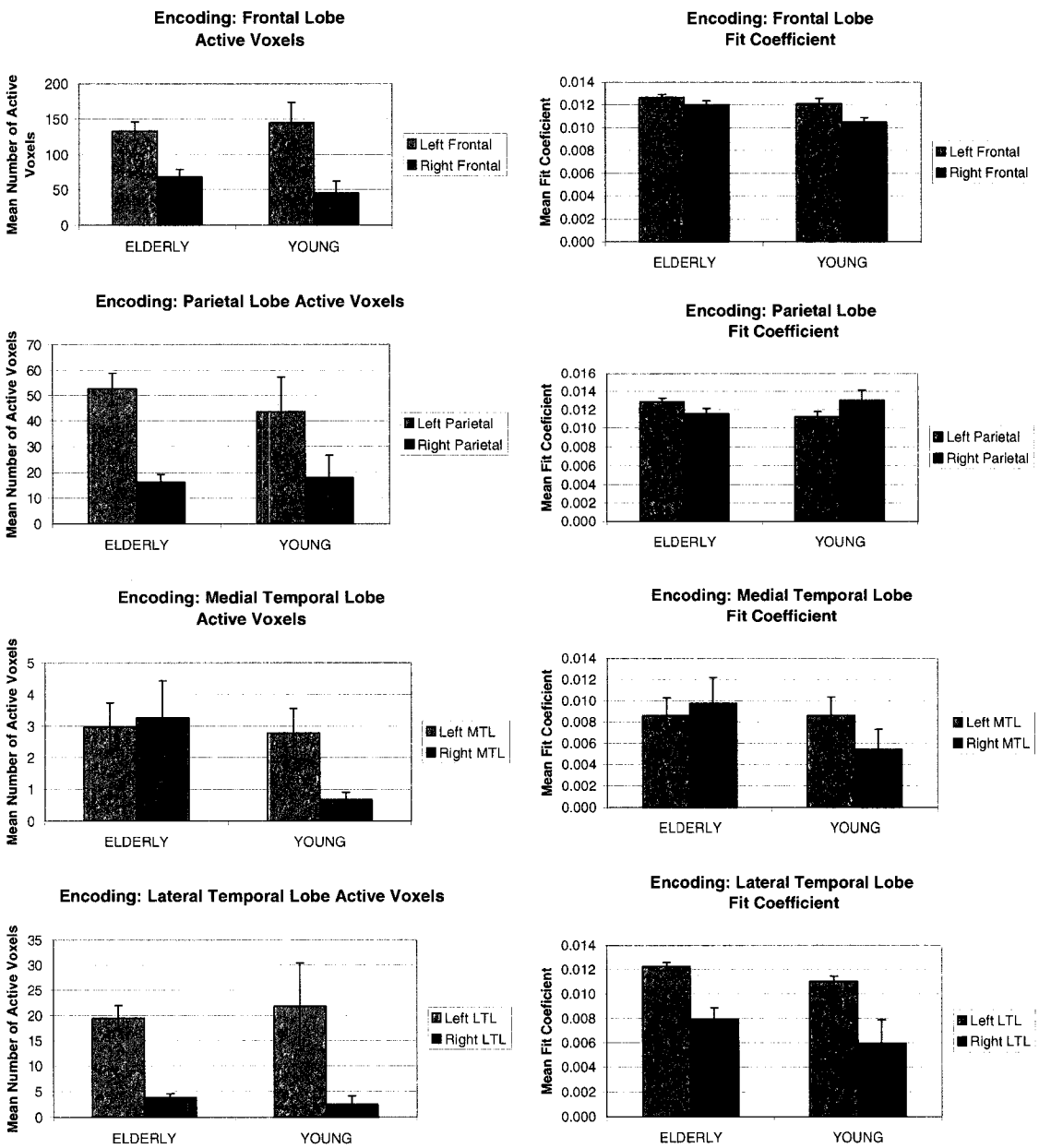


Figure 9. Mean suprathreshold voxels and fit coefficient for left and right regions of interest during encoding. Error bars are standard error of the mean. Note that due to the inherent differences in the number of voxels possible in each region of interest, the scale of the Y-axis varies for each region of interest.

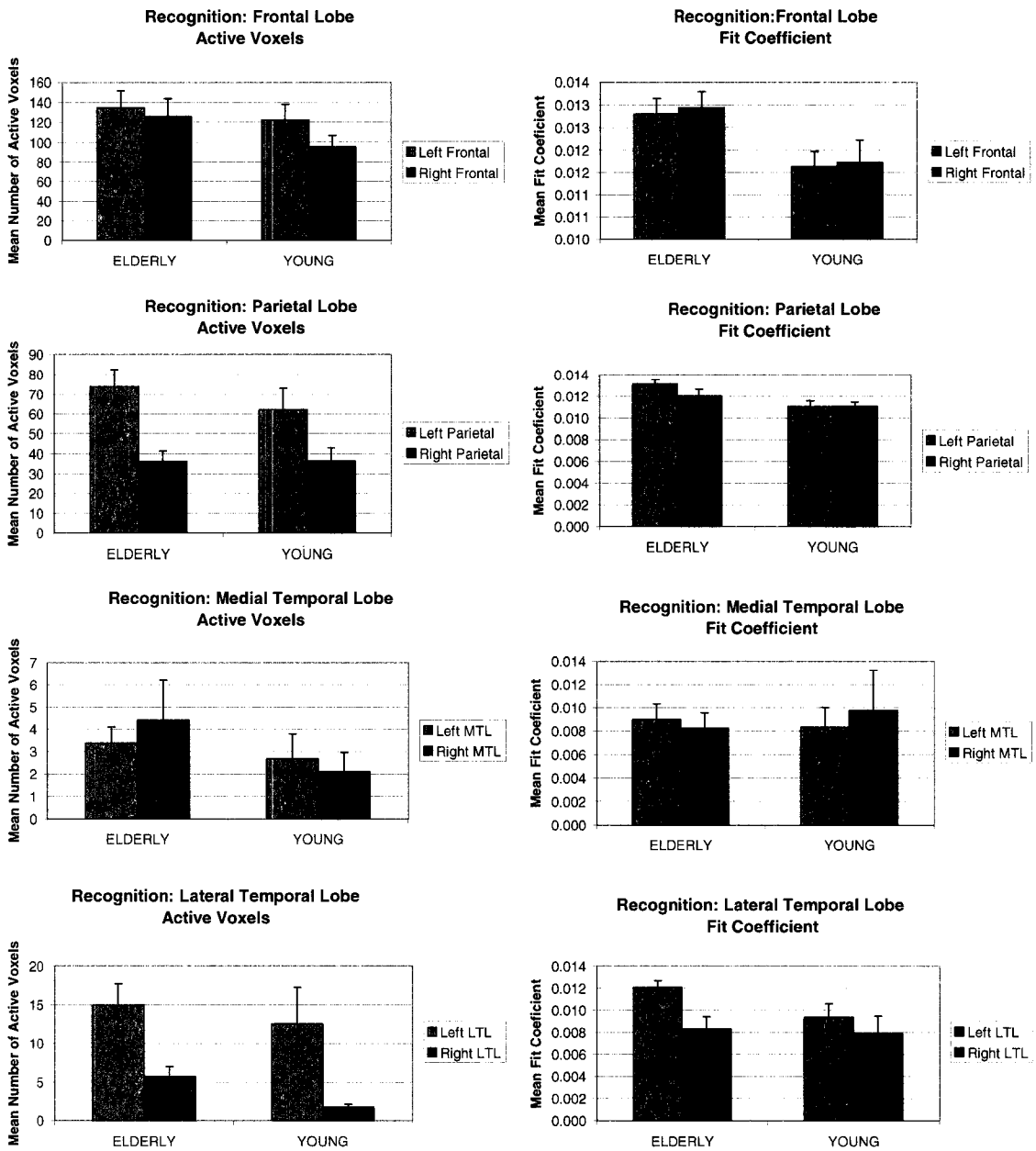


Figure 10. Mean suprathreshold voxels and fit coefficient for left and right regions of interest during recognition. Error bars are standard error of the mean. Note that due to the inherent differences in the number of voxels possible in each region of interest, the scale of the Y-axis varies for each region of interest.

Table 6.

Pearson R Correlation Between Factor Scores and Left and Right Region of Interest Raw Scores in Older Adults.

		Frontal Factor			
		voxel r		fit r	
ENCODING	N	left ROI	right ROI	left ROI	right ROI
Frontal Lobe	32	0.03	0.10	-0.01	0.04
Parietal Lobe	32	0.13	0.13	0.04	0.06
Medial Temporal Lobe	32	0.00	-0.14	0.08	0.16
Lateral Temporal Lobe	32	0.15	0.34*	0.01	0.21
RECOGNITION					
Frontal Lobe	30	-0.45*	-0.40*	-0.29	-0.23
Parietal Lobe	30	-0.27	-0.35*	-0.04	-0.28
Medial Temporal Lobe	30	-0.34	-0.19	-0.14	-0.19
Lateral Temporal Lobe	30	-0.32	-0.30	-0.20	0.11
		MTL Factor			
		voxel r		**fit r**	
ENCODING	N	left ROI	right ROI	left ROI	right ROI
Frontal Lobe	32	0.06	-0.08	0.43*	0.25
Parietal Lobe	32	0.12	0.30	0.41*	0.34*
Medial Temporal Lobe	32	-0.09	-0.17	0.06	0.11
Lateral Temporal Lobe	32	0.09	0.27	0.15	0.43*
RECOGNITION					
Frontal Lobe	30	0.00	-0.03	0.27	0.11
Parietal Lobe	30	0.16	0.35*	0.41*	0.17
Medial Temporal Lobe	30	0.13	0.11	0.21	0.06
Lateral Temporal Lobe	30	-0.01	0.18	0.01	0.06

* p<.05

Predicting MTL factor scores

It was originally proposed to use regression analyses to predict neuropsychological performance from lateralization indices. However, simple correlation matrices showed that few variables met the significance criterion of p<.05. Surprisingly, the number of cases included in the analyses dramatically dropped when only a subset of the variables was included. Several participants lacked medial temporal

lobe activation at encoding, recognition, or both. Consequently, the correlation values changed when the analyses were completed using a reduced number of subjects. For example, the Pearson r correlation between MTL factor score and parietal lateralization index at encoding changed from r = .25 with all older adults to r = .42 with the subset of participants included in a regression analysis. To determine whether other variables were similarly affected, the group of older adults was divided into two subgroups depending on whether any MTL activation was observed during encoding (number of active voxels > 0). The encoding measure was chosen because more participants lacked MTL activation at encoding than during recognition. Finding variable MTL activation among older adults was consistent with Daselaar et al. (2003) who found less MTL activation in older adults compared to young adults. This division resulted in a group of 10 older adults without MTL activation; and 19 elderly participants with MTL activation. Tables 7, 8, and 9 compare characteristics of the participants with and without MTL activation at encoding. New correlation tables were generated for each group (with and without MTL activation during encoding), in which FL and MTL factor scores were correlated with all lateralization indices (Table 10).

Table 7.
Characteristics. Mean, sd and significance tests between older adults with and without MTL activation during encoding.

	Older Adults Without MTL Activation at Encoding			Older Adults With MTL Activation at Encoding			t-test
	N	Mean	sd	N	Mean	sd	p
Demographics							
Age	10	71.10	5.53	19	72.79	5.73	ns
Education (years)	10	15.80	1.48	19	16.05	3.06	ns
Cognitive Measures							
Frontal Factor	10	-0.04	0.67	19	-0.06	0.63	ns
Memory Factor	10	-0.10	0.82	19	-0.06	0.56	ns
WASI Verbal IQ	10	117.50	12.48	19	118.42	10.07	ns
WASI Performance IQ	10	118.10	11.61	19	114.68	12.72	ns
WASI Full Scale IQ	10	120.30	12.18	19	118.63	10.47	ns
Recognition Performance							
Hit Rate (H)	10	0.81	0.13	16	0.80	0.09	ns
False Alarm Rate (FA)	10	0.22	0.13	16	0.22	0.11	ns
Percent Correct	10	79.61	7.50	16	79.65	6.16	ns
H - FA	10	0.58	0.14	16	0.59	0.12	ns

Table 8.

