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MOTIVATIONAL INCENTIVES ENHANCE TOP-DOWN MODULATION OF VISUAL SPATIAL ATTENTION IN HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT BUT NOT PROBABLE ALZHEIMER'S DISEASE

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ABSTRACT

Motivational Incentives Enhance Top-Down Modulation of Visual Spatial Attention in Healthy Aging and Mild Cognitive Impairment but not Probable Alzheimer's Disease

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The goal of this dissertation was to examine the influence of motivational incentives on visual spatial attention in patients with probable Alzheimer's Disease (PRAD), patients with mild cognitive impairment (MCI) and healthy age-matched control subjects (EC). Specifically, I compared the ability of monetary incentives to influence behavioral and neural performance on a covert visual spatial attention task while participants were scanned using functional magnetic resonance imaging (fMRI). A volumetric MRI study was also conducted to test for potential group differences in brain atrophy. The results from the experiments presented in this dissertation reveal that: 1) motivational incentives can influence top-down modulation of visual spatial expectancy in EC and MCI, but not PRAD; 2) the enhancement of spatial expectancy by incentives is regulated by the PCC in the EC and MCI subject groups; 3) disengaging attention is specifically impaired in the PRAD population; 4) EC, but not MCI or PRAD subjects can disengage and reorient attention quicker when incentives are present; 5) the OFC controls the influence of motivation on disengagement; and 6) hippocampal atrophy and the associated memory impairments in the PRAD group may account for the inability of monetary incentives to enhance spatial attention in this population. I conclude that monetary incentives are effective in motivating elder controls and MCI subjects to enhance visual spatial attention processes and that the PCC and OFC areas responsible for this enhancement are the same as those in young adults.

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CHAPTER 1: GENERAL INTRODUCTION

1.1 Selective Visual Spatial Attention

In daily life, what we perceive depends on where we direct our attention. Despite the large amount of information in our environment, attention allows us to focus so that only relevant events enter awareness. Attention acts in all sensory modalities; however, the focus of this dissertation will be on visual spatial attention. Visual spatial attention is the ability to focus on a specific event while avoiding distractions and shifting attentional awareness from one focal point in the visual field to another according to internal needs and past experiences (Mesulam, 2000). Visual attention can be directed towards external sensory stimuli via bottom-up processes (exogenous orienting) or via internal thoughts and feelings by top-down processes (endogenous orienting).

1.1.1 Exogenous Orienting

Exogenous orienting is a bottom-up process driven by the features of a stimulus. The sensory stimulus is either unexpected or different from its background and therefore captures attention automatically. A fire alarm is an example of a sudden, unexpected stimulus that grabs attention. In this case, the emotional relevance of the stimulus is important. Bottom-up mechanisms also regulate attention to distinctive stimuli such as a red tulip in a field of green grass, which is detected quicker than a red tulip in a field of colored flowers. The distinctiveness and unexpectedness of an exogenous stimulus determines how fast attention is shifted towards it (Duncan et al., 1992).

Exogenous orienting is usually accompanied by an overt eye movement towards the stimulus (referred to as a saccade). Saccadic eye movements were first studied in nonhuman primates using neurophysiological recordings (Goldberg et al., 1972; Lynch et al., 1977; Goldberg et al., 1981; Petersen et al., 1987). The bottom-up mechanisms of exogenous orienting have also been studied in normal subjects using a task developed by Posner and colleagues that examined the relationship between attention shifts and eye movements (Posner, 1980). The task included a one degree clear box that was used as the central fixation point. A similar box was used as the peripheral exogenous cue and appeared eight degrees either to the left or right of fixation after a variable inter-trial interval (ITI). The subjects were asked to respond to a target stimulus (black circle) that appeared either in the fixation box or the peripheral box with equal probability. The results showed that subjects responded faster to the target stimulus when it was presented in the exogenously cued peripheral box compared with the fixation box. The reaction time benefits were explained to have occurred due to attention shifts preceding eye movements. After the peripheral cue appeared, subjects shifted attention towards that location so that if the target appeared there, they were quickly able to make a saccade and detect it. If, on the other hand, the target appeared in the central fixation box, the previous attention shift would not benefit target detection and would not be accompanied by a saccade. These results provided evidence for attention shifts to precede eye movements and their independent processes.

Recent neuroimaging studies have shown that a salient unexpected stimulus attracts attention by engaging bottom-up processes in the tempero-parietal junction (TPJ) and inferior frontal gyrus (IFG) (Corbetta et al., 2000; Corbetta et al., 2002). This ventral fronto-parietal network is modulated by target detection and is thought to be strongly lateralized to the right

hemisphere. These findings will be discussed in more detail below in the section on the spatial attention network.

1.1.2 Endogenous Orienting

Endogenous orienting is regulated by top-down processes that selectively allocate attentional resources to a specific location for further processing in the service of goal-directed behavior. In this case, the cue provides information about the most likely location at which a target will appear. The top-down information from the cue is used to bias attention towards that location. For example, while searching for a friend in a crowd, remembering that your friend likes to sit near fountains will orient attention to that location. During this real life visual search, attention shifts are accompanied by overt saccadic eye movements. In the laboratory, attention shifts can be studied in the absence of saccades; referred to as covert shifts of attention. The Posner exogenous orienting paradigm described above was modified to present cues at the center of fixation so that they provided endogenous information about the location of the subsequent target without requiring a saccade (Posner, 1980). The cue was either an arrow pointing to the left or right of fixation or a plus-sign that provided no directional information. The target was a solid black box that appeared either to the left or right of fixation. The subjects were required to maintain fixation in the center and learned that the cue correctly predicted the location of the target most of the time (80%). The researchers were interested in measuring the benefits from knowing where the target would occur (valid trials), and the costs when the target occurred at an unexpected location (invalid trials). They found that the costs and benefits in reaction time were roughly the same magnitude (although different direction) when compared to non-directional trials. The valid directional cue caused a covert attentional shift so the valid target was detected

faster compared with the target following the non-directional cue, referred to as the validity effect. The invalid target required attention to be reoriented to the new location, so the invalid target was detected slower than the target following the non-directional cue, referred to as the invalidity effect. Both valid and invalid trials required attention to be shifted and then engaged at the target, however, the invalid trials also required attention to be disengaged. Posner concluded that orienting attention to an unexpected stimulus requires three mental operations: 1) disengagement of attention from its current location, 2) movement of attention to the target, and 3) engagement of attention at the target (Posner et al., 1984).

1.2 Neural Network for Visual Spatial Attention

Early evidence for a network of brain regions controlling visual spatial attention came from patients who demonstrated deficits in orienting attention within space, a phenomenon termed neglect. Neglect has been shown to occur more often after lesions in the right hemisphere and Mesulam suggested that this is because the left hemisphere shifts attention in the contralateral hemispace, while the right hemisphere distributes attention more evenly in both hemispaces and in both directions (Mesulam, 1981). Patients with unilateral neglect tend to ignore objects in their left extrapersonal space, especially if there is competing stimuli in the right hemispace. For example, he reported that some patients only eat the food on the right side of their plate, or only write on the right side of a piece of paper (Mesulam, 1981). Neglect has been shown to occur most often after lesions in the parietal lobe, but can also occur after lesions in the frontal lobes, cingulate gyrus, or thalamus (Nobre et al., 1999). Experiments with rhesus monkeys have demonstrated that each of these areas makes a specific contribution to the neural organization of spatial attention and that together they form an interconnected network for

selective attention (Mesulam, 1981) (see Figure 1). Numerous functional neuroimaging studies have also been used to examine this network (Posner et al., 1994; Nobre et al., 1997; Corbetta, 1998; Gitelman et al., 1999; Kim et al., 1999); however, evidence for right hemisphere dominance in spatial attention is less conclusive.

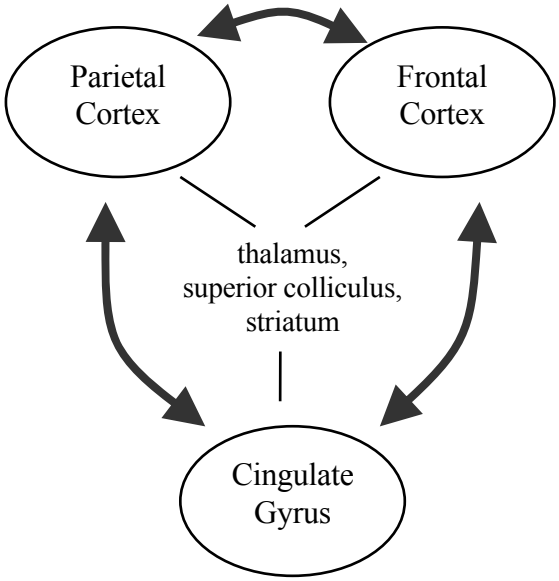

Figure 1. The network for spatial attention includes the parietal, frontal, and cingulate cortices. These areas are interconnected with each other and to subcortical regions in the thalamus, superior colliculus, and striatum. (reproduced with permission from (Mesulam, 1999)).

1.2.1 Posterior Parietal Lobe

Lesions in the posterior parietal lobe have long been shown to cause deficits in attention, the most common being unilateral neglect after right parietal damage (Mesulam, 1981). Bilateral parietal lesions are associated with a severe form of neglect, termed Balint's syndrome. This condition causes an impairment of shifting attention in the entire visual field and an inability to perceive more than one object at a time (Verfaellie et al., 1990).

The human posterior parietal lobe consists of four areas; the superior and inferior parietal lobes, the intraparietal sulcus (IPS) and the medial parietal cortex (Nobre et al., 1999). The posterior parietal region is located at the convergence of visual, auditory, somatosensory, and vestibular unimodal areas and participates in multimodal integration (Mesulam, 1981).

Experiments in rhesus monkeys have shown that the parietal lobe is also interconnected with the premotor cortex, frontal eye fields (FEF), superior colliculus, cingulate gyrus, insula, and orbitofrontal cortex (OFC) (Mesulam et al., 1977; Barbas et al., 1985; Morecraft et al., 1992). The monkey parietal lobe consists of the same divisions as the human parietal lobe, however, the IPS is further subdivided into lateral, medial, ventral, anterior, and posterior regions (Sakata et al., 1997). The human IPS is also subdivided into similar regions, however the lateral and posterior segments appear more medially in humans (Grefkes et al., 2005). Despite the differences in anatomy between species (Rushworth et al., 2001), the behavioral modulation of visuospatial attention is relatively similar.

1.2.1.1 Intraparietal Sulcus

Electrophysiological studies in rhesus monkeys have suggested that the IPS and area 7 of the parietal lobe are associated with shifting the attentional focus. Neurons in these regions have been shown to increase firing during covert attention (Petersen et al., 1987), specifically when the target appears in a different spatial location from the cue (Petersen et al., 1987). Functional imaging experiments have confirmed this association. During tasks of covert visuospatial attention, activity has been observed in the superior and inferior parietal lobes as well as the IPS (Nobre et al., 1997; Gitelman et al., 1999; Kim et al., 1999; Hopfinger et al., 2000; Vandenberghe et al., 2001). Additional neuroimaging studies have demonstrated that the IPS is specifically active when attention is voluntarily shifted to a particular location in space using a cue (Corbetta et al., 2000; Corbetta et al., 2002; Kincade et al., 2005; Hahn et al., 2006). These studies suggest that the IPS plays an important role during top-down modulation of spatial attention when attention is shifted voluntarily.

