EFFECTS OF GOAL-SETTING ON MEMORY PERFORMANCE IN YOUNG AND OLDER ADULTS: A FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI) STUDY

By

MICHAEL A. COLE

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I dedicate this dissertation to my wife, Heather Graham Cole,
and to my daughter, Tiana Cassidy Cole.

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By

Michael A. Cole

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Chair: William Perlstein
Cochair: Bruce Crosson
Major Department: Clinical and Health Psychology

Episodic memory decline in late life can be improved by use of explicit goal-setting for performance. The neural correlates that underlie the benefits of goal-setting on memory performance have yet to be examined. Event-related functional magnetic resonance imaging (fMRI) was employed to investigate the neural correlates of memory encoding as a function of age and memory enhancement by goal-setting. FMRI data were obtained while 20 young adults (ages 18 – 28) and 20 older adults (ages 60 – 70) performed 3 trials of a list-learning task that was comprised of grocery items. Half of the young adult and half of the older adult groups received goals for performance achievement prior to each of the 3 trials, whereas the other half of the young adult and older adult groups did not receive performance goals. FMRI data were analyzed for signal increases related to the encoding period, as well as signal increases that correlated with subsequent recall performance of the word-lists. Young adults remembered a

significantly greater number of words than older adults. Significant performance improvement derived from goal-setting was equivalent between young and older adults. Functional MRI findings revealed left lateralized prefrontal cortex (PFC) activation in young adults (not receiving goals), which is consistent with predictions of the hemispheric encoding and retrieval asymmetry (HERA) model. Older adults demonstrated left lateralized PFC activation as well. Consistent with predications of the hemispheric asymmetry reduction in older adults (HAROLD) model, the left PFC activity was significantly dampened in older adults. The effect of goal-setting on encoding activity was primarily constrained to the frontal lobes. Regions that demonstrated significantly greater activity in the goal group than in the no-goal group included the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), and Broca's area. Engagement of these regions likely reflects increased motivation and increased mnemonic processes, such as subvocal rehearsal. In conjunction with goal-setting, older adults activated several different regions to a greater extent than young adults. As these regions were observed to be activated during encoding in the absence of goal-setting, the differentially greater activation in older adults may reflect increased resources put toward mnemonic processing in older adults or perhaps decreased overall efficiency.

CHAPTER 1
INTRODUCTION

Overview

As advances in modern medicine have enabled individuals to reach later and later decades in their lives, much interest has accumulated into the physical and psychological changes that take place in these late stages of life. Many remain highly inventive and ingenious in their work well into the late stages of their life, such as Michelangelo, Claude Monet, Frank Lloyd Wright, and Joseph Campbell, but these are unique examples of notables who unfortunately are not representative of typical cognitive aging. A particular area of interest in cognitive aging that has evolved is that of episodic memory, a cognitive domain that experiences one of the steepest trajectories of decline with increasing age (Connor, 2001; Luszcz and Bryan, 1999). The declines in episodic memory performance have been firmly demonstrated, but less is known about the neural substrates that underlie this decrease in behavioral performance. Anatomical findings have revealed correlations between volumetric measures of the prefrontal cortex (PFC) and the rate of decline in episodic memory (Raz, 2000). Additional evidence suggests decreased activity (e.g., neural engagement) occurring in the PFC, as well as the temporal lobes, during memory tasks (Grady, 2000).

Some strategic techniques have been shown to be effective in improving episodic memory performance in both young and older adults. One such technique is goal-setting, which provides a challenge to the individual and often results in improved episodic memory performance (Linnenbrink et al., 1999; West et al., in press). Findings show that both young and older adults can improve memory performance through the provision of

explicit goals, which clearly has a neural origin. Although the neural underpinnings of the effect of explicit goal-setting on cognition has yet to be elucidated, evidence suggests a role for the orbito frontal cortex (OFC) and the dorsolateral prefrontal cortex (dlPFC; Jahanshanhi and Frith, 1998; Tremblay and Schultz, 1999).

The effect of goal-setting has generally been found to be as strong in older adults as in young adults (West and Thorn, 2001; West et al., in press). This finding is perhaps surprising in light of the fact that the two primary areas that likely participate in the goal-setting effect on memory, the OFC and dlPFC, undergo the steepest rate of degradation toward the latter stages of the lifespan (Band et al., 2001). It is therefore important to examine if an equal extent of activation exists in the OFC and dlPFC in young and older adults resulting from goal-setting. Alternatively, compensatory mechanisms may be taking place, allowing older adults to gain equal benefit by greater activation and/or recruitment of other regions to compensate for atrophy taking place in the OFC and the dlPFC.

The present research first reevaluated previous findings that episodic memory encoding in young adults is primarily lateralized to the left prefrontal cortex and that older adults engage the left prefrontal cortex to a lesser extent. This research also evaluated the role of the frontal cortex, specifically the OFC and the dlPFC, in the memory enhancing effects of goal-setting. Prior studies indicate that both these regions are involved with goal-directed behaviors. But the potential role for these frontal cortex regions in mediating the influence of explicit goal-setting on memory performance remains to be examined. It was hypothesized that the increased challenge resulting from explicit goal-setting would be accompanied by significant increases in dlPFC and OFC

activity. Additionally, it was hypothesized that older adults would show greater activation in these regions and perhaps more widespread activation to generate the equal benefit of explicit goal-setting on memory performance, compensating for the age-related declines seen in the OFC and dlPFC (Band et al., 2001).

Episodic Memory in Young and Older Adults

Different memory domains are not equally vulnerable to the declines occurring in older age. In fact, the integrity of some memory domains remains highly intact, while others are particularly susceptible to aging. A major distinction between memory types, and domains that demonstrate this differential vulnerability to aging, are the two types of declarative memory: semantic memory and episodic memory (Tulving, 1987). Semantic memory pertains to an individual's general knowledge about the world. This information includes, but is not limited to, vocabulary, facts, and concepts. Semantic memories are ones that an individual can volitionally bring to consciousness, but typically cannot report where the specific knowledge unit was obtained. This knowledge is therefore not associated with specific learning contexts or events, as it is in episodic memories. Overall, studies of semantic memory integrity in older adults show very little difference from young adults in the retrieval and use of semantic information (Madden et al., 1993).

On the other hand, older adults do experience declines in episodic memory, which refers to the ability to remember specific events situated in time and place. Episodic memory is commonly thought of as the acquisition, storage, and retrieval of information that refers to a specific context and is consciously and intentionally recollected (Tulving et al., 1994). Studies consistently show declines in episodic memory performance in older adults (Craik and Jennings, 1992; Smith, 1996). Findings indicate that older adults often have difficulty with encoding (the initial storage of information), as well as retrieval

(Craik and Jennings, 1992). This decline has been observed with virtually every type of stimulus, such as prose passages, single words, spatial locations, pictures, faces, and activities (Burke and Light, 1981; Light, 1991; Smith, 1996). Additionally, age differences have been demonstrated for spontaneously used elaborative and organizational strategies to store and retrieve information, as older adults are less likely to engage in these sorts of mnemonics. The greatest age differences are observed in tests of recall. Tests of cued recall and recognition reveal less substantial, but significant differences between young and older adults (Smith, 1996). These age-related changes are not peculiar to the artificial nature of memory tests that are administered in laboratory settings because they also occur in tasks that are designed to emulate memory in everyday life (Kirasic et al., 1996).

Strong evidence exists that these age-related declines in episodic memory are not due to older adults being less motivated to remember unfamiliar or unimportant stimuli of laboratory tasks because the memory decline still exists for more naturalistic stimuli. These stimuli include such examples as hands in bridge, groceries on a shelf (Read, 1987), board positions in chess (Charness, 1981), instructions on bottles of prescription medicine (Morrell et al., 1990), people's names (Cohen and Faulkner, 1986), and golf shots (Backman and Molander, 1986). A meta-analysis by Verhaeghen et al. (1993) confirmed results from individual experiments by reporting a negative relationship between age and episodic memory test performance with recall and recognition. They found that the average older adult above the age of 60 performed at a level between the 16th and 25th percentile of the young adults' performance distribution on various measures of recall. This result suggests that the average older adult's performance on

episodic memory tasks is approximately one standard deviation lower than that of the average performance of a young adult (Verhaeghen et al., 1993).

Especially in the last decade, researchers have begun to examine the neural substrates that might underlie these changes in memory performance across the lifespan. Studies have focused on the neuroanatomical changes that exist in older adults in addition to investigations of functional activation of brain regions *in vivo* as a subject performs an episodic memory task. Research identifying these neuroanatomical and functional changes has been successful in implicating likely mechanisms that may account for the decline in episodic memory performance in older age.

Neural Substrates of Episodic Memory Encoding

Overview

For some time it has been known that a person who has suffered a traumatic brain injury can have selective memory loss for events that occurred before (retrograde amnesia) and after (anterograde amnesia) the event that precipitated the traumatic brain injury. This phenomenon has been investigated thoroughly in animal studies using approaches such as electroconvulsive shock, physical trauma to the brain, and drugs that depress neuronal activity or inhibit protein synthesis in the brain. Clinical studies also indicate that brain trauma can produce amnesia that is particularly prevalent for recent events. Findings indicate that more recent memories are more susceptible to disruption, whereas older memories remain quite intact (Kupfermann, 1991). Squire et al. (1975) investigated this phenomenon in patients with depression who received electroconvulsive treatment. They used a memory test that could reliably quantify the degree of memory for relatively recent events (1-2 years old), old events (3-9 years old), and very old events (9-16 years old). Patients were asked to name television programs that were broadcast

during a single year between 1957 and 1972. The patients were initially tested and then tested again (with a different set of television programs) after the electroconvulsive therapy. After patients received electroconvulsive therapy, memory for television shows from less than 2 years removed were selectively impaired, whereas memory performance for more temporally removed programs remained consistent with performance levels observed prior to electroconvulsive therapy.

The differential susceptibility to disruption of memory that is dependent on the time of acquisition brings about possible explanations for how memories are stored and how neural changes that are associated with memories are maintained for years. One possibility is that the dynamic change that underlies the initial encoding of a memory persists and represents the long-term memory as well, such as a reverberating circuit. Another possibility is that long-term memories are related to some plastic rather than dynamic change (e.g., a persistent functional change within the brain). The extent literature provides strong support for the latter possibility. Studies have shown that by silencing the brain through use of deep anesthesia, anoxia, or by cooling the brain, short-term memories or recent memories are disrupted, but older memories are not. Therefore, it can be concluded that at least older memories are not mediated by dynamic change, but involve physical changes in the brain. It is thought that the storage of long-term memories is in part mediated by processes such as increased protein synthesis, growth of new synaptic connections, and increased synaptic efficacy (such as long-term potentiation; Kupfermann et al., 1991).

A central region in the facilitation of memory storage is the medial temporal lobe. The medial temporal lobe is needed at the time of learning to establish functional

connections with widespread areas of neocortex, based on neural activity that occurs at the time of learning. Medial temporal lobe lesions spare short-term (immediate) memory, presumably because the neocortex can support short-term memory. Therefore, it is thought that the medial temporal lobe is involved with processing and analyzing. This function begins at the time of learning as it receives highly processed input from neocortical association areas and continues to interact with the neocortex as it processes the information. Deficits from medial temporal lobe lesions have been described as extreme forgetfulness, and these deficits are most salient after some time has elapsed after the point of learning. This dissociation between perception and short-term memory and long-term-memory has been well established in humans, monkeys, and rats (Squire and Zola, 1997). In contrast, lesions in the neocortex impair memory abilities at both short and long delays (Goldman-Rakic, 1987; Fuster, 1995.)

The medial temporal lobe is involved in memory for a limited period of time after learning. As time passes, memory is slowly consolidated, and information storage in the neocortex becomes independent of the medial temporal lobe system. This is evidenced by the finding that if a medial temporal lobe lesion is sufficiently delayed after learning, memory is not affected. For instance, object discrimination tasks in monkeys demonstrated this temporally graded amnesia with lesions at different times following learning (Zola-Morgan et al., 1986). In contrast, there is no evidence of temporally graded amnesia in the neocortex (Squire and Zola, 1997).

Another important characteristic of the medial temporal lobe is that damage to this region produces memory deficits that are global and multimodal. That is, the memory impairments are present regardless of the type of material to be remembered, such as

objects, words, or designs, or the sensory modality in which information is presented (Baltes, 1993). In contrast, memory deficits associated with neocortical lesions are domain specific. That is, they are specific to the kind of material that is ordinarily processed by the damaged area.

The global and multimodal functioning of the medial temporal lobe is an important characteristic for theoretical accounts of memory consolidation, which assert that the medial temporal lobe directs consolidation in the neocortex by gradually binding together the multiple cortical regions located in different areas, storing a memory for a whole event (Squire and Alvarez, 1995).

Much like the medial temporal lobe, the basal forebrain is also thought to participate in the storage of memories in the neocortex. Neurons of the basal forebrain are activated by sustained attention in learning (Muir et al., 1993), which is a condition during which cortical plasticity often takes place. Evidence suggests that cholinergic and GABAergic neurons projecting from the basal forebrain (and in particular the nucleus basalis) can induce experience-induced plasticity changes in, for instance, auditory cortical responses. Response characteristics of the auditory cortex can be altered by repeatedly pairing of sounds with basal forebrain stimulation (Kilgard and Merzenich, 1998). Additionally, it has been shown that experience-induced plasticity can be blocked by lesioning the basal forebrain (Kilgard and Merzenich, 1998) or blocking cholinergic effects (Baskin and Weinberger, 1996).

Study of Korsakoff's syndrome patients has been informative in elucidating the role of the other structures important to memory function. Patients with Korsakoff's syndrome suffer from similar amnestic features as do patients who have had damage to

temporal lobe structures. Korsakoff's syndrome, which is caused by chronic alcoholism and associated nutritional deficiency, is associated with signs of frontal lobe dysfunction in addition to severe memory deficits. Patients exhibit pathological changes in diencephalic structures such as the mammillary bodies of the hypothalamus and the medial dorsal nucleus of the thalamus. Warrington and Weiskrantz (1982) found that when patients with Korsakoff's syndrome are given a list of words to remember, they do poorly on a simple recall task, but their performance is significantly improved when recall is tested by the use of prompts or partial cues. The authors concluded that this finding represents intact priming in the Korsakoff's syndrome patients in the presence of poor episodic memory abilities.

Evidence for thalamic involvement in memory is also derived from patients with infarctions, haemorrhages, mechanical injury, or tumor interfering with the integrity of the thalamus. Studies have shown a role for the thalamus in various cognitive functions related to memory such as the formation of new memories, attention to stimuli and events, and the use of memory strategies (Van Der Werf et al., 2003). Studies in animals indicate that a large lesion of the medial dorsal region of the thalamus is sufficient to produce learning deficits analogous to those exhibited by amnesic patients (Kupfermann, 1991; Van Der Werf et al., 2003).

Evidence outside of Korsakoff's syndrome patients exists for a role of mammillary bodies in memory. For instance, two cases of well documented amnesia have been reported in which marked neuronal loss was found within the mammillary bodies (Mayes et al., 1988). In addition, lesioning of the mammillary bodies in animals results in

significant impairments in the performance of spatial delayed alternation tasks in rats, cats, and monkeys (Sziklas and Petrides, 1998).

The above brief overview of neural substrates underlying memory function was primarily limited to animal and neuropsychological studies. Differentiating the role of these regions in encoding versus retrieval is difficult as the approaches are based primarily on lesion studies. With functional neuroimaging, cerebral metabolic activity is measured "on-line" as a cognitive task is being performed, and, in this way, the brain regions recruited for specific memory processes can be identified. Functional neuroimaging studies have played an important role in evaluating the neural substrates of memory because, in part, the encoding and retrieval processes of memory can be observed independently in real-time. As the present research evaluates episodic memory encoding, the following sections provide a focused review of primarily functional neuroimaging findings relating to the encoding phase of episodic memory.

Temporal Lobes

As mentioned above, the medial temporal lobe is central to memory function. The report by Scoville and Milner (1957) of impaired memory in patient H.M., who had a medial temporal lobe resection, was the first to highlight this region's importance in memory. Later neuropsychological, neuroscientific, and psychological research all converged on the medial temporal lobe, especially the hippocampal portion, as the site that mediates the storage of memories for episodes and factual knowledge of the world (Squire, 1987; Tulving, 1987). With the advent of neuroimaging, a logical region to begin the study of episodic memory would be the medial temporal lobe. The memory literature would suggest that episodic memory tasks would surely induce activation of the hippocampal complex. Surprisingly, though, many initial studies did not report

significant activation in this region (Buckner et al., 1995; Petersen et al., 1988; Frith et al., 1991; Demonet et al., 1992; Grasby et al., 1993, 1994). Several possible explanations exist that could account for these surprising findings. First, signal difference between experimental conditions is often only 1% to 2%, and even lower in the hippocampus because it resides in a region that is close to sinus cavities and subsequently subject to more noise. Thus, there may not have been sufficient signal over increased background noise to detect activations that may have been present. Additionally, some researchers have asserted that the nature of hippocampal neural functioning itself may have contributed to the inability to detect hippocampal activation between conditions (Cabeza and Kingstone, 2001). The hippocampus is central to information processing. Therefore it is frequently active, perhaps making it difficult to detect any increases in activation in an episodic memory condition.

Many more recent neuroimaging studies, which have investigated hippocampal involvement in episodic memory, have attempted a more nuanced assessment of hippocampal functioning. It was initially assumed that effort directed toward encoding and recollection should result in increased hippocampal activity. However, neuroimaging studies thus far have not found effort in encoding and recall/recognition to be an important factor as success in recollection. Specifically, hippocampal activation has been shown to be significantly correlated to success of memory performance (Fernandez et al., 1998; Yancey and Phelps, 2001).

A study by Fernandez et al. (1998) found that activation in the posterior hippocampus was significantly correlated with successful encoding of verbal stimuli. In a follow-up study, this same group compared results using the correlational method

between encoding activation and performance with the more traditional method of cognitive subtraction. The cognitive subtraction approach entails, in this context, the activation of the episodic memory encoding component process having an identical task, but without the mnemonic functions subtracted from it (Fernandez et al., 1999). They found that the entorhinal cortex did not respond transiently as the study word appeared (as assessed using the cognitive subtraction technique), but did correlate positively with subsequent test performance. This study was the first to directly compare these two techniques finding that the correlation with performance technique is able to much more reliably detect medial temporal lobe activation related to encoding.

With this novel approach, Brewer et al. (1998) demonstrated that the strength of medial temporal lobe activity during encoding predicts not only what items will be remembered, but also how well they will be remembered. They found that the magnitude of activation in the bilateral parahippocampal cortex predicted which picture stimuli were later remembered well, remembered less well, or forgotten. The distinction between remembering well and remembering less well was provided by a subjective report by the participant.

Schacter and Wagner (1999) reviewed all fMRI studies of memory encoding and compared them to results of a meta-analysis of positron emission tomography (PET) studies of episodic memory encoding (Lepage et al., 1998). Schacter and Wagner's review found that encoding processes resulted in more posterior medial temporal lobe activation across various materials and conditions (Schacter and Wagner, 1999). The meta-analysis by Lepage et al. (1998) of PET studies found a slightly different conclusion: episodic encoding is associated with more anterior medial temporal lobe

activation. Therefore, both methodologies converge in identifying the medial temporal lobe as an important region in encoding. The discrepancy between more anterior medial temporal lobe regions being activated in PET studies and more posterior medial temporal lobe regions in fMRI studies can likely be accounted for by the fact that PET is more sensitive to activation in the anterior portions of the medial temporal lobe. FMRI is known to be characterized by susceptibility artifacts that can be pronounced in the anterior medial temporal lobe, resulting in less sensitivity (Ojemann et al., 1997).

Frontal Lobes

Lack of activation of the hippocampus in many early neuroimaging studies was perplexing to those performing these experiments. Equally perplexing was the consistent and robust activation found in the frontal lobes. Prior to these studies, the frontal lobes were not necessarily thought to be major contributors to episodic memory. Patients who suffer damage to the frontal lobes, for instance, do not exhibit the pervasive and disabling amnesia that is characteristic of patients with hippocampal lesions (Wheeler et al., 1995). In functional neuroimaging studies, a highly consistent, lateralization of frontal lobe function has been found with the left frontal cortex showing predominant activation in association with learning or encoding tasks. The primary areas within the frontal cortex where this lateralized contribution to episodic memory encoding has been found are in ventral regions (Brodmann's areas 44, 45, and 47) and dorsal regions (Brodmann's areas 9 and 46) of the PFC. These findings have been integrated in the HERA (hemispheric encoding and retrieval asymmetry) model, which states that the left prefrontal cortex is more involved in episodic encoding (Tulving et al., 1994).

Though ventral PFC appears to contribute to episodic memory encoding, it has not been consistently found to be activated across experiments. Wagner et al. (1999) found

significant activation in the left ventral lateral frontal cortex, posteriorly in Brodmann's area (BA) 44 and anteriorly in BA 45/47, for encoding words that would later be remembered well versus words that would later be forgotten. Another study by Hensen et al. (1999) found that words that would be later specifically recalled as having been seen in the study phase exhibited significantly greater correlation with activation in the ventral PFC than words being classified as having been seen in the study phase but not specifically remembered. Fernandez et al. (1999) found that only the left BA 45 exhibited transient hemodynamic responses during encoding of verbal information.

The dorsal PFC, on the other hand, is reliably activated during encoding of episodic memories. Studies have demonstrated activation in the left dorsal PFC during the encoding of words (Grady et al., 1998; Kelley et al., 1998; Kopelman et al., 1998; Nyberg et al., 1996; Wagner et al., 1998); word pairs (Dolan and Fletcher, 1997; Fletcher et al., 1995; Halsband et al., 1998; Kapur et al., 1996); and word lists (Fletcher et al., 1998).

The left dorsolateral prefrontal cortex (dlPFC) has also been shown to contribute specifically to the implementation of strategic processes for the encoding of episodic memories. In a PET study, Fletcher and colleagues manipulated the level of attention to and the degree of organization of study material (Fletcher et al., 1998). The degree to which the subjects were required to organize word lists semantically was systematically varied across three experimental conditions. Left dlPFC activity reached its highest levels when organizational demands were the greatest. A role for the dlPFC in attention was suggested by dlPFC activity being attenuated by a concurrent motor distraction task during the most organizationally demanding task. Subsequent retrieval was also

correspondingly attenuated under this condition. Wagner et al. (1999) also found dlPFC activation during the implementation of strategic memory processes that improved memory performance. Subjects were presented with three words that they had to maintain either in the same order for a short period by means of subvocal rehearsal or to reorder along an abstract semantic dimension (e.g., pleasantness). Both activities engaged the dlPFC, but the semantic reordering of the words resulted in greater activation of the dlPFC. The semantic reordering of the words subsequently led to better memory as well.

In summary, neuropsychological and non-primate animal studies have documented the important role of the temporal lobes, diencephalon, and basal forebrain in memory function. Neuroimaging studies have allowed for a greater ability to evaluate the neural substrates of specific components of memory function, such as encoding. Neuroimaging findings have confirmed the role of temporal lobe structures in encoding. Additionally, neuroimaging studies have revealed the importance of the left PFC in encoding. Both the temporal lobe and PFC undergo significant changes in aging. The next section will discuss these changes and how they relate to episodic memory performance in older adults.

Neural Changes in Aging Affecting Episodic Memory Encoding

This section describes the multiple neuronal changes that take place in aging in the context of the effects on episodic memory encoding. Two key regions involved in episodic memory (temporal lobe and PFC) appear to experience both anatomical and physiological changes with aging that likely serve as the underpinnings of episodic memory performance declines.

Temporal Lobes

Several studies demonstrated modest structural and physiological changes in the temporal lobe regions in aging. Post-mortem studies of animal and human brains reveal age-associated changes in the hippocampal size (Geinisman et al., 1995). In one of the most comprehensive human post-mortem studies, the correlation value between neural counts in the hippocampus and age was r = -.21 (West, 1993). Aging also affects the neuronal architecture of the hippocampus. Although not as rampant in the normal aging brain as in Alzheimer's disease, neurofibrillary tangles display a similar characteristic regional distribution with the highest concentration in the hippocampus (Kemper, 1994). The hippocampus shares other architectural deformities, such as Hirano bodies and granulovacular degeneration (Kemper, 1994). The hippocampus is therefore the focal point of several deleterious events associated with aging. However, the magnitude of these age-related effects is thought to be within the mild range, as compared to effects in other brain regions (Raz, 2000). In keeping with this estimate, *in vivo* neuroimaging studies reveal only mild age-associated shrinkage of the broadly defined hippocampal formation (Raz, 2000).