FMRI encoding. Mean, sd and independent samples t-test between older adults with and without MTL activation during encoding.

			Older Adults Without MTL Activation at			Older Adults With MTL Activation at Encoding			t-test
FMRI: ENCODING			N	Mean	sd	N	Mean	sd	p
Frontal Lobe	Laterality Indicies	Enc-Flfit	10	-2.06	6.51	19	-3.97	4.75	ns
		Enc-FLvox	10	-55.71	22.40	19	-33.83	22.48	0.02
	Raw Values Enc-FL	Enc-FL fit left	10	0.01	0.00	19	0.01	0.00	ns
		Enc-FL vox left	10	83.30	45.69	19	143.05	64.51	0.02
		Enc-FL fit right	10	0.01	0.00	19	0.01	0.00	ns
		Enc-FL vox right	10	20.00	11.21	19	73.21	49.18	0.00
		Total Voxels (L+R)	10	103.30	49.04	19	216.26	100.88	0.00
Parietal Lobe	Laterality Indicies	Enc-PLfit	10	0.88	8.77	19	-10.12	23.44	ns
		Enc-PLvox	10	-56.92	24.67	19	-54.81	34.27	ns
	Raw Values Enc-PL	Enc-PL fit left	10	0.01	0.00	19	0.01	0.00	0.02
		Enc-PL vox left	10	23.50	16.61	19	62.00	35.93	0.00
		Enc-PL fit right	10	0.01	0.00	19	0.01	0.00	ns
		Enc-PL vox right	10	6.20	4.96	19	16.63	13.60	0.03
		Total Voxels (L+R)	10	29.70	18.61	19	78.63	44.76	0.00
Medial Temporal Lobe	Laterality Indicies	Enc-MTLfit	n/a	n/a	n/a	19	0.83	58.37	N/A
		Enc-MTLvox	n/a	n/a	n/a	19	-7.44	68.03	N/A
	Raw Values Enc-MTL	Enc-MTL fit left	10	0.00	0.00	19	0.01	0.01	N/A
		Enc-MTL vox left	10	0.00	0.00	19	3.79	3.88	N/A
		Enc-MTL fit right	10	0.00	0.00	19	0.01	0.02	N/A
		Enc-MTL vox right	10	0.00	0.00	19	3.95	5.86	N/A
		Total Voxels (L+R)	10	0.00	0.00	19	7.74	8.22	N/A
Lateral Temporal Lobe	Laterality Indicies	Enc-LTLfit	10	-34.30	45.56	19	-35.96	45.11	ns
		Enc-LTLvox	10	-60.99	40.52	19	-71.34	33.18	ns
	Raw Values Enc-LTL	Enc-LTL fit left	10	0.01	0.00	19	0.01	0.00	ns
		Enc-LTL vox left	10	17.30	15.73	19	17.42	11.16	ns
		Enc-LTL fit right	10	0.01	0.01	19	0.01	0.01	ns
		Enc-LTL vox right	10	3.80	3.77	19	2.68	2.71	ns
		Total Voxels (L+R)	10	21.10	18.62	19	20.11	12.03	ns

Table 9.

FMRI recognition. Mean, sd and independent samples t-test between older adults with and without MTL activation during encoding.

			Older Adults Without MTL Activation at			Older Adults With MTL Activation at Encoding			t-test
FMRI: RECOGNITION			N	Mean	sd	N	Mean	sd	p
Frontal Lobe	Laterality Indicies	Rec-Flfit	10	1.94	3.46	19	0.54	3.24	ns
		Rec-FLvox	10	-3.36	18.83	19	-5.04	20.15	ns
	Raw Values Rec-FL	Rec-FL fit left	10	0.01	0.00	19	0.01	0.00	0.05
		Rec-FL vox left	10	116.40	73.25	19	149.21	99.37	ns
		Rec-FL fit right	10	0.01	0.00	19	0.01	0.00	ns
		Rec-FL vox right	10	100.70	70.92	19	144.89	104.37	ns
		Total Voxels (L+R)	10	217.10	141.57	19	294.11	195.23	ns
Parietal Lobe	Laterality Indicies	Rec-PLfit	10	-9.93	32.28	19	-4.52	6.84	ns
		Rec-PLvox	10	-36.02	34.95	19	-37.49	25.77	ns
	Raw Values Rec-PL	Rec-PL fit left	10	0.01	0.00	19	0.01	0.00	0.09
		Rec-PL vox left	10	57.50	46.40	19	85.47	47.37	ns
		Rec-PL fit right	10	0.01	0.00	19	0.01	0.00	ns
		Rec-PL vox right	10	33.00	34.45	19	38.21	23.82	ns
		Total Voxels (L+R)	10	90.50	76.29	19	123.68	61.50	ns
Medial Temporal Lobe	Laterality Indicies	Rec-MTLfit	6	20.46	74.53	16	-7.13	44.84	ns
		Rec-MTLvox	6	27.14	73.48	16	-8.96	59.75	ns
	Raw Values Rec-MTL	Rec-MTL fit left	10	0.00	0.01	19	0.01	0.01	0.01
		Rec-MTL vox left	10	1.50	2.27	19	4.42	4.49	0.07
		Rec-MTL fit right	10	0.01	0.01	19	0.01	0.01	ns
		Rec-MTL vox right	10	2.30	3.43	19	5.74	12.17	ns
		Total Voxels (L+R)	10	3.80	5.59	19	10.16	15.46	ns
Lateral Temporal Lobe	Laterality Indicies	Rec-LTLfit	10	-30.77	48.39	19	-27.76	55.86	ns
		Rec-LTLvox	10	-52.30	40.49	19	-49.65	54.54	ns
	Raw Values Rec-LTL	Rec-LTL fit left	10	0.01	0.00	19	0.01	0.00	ns
		Rec-LTL vox left	10	12.90	16.06	19	16.32	15.39	ns
		Rec-LTL fit right	10	0.01	0.01	19	0.01	0.01	ns
		Rec-LTL vox right	10	6.00	6.60	19	5.68	7.65	ns
		Total Voxels (L+R)	10	18.90	22.03	19	22.00	19.44	ns

Table 10.

Pearson R Correlation between Factor Scores and Lateralization Indices in Older Adults with and without MTL activation during encoding.

Without MTL Activation During Encoding					
		Frontal Factor		MTL Factor	
ENCODING	**N**	voxel r	fit r	voxel r	fit r
Frontal Lobe	10	-0.50	-0.45	-0.49	-0.43
Parietal Lobe	10	0.17	-0.57	-0.03	0.14
Medial Temporal Lobe	0	N/A	N/A	N/A	N/A
Lateral Temporal Lobe	10	-0.12	0.40	-0.06	0.23
RECOGNITION	**N**	voxel r	fit r	voxel r	fit r
Frontal Lobe	10	0.24	0.03	0.21	-0.15
Parietal Lobe	10	-0.50	-0.58	0.09	-0.34
Medial Temporal Lobe	6	-0.65	-0.72	-0.57	-0.66
Lateral Temporal Lobe	10	-0.05	0.05	0.17	-0.05
With MTL Activation During Encoding					
		Frontal Factor		MTL Factor	
ENCODING	**N**	voxel r	fit r	voxel r	fit r
Frontal Lobe	19	0.56*	0.38	0.18	0.36
Parietal Lobe	19	0.18	0.16	0.32	0.08
Medial Temporal Lobe	19	0.21	0.30	0.06	0.14
Lateral Temporal Lobe	19	0.23	0.15	0.26	0.48*
RECOGNITION	**N**	voxel r	fit r	voxel r	fit r
Frontal Lobe	19	0.14	0.13	-0.13	-0.23
Parietal Lobe	19	-0.19	-0.01	0.28	0.18
Medial Temporal Lobe	16	0.16	0.13	0.14	0.08
Lateral Temporal Lobe	19	0.15	0.27	0.05	0.01

* $p < .05$

Split by MTL Activation During Encoding

Dividing older adults by the presence or absence of MTL activation during encoding revealed an important interaction between frontal lateralization and frontal factor scores. In participants without MTL activation, frontal factor scores were strongly correlated with frontal lobe activation during encoding (Enc-FLvox: $r = -.50$, $p = .14$). This

correlation was particularly striking because when all older adults were included, the correlation between the FL factor and FLI at encoding was substantially lower (see Table 5, $r = .10$). In contrast, older adults who had MTL activation during encoding had a positive correlation with FL factor scores (Enc-FLvox: $r = .56$, $p < .05$). Figure 11 shows the correlation of frontal factor score and frontal lobe lateralization scores during encoding for young and older adults. In older adults who did not activate the MTL during encoding, left-lateralized activity in the frontal lobe was associated with higher FL factor scores. In older adults who had MTL activation during encoding, participants with higher FL factor scores had more bilateral activation in the frontal lobes. Statistical comparison of Pearson r's confirmed that there was a significant difference between frontal lobe lateralization in participants with and without MTL activation during encoding (Enc-FLvox: $z' = -2.61$, $p<.01$; Enc-FLfit: $z' = -1.95$, $p<.05$). The low correlation between FLI and factor score originally observed in the entire older adult group (Enc-Flvox: $r = .10$, Enc-Flfit: $r = .03$), actually reflected a combination of two subgroups with opposite correlations to the frontal factor score.

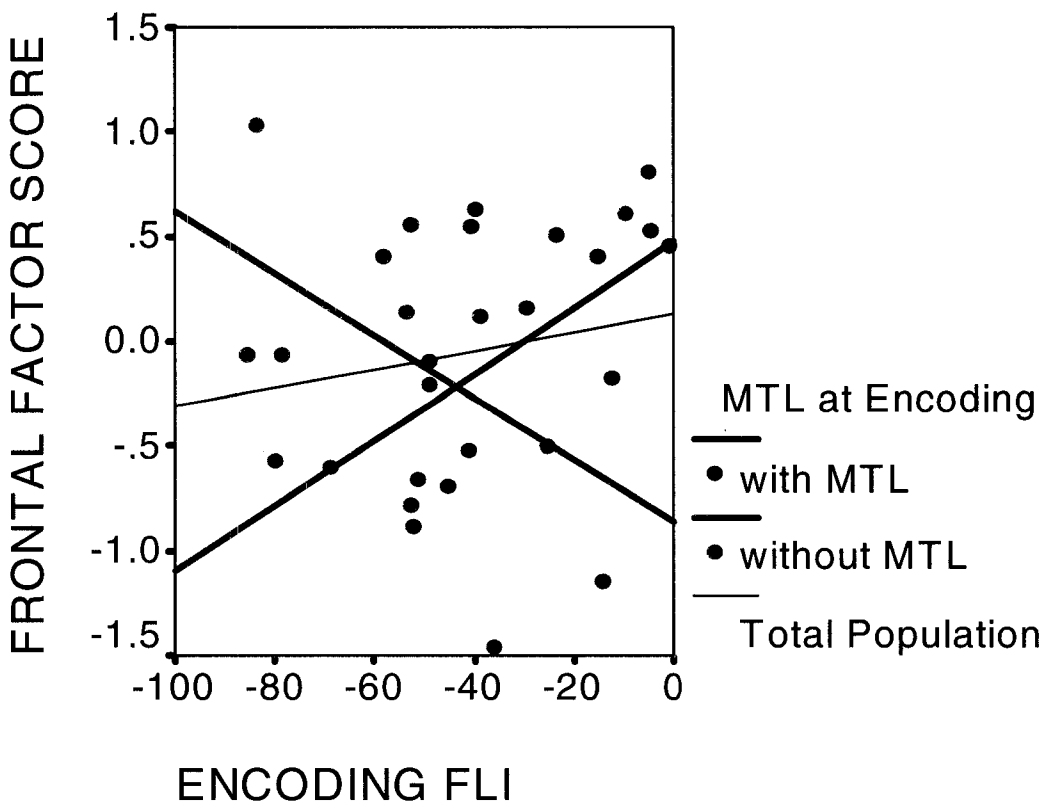


Figure 11. Pearson r correlation between frontal lobe factor score and frontal lobe lateralization index by voxel count (Enc-FLvox) during encoding in older adults grouped by presence and absence of MTL activation at encoding. Lower factor scores represent lower performance on factor score tests. Lower lateralization index scores indicate greater left lateralization (-100 = completely left lateralized activity, 0 = equally bilateral activation). Green line and markers represent older adults with MTL activation during encoding. Red line and markers represent older adults without MTL activation at encoding.