1.2.1.2 Tempero-Parietal Junction

Functional neuroimaging studies using the Posner attention task have demonstrated that the tempero-parietal junction (TPJ), encompassing the inferior parietal lobule (IPL) along the supramarginal gyrus (SMG), and the superior temporal gyrus (STG) are involved in reorienting attention within space; especially during invalidly cued trials when the target appears at an unattended location (Corbetta et al., 2000; Corbetta et al., 2002; Thiel et al., 2004; Kincade et al., 2005; Hahn et al., 2006; Vossel et al., 2006). Some studies have suggested that the TPJ is specifically involved in reorienting attention (Thiel et al., 2004; Kincade et al., 2005; Vossel et al., 2006) while other studies have suggested that this region is specific for detecting targets at unexpected locations (Corbetta et al., 2000; Corbetta et al., 2002; Hahn et al., 2006). Moreover, patients with lesions in the TPJ were unable to detect targets in the contralesional visual field, especially if they were cued to the ipsilesional visual field (Friedrich et al., 1998) . Whether the TPJ plays a specific role in reorienting attention or target detection is unclear, however, these studies demonstrate its importance during bottom-up modulation of attention to unexpected salient stimuli.

1.2.1.3 Summary

The parietal lobe plays a fundamental role in both top-down and bottom-up modulation of selective attention processes. Early lesion studies have shown that parietal damage results in the inability to direct attention to the contralesional visual field especially if attention needs to be disengaged from the ipsilesional hemifield (Posner et al., 1984; Rafal et al., 1987). A more recent lesion study has shown that damage in the TPJ causes an inability to detect targets even when correctly cued to their location (Friedrich et al., 1998). The role of the TPJ in detecting

targets at unattended or unexpected locations has been confirmed with neuroimaging studies that report its activation during invalidly cued targets (Corbetta et al., 2000; Corbetta et al., 2002; Hahn et al., 2006). Valid cues, on the other hand, are used to shift attention to the appropriate location and this has consistently been associated with IPS activity (Gitelman et al., 1999; Corbetta et al., 2000; Corbetta et al., 2002; Kincade et al., 2005; Hahn et al., 2006). These studies demonstrate that the IPS is responsible for shifting attention in a top-down fashion, while the TPJ is associated with orienting in a bottom-up manner.

1.2.2 Frontal Lobe

Neglect, the inability to direct attention within space, can also occur after lesions in the frontal cortex (Mesulam, 1981; Nobre et al., 1999; Mort et al., 2003). Lesions in the dorsal part of the inferior frontal gyrus (IFG) have been shown to cause an impairment in shifting attention (Mort et al., 2003). Neuroimaging studies have confirmed this association and demonstrated that the IFG is particularly active when subjects needed to reorient attention to an unattended location (Corbetta et al., 2002).

1.2.2.1 Orbitofrontal Cortex

A more medial and ventral region of the prefrontal cortex around the orbital sulcus, defined as the orbitofrontal cortex (OFC) was found to be active when stimulus contingencies changed and subjects needed to redirect their attention to respond to these changes (Nobre et al., 1999). OFC activity was greatest during invalidly cued trials when attention needed to be disengaged and reoriented. The authors concluded that the OFC is important for identifying and responding to breaches of expectation by interacting with the neural systems that direct attention. A more recent neuroimaging study has confirmed that the OFC is specifically active during

invalidly cued trials when generating spatial expectancy does not benefit target detection and attention needs to be redirected to the correct location (Small et al., 2005).

OFC involvement in attention processes is further enhanced during high incentive conditions. Single-cell recording studies in monkeys have demonstrated increased activity in prefrontal cortex regions during reward-related behavior (Watanabe et al., 2002), while lesion studies have demonstrated that patients can predict reward without a prefrontal cortex but are unable to correct their behavior when predictions are violated (Knutson et al., 2005). Both of these studies reported the involvement of the prefrontal cortex in reward-related behavior, but did not specify whether the region involved included the OFC or IFG. A neuroimaging study conducted by Elliott and colleagues revealed that the OFC, but no other prefrontal region, was more likely to be activated when the problem of what to do next was resolved by taking into account the reward value of a stimulus rather than its identity or location (Elliott et al., 2000). These results suggest that the OFC is involved in decision making when emotional influences are present. Damasio and colleagues confirmed these findings by examining patients with OFC lesions on a gambling task that modeled real life conditions (Bechara et al., 2000). They found that patients with such lesions made choices that yielded high immediate gains, despite the possibility of getting higher future losses (Bechara et al., 2005). The authors concluded that these patients were insensitive to future consequences, whether positive or negative, and were primarily guided by immediate reward. In summary, these findings suggest that the OFC plays an important role in decision making when expectations are violated and need to be corrected (as in the case of invalidly cued trials) or when incentives are involved in the decision making process.

1.2.2.2 Frontal Eye Fields

Experiments with alert, behaving monkeys have shown that shifting attention causes an increase of neuronal firing in the frontal eye fields (FEF) (Goldberg et al., 1981), a region located at the intersection of the superior frontal sulcus and precentral sulcus (Paus, 1996). Moreover, lesions in the FEF of both humans and monkeys are associated with symptoms of neglect, specifically the inability to make saccades to, or in, the contralesional hemispace (Mesulam, 1981; Nobre et al., 1999). These studies suggested that the FEF plays an important role in both attention shifts and eye movements. However, electrophysiological recordings in monkey FEF revealed neuronal firing during overt saccadic eye movements, but not covert shifts of attention (Goldberg et al., 1981) raising the possibility that this region is important for eye-movements rather than attention. This conflict was resolved with evidence from more recent neuroimaging studies that demonstrated the importance of the FEF during attention shifts, whether or not they were accompanied by saccades (Gitelman et al., 1999; Nobre et al., 2000). Visual search tasks requiring subjects to use a cue to shift attention throughout the visual field using eye movements have reported FEF activity as well (Gitelman et al., 2002). Other studies that have examined both covert and overt shifts of attention have reported activity in overlapping regions of the FEF (Nobre et al., 1997; Kim et al., 1999), however, direct comparison between the FEF areas associated with attention shifts versus eye movements has revealed FEF activity that is specific to covert attention shifts (Nobre et al., 2000). These results demonstrate that the FEF plays an important role in selective visual spatial attention processes, specifically during attention shifts that may or may not be accompanied by eye movements.

1.2.3 Cingulate Gyrus

The cingulate gyrus is thought to be the most important limbic component of the spatial attention network because of its strong monosynaptic connections with the parietal lobe and FEF (Mesulam et al., 1977; Barbas et al., 1985). The cingulate plays a major role in directing attention by sending information about the behavioral relevance of extrapersonal events to other regions of the spatial attention network (Mesulam, 1999). Neglect associated with cingulate damage provides further evidence for the role of the cingulate in spatial attention. Cingulate lesions have been shown to impair the ability to voluntarily shift attention to motivationally relevant events (Mesulam, 1981).

The cingulate cortex has functionally distinct anterior and posterior subregions. Single unit recordings in monkeys have demonstrated that each component modulates attention somewhat differently (Bush et al., 2002). While neurons in the anterior cingulate cortex (ACC) fire when attention remains focused, neurons in the posterior cingulate cortex (PCC) fire when eye movements are monitored (Bush et al., 2002).

1.2.3.1 Anterior Cingulate Cortex

Neuroimaging studies have reported functionally distinct regions in the cingulate cortex (Mesulam et al., 2001). Paus and colleagues (1993) performed a PET study where they found that the ACC participates in motor control by facilitating the execution of appropriate responses and suppressing the execution of inappropriate responses. The ACC was also found to be highly active during interference in the Stroop color/word naming task when subjects were asked to name the color of a word that was incongruent with the name of the word (e.g. the word “red” printed in “green” color) (Pardo et al., 1990). These studies suggest that the ACC plays an

important role in monitoring conflict and evaluating performance when competing stimuli are present. Conflict monitoring has been extensively studied by Cohen and colleagues who suggested that the ACC may serve to detect events or internal states which require a shift of the attentional focus, thereby influencing top-down attentional control (Botvinick et al., 2004). ACC function has been further examined in tasks which include reward-related outcomes (Bush et al., 2002; Liddell et al., 2005). The data from these neuroimaging studies illustrate that the ACC plays a critical role in reward-related decision making and increases activity to outcomes that represent a decrease in reward value.

1.2.3.2 Posterior Cingulate Cortex

The PCC is thought to play an important role in top-down modulation of visual spatial expectancy. The efficiency of anticipatory attentional allocation during validly cued trials has been shown to correlate with PCC activity (Mesulam et al., 2001). In fact, the PCC was the only region that significantly correlated with the speed of target detection. Since there was a positive relationship with speed and activity in the PCC the authors argued for a role for PCC in visual spatial expectancy (Mesulam et al., 2001). Subjects who were most effective at shifting attention showed significantly greater activation in the PCC. This finding was replicated in a more recent neuroimaging study using a modified version of the Posner covert attention task (Small et al., 2003). Not only did the subjects respond significantly faster during the valid cues compared with the non-directional cues, activity in the PCC also increased as reaction time decreased. Small and colleagues then conducted a similar neuroimaging experiment using the same Posner paradigm; however, monetary incentives were now awarded to subjects for faster than average response times (Small et al., 2005). The authors were interested in examining the behavioral and

neural effects that abstract incentives had on top-down modulation of selective attention. They found that subjects responded faster to validly cued trials and generated a greater amount of spatial expectancy when money was offered compared to when it was not offered. Moreover, this behavioral enhancement was found to correlate linearly with increased neuronal firing in the PCC. Valid trials in which incentives caused the greatest degree of spatial expectancy and fastest target detection were associated with the largest amount of PCC activity (Small et al., 2005). Taken together, these studies demonstrate that the PCC plays an integral role in selective visual attention by modulating the interaction of spatial expectancy and motivational relevance.

1.2.4 Visual Cortex

An important aspect of attention is that the threshold for activating sensory neurons decreases so that relevant information is detected more rapidly (Shulman et al., 1997). As such, it is important to consider the visual cortex as an integral component of the visual spatial attention network. Salient sensory information has been shown to capture attention via bottom-up mechanisms originating in early visual cortical areas responsible for basic sensory analysis (Shulman et al., 1997). In addition, the visual system uses attention as a top-down mechanism to optimize its use of neural resources by allowing us to concentrate processing on a small portion of the incoming information (Pessoa et al., 2003). In the case of selective visual spatial attention, posterior parietal and frontal areas of the attention network influence where attention is directed by top-down modulation of visual cortex (Kastner et al., 2000). The visual cortex receives feedback signals from higher level association cortices regarding where attention needs to be directed. In this way, selective attention changes how sensory information is processed by

enhancing the influence of the attended stimulus at the expense of unattended stimuli (Shulman et al., 1997; Kastner et al., 2000; Pessoa et al., 2003).

1.2.5 Thalamus

The thalamus is a subcortical region involved in spatial attention processes. Damage to the thalamus has been associated with symptoms of neglect (Watson et al., 1979). Electrophysiological studies with monkeys have shown that neurons in the lateral pulvinar nucleus of the thalamus increase activity during tasks of visual spatial attention (Petersen et al., 1985) and recent neuroimaging studies have reported thalamic activity during tasks of covert spatial attention (Gitelman et al., 1999; Kim et al., 1999; Small et al., 2000).

Patients with unilateral thalamic damage demonstrate similar impairments as patients with right parietal lesions. Both lesion groups reveal an impairment in detecting invalidly cued targets in the contralesional visual field, however, unlike patients with parietal lesions, patients with thalamic lesions are slower at detecting targets in the contralesional hemifield, even when they are correctly cued to that location (Rafal et al., 1987). The authors suggested that even though the thalamus may participate in disengaging attention, damage to this area specifically impairs engaging attention at the target.