Age-associated volume reduction takes place in other temporal lobes regions outside the hippocampus as well, and this reduction has been estimated to be about 1% (Haug and Eggers, 1991). The reduction is thought to result primarily from a decrease in neuron size rather than an actual loss of neurons (Haug and Eggers, 1991). Three research groups (Coffey et al., 1992; Cowell et al., 1994; Murphy et al., 1996) found similar correlations between age and temporal lobe volume, having a combined average correlation of r = -.25. Raz et al. (1997) found a correlation between inferior temporal lobe volume and age of r = -.32.

These modest structural changes observed in the temporal lobes are accompanied by physiological changes as well. An fMRI study conducted by Iidaka et al. (2001) provided evidence for functional changes in older adults taking place in the medial temporal lobe during episodic memory encoding. Young and older adults were studied while they encoded pairs of concrete and abstract pictures. Age differences were found in correlations between memory performance and amplitude of signal change in the parahippocampal gyrus under both concrete and abstract picture conditions. Specifically, medial temporal lobe regions were demonstrated to experience reduced activation in older adults during encoding.

A decrease in activity in the medial temporal lobe during episodic encoding was also found in a study by Bennett et al. (2001). PET was used to measure activational differences between young and older participants during encoding of simple visual attributes of a sine wave gradient screen. They found that there was a significant decrease in activation in the left medial temporal gyrus in older adults.

Application of covariance analysis to human neuroimaging data suggests that age modifies the relationship between the hippocampus/medial temporal lobes and other brain regions. Age-related differences in the relationship between the hippocampus and the cingulate gyrus during episodic memory encoding have been suggested by Grady et al. (1995). An age-associated change in neural interactions between the hippocampus and the dlPFC during episodic encoding has also been suggested by D'Esposito el al. (1999). However, these findings are controversial because they use statistical methods to parse out purported functional interactions between regions in neuroimaging studies that are based on independent observations of activations.

Overall, the age-associated decline in episodic memory encoding in older adults appears to be accompanied by a slight decrease in activation of the hippocampal/temporal lobe regions as well as modest morphological changes. It should be noted that the above functional neuroimaging studies reporting amplitude of activity differences between young and older adults are based on the assumption that the measured signal intensity differences genuinely reflect differences in neural activity. Given that these functional neuroimaging studies are based on cerebral blow flow, it is possible that differences between young and older adults are indicative of reduced vascular responsivity to neural activation that is due to compromised cerebrovascular function (D'Esposito et al., 1999). This possible interpretation will later be discussed at length in the context of the present research.

Frontal Lobes

Episodic memory, as previously stated, experiences one of the steepest trajectories of decline of all the cognitive domains. Perhaps not coincidentally, the frontal lobes too experience one of the steepest trajectories of decline in older age. Ample evidence suggests that structural and functional changes in the frontal lobes experienced in older age do indeed contribute to the decreased memory performance observed in older adults.

Age-associated volume reduction in the frontal lobes has been estimated to be from 10% to 17% (Haug and Eggers, 1991). This reduction may result from a reduction in neuron size rather than from an actual loss of neurons, similarly to what is observed in the temporal lobe (Haug and Eggers, 1991). Shrinkage of cells in the frontal lobes appears to begin earlier and is more severe than in any other region. An estimated 22% shrinkage in cells outside of the pyramidal layer of the PFC occurs within the fifth to seventh decades of life. Above the age of 65, the reduction in cell size becomes more

pronounced, reaching a 43% reduction in cells outside of the pyramidal cell layer in the prefrontal cortex (Haug and Eggers, 1991).

Several studies have also found significant differences between young and older adults in the degree to which they engage these frontal regions during memory encoding. Grady et al. (1995) performed the first study demonstrating a functional neuronal basis for why older adults perform worse on memory tasks. This study utilized an episodic memory task that entailed memorizing faces and then later choosing the ones that were previously seen. The left prefrontal cortex was activated during encoding in young adults. In older adults, however, there was no significant activation observed in the left prefrontal cortex during encoding. Studies that followed also found this difference between young and older adults. It should be noted, however, that while finding a significant difference between young and older adults in the left PFC, there was still significant activation in the left PFC of older adults in studies that followed. This difference may likely be attributed to the statistical power of the experiment in conjunction with the conservative significance threshold used (Cabeza, 2002).

Studies that found the dampened, but still significant, left PFC activation in older adults include the previously mentioned fMRI study conducted by Iidaka et al. (2001). Young and older adults were studied while they encoded pairs of concrete and abstract pictures. Older adults showed significant activation of the left dorsal PFC during encoding of both concrete and abstract pictures. This activation in older adults was reduced as compared to young adults.

Several other studies have looked specifically at left PFC activation during encoding in older adults as compared to young adults. These studies consistently found

age-related decreases in activation of left prefrontal areas: BA 6 (Cabeza et al., 1997; Cabeza et al., 1997); BA 10 (Madden et al., 1996); BA 45 (Grady et al., 1995); and BA 46 (Cabeza et al., 1997).

Cabeza et al. (1997) conducted a unique approach in their PET study of episodic memory in an attempt to explain the differences between memory activations in young adults and those observed in older adults. They aimed to determine if the changes in activation observed in older adults were a result of local neural changes or if there were more global changes taking place in the way that regions interact. In order to test this, they performed a path analysis on the areas of activation observed during encoding and retrieval during an episodic memory task. Their path analysis indicated that the patterns of activation in older adults reflected a global shift in processing of the memory information. The authors concluded that the neural changes in memory encoding that take place in older adults is not limited to a few discrete regions in the brain in isolation, but rather is a global alteration in the way the many neural networks behind memory encoding interact with each other. This conclusion is perhaps premature, however, given that nothing implicit in the design of their study would allow them to exploit possible connectivity changes between brain region activations.

Other methods have been used to investigate whether global shifts in neural processing can account for the activational changes observed in older adults during mnemonic tasks, or if theses changes are specific to only a few discrete brain regions. Evidence for a “common cause” behind the episodic memory declines was found in some studies (Cabeza et al., 1997; Grady et al., 1995), as evidenced by a decreased activation seen in the older adults’ fusiform and/or the lingual gyrus. On the other hand, evidence in

other studies suggested specific processes as a possible etiology, in which equal activation across age groups in the same regions of visual association areas was observed (BA 19 and BA 37; Cabeza et al., 1997; Madden et al., 1999). Further support for the specific-process hypothesis can be taken from activation changes observed in the left and right PFC during retrieval of episodic memories. Specifically, significant lateralized activation in the right PFC is observed during retrieval in young adults, but older adults show left and right PFC activation during retrieval of episodic information (Cabeza, 2001, 2002; Madden et al., 1999). Based on this finding, the left PFC does not suffer from a generalized reduction in activity during memory tasks in older adults because it is consistently shown to have an increased activation in older adults during retrieval of episodic information. Overall, the decrease in activation of the left PFC during encoding observed in older adults is therefore likely related to process-specific changes observed in aging.

The findings of reduced left prefrontal activity during encoding in older adults compared to young adults have been integrated in the HAROLD (hemispheric asymmetry reduction in old adults) model. The HAROLD model states that young subjects, in line with the HERA model, engage the left frontal cortex more heavily during encoding, whereas older subjects experience reduced left prefrontal activity (Cabeza et al., 2001).

Numerous pharmacological and behavioral interventions have been developed in order to attempt to address these deleterious changes related to episodic memory performance decline in late life. One such intervention that appears promising is goal-setting.

Effect of Enhanced Goal-directed Action on Cognition

The use of explicit goals has proven to be an effective approach to improving cognitive performance, especially memory performance. Certain parameters of goals have been identified that result in the goal being more efficacious. Goal-theory directly addresses these parameters indicating that goals must have a certain degree of specificity, difficulty, and proximity to be effective in optimizing behavioral performance (West and Thorn, 2001). Goals that are difficult and at the same time attainable tend to motivate improvement in performance (Lee et al., 1989). Research has shown that goals that are not attainable may serve to be more discouraging than motivating (Bandura, 1989). Support for the importance of specificity of goals has been provided by areas of education (Schunk, 1990) and organizational management (Lee et al., 1989). These authors found that goals directed toward specific performance levels, which contain measurable outcomes, proved to be the most efficacious. The greater clarity in the performance level expected for the goal, as well as the goal being clearly measurable, results in greater performance increases than do more general goals in which the outcome is less clearly ascertained. Proximal goals have been found to be more effective than distal goals in increasing an individual's motivation and expectations regarding task performance and self-efficacy on tasks that are even easy and intrinsically interesting (Madderlink and Harackiewicz, 1984). Lastly, Bandura (1989) found that short-term goals are more effective than long-term goals because they allow the individual to track more effectively the progress that is made.

Goals have the effect of increasing the challenge to the individual for the cognitive task at hand. When a goal is utilized for a specific task, the performance requirements for the individual are raised above the otherwise implicit assumption that

she/he is to perform well. Research has shown that this increase in challenge results in performance advantages. It has been shown that individuals will work towards achieving their goals (Bandura and Cervone, 1983; Elliott and Dweck, 1988). Stock and Cervone (1990) have also shown that goals are strongly related to the task-associated effort and persistence. Goals provide not only an increase in motivation for achieving success in the task at hand, but they also increase cognitive activity in efforts to achieve the goal, that is, greater use of strategies (Elliott and Dweck, 1988). A study by Hinsz and Ployhart (1998) evaluated the effects of goals on the performance of a word pair memory task. They measured "trying" in this task, which they operationalized in terms of effort, persistence, attention, and the use of effective strategies while performing a task. They found that subjects provided with goals significantly increased "trying" in the verbal memory task.

A study by Juergen et al. (2001) found that goal-setting substantially improved performance in two types of memory tasks. Two conditions of goal-setting were employed: do your best versus specific and difficult goals. The first of the two memory tasks was a reading span test that required reading aloud sets of sentences continuously. The subject then had to recall the final words of every sentence each time all sentences of a set were processed. In the second task, a memory span test with lists of one-syllable words was used. The goal-setting condition resulted in greater motivation, as well as significantly greater memory performance in both of the memory tasks. Because evidence suggested that increased memory performance was not precipitated by different encoding or recall strategies, the authors concluded that goal-setting resulted in temporary cognitive arousal. A study by Linnenbrink et al. (1999) found that the setting of mastery goals in a working memory paradigm also improved performance. Task-irrelevant

thoughts were decreased and motivation for higher achievement was increased in the mastery goals condition, which the authors asserted to be a major contributor to the greater memory success.

One's progress on goal attainment can be monitored either through attending to their progress as they proceed through the task (assuming the performance is readily discernable by the subject) or by means of explicit, external feedback. Cognitive performance can be further improved by providing external feedback in addition to the increased challenge in a task provided by goals. In general, explicit feedback in conjunction with goal-setting has been shown to be more effective than goal-setting alone for enhancing performance and efficacy (Bandura, 1989; Bandura and Cervone, 1983).

These studies indicate that a specific goal coupled with the ability to monitor performance is the most effect approach to improvement memory performance through goal-setting. The underlying neural substrates that mediate the effect of goal-setting remain to be elucidated. Several areas of research exist, however, that bring the OFC and the dlPFC into light as being likely candidates in mediating the effect of goal enhancement of memory performance.

Neural Substrates of Goal-directed Action in Cognitive Operations

The neural substrates supporting the *explicit* use of goals in the improvement of cognitive performance remain to be clearly elucidated. Ample literature exists, though, evaluating the contribution of goal-directed behavior and willed action to cognition. More specifically, studies have elucidated the neural substrates involved in motivation, drive, and/or effort arising from *implicit* goals that influence cognition. Interestingly, findings from diverse methodologies and paradigms all converge to suggest a role for the dlPFC and OFC as major participants in goal-directed behavior and willed action. These studies

serve to reveal the possible neural substrates supporting the explicit use of goals in the improvement of memory.

Stuss and Levine (2002) primarily utilized neuropsychological evidence to inform their conceptualization of ventral PFC functions in goal-directed behavior. They coined the term “self-regulatory disorder” (SRD) to characterize the clinical manifestation of individuals having suffered an insult to the ventral PFC. They define SRD as “the inability to regulate behavior according to internal goals and constraints” (Stuss and Levine, 2002, p. 405). Damage to the ventral PFC impairs an individual’s ability to maintain goals internally, which results in highly disorganized behavior. Their findings show that patients with this neuropsychological deficit remain largely unable to perform complex goal-directed behavior.

Barrash et al. (2000) performed a study including 7 participants with bilateral ventromedial PFC lesions, 14 participants with PFC lesions but no ventromedial involvement, and 36 participants with nonfrontal lesions. Subjects were administered the Iowa Rating Scales of Personality Change in which informants rated 30 specific characteristics for degree of disturbance and change from premorbid personality. They found that only the bilateral ventromedial lesioned group had significant impairments in goal-directed behaviors. Specifically, bilateral ventromedial patients had significant problems in planning, initiation, and persistence.

Tamm et al. (2002) investigated neural activation in females with Fragile X Syndrome and normal controls while performing a counting Stroop interference task. Fragile X Syndrome is an X-chromosome linked syndrome that results in mild mental retardation in females. The authors found that the experimental group had a decreased

ability for goal-directed behaviors and consequently a decrease in performance, which was associated specifically with a reduced activation in the left orbitofrontal gyrus.

Many studies have demonstrated the involvement of the OFC in the reward circuit, but a study by Tremblay and Schultz (1999) was able to demonstrate its direct involvement in the motivational aspects of appetitive behavior. They investigated goal-directed behaviors in non-human primates, recording neuronal activity in the OFC during a spatial delayed responding task. Neurons of the OFC selectively became more excited in response to reward-predicting signals, during the expectation of rewards, and after the receipt of rewards. The authors concluded that neurons in the OFC appear to process the motivational value regarding outcomes of voluntary action.

The previous studies demonstrate that the OFC participates in goal-directed actions. As stated earlier, the dlPFC has also been shown to be involved in goal-directed activities. For instance, Jahanshai and Frith (1998) reviewed studies in which they found the dlPFC to play a critical role in willed action, which they defined as (1) conscious awareness and attention, (2) choice and control, and (3) intentionality. Several lines of studies are cited by these authors that meet these criteria for willed action, and in these studies the dlPFC has been found to be the primary contributor to this function.

Frith et al. (1991) used PET to study a motor task that required the subject to move the first or second finger of the right hand at will in a random order, paced by touches to the fingers made by the experimenter. This condition was compared to a control condition that had the subject lift his/her finger after the experimenter touched it. Random finger lifting was associated with significantly greater dlPFC activation, as compared to the control condition. Another approach to examining willed action was to have subjects

make random movements on a joystick in one of four possible directions: up, down, left, and right (Playford et al., 1992). Compared to rest condition, movements of the joystick resulted in activation of the dlPFC.

The task of random number generation has also been used to study willed action (Jahanshanhi et al., 1997). Random number generation involves operations characteristic of willed action, such as the selection and maintenance of strategies, holding information in attention, suppression of habitual counting, internally driven response generation, and monitoring of responses. This task, as compared to counting, activated the right dlPFC, as well as the right inferior PFC.

Transcranial magnetic stimulation (TMS) has been used in research as a transient "lesion" model where it allows for the temporary disruption of neural processing during focal stimulation of a local brain region. Ro et al. (1997) found that the latency increased for volitional saccades made to a central arrowhead (endogenous go signal) that indicated the location of the required response in the right or left visual field as a result of TMS over the superior PFC. TMS over the superior PFC had no effect on the saccades triggered by a peripheral asterisk (exogenous go signal) that marked the hemifield where a response was required. This indicates that the effect was not a function of disrupting visual tracking abilities due to diffuse effects of the TMS at the frontal eye fields. Additionally, TMS over the parietal cortex had no effect on either the volitional or triggered saccades. The transient "lesion" to the dorsal PFC region therefore resulted in an interruption of the willed action of making the saccade.

Other groups have looked at the functioning of the dlPFC in the context of cognitive control. Jonathan Cohen, Earl Miller, William Perlstein, and others have

conceptualized the role of the prefrontal cortex as being responsible for activities such as internal representation, maintenance, and updating of contextual information in the service of exerting control over thoughts and behavior, or “cognitive control” (Braver et al., 2001; Miller and Cohen, 2001; Perlstein et al., 2002). Context is referred to as any task-relevant information that is internally represented in a way that it can bias processing in the pathways responsible for the performance of a task. Goal representations are one form that this information can take, as they have influence on planning and cognitive operations. Within this line of thinking, context is viewed as the subset of representations within working memory that governs how other representations are used. These context representations are thought to subserve both mnemonic and control functions. Support for this conceptualization and the role of the dlPFC in context maintenance is obtained from several different domains. Neuropsychological evidence comes in part from findings that led to the development of the term “frontal syndrome,” which refers to a particular impairment in which the normal control over social and sexual behavior is dysregulated (Stuss and Benson, 1986). Neuropsychological studies have demonstrated that patients with PFC lesions show impairments on tasks involving cognitive control, such as the Stroop test and the Wisconsin Card Sorting Test. Neurophysiological studies with non-human primates have provided direct evidence of the dlPFC involvement with cognitive control. In experiments such as the delayed task paradigm, neurons in the dlPFC have been found to exhibit sustained, stimulus-specific activity during the delay periods of simple tasks requiring the active maintenance of task relevant information (Fuster, 1989; Goldman-Rakic, 1987). More recent neuroimaging studies have corroborated these previous findings from the neuropsychological and neurophysiological literature. PFC

activity has been demonstrated during a wide range of tasks involving a cognitive control component (Cabeza and Nyberg, 2000; Cohen et al., 1997; Perlstein et al., 2002). Neuroimaging studies have also confirmed that the dlPFC is specifically involved in active maintenance functions by demonstrating sustained activity in this region during the maintenance period of working memory tasks (Braver and Cohen, 2001; Cohen et al., 1997; Perlstein et al., 2002).

Significant evidence exists to suggest a role for both the dlPFC and OFC regions in goal-directed behaviors. Notably, Perlstein et al. (2002) provided evidence that both the dlPFC and OFC are sensitive to contextual motivational characteristics in which higher-level cognitive tasks are performed. Overall, these two regions appear to subsume slightly different aspects of goal-directed action. The OFC appears to be involved in biasing volitional aspects of behavior by the underlying motivational state (Bechara et al., 2000). The dlPFC, on the other hand, appears to play a role in the more conscious, or salient, aspects of goal-directed behavior, such as keeping the context in mind through active goal representation (Miller and Cohen, 2001).

Many studies have evaluated the role of the OFC and dlPFC in goal-directed behavior, willed action and context maintenance, but the role of these two regions in the improvement of episodic memory by use of explicit goal-setting has yet to be systematically evaluated. Further, these two likely candidates for contributing to the positive effects of goal-setting undergo the steepest rate of decline in older adults. Specifically, the dlPFC and the OFC are thought by many to be the most susceptible regions in the brain to neuronal degeneration with age (Band et al., 2001). Huttenlocher (1979) found a 13% decrease of the synaptic density in Brodmann's area (BA) 46.

Ulyings et al. (2000; 2002) showed that age-related dendritic change in BA 9 and 46 are large in the pyramidal cells of layer V. An approximate loss of 20% of layer V spines in the OFC has been found (Band et al., 2001). Above the age of 65, a pronounced reduction in cell size exists where, for example, there is a 25% reduction in cells outside of the pyramidal layer of the OFC (Haug and Eggers, 1991). In light of these findings, the potential for the beneficial effects of goal-setting in young adults extending to older adults may appear dubious. However, as the next section will detail, enhancing goal-directed action by goal-setting and other techniques does in fact help older adults in cognitive tasks to an equal extent as young adults.

Effect of Enhanced Goal-directed Action on Cognition in Older Adults

Evidence suggests that older adults may have greater difficulties with maintaining the context of a cognitive task (e.g., important features in generating successful responses for the task). However, it has generally been found that improving the salience of those features important for a task, or increasing the challenge to the individual by techniques such as goal-setting, can compensate for decreased task performance.

De Jong (2001) asserted a goal-neglect hypothesis of age-related decrements in cognitive control. He stated that decrements in cognitive control could be characterized by a reduced capacity for goal selection and goal maintenance in working memory. In particular, De Jong stated that under conditions of novelty or of weak environmental stimulation (i.e., reduced environmental cues that support cognitive operations), pronounced goal neglect results. Goal neglect is defined as “disregard of a task requirement even if it has been understood, resulting in a mismatch between what is known about task requirements and what can be done in principle, and what is actually attempted in behavior” (De Jong, 2001, p. 71). Evidence indicates that older adults tend

to be more dependent on and more sensitive to means for external support offered by the context of the task so that they might compensate for a reduced capacity for cognitive control (Hultsch et al., 1987).

Evidence for the goal-neglect hypothesis comes in part from task-switching paradigms. In task-switching paradigms, the task to be performed on each trial is selected by the subject from a set of alternative tasks. The tasks are presented in an unpredictable order, and each trial starts with the presentation of a cue that signals the task to be performed. The cue is followed by either a fixed or random delay, which is called the preparation interval. Then the stimulus is presented in which the subject must perform the task. This stimulus is typically ambiguous as to which task is to be performed, rendering it necessary to keep track of the task sequence and/or process the cue effectively (De Jong, 2001). De Jong (2000) found that older adults experienced a failure to engage in advance preparation in task-switching in which he proposed an intention-activation account. According to this account, the effective utilization of advanced preparation depends on two components. The first component is an explicit goal or intention to be added to the basic goal structure that governs performance in the task-switching paradigm. The second required component is the retrieval and carrying out of this intention at the proper time. Success of the intention retrieval is thought to depend on the activation level of the intention and the characteristics or triggering power of the retrieval cue. Therefore, De Jong asserted that the frequent failures to engage in advance preparation in older adults may be due to low levels of intention activation, which would reflect goal neglect. Interestingly, the number of errors committed by older adults in the task-switching paradigm can be reduced to the level observed in young adults by straight

forward speed manipulations. Specifically, if the delay period between the cue and the stimulus to perform the task is shortened, older adults perform as well as young adults. By shortening the time delay, there was an increase in challenge for older adults. According to De Jong, this increase in challenge resulted in older adults being better able to utilize available control capabilities in order to optimize performance. Importantly, the increase in challenge decreased the possibility of goal neglect (De Jong, 2001).

Several studies have investigated the use of explicit goals to improve performance on a cognitive task in young and older adults. That is, a specific goal for performance achievement on a cognitive task is provided, and then the impact of the explicit goal on performance is measured. According to De Jong's goal-neglect hypothesis of older adults, the use of an explicit goal would provide important exogenous environmental structure that would serve to help older adults compensate for a reduced capacity for goal selection and goal maintenance during cognitive tasks. One study tested young and older adults in a free-recall task in which one subgroup established a performance goal for blocks of trials and received feedback on a trial-by-trial basis. The other subgroup neither established goals nor received feedback (Stadtlander and Coyne, 1990). Memory for random letter strings of 5 letters in 3 blocks of 50 trials was measured. The use of the motivational technique of explicit goal-setting and feedback increased memory performance in both young and older adults above that of the no-goal condition.

West et al. (2001; 2003) reported similar findings, showing that an increase in challenge to older adults by means of explicit goals significantly increases performance in a memory task. These studies examined the impact of goal-setting on memory and memory beliefs across adult age groups. In one study (West et al., 2001), a baseline

memory trial was administered, followed by three additional recall trials. All four memory trials entailed memorization of a grocery item list and subsequent free recall of the items. Young and older adults were placed in one of three conditions: goal-setting, goal-setting with feedback, or no goals. Goal-setting was initiated after the baseline trial. An assessment of memory beliefs, self-efficacy, and motivation was performed in conjunction with memory performance measurement. As was expected, young adults remembered a significantly greater number of items from the word list than did older adults across trials. Goal-setting significantly improved memory performance in both young and older adults. The increase in challenge on the memory task provided by the explicit goal resulted in equal memory performance enhancement for young and older adults. Additionally, motivation and self-efficacy were both positively affected by goal-setting. The results for the goal-setting plus feedback group were mixed. The variable outcome is thought to be related to the differing performance outcomes for each subject and the subsequent individual feedback that they received. For instance, subjects not meeting their goal would receive negative feedback and often would have a poorer performance in the subsequent trial, particularly in the older adult group. Overall, the primary finding of this study was that performance was positively affected by goal-setting in both age groups, and self-efficacy and motivation were also higher after goal-setting.