Split by MTL activation during encoding: FL Factor

Subgroup Without MTL Activation. Splitting the older adult group by MTL activation during encoding also affected correlation values of other lateralization indices. When all older adults were included in the series of Pearson correlation analyses, the FL factor score was correlated with MTL activation intensity at encoding (Enc-MTLfit) and parietal lateralization indices at recognition (Rec-PLfit; see Table 5). Although the correlation interaction in the frontal lobe was the most notable change, the subgroup of older adults without MTL activation during encoding also showed a stronger correlation between PLI at recognition and FL factor score (Rec-PLvox: $r = -.50$, $p = .14$; Rec-PLfit: $r = -.58$, $p = .08$). The difference between correlation from encoding and recognition for parietal lobe lateralization and frontal factor was not significant. Additional variables strongly correlated with FL factor score included MTL activation during recognition (Rec-MTLvox: $r = -.65$, $p = .16$; Rec-MTLfit: $r = -.72$, $p = .11$), and parietal activation during encoding (Enc-PLfit: $r = -.57$, $p = .09$). Although the correlation values are relatively strong, none of the variables from this small group reached significance criteria to enter into a regression analysis.

Subgroup With MTL Activation. In addition to the strong correlation with FL activation (above), participants with activation in the MTL also showed a moderate correlation between the FL factor and MTL intensity at encoding (Enc-MTLfit: $r = .30$, $p = .21$), and lateral temporal lobe intensity during recognition (Rec-LTLfit: $r = .27$, $p = .26$). Again, a forward selection regression was not completed in this subset of the

sample, because only one variable reached the significance level required to enter a regression analysis.

Split by MTL activation during encoding: MTL Factor

Dividing older adults by MTL activation at encoding also changed the pattern of regions correlated to the MTL factor scores. Similar to the correlation reported between FL factor score and FL activation, activation in the frontal lobes was variably correlated with MTL factor scores as a function of MTL activation during encoding. In older adults without MTL activation, lateralization of frontal lobe activity during encoding was negatively correlated with MTL factor scores (Enc-FLfit: $r = -.43$, $p = .22$; Enc-FLvox: $r = -.49$, $p = .15$). In contrast, for subjects who had MTL activation during encoding, the same variables were positively correlated (Enc-FLfit: $r = .36$, $p = .13$; Enc-FLvox: $r = .18$, $p = .46$). The difference between Pearson r's was significant ($z' = -1.85$, $p < .05$).

Initial calculation of Pearson r for all older adults combined (table 5 above) showed that MTL factor scores had the strongest correlation to the lateralization of activation intensity in the lateral temporal lobe during encoding (Enc-LTLfit: $r = .36$, $p<.05$). In the re-analyses splitting the groups by MTL activation during encoding (Table 10), activation intensity in the lateral temporal lobe was still correlated to MTL factor scores. However, the correlation was not dependent on MTL activation during encoding. The correlation value was higher in older adults with MTL activation during encoding (Enc-LTLfit: $r = .48$, $p < .05$) than in participants without MTL activation at encoding (Enc-LTLfit: $r = .23$, $p = .53$). The strength of the correlation here could simply be a reflection of the number of cases in each group (without MTL, N = 10, with MTL, N =

19). Although activation in the LTL during encoding did not differ as a function of MTL activation during encoding, other variables revealed differences between the subgroups. Both measures of medial temporal activation during recognition were negatively correlated to MTL factor score in the group of subjects without MTL activation at encoding (Rec-MTLfit: r = -.66; Rec-MTLvox: r = -.57), but showed a weak positive correlation in subjects with MTL activation at encoding (Rec-MTLfit: r = .08; -vox: r = .14). Lateralization indices of parietal lobe activation also showed moderate correlation differences between the subgroups, however the results were mixed between fit coefficient and voxel count data (see Table 10). Forward selection regression analyses were not completed because only one variable (ELTL-fit) met significance criteria to be included in a model to predict factor scores.

Question 3:

Is recognition performance better predicted by fMRI activation at encoding, retrieval, or a combination of both?

The third issue compared imaging data from encoding and recognition with recognition performance. One advantage of the present study was that fMRI data was collected during both encoding and recognition. Based on previous research (Daselaar *et al.*, 2003), decreased amount (voxel count) or level (fit coefficient) of MTL activation at encoding was hypothesized to correlate with lower recognition performance scores, and increased activation during retrieval may also correlate with lower recognition performance scores. Given the variability of previous findings, it was possible that increased activation will reflect difficulty during the recognition performance, but it was

also possible that those older adults with better recognition performance may have increased activation reflecting successful compensation.

A series of forward selection regression analyses, in which recognition performance was predicted by lateralization indices from both encoding and recognition were planned to examine the relationship between recognition performance during fMRI and lateralization index scores. Results from young and older adults were compared. The proposed analyses of separating regression analyses by encoding variables alone and by recognition variables alone, was not performed because correlation values were strong, but generally would not meet criteria to enter the regression model (set at $p < .05$). Data from older adults were also compared across two sets of subgroups: 1) groups based on factor scores (high, low FL function; high, low MTL function), and 2) groups divided by the presence or absence of MTL activation during encoding. The latter set of subgroups was based on the earlier finding that factor scores were predicted by different variables in older adults with MTL activation than older adults who did not show MTL activation during encoding. Recognition performance was measured by adjusting the hit rate (H) by subtracting the false alarm rate (FA) to provide a better accuracy measure (H-FA).

Question 3 – Results

Figure 12 shows the Pearson r correlation values calculated between H-FA and each lateralization index. Similar to the relationship between factor scores and lateralization indices, a positive correlation indicates that better recognition performance was related to more right-lateralized activation, and a negative correlation between

recognition performance and a lateralization index indicates that better recognition performance was associated with greater left-lateralized activation in a given region.

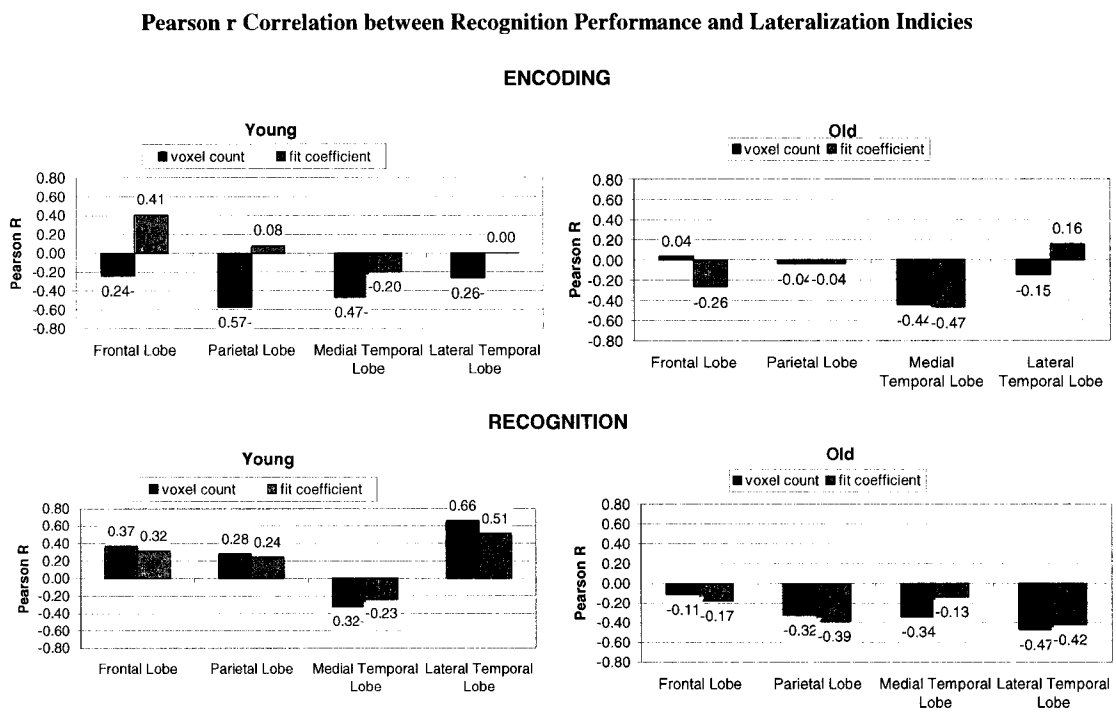


Figure 12. Pearson r correlation for A) Encoding and B) Recognition, in young and older adults by region of interest. Puple bars are correlation between voxel count lateralization index of the given region (x-axis) and recognition performance (H-FA) during fMRI. A positive correlation indicates that better recognition performance was related to more right-lateralized activation. A negative correlation reflects better recognition performance associated with greater left-lateralized activation.

Older Adults. In older adults, recognition performance was negatively correlated with several lateralization indices including MTL activation at encoding (Enc-MTLfit: r = -.47, p = < .05; Enc-MTLvox: r = -.44, p = .06) and at recognition (Rec-MTLvox: r = -.34, p = .14), parietal lobe activation at recognition (Rec-PLfit: r = -.39, p = .05; Rec-PLvox: r = -.32, p = .11), lateral temporal lobe activation during recognition (Rec-LTLfit:

r = -.42, p < .05; Rec-LTLvox: r = -.47, p <.05), and frontal lobe activation during encoding (Enc-FLvox: r = -.27, p = .17; see Figure 12).

Young Adults. Figure 12 shows Pearson correlation coefficients for each lateralization index compared to H-FA in young adults. Many lateralization indices were moderately correlated to H-FA score. The amount of activation in the lateral temporal lobe during recognition had the strongest correlation with H-FA score (Rec-LTLvox: r = .66, p = .05). Additionally H-FA was negatively correlated with the lateralization of activation amount in parietal and medial temporal during encoding (Enc-PLvox: r = -.57, p=.11; Enc-MTLvox: r = -.47, p = .29), activation intensity in the frontal lobe (Enc-FLfit: r = .41, p = .28), all variables based on recognition data were at least moderately correlated (range r = .23 to .66, see Figure 12). A regression analysis was not performed with these data because, although several variables were strongly correlated with recognition performance, only the RLTL measures (fit and voxel) met significance criteria to enter into the regression model and these two measures were highly inter-correlated (r = 0.87).

Interestingly, although lateralization indices from many of the same regions were correlated with recognition performance in young and older adults, the direction of the correlation was reversed. The greatest difference was observed in posterior regions during recognition. Older adults showed a negative correlation between H-FA and lateralization indices in the lateral temporal lobe during recognition (Rec-LTLvox: r = -.47, p < .05), and young adults showed a positive correlation (Rec-LTLvox: r = .66, p = .053). The difference between young and older adults' Pearson r's was significant

(Fisher's z' = 2.84, p<.01). Figure 13 shows that one young subject appears to be an outlier. However, re-plotting the data without this subject did not change the slope of the young adult data. Opposite correlations were also observed in the parietal lobe during recognition and frontal lateralization indices during both recognition and encoding. Young and older adults both showed a negative correlation between the laterality index for MTL activation and H-FA at encoding and recognition (see Figure 12).