1.2.6 Superior Colliculus

The superior colliculus is located in the midbrain and responds to highly emotional stimuli that requires immediate attention. Threatening or fearful stimuli is processed very quickly in the amygdala and elicits eye movements which are controlled by the superior colliculus (Liddell et al., 2005). Electrophysiological recordings of the superior colliculus in the monkey have shown bursts of activity when the monkey shifts attention, but only when the shift

is accompanied by a saccade (Dorris et al., 1997). The superior colliculus of the human is also more closely related to overt saccadic shifts of attention compared with covert attention shifts (Gitelman et al., 2002). Moreover, lesions in the this area have been shown to lead to progressive supranuclear palsy which impairs the ability to reflexively shift attention with saccades (Posner et al., 1982; Pierrot-Deseilligny et al., 1989).

1.2.7 Summary of Attention Network

Lesion, electrophysiological, and functional neuroimaging experiments have all been used to demonstrate that selective spatial attention is controlled by a large scale network of brain regions in the parietal lobe, frontal lobe, and cingulate cortex and is modulated by information from the visual cortex (see Figure 1). Visual spatial information first enters primary unimodal visual areas, and then travels to the posterior parietal lobe where it participates in heteromodal integration. This region also receives information from the cingulate cortex regarding motivational relevance and frontal lobe regarding attention shifts. During top-down processing, the parietal lobe integrates the information about the relevance of the target and its location, thereby modulating where attention is directed. During bottom-up processing, the superior colliculus receives information about a highly salient stimulus from the amygdala and regulates the eye movements needed to shift attention to that location.

1.3 Healthy Aging, MCI, and PRAD

In this dissertation, I examined the role of incentives on top-down modulation of visual spatial attention in healthy aging and mild dementia. Functional magnetic resonance imaging was used to test for structural and functional differences in the attention network of these populations compared to young controls. The individuals that participated in the experiments

reported in this dissertation were categorized into three different groups based on their level of cognitive impairment: normal healthy aging, mild cognitive impairment (MCI), or probable Alzheimer's disease (PRAD). I was interested in testing these populations because spatial attention is thought to be one of the first non-memory domains to be affected in early dementia. Moreover, patients with MCI and early PRAD show reduced interest in normal everyday living activities that were previously performed without problems. This lack of motivation or interest in everyday activities is referred to as apathy and will be discussed in more detail below.

1.3.1 Attention in Aging and Dementia

Visuospatial attention is among the first non-memory cognitive functions to be impaired in MCI and early AD and several studies have demonstrated these impairments (Parasuraman et al., 1992; Lorenzo-Lopez et al., 2002; Rizzo et al., 2002). The deficits in attention may contribute to the impairments in daily living activities, decision making, and problem solving often observed in these conditions. AD patients have been shown to perform worse on tasks of sustained, divided, and selective attention compared with age-matched controls (Rizzo et al., 2002); with selective attention being the most impaired (Parasuraman et al., 1992). As discussed previously, the selective orienting of attention from a miscued spatial location towards a salient stimulus requires disengaging, shifting, and engaging attention and these components of attention are assessed with the Posner covert attention task (Posner, 1980). Parasuraman and colleagues examined these processes in healthy aging and persons with mild PRAD and found that PRAD subjects were much slower at detecting invalidly cued targets than validly cued targets compared with the elderly controls and this was associated with hypo-metabolism in the superior parietal lobe (Parasuraman et al., 1992). Even though PRAD subjects were only slightly

slower than controls on validly cued trials, they were significantly slower on invalidly cued trials (Parasuraman et al., 1992). Thus both groups showed evidence for generating spatial expectancy following the valid cues and detected targets faster than if no cue was present; however, PRAD subjects were much slower at detecting targets that were invalidly cued and required attention be disengaged and reoriented. The results suggest that shifting and engaging attention are preserved, while disengaging attention is impaired in early PRAD.

The deficits in disengagement may be associated with reduced activity in the orbitofrontal cortex (OFC). Patients diagnosed with AD at autopsy have shown a large amount of neurofibrillary tangle pathology in the OFC region (Mesulam et al., 1977; Tekin et al., 2001). Moreover, examination of the OFC using VBM measurements has revealed a significant amount of atrophy in PRAD subjects compared with normal age-matched controls (Callen et al., 2001). Metabolic activity in the prefrontal cortex has been shown to decline in PRAD patients during response inhibition tasks which require subjects to inhibit the allocation of spatial attention to irrelevant stimuli and reorient their attention to relevant stimuli (Slavin et al., 2002). Moreover, the hypo-activity that is observed in the prefrontal cortex is thought to be as severe as that seen in the parietal lobe (Haxby et al., 1986). The inability to inhibit attention to irrelevant stimuli was further examined in a more recent study investigating disorientation, defined as a failure to select the appropriate actions for ongoing behavior (Joray et al., 2004). The authors found that disorientation was frequent in PRAD patients and was associated with reduced OFC activity. Hypo-perfusion in the OFC and prefrontal regions have also been shown to correlate with a lack of motivation or interest, referred to as apathy (Benoit et al., 2004)

Metabolic reductions in the PCC have been observed in patients with mild dementia (Minoshima et al., 1997) and may contribute to the reduction of top-down attentional control on visual spatial expectancy. PCC hypo-activity has also been observed in adults that are carriers of the Apolipoprotein ε4 allele but do not show any cognitive impairments (Small et al., 2000; Alexander et al., 2002; Reiman et al., 2004). Moreover, the severity of AD symptoms has been shown to correlate better with hypo-activity in the PCC than in temporal regions (Ishii et al., 1997), suggesting that metabolic decline in the PCC may be an early indicator in the progression of AD.

1.3.2 Apathy

Apathy, or lack of motivation, is one of the most frequent behavioral disturbances in AD and has been shown to contribute to the decline in normal everyday activities (Holthoff et al., 2005). Apathy was determined to be a distinct syndrome from depression based on the negative correlation between an apathy evaluation scale and a rating scale for depression (Marin et al., 1994). Specifically, patients with AD were shown to have high apathy scores and low depression scores and only apathy correlated with impairments in cognitive functioning. In a separate PET study, PRAD patients with apathy showed hypo-perfusion in the OFC and ACC regions compared to PRAD patients without apathy (Benoit et al., 2002). Several other studies have also demonstrated that apathy results in reduced activity in the OFC and ACC (Landes et al., 2001; Migneco et al., 2001; Benoit et al., 2004). The apathetic behavior observed in PRADs is due to a problem with generating motivation internally. In other words, they have difficulty in orienting their attention to internal neural resources to carry out cognitive tasks.

Conversely, orienting to motivationally relevant stimuli in the environment has been shown to be intact in persons with PRAD (LaBar et al., 2000; LaBar et al., 2005). Subjects were able to direct their attention to emotionally arousing aversive stimuli even when they were attending elsewhere. Young controls also demonstrated this response (Armony et al., 2002), indicating that attentional modulation of fearful stimuli is preserved in PRAD. In a separate study with young control subjects, Vuilleumier and colleagues found that the amygdala response to fearful faces was not influenced by attention but the response in the fusiform face area of the visual cortex was influenced by attention (Vuilleumier et al., 2001). Since the amygdala responded to emotionally aversive stimuli independent of attentional allocation, the authors concluded that threat-related stimuli can be processed automatically via bottom-up mechanisms originating in the amygdala and modulated by the visual cortex. However, more recent studies have demonstrated that processing emotional faces requires some degree of attention (Pessoa et al., 2003). Pessoa and colleagues have found that the neural response to emotional expressions is modulated by top-down processes in the parietal and frontal regions of the spatial attention network. They also showed that the amygdala responds to emotional faces only when sufficient attentional resources are available to process those faces, providing further evidence for the involvement of attention to detect motivationally relevant stimuli. In PRAD patients, this relationship is true for external stimuli present in the environment but is unclear for internal modulation of spatial attention.

1.4 Goals and Predictions

The experiments that comprise this dissertation were conducted in order to examine the behavioral and neural correlates of motivational incentives on visual spatial attention processes in healthy aging, MCI, and PRAD. As outlined above attention has several components including disengagement, shifting, and engagement of attention (Posner, 1980). The Posner task has been used to evaluate these components successfully in young subjects (Small et al., 2000) and also in behavioral studies of patients with PRAD (Parasuraman et al., 1992). PRAD patients have demonstrated a selective impairment during invalidly cued trials when attention needs to be disengaged from an incorrect location (Parasuraman et al., 1992), however, no study has examined the neural correlates of this deficit in the PRAD population. On the other hand, a modified version of the Posner task has been used to examine top-down motivational influences on spatial attention processes including expectancy and disengagement in young controls (Small et al., 2005). Specifically, subjects were told that they could win money for fast responses and this was associated with improved performance and enhanced activity in the attention network. Taken together, I predicted that monetary incentives would enhance performance by reducing target detection times for all trials. This enhancement is expected to be most effective in EC subjects and least effective in PRAD subjects, with the MCI subjects showing some improvements.

The next chapter describes pilot studies during which we tested and developed the task for use in the PRAD population. The first pilot study was conducted to confirm that patients with PRAD were able to use a valid directional cue to bias attention and improve target detection and also to demonstrate the behavioral deficits of disengagement from invalid cues. Moreover, I was

also interested in examining the behavioral effect that motivational incentives had on these spatial attention processes. I predicted that incentives would improve target detection on all trials but would have the greatest effect on invalidly cued trials by reducing some of the deficits due to disengagement. The second pilot study was conducted in healthy young subjects to verify that the task modifications and online feedback did not reduce the effectiveness of the Posner task. The third pilot study was conducted on one subject from each group (healthy aging, MCI, PRAD) to confirm their ability to perform the modified Posner task and understand the online feedback.

In the main experiment, I used functional magnetic resonance imaging (fMRI) to study the brain responses of motivational influences on the top-down modulation of selective spatial attention processes. Thirty-one subjects (12 healthy aging, 12 MCI, 7 PRAD) participated in the fMRI experiment while performing the modified Posner task with feedback under the three incentive conditions, WIN, LOSE, and NEUTRAL. As demonstrated in previous studies with healthy aging and mild dementia subject groups (Parasuraman et al., 1992), I predicted that spatial expectancy would be intact in these groups, but disengagement would be specifically impaired in the PRAD group. Incentives are predicted to enhance the amount of spatial expectancy generated during the valid cues and this enhancement is predicted to engage the PCC. The PCC is predicted to only respond when incentives are used to effectively allocate attentional resources to a valid location and this will be associated with faster reaction times.

Disengagement is predicted to activate the OFC and tempero-parietal junction in healthy aging subjects and patients with MCI. PRAD subjects, on the other hand, will not recruit parietal or frontal regions during disengagement due to the evidence from VBM studies that show their

atrophy. Instead, they are predicted to engage the ventral visual pathway that includes the tempero-occipital cortex. This alternate pattern of activation will be apparent from the relatively slower reaction times during invalidly cued trials.

Unlike the predicted enhancement of spatial expectancy, incentives are predicted to have a small influence on response time to invalid targets in all three subject groups. Early visual cortical areas (corresponding to Brodman's areas 18 and 19) are also expected to be recruited for extensive visual spatial processing or as a compensatory mechanism for dysfunction in the spatial attention network.