In another study by West et al. (in press), two different experiments investigated different levels of goal-setting/challenge in older and young adults in a similar shopping list recall task. In both experiments, older and young adults completed a baseline shopping list recall task to begin. Three more shopping list recall trials were completed

following the baseline. For goal conditions in both experiments, subjects were given a specific recall goal based on their own prior performance prior to each of the trials (excluding the baseline trial). Additionally, all subjects in goal conditions received positive feedback for their memory gains over trials. In the first experiment, subjects were assigned a low-challenge or high-challenge goal. Both young and older adults clearly benefited from the higher challenge goal. Further, older adults experienced an equal degree of memory performance improvement from the higher challenge goal condition as did young adults.

In the second experiment of this same study, a moderate challenge goal condition was compared to a no-goal condition. Results indicated that performance gains in the goal-setting condition exceeded the gains in the control group for both young and older adults. The average score gain per trial in the control condition (no goals) was 4.6 words for young adults and 2.1 words for older adults. In the goal-setting condition, the average score gain for young adults was 5.6 words and 4.0 words for older adults. These score gain increases were significant for both young and older adults. Further, a significant difference was not found between young and older adults in these positive effects of goal-setting.

Summary and Predictions

Evidence clearly indicates that older and young adults can benefit from explicit goal-setting in episodic memory tasks. The OFC and dlPFC are likely contributors to the improvement of episodic memory performance associated with explicit goal-setting, but this has yet to be tested. As noted previously, the two regions of the brain demonstrating the steepest trajectory of decline in aging are the OFC and the dlPFC (Band et al., 2001). This is of substantial interest because if these two regions do in fact correlate with the

performance improving effects of goal-setting, then it would be important to determine if the OFC and dlPFC sustained equal activation increases in young and older adults as a result of goal-setting. Perhaps activity in the OFC and dlPFC in older adults increases to a greater extent than in young adults in order to receive equal benefit from explicit goal-setting, compensating for the age-associated atrophy in these two regions. Alternatively, compensation could be achieved by greater activation in regions involved with motivation and/or mnemonic processes in older adults in order to generate equal benefit from goal-setting conditions as young adults.

In order to investigate these possibilities, a pilot study was performed in which 20 older adults and 20 young adults were recruited to undergo fMRI to examine the neural substrates that underlie the memory enhancing effects of goal-setting. Both young and older adults were assigned to one of two groups: a goal-setting group and a no-goal group. Four memory trials were conducted with brain-related encoding activity being measured in the last three trials by fMRI. Activations of the left PFC and the temporal lobe, bilaterally, were anticipated during the verbal memory encoding task. Activation in these two regions was predicted to be dampened in older adults, corresponding to the decreased memory performance anticipated for older adults. Goal-setting was hypothesized to increase performance in both young and older adults. It was hypothesized that gains in memory performance through goal-setting would be coupled with increased activation in the OFC and dlPFC, among other regions in the PFC. In older adults, compensation for the decline in these two regions was hypothesized by means of greater activation in the OFC and dlPFC and/or greater activation in other important motivation or mnemonic-related regions.

CHAPTER 2
METHODS

Overview

A between group design was used with four groups: young adult/goal, young adult/no-goal, older adult/goal, and older adult/no-goal. Subjects performed a memory task that entailed studying a list of grocery items that they were later asked to recall. Brain activity during encoding was measured by fMRI and behavioral performance was measured by recall accuracy. Subjects also performed a motor task that required a button press in response to a visual stimulus in order to assess for the possibility of a generalized lesser magnitude fMRI hemodynamic response in older adults. Motor response time was measured in the motor task. It should be noted that a fixed-effects statistical approach was used for the behavioral and fMRI data due to power considerations, thus limiting the ability to generalize findings.

General Methods

Subjects

Subjects were 20 young adults (ages 18-28) and 20 older adults (ages 60-70) with members of each age group pseudo-randomly assigned to one of two goal groups (goal, no-goal). Young adult subjects were primarily undergraduate and graduate students at the University of Florida. Older adult subjects were high-functioning, community-dwelling individuals. Young adults were matched to older adults in education and self-rated health (see Table 2-1). Self-rated health was assessed by asking the subject to circle a number on a scale of 1 to 10, 1 being excellent health and 10 being very poor health, indicating how healthy they are in general. Older and young adults were administered the Shipley

vocabulary test (Shipley, 1940; Appendix A), on which older adults scored significantly better than young adults, t (1,38) = 7.6, p = .009 (Table 2-1).

Exclusion Criteria

All subjects were right-handed. Subjects were excluded if they reported any history of neurological illness (including strokes or traumatic brain injury) or psychiatric illness. Subjects were also excluded if taking psychoactive or anticholinergic medications. Subjects taking blood pressure medication were not excluded if their blood pressure had been stable for the previous 6 months while taking the medication. Subjects having a history of substance abuse or previous treatment for substance abuse were excluded. Participants with a history of epilepsy or a seizure disorder were excluded. Subjects were administered the Telephone Interview for Cognitive Status (TICS; Brandt et al., 1988) and were excluded if their score reflected the possible presence of a cognitive impairments (as defined by a score of $<15^{th}$ percentile). Subjects were also excluded for any MRI environment contraindications (e.g., cardiac pacemaker, implanted cardiac defibrillator, aneurysm clip, claustrophobia, non-removable ferromagnetic dental work such as bridges, etc.). Lastly, subjects were not permitted to ingest caffeine or nicotine within a 60 minute time period prior to the MRI session. This criteria reduced the risk of confounded cerebral blood flow measurements by allowing time for at least partial clearance of any potentially high levels of circulating caffeine or nicotine, which are vasoactive agents (caffeine half life = 3.5 hours and nicotine half life = 2 hours).

High resolution T1 weighted structural MRI scans were used to determine the presence of any structural abnormalities. One older adult was excluded after a significant lesion was identified.

Table 2-1 Mean (Standard Error) Demographic Characteristics of Experimental Participants.

	Young Adults	Older Adults
N	20	20
Age	22.3 (0.62)	64.8 (0.55)
Age Range	18-28	60-70
Sex (Men/Women)	9/11	6/14
Education	15.6 (0.41)	15.5 (0.69)
Self-Reported Health	2.55 (0.33)	2.40 (0.35)
Vocabulary[a]	33.0 (0.56)	35.2 (0.60)

[a]Older adults significantly greater than young adults: t (1,38) = 7.6, p = .009.

Three older adults and two young adults were excluded due to image distortion that was caused by an inability to position the head far enough into the scanner bore longitudinally to be within the optimal image acquisition range. On account of the positioning difficulty, images were subjected to large field inhomogeneity and distortion. One older adult was excluded due to a claustrophobic reaction to the scanner. Lastly, collection of data from one subject was terminated in the middle of testing due to an MRI schedule conflict.

Experimental Task and Procedures

Participants performed a free-recall episodic memory task modeled after that employed by West (2001; 2002). Word lists, comprised of categorizable grocery items, were presented.

This task was originally developed as follows. In order to create a large pool of categorizable items, four research assistants listed all items they found in grocery stores and also identified a large number of narrowly defined categories for those items. Nine independent raters then determined the most suitable category for each item and rated each item as a high, moderate, or low frequency exemplar of its category. In order for an

item to be included in the final word list, the word must have met a predetermined criterion rating such that seven of nine raters rated the item as a "high frequency" exemplar of its category (West and Thorn, 2001).

The episodic memory task was modified from its original form for administration in the imaging context. Four memory trials were performed (Baseline Trial and Trials 1 through 3). All four groups (young adult/goal, young adult/no-goal, older adult/goal, older adult/no-goal) were administered identical memory trials and word lists.

The Baseline Trial was administered prior to entering the scanner and was comprised of a 15-word list presented on a single sheet of paper (Appendix B). Participants were given a one-minute study period, and then were prompted to write out all the words that they could remember on a numbered sheet of paper. Instructions given to the participant were as follows: "On this task, you will be asked to study a list of items that can be bought at a store. You are not expected to remember every item on the list. Just do your best. I will tell you when to begin studying the list and I will also let you know when your study time has ended. You will be given approximately 1 to 3 minutes to study the list. You may not write during the study time. After the study period is done, I will ask you to write down all of the items that you remember from that list. You will write the remembered items on this page."

Following the Baseline Trial, participants were placed in the MR scanner and performed the remaining three memory trials (Trials 1 through 3). Memory trials were computer controlled by the software package PsyScope (Cohen et al., 1993). Participants were presented with the identical 42-item grocery list for Trials 1 through 3 (Appendix B). Included in the 42-item list were all 15 items contained in the Baseline Trial list. For

each of the three trials, word-list content of the 7 blocks was identical. However, the order of presentation for the 6 words within each block was randomized for each trial. The word content of each of the three trials was identical in order to observe continued improvement across trials in conjunction with the goal-setting condition. The content of the word list is detailed in Appendix B. Instructions given prior to Trial 1 were as follows: “In these next activities, you will again be asked to study a list of items that can be bought at a store, except this time they will be presented on a screen. After an item is presented, there will sometimes be a short delay before another item is presented on the screen, and other times there will be a little longer delay. During these delays, you are asked to attend to the target in the center of the screen. When all the items have been presented, I will ask you to tell me back as many as you can remember. You will not be expected to remember all of them.” Instructions prior to Trials 2 and 3 were not stated vocally but appeared on a liquid crystal display (LCD) screen (described below). The instructions read: “Study the following list of words.” The vocal recall of word lists by the subjects and task instruction delivery were achieved by a bi-directional in-scanner microphone and receiver.

The 42-word trials were presented singly in 6-word blocks, for a total of 7 blocks per trial (see Figure 2-1). Words were presented singly for a 2 s duration with a 2 s interstimulus interval (ISI). Subjects were presented the words through a mirror system orientated towards an LCD screen mounted in the radio frequency coil (RF) 4 in. behind the top of the subjects’ head (approximate visual angle = 41 degrees). All 6-word blocks lasted a total duration of 24 s, followed by a 10 s interblock interval. During the interblock interval, subjects were asked to attend to a fixation point (“+”) in the middle of

the screen. All three trials were initiated by a 16 s baseline fixation period during which the subjects were asked to attend to a fixation point ("+") in the middle of the screen. Image acquisition began at the onset of the baseline fixation period. The first 2 image volumes were automatically discarded (TR=2 s), so the first image that was collected for later analysis was the 3rd image volume. Consequently, 12 s (6 image volumes) of the 16 s baseline fixation period were analyzed. After the seventh block of words, there was a 16 s recovery fixation period when the subject was again asked to attend to the fixation point. Image acquisition terminated at the conclusion of the recovery period. Free recall of the 42-item list began immediately following the recovery fixation period and subjects were given a maximum of 4 min for recall. During the recall period, subjects verbally recalled as many of the 42 items as they could remember, in any order. Vocal responses were digitally recorded and immediately scored for accuracy. Image volumes were not collected during the recall period. In total, 133 images were collected per trial, yielding 399 images for each subject.

All groups performed the above described memory task. The only procedural difference was between the goal and no-goal groups, which was implemented between the memory trials. Prior to Trials 1, 2 and 3, subjects in the goal group received feedback regarding the number of items they remembered correctly from the previous trial in addition to a goal statement for that trial: "Your goal is to achieve a 50% improvement in your score." Prior to Trials 2 and Trial 3, subjects in the goal groups also received a positive feedback statement (e.g., "Good job - that's a great score") and after the goal statement, "Keep trying" was written. Following the final trial, Trial 3, these statements and feedback were given again. All statements and feedback were provided on the LCD

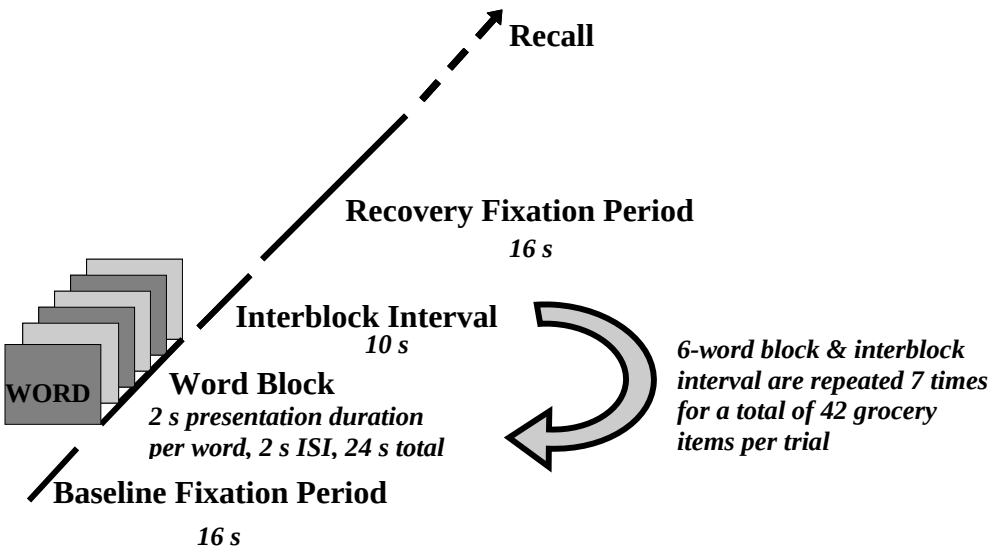

Figure 2-1**.** Graphical representation of the memory task for Trials 1 through 3.

screen. Subjects alerted the experimenter verbally when they completed reading each screen. Subjects in the no-goal group did not receive any of the feedback described above. Feedback was not included for the goal group in order to maintain paradigmatic consistency with previous studies finding improved performance from goal-setting (West et al., 2002, 2003). However, communications with the goal group were equated in the no-goal group by inserting the statements: "You have completed trial number *x*" and "We are now ready to begin the next trial."

The Baseline Trial contained only 15 words, as compared to 42 words in the following 3 trials, so that subjects would not be overwhelmed by the task (as was observed in pilot versions of this paradigm). Also, the initial goal of 50% improvement would be more easily attainable, again reducing the risk of overwhelming the subject at the onset of the memory trials.

All experimentation was performed during one visit to the MRI facility. The first portion of experimentation took place in a testing room inside the MRI facility (although outside the scanning environment). To begin, informed consent was obtained from the participant in a manner consistent with the University of Florida Institutional Review Board regulations. Subjects then completed several questionnaires that inquired about their opinions about their memory, demographic information, among other similar information (Appendix C). Then the Baseline Trial was conducted with recall immediately following. Following the baseline trial, another questionnaire was administered, which was also related to the participants' opinion of their memory.

The next procedure varied depending on whether the subject was in the older adult group or the young adult group. Because all 15 words from the Baseline Trial were included in subsequent memory trials, it was important that a consistent time frame be maintained between the administration of the Baseline Trial and the commencement of Trial 1 for all participants. (It should be noted that the subjects were not made aware that the exact same words would be repeated in subsequent trials). The older adults, on average, require a greater amount of time to complete the questionnaires following the Baseline trial. Thus, a temporal window of 30 - 40 minutes between the completion of the Baseline Trial and the start of Trial 1 was maintained for both young and older adults by giving the young adults a participant information form and the vocabulary test to complete before proceeding to the MRI scanner. Older adults, on the other hand, proceeded directly to the MRI scanner after completion of the initial questionnaire. (Older adults instead completed the vocabulary test and participant information sheet after the MRI testing was complete.) Consequently, the time between the Baseline Trial

and Trial 1 were matched between young and older adults in temporal length and activity, as both were completing questionnaires. After completing their respective questionnaires, subjects were then prepared for the scanning environment and placed in the scanner bore. After localizing sequences were performed, Trials 1 through 3 were administered.

After completion of the three memory trials in the scanner, subjects then completed a motor task consisting of pressing the right index finger button of a Button Response Unit (BRU) every time a large white square appears on the LCD screen. The stimulus duration was 1s followed by a fixation period of 9 s. Each motor task session contained 9 trials and there were a total of 3 motor task sessions completed (e.g., 27 total motor responses). This task served as an internal activation standard (described in further detail shortly).

Subjects then completed 5 more questionnaires following the scanning portion of the experiment that again asked for their opinions about their memory and also how they felt they performed on the memory task. An additional questionnaire asked about strategies utilized to complete the memory task (Appendix D).

Behavioral Data Analysis

The percent of items recalled from each 6-word block served as the dependent variable. The Baseline Trial was excluded because it was conducted outside the scanner and procedures for the goal and no-goal groups were identical. Due to power considerations, a fixed-effects analysis was conducted. The error variance term was estimated on a block by block basis with each block representing an independent observation. The percent of items recalled for each block was evaluated by analysis of variance (ANOVA) with Group (young adults, older adults) and Condition (goal, no-

goal) as the between-subjects factors and trial (trials 1 – 3) and block (blocks 1 –7) as within-subjects factors.

Magnetic Resonance (MR) Acquisition

Scanning was conducted in a Siemens Allegra 3.0 Tesla head-only MR superconducting system (128 MHz; 60cm bore) at the University of Florida McKnight Brain Institute MR Facility. Images were acquired using a Siemens quadrature head radio frequency (RF) coil. A BOLD sensitive echo-planar imaging pulse sequence (EPI; Siemens; TR=2000 ms, TE=30 ms, FOV=240 mm, flip angle=90°, 64 x 64 matrix) was used to acquire 31 slices (voxels = 3.75 mm^2 in-plane, 3.2 mm thick, 0.32 mm gap) in the axial oblique plane. A 3-plane localizer was first acquired onto which a sagigittal scout was prescribed. The prescription was acquired with 31 contiguous slices perpendicular to the anterior commissure-posterior commissure line. A double-oblique prescription was collected in order to reduce potential image misregistration across subjects due to differences in ventral head orientation. Functional scanning was synchronized to trial onset (baseline fixation period) and terminated at the end of the recovery fixation period. Following functional scanning, structural images were acquired with a 3-D magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted pulse sequence (128 slices, 1.3 mm slice thickness, TE=4.13 ms, FOV=240 mm, flip angle=8°, 512 x 512 matrix).

It is important to note that an area of specific interest in this study, the orbital frontal cortex, contains a high potential for signal drop off, especially in the high magnetic field strength of 3 tesla. The orbito frontal cortex borders the orbital sinus and the auditory meatus, creating susceptibility artifacts at the tissue-air interfaces. Indeed,

signal loss was observed in the most ventral and anterior portions of the OFC, as pictured in Appendix E.

FMRI Data Analysis

Data analysis, registration and visualization were performed with the fMRI software package BrainVoyager 2000 (Brain Innovation, Maastricht, The Netherlands).

FMRI data reduction. The first two volumes (4 s) of each functional scanning run were automatically discarded by the Siemens scanner to allow for T1 equilibrium and thus were not included in any of the analyses. Prior to data analysis, functional images were aligned to the last volume for each slice in order to minimize the signal changes related to rigid body rotation and translation during the acquisition. Following movement correction, images were spatially smoothed with a Gaussian kernel, FWHM = 8 mm, to accommodate for differences in anatomy. Three-dimensional motion correction and Talairach transformation were performed for the functional data of each subject. Linear drifts of the signal with respect to time were removed from each pixel's time course.

The 3-D anatomical volumes and 2-D functional volumes were resliced to a 256 x 256 matrix size. Reslicing of functional volumes took place before statistical analysis. The functional volumes were analyzed in 3-D space. Statistical maps were superimposed onto 3-D anatomical data sets. Since the EPI functional scans and 3-D structural measurements were performed within the same recording session and contained the exact same positioning parameters, co-registration of the respective data sets were performed semi-automatically based on the Siemens slice position parameters of the T2*-weighted measurement (number of slices, slice thickness, distance factor, pitch angle (axial – coronal angle), FOV, shift mean, off-centre read, off-centre phase, in plane resolution) and on parameters of the T1-weighted 3-D measurement (number of sagittal partitions,

shift mean, off-centre read, off-centre phase, resolution) with respect to the initial overview measurement (prescription). Manual co-registering corrections in the x, y, and z planes and in the pitch angle were required to optimize final alignment.

For each subject, the structural 3-D data sets were transformed into Talairach space using a two step process. The first step consisted of rotating the 3-D data set of each subject to be aligned with the stereotaxic atlas. For this step the location of the anterior commissure (AC), the posterior commissure (PC), and two rotation parameters for midsagittal alignment had to be specified manually in the high resolution 3-D volumetrics. In the second step the extreme points of the cerebrum were specified. These points together with the AC and PC coordinates were then used to scale the 3-D data sets into the dimensions of the standard brain of the Talairach and Tournaux atlas (Talairach and Tournaux, 1988) using a piecewise affine and continuous transformation for each of the 12 defined cerebral borders.

FMRI data analyses. Statistical analyses were performed using BrainVoyager by fitting a general linear model to the individual fMRI time series data (e.g., multiple regression analysis). The predictor variables were created for each condition creating the idealized time series that represented the response to the condition (e.g. encoding period or motor response) in each group. The hemodynamic response for predictor variables was estimated by convolving each regressor with a standard gamma variate function that shifted the estimated hemodynamic response approximately 6 seconds to account for the expected delay. A weighted sum of the predictor variables was created that produced the closest match to the actual data time series. A parameter estimate (e.g., beta weight) was generated for each model that estimated the strength of covariance between the actual

data and the modeled hemodynamic response function. Parameter estimates were calculated for each participant, which were then subjected to group analysis.

For all analyses, statistical maps generated for each pattern of interest were thresholded for significance using a cluster-size algorithm (Forman et al., 1995) of 80 voxels, which protects against an inflation of a false-positive rate with multiple comparisons. The voxel size was 0.9375 mm^2 in plane and 1.3 mm thick. Due to power considerations, a fixed-effect analysis approach was utilized, which estimates the error variance on a scan to scan basis. Significant effects are shown only if the associated *P* valued yielded $P < 0.01$ (Bonferroni corrected for multiple comparisons using the number of voxels exceeding the minimum in brain threshold signal criteria intensity of 250).

It is important to note that relative differences between groups reflect differential activation intensity for a specific prescribed area, and do not indicate a greater or lesser spatial extent of activation. That is, relative differences of activation asserted to be present between groups reflect a significantly greater or lesser signal intensity measured for a discrete group of voxels.

Internal activation standard

In order to establish that differential activation observed in older adults is not simply a generalized change in neural activation, an “internal activation standard” (Weinberger et al., 1996) was utilized. The blood oxygen level dependent (BOLD) signal of fMRI depends on neurovascular coupling, which is a process in which neural activity influences the hemodynamic properties of the surrounding vasculature. There could be direct changes in the cerebral vasculature as well as alterations in the complex neurochemical transformation of neural activity into changes in blood flow that might affect the measured BOLD response (D’Esposito, 2003). Age-associated signal

differences have not been demonstrated in components of the BOLD hemodynamic response function in the motor cortex in response to a buttonpress (D'Esposito et al., 1999). Thus, the neural activation in the precentral gyrus, Brodmann's area 4 (BA 4), in response to subjects' buttonpress was utilized as the internal activation standard. Absence of age-related BA 4 signal intensity differences supports the specificity of any differences observed between young and older adults in the memory task.

The general linear model (GLM) of the experiment was computed from the 40 (40 subjects; 3 motor trials per subject collapsed) z-normalized volume time courses. For each time course, the 1 s period of stimulus presentation (white square to which the subject responds with a button press) was defined to represent motor activity. The signal values during this phase were considered the effects of interest. Response latencies in older adults (median = 404 ms, standard error = 24 ms) and young adults (median = 397 ms, standard error = 22 ms) occurred well within the temporal frame of the defined predictor response of the GLM model. The baseline fixation period (9 s following the motor stimulus cue) was defined as the baseline (non-motor) period. For each trial, 90 volumes were collected. There were a total of three trials so 270 volumes were collected for each subject. The resulting predictor was obtained by shifting an ideal box-car response (assuming a value of 1 for the volumes of the respective motor periods and a value of 0 for the baseline periods) by a standard gamma variate function prescribed by Brainvoyager (in order to account for the hemodynamic delay). This predictor, which was identical for all subjects across all groups, was used to build the design matrix of the experiment (see Figure 2-2).