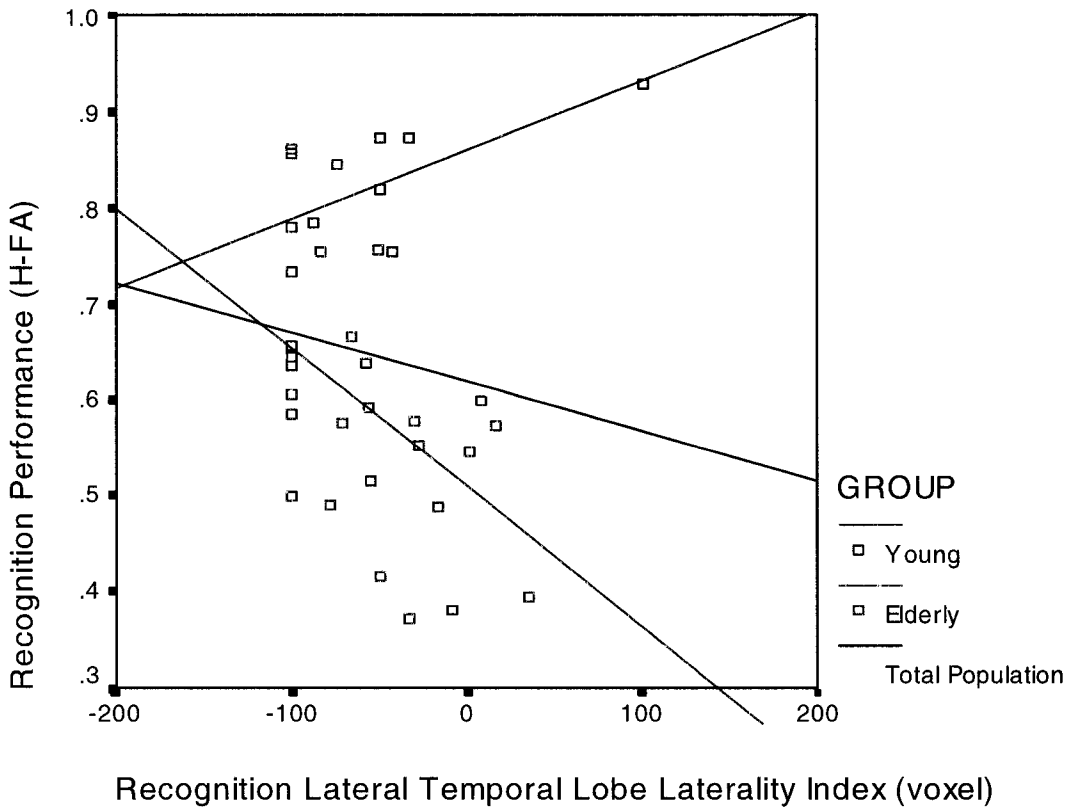


Figure 13. Pearson's correlation between recognition performance and activation lateralization in lateral temporal lobe in young (green) and older (red) adults.

Recognition Performance: Split by MTL Activation at Encoding.

A series of Pearson r correlation analyses were performed to determine whether an interaction existed between older adults' recognition performance score (H-FA) and MTL activation (as was found from Pearson correlation analyses of neuropsychological FL factor score data and MTL activation during encoding). Since this analysis was split on the basis of MTL activation during encoding, lateralization indices from MTL encoding data were not included. Regardless of MTL activation during encoding, frontal lobe activation during recognition had the strongest correlation value with H-FA rate. (Table 11. Rec-FLvox, without MTL activation: $r = .38$, $p = .27$; Rec-FLvox with EMTL activation: $r = -.43$, $p = .10$). Note that six people were dropped from the analysis because they lacked MTL activation during recognition. However, in older adults who lacked MTL activation during encoding, the recognition MTL laterality indices had the next highest correlation to H-FA (Rec-MTLvox: without EMTL activation, $N=6$, $r = -.73$, $p=.05$). Since this correlation existed, it would not have been justified to remove the recognition MTLI to increase the number of cases included in the regression.

Table 11.

Correlation between recognition performance (H-FA) and laterality indices by condition and ROI for elderly with and without MTL activation during encoding and young participants.

		Older Adults				Young	
		Without MTL at Enccoding		With MTL at Encoding			
		N	r	N	r	N	r
Encoding							
Frontal Lobe	fit	10	-0.79	16	-0.11	9	0.41
	vox	10	-0.20	16	0.67	9	-0.24
Parietal Lobe	fit	10	-0.14	16	-0.03	9	0.08
	vox	10	-0.18	16	-0.10	9	-0.57
Medial	fit	.	n/a	16	-0.60	7	-0.20
Temporal Lobe	vox	.	n/a	16	-0.56	7	-0.47
Lateral	fit	10	0.26	16	-0.03	9	0.00
Temporal Lobe	vox	10	-0.16	16	-0.30	9	-0.26
Recognition							
Frontal Lobe	fit	10	0.17	16	-0.45	9	0.32
	vox	10	0.38	16	-0.43	9	0.37
Parietal Lobe	fit	10	-0.49	16	-0.45	9	0.24
	vox	10	-0.39	16	-0.26	9	0.28
Medial	fit	6	-0.68	14	0.12	7	-0.23
Temporal Lobe	vox	6	-0.73	14	-0.25	7	-0.32
Lateral	fit	10	-0.37	16	-0.45	9	0.51
Temporal Lobe	vox	10	-0.36	16	-0.54	9	0.66

Question 4:

Does the present study provide evidence of frontal lobe compensation either for the contralateral region in the non-dominant hemisphere, or in relationship to other regions of interest?

Finally, the fourth issue is aimed to address a suggestion raised in a previous study (Cabeza *et al.*, 2002) that bilateral activation in the frontal lobe may be evidence of reorganization of memory networks. To test this hypothesis, a Pearson correlation

between FLI and MTLI was calculated separately for older and younger adults (by both lateralization measures, at encoding and recognition separately). Several of the previous analyses may lend information to this issue as well, such as the comparison between frontal activation and MTL factor scores, and analyses of recognition performance.

The above analyses get to the heart of the debate in the cognitive neuroscience of aging: is increased activation in contralateral regions evidence for compensation? To address this issue further, first the correlation between activation in frontal and medial temporal lobes was examined. FLI and MTLI were compared with separate bivariate correlation analysis in young and older adults.

Question 4 – Results

In older adults, intensity of frontal lobe activation during encoding was significantly correlated with intensity of activation in the medial temporal lobe (Enc-FL and Enc-MTL by fit coefficient: $r = .46$, $p<.05$). This relationship was not reflected in the same comparison in younger adults (young Enc-FL to Enc-MTL by fit coefficient: $r = -.02$). No significant correlations were found between Enc-FL and Enc-MTL in older adults during recognition. In young adults, a strong correlation was found between FLI and MTLI as calculated by both fit coefficient and voxel count, however no correlation was statistically significant (FLI-fit to MTLI-fit: $r = .52$; FLI-vox to MTLI-vox: $r = .42$).

Second, percent correct on the recognition task was negatively correlated with MTLI intensity during encoding in older adults. That is, individuals with lower recognition performance scores had more right lateralized signal intensity in the MTL during encoding ($r = -.47$, $p<.05$). Similar correlations existed for the correlation to

MTLI by voxel counts (r = -.46). Young adults had similar correlation values (MTLI by voxels: r = -.54). Additionally, young participants' recognition performance was positively correlated with FLI intensity during encoding (r = .51). Again, neither correlation reached criteria for significance. Significant results may have been found with a larger sample of younger adults.

Total number of voxels at encoding and recognition

One methodological question that is raised in group comparisons of neuroimaging data is whether the two groups generally have the same amount of activation. There are several biological factors that could affect the fMRI BOLD signal observed in older adults, including cardiovascular disease, hypertension, decreased motor control, and others (D'Esposito, 2003). A concern for the present study was whether there was a difference between young and older adults, and further whether there were general activation differences among older adults as a function of FL or MTL factor scores. Group differences in the present study were assessed by comparing the total number of voxels active during encoding and recognition for each group. The total number of active voxels was calculated for each participant by summing the number of active voxels for each ROI, within each experimental condition (encoding and recognition). An independent samples t-test was used to compare total active voxels between young and older adults. A 2x2 between-subjects ANOVA was used to compare the number of total active voxels across the FL and MTL factor score groups.

On average, young and older adults had equal amounts of activation across all regions of interest combined. The average number of voxels active did not differ between

the age groups at encoding (elderly mean = 299.00, sd = 175.5; young mean = 278.89, sd = 224.3; $t(39) < 1$, SE = 70.38); or during recognition (elderly mean = 408.21, sd = 241.0; young mean = 345.56, sd = 97.3; $t(36) < 1$, SE = 82.98). No significant main effects or interaction were found among the older adult group as a function of FL or MTL factor scores.

Although differences were not observed within each experimental condition, an interesting pattern was revealed when mean number of active voxels during encoding and recognition were compared (see Figure 10). Older adults with high FL factor scores had more active voxels during encoding than adults with low FL factor scores. The opposite pattern occurred in recognition data; older adults with high FL factor scores showed less overall activation during recognition than subjects with low FL factor scores. A repeated measures ANOVA comparing average number of active voxels for each condition (encoding, recognition), by one between-subjects factor, group (young, elderly), revealed a significant main effect of condition ($F(1,36) = 5.34$, MSE = 28451.71, $p < .05$) but not a significant interaction between condition and group ($F < 1$, MSE = 28451.71, ns). Differences among older adults as a function of factor scores was assessed by a 1 within- (condition: encoding, recognition) and 2 between- subjects (FL factor: low, high; MTL factor: low, high) factors repeated measures ANOVA. Significant results included a main effect of condition ($F(1,25)=10.21$, MSE=28495.61, $p<.01$) and an interaction between condition and FL factor ($F(1,25)=6.13$, MSE=28495.61, $p<.05$). Follow-up paired t-tests showed that participants with low FL factor scores had significantly more

voxels active overall during recognition than during encoding (t(14) = -3.60, SE = 68.79, p<.01) No other interactions were significant.

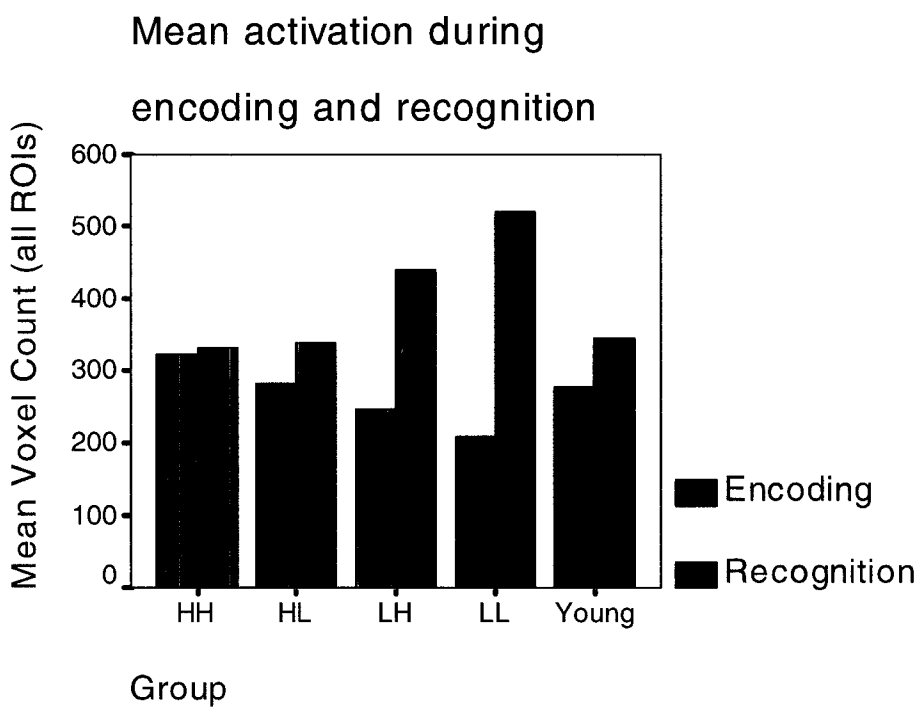


Figure 14. Mean number of voxels active across all ROIs during encoding (blue) and recognition (orange) for young adults and older adults by factor score groups. HH=high frontal, low memory; HL= high frontal, low memory; LH=low frontal, high memory; LL=low frontal, low memory.