As a final measurement, voxel based morphometry (VBM) was performed on the anatomical images to examine and compare the atrophic areas between PRAD, MCI, and healthy aging. As demonstrated in previous VBM studies, the hippocampus and posterior parietal cortex are predicted to show the greatest amount of atrophy in PRAD subjects compared with the healthy aging subjects (Frisoni et al., 2002; Busatto et al., 2003). Due to the heterogeneity of the MCI subjects, it was uncertain whether or not they would show atrophy in these regions.

CHAPTER 2: PILOT EXPERIMENTS

2.1 Introduction

The primary goal of these pilot studies was to confirm that patients with probable Alzheimer's disease (PRAD), mild cognitive impairment (MCI) and age-matched controls were able to perform a version of the Posner covert spatial attention task and demonstrate the validity and invalidity effects. I was also interested in examining the behavioral effects of motivational incentives on selective spatial attention in these subjects. To evaluate the influence of incentives, subjects were rewarded when they used the valid directional cues to detect targets faster than non-directional, uninformative cues. As demonstrated in healthy young subjects (Small et al., 2005), I predicted that monetary incentives would improve target detection on all trials. This benefit would be most evident in the healthy aging group and least evident in the PRAD group, with MCI subjects showing some improvements.

The first pilot study was conducted to confirm that patients with PRAD demonstrated the validity and invalidity effects under the different incentive conditions. I predicted that reward would decrease some of the deficits in disengagement observed during invalidly cued trials by reducing response times. The second pilot study was conducted in healthy young subjects to verify that the task modifications and online feedback did not reduce the effectiveness of the Posner task. The third pilot study was conducted on one subject from each group (healthy aging, MCI, PRAD) to ensure that they were still able to perform the modified task with feedback.

2.2 Cognitive Laboratory

The first pilot study was needed to examine the influence of incentives on spatial expectancy and disengagement in patients with PRAD by comparing reaction times for each trial type. The goals of this study were to 1) ensure that patients with probable Alzheimer's disease are able to perform the modified version of the Posner covert spatial attention task, 2) replicate previous findings that suggest disengaging and reorienting attention from an incorrect spatial location are specifically impaired in patients with AD (Parasuraman et al., 1992) , and 3) test whether motivational incentives can help reduce the RT costs due to disengaging attention from an invalid location.

2.2.1 Participants

In the initial experiment three patients with probable Alzheimer's disease (PRAD) (2 males) were tested in the cognitive laboratory (see **Table 1**). Subjects were recruited from the Alzheimer's Disease Clinical Core (ADCC) subject registry at Northwestern University. Individuals that participate in this clinical core program undergo neurological exams and neuropsychological tests to determine their level of cognitive impairment, thereby providing a diagnosis. Testing includes the Mini-Mental State Examination (MMSE), which assesses a patient's basic cognitive skills, such as short and long-term memory, orientation, attention, writing, language, and the ability to follow simple verbal and written commands (Folstein et al., 1975) (see Appendix A). In a separate exam, the neurologist interviews the patient and assigns a clinical dementia rating (CDR) (Morris, 1993) (see Appendix B). The CDR is a clinical rating of dementia based on interview data from the patient and an informant and characterizes six domains of cognitive and functional performance: memory, orientation, judgment & problem

solving, community affairs, home & hobbies, and personal care. The score represents the level of impairment: 0 = no impairment, 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively. The patient's primary caregiver is asked to complete the Activities of Daily Living Questionnaire (ADLQ), a measure of the patient's need for assistance with routine activities (Johnson et al., 2004) (see Appendix C). The ADLQ measures functioning in six areas: self-care, household care, employment and recreation, shopping and money, travel, and communication. A score between 0 and 33% indicates mild impairment, between 34 and 66% indicates moderate impairment, and above 67% indicates severe impairment.

The neuropsychological evaluation also includes several subtests from the Consortium to establish a registry for Alzheimer's Disease (CERAD) (Morris et al., 1989). The 'word list generation' (see Appendix H) assesses immediate and delayed memory recall (see Appendix I) and recognition (see Appendix J). The 'semantic fluency' subtest assesses executive function and requires subjects to generate a list of animals as quickly as possible within 60 seconds (Appendix K). In addition, visuoperceptual skills are tested with the 'constructions' subtest, which asks participants to copy figures of specific shapes (see Appendix L). Attention is evaluated with the trail making tests. Subjects are required to draw a line connecting circles in a specified sequence. Part A is used to assess motor speed and sequencing ability (see Appendix M), while part B assesses the ability to switch between two categories (see Appendix N). The amount of time taken to complete the trail making tests is their score.

The diagnosis of definite AD can not be made until autopsy, so the term probable is used to define this patient group (McKhann et al., 1984). PRAD is characterized by a gradual onset and progression of impairments in memory and at least three other cognitive domains as well as

the absence of other brain diseases that may account for the cognitive deficits (McKhann et al., 1984). The clinical diagnosis of PRAD is based on several factors including medical history, clinical examination, and neuropsychological testing which are used to assess impairments in daily living activities and altered behavior patterns. These criteria were used to determine enrollment to the ADCC as a PRAD subject with a certain level of functioning as demonstrated by: 1) MMSE score > 24; 2) CDR of ≤ 1; 3) either a CT or MRI scan within the past two years, documenting absence of strokes or other structural lesions; and 4) availability of a caregiver who is willing to accompany the patient and complete the ADLQ.

We recruited only right-handed subjects, as determined by the Edinburgh handedness inventory (Oldfield, 1971) (see Appendix D), with corrected visual acuity of at least 20/40 with full visual fields. To rule out depression, each subject's mood was rated on the geriatric depression scale (see Appendix O). Other exclusion criteria included: 1) history of CNS disease; 2) history of DSM-IV criteria for any major psychiatric disorder, or alcohol or substance abuse; 3) history of concurrent, unstable or serious medical condition; 4) chronic use of psychoactive medications; 5) concurrent use of medications that affect eye movements; 6) presence of visual impairments/disorders such as cataracts, macular degeneration or physical impediments to data collection; 7) known claustrophobia; or 8) the presence of metal in the body including excessive dental work, which may effect the MR signal (see Appendix E).

Subject	Age	Sex	CDR	MMSE	Race	Handedness	Education	ADL
BB	70	M	1	26	Cauc	75	16	17.4%
LD	66	M	1	22	Cauc	100	18	42%
LG	85	F	1	16	Cauc	100	18	61.1%

Table 1. Demographic data for 3 PRAD subjects tested in the cognitive laboratory

2.2.2 Procedure

Upon arrival participants were escorted to the cognitive laboratory for the experiment. After giving informed written consent (see Appendix F), they were seated 40 cm away from a 21-inch monitor, with their head placed in a chin rest to minimize head movements (see Figure 2).

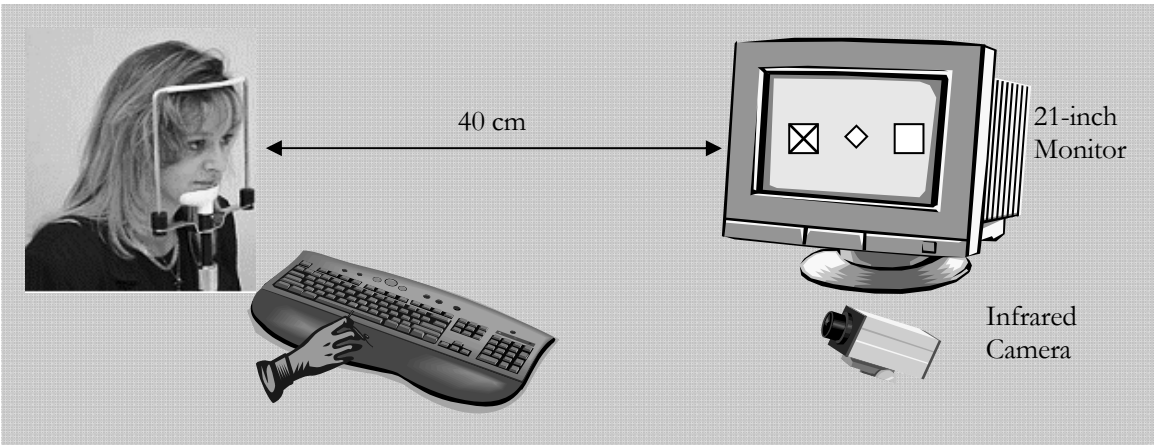

Figure 2. Depiction of the experimental set-up in the cognitive laboratory (created from pictures found in Microsoft clip art). Subjects are seated 40 cm away from a computer screen with their head in a chin rest. They respond to the task by pressing the spacebar with their right hand while an infrared camera records their eye movements.

2.2.2.1 The Modified Posner Task

Figure 3 depicts the basic features of the Posner task (Posner, 1980).

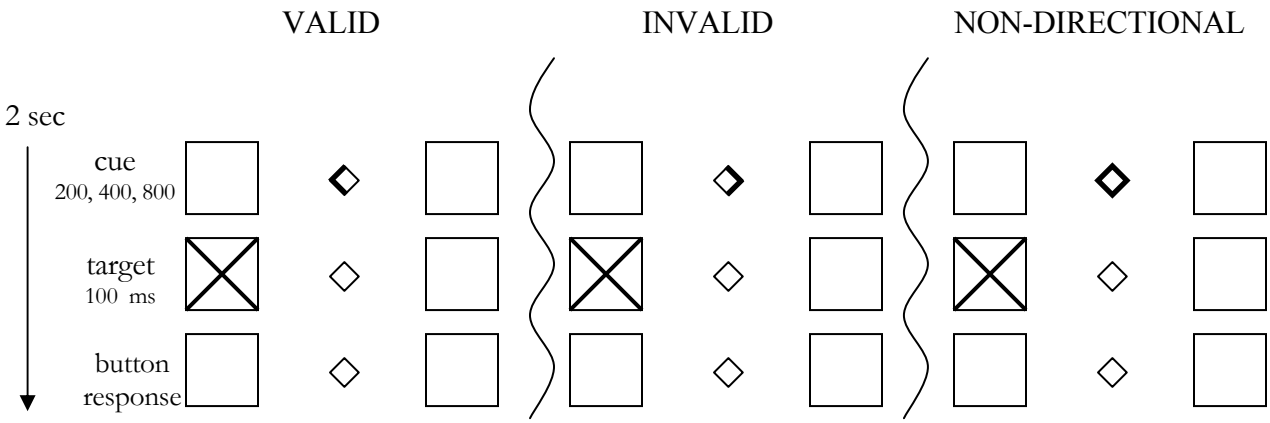

Figure 3. Modified Posner target detection task. Subjects fixate on the central diamond throughout the experiment. Bolding of the left side or right side of the diamond provides a directional cue that can either be VALID or INVALID while bolding of the entire diamond provides a NON-DIRECTIONAL cue. Cues appear for 200, 400 or 800 msec. The target X appears for 100 msec in one of two boxes. Subjects have 1000 msec to respond and each trial lasts 2 sec.