The above steps generated a 4-D functional time series (volume time course: 3 x

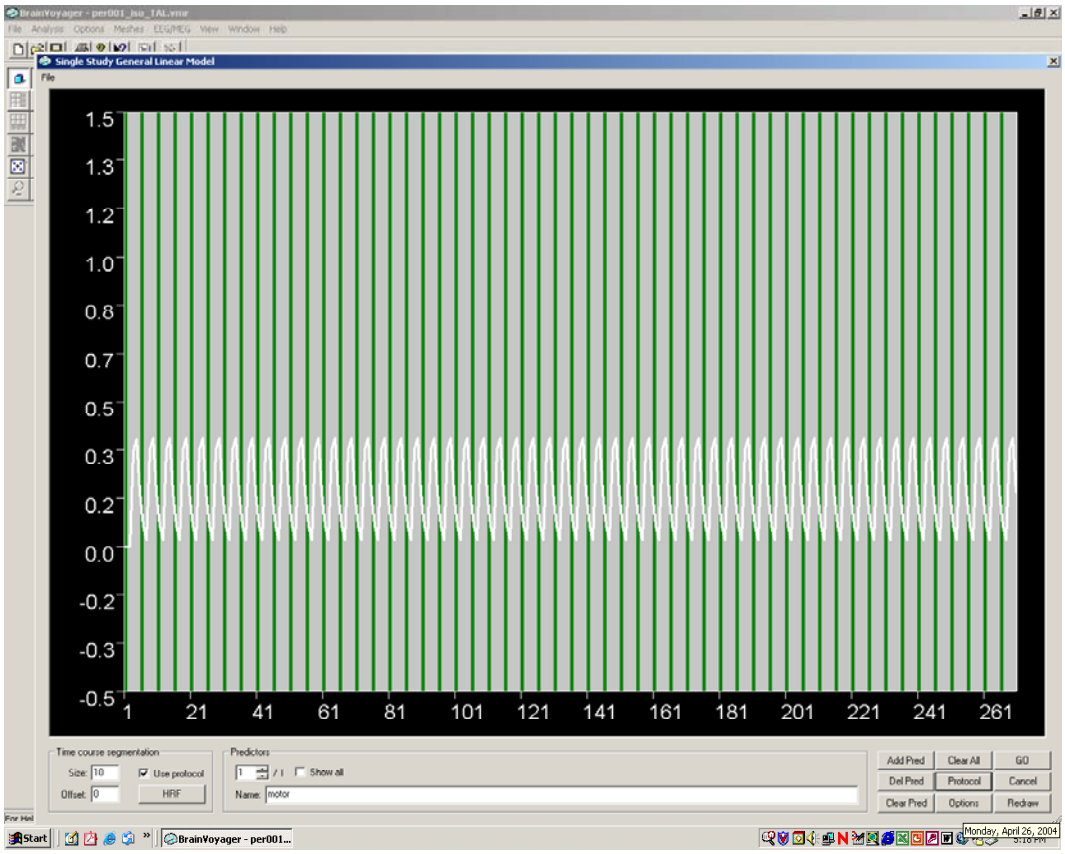

Figure 2-2. GLM predictor model for signal intensity increases corresponding to the motor response of a button press for a single subject. The model represented here was identical for all subjects. The green shading represents the presence of the predictor, in this case a motor response, and the gray area indicates the rest period.

space, 1 x time) for the predictors of the model. Statistical analysis of 4-D functional time series included first single-subject multiple regression analysis, followed by multi-subject multiple regression analysis that concatenated the single-subject analyses. The global level of the signal time course in each session was considered to be a confounding effect and was entered as such into the GLM model. A fixed effects analysis was employed. Statistical maps generated from the multi-subject analyses were projected on the flattened surface of a volumetric rendering of all 40 subjects' high resolution 3-D volumes averaged together in Talairach space. Three statistical maps were generated for the motor

predictor model: 1) young adults, 2) older adults, and 3) young adults directly compared to older adults (contrast map).

Button press response latencies to the visual cue were measured in all subjects. A comparison between young and older adult response latencies was conducted by first determining the median response time for each subject. A between subjects (young and older adults) analysis of variance was conducted on the median reaction time for each subject.

The motor task was employed for an additional analysis to evaluate the possibility of an altered hemodynamic response in older adults taking blood pressure medication. The hemodynamic response during the motor task in the 6 older adults taking blood pressure medication and 6 pseudo-randomly selected older adults not taking blood pressure medication were compared.

Memory Encoding Experiment

Data were analyzed separately for encoding and for relation of encoding to blockwise memory recall performance.

Encoding-related activity. A general linear model (GLM) for the experiment was computed from the 40 (40 subjects; 3 memory trials per subject collapsed) z-normalized volume time courses. For each time course, the 24 s period of word presentation was defined to represent encoding. The signal values during these phases were considered effects of interest. The baseline fixation period (12 s), interblock intervals (10 s), and recovery fixation period (16 s) were defined as the rest (non-encoding) period. The resulting predictor was obtained by shifting an ideal box-car response (assuming a value of 1 for the volumes of the respective encoding phases and a value of 0 for the baseline time points) by a standard gamma variate function prescribed by Brainvoyager (in order

to account for the hemodynamic delay and form approximate hemodynamic rise and fall times). This predictor, which was identical for all subjects across all groups, was used to build the design matrix of the experiment (see Figure 2-3).

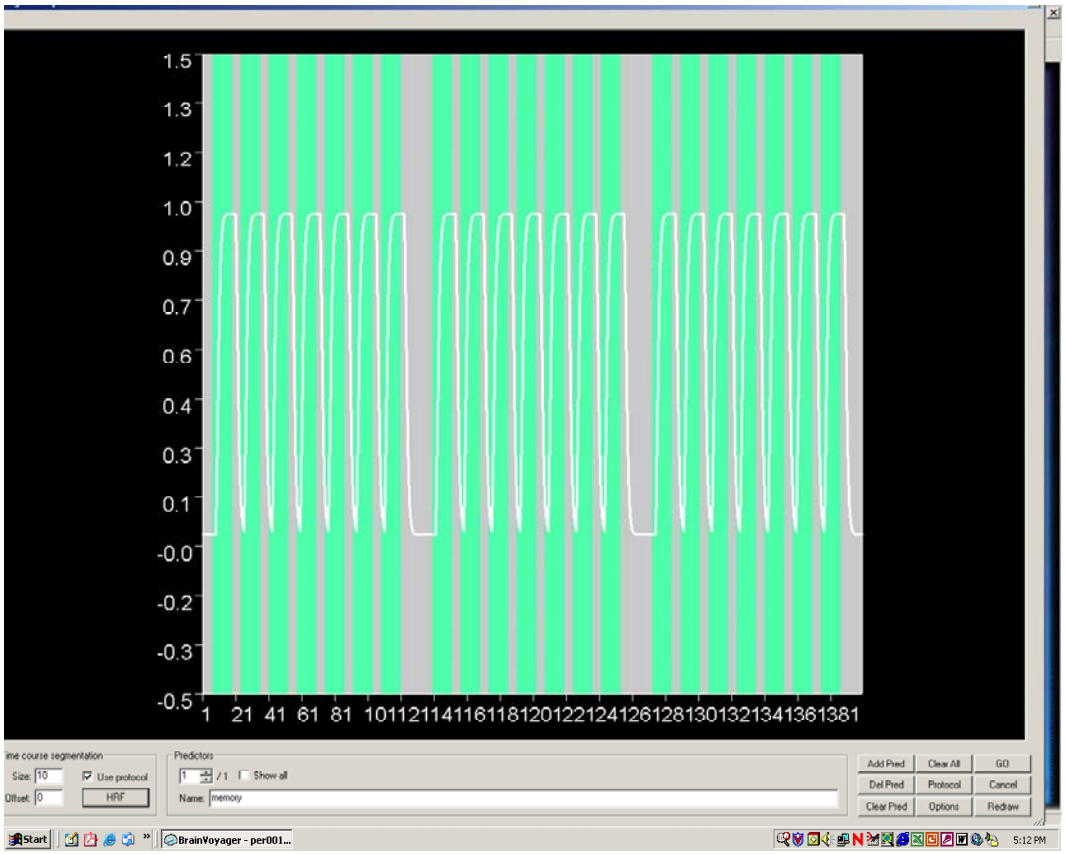

Figure 2-3. GLM model for the multiple regression analysis of overall memory encoding for a single subject. The model represented here was identical for all subjects. The green shading represents the presence of the predictor, in this case encoding activity, and the gray area indicates the rest period.

Subsequent memory activity. The above model reflected overall neural activity corresponding to encoding the 6-word blocks. In order to evaluate how encoding activity related to subjects' recall performance, an additional GLM model was used that correlated voxel signal intensity with recall performance on each of the 6-word blocks. This approach has become known as the 'subsequent memory' effects approach to analyzing encoding (Rugg et al., 2002). In the subsequent memory procedure, event-related activity elicited by a series of study items is contrasted according to the number of

items remembered or forgotten on a subsequent memory test. The assumption behind this analysis is that differences in activity that predict successful versus unsuccessful memory reflect the different levels of engagement of processes supporting effective encoding. As an example of this approach, a subject may have remembered 5 of 6 words on the first block of a trial, so .83 (83% correct) is entered for each of the 12 volumes (covering the 24 s period when the 6 words were presented) for the encoding predictor. Likewise, recall performance values are entered into the encoding predictor for each of the following 6-word blocks. The resulting predictor for the GLM model represents higher signal intensity for blocks in which the subject performed well, and lower signal intensity for blocks in which the subject performed poorly. In other words, the model represents a correlation of recall performance for each 6-word block and signal intensity increases above baseline during encoding periods. Encoding time periods are thus set as relative increases in signal intensity corresponding to recall performance for each respective 6-word block and are corrected for the hemodynamic response delay (see Figure 2-4).

For both the encoding activity model and the subsequent memory activity model, the global level of the signal time course in each session was considered to be a confounding effect and was entered as such into the GLM model. A fixed effects analysis was employed. The creation of other alternative GLM models further evaluating encoding was constrained by software limitations. For instance, creation of a model investigating purely recall performance correlation with signal intensity was not possible because it was necessary to include rest periods into the model.

The above steps generated a 4-D functional time series (volume time course: 3 x space, 1 x time) for the predictors of the 2 models. Statistical analysis of 4-D functional

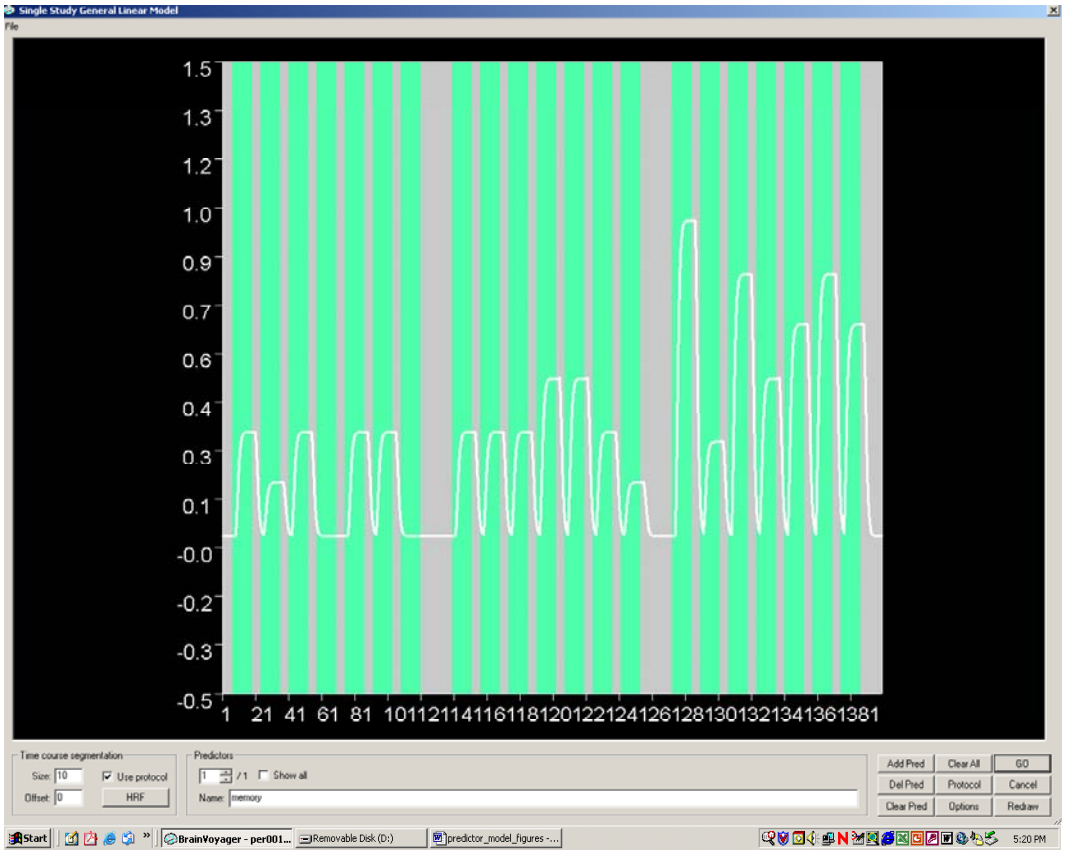

Figure 2-4. GLM model of the multiple regression analysis of memory recall performance correlated with signal intensity. The green shading represents the presence of the predictor, in this case encoding activity correlated with subsequent memory performance, and the gray area indicates the rest period. The illustrated model is an exemplar for a single subject. A separate model was calculated for each subject that was based on their individual recall performance during each of the 21 blocks.

time series included first single-subject multiple regression analysis, followed by multi-subject multiple regression analysis that concatenated the single-subject analyses. Statistical maps generated from the multi-subject analysis were projected on the flattened surface of a volumetric rendering of all 40 subjects' high resolution 3-D volumes averaged together in Talairach space. Seven statistical maps were generated for each model (e.g., encoding activity model and subsequent memory activity model): 1) young adult/no-goal, 2) older adult/no-goal, 3) young adult/no-goal compared directly to older adult/no-goal (contrast map), 4) goal group, 5) no-goal group, 6) goal group compared

directly to the no-goal group (contrast map), and 7) interaction of goal-setting group by age.

CHAPTER 3
RESULTS

Behavioral Performance

Encoding accuracy was scored as the percent of words correctly recalled for each block of words (21 blocks per subject). Data were analyzed with a fixed-effects ANOVA with between-subjects factors of age (young adults, older adults), goal (goal, no-goal) and within subjects factors of trial (trials 1 through 3) and block (blocks 1 through 7). Group means and standard errors are reported in Table 3-1. There was a main effect of age: $F[1,756] = 7.31$, $P = 0.007$, Cohen's $d = 0.16$, reflecting better recall memory performance in young adults than in the older adults (see Figure 3-1). There was a main effect of goal-setting: $F[1,756] = 9.13$, $P = 0.003$, Cohen's $d = 0.18$, reflecting better performance in the goal than no-goal group (see Figure 3-1). A main effect of trial, $F[2,756] = 77.33$, $P < 0.001$, reflected subjects being able to perform progressively better on each successive trial, as lists were identical in content for each trial (see Figure 3-1). There was a main effect of block: $F[6,756] = 12.16$, $P < 0.001$, reflecting subjects' tendency to recall words better in the earlier than later blocks (e.g., primacy effects; see Figure 3-1). Notably, there was not a significant interaction between goal-setting and age groups: $F[1,756] = 0.652$, $P = 0.420$, indicating that neither age group benefited disproportionately from the provision of goals. Interestingly, the effect of goal-setting in older adults brought their performance up to levels of performance in young adults without goal-setting.

Following testing, subjects reported all the strategies they used for performing the memory task. The number of strategies used by subjects was analyzed using an ANOVA

with factors of age (young adults, older adults) and goal (goal, no-goal). A main effect of goal was not found, as subjects in each group used, on average, the same number of

Table 3-1. Mean Percent (Standard Error) of Recall Performance for Each Group

Goal-setting	Age	Mean
Goal	Older Adults	49.5 (1.7)
	Young Adults	55.0 (1.7)
	Total	52.2 (1.2)
No-Goal	Older Adults	46.2 (1.7)
	Young Adults	49.0 (1.7)
	Total	47.6 (1.2)
Total	Older Adults	47.8 (1.2)
	Young Adults	52.9 (1.2)
	Total	49.9 (0. 8)

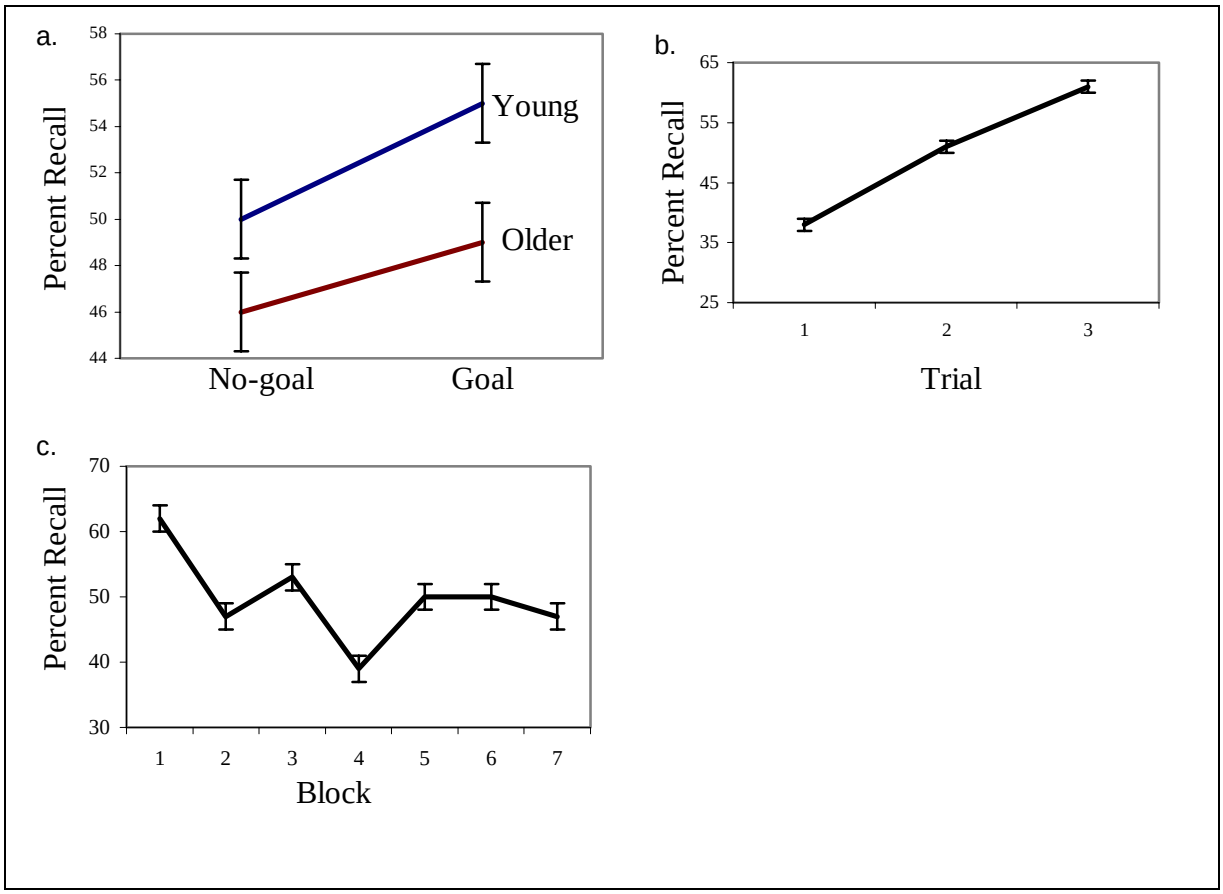

Figure 3-1. Summary of memory recall percent in a) young adult/goal, young adult/no-goal, older adult/goal, and older adult/no-goal groups, b) memory trials, and c) blocks within each trial. Standard error bars are shown.

strategies to approach the task. However, a trend was observed for young adults to use a greater number of strategies in performing the memory task than older adults, $F(1,36)$ =

3.53, $P = 0.068$. Young adults used a mean of 7.0 strategies (standard error = 0.4), as compared to 6.4 (standard error = 0.3) strategies used by older adults. Follow-up analysis revealed a significant difference between the young adult/no-goal (mean = 7.8) and the older adult/no-goal (mean = 6.2) groups, (Student's *t*-test, $t(1,19) = 13.9$, $P < 0.001$, Cohen's $d = 0.54$).

Functional MRI Findings

Internal Activation Standard

The motor task was employed to assess for generalized lesser-magnitude signal increase in older adults. The statistical threshold that was used for the memory study analyses ($P > 0.01$, Bonferroni corrected for multiple comparisons; minimum threshold of 80 contiguous voxels) was used for the motor task study in order to facilitate cross study comparison of potential lesser-magnitude signal increases in older adults. Activation in the left precentral gyrus (BA 4) was selectively examined as the task involved the contralateral right index finger response. Left BA 4 activation in young adults (center of gravity: x = -41, y = -17, z = 48; 3241voxels; center of gravity refers to the geographical center of a significantly activated cluster, independent of the relative statistical significance magnitude) and older adults (center of gravity: x = -41, y = -17, z = 46; 2502 voxels) was significant (see Figure 3-2; $P > 0.01$, Bonferroni corrected for multiple comparisons; minimum threshold of 80 contiguous voxels). A follow-up analysis, which directly compared activation in young adults to older adults, revealed no significant differences between young and older adults in BA 4 (see Figure 3-1; $P > 0.01$, Bonferroni corrected for multiple comparisons; minimum threshold of 80 contiguous voxels). Figure 3-3 illustrates the hemodynamic response to the button press in young and older adults. A group by linear trend over scan analysis of signal intensity was not

significant, suggesting that young and older adults did not differ significantly in the hemodynamic response curve characteristics (group x linear trend over scan analysis: $F(1,38) = 0.08$, $P = 0.785$).

A random effects analysis of the median reaction time of each subject comparing young and older adults revealed that there was not a significant difference in the time taken for the button press response after the visual cue ($F[1,38] = 0.07$, $P = 0.79$). The response latency median values were 404 ms (standard error = 24 ms) for older adults and 397 ms (standard error = 22 ms) for young adults.

In order to address concerns regarding the possibility of altered hemodynamic response in older adults taking blood pressure medication, their BOLD response during the motor task was compared to 6 pseudo-randomly selected older adults not taking blood pressure medication. There was significant activation in the contralateral left primary motor cortex (BA 4) in blood pressure medication free older adults (center of gravity: x = -42, y = -18, z = 48; 1204 voxels). Significant activation of left BA 4 was also observed in older adults taking blood pressure medications (center of gravity: x = -37, y = -22, z = 56; 435 voxels). Importantly, there were no significant differences between subjects taking blood pressure medications and subjects that were blood pressure medication free older adults in left BA 4, or any other regions ($P > .01$, Bonferroni corrected; threshold of 80 contiguous voxels). As this analysis is susceptible to a Type II statistical error due to low power (e.g., each group had 6 subjects), a much more liberal threshold was utilized as well. There again was no significant difference observed at a threshold of $P < 0.01$, uncorrected for multiple comparisons, and a minimum of 10 contiguous voxels.

Age Effect on Encoding Activity

In order to evaluate the effect of aging on encoding, only the young adult and older adult no-goal groups were compared so as not to confound this comparison with the

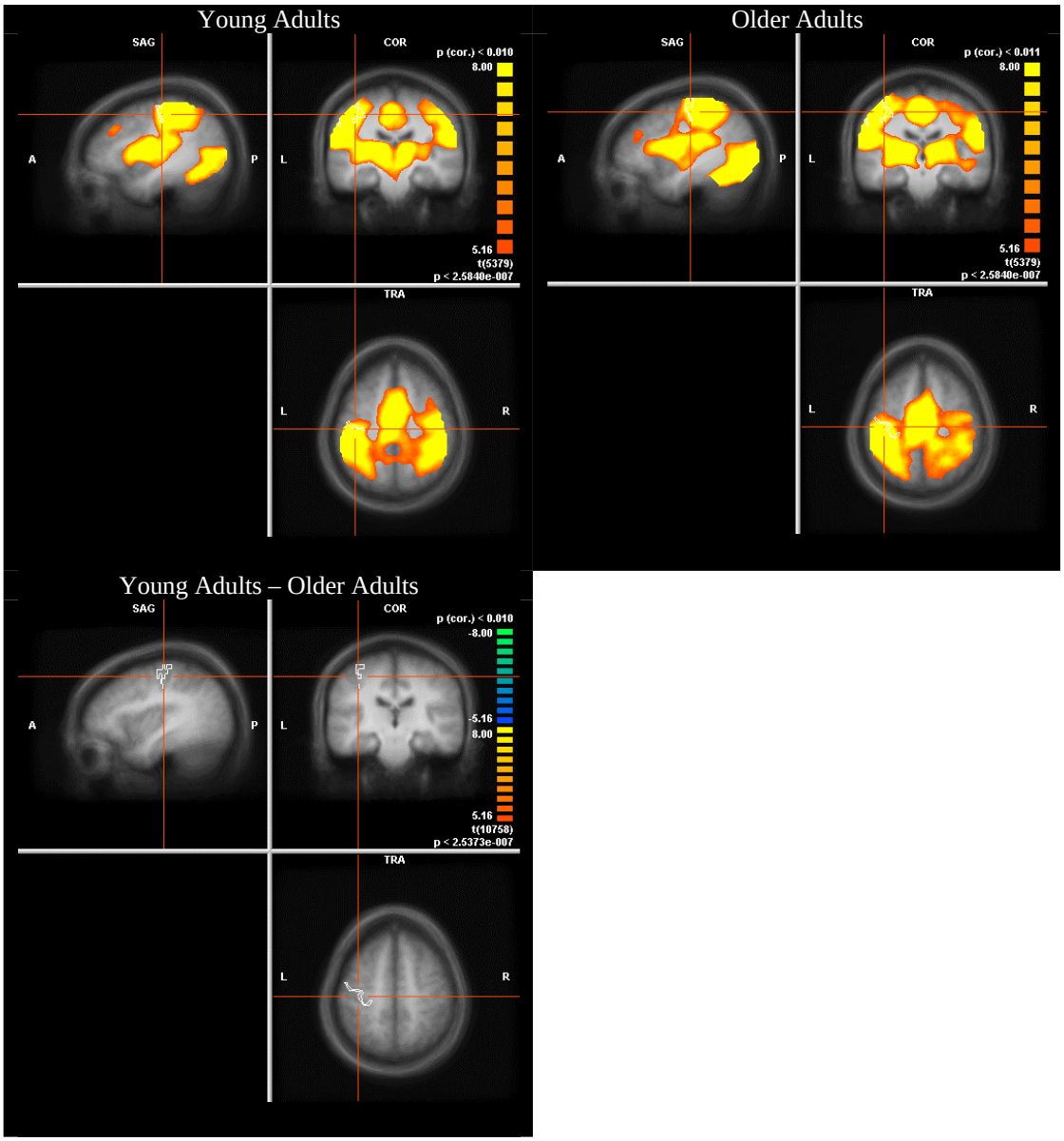

Figure 3-2. Left primary motor cortex (BA 4) activation during the motor task in young adults, older adults, and older adults subtracted from young adults. Statistical threshold was set at $P < 0.01$ (Bonferroni corrected for multiple comparisons; minimum of 80 contiguous voxels). Activation statistical maps are displayed on the smoothed, averaged T_1 image for all subjects in the analysis. Central point of the cross-hairs indicates the center of gravity for activation within BA 4.