Since the above analyses were based on the sum of active voxels from each ROI, an obvious question is whether this overall pattern, is consistent in each ROI, or if the overall difference reflects a change in a subset of regions. The pattern observed for all ROIs combined was also seen within each ROI (Figures 15-18).

Mean frontal lobe activation during encoding and recognition

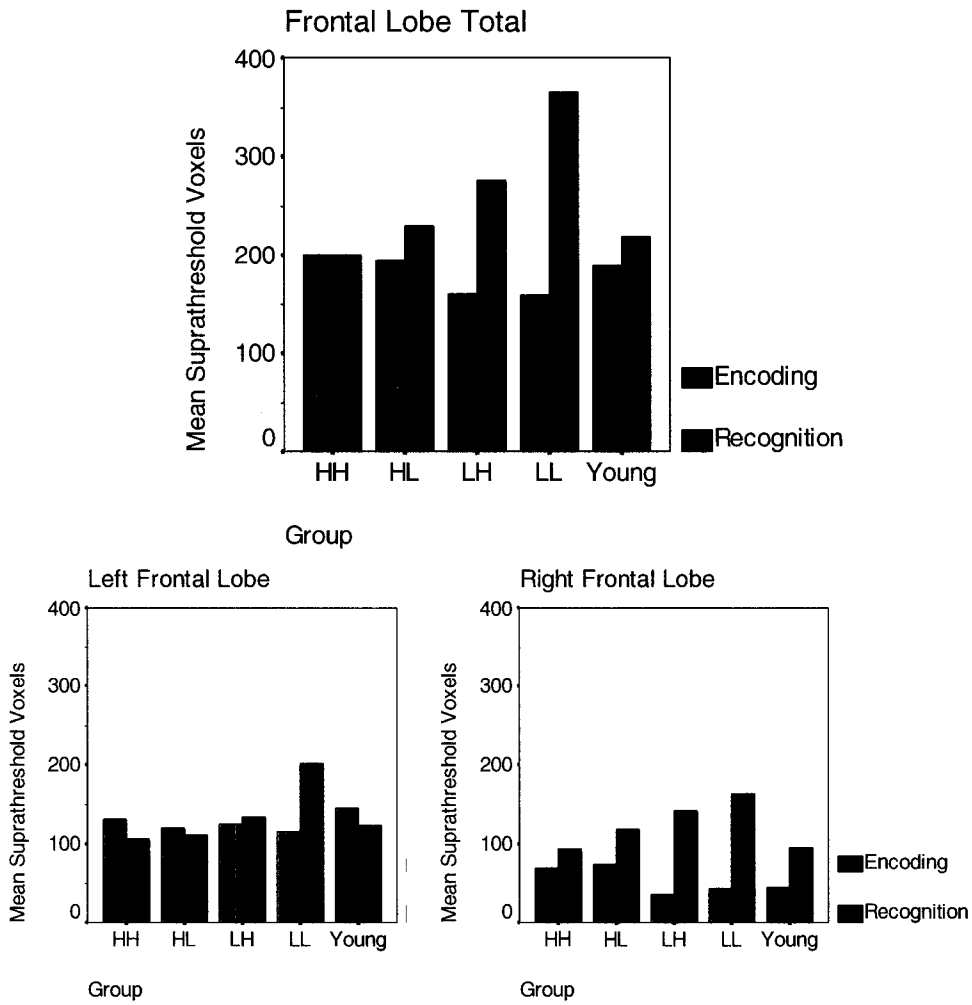


Figure 15. Mean suprathreshold voxels in the frontal lobe. Groups: HH=high frontal, high memory: HL=high frontal, low memory; LH=low frontal, high memory; LL=low frontal, low memory.

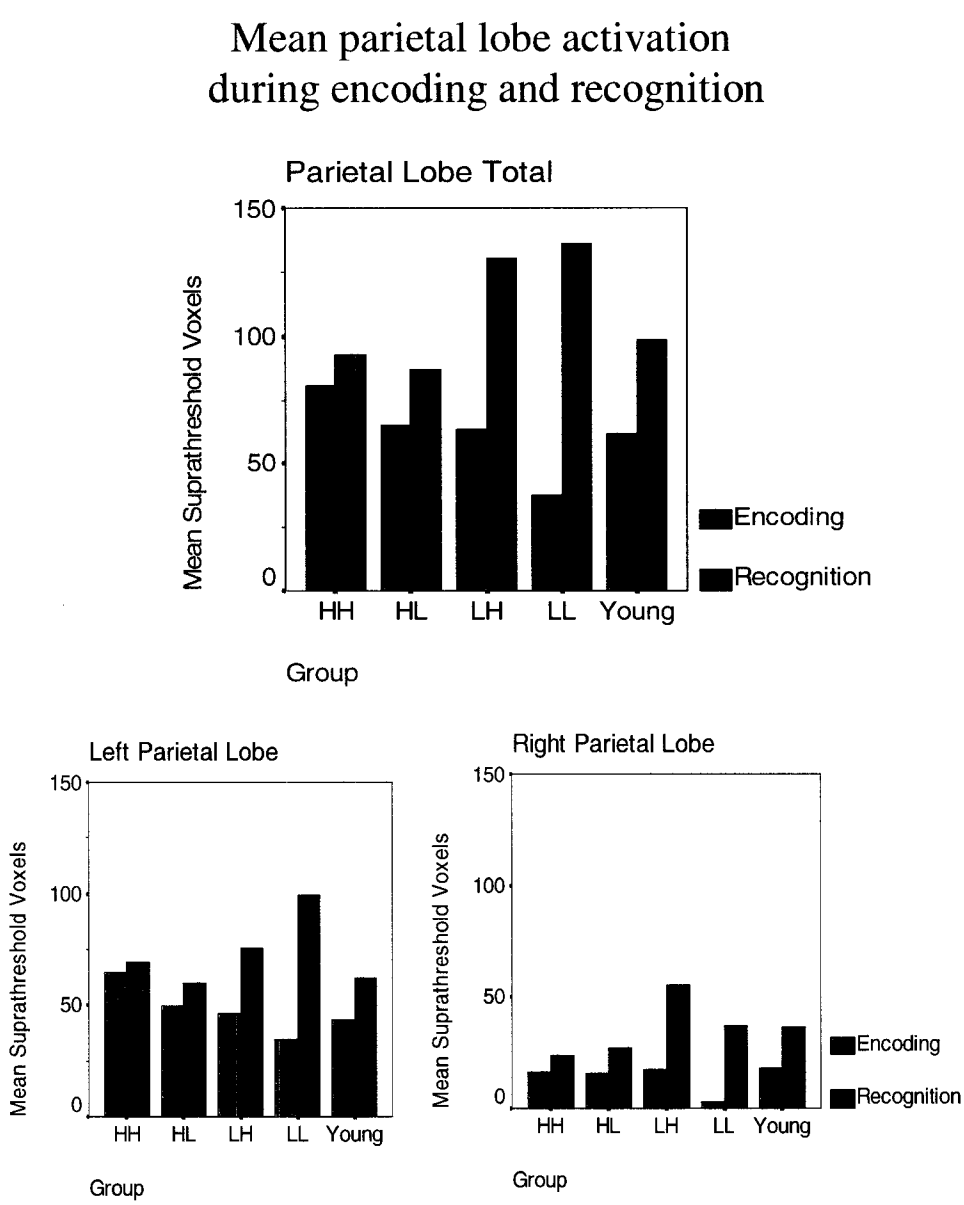


Figure 16. Mean suprathreshold voxels in the parietal lobe. Groups: HH=high frontal, high memory: HL=high frontal, low memory; LH=low frontal, high memory; LL=low frontal, low memory.

Mean medial temporal lobe activation during encoding and recognition

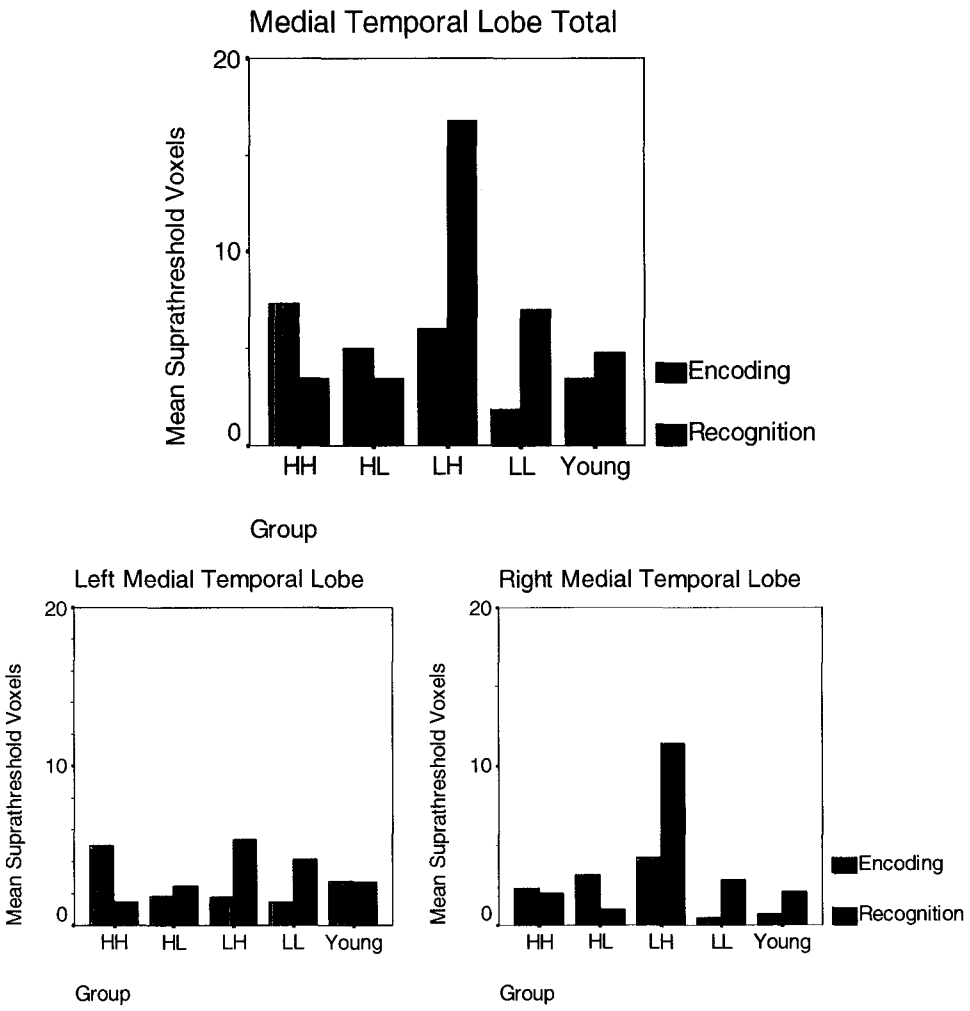


Figure 17. Mean suprathreshold voxels in the medial temporal lobe. Groups: HH=high frontal, high memory: HL=high frontal, low memory; LH=low frontal, high memory; LL=low frontal, low memory.