Stimuli were presented using Superlab software running on a Macintosh computer. Participants were required to fixate on the central diamond (1° wide) during the entire task (Figure 3). They were instructed to respond to targets (Xs) but not foils (+s) by pressing a keyboard spacebar. Targets and foils appeared for 100 msec in one of two peripheral squares (one on the left and one on the right, each 1.5° wide) displaced 7.5 degrees from the central diamond, with equal frequency on both sides. Targets and foils were preceded by cues that could: 1) validly predict the target location (validly cued trials—central diamond is bolded on side of subsequent target appearance); 2) incorrectly predict target location (invalidly cued trials—diamond is bolded on opposite side of subsequent target appearance); or 3) provide an alerting but non-directional cue (entire diamond is bolded). Performance was measured by speed

of RT to the target X. The non-directional trials constituted a baseline for comparison since no directional information, and thus no performance benefit, could be derived from the cue. To minimize the potential role of working memory, the cue remained visible until the target appeared. In addition, three different intervals of stimulus onset asynchrony (SOA), the time between cue and target, were used in order to prevent temporal predictability: 200 msec, 400 msec, and 800 msec. Each trial lasted 2 sec and each experimental "run" consisted of 152 trials, with 138 targets (X) and 14 foils (+). Each run lasted 5 min and 4 sec. Foils were employed to make sure that the subject was actively attending to the periphery rather than just responding to any peripheral stimulus. Fifty-two percent of the 152 trials were validly cued (72 targets, 8 foils), 13% were invalidly cued (18 targets, 2 foils) and 35% had a non-directional alerting cue (48 targets, 4 foils).

Each subject performed 4 runs; an initial practice run followed by three runs corresponding to incentive conditions, WIN, LOSE, and NEUTRAL. Subjects could win money during the WIN run, lose money during the LOSE run, or neither win nor lose money during the NEUTRAL run. The order of the conditions was counterbalanced between subjects. A practice session was first administered to familiarize the subject with the task. This run was also used to calculate RT to be used to determine a cut-off RT indicating whether the subject won or lost money. Cut-offs differed for WIN and LOSE to maximize winning during the win condition and losing during the lose condition. For WIN, the cutoff was the mean RT plus 2 standard errors of the mean, whereas for LOSE, the cutoff was the mean RT minus 2 standard errors of the mean.

After the cut-offs had been determined in the initial run, subjects were informed about the monetary incentives they would receive. They were told that during one run "WIN", they could

earn 18 cents if they responded faster than a cut off for a total potential winning of $24.84. In contrast, subjects were told that during another run "LOSE", they would start with $24.84 and would lose 18 cents for responses slower than a cut off. During another run "NEUTRAL", subjects were instructed that they would neither win nor lose money.

2.2.2.2 Eye Movements

To insure that subjects were fixating on the central diamond, eye movements were monitored with the ISCAN infrared monitoring system (model RK-426PC; ISCAN Co., Burlington, MA). The eye movement data was then analyzed with custom-designed software, ILAB (Gitelman, 2002) running in the MATLAB environment (Mathworks, Natick, MA) to identify the number of saccades and the amount of time that fixations were maintained. As mentioned previously, maintaining fixation is important in this task because we are examining covert (without eye movement) attention. Eye data was designated as interpretable if there was eye information for at least 90% of the trials. Saccades or rapid eye movements made in the horizontal direction were important to the study but vertical eye movements, indicating blinks, were filtered out. The data were further analyzed by defining a region of fixation which took into account the central fixation diamond plus 3° in either direction. The modification allowed saccades to be identified. Saccades were reported to have occurred if they fell outside of the fixation region and in a horizontal direction towards the target.

2.2.2.3 Debriefing

Following the experiment, subjects were paid for their participation. Compensation was based on performance during the WIN and LOSE conditions. Maximum compensation was $50.

2.2.3 Results

2.2.3.1 Accuracy

Responses less than 100 msec and greater than 1000 msec were omitted because they indicate that the subject is not responding to or paying attention to the target. All three subjects responded to over 80% of the trials during the WIN condition (**Table 2**). Subjects BB and LD responded to over 90% of trials during the LOSE and NEUTRAL conditions, while subject LG responded to only 25% and 22%, respectively. Since WIN was the first condition for subject LG, the low accuracy scores on the other two conditions could be due to fatigue or forgetting what the task was. Across all three conditions, subjects BB and LD responded to over 87% of the valid, invalid, and non-directional trials, while subject LG responded to only 30%, 33%, and 71%, respectively. This data also suggests that subject LG forgot the task. Accuracy scores from a similar study conducted with healthy young controls (Small et al., 2005) are shown in **Table 2** for comparison.

Subject	Win	Lose	Neutral	Valid	Invalid	Non-Directional
BB	96%	91%	94%	94%	94%	93%
LD	81%	92%	97%	90%	87%	91%
LG	86%	25%	22%	30%	33%	71%
Young Controls	97%	97%	98%	98%	97%	98%

Table 2. Mean accuracy scores for the 3 PRAD subject in the pilot study and 9 healthy young controls (from (Small et al., 2005)).

2.2.3.2 Reaction Times

Each subject's RT dataset was analyzed individually using separate repeated measures ANOVAs with planned comparisons (SPSS Inc., 2004). Since subject LG showed poor accuracy

during the LOSE and NEUTRAL conditions (see **Table 2**), only the WIN condition was analyzed.

A main effect of trial type was found for subject BB's RT data ($F_{(2,100)}$= 3.21, p=.045), such that validly cued trials were responded to significantly faster than invalidly cued trials (p=.011). The result is termed a validity effect because the valid cue is used to generate spatial expectancy and reduce RTs to the target. Neither of the other two subjects showed a validity effect {LD: ($F_{(2,92)}$=.338, p=.714); LG: ($F_{(2,34)}$=1.56 , p=.11)}.

A main effect of motivational condition was found for subjects BB and LD {BB: ($F_{(2,250)}$= 6.89, p=.001); LD: ($F_{(2,222)}$= 14.57, p=.0001)} (see Figure 4). Planned comparisons revealed that for both subjects, RTs were fastest for WIN compared to LOSE {BB: (p=.001); LD: (p=.0001)} and WIN compared to NEUTRAL {BB: (p=.001); LD: (p=.0001)}. Subject LG showed a trial by motivation condition interaction ($F_{(2,30)}$= 4.32, p=.022), responding to the non-directionally cued trials faster than to the invalidly cued trials during the win condition (p=.005). In summary, one subject demonstrated a validity effect, two subjects exhibited a motivational effect and one showed an invalidity effect during WIN.

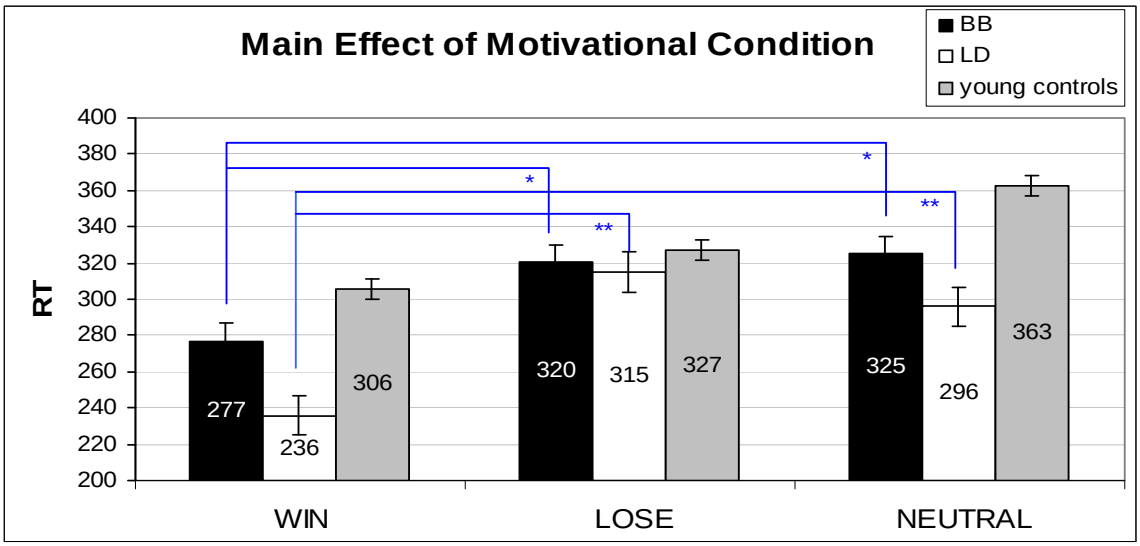

Figure 4. Main effect of motivational condition for PRAD subjects BB, LD and 9 healthy young control subjects from Small, et al., 2005. Error bars represent the standard error of the mean. *p=.001, **p=.0001

2.2.3.3 Maintenance of fixation

Eye data was successfully recorded for all three subjects. The percentage of time subjects were able to maintain fixation is shown in **Table 3**. Inspection of this table clearly shows that subjects were able to maintain fixation.

Subject	Win	Lose	Neutral	Valid	Invalid	Non-Directional
BB	81%	79%	78%	77%	69%	83%
LD	86%	90%	87%	89%	80%	88%
LG	78%	89%	92%	92%	82%	78%

Table 3. Average amount of time each PRAD subject maintained fixation

2.2.3.4 Debriefing

After completing the experiment, subjects were given their earnings. During the WIN and LOSE conditions, subject BB earned $17.64 and $15.30, subject LD earned $18.90 and $17.10, and subject LG earned $16.38 and $4.50. However, all subjects displayed surprise, and delight,

at receiving the money. Thus it was clear that they did not remember the monetary contingency. This was true even for the two subjects who clearly responded faster when money could be won. It is possible that these subjects remembered the monetary incentives at the beginning of the experiment but by the end of the experiment, they had forgotten. Alternatively, these subjects may never have consolidated the instructions regarding the possibility of winning or losing money. In that case, the effect of monetary incentive must have been based on implicit processing.

2.2.4 Discussion

The results from this preliminary experiment suggest that PRAD subjects will be able to perform the modified version of the Posner covert visual spatial attention task and some subjects may even benefit from motivational incentives. The validity and invalidity effects that were seen in 2 out of 3 patients are in accordance with an earlier study that found attentional focusing to be intact but attentional reorienting to be impaired in this population (Parasuraman et al., 1992). In addition, motivational incentives, specifically reward, influenced performance on the invalidly cued trials in 2/3 subjects by reducing some of the deficits associated with disengagement, thereby, speeding up target detection.

Although these behavioral results were encouraging, I felt it was problematic that subjects were not explicitly aware of the monetary reward given that the primary goal of this project was to evaluate the influence of explicit motivational incentives on top-down control of attention. Therefore a decision was made to revise the task to include online feedback about the monetary components.

2.3 Task Modifications

2.3.1 Online Feedback

The primary modification was the inclusion of feedback cues following each response. During the WIN condition, responses resulting in monetary gains were followed by a dollar sign. During the LOSE condition, responses resulting in monetary loss were followed by a dollar sign with ah X through it. In both conditions, responses that did not result in monetary gains or losses were followed by an equal sign. During the NEUTRAL condition all responses were followed by the appearance of an equal sign to signify that no money had been won or lost. (Figure 5).

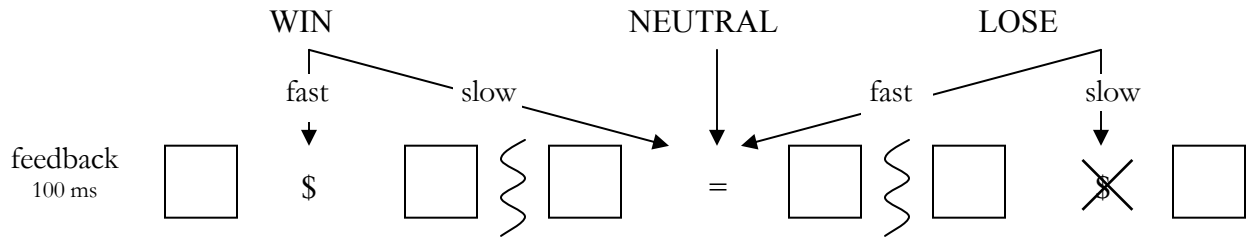

Figure 5. Subjects see the appropriate feedback symbol after each trial depending on if they responded faster than the cutoff or slower than the cutoff during WIN and LOSE. The dollar sign represents winning money, the dollar sign with an X represents losing money and the equal sign represents neither winning nor losing money. Subjects will see an equal sign during NEUTRAL whether they are fast or slow since there are no monetary incentives during NEUTRAL.