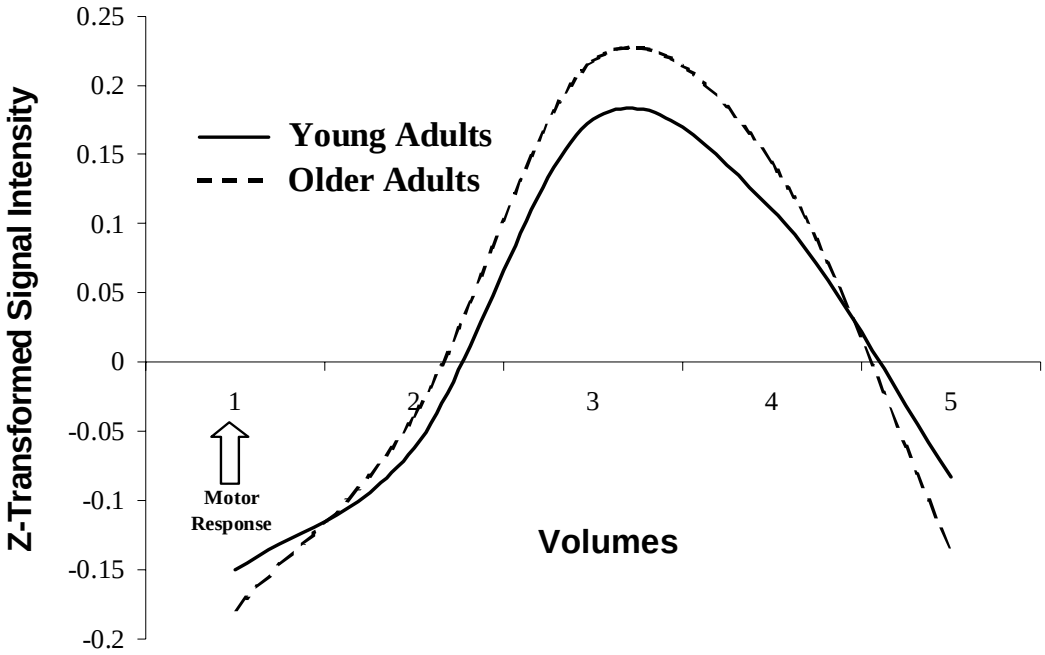

Figure 3-3. Motor task-related z-transformed signal intensity change as a function of scan-in-trial is displayed. Data were obtained from the left BA 4 in young adults (n=20) and older adults (n=20). Scan by group analysis revealed no significant differences in the curvature of the hemodynamic response between young and older adults.

presence of goals. Brain regions demonstrating significant activations for encoding in young and older adults are presented in Table 3-2. Direct comparisons between young and older adults' encoding-related activation levels are presented in Table 3-3. Figures F-1 and F-2 of Appendix F show the 3-dimensional spatial extent of activation in older and young adults, as well as activation differences between the two groups.

A priori findings. The effects of memory encoding were pronounced and statistically significant in both older and young adults in the prefrontal cortex. Encoding was associated with several prefrontal foci in both groups. Much of this activity was in the left middle frontal gyrus (BA 6, 8, 9, and 10). Left BA 8 of the medial frontal gyrus was activated only in younger adults. Broca's area was additionally activated in both

groups. Right middle frontal gyrus activation was observed in both groups, although to a much lesser extent. In the BA 6 portion of the right middle frontal gyrus, activation was greater in older adults. In the BA 8 portion of the right middle frontal gyrus, activation was greater in young adults. Left anterior cingulate (BA 32) was activated in young adults, but not older adults. A small, bilateral region of BA 10 in the middle frontal gyrus was also activated only in younger adults. Based on qualitative observations of the final statistical maps, activation was left lateralized in young adults, and to a lesser extent in older adults. When activation levels between young and older adults were compared directly, regions of the left medial frontal gyrus (BA 6, 8, and 9) were greater in young adults than in older adults. Activations were also greater in young adults in bilateral anterior cingulate cortex (BA 32). Right lateralized medial prefrontal gyrus regions (BA 6 and 8) and middle frontal gyrus (BA 6) demonstrated greater activation in young adults.

Temporal lobe involvement was observed in young and older adults extending from BA 20 to BA 21. This activation was bilateral in BA 20. Activation in the bilateral parahippocampal gyrus and left hippocampus was found only in older adults. Activation in the left BA 22 region of the superior temporal gyrus was only observed in the young adults. Overall, greater spatial extent of activation was observed in the temporal lobe regions for the young adults, but signal intensity-based comparisons did not reveal any significant differences between the two groups.

It should be noted that regions located in the occipital lobe were activated as well in both young and older adults. The encoding period is time-locked to the presentation of the words to be remembered. Consequently, visual stimulation occurred in conjunction with encoding. As was expected, several occipital regions were activated (precuneus,

fusiform gyrus, and lingual gyrus). These areas will not be a direct focus of evaluation and therefore are not listed in the following tables.

A posteriori findings. Bilateral activation of the angular gyrus (BA 39), as well as left lateralized supramarginal gyrus (BA 40), was found in both groups. Activation was also observed in the transverse temporal gyrus (BA 41), also referred to as the primary auditory receiving cortex. Lastly, activation was observed in the precentral and postcentral gyri (BA 3 and 4) in older adults. When directly comparing young and older adults, greater activity was observed in bilateral posterior cingulate cortex (BA 31) and bilateral supramarginal gyrus (BA 40) in young adults.

Age Effect on Subsequent Memory Activity (Encoding Activity Correlated with Recall Performance)

Brain regions demonstrating significant subsequent memory effects in young and older adults are presented in Table 3-4. Direct comparisons between young and older adults on subsequent memory effects are presented in Table 3-5. Figures F-3 and F-4 of Appendix F show the 3-dimensional spatial extent of activation in older and young adults, as well as activation differences between the two groups.

A priori findings. The effects of memory encoding were pronounced and statistically significant for both older and young adults in the prefrontal cortex. Subsequent memory was associated with several prefrontal foci in both groups, including the middle frontal gyrus (BA 6, 8, and 9; see Figure 3-4). Left anterior cingulate (BA 32) and right middle frontal gyrus (BA 9) were activated only in young adults. Right supplementary motor area (BA 6) was activated only in older adults. When activation in young and older adults was directly compared, greater activation in young adults was observed in the medial frontal gyrus (BA 6, bilaterally; left BA 8 and 9) and anterior

Table 3-2. Comparison of Activation during Encoding in Young and Older Adult Groups Not Receiving Goal-setting

Region (BA)	Young		Older	
	Talairach (x,y,z)	Voxels	Talairach (x,y,z)	Voxels
Left				
Postcentral gyrus (3)			-55,-10,46	112
Precentral gyrus (4)	-55,-10,35	126	-52,-7,45	257
Middle frontal gyrus (6)	-29,5,43	1220	-48,0,38	2278
Medial frontal gyrus (8)	-9,30,42	477		
Middle frontal gyrus (8)			-49,12,40	236
Middle frontal gyrus (9)	-48,10,31	734	-49,10,33	973
Middle frontal gyrus (10)	-36,47,12	101		
Middle temporal gyrus (20)	-36,-36,-15	207	-35,-36,-15	292
Middle temporal gyrus (21)	-60,-27,0	887	-64,-26,0	113
Superior temporal gyrus (22)	-59,-33,5	1165		
Anterior cingulate cortex (32)	-12,19,42	268		
Parahippocampal gyrus (36)			-34,-29,-16	230
Angular gyrus (39)	-41,-61,37	562	-37,-60,37	324
Supramarginal gyrus (40)	-47,-59,43	114	-43,-47,42	1054
Inferior frontal gyrus (44)	-52,15,9	92		
Broca's area (45)	-48,22,5	205	-42,28,16	1623
Hippocampus			-25,-21,-4	165
Right				
Middle frontal gyrus (6)			40,-4,33	257
Middle frontal gyrus (8)	34,24,34	166		
Middle temporal gyrus (20)	31,-36,-15	233	32,-37,-15	250
Parahippocampal gyrus (36)			29,-31,-13	431
Angular gyrus (39)	33,-60,38	204	31,-59,36	126
Transverse temporal gyrus (41)	41,-31,9	94		

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxel = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels.

Table 3-3. Encoding Related Activity Differences between Young and Older Adult Groups Not Receiving Goal-setting

Region (BA)	Young - Older		
	Talairach (x,y,z)	Voxels	Direction of Effect
Left			
Medial frontal gyrus (6)	-6,24,46	570	Y > O
Medial frontal gyrus (8)	-6,32,43	818	Y > O
Medial frontal gyrus (9)	-6,43,28	830	Y > O
Posterior cingulate cortex (31)	-7,-63,27	518	Y > O
Anterior cingulate (32)	-6,29,31	609	Y > O
Supramarginal gyrus (40)	-58,-46,26	119	Y > O
Right			
Middle frontal gyrus (6)	21,17,47	811	Y > O
Medial frontal gyrus (8)	14,28,45	1011	Y > O
Medial frontal gyrus (9)	10,41,32	736	Y > O
Posterior cingulate cortex (31)	1,-59,27	697	Y > O
Anterior cingulate cortex (32)	2,30,29	347	Y > O
Supramarginal gyrus (40)	53,-29,33	117	Y > O

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxel = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels. Y = young adults; O = older adults.

cingulate (left BA 24 and bilateral BA 32). Figure 3-5 illustrates a PFC cluster including portions of the anterior cingulate cortex and medial frontal gyrus that exhibited significant task-related changes in signal intensity that were correlated with subsequent performance.

Extensive temporal lobe involvement, which was mostly left lateralized, was observed in young and older adults. Bilateral activations were observed in the parahippocampal gyrus (BA 36) in both groups. Bilateral activation in the middle temporal lobe was observed in BA 20 for both groups. Right BA 21 and 22 of the middle temporal gyrus were activated only in young adults. Hippocampal activation was bilateral in young and older adults. The spatial extent of activation was somewhat greater in young

Table 3-4. Comparison of Subsequent Memory Effect in Young and Older Adult Groups Not Receiving Goal-setting

Region (BA)	Young		Older	
	Talairach (x,y,z)	Voxels	Talairach (x,y,z)	Voxels
Left				
Postcentral gyrus (3)			-55,-10,46	84
Precentral gyrus (4)			-51,-6,47	167
Middle frontal gyrus (6)	-37,4,41	1576	-50,0,41	1438
Middle frontal gyrus (8)	-26,21,41	480	-50,13,40	160
Middle frontal gyrus (9)	-44,9,35	486	-54,9,34	251
Middle temporal gyrus (20)	-35,-36,-15	250	-36,-36,-15	238
Middle temporal gyrus (21)	-59,-29,0	573		
Superior temporal gyrus (22)	-58,-34,4	501		
Anterior cingulate cortex (32)	-11,19,42	264		
Parahippocampal gyrus (36)	-37,-31,-13	78	-35,-28,-17	150
Angular gyrus (39)	-38,-61,38	391	-36,-60,37	237
Supramarginal gyrus (40)	-45,-58,43	102	-42,-48,42	948
Hippocampus	-26,-12,-9	1770	-27,-23,-4	422
Right				
Supplementary motor areas (6)			40,-2,35	156
Middle frontal gyrus (9)	37,24,33	117		
Middle temporal gyrus (20)	32,-36,-15	237	32,-37,-15	245
Parahippocampal gyrus (35)			25,-25,-17	104
Parahippocampal gyrus (36)	33,-31,-13	133	28,-31,-13	455
Angular gyrus (39)	35,-61,39	243	32,-60,38	115
Hippocampus	21,-12,-6	1003		

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels.

Table 3-5. Subsequent Memory Differences between Young and Older Adult Groups Not Receiving Goal-setting

Region (BA)	Young - Older		
	Talairach (x,y,z)	Voxels	Direction of Effect
Left			
Medial frontal gyrus (6)	-8,29,36	118	Y > O
Medial frontal gyrus (8)	-7,29,42	321	Y > O
Medial frontal gyrus (9)	-8,30,32	84	Y > O
Anterior cingulate cortex (24)	-7,23,25	113	Y > O
Posterior cingulate cortex (31)	-4,-66,29	89	Y > O
Anterior cingulate cortex (32)	-7,26,31	838	Y > O
Supramarginal gyrus (39)	-52,-60,23	83	Y > O
Supramarginal gyrus (40)	-58,-46,27	85	Y > O
Putamen	-20,7,5	219	Y > O
Right			
Middle frontal gyrus (6)	27,10,45	180	Y > O
Posterior cingulate cortex (31)	2,-56,28	293	Y > O
Anterior cingulate cortex (32)	1,26,29	137	Y > O

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels. Y = young adults; O = older adults.

adults in temporal regions, including the hippocampus (see Figure 3-4).

Several occipital regions were additionally activated (precuneus, fusiform gyrus, and lingual gyrus).

A posteriori findings. Activation of the precentral (BA 4) and postcentral (BA 3) gyri was found only in older adults. Bilateral angular gyrus (BA 39) and left supramarginal gyrus activity (BA 40) was found in young and older adults. When activation in young and older adults was compared directly, bilateral posterior cingulate (BA 31), left supramarginal gyrus (BA 39 and 40), and left putamen were found to be greater in young adults.

Goal-setting Effect on Encoding Activity

In order to evaluate the effect of goal-setting on encoding, young and older adult

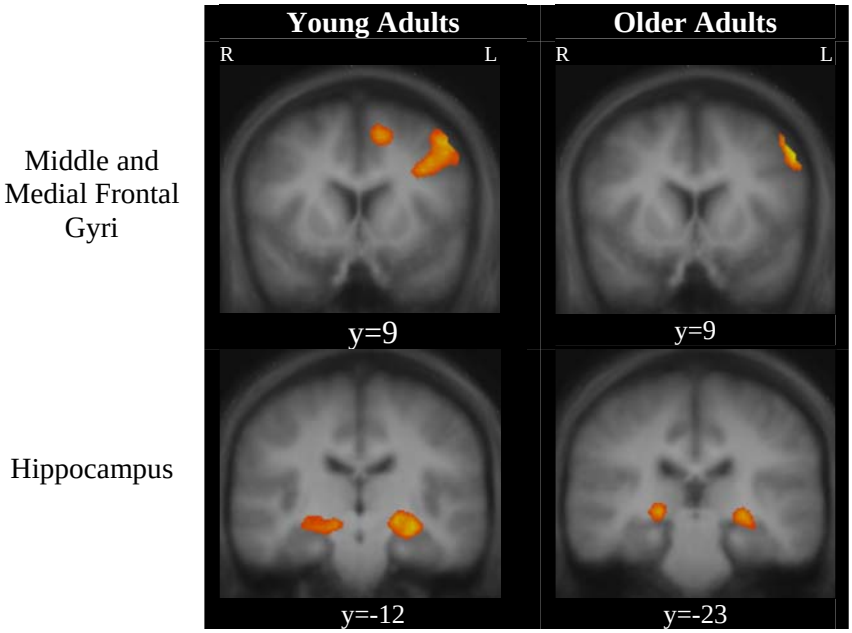

Figure 3-4. Effect of subsequent memory in young (n=10) and older (n=10) adults. Coronal slice images illustrate regions in the medial and middle frontal gyri and hippocampus that exhibited significant task-related changes in signal intensity that were correlated with subsequent performance ($P<0.01$, Bonferroni corrected; minimum of 80 contiguous voxels). Activation statistical maps are displayed on the smoothed, averaged T_1 image for all subjects in the analysis.

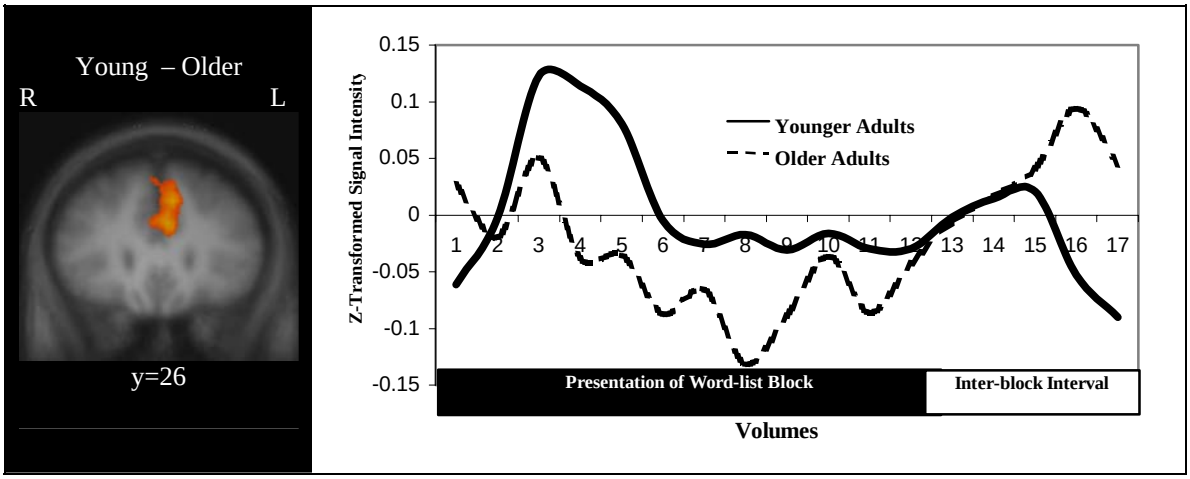

Figure 3-5. Effect of subsequent memory: older adults subtracted from young adults. Coronal slice image illustrates PFC cluster (extending from the medial frontal gyrus to the anterior cingulate cortex) that exhibited significant group differences in signal intensity that were correlated with subsequent performance (P<0.01, Bonferroni corrected; minimum of 80 contiguous voxels). Activation statistical maps are displayed on the smoothed, averaged T_1 image for all subjects in the analysis. Task-related z-transformed signal intensity as a function of scan-in-trial is displayed in the graphical illustration. Data were obtained from the contiguous cluster of 7 voxels that had the highest t-values of the overall cluster (x = -6, y = 26, z = 29).

groups were collapsed across goal (n = 20) and no-goal (n = 20) groups. Brain regions demonstrating significant activations for encoding in the goal and no-goal groups are presented in Table 3-6. Data reflecting significant differences between groups are not presented in tabular format as there was only one region demonstrating a significant difference. Figures F-5 and F-6 of Appendix F show the 3-dimensional spatial extent of activation in the goal and no-goal groups, as well as activation differences between the two groups.

A priori findings. In the individual group analyses, activation was observed in bilateral dlPFC regions in the goal and no-goal groups. Specifically, bilateral activation was found in the BA 9 region of the middle frontal gyrus, and left BA 46 activation was found in the middle frontal gyrus. Orbitofrontal cortex activation was observed in the left BA 10 region of the middle frontal gyrus and left BA 47 regions of the inferior frontal gyrus in both groups. However, only in the goal group was right BA 10 activation found. Broca's area (BA 45), left BA 8 of the middle frontal gyrus, and left supplementary motor area (BA 6) include other frontal regions activated in both groups. Right BA 6 was additionally activated in the goal group. The left BA 32 region of the anterior cingulate was activated in both groups, whereas activation in the right anterior cingulate (BA 24 and 32) was observed only in the goal group. No significant differences were found between the goal and no-goal groups in any frontal lobe regions.

Bilateral temporal lobe involvement was observed in the hippocampus, parahippocampal gyrus (BA 36), and BA 20 of the middle temporal gyrus in both groups. Greater spatial extent of the hippocampal activation was observed in the goal group; however, differences in signal intensity in this region were not significant. Activation in

the left insula (BA 13), left superior temporal gyrus (BA 22), and left middle temporal gyrus (BA 21) was observed in both groups as well. When goal and no-goal groups were compared directly, BA 20 activation of the middle temporal gyrus was found to be greater in the goal group.

Several occipital regions were additionally activated (precuneus, fusiform gyrus, and lingual gyrus).

A posteriori findings. Bilateral angular gyrus (BA 39) and supramarginal gyrus (BA 40) activity was observed in both groups. Bilateral posterior cingulate cortex (BA 23 and 31) was activated in the goal group, but not in the no-goal group. Left precentral (BA 4) and postcentral (BA 3) gyri were activated in both groups. Activation was also observed in the right transverse temporal gyrus (BA 41) in the no-goal group.

Goal-setting Effect on Subsequent Memory Activity (Encoding Activity Correlated with Recall Performance)

Brain regions demonstrating significant subsequent memory activations are presented in Table 3-7. Direct comparisons between goal and no-goal groups' subsequent memory activation level differences are presented in Table 3-8. Figures F-7 and F-8 of Appendix F show the 3-dimensional spatial extent of activation in the goal and no-goal groups, as well as activation differences between the two groups.

A priori findings. In the individual group analyses, activation was observed in bilateral dlPFC regions in goal and no-goal groups. Specifically, there was bilateral activation in the BA 9 region of the middle frontal gyrus. Only in the goal group was activation in the left BA 46 region of the middle frontal gyrus found. In the goal group, orbitofrontal cortex activation was observed in the left BA 10 region of the middle frontal gyrus and in the left BA 47 regions of the inferior frontal gyrus. Broca's area (BA 45),

Table 3-6. Comparison of Activation during Encoding in the Goal and No-goal Groups

Region (BA)	Goal		No-goal	
	Talairach (x,y,z)	Voxels	Talairach (x,y,z)	Voxels
Left				
Frontal Lobe				
Precental gyrus (4)	-52,-9,42	736	-54,-9,39	679
Supplementary motor area (6)	-36,0,45	3684	-45,0,40	3155
Middle frontal gyrus (8)	-39,16,40	333	-41,16,41	317
Middle frontal gyrus (9)	-48,13,32	1820	-48,11,32	1671
Middle frontal gyrus (10)	-38,45,13	854	-39,45,12	341
Broca's area (45)	-50,22,14	390	-44,24,6	203
Middle frontal gyrus (46)	-47,34,16	1059	-45,32,16	432
Anterior cingulate cortex (32)	-13,17,41	368	-13,13,45	141
Inferior frontal gyrus (47)	-36,27,-1	107	-42,25,0	201
Temporal Lobe				
Insula (13)	-37,12,10	393	-37,22,7	374
Middle temporal gyrus (20)	-35,-35,-15	317	-35,-36,-15	288
Middle temporal gyrus (21)	-60,-26,0	514	-60,-27,0	764
Superior temporal gyrus (22)	-60,-30,5	766	-59,-31,4	801
Parahippocampal gyrus (36)	-36,-29,-14	313	-35,-29,-16	193
Hippocampus	-35,-21,-9	1991	-25,-22,-5	525
Parietal Lobe				
Supramarginal gyrus (40)	-44,-49,44	1389	-44,-51,43	853
Posterior cingulate cortex (23)	-9,-72,12	144		
Angular gyrus (39)	-41,-61,33	976	-40,-61,37	601
Postcentral gyrus (3)	-55,-11,41	266	-56,-11,39	253
Right				
Frontal Lobe				
Supplementary motor area (6)	41,-5,34	583		
Middle frontal gyrus (9)	37,24,33	680	35,24,33	287
Middle frontal gyrus (10)	30,47,9	150		
Anterior cingulate cortex (24)	14,2,38	116		
Anterior cingulate cortex (32)	11,17,35	471		
Temporal Lobe				
Middle temporal gyrus (20)	32,-37,-15	250	32,-36,-15	254
Transverse temporal gyrus (41)			42,-29,8	104
Parahippocampal gyrus (36)	31,-30,-14	342	30,-30,-14	427
Hippocampus	28,-23,-4	1100	23,-19,-4	515
Parietal Lobe				
Angular gyrus (39)	33,-59,36	231	33,-60,37	275
Supramarginal gyrus (40)	39,-47,42	1017	35,-51,43	132
Posterior cingulate cortex (31)	16,-58,24	177		
Posterior cingulate cortex (23)	7,-71,12	191		

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels.

left BA 8 of the middle frontal cortex, and left supplementary motor area (BA 6) include other frontal regions activated in both groups. Right BA 6 and Broca's homologue (right BA 45) were additionally activated in the goal group. The left BA 32 region of the anterior cingulate was activated in both groups.