Mean lateral temporal lobe activation during encoding and recognition

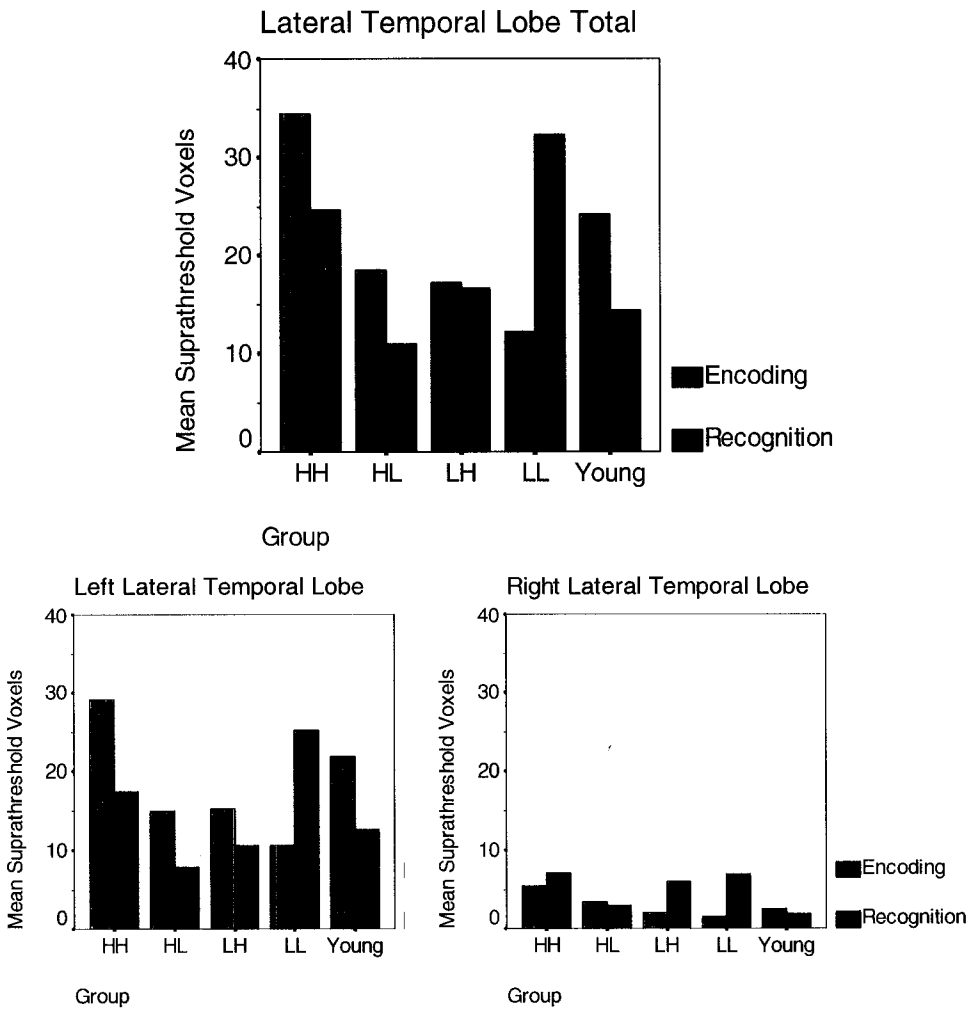


Figure 18. Mean suprathreshold voxels in the lateral temporal lobe. Groups: HH=high frontal, high memory: HL=high frontal, low memory; LH=low frontal, high memory; LL=low frontal, low memory.

DISCUSSION

HAROLD model

Consistent with the HAROLD model, older adults showed greater bilateral fMRI activation in the frontal lobes during encoding than young adults. Frontal activation in young adults was greater on the left than on the right during encoding. Surprisingly, however, when analyses were extended to include regions of interest beyond the frontal lobes, a different picture emerged. In older adults, the relationship between executive function and frontal lobe activation during semantic encoding was dependent upon whether the medial temporal lobe was also active. This finding was not predicted by the present study; nonetheless, it suggests that age-related changes of frontal activation patterns are more complex than what is explained by the HAROLD model.

Participants with MTL activation, showed a strong positive correlation between the frontal factor score and lateralization of frontal lobe activation. That is, within this group, bilateral activation in the frontal lobe increased with frontal factor score: older adults with higher frontal factor scores showed more bilateral frontal activation, and those with lower frontal factor scores showed more left-lateralized activation. In contrast, participants who lacked MTL activation had the opposite pattern: higher frontal factor scores were associated with greater left-lateralization. Additionally, among adults without MTL activation, bilateral frontal activation was related to low MTL factor scores (Figure 11).

Thus, bilateral activation in the frontal lobes during semantic encoding was associated with two different activation patterns: 1) when MTL activation was present,

bilateral frontal activation was observed in older adults with high FL factor scores; 2) when the MTL was not active, bilateral frontal activation was found in older adults with low MTL factor scores. Older adults with high FL factor scores but who did not activate MTL had left lateralized frontal activation (see Figures 11). Importantly, older adults with and without MTL activation did not differ in recognition performance scores. Furthermore, each group included participants across the range of FL and MTL factor scores, and there was no correlation between lack of MTL activation and activation amount in other regions.

These results suggest that bilateral frontal activation patterns in older adults cannot be explained by a single model. The HAROLD model fits data from a majority (19/29) of the participants in the present study, yet a sizeable minority (10/29) cannot be explained by the HAROLD model. Although it should be kept in mind that each subgroup in Figure 6 represents only a few subjects, there was a marginally significant main effect of frontal factor score, which indicates lateralization differences within each group (with and without MTL activation during encoding) may be differentiated by frontal factor scores in a larger sample. The pattern observed was that differences among adults with MTL activation were divided across high and low frontal factor scores and adults without MTL activation were differentiated by high and low memory factor scores. This finding suggests an interesting pattern that needs to be confirmed in another sample.

Any explanation of the two patterns observed here must take into account that older adults with and without MTL activation performed equally well on the recognition test during fMRI. Several explanations are possible. Among individuals with high

frontal factor scores, finding bilateral frontal activation in older adults with MTL activation indicates that either: 1) older adults with high frontal factors invoke different strategies or processes at encoding that recruit the right hemisphere, or 2) that these older adults succeed because they successfully compensate for lowered left-hemisphere activation. It is possible that these two explanations are related. That is, different strategies are utilized because old strategies presumably reliant on the left hemisphere are no longer effective. In contrast, older adults with high frontal factor scores but without MTL activation, left-lateralized frontal activation is indicative of normal performance, similar to young adults, who show strong left lateralized frontal activation regardless of MTL activation. Among young adults, seven out of nine subjects showed activation in the MTL. Finally, an intuitive explanation for bilateral frontal activation in older adults without MTL activation is that they are able to succeed on the recognition memory test by recruiting the right hemisphere.

Finding differences within a group of older adults is not new. Two other explanations of differences among older have been based on differences between fluid and crystallized intelligence measures (Li, S-C; Lindenberber, Hommel, Aschersleben, Prinz, & Baltes, 2004), reaction time (Rympa & D'Esposito, 2000), or brain volumes, particularly differences in the MTL (Rosen et al., 2002). Another possible explanation for increased bilateral activation observed in older adults but not young adults during recognition, is that the task is more demanding for older adults. It has been shown in other studies that bilateral frontal activation was associated with demanding executive function tasks (Shaywitz, Shaywitz, Pugh, Fulbright, Skudlarski, et al., 2001).

Unfortunately, the present study does not expose possible neurological or cognitive basis for the variable patterns found in older adults. Future analyses to determine differences between adults with and without MTL activation could include using voxel based morphometry or PLS analyses to further examine differences between whole-brain networks in each group; or by using standard mophometric analyses to measure the volume of MTL structures. One limitation of the current study is that frontal lobe regions were intentionally broadly defined to address the HAROLD issue. More precisely delineated areas using morphometry may be better suited to reveal more subtle differences between groups. Previous reports in the literature that only examined FL activation may have found the HAROLD pattern if they had included other ROIs or may have obscured significant relationships between frontal activation and cognitive performance by failing to include MTL as a region of interest.

Amount of Activation: Differences between encoding and recognition

Another important finding was that the overall amount of fMRI activation found during encoding and recognition varied across older adults by factor scores (see Figures 14-18). Compared to all other groups (other factor score groups and young), older adults with low FL factor scores showed the lowest amount of activation during encoding, but the most activation during recognition. This finding is consistent with results reported by Daselaar et al.2003), who found dramatic global increase of fMRI activation across all regions in older adults who had low memory as measured by recognition performance. Although significant differences in recognition performance were not found among older adults in the present study, adults with lower MTL factor scores performed numerically

worse at recognition than older adults with high MTL factor scores. The small subject sample may contribute to the lack of significant findings. Also, two older adults from the LL group were dropped from analyses because of recognition scores that appeared to be outliers in comparison to the rest of the LL group. Similarly, Daselaar et al. (2003) and Rosen et al. (2002) also showed reduced activation during encoding in older adults with low memory performance. Together, these data suggest that older adults with poor memory function do not sufficiently activate efficient encoding networks, such that they have to activate broader networks during recognition.

Both key findings from this study suggest that deficits during encoding processes are responsible for memory decline in normal aging. First, frontal laterality differences were observed between age groups during encoding but not during recognition. Second, older adults with lower memory show decreased activation during encoding.

Cognitive Neuroscience of Aging - Questions Answered

One aim of the present study was to address four primary questions: 1) was hemispheric asymmetry reduction observed in the frontal lobe of older adults compared to younger adults during encoding and recognition; and if so, did frontal lobe activation patterns differ among older adult groups as a function of neuropsychological factor score? 2) What is the relationship between memory, executive function and fMRI lateralization patterns when ROIs beyond the frontal lobe are included? 3) Was recognition performance better predicted by fMRI activation at encoding, retrieval, or a combination of both? 4) Does the present study provide evidence for a compensatory

role for increased frontal lobe activation? Answers to each question will be discussed in the context of how results relate to existing literature.

First, the HAROLD pattern was observed in the frontal lobe during semantic encoding but not during recognition (see discussion above). This finding is consistent with Rosen et al. (2002) who also required participants to make natural/manmade judgments, and found greater bilateral frontal activation in older adults with good memory during encoding. During a similar semantic encoding task (pleasantness judgment) Daselaar et al. (2003) also found a trend toward greater bilateral frontal activation during encoding, in older adults with better memory performance. Cabeza et al. (2002) did not scan during encoding, and tested memory for paired associates and source. In that study, the HAROLD pattern was not found during a paired associates recall task, but was found during a source memory task. When other ROIs were examined, the HAROLD pattern was also found in the medial temporal lobe and lateral temporal lobe during encoding. No region of interest showed evidence for the HAROLD pattern during recognition.

Second, including ROIs beyond the frontal lobe revealed that the relationship between frontal activation patterns and factor scores was dependent on whether MTL activation was also found. Cabeza suggested that the HAROLD pattern was found during the source task because it was more difficult than paired associates recall (Cabeza et al., 2002). The present findings are not consistent with a difficulty explanation. If the HAROLD pattern was found only in tasks that are more difficult, why then would it be found during encoding, when both young and older participants performed near ceiling

levels on the semantic classification task? Furthermore, recognition performance was equal across groups of older adults with and without MTL activation during encoding, who showed opposite lateralization patterns.

Third, recognition performance was associated with bilateral or right-lateralized activation of the lateral temporal lobe during recognition in young adults (Figures 12 and 13). Successful recognition performance in older adults' was moderately correlated with left-lateralized activation in the lateral temporal lobe during recognition and left-lateralized medial temporal lobe activation during encoding (Figure 13). Young and older adults had opposite correlations between laterality indices in the lateral temporal lobe during recognition (Figure 13).

Fourth, the HAROLD pattern was found in 2 subsets of older adults: those with high FL factor scores and who also had activation in MTL, and those with low MTL scores and who lacked MTL activation (see Figure 11). Increased bilateral frontal activation in older adults has been suggested to be a compensatory mechanism (Cabeza, Grady, Nyberg, McIntosh, Tulving, Kapur, et al., 1997; Cabeza, 2002; Cabeza et al., 2002). Bilateral activation is expected in better performing older adults, presumably because they are able to meet the demands of a difficult task by recruiting the non-dominant hemisphere (Cabeza et al., 2002). Additionally, Cabeza et al. (2002) suggested that increased activation within the same hemisphere is less effective than recruitment of non-dominant hemisphere. Cabeza's interpretation was that older adults with high memory "compensated age-related memory decline by reorganizing memory networks." Results from the present study suggest a more complex relationship.

Although there is evidence that older adults in the present study utilized two different networks, it is not evident that the recruitment of one network over the other was related to task difficulty. First, there were no group differences for accuracy of semantic classification during the encoding phase. Second, recognition performance did not differ across groups of older adults split by MTL activation during encoding, yet the same two groups showed opposite frontal lateralization patterns. Regarding the claim that additional recruitment within hemisphere is inefficient, again it depends on the whole network. Among older adults without MTL activation during encoding, the greatest left-lateralized activation was found in older adults with high MTL function, whereas greater bilateral activation was seen in subjects with low MTL factor scores.