It was not possible to generate online feedback using the Superlab software, so I reprogrammed the Posner task using Cogent software (Cogent2000 developed by the Cogent team at the Wellcome Department of Imaging Neuroscience) running in the Matlab environment (Mathworks, Natick, MA). One feedback symbol was displayed for 100 msec immediately following each trial and the type of symbol displayed was determined by online comparison with the cut-off scores (see Figure 5).

2.3.2 HRF and Null Events

When creating fMRI experiments, it is important to present the stimuli in such a way as to maximize the ability to detect events of interest. In order to extract activity related to each event type, the hemodynamic response function (HRF) needs to be measured for the event. The HRF is the basis of the blood oxygen-level dependent (BOLD) signal in fMRI measurements and evolves over a period of 10-12sec following an event. Sequential events would need to occur every 12sec to avoid overlapping hemodynamic responses however, presenting trials every 12sec is not optimal because it greatly limits the number of trials available for averaging, and thus reduces statistical power. The considerable amount of time between trials may also cause problems related to keeping the subject engaged in the task. In order to avoid overlapping HRFs from limiting presentation rate, Burock & colleagues (1998) found that using randomized experimental designs allowed events to be rapidly presented. The event of interest occurs at random time points throughout the experiment and the event-related design is based on averaging these events. Since response overlap is approximately the same for different event types, it would subtract out in a contrast, resulting in differential response activity between the event types. Moreover, events with short and variable inter-trial intervals increase the accuracy of estimating the HRF (Dale, 1999). These procedures allow neural responses based on different cognitive events to be separated and analyzed.

In addition to examining differential activity between trial types, the response of individual event types can be extracted by including "null events" in the trial sequence at random series of time points (Buckner, 1998; Burock et al., 1998). The null event acts as an implicit baseline and does not include any stimuli. In this experiment, the null event comprises of the

central diamond and peripheral boxes of the Posner task, but no cue or target. Null events are important in fast-rate event-related fMRI experiments because, on average, they contain the same overlap from adjacent trials as any other trial type. Thus, to examine the main effect of an event of interest, a contrast is created between that event and null events in order to subtract out the overlap and thereby, reveal the full HRF for the event of interest. Assuming that the null events do not evoke a response themselves, they also allow the HRF to return to baseline (Burock et al., 1998) . Trial sequences are created by randomizing the different event types and adding null events throughout the sequence to optimize HRFs.

2.3.3 Optimal Trial Sequences

The original event presentations had been optimized for the trials without feedback. Since the addition of the feedback symbols lengthened the overall trial to 2.3 sec, I needed to re-optimize event presentation order and null event distribution using the OptSeq software, distributed by Massachusetts General Hospital (MGH) (Dale, 1999). This process generated three random series of 152 trials with 43 null events distributed evenly, for each fMRI script, which lasted 6 min 39 sec. The behavioral versions of the scripts were the same random series of 152 trials without null events and lasted 5 min 50 sec.

2.3.4 Questionnaire

A second modification was the creation and inclusion of a questionnaire to assess subjects' awareness of the various components of the task (see Appendix G). The questionnaire was to be filled out by all subjects at the end of the experiment.

2.4 Retesting in the Cognitive Laboratory

2.4.1 Introduction

In the previous pilot study we demonstrated that the performance of two patients with PRAD on the Posner covert visual spatial attention task is improved when they were offered money. This was true despite the fact that patients did not show explicit awareness of the monetary incentives. Since the main goal was to evaluate the influence of explicit motivational factors on top down control of attention, I modified the task to include online feedback about winning and losing to increase subjects' awareness of the monetary incentives. Before testing more PRAD patients, I wanted to verify that the motivational effect could be obtained in young controls when using feedback. A previous study with young controls on a similar paradigm without feedback revealed a main effect of motivational incentive, such that overall RT was faster when monetary incentives were offered (Small et al., 2005). The current goal was to verify that the updated version of the Posner paradigm with online feedback would produce similar results in young controls. I predicted that subjects would benefit from the feedback by responding faster when there was a possibility of winning and losing money compared to neither winning nor losing money (as measured with neutral). I also predicted that they would be explicitly aware of the feedback symbols and respond 100% accurately on the questionnaire.

2.4.2 Participants

Fourteen healthy young volunteers (10 women, 4 men) with a mean age of 27 years (22-39) were recruited from Northwestern University. All subjects reported being right-handed and were classified as right-handed by the Edinburgh inventory (Oldfield, 1971) (see Appendix E). The average handedness score was 88 out of a possible 100, with a range of 70-100.

2.4.3 Procedure

Upon arrival participants were escorted to the cognitive laboratory for the experiment. After giving informed written consent (see Appendix F), they were explained the task they would be performing. The set-up was identical to the previous pilot study (see Figure 2). A sample of the task was displayed on the screen and subjects were asked to fixate on the central diamond while responding to the target (X) by pressing the space bar. RTs and eye movements were recorded.

2.4.3.1 The Modified Posner Task with Feedback

The basic features of the Posner task were the same as those used in the previous pilot experiment with the exception of online feedback (Figure 6).

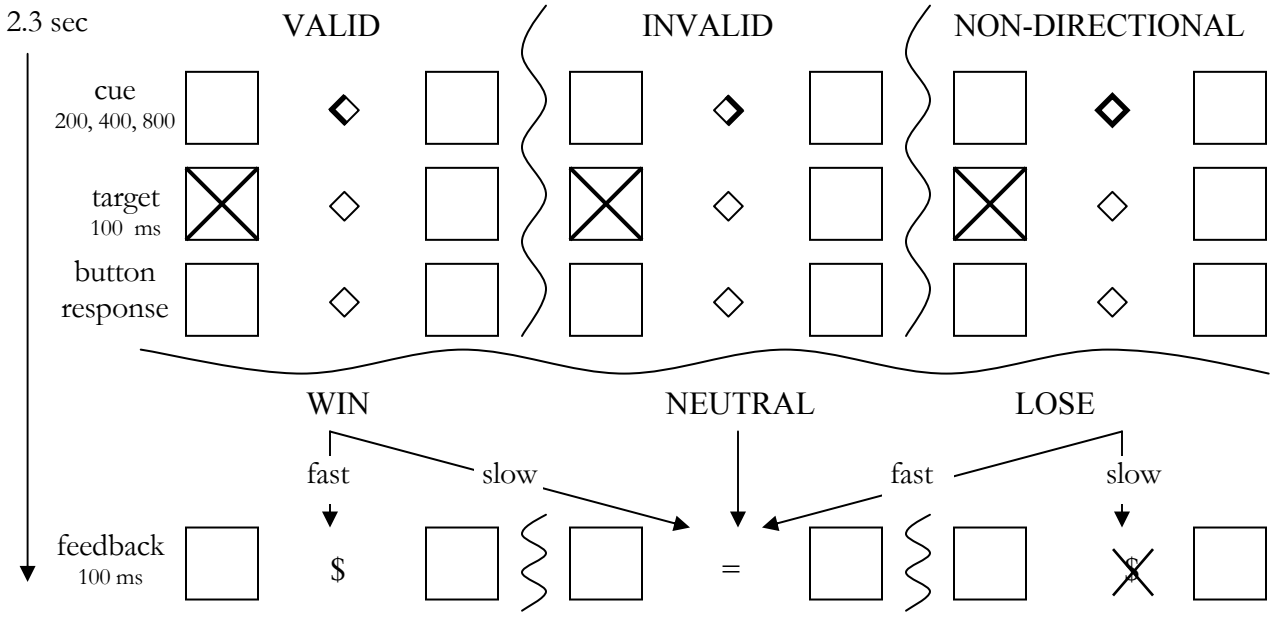

Figure 6. Modified Posner paradigm with feedback. Subjects will see the appropriate feedback symbol after each trial depending on if they responded faster than the cutoff or slower than the cutoff during WIN and LOSE. Subjects will see the same symbol (=) during NEUTRAL whether they are fast or slow since there are no monetary incentives during NEUTRAL.

After the cut-offs had been determined in the initial run (see above for details for determining cut-offs), subjects were informed about the three monetary incentive conditions and the amount of money they could win or lose, just as in the previous experiment. They were also informed about the feedback symbols they would see following their responses (see Figure 6). They were told that during the "WIN" run, they would see a dollar sign after their response if they had won money or an equal sign if they had not. During the "LOSE" run, they would see an X through a dollar sign for each response that would cost them 18 cents and an equal sign for responses that were equal to or faster than the cut-off, indicating no money had been won or lost. During NEUTRAL, subjects were instructed that they would neither win nor lose money, and would see an equal sign following each response. Eye movements were monitored as previously described. After the experiment, subjects were asked to fill out the questionnaire (see Appendix G). They were then paid for their participation and given their total earnings.

2.4.4 Results

2.4.4.1 Accuracy

RTs greater than 1000 msec and less than 100 msec were omitted from analysis. Accuracy was measured as described above. Accuracy of target detection was > 97% in all runs and all trial types (**Table 4**).

Win	Lose	Neutral	Valid	Invalid	Non-Directional
98%	97%	98%	98%	97%	98%

Table 4. Mean accuracy scores for the 14 young controls during each condition and trial type

A within-subjects repeated-measure ANOVA indicated that accuracy did not differ across trial type ($F_{(2,26)}$= 1.95, p=.16) or monetary incentive condition ($F_{(2,26)}$= 2.49, p=.10). Since, the p-

values might have indicated a trend, planned comparisons were carried out but no significant differences were observed. These accuracy scores are similar to what was shown in a previous experiment with the Posner paradigm plus monetary incentives but no feedback (Small et al., 2005).

2.4.4.2 Reaction Times

A separate within-subjects repeated-measures ANOVA with planned comparisons was used to determine if there were RT differences between trial types, motivational conditions, stimulus onset asynchrony and their interactions. This analysis revealed an overall validity effect ($F_{(2,26)}$= 15.7, p=3.4x10^{-5}) such that subjects responded faster to validly cued trials than invalidly cued trials (p=3.1x10^{-4}). However, RTs did not differ between validly cued trials and non-directional trials (p=.154), whereas invalidly cued trials did differ from non-directional trials (p=.003) (Figure 7). These data indicate that the invalid cue had a greater effect on response times than did the valid cue.

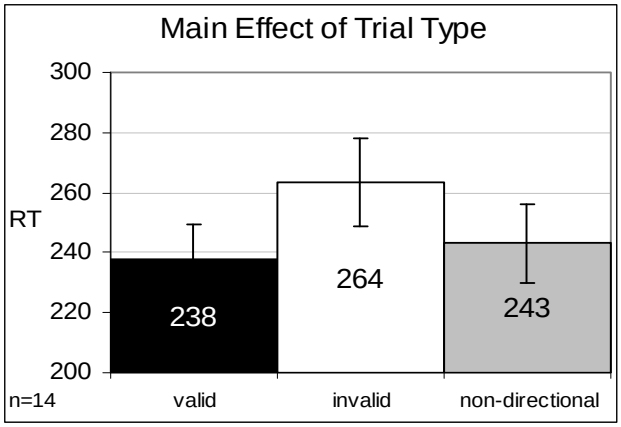

Figure 7. Mean RT of each trial type for 14 young subjects. RTs are faster during valid (p=3.1x10^{-4}) and non-directional trials (p=.003) compared to invalid trials. Error bars represent standard errors of the mean.