When the goal and no-goal groups were compared directly, there was significantly greater activity in the bilateral orbitofrontal cortex (BA 10; x=-32, y=49, z=16), dlPFC (BA 46; x =-47, y=28, z=19), and Broca's area (BA 45; x=-50, y=19, z=18) in the goal-group (see Figure 3-6).

Bilateral temporal lobe involvement was observed in the hippocampus, parahippocampal gyrus (BA 36), and BA 20 of the middle temporal gyrus in both groups. Activation in the left insula (BA 13), left superior temporal gyrus (BA 22), and left middle temporal gyrus (BA 21) was observed in both groups as well. When goal and no-goal groups were compared directly, BA 20 of the middle temporal gyrus was found to be greater in the no-goal group bilaterally and activation in the right hippocampus was greater in the goal group.

Several occipital regions were additionally activated (precuneus, fusiform gyrus, and lingual gyrus).

A posteriori findings. Bilateral angular gyrus (BA 39) and supramarginal gyrus (BA 40) activity was observed in both groups. Left posterior cingulate cortex (BA 30) was activated in the goal group, but not in the no-goal group. Left precentral and postcentral gyri were activated in both groups. Activation was also observed in the right transverse temporal gyrus (BA 41). Amygdalar activation was observed in the left

hemisphere of the goal group only. There were no significant differences between groups in any of these regions.

Interaction of Goal-setting and Age during Encoding Activity

Brain regions demonstrating significant interactions during encoding activation are presented in Table 3-9 with parameter estimates listed for each group. Figure F-9 of Appendix F shows the 3-dimensional spatial extent of activation in regions that demonstrated a significant age by goal-setting interaction.

Regions that were identified as having a significant interaction demonstrated, without exception, the same pattern of relative increases or decreases within age groups. More specifically, regions with a significant interaction showed decreases in activity in young adults as a function of goal-setting, whereas activation in older adults increased as a function of goal-setting. The observed pattern of activation differences between young and older adults in response to goal-setting indicated that older adults activated these regions to a greater extent during goal-setting relative to activity observed in the no-goal group.

Beta weights provided in Table 3-9 are products of the multiple-regression analysis performed on the interaction of age by goal-setting. Beta weights are interpreted only to the extent that they show relative increases or decreases in encoding-related activity within an age group as a function of goal-setting. For regions demonstrating a significant interaction, relative increases or decreases in encoding-related activity as a consequence of goal-setting in one age group are then compared to the pattern observed in the other age group.

A priori findings. In frontal regions, activation was observed in bilateral medial frontal gyrus (BA 9; see Figure 3-7), BA 8 of the left medial frontal gyrus, and left

Table 3-7. Comparison of Subsequent Memory Effect in Goal and No-goal Groups

Region (BA)	Goal		No-Goal	
	Talairach (x,y,z)	Voxels	Talairach (x,y,z)	Voxels
Left				
Frontal Lobe				
Precentral gyrus (4)	-51,-8,44	264	-51,-7,46	272
Supplementary motor area (6)	-40,0,39	2059	-45,0,40	2932
Middle frontal gyrus (8)	-33,19,40	413	-47,14,41	282
Middle frontal gyrus (9)	-47,13,32	1859	-48,9,33	1031
Middle frontal gyrus (10)	-36,48,10	1181		
Anterior cingulate cortex (32)	-13,18,41	368	-13,13,45	130
Broca's area (45)	-37,29,11	9181	-27,32,2	370
Middle frontal gyrus (46)	-47,34,16	1045		
Inferior frontal gyrus (47)	-39,27,-3	129		
Temporal Lobe				
Insula (13)	-37,23,7	258		
Middle temporal gyrus (20)	-36,-34,-15	324	-35,-36,-15	290
Middle temporal gyrus (21)	-62,-25,0	212	-60,-28,0	363
Superior temporal gyrus (22)	-63,-28,3	145	-58,-30,3	133
Parahippocampal gyrus (36)	-36,-28,-15	273	-36,-29,-15	276
Hippocampus	-24,-28,0	1141	-29,-14,-9	2315
Parietal Lobe				
Angular gyrus (39)	-40,-61,35	753	-39,-61,37	504
Supramarginal gyrus (40)	-43,-52,43	585	-43,-49,43	1119
Postcentral gyrus (3)			-55,-10,46	112
Right				
Frontal Lobe				
Supplementary motor area (6)	39,-5,34	342		
Middle frontal gyrus (9)	39,19,34	609	38,25,34	249
Broca's homologue (45)	25,31,8	3632	22,33,2	197
Temporal Lobe				
Middle temporal gyrus (20)	32,-37,-15	252	32,-36,-15	254
Parahippocampal gyrus (36)	31,-30,-14	306	29,-30,-13	537
Parahippocampal gyrus (35)			24,-25,-15	86
Amygdala	29,-4,-17	398		
Hippocampus	23,-25,-2	710	25,-16,-8	820
Parietal Lobe				
Angular gyrus (39)	32,-59,36	220	35,-61,37	378
Supramarginal gyrus (40)	38,-46,40	615	36,-47,44	515
Posterior cingulate cortex (30)	22,-67,11	112		

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels.

Table 3-8. Subsequent Memory Effect Differences between Goal and No-goal Groups

Region (BA)	Goal – No-goal		
	Talairach (x,y,z)	Voxels	Direction of Effect
Left			
Supplementary motor area (6)	-41,4,52	210	NG > G
Middle frontal gyrus (10)	-32,49,16	826	G > NG
Middle temporal gyrus (20)	-25,-84,-12	117	NG > G
Broca's area (45)	-39,31,7	1680	G > NG
Inferior frontal gyrus (46)	-45,40,11	153	G > NG
Right			
Middle frontal gyrus (10)	36,45,20	103	G > NG
Middle temporal gyrus (20)	27,-79,-10	150	NG > G
Hippocampus	38,25,8	507	G > NG

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels. G = goal group, NG = no-goal group

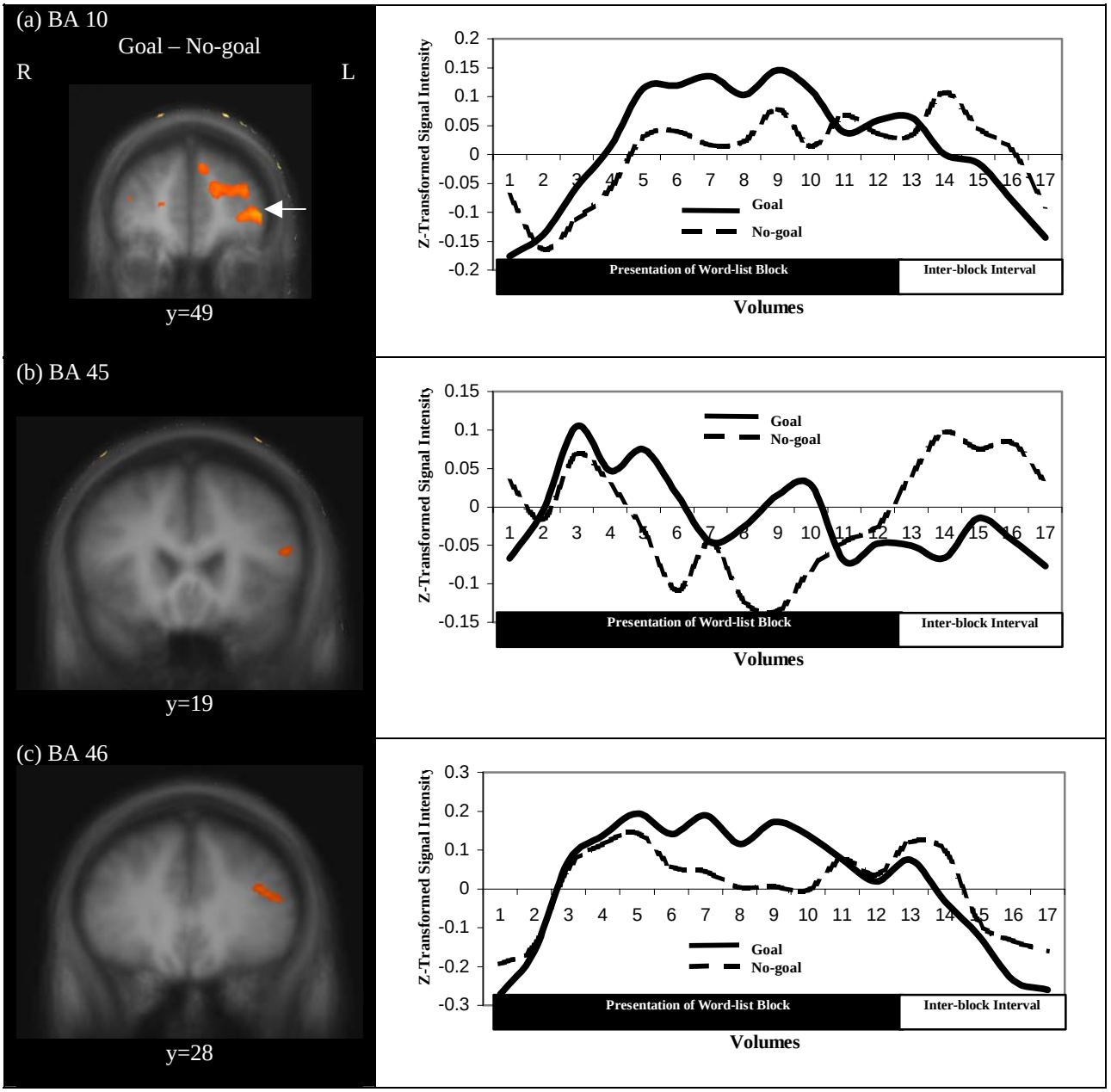

Figure 3-6. Effect of subsequent memory: no-goal group subtracted from the goal group. Coronal slice images illustrate frontal cortex clusters that exhibited significant activation (P<0.01, Bonferroni corrected; minimum of 80 contiguous voxels). Clusters depicted are (a) orbitofrontal cortex (BA 10; x=-32, y=49, z=16); (b) Broca's area (BA 45; x=-50, y=19, z=18); and (c) dorsolateral prefrontal cortex (BA 46; x =-47, y=28, z=19). Activation statistical maps are displayed on the smoothed averaged T1 image for all subjects in the analysis. Task-related z-transformed signal intensity as a function of scan-in-trial is displayed in the graphical illustrations. Data were obtained from the contiguous cluster of 7 voxels that had the highest t-values of the overall cluster.

supplementary motor area (BA 6). Activation in the temporal lobe was limited to the left superior temporal gyrus (BA 22). Significant interactions were not observed in the OFC or dlPFC.

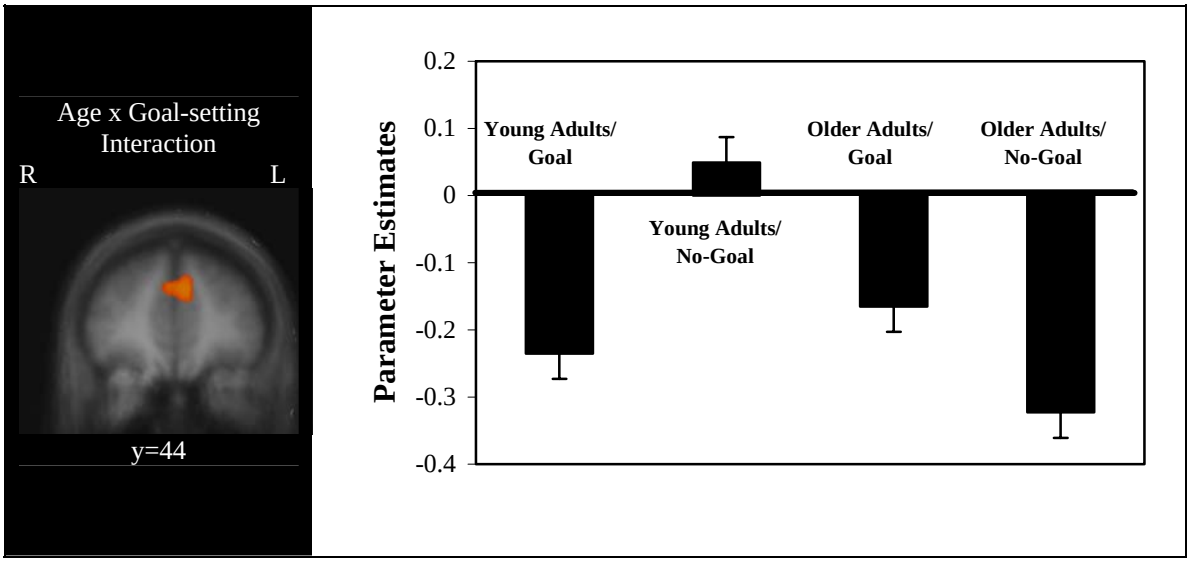

Figure 3-7. Coronal slice image illustrates PFC cluster (BA 9) that exhibited significant task-related interaction of age by goal-setting (P<0.01; Bonferroni corrected, minimum of 80 contiguous voxels). Activation statistical maps are displayed on the smoothed, averaged T_1 image for all subjects in the analysis. Parameter estimates (e.g., beta weights) for each group are displayed in the graphical illustration. Data were obtained from the contiguous cluster of 7 voxels that had the highest *t*-values of the overall cluster (x=-5, y=44, z=29). Standard error bars are shown.

A posteriori findings. An interaction effect was found in bilateral supramarginal gyrus (BA 40), left angular gyrus (BA 39), and left posterior cingulate cortex (BA 31).

Interaction of Goal-setting and Age for Subsequent Memory Activity (Encoding Activity Correlated with Recall Performance)

Brain regions demonstrating significant subsequent memory interactions are presented in Table 3-10 with parameter estimates listed for each group. Figure F-10 of Appendix F shows the 3-dimensional spatial extent of activation in regions that demonstrated a significant age by goal-setting interaction. Beta weights are again used for interpretation of regions that demonstrate a significant interaction.

Table 3-9. Interaction of Age and Goal-setting during Memory Encoding

Region (BA)	Talairach (x,y,z)	Voxels	Parameter Estimates (beta weights)			
			YA/G	YA/NG	OA/G	OA/NG
Left						
Supplementary motor area (6)	-6,33,39	169	-0.09	0.14	0.00	-0.26
Medial frontal gyrus (8)	-8,31,41	277	0.04	0.29	0.10	-0.13
Medial frontal gyrus (9)	-5,44,29	348	-0.21	0.08	-0.12	-0.31
Superior temporal gyrus (22)	-55,-50,17	178	-0.28	0.08	0.04	-0.04
Posterior cingulate cortex (31)	-6,-55,25	196	-0.18	0.10	-0.06	-0.18
Angular gyrus (39)	-50,-61,18	477	-0.15	0.11	0.12	-0.15
Supramarginal gyrus (40)	-59,-40,26	485	-0.25	-0.04	0.020	-0.29
Right						
Medial frontal gyrus (9)	2,43,31	175	-0.24	0.03	-0.16	-0.34
Supramarginal gyrus (40)	52,-29,33	242	-0.28	-0.15	-0.09	-0.46

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels. YA = young adults, OA = older adult, G = goal group, NG = no-goal group.

A priori findings. Frontal regions that demonstrated a significant interaction included Broca's homologue (BA 45) and the anterior cingulate cortex (BA 31). The left superior temporal gyrus (BA 22) was also activated.

A posteriori findings. The left angular gyrus (BA 39) demonstrated a significant interaction.

Table 3-10. Interaction of Age and Goal-setting during Encoding for Subsequent Memory Effects

Region (BA)	Talairach (x,y,z)	Voxels	Parameter Estimates (beta weights)			
			YA/G	YA/NG	OA/G	OA/NG
Left						
Superior temporal gyrus (22)	-52,-56,16	83	-0.34	0.18	0.09	-0.26
Posterior cingulate cortex (31)	-5,-12,45	167	-0.37	-0.12	0.01	-0.44
Angular gyrus (39)	-50,-60,19	260	-0.30	.14	.14	-0.33
Right						
Broca's homologue (45)	45,34,3	207	-0.21	-0.07	0.09	-0.33

BA = Brodmann's Area. Talairach = 3-dimensional coordinates for the center of gravity in each activation cluster given the stereotactic space of Talairach and Tournoux (1988). Voxels = number of voxels in each cluster exceeding height threshold $P < 0.01$, Bonferroni corrected in the whole brain volume; exceeding minimum threshold of 80 contiguous voxels. YA = young adults, OA = older adult, G = goal group, NG = no-goal group.

CHAPTER 4
DISCUSSION

Despite their high levels of self-reported general health and greater vocabulary skills, older subjects exhibited a pattern of episodic memory performance typical of that reported in behavioral studies of aging (Light, 1991). In particular, older subjects' performances were below those of young subjects on a word list recall task. The provision of goals for performing the task resulted in a significant increase in the number of words recalled in both young and older adults. Further, the increase in performance as a result of goal-setting was equivalent between young and older adults. These findings are consistent with other studies that utilized an analogous paradigm (West et al., 2002; 2003).

Encoding of the word list was associated with highly left-lateralized activity in the prefrontal cortex (PFC) of young adults. PFC activity in older adults was dampened compared to young adults. When correlating recall performance with signal intensity (e.g., subsequent memory effects), bilateral temporal lobe and hippocampal activity was also observed in young and older adults. Volume distribution of the activation was larger in young adults; however, a signal-intensity based comparison did not reveal a significant difference.

The effect of goal-setting on subsequent memory activation was only found in the frontal lobes. Specifically, regions that demonstrated higher levels of activity from goal-setting included the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), as well as Broca's area. A significant increase in the right hippocampal region as a result of

goal-setting was observed as well. When comparing young and older adults' response to goal-setting, older adults were found to recruit several different regions to a greater extent than young adults.

Encoding in Young Adults

A leading model describing the cortical neural substrates of encoding is the hemispheric encoding/retrieval asymmetry (HERA) model (Tulving, 1994). The HERA model proposes that the left PFC is more involved than the right PFC in encoding, whereas the right PFC is more involved than the left PFC in episodic memory retrieval. However, more recent studies of spatial (as opposed to verbal) material find greater right-lateralized PFC activity during encoding, presenting a formidable challenge to the HERA model. Thus, Tulving and colleagues (Habib et al., 2003) recently asserted a revised formulation of the HERA model in order to accommodate these conflicting results. They assert that encoding and retrieval processes must be systematically varied in their interaction with hemispheric interactions. Specifically, to test for asymmetry in encoding, the following formulation must be met: left hemisphere encoding minus left hemisphere retrieval is greater than right hemisphere encoding minus right hemisphere retrieval.

Findings from the present study are generally consistent with the HERA model as strongly left-lateralized PFC activation was observed during encoding. However, the design of the present study does not allow for evaluation of retrieval-related neural activation. Consequently, findings only partially address the HERA model as an evaluation of the present data set with the more stringent reformulation of the HERA model is not possible.

The present study found less than robust temporal lobe activation in the encoding-related activity analysis. Extensive neuropsychological and physiological evidence points

to a clear role of temporal lobe involvement in encoding; however, many other fMRI studies exist that found little or no encoding-related medial temporal lobe activation (Petersen et al., 1988; Frith et al., 1991; Demonet et al., 1992; Grasby et al., 1993, 1994; Kapur et al., 1994, 1996; Raichle et al., 1994; Shallice et al., 1994; Tulving et al., 1994; Fletcher et al., 1995; Nyberg et al., 1996). In addition to the dubious finding of little or no involvement of the medial temporal lobe in encoding, this approach – measuring encoding-related activity – is questionable to the extent that encoding activities are genuinely being assessed. For instance, encoding related activity in the hippocampus could reflect a response to novelty unrelated to the encoding of a memory, or it could reflect habituation or reduced attention. To address these important issues, the present study also employed an approach that correlated subsequent memory performance with signal intensity during encoding. In this way, one can be more confident that a particular region of activation signifies processes important for encoding an episodic memory. When using the correlative approach between memory performance and signal intensity, robust activation was found in the temporal lobe/hippocampus regions, which is consistent with other studies that employed this approach (Brewer et al., 1998; Gabrieli et al., 1997; Fernandez et al., 1998, 1999).

Activation was observed bilaterally in the angular gyrus and the supramarginal gyrus, which likely reflects reading processes taking place during the word list presentation (Price, 2000). Activation also occurred in the transverse temporal gyrus, which may be accounted for by the loud scanner environment.

Encoding in Older Adults and Age-related Changes

The predicted reduction in left PFC activity observed during encoding for older adults compared with young adults is in line with the HAROLD (hemispheric asymmetry

reduction in older adults) model. The HAROLD model states that young subjects, consistent with the HERA model, engage the left PFC more extensively during encoding, whereas older subjects show dampened left PFC activity during encoding (Cabeza et al., 2001). Even though the present study, among many others (see Grady, 2000 for review), showed decreased left PFC activation in older adults during encoding, it is worthwhile noting two recent studies that showed a similar level of activation in the left PFC in young and older adults. Daselaar et al. (2003) compared brain activity patterns obtained during incidental encoding in which subjects were not asked to learn the words presented, but instead were asked to make pleasant/unpleasant judgments about the words. They found equivalent left PFC encoding activation in young subjects and older subjects when correlating encoding activity with subsequent memory of the words. Morcum et al. (2003) also found equivalent left PFC activation when subjects were asked to make animacy decisions about words. Subjects later underwent a recognition memory test for these words that was correlated with activity during the encoding period.

A common thread can be found between these two studies that reported equivalent left PFC activation between young and older adults during encoding. Both of these studies involved incidental learning, as opposed to the intentional learning approach that was utilized by other studies, including the present one. This account for the differential findings is further supported by a study by Buckner and colleagues (Logan et al., 2002), which showed less prefrontal activity in older adults compared with young adults under intentional learning instructions. Importantly, this difference was not observed when a semantic-orienting task was used to support episodic encoding (e.g., incidental encoding). This interpretation of the seemingly disparate findings in the left PFC is in agreement

with a production deficiency account of age-related impairments in episodic encoding. This account asserts that older adults do not employ semantic elaboration strategies spontaneously but are able to make use of them when forced to do so (Burke and Light, 1981). The production deficiency account is particularly interesting in light of the differential use of strategies between young and older adults observed in the present study. Older adults utilized less strategies in performing the intentional memory encoding task. The decreased use of strategies is consistent with the production deficiency account and is likely reflected by the decreased left PFC activation observed in older adults.

Greater activation was found in the anterior and posterior portions of the cingulate cortex in young adults. A significant scan by age interaction existed in a cluster of voxels that included regions of the anterior cingulate and medial frontal gyrus. The greater level of sustained activity in the young adults suggests greater attentional resources dedicated to the task and perhaps more concentrated performance monitoring (Tisserand and Jolles, 2003). In regards to the increased level of activation in the posterior cingulate in young adults, several studies have asserted a role for this region being involved in encoding (Hunkin et al., 2002; Hofer et al., 2003). However, Otten and Rugg (2001) found that encoding activation in the posterior cingulate was associated with recall failure on subsequent memory tests. At present, the role of the posterior cingulate in encoding is unclear and is need of further elucidation.