Regarding recruitment of alternative memory networks (Cabeza et al., 2002), it would seem that one may have expected the reverse pattern of MTL activation in the current study. Given that it is widely accepted that MTL regions are part of a normal memory network, it seems more likely that the group of older adults *without* MTL activation would require recruitment of additional different networks. Yet, among older adults without MTL activation, subjects with better general memory performance did not recruit the contralateral hemisphere. In fact, the opposite is true: they have the strongest left-lateralized activation of any of the older adult groups. Daselaar's report of nearly absent anterior MTL activation in older adults with reduced memory would also support that disrupted memory networks are more likely to be associated with individuals with poor memory than in individuals that have improved memory.

Compensation or Dedifferentiation?

Several recent imaging studies in the cognitive neuroscience of aging have attempted to pit "compensation" and "dedifferentiation" hypotheses of reduced asymmetry in older adults (HAROLD model) against one another. Results from the present study were mixed. No strong evidence was found to support either view. Unilateral and bilateral frontal activation patterns in older adults were not isolated to a specific subgroup of older adults (i.e. low-functioning or high functioning). Therefore, it cannot be concluded that better memory or executive function in older adults is related to recruitment of additional brain regions.

Additionally, the current findings did not show direct support for the dedifferentiation view. Although two different activation networks were observed during encoding, there were not neuropsychological differences between the two groups of participants with or without MTL activation. Furthermore, MTL activation was not found for two young adults. This could be an indication that the two network patterns do not differentiate across the age range.

Additionally a better consensus of the definition of dedifferentiation among researchers is needed. It seems that often a single result could be explained by either compensation or dedifferentiation.

Future Research

Further research in which data could be combined from multiple methods is needed to adequately distinguish whether aging is better characterized by a compensation or dedifferentiation view. One possible combination of methods is to use an event related design or to combine EEG or MEG methods with fMRI to examine the time course

activation. Such studies could provide valuable information about activation timing within dominant and non-dominant hemispheres. If bilateral frontal activation was a form of compensation, one might expect the dominant hemisphere to show activation first, and "recruitment" of the non-dominant hemisphere would be expected to be evidenced by a short delay in activation onset compared to the dominant hemisphere. If, however, bilateral frontal activation was evidence for dedifferentiation, it would be expected that activation across hemispheres would be more simultaneous.

Another issue for future research would be to re-evaluate whether the experimental design and image processing allowed for the maximum number of voxels to be reported. Finding a lack of activation in fMRI research could be indicative of a separate network, but there is also a chance that a Type II error occurred. In particular it can be difficult to collect fMRI data from the hippocampus (Grecicius, Krasnow, Boyett-Anderson, Elez, Schatzberg, et al., 2003). A limitation of the present study is that scanning parameters were not optimized for acquiring MTL activation. In the current study, images were acquired parallel to the anterior commisure – posterior commisure (AC-PC) plane to maximize whole-brain coverage. Future studies may benefit from using an oblique slice selection selectively in medial temporal lobe, to increase the number of voxels of fully-volumed hippocampus, and to reduce susceptibility artifacts (but see also Grecicius, et al., 2003).

Finally, one of the goals of the cognitive neuroscience of aging is to distinguish brain activation differences that are a part of normal aging from activation patterns indicative of age-related disease processes, such as Alzheimer's disease. Further research

could be directed to determine whether one of the patterns observed in older adults in the present study is indicative of mild cognitive impairment or Alzheimer's disease. Incidentally, two participants who were excluded due to exceptionally poor recognition performance were the only two subjects to show right-lateralized activation during encoding. Together with the finding that adults with low memory factor scores also had more activation in the right hemisphere, a hypothesis to test in future studies would be whether adults with MCI or Alzheimer's disease show greater right-hemisphere activation and no MTL activation during encoding.

Conclusions

Results from the present study provide insight to discrepant findings in cognitive neuroscience of aging research. Two important findings include: 1) Support for the HAROLD model was only found in older adults who also showed activation in the MTL during encoding (i.e. greater bilateral frontal activation in higher performing older adults), 2) the amount of activation during encoding and recognition was dependent on FL factor score. During encoding, older adults with high FL factor scores had more global activation than older adults with low FL factor scores, and the inverse pattern was observed during recognition. These data support encoding deficit hypotheses of age-related memory decline. Further, a single model cannot account for the variability of frontal activation patterns observed in older adults.

APPENDIX A

Lateralization Calculation. Lateralization indices used in this dissertation were calculated based on the fit coefficient and voxel count values for each individual. Another possibility would have been base a lateralization index on the area under the curve value, which is a combination of fit coefficient and voxel count values. The area under the curve was calculated for frontal lobe values during encoding and recognition. The area under the curve was obtained by multiplying the mean fit coefficient value by the total number of voxels active in the region of interest. Area under the curve was calculated for the each individual's left and right frontal lobe ROIs. These values were then used to calculate a laterality index: ((Eauc_rf – Eauc_lf)(Eauc_rf + Eauc_lf))X100, where Eauc = Encoding area under the curve, rf = right frontal, lf = left frontal.

Figure A.1 shows a comparison of the three methods used to calculate laterality indices. The laterality index based on the area under the curve values consistently indicated greater left-laterality (values closer to -100), and had the same overall pattern as the laterality index based on voxel count data.

Although the area under the curve measure combines the intensity (fit coefficient) and extent (voxel count) information, it is informative to separately examine intensity and extent data. The fit coefficient laterality index values were consistently closer to 0, indicating that mean intensity of active voxels was similar in left and right regions of interest. Cohen has found through both human fMRI experiments and Monte Carlo simulation experiments that the fit coefficient is a more stable measure than voxel count

(Cohen, 1997; Cohen & DuBois, 1999). For this reason was decided to report fit coefficient and voxel count information separately in this dissertation.

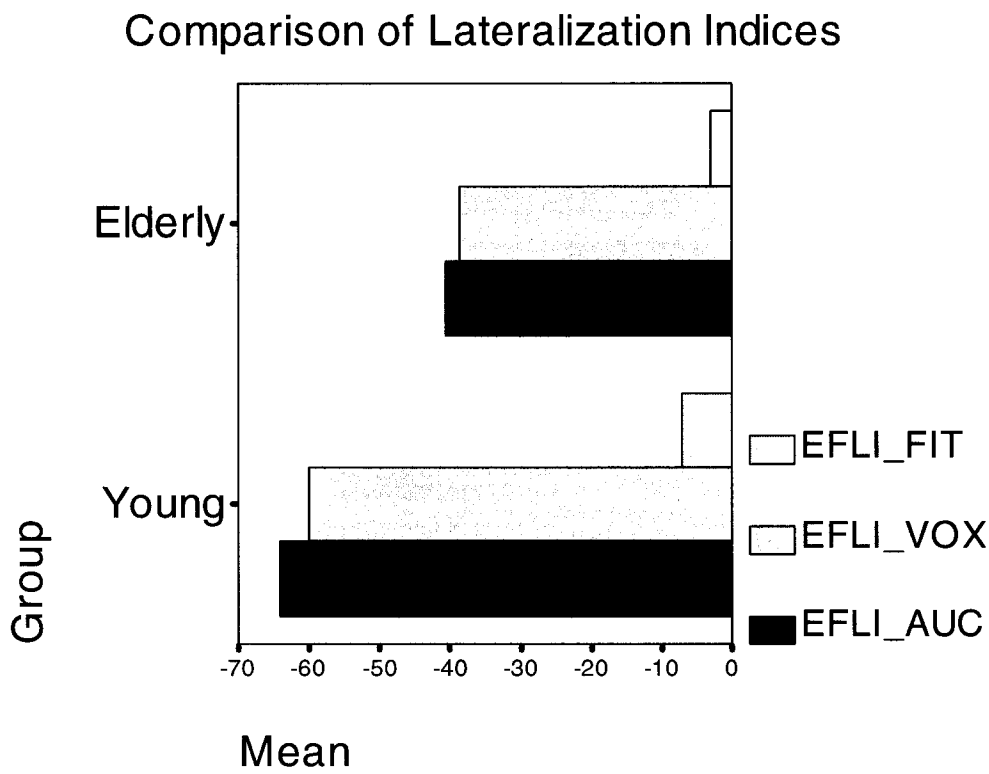


Figure A.1. Comparison of frontal lobe laterality indices for encoding in young and elderly participants. EFLI_FIT = encoding frontal lobe lateralization index by fit coefficient, EFLI_VOX = encoding frontal lobe lateralization index by voxel count, EFLI_AUC = encoding frontal lobe lateralization index by area under the curve.

REFERENCES

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. Neuroimage, 8, 360-369.

Anderson, N. D. & Grady, C. L. (2001). Functional Imaging in Cognitively Intact Aged People. In P.R.Hoff & C. V. Mobbs (Eds.), Functional Neurobiology of Aging (pp. 211-225). San Diego: Academic Press.

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). Memory changes in healthy older adults. In E.Tulving & F. I. M. Craik (Eds.), The Oxford handbook of memory (pp. 395-409). London: Oxford University Press.

Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for time-course data sets in functional MRI of the human brain. Magnetic Resonance in Medicine, 30, 161-173.

Blanchet, S., Desgranges, B., Denise, P., Lechevalier, B., Eustache, F., & Faure, S. (2001). New questions on the hemispheric encoding/retrieval asymmetry (HERA) model assessed by divided visual-field tachistoscopy in normal subjects. Neuropsychologia., 39, 502-509.

Cabeza, R. (2001). Cognitive neuroscience of aging: Contributions of functional neuroimaging. Scandinavian Journal of Psychology, 42, 277-286.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychology and Aging, 17, 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high- performing older adults. Neuroimage, 17, 1394-1402.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., Houle, S., & Craik, F. I. M. (1997). Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. Journal of Neuroscience, 17, 391-400.

Carusone, L. M., Srinivasan, J., Gitelman, D. R., Mesulam, M. M., & Parrish, T. B. (2002). Hemodynamic response changes in cerebrovascular disease: implications for functional MR imaging. Ajnr: American Journal of Neuroradiology., 23, 1222-1228.

Cohen, M. S. (1997). Parametric analysis of fMRI data using linear systems methods. Neuroimage., 6, 93-103.

Cohen, M. S. & DuBois, R. M. (1999). Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging. Journal of Magnetic Resonance Imaging., 10, 33-40.

Craik, F. I. M. & Lockhart, R. S. (1972). Levels Of Processing - Framework For Memory Research. Journal of Verbal Learning and Verbal Behavior, 11, 671-684.

Craik, F. I. M., Morris, L. W., Morris, R. G., & Loewen, E. R. (1990). Relations Between Source Amnesia And Frontal-Lobe Functioning In Older Adults. Psychology and Aging, 5, 148-151.

Craik, F. I. M. & Rabinowitz, J. C. (1985). The effects of presentation rate and encoding task on age-related memory deficits. Journal of Gerontology., 40, 309-315.

Craik, F. I. M. & Simon, E. (1980). Age differneces in memory: The roles of attention and depth of processing. In L.W.Poon, J.L.Fozard, L.E.Cermak, D.Arenberg, & .W.Thompson (Eds.), New Directions in memory and aging: proceedings of the George A. Talland Memorial Conference (pp. 95-113). Hillsdale, N.J: Lawrence Erlbaum Associates.

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the bold FMRI signal with ageing and disease: A challenge for neuroimaging. Nature Reviews Neuroscience, 4, 863-872.

D'Esposito, M., Zarahn, E., Aguirre, G. K., & Rypma, B. (1999). The variability of bold hemodynamic responses in young and elderly subjects: Implications for FMRI studies of normal aging. Journal of Cognitive Neuroscience 72.

Dale, A. M. & Buckner, R. L. (1997). Selective averaging of rapidly presented individual trials using fMRI. Human Brain Mapping, 5, 329-340.

Daselaar, S. M., Veltman, D. J., Rombouts, S. A. R. B., Raaijmakers, J. G. W., & Jonker, C. (2003). Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain, 126, 43-56.