Additionally, the ANOVA revealed a main effect of motivational condition ($F_{(2,26)}$= 13.8, p=8.2x10^{-5}), with RTs slower for all trials during NEUTRAL compared to all trials during WIN (p=.004) and LOSE (p=.001) (Figure 8).

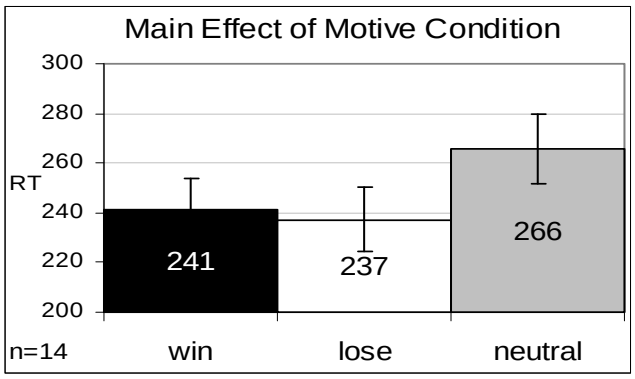

Figure 8. Mean RT of each motive condition for 14 young subjects. RTs are faster during WIN (p=.004) and LOSE (p=.001) compared to NEUTRAL. Error bars represent standard errors of the mean.

A main effect for stimulus onset asynchrony (SOA) was also demonstrated ($F_{(2,26)}$= 6.2, p=.006), such that RTs were faster when cues appeared following 800 msec compared to 200 msec (p=.007) (Figure 9).

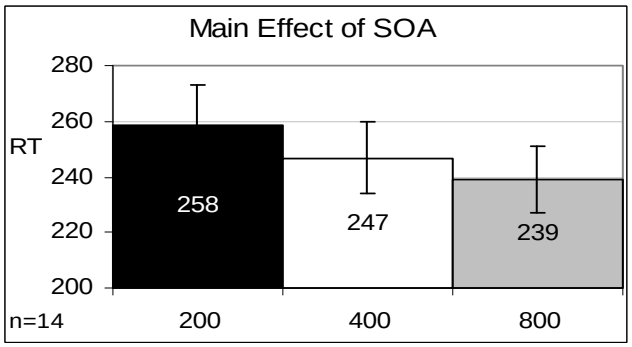

Figure 9. Mean RT of each SOA for 14 young subjects. RTs are faster when the cue appeared for 800 msec compared to 200 msec (p=.007). Error bars represent standard errors of the mean.

Planned comparisons also revealed a significant interaction between trial type and soa ($F_{(4,52)}$= 6.3, p=$3.4x10^{-4}$); trials with valid and non-directional cues that appeared for 200 msec were responded to slower than those that appeared for 400 (p< .003) and 800 msec (p< .019). No other interactions were seen; motive by trial type ($F_{(4,52)}$= .51, p=.73), motive by SOA ($F_{(4,52)}$= .99, p=.42), or motive by trial by SOA ($F_{(8,104)}$= 1.51, p=.16).

2.4.4.3 Maintenance of Fixation

The eye movement data indicated that subjects had no difficulty maintaining fixation throughout the experiment (**Table 5**). Since very few trials were contaminated with a saccade, they were all included in the analysis.

Win	Lose	Neutral	Valid	Invalid	Non-Directional
4	5	11	3	9	8

Table 5. Total number of saccades made by 14 young controls during each condition and trial

2.4.4.4 Debriefing

At the end of the experiment, subjects were given the questionnaire regarding various features of the task (see Appendix G). They all responded with 100% accuracy, suggesting that they understood the monetary components of the task. For example, they correctly defined the meaning of the three feedback symbols and when asked about the amount of money they could earn, they all correctly indicated that they could earn up to $50. Subjects earned an average of $22.97 in the WIN condition and $22.37 in the LOSE condition. A paired t-test revealed a significant difference between WIN and LOSE ($t_{(1,13)}$ =2.14; p=.052); more money was earned in the WIN condition than in the LOSE condition.

2.4.5 Discussion

The goal of this pilot study was to determine the effectiveness of the modified Posner paradigm with monetary incentives and online feedback. The results revealed that motivation influences top-down control of attention as shown by faster RTs when there was a chance to win or lose money compared to when there was no incentive. Moreover, subjects' responses on the questionnaire indicated explicit awareness of the monetary incentives. A previous study without

online feedback found that subjects responded faster only when there was a chance of losing money (Small et al., 2005). However, this experiment shows that the presence of online feedback caused faster responses when there was a chance of either winning (p=.004) or losing money (p=.001). These results suggest that providing explicit awareness about monetary incentives may be a better way for motivation to influence attention.

2.5 Testing Patients

2.5.1 Introduction

The updated feedback version of the modified Posner paradigm was successful at achieving explicit awareness of the monetary components of the task in young control subjects. This was demonstrated by faster RTs during WIN and LOSE compared to NEUTRAL as well as correct knowledge of the feedback symbols on the questionnaire. Additionally, since motivation affected all trial types, it is possible that the online feedback made the monetary incentives a more effective performance enhancer than in previous studies. The following experiment was conducted to determine if the inclusion of on-line feedback would help patients with probable Alzheimer's disease (PRAD), patients with mild cognitive impairment (MCI) and healthy age matched controls have explicit awareness of the monetary incentives.

2.5.2 Participants

One patient with PRAD, one patient with MCI, and one elderly control (EC) subject were tested in the cognitive laboratory (see **Table 6**). Subjects were again recruited from the Alzheimer's Disease Clinical Core (ADCC) subject registry at Northwestern University as mentioned in the first set of pilot experiments, and they all underwent neurological examinations and neuropsychological testing as part of the Northwestern ADCC methods for establishing a

diagnosis. The criteria for the diagnosis of PRAD is described in the first set of pilot experiments.

2.5.2.1 Mild Cognitive Impairment

MCI is defined as a transitional stage between healthy aging and PRAD (Petersen et al., 1999; Petersen et al., 2001; Petersen, 2004). MCI is associated with memory impairments similar to PRAD, however, unlike patients with PRAD, the diagnosis of MCI includes preservation of general cognitive and functional abilities and the absence of clinical dementia and is associated with a CDR ≤ 0.5 (Morris, 1993). Since the CDR is not the only measurement for dementia, a CDR score of 0.5 can be associated with PRAD, instead of MCI, if other areas of cognitive function are also impaired.

Patients with MCI are a heterogeneous group with different levels and areas of cognitive decline (Petersen, 2004). Even though MCI is most often associated with memory impairments (amnestic MCI), MCI can also occur because of deficits in other cognitive domains (multiple-domain MCI), such as language, attention, or visuospatial skills and can occur with or without memory impairments. MCI patients with memory impairments are more likely to progress to PRAD, while MCI patients with non-memory impairments are more likely to progress to non-AD dementias, such as dementia with lewy bodies (Petersen et al., 2001). Other risk factors that contribute to the progression of AD include family history of AD and the presence of the ε4 allele of the ApoE gene (Saunders et al., 1993). The rates of conversion from MCI to PRAD and healthy aging to PRAD were investigated in a longitudinal study by Petersen and colleagues (1999). Four years after initial testing, the conversion rate from MCI to PRAD was 12% per year. The progression rate from healthy aging to PRAD was much lower at only 1% to 2% per

year for the four years. A separate longitudinal study found that more than half of the MCI patients (CDR = 0.5) converted to PRAD (CDR ≥ 1) over a 5 year period, while only 7% of age-matched controls (CDR = 0) converted to PRAD (Morris et al., 2001). These rates of progression were confirmed at autopsy by examining the pathologic features and regional atrophy of 10 representative brains from each group.

Subject	Age	Sex	CDR	MMSE	Race	Handedness	Education	ADL
PRAD	73	F	0.5	28	African	+100	14	N/A
MCI	75	F	0	29	Cauc	+100	16	N/A
EC	77	F	0	30	Cauc	+100	16	N/A

Table 6. Demographics of one subject from each group tested on the feedback version of the Posner covert attention task in the cognitive laboratory

2.5.3 Procedure

The experimental set-up and procedure were the same as in the last two experiments.

2.5.4 Results

2.5.4.1 Accuracy

Accuracy was measured as in the previous experiments. Accuracy of target detection was > 83% in all runs and >85% for all trials (**Table 7**).

Subject	Win	Lose	Neutral	Valid	Invalid	Non-Directional
PRAD	91%	84%	87%	88%	89%	85%
MCI	96%	99%	93%	97%	93%	97%
EC	96%	88%	83%	88%	93%	89%

Table 7. Mean accuracy scores for a subject from each group tested in the cognitive laboratory

2.5.4.2 Reaction times

Each subject's RT dataset was analyzed individually since group statistics could not be performed with three subjects. The EC subject did not show a validity effect (p=.231). In contrast, this subject did reveal an overall invalidity effect ($F_{(2,98)}$=12.1, p=2.1x10^{-5}) with response times slowest during invalidly cued trials compared to validly cued trials (p=1.8x10^{-4}) and non-directional trials (p=.001) (Figure 10).

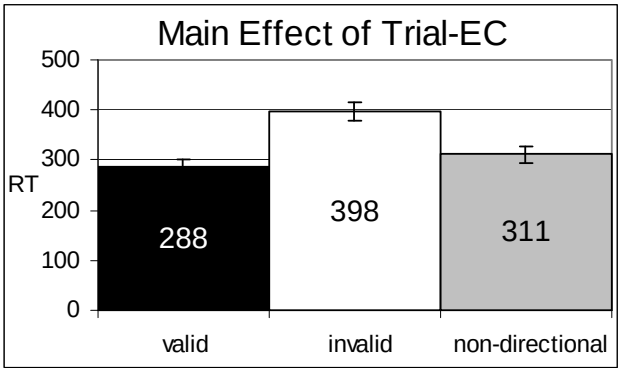

Figure 10. EC subject's mean RT for each trial type. Invalid RT is slowest compared to valid RT (p=1.8x10^{-4}) and non-directional RT (p=.001). Error bars represent the standard error of the mean.

This subject's data also revealed a main effect of motivational condition ($F_{(2,228)}$=11.9, p=1.2x10^{-5}); WIN generated the fastest RTs compared to LOSE (p=.025) and NEUTRAL (p=1.2x10^{-5}) (Figure 11).

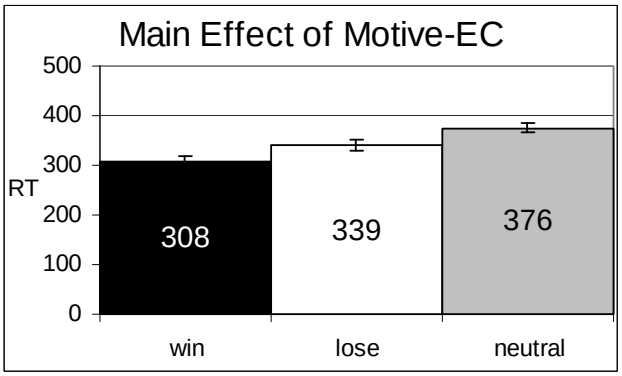

Figure 11. EC subject's mean RT for each motive condition. WIN RT is fastest compared to LOSE (p=.025) and NEUTRAL (p=1.2x10^{-5}). Error bars represent the standard error of the mean.