Older adults demonstrated encoding activity in the temporal lobe (primarily in the middle temporal gyrus and hippocampus), which was to a lesser spatial extent than young adults. There were no significant signal intensity differences between young and older adults, though significant activation present in BA 21 of the middle temporal gyrus and

right hippocampus in the young adults was absent in older adults. It has been suggested that the medial temporal lobe operates by forming associations between sensory, cognitive and emotional processes that make up an episode in memory (Alvarez and Squire, 1994; Eichembaum, 1996). Accordingly, it has been suggested that there is a relation between the amount of medial temporal lobe activity and the number of associations that are formed during encoding of study material (Henke et al., 1997, 1999). Given the presence of medial temporal lobe activity during encoding, this would imply that the older adults formed fewer memory associations.

In addition to the PFC and temporal lobes, older adults engaged other regions that were in common with young adults. Activation was observed in the angular gyrus and supramarginal gyrus regions in the encoding-related and subsequent memory analyses. This activation, as previously stated, was likely associated with reading processes required for list learning (Price, 2002).

Taken together, data from this pilot study suggest that older subjects engage much of the same neural circuitry as young subjects when encoding new memories. However, the findings also point to the possible presence of age-related differences in both prefrontal and temporal activity during episodic encoding. Further, these findings suggest that the age-related declines in episodic encoding may be related to strategic encoding and attentional differences, as well as fewer memory associations formed.

Goal-setting Influence on Encoding

Predicted associations were found between OFC and dlPFC activation and the presence of goal-setting during encoding. Additional regions of the prefrontal cortex were also found to be involved with subsequent memory performance, including the supplementary motor cortex and a large portion of Broca’s area.

In further evaluating areas engaged by goal-setting, it is impossible to separate which regions underlie the motivation properties of goal-setting and which regions underlie increased mnemonic processing, facilitated by increased motivation. However, comparing the results to the extent literature provides a likely framework in which the goal-setting effect is mediated.

The generally agreed upon role of the OFC in motivation and the pattern of activation observed in the OFC suggest that this region supports the motivational component of goal-setting. In the subsequent memory effect analysis of goal-setting, activation in the OFC was not observed in the no-goal group, indicating that this region was likely not associated with successful or unsuccessful encoding. Consequently, it is unlikely that the engagement of the OFC directly reflects mnemonic processes. It is likely, however, that the OFC is associated with the motivational aspect of goal-directed improvement of the performance, which is supported by several lines of evidence. Stuss and Levine (2002) put forward the concept of the self-regulatory disorder, which is characterized by an inability to regulate behavior according to internal goals and constraints. They observed this disorder after discrete lesioning to the ventral frontal cortex. Humans with ventral frontal lobe damage can show impairments in a number of tasks in which an alteration of behavioral strategy is required in response to a change in environmental context or expectations (Damasio, 1994; Rolls, 2000). Activity in this region in the present study likely reflects the other end of the spectrum from what these studies report: increased activity in the OFC mediates increases in goal-directed/contextually-guided behavior.

A more difficult region to elucidate the contribution to the goal-setting effect is the dlPFC. Extensive work demonstrates the role of the dlPFC in cognitive control (see Miller and Cohen, 2002 for review). Cognitive control includes the ability to maintain context, or a goal, by which behavior is then biased. Certainly it is plausible that the increased dlPFC activation subserved the function of maintaining the idea of the goal on-line while performing the task. However, being that the dlPFC subserved mnemonic processes as well in the absence of goal-setting, it is difficult to ascertain whether this region helped to improve memory performance by enhanced mnemonic processing or maintenance of goal intent, or a combination of these factors.

Goal-setting also produced substantially greater activation in Broca's area and supplementary motor areas. As activation in motor regions and Broca's area has been implicated in subvocalization (Sweet et al., 2004; Gruber, 2001), these regions could be involved in an increase in subvocal rehearsal in the goal group as a result of increased motivation. This finding suggests that the goal group may have gained in performance over the no-goal group by greater subvocal rehearsal during the encoding period.

Interestingly, none of the frontal regions observed to be significantly greater in the goal-setting group in the subsequent memory analysis were significant in the encoding-related activity analysis. Changes that occur during goal-setting are therefore not reflected by general activity during encoding, but more likely reflect neural processes directly related to successful or unsuccessful encoding.

Differential Neural Response to Goal-setting in Young and Older Adults

Older adults did not show the predicted differential activation of the OFC or dlPFC in response to goal-setting, as compared to young adults. However, older adults recruited several other regions to a greater extent than young adults to achieve the performance

enhancing effects of goal-setting. Interestingly, there were no regions that exhibited significantly greater activity in young adults in conjunction with goal-setting, as compared to older adults. This result is consistent with the hypothesis that older adults would compensate for the age-related atrophy in the OFC and dlPFC. Each of the regions demonstrating an age by goal-setting interaction was previously shown to be involved in mnemonic processes. Therefore, the overall pattern of differentially greater activation in older adults may reflect greater increases in mnemonic processing that are precipitated by increases in motivation. However, it is also possible that greater activation in these regions in older adults reflects less efficient recruitment of neural resources.

In the encoding-related activity analysis, increases in activity in the prefrontal, temporal and posterior cingulate regions perhaps reflect increased resources committed toward memory encoding processes. Activation in the supplementary motor area could reflect increased subvocal rehearsal of the word list by older adults. The differential increased activity in older adults in the angular gyrus and the supramarginal gyrus may reflect an increased level of focus on reading the words as they are presented. Again, these increases in activation in the above mentioned regions could also represent inefficient recruitment of neural resources in older adults.

It should be noted that activation in all the previously mentioned regions, with the exception of the temporal lobe and angular gyrus, does not reach significance in the subsequent memory analysis. This may indicate that even though the regions are recruited more heavily as compared to young adults, only activations in the angular gyrus and superior temporal gyrus have a genuine impact on subsequent recall performance. Additionally, results from the subsequent memory analysis revealed that older adults

recruit the anterior cingulate and Broca's homologue to a greater extent than young adults, perhaps reflecting increased attention.

The suggestion that the older adults had greater increases in use of mnemonic processes than the young adults as a consequence of goal-setting is consistent with De Jong's goal neglect hypothesis. It has been shown that increasing the challenge to older adults can compensate for difficulties maintaining the context of a cognitive task (e.g. compensate for neglect of salient processes necessary for successful task performance; De Jong, 2001). In the present study, it appears as though the increased challenge provided by goal-setting enabled older adults to generate disproportionately greater focus towards important mnemonic processes for the episodic memory task, which helped them improve their performance levels to that of the young adults not receiving goal-setting.

Potential Limitations

Group membership in the present study was limited to 10 subjects, which gives rise to restricted power. In order to address this power consideration, a fixed-effects analysis approach was utilized for both fMRI and behavioral data. Thus, error variance was estimated on a data point by data point basis for each subject with each data point representing an independent observation. In contrast to a random-effects analysis in which generalizations can be inferred about the population(s) studied, generalizations from the present research must be considered more cautiously.

It is also important to highlight that the goal-setting condition was accompanied by performance feedback, as well as encouraging statements for achieving the goal. The feedback and encouragement was not controlled for in the no-goal group, thus constraining conclusions regarding goal-setting to this context. The ultimate aim of this research is to provide a better understanding of the positive effects of the goal-setting

paradigm utilized in the previously mentioned studies by West et al. (2002, 2003) such that it might be utilized in an applied setting. To this end, goal theory asserts that knowledge of progress toward a goal improves the efficacy of the goal. In regards to the positive encouragement provided, West and colleagues (Dark-Freidman et al., 2004) recently found no memory recall performance differences between individuals receiving positive encouragement and progress feedback with goal-setting and individuals who receive "realistic" feedback in conjunction with goal-setting (e.g., subjects are told whether or not they met their goal and are not given encouragement before goals). Thus, it is unlikely that the encouraging remarks significantly influenced performance outcome.

Another consideration of the present findings worth elucidating is that groups, whether it be the goal and no-goal groups or the young and older adults, demonstrated differential behavioral performance on the memory task that subsequently could result in different cognitive operations being measured. For instance, the comparison of older adults and young adults could be measuring differences between poor encoding and successful encoding, as opposed to age-related changes in encoding activity. This potential confound was addressed, in part, by the subsequent memory analyses performed that correlated recall performance with signal intensity. Even though this analysis takes into consideration changes in signal intensity relative to differential performance, it still does not account for the overall poorer performance in older adults and no-goal groups. Follow-up studies would benefit from a design that allows for only correct responses to be subjected to fMRI analysis. In such a case, direct comparisons can be made between groups relative to the cognitive process of successful encoding.

Findings of the present research should also be considered in the context of important factors related to the use of fMRI in studying aging. The older adults' hemodynamic response to several sensorimotor tasks shows that the neural circuitry of healthy older adults may produce greater noise while keeping the signal at the same level as young adults (Raz, 2000). Consequently, a lower signal-to-noise ratio is observed in the older cohort, and fewer (by a factor of four) pixels on their fMRI images pass the threshold for activation (D'Esposito et al., 1999). When performing a group analysis, an activation focus emerges to the extent that each member of the group exhibits greater activation for one condition relative to another in a particular brain region. In theory, a group of older subjects could have equal spatial extent and intensity of activation as young subjects, but if the older participants were more variable from one to another in the locations of activation, activation in significantly fewer voxels would surpass a statistical threshold. In this case, the group activation would be incorrectly characterized, since greater variability across participants in activation loci would appear as reduced activation (Stebbins et al., 2002).

A further methodological consideration, as previously discussed, is that of differential neurovascular coupling between young and older adults. FMRI does not measure brain activity directly, but changes in blood oxygen level dependent (BOLD) signal that are strongly associated with neural activity (Logothetis, 2001). As this is the case, it gives rise to the possibility that differences between young and older adults may not be due to differences in neural activation, but to secondary factors associated with the BOLD response. The BOLD signal is a reflection of interactions between cerebral blood flow, cerebral blood volume, blood oxygen extraction, and local metabolism that occur as

a consequence of neural activity. The possibility therefore exists that age-associated changes observed in this research could be influenced by age-related changes in vascular processes (D'Esposito et al., 1999, 2003). It is noteworthy that the regions of greatest interest in the present research, the PFC and OFC, experience the steepest trajectory of atrophy of all brain regions in aging (Raz, 2000) and consequently may have a heightened susceptibility to neurovascular changes as well.

These concerns regarding greater intra-group variability in the older adults and differential neurovascular coupling between young and older adults were addressed in part by use of the internal activation standard. Activation occurring in response to the motor task was equivalent between young and older adults. Demonstration of equivalent activation helps to vitiate these concerns; however, it is conceivable that differential neurovascular coupling between young and older adults exists throughout the brain. Nonetheless, a clear absence of activation differences between young and older adults during the motor task (see Figure 3-1) supports the assertion that the findings of the present research do not represent neurovascular coupling differences or intra-group variability differences between young and older adults.

Steps were taken in the data analysis of the present research as well to minimize the concern of intra-group variability and differential neurovascular coupling. An important comparison was that of possible differential responses to goal-setting between young and older adults. Instead of testing for direct group differences in young and older adults who received goals (e.g., young adult/goal subtracted by older adult/goal), a safer approach was used - testing for an age by goal-setting interaction. That is, differences in the

relative activation between no-goal and goal groups within each age group was evaluated rather than a direct comparison between the two groups.

Concluding Remarks

The present research findings are consistent with the left lateralized PFC activation proposed by the HERA model of episodic memory encoding. These findings are also consistent with the proposition of the HAROLD model that this lateralized PFC activation during encoding is suppressed in older adults. Decreased left PFC activation in older adults was accompanied by a poorer performance on the episodic memory task. Previous findings of the improvement of memory performance by goal-setting in young and older adults were replicated here. The use of explicit goals to improve memory performance was, as hypothesized, associated with the dlPFC and the OFC. However, especially in the case of the dlPFC, it remains somewhat unclear as to the extent these regions contribute to increased motivation and/or increased mnemonic processing resulting from increased motivation. Dissociation of these roles may be achieved in future studies by parametrically manipulating the level of motivation, perhaps by differential monetary rewards, and parametrically manipulating the level of challenge in mnemonic processing.

Older adults showed a pattern of differential activation in response to goal-setting, as compared to young adults, that entailed greater recruitment of several regions during encoding. The pattern of activation suggests possible cognitive processes that are producing the beneficial effects of goal-setting. For instance, activation in the anterior cingulate cortex likely underlies greater attentional resources and performance monitoring committed to the list learning task. Activation of Broca's homologue could reflect greater use of strategies. These possibilities could be capitalized upon to refine and

improve behavioral interventions that improve memory. For instance, goal-setting can be combined with attention focusing training and specific strategies, such as rehearsal, to optimize the efficacy of memory training. In addition, regions disproportionately activated in older adults during goal-setting, as well as regions that demonstrated reduced activation during encoding, are potentially promising targets for possible pharmaceutical interventions in normal and clinically significant memory declines.

APPENDIX A
SHIPLEY VOCABULARY TEST

VOCABULARY

On this questionnaire, the first word in each line is printed in capital letters. Opposite it are four other words. Draw a line under the one word which means the same thing, or most nearly the same thing, as the first word. A sample has been worked out for you, with the right answer underlined. If you don't know, guess. Be sure to underline the one word in each line which means the same thing as the first word.

sample:				
LARGE	**red**	**big**		**silent**
wet				
1. TALK	draw	eat	speak	sleep
2. PERMIT	allow	sew	cut	drive
3. PARDON	forgive	pound	divide	tell
4. COUCH	pin	eraser	sofa	glass
5. REMEMBER	swim	recall	number	defy
6. TUMBLE	drink	dress	fall	think
7. HIDEOUS	silvery	tilted	young	dreadful
8. CORDIAL	swift	muddy	leafy	hearty
9. EVIDENT	green	obvious	skeptical	afraid
10. IMPOSTOR	conductor	officer	book	pretender
11. MERIT	deserve	distrust	fight	separate
12. FASCINATE	welcome	fix	stir	enchant
13. INDICATE	defy	excite	signify	bicker
14. IGNORANT	red	sharp	uninformed	precise
15. FORTIFY	submerge	strengthen	vent	deaden

16. RENOWN	length	head	fame	loyalty
17. NARRATE	yield	buy	associate	tell
18. MASSIVE	bright	large	speedy	low
19. HILARITY	laughter	speed	grace	malice
20. SMIRCHED	stolen	pointed	remade	soiled
21. SQUANDER	tease	belittle	cut	waste
22. CAPTION	drum	ballast	heading	ape
23. FACILITATE	help	turn	strip	bewilder
24. JOCOSE	humorous	paltry	fervid	plain
25. APPRISE	reduce	strew	inform	delight
26. RUE	eat	lament	dominate	cure
27. DENIZEN	senator	inhabitant	fish	atom
28. DIVEST	dispossess	intrude	rally	pledge
29. AMULET	charm	orphan	dingo	pond
30. INEXORABLE	untidy	involatile	rigid	sparse
31. SERRATED	dried	notched	armed	blunt
32. LISSOM	moldy	loose	supple	convex
33. MOLLIFY	mitigate	direct	pertain	abuse
34. PLAGIARIZE	appropriate	intend	revoke	maintain
35. ORIFICE	brush	hole	building	lute
36. QUERULOUS	maniacal	curious	devout	complaining
37. PARIAH	outcast	priest	lentil	locker
38. ABET	waken	ensue	incite	placate
39. TEMERITY	rashness	timidity	desire	kindness
40. PRISTINE	vain	sound	first	level

APPENDIX B
WORD LISTS FOR MEMORY TRIALS

Baseline Trial

Tomatoes
Cauliflower
Broccoli
Cucumbers
Roast
Ribs
Bacon
Ham
Mayonnaise
Antacid
Detergent
Hammer
Jelly Beans
Thread
Magazine

Trials 1, 2 and 3

Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7
Tomatoes	Antacid	Thread	Rolls	Broccoli	Pears	Foil
Bacon	Detergent	Cauliflower	Envelope	Salt	Ham	Cologne
Mayonnaise	Hammer	Magazine	Popcorn	Cola	Mop	Pineapple
Pens	Scissors	Roast	Oranges	Bananas	Peanuts	Beer
Cucumbers	Jelly Beans	Eraser	Shampoo	Ribs	Chili	Macaroni
Iron	Cheese	Dog Food	Teaspoon	Razor	Conditioner	Scarf

APPENDIX C
QUESTIONNAIRES

MEMORY QUESTIONNAIRE

DIRECTIONS:

Different people use their memory in different ways in their everyday lives. For example, some people make shopping lists, whereas others do not. Some people are good at remembering names, whereas others are not.

In this questionnaire, we would like you to tell us how you use your memory and how you feel about it. There are no right or wrong answers to these questions because people are different. Please take your time and answer *each* of these questions to the best of your ability.

Each question is followed by five choices. Draw a circle around the number corresponding to your choice. Mark *only* one number for each statement.

For example:

My memory will get worse as I get older.	1. agree strongly 2. agree 3. undecided 4. disagree 5. disagree strongly

In this example you could, of course, choose any one of the answers. If you agree strongly with the statement you would circle the "1." If you disagree strongly you would circle the "5." The answers of "2" and "4" indicate less strong agreement or disagreement. The "3" gives you a middle choice, but don't use the "3" unless you really can't decide on any of the other responses.

Keep these points in mind:

Answer *every* question, even if it doesn't seem to apply to you very well. Answer as honestly as you can what is true for *you*. Please do not mark something because it seems like the "right thing to say."

		Agree Strongly	Agree	Undecided	Disagree	Disagree Strongly
1.	It is important to me to have a good memory.	1	2	3	4	5
2.	I have little control over my memory ability.	1	2	3	4	5
3.	I think a good memory is	1	2	3	4	5

something of which to be proud.					
4. I find it harder to remember things when I am upset.	1	2	3	4	5
5. I get anxious when I am asked to remember something.	1	2	3	4	5
6. It bothers me when others notice my memory failures.	1	2	3	4	5
7. My friends often notice my memory ability.	1	2	3	4	5
8. I am usually uneasy when I attempt a problem that requires me to use my memory.	1	2	3	4	5
9. I know if I keep using my memory I will never lose it.	1	2	3	4	5
10. Having a better memory would be nice but it is not very important.	1	2	3	4	5
11. It doesn't bother me when my memory fails.	1	2	3	4	5
12. I can't expect to be good at remembering zip codes at my age.	1	2	3	4	5
13. I get upset when I cannot remember something.	1	2	3	4	5
14. I think it is important to work at sustaining my memory abilities.	1	2	3	4	5
15. I work hard at trying to improve my memory.	1	2	3	4	5
16. If I am put on the spot to remember names, I know I will have difficulty doing it.	1	2	3	4	5
17. I admire people who have good memories.	1	2	3	4	5
18. I have difficulty remembering things when I am anxious.	1	2	3	4	5
19. I would feel on edge right now if I had to take a memory test or something similar.	1	2	3	4	5
20. I often notice my friends' memory ability.	1	2	3	4	5

21. As long as I exercise my memory it will not decline.	1	2	3	4	5
22. I feel jittery if I have to introduce someone I just met.	1	2	3	4	5
23. It's important that I am very accurate when remembering names of people.	1	2	3	4	5
24. When I am tense and uneasy at a social gathering, I cannot remember names very well.	1	2	3	4	5
25. I'm highly motivated to remember new things I learn.	1	2	3	4	5
26. It's up to me to keep my remembering abilities from deteriorating.	1	2	3	4	5
27. When someone I don't know very well asks me to remember something, I get nervous.	1	2	3	4	5
28. Even if I work on it, my memory ability will go downhill.	1	2	3	4	5
29. I get anxious when I have to do something I haven't done for a long time.	1	2	3	4	5
30. It bothers me when I forget an appointment.	1	2	3	4	5
31. I like to remember things on my own, without relying on other people to remind me.	1	2	3	4	5
32. I get tense and anxious when I feel my memory is not as good as other people's.	1	2	3	4	5
33. It's important that I am very accurate when remembering significant dates.	1	2	3	4	5
34. I do not get flustered when I am put on the spot to remember new things.	1	2	3	4	5
35. I would feel very anxious if I visited a new place and had to remember how to find my way back.	1	2	3	4	5
36. No matter how hard a person works on his memory, it cannot be	1	2	3	4	5

	improved very much.				
37.	If I were to work on my memory I could improve it.	1	2	3	4	5
38.	It gives me great satisfaction to remember things I thought I had forgotten.	1	2	3	4	5
39.	I think a good memory comes mostly from working at it.	1	2	3	4	5

QUESTIONS ABOUT RECENT MEMORY PERFORMANCE

On this page, there are some questions asking for your opinions. To answer each question, you should circle the number that best indicates your opinion. Please read each question carefully before you decide how to answer. There are no right or wrong answers on these questions.

First, do the EXAMPLE:

Please give us your opinion about the weather.
What do you think about the weather outside today?

1	2	3	4	5	6	7
Wonderful						Horrible

QUESTIONS ABOUT RECENT MEMORY PERFORMANCE

1. How important has it been to you to perform well on memory activities in your everyday life?

1	2	3	4	5	6	7
Not at all Important					Very Important	

2. How have you performed on most memory tasks you have done recently?

1	2	3	4	5	6	7
Very Poor					Very Good	

3. How do you think your memory compares with most other people your age?

1	2	3	4	5	6	7
Much worse					Much better	

4. How satisfied are you with your recent memory performance?

1	2	3	4	5	6	7
Very unsatisfied					Very satisfied	

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

1. I feel calm
2. I feel secure
3. I am tense
4. I feel strained
5. I feel at ease
6. I feel upset
7. I am presently worrying over possible misfortunes
8. I feel satisfied
9. I feel frightened
10. I feel comfortable
11. I feel self-confident
12. I feel nervous
13. I am jittery
14. I feel indecisive
15. I am relaxed
16. I feel content
17. I am worried
18. I feel confused
19. I feel steady
20. I feel pleasant

PARTICIPANT INFORMATION

Please give us the following information about yourself.

1. Your date of birth: _____

2. Sex (circle one): male female

3. Marital status (circle one): single married separated divorced widowed

4. Race: _____

5. Current job status (circle all that apply): work full-time work part-time retired student

Occupation and/or job position that you held for the longest time (please describe):

6. Total years of education, beginning with Grade 1: _____

Highest educational degree or diploma that you hold: _____

7. Health: Circle one number below to indicate how healthy you are in general:

1	2	3	4	5	6	7	8	9	10
Excellent health									Very poor health

8. Have you been hospitalized in the last 5 years? (circle one) YES NO

If YES, please describe the reason(s) for each hospitalization (if needed, you can use more space on the back of this page):

9. Please list any medications you take regularly. If you do not take any medications, write “none.” If you do take something regularly, please give the names of the medications and describe your reason for taking each one. If you do not know the names, just list the reason. For example -- "I take 2 pills each day for high blood pressure." (if needed, you can use more space on the back of this page)

GOAL REVIEW SHEET

The experimenter gave you a goal. Please indicate how you feel about this goal.

---

1. I am committed to achieving this goal.

1	2	3	4	5	6	7
Strongly agree					Strongly disagree	

2. It is realistic to expect me to reach this goal.

1	2	3	4	5	6	7
Yes, I can reach it easily					No, I will never reach it	

3. The goal for me should be changed.

1	2	3	4	5	6	7
Strongly agree					Strongly disagree	

4. I will make an effort to reach this goal.

1	2	3	4	5	6	7
No, I won't make any effort					Yes, I will put forth maximum effort	

5. It is important to me to achieve this goal.

1	2	3	4	5	6	7
Strongly agree					Strongly disagree	

6. I will never be able to reach this goal.

1	2	3	4	5	6	7
Strongly agree					Strongly disagree	

7. This goal is personally meaningful to me.

1	2	3	4	5	6	7
Strongly agree					Strongly disagree	

8. I am motivated to reach the goal.

1	2	3	4	5	6	7
Yes, highly motivated					Not at all motivated	

QUESTIONS

Please circle the answer that best represents your opinion for each question.

---

1. If you had an opportunity to work on another memory list today, to try to improve your performance, would you want to do it?

1	2	3	4	5	6	7
Definitely would try					Definitely would not try	

2. How difficult were the memory tasks that you completed today?

1	2	3	4	5	6	7
Very difficult					Very easy	

3. How much effort did you make on the memory tasks today?

1	2	3	4	5	6	7
Very high effort					No effort at all	

4. Did you achieve your goals today?

1	2	3	4	5	6	7
Definitely					Definitely not	

5. How satisfied are you with your memory performance today?

1	2	3	4	5	6	7
Highly satisfied					Highly dissatisfied	

APPENDIX D
STRATEGY USE QUESTIONNAIRE

Techniques or Strategies for Recalling a Shopping List

Some people are able to use special techniques to help them to remember. Here is a long list of many memory techniques that could be used. You may have concentrated on the words while you were studying, and did not do anything else. Or you may have tried many different strategies to try to improve your score. Either way is fine. We are interested only in finding out exactly what you did while you were studying.