Fergus, I. M. C. (2002). Levels of processing: Past, present ... and future? Memory, 10, 305-318.

Folstein, M.F., Folstein, S.E., McHugh, P.R. (1975). 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatry Research, 12, 189-198.

Forster, K. I. & Forster, J. C. (2003). A Windows display program with millisecond accuracy. Behavior Research Methods Instruments & Computers, 35, 116-124.

Glisky, E. L., Polster, M. R., & Routhieaux, B. C. (1995). Double Dissociation Between Item And Source Memory. Neuropsychology, 9, 229-235.

Glisky, E. L., Rubin, S. R., & Davidson, P. S. R. (2001). Source memory in older adults: An encoding or retrieval problem? Journal of Experimental Psychology-Learning Memory and Cognition, 27, 1131-1146.

Glover, G. H. and Lee, A. T. 1995. Motion artifacts in fMRI: comparison of 2DFT with PR and spiral scan methods. *Magn. Res. Med.* **33:** 624-635.

Grady, C. L. (2002). Age-related differences in face processing: A meta-analysis of three functional neuroimaging experiments. Canadian Journal of Experimental Psychology-Revue Canadienne de Psychologie Experimentale, 56, 208-220.

Grady, C. L., Bernstein, L. J., Beig, S., & Siegenthaler, A. L. (2002). The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. Psychology and Aging, 17, 7-23.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., Pietrini, P., Wagner, E., & Haxby, J. V. (1994). Age-related-changes in cortical blood-flow activation during visual processing of faces and location. Journal of Neuroscience, 14, 1450-1462.

Grady, C. L., McIntosh, A. R., Beig, S., & Craik, F. I. M. (2001). An examination of the effects of stimulus type, encoding task, and functional connectivity on the role of right prefrontal cortex in recognition memory. Neuroimage, 14, 556-571.

Grady, C. L., McIntosh, A. R., Bookstein, F., Horwitz, B., Rapoport, S. I., & Haxby, J. V. (1998). Age-related changes in regional cerebral blood flow during working memory for faces. Neuroimage, 8, 409-425.

Grady, C. L., McIntosh, A. R., & Craik, F. I. M. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. Hippocampus, 13, 572-586.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., Pietrini, P., Schapiro, M. B., & Haxby, J. V. (1995). Age-related reductions in human recognition memory due to impaired encoding. Science, 269, 218-221.

Greicius, M.D., Krasnow, B., Boyett-Anderson, J.M., Eliez, S., Schatzberg, A.F., Reiss, A.L., & Menon, V. (2003). Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI Study. Hippocampus, 13, 164-174.

Gunning-Dixon, F. M. & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. Neuropsychology, 14, 224-232.

Hart, R.P., Kwentus, J.a., wade, J.B., & Taylor, J.R. (1998). Modified Wisconsin Card Sorting Test in elderly normal, depressed, and demented patients. Clinical Neuropsychologist, 2, 49-56.

Hasher, L. & Zacks, R. T. (1979). Automatic And Effortful Processes In Memory. Journal of Experimental Psychology-General, 108, 356-388.

Hashtroudi, S., Johnson, M. K., & Chrosniak, L. D. (1989). Aging And Source Monitoring. Psychology and Aging, 4, 106-112.

Head, D., Raz, N., Gunning-Dixon, F., Williamson, A., & Acker, J. D. (2002). Age-related differences in the course of cognitive skill acquisition: The role of regional cortical shrinkage and cognitive resources. Psychology and Aging, 17, 72-84.

Hedden, T. & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. Nature Reviews Neuroscience, 5, 87-U12.

Huettel, S. A., Singerman, J. D., & McCarthy, G. (2001). The effects of aging upon the hemodynamic response measured by functional MRI. Neuroimage, 13, 161-175.

Jennings, J. M. & Jacoby, L. L. (1993). Automatic Versus Intentional Uses Of Memory - Aging, Attention, And Control. Psychology and Aging, 8, 283-293.

Kray, J., Li, K. Z. H., & Lindenberger, U. (2002). Age-related changes in task-switching components: The role of task uncertainty. Brain and Cognition, 49, 363-381.

Kucera H and Francis WN. Computational Analysis of Present-day American English. Providence, RI: Brown University Press; 1967.

Lars, N. (2002). Levels of processing: A view from functional brain imaging. Memory, 10, 345-348.

Li, K. Z. H., Lindenberger, U., Freund, A. M., & Baltes, P. B. (2001). Walking while memorizing: Age-related differences in compensatory behavior. Psychological Science, 12, 230-237.

Li, S. C. & Lindenberger, U. (2000). Lifespan differences in the relationships between interindividual differences in intellectual abilities and cognitive task demands. International Journal of Psychology, 35, 386.

Li, S. C., Lindenberger, U., & Sikstrom, S. (2001). Aging cognition: from neuromodulation to representation. Trends in Cognitive Sciences, 5, 479-486.

Light, L. L., & LaVoie, D. (1993). Direct and indirect measures of memory in old age. In P. Graf & M. E. J. Masson (Eds.), *Implicit memory: New directions in cognition, development, and neuropsy-chology (pp. 207-230). Hillsdale, NJ: Erlbaum.*

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. Neuron, 33, 827-840.

Madden, D. J., Gottlob, L. R., Denny, L. L., Turkington, T. G., Provenzale, J. M., Hawk, T. C., & Coleman, R. E. (1999). Aging and recognition memory: Changes in regional cerebral blood flow associated with components of reaction time distributions. Journal of Cognitive Neuroscience, 11, 511-520.

Madden, D. J., Turkington, T. G., Provenzale, J. M., Denny, L. L., Langley, L. K., Hawk, T. C., & Coleman, R. E. (2002). Aging and attentional guidance during visual search: Functional neuroanatomy by positron emission tomography. Psychology and Aging, 17, 24-43.

Maguire, E. A. & Frith, C. D. (2003). Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain, 126, 1511-1523.

McConnell, K. A., Bohning, D. E., Nahas, Z., Shastri, A., Teneback, C., Lorberbaum, J. P., Lomarev, M. P., Vincent, D. J., & George, M. S. (2003). BOLD fMRI response to direct stimulation (transcranial magnetic stimulation) of the motor cortex shows no decline with age. Journal of Neural Transmission, 110, 495-507.

McGonigle, D. J., Howseman, A. M., Athwal, B. S., Friston, K. J., Frackowiak, R. S. J., & Holmes, A. P. (2000). Variability in fMRI: An examination of intersession differences. Neuroimage, 11, 708-734.

Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. Psychology and Aging, 17, 56-71.

Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. Psychonomic Bulletin & Review, 3, 135-148.

Park, D. C., Smith, A. D., Morrell, R. W., Puglisi, J. T., & Dudley, W. N. (1990). Effects Of Contextual Integration On Recall Of Pictures By Older Adults. Journals of Gerontology, 45, 52-57.

Raz, N. (2000). Differential aging of the cerebral cortex: Implications for age-related differences in memory. International Journal of Psychology, 35, 183-184.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., Thornton, A. E., & Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. Cerebral Cortex, 7, 268-282.

Raz, N., Rodrigue, K. M., & Acker, J. D. (2003). Hypertension and the brain: Vulnerability of the prefrontal regions and executive functions. Behavioral Neuroscience, 117, 1169-1180.

Reuter-Lorenz, P. A. (2002). New visions of the aging mind and brain. Trends in Cognitive Sciences, 6, 394-400.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. Journal of Cognitive Neuroscience, 12, 174-187.

Rosen, A. C., Prull, M. W., O'Hara, R., Race, E. A., Desmond, J. E., Glover, G. H., Yesavage, J. A., & Gabrieli, J. D. E. (2002). Variable effects of aging on frontal lobe contributions to memory. Neuroreport, 13, 2425-2428.

Rypma, B. & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. Nature Neuroscience, 3, 509-515.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. Psychological Review, 103, 403-428.

Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L., & Albert, M. S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. Proceedings of the National Academy of Sciences of the United States of America, 93, 321-325.

Schacter, D.L., Harbluk, J.L., & McLachlan, D.R. (1984). Retrieval without recollection: an experimental analysis of source amnesia. Journal of Verbal Learning and Verbal Behavior, 23, 593-611.

Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Fulbright, R.K., Skudlarski, P., Mencl, W.E., Constable, T., Marchione, K.E., Fletcher, J.M., Klorman, R., Lacadie, C., & Gore, J.C. (2001). The functional neural architecture of components of attention in language processing tasks. Neuroimage, 13, 601-612.

Scheibel, A.B. (1996). Structural and functional changes in the aging brain. In: Handbook of the Psychology of Aging, Fourth Edition. J.E. Birren, K.W. Schaie (Eds.). San Diego, CA, Academic Press, 105-128.

Shimamura, A. P., & Squire, L.R. (1987). A neuropsychological study of fact memory and source amnesia. Journal of Experimental Psychology: Learning, Memory, and Cognition, 13, 464-473.

Spreen, O., & Benton, A. L., (1997) *Neurosensory Center Comprehensive Examination for Aphasia* (Rev. ed.). Victoria, British Columbia: University of Victoria Neuropsychology Laboratory.

Stebbins, G. T., Carrillo, M. C., Dorfman, J., Dirksen, C., Desmond, J. E., Turner, D. A., Bennett, D. A., Wilson, R. S., Glover, G., & Gabrieli, J. D. E. (2002). Aging effects on memory encoding in the frontal lobes. Psychology and Aging, 17, 44-55.

Stebbins, G. T., Gabrieli, J. D. E., Carrillo, M. C., Dorfman, J., Dirksen, C., Turner, D., Glover, G., & Desmond, J. (1998). Influence of aging on semantic and episodic memory: A functional magnetic resonance imaging (fMRI) study. Journal of Cognitive Neuroscience 52.

Sullivan, E. V., Marsh, L., Mathalon, D. H., Lim, K. O., & Pfefferbaum, A. (1995). Age-Related Decline In Mri Volumes Of Temporal-Lobe Gray-Matter But Not Hippocampus. Neurobiology of Aging, 16, 591-606.

Talairach, J. and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain.* Thieme, Stuttgart.

Tulving, E. (1972). Episodic and semantic memory. In: E. Tulving and W. Donaldson (Eds.). Organization of Memory. Academic Press: New York, 381-403.

Van Petten, C., Plante, E., Davidson, P.S.R., Kuo, T.Y., Bajuscak, L., and Glisky, E.L. (in press). Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes.

Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: Psychological Corporation, Harcourt Brace, 1999.

Wechsler, D., (1981). Wechsler Adult Intelligence Scale—Revised. New York: Psychological Corporation.

Wechsler, D., (1987). Wechsler Memory Scale—Revised. New York: Psychological Corporation.

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1350 N. Vine Avenue
P.O. Box 245137
Tucson, AZ 85724-5137
(520) 626-6721

7 April 2003

Jennifer Johnson, M.A.
Lee Ryan, Ph.D.
Elizabeth Glisky, Ph.D.
Department of Psychology
PO Box 210068

RE: **BSC #03-21** THE EFFECTS OF AGING AND COGNITIVE PERFORMANCE ON PATTERNS OF NEURAL ACTIVITY MEASURED BY FUNCTIONAL MAGNETIC RESONANCE

Dear Ms. Johnson, Dr. Ryan and Dr. Glisky:

The above referenced project was reviewed by Full committee for a second time and approval for this subjects-at-risk project is granted as submitted **effective 7 April 2003** for a period of one year.

The Human Subjects Committee (Institutional Review Board) of the University of Arizona has a current assurance of compliance, number FWA00004218, which is on file with the Department of Health and Human Services and covers this activity.

Approval is granted with the understanding that no further changes or additions will be made either to the procedures followed or to the consent form(s) used (copies of which we have on file) without the knowledge and approval of the Human Subjects Committee and your College or Departmental Review Committee. Any research related physical or psychological harm to any subject must also be reported to each committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Theodore J. Glattke, Ph.D.
Chair
Social and Behavioral Sciences Human Subjects Committee

TJG:tl
cc: Departmental/College Review Committee

Enclosures