Please place a checkmark by all of the methods that you used while you were studying the shopping lists.

---

1. _____ I concentrated and paid attention to each word.

2. _____ I thought about how I might make a meal out of some items (e.g., "eggs, cereal, orange juice are my breakfast").

3. _____ I repeated single words over and over to myself (e.g., "peas," "peas," "peas," "peas").

4. _____ I repeated groups or sets of words over and over to myself (e.g., "pears, pizza, bags," "pears, pizza, bags," "pears, pizza, bags").

5. _____ I grouped items together in my mind into categories (e.g., meats, beverages, and fruits were grouped).

6. _____ I put together items in my mind that began with the same letter of the alphabet.

7. _____ I put together items that a person might use together in daily life (e.g., use a hammer, pencil, and nail to mount a picture frame in a certain place).

8. _____ I made up sentences or stories to connect the items (e.g., "the candy apple was on a plate pierced by a fork."

9. _____ In my mind, I pictured each individual item.

10. _____ In my mind, I pictured sets of items together (e.g., sugar in a bowl with a spoon).

11. _____ In my mind, I pictured items interacting in an active video (e.g., the coffee is being poured into the mug, with milk, and a chocolate drop).

12. _____ I connected the first letters of the items (e.g., "HOT reminds me of Honey, Onion, T-shirt").

13. _____ I thought about where the items are located in the grocery store where I usually shop.

14. _____ I looked away from the list and tested myself to see how many items I could recall.

15. _____ Other method: please describe

Now go back through and review the list of things you checked.
Circle the 1 or 2 methods that you used the most often for remembering.

APPENDIX E
TISSUE-AIR INTERFACE SIGNAL DROP OFF

Regions that border tissue-air interfaces, such as the orbitofrontal cortex, experience field inhomogeneities that result in signal loss and mismapping artifacts. The orbitofrontal cortex borders the orbito sinus and the auditory meatus, creating susceptibility artifacts at the tissue-air interfaces. Figure F-1 shows the degree of signal loss in the echo planar (functional) scans as compared to the high resolution (MPRAGE) structural image, both in the same 3-D orientation in an example subject.

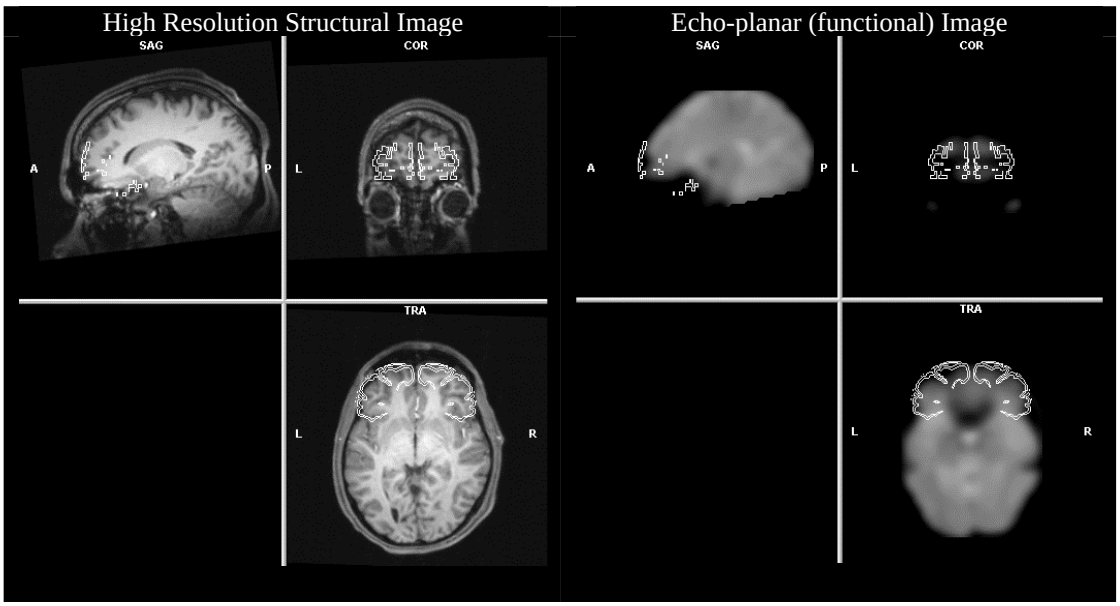

Figure E-1. Illustration of signal drop off in portions of the orbitofrontal cortex in a single subject. The white highlighted area depicts Brodmann's area 10 and 47 for purposes of anatomical reference and image comparison. Considerable signal loss is observed in ventral and anterior portions of the orbitofrontal cortex.

APPENDIX F
GLASS BRAIN ILLUSTRATIONS

DESCRIPTION OF GLASS BRAIN ILLUSTRATIONS

"Glass-brain" illustrations of the primary statistical analyses visualize activated regions in 3-dimentional space. Glass brain depictions are constructed using a wire mesh outline of the brain and red-green stereo coloring of activated regions in efforts to better visualize activated regions in 3-dimentional space. Directionality of effect is not represented in the figures. Presentation of the glass brain illustrations follow the order in which the statistical analyses were presented in the *Results* chapter: 1) effect of age on encoding, 2) effect of goal-setting on encoding, and 3) the interaction of age and goal-setting in encoding. Statistical threshold for glass brain figures are $P < 0.01$, Bonferroni corrected, and 80 contiguous voxels, unless otherwise noted.

Age Effects on Encoding-related Activity

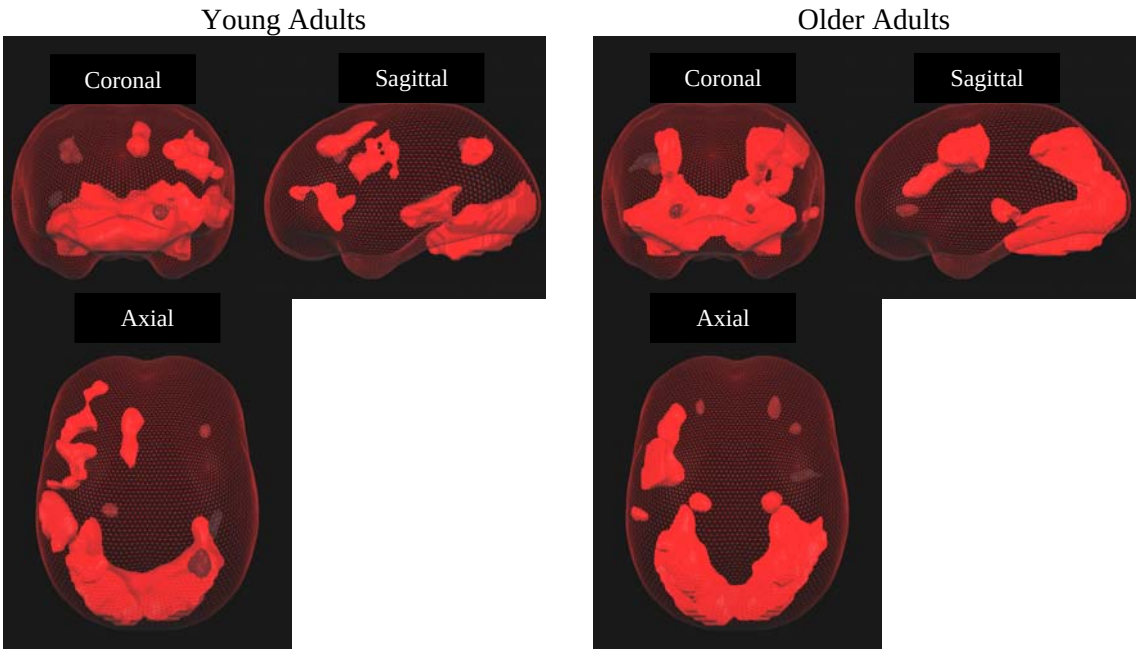

Figure F-1. Glass-brain representation of regional activations during encoding in older and young adults.

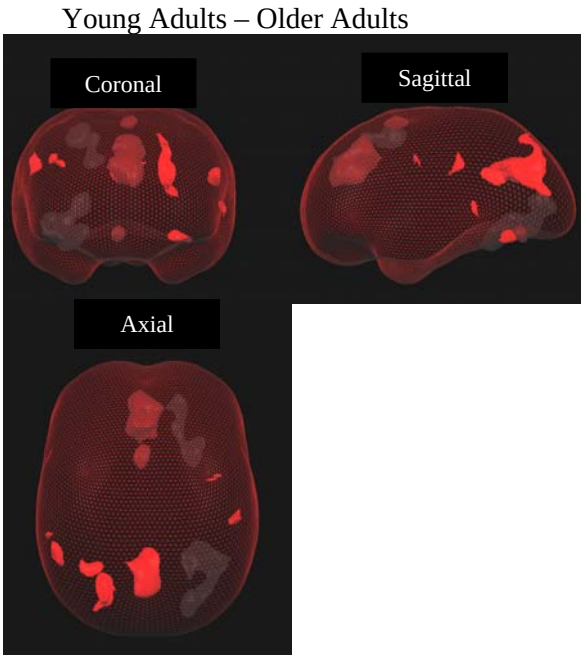

Figure F-2. Glass-brain representation of the regions showing significantly different activation between young and older adults during encoding.

Age Effects on Subsequent Memory

Young Adults Older Adults

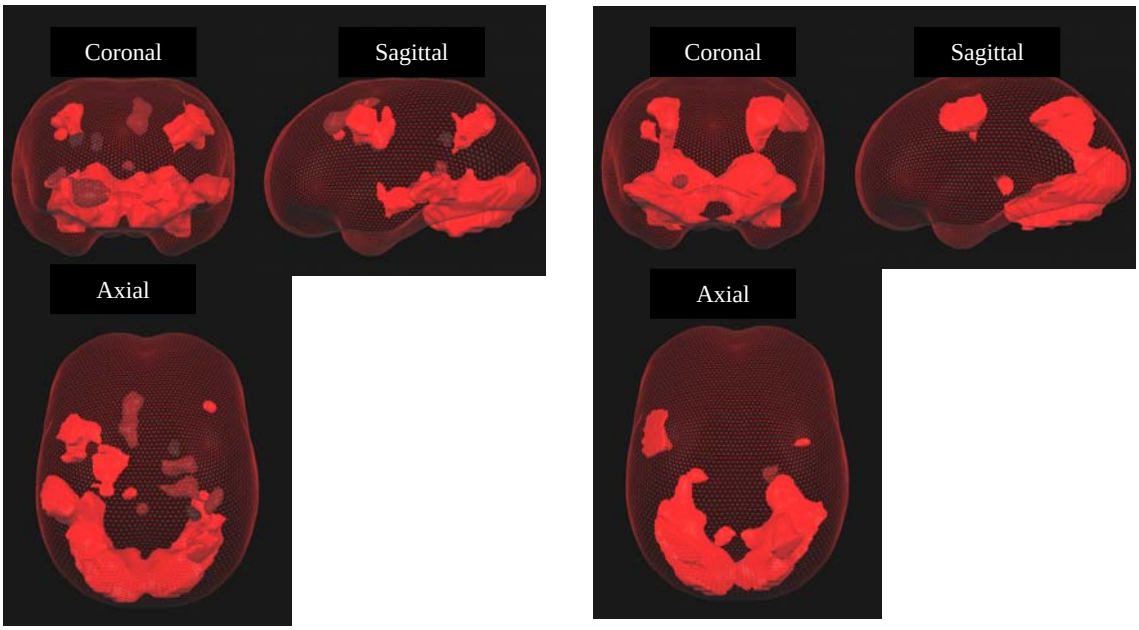

Figure F-3. Glass-brain representation of encoding activity correlated with subsequent recall performance in young and older adults.

Young Adults – Older Adults

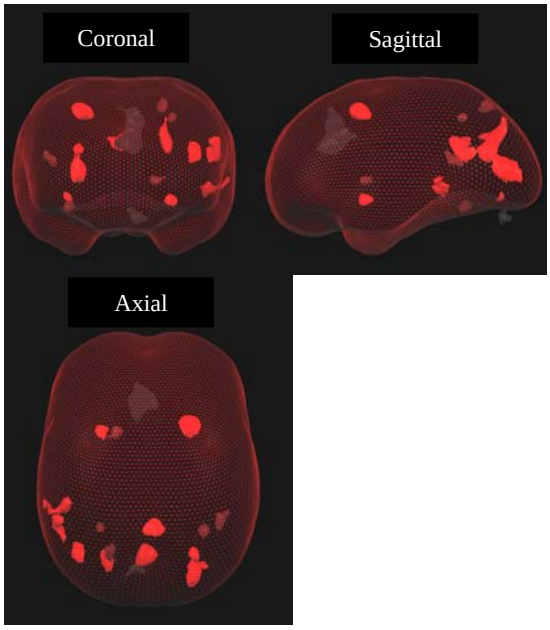

Figure F-4. Glass-brain representation showing significant differences between young and older adults for encoding activity correlated with subsequent recall performance.

Goal-setting Effects on Encoding

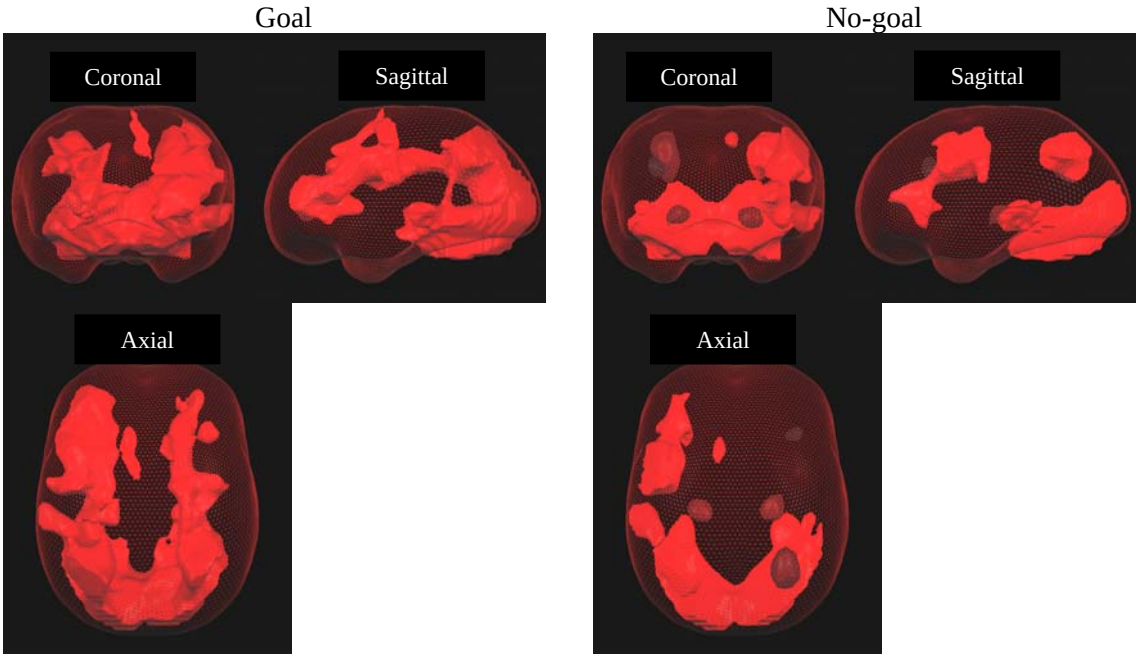

Figure F-5. Glass-brain representation of regional activations during encoding in goal and no-goal groups ($P < 0.001$, corrected; minimum threshold of 250 contiguous voxels). Due to the extensive activation observed in goal and no-goal groups, it was necessary to set the threshold, for viewing purposes only, higher for these two groups than the statistical threshold used for all other statistical maps and tables. The extensive activation is a consequence of increased power and use of the fixed-effects analysis. These analyses are conducted with 20 subjects per group, as compared to the age analyses, which contained 10 subjects per group. It should be noted that the contrast glass brain statistical maps for goal and no-goal groups (e.g., goal – no-goal) employs the other statistical threshold ($P < 0.01$, corrected; 80 contiguous voxels).

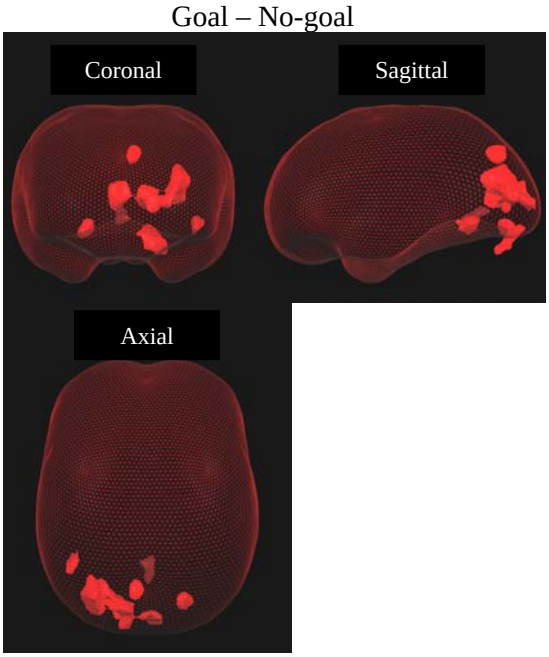

Figure F-6. Glass-brain representation of the regions showing significantly different levels of activation between goal and no-goal groups during encoding.

Goals-setting Effects for Subsequent Memory

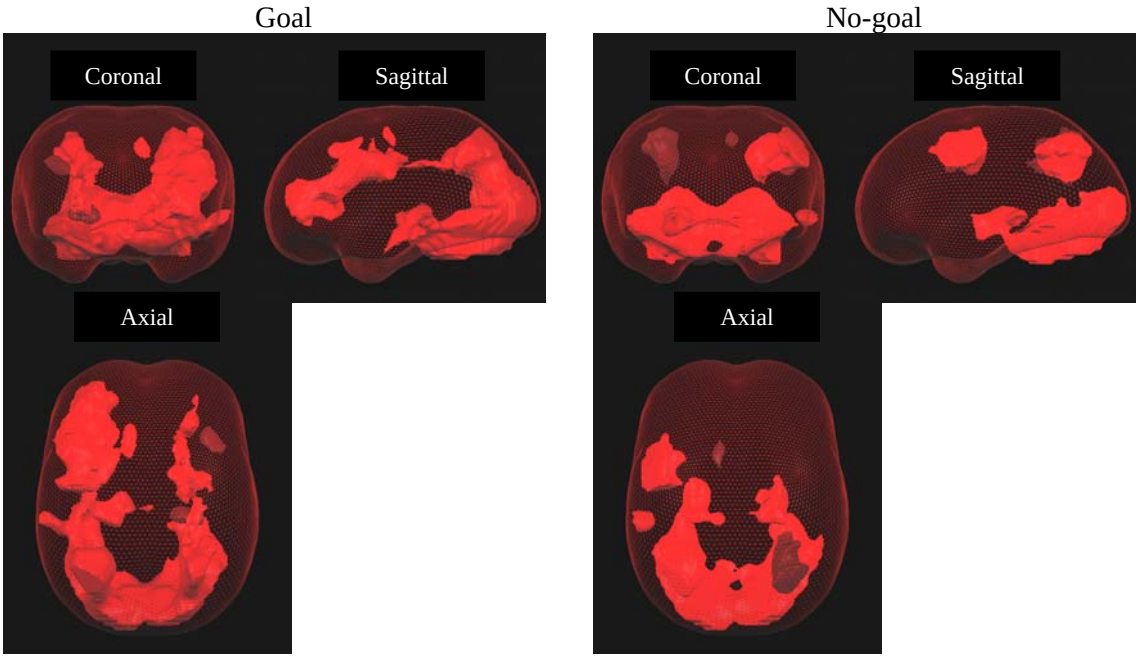

Figure F-7. Glass-brain representation of encoding activity correlated with subsequent recall performance in goal and no-goal groups ($P < 0.001$, Bonferroni corrected; minimum threshold of 250 contiguous voxels).

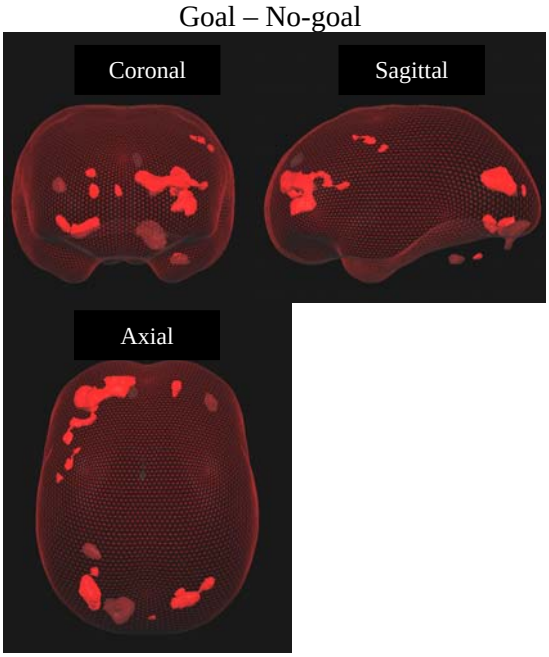

Figure F-8. Glass-brain representation showing significant differences between goal and no-goal groups for encoding activity correlated with subsequent recall performance.

Interaction of Goal-setting and Age

Age x Goal-setting

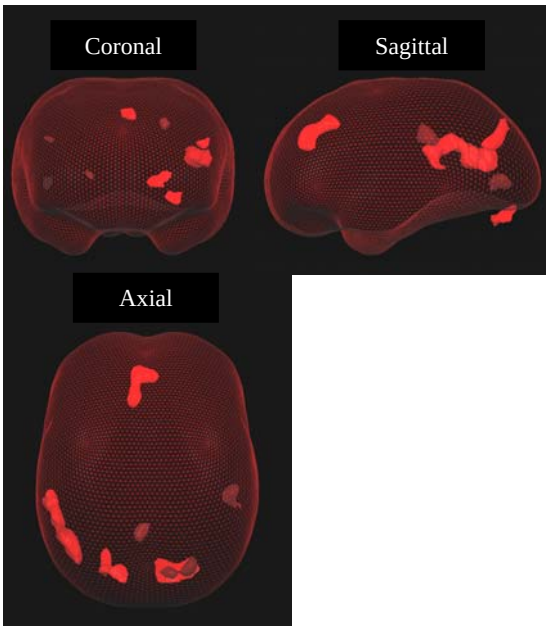

Figure F-9. Glass-brain representation of regions showing a significant interaction between age and goal-setting during encoding.

Interaction of Goal-setting and Age for Subsequent Memory

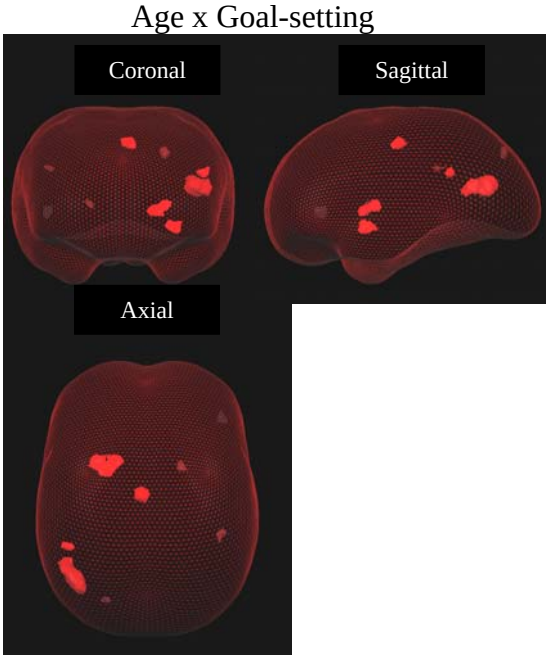

Figure F-10. Glass-brain representation of regions showing a significant interaction between age and goal-setting for encoding activity that was correlated with subsequent recall performance.

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BIOGRAPHICAL SKETCH

Michael Cole graduated with honors from the University of Colorado, Boulder, in 1996 majoring in psychology. Michael continued his studies at the University of Colorado, Boulder, obtaining a master's degree in behavioral neuroscience in 1999. He began his predoctoral training at the University of Florida in 2000 in clinical psychology with focuses on clinical neuropsychology and cognitive neuroscience. Michael pursued his interest in executive functions and affective/motivational influences on cognition in aging and in traumatic brain injury populations using neuroimaging and neuropsychological research techniques. Michael will continue his training at the University of California Los Angeles Clinical Psychology Internship Program in the clinical neuropsychology track.