The MCI subject's RT data revealed a main effect of trial type ($F_{(2,98)}$=5.91, p=.004); non-directional trials were responded to faster than valid trials (p=.001) and invalid trials (p=.034)

(Figure 12). In contrast, the MCI subject did not reveal an effect for motivation ($F_{(2,256)}$=.701, p=.497).

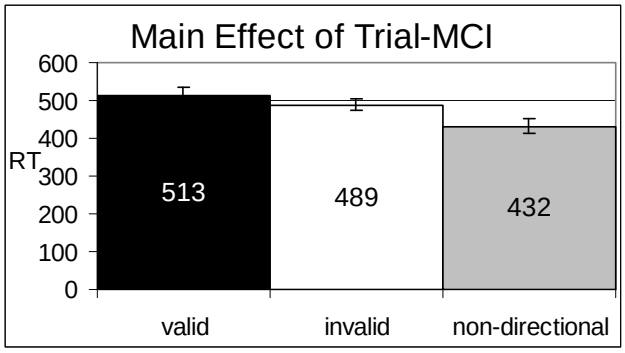

Figure 12. MCI subject's mean RT for each trial type. Non-directional RT is fastest compared to valid RT (p=.001) and invalid RT (p=.034). Error bars represent the standard error of the mean.

The PRAD subject's RT data revealed no significant RT differences among the three trial types ($F_{(2,94)}$=.86, p=.43) or the three motive conditions ($F_{(2,230)}$=1.02, p=.36).

2.5.4.3 Maintenance of Fixation

Eye tracking data was successfully recorded from the PRAD and EC subjects (**Table 8**). Since very few trials were contaminated with a saccade, no trials were excluded from the analysis.

Subject	Win	Lose	Neutral
PRAD	3	3	1
EC	9	13	18

Table 8. Number of saccades made in each condition

2.5.4.4 Debriefing

The questionnaires revealed that the EC and MCI subjects were aware of the monetary components of the task and defined the feedback symbols correctly. The PRAD subject was aware that money could be won or lost during the experiment, but did not remember how much or what the feedback symbols represented.

2.5.5 Discussion

The results from this pilot study suggested that online feedback increased awareness about monetary incentives. Furthermore, although the degree of awareness varied between subjects, we reasoned that we would be able to use the data collected on the questionnaire to evaluate this effect. Therefore a decision was made to begin the main phase of testing with the knowledge that the PRAD patients might not have the memory capacity required to examine endogenous motivational manipulations. Therefore I suspected that while between-group comparisons on the attention task would be valid the comparisons of the influence of motivation on attention might have to be limited to EC vs. MCI.

CHAPTER 3: FMRI EXPERIMENT

3.1 Introduction

The present experiment was conducted to examine the behavioral and neural correlates of motivational influences on the top-down control of covert visual spatial attention processes in patients with probable Alzheimer's disease (PRAD), patients with mild cognitive impairment (MCI), and healthy age-matched controls (EC). Previous experiments have found that attentional focusing upon spatial location is intact in aging subjects and in patients in early stages of dementia. However, disengaging or reorienting attention from an incorrect spatial location to another location is specifically impaired in patients with mild Alzheimer's type dementia (AD) (Parasuraman et al., 1992; Tales et al., 2005). This is demonstrated by significantly slower RTs following invalid directional cueing in AD compared to age-matched controls. In young controls, motivational incentives have been shown to alleviate the RT costs associated with disengaging attention during invalidly cued trials (Small et al., 2005). Specifically, subjects responded faster to invalidly cued trials when there was a possibility of losing money compared to when no monetary incentives were offered. Furthermore, the data presented in the pilot studies indicate that when feedback about performance is provided, subjects benefit even more from monetary incentives. Specifically, subjects responded faster to validly cued and invalidly cued trials when there was a possibility of winning or losing money compared to receiving no incentives (see Figure 7).

The goal of the current experiment was to test patients with PRAD, patients with MCI, and aged-matched controls on the modified Posner paradigm with feedback while being scanned

with functional magnetic resonance imaging (fMRI). Since attentional focusing is reported to be intact in the aging and mild Alzheimer's populations (Parasuraman et al., 1992; Tales et al., 2005), I predict that all three groups of subjects will respond faster to the validly cued trials than non-directionally cued trials, however, overall RTs will be slower in patients with PRAD, presumably due to deficits in areas of the spatial attention network. The valid cue acts as a top-down mechanism of attention by generating visual spatial expectancy towards the target, thereby decreasing RT. I predict that this validity effect will be associated with activity in the canonical spatial attention network including regions of the posterior parietal cortex, the frontal cortex, and the cingulate gyrus (Gitelman et al., 1999; Small et al., 2003) in EC and MCI subjects. Patients with PRAD, however, will not show activity in regions of the posterior parietal cortex and cingulate gyrus because hypoperfusion has been reported in these areas (Buck et al., 1997; Prvulovic et al., 2002; Boxer et al., 2003; Miller et al., 2003). The deficits will be observed with slower response times.

I predict that in patients with MCI and age-matched controls disengagement from an invalidly cued location will activate regions of the inferior parietal lobule (IPL) near the tempero-parietal junction (TPJ), the intraparietal sulcus (IPS), and the orbitofrontal cortex (OFC) similar to young controls (Nobre et al., 1999; Corbetta et al., 2002; Small et al., 2003). In contrast, I predict that patients with PRAD will respond significantly slower to invalidly cued trials compared with age-matched controls and that this will be associated with reduced activation in regions important for disengaging attention (Parasuraman et al., 1992). All groups are predicted to activate regions in early visual cortex corresponding to areas 18 and 19 during sensory analysis of the cue (Shulman et al., 1997; Hopfinger et al., 2000; Pessoa et al., 2003).

The visual cortex is also upregulated during top-down modulation of spatial attention via information from the frontal and parietal cortices. Moreover, PRAD subjects are thought to recruit the ventral visual pathway and occipito-temporal regions to compensate for the dysfunction of the dorsal visual pathway leading into the parietal cortex.

Motivational incentives are predicted to influence the top-down control of spatial attention by speeding up target detection times for EC and MCI subjects. This will be associated with greater activity in regions that modulate the interaction of motivation and attention, specifically the posterior cingulate cortex (PCC) during visual spatial expectancy and the inferior parietal lobule (IPL) during disengagement. These regions show reduced activity in PRAD subjects which may be due to the loss of inputs from the orbitofrontal cortex (OFC). As mentioned previously, the OFC is important for goal-directed behavior and its deterioration results in apathy while the PCC is thought to modulate the interaction between motivation and attention. Moreover, atrophy and AD pathology in these regions may influence the slower reaction times and reduced neural activity in the PRAD group, even when incentives are present (Van Hoesen et al., 2000; Callen et al., 2001). In the healthy aging and MCI groups, I predict that motivation will influence the top-down control of spatial attention by improving response time and enhancing neural activity in regions that modulate this interaction, however, the influence will be less pronounced or absent in the PRAD group.

3.2 Participants

Twelve EC subjects (9 women, 3 men) with a mean age of 73 (63-91), 12 MCI patients (10 women, 2 men) with a mean age of 71 (65-83), and 7 PRAD patients (6 women, 1 man) with a mean age of 75 (61-86) participated in the study (see **Error! Reference source not found.**).

As mentioned in the pilot studies, we recruited participants from the Alzheimer's Disease Center Clinical Core subject registry at Northwestern University (NADC) who underwent neurological exams and neuropsychological testing to determine level of cognitive impairment. Details regarding these rating scales and test scores are specified in the first set of pilot experiments. Each subject's test scores are reported in Error! Reference source not found. along with the cutoff scores needed to be classified as EC, MCI, or PRAD.

Individuals that are identified as EC meet the following criteria: 1) at least 10 years of formal education; 2) live independently in the community with no need for assistance in activities of daily living, as confirmed by a caregiver; 3) MMSE score >28, CDR = 0, indicating no dementia; and 4) scores on the specified neuropsychological tests within 1 SD of average for their age.

The diagnosis of MCI comprises criteria recommended by Petersen and colleagues (Petersen et al., 1999; Shah et al., 2000; Petersen et al., 2001; Petersen, 2004). These include: 1) MMSE score > 28 and CDR = 0 or 0.5, indicating questionable dementia; 2) availability of an informant to verify the absence of impairments in daily living activities; 3) a score on Logical Memory II of the Wechsler Memory Scale Revised (WMS-R) of 1.5 SD or more below average for age; and 4) scores on tests of other cognitive functions within 1.0 SD of the average for age or better. During the Wechsler logical memory tests, the examiner reads two stories to the subject and asks them to recall as much as possible. The first subtest is administered immediately after both stories are read and the second subtest is conducted at least 30 minutes later. Scoring is based on 25 key points from each story for a max score of 50 points (Sullivan, 1996).

As mentioned in the first set of pilot experiments, the diagnosis of PRAD was based on criteria proposed by McKhann and colleagues (McKhann et al., 1984). Furthermore, other inclusion and exclusion criteria for the participants are also specified in the first set of pilot experiments.

3.3 Procedure

Prior to the experiment, subjects were told that they would be participating in two sessions on the same day lasting between 90 minutes and 2 hours. The first session took place at the cognitive laboratory and the second session at the 3T Trio magnet in the Olson Pavilion.

3.3.1 Cognitive Laboratory

After signing the consent forms (see Appendix F) and filling out the MRI screening forms (see Appendix E), detailed instructions about the task are given. The experimental set-up and methods for measuring eye-movements are the same as those described in the pilot study (see Figure 2). Since eye-tracking equipment was not available in the 3T magnet at the time this study was conducted, this was our only measurement of eye-movement. After the eyes were calibrated the task was explained again (see Figure 3). Subjects then performed a full run of 152 trials without feedback while eye-movements were recorded. As detailed in the pilot experiments, RTs from this run were used to calculate cut-off RTs upon which to base wins and loses.

3.3.2 3T Imaging Laboratory

After the cut-offs were determined, subjects were escorted to the 3T magnet where they performed the second part of the experiment. Prior to entering the scanner, task instructions were provided again. Subjects were familiarized with the feedback symbols and the reward

contingencies (see Figure 5). The scanning procedure was then thoroughly explained to the subject. They were asked to lie on the MRI patient table with their head placed in the 8-channel head coil used to record the imaging signal. A vacuum pillow was used to stabilize their head and minimize head movements. Subjects were able to view the stimuli projected onto a non-magnetic screen through an angled mirror that rested on the head coil. They were asked to respond to the stimuli using a fiber optic button box connected to a Dell computer in the viewing room that presented the visual stimuli and recorded the RTs. Since the MRI scanner makes loud banging noises while performing measurements, the subject wore specially designed headphones to reduce the noise. They were still able to communicate freely with the experimenters through an intercom system.

Three functional imaging runs were administered to the subject (corresponding to each of the three motivational conditions). These were followed by a T1 volume scan for anatomic reference. For the functional scans, thirty-four contiguous 3 mm slices aligned to the AC-PC line were acquired using a susceptibility weighted single shot EPI method to image the regional distribution of the Blood Oxygen Level Dependent (BOLD) signal (TR/TE 2100/30ms, flip angle 90, FOV 240, 64 x 64 matrix). Each of the functional runs consisted of 196 scans; however, the MR signal was allowed to achieve equilibrium over six initial scans that were excluded from analysis, resulting in 190 scans for each run.

After the experiment, subjects were asked to fill out the questionnaire (see Appendix G). This was used as a post hoc measurement to assess the different populations' awareness of the task. They were then paid for their participation and given their total earnings, out of a possible $50.

3.3.3 Analysis of Eye Movement Data

As in the pilot experiments, eye-movement data was analyzed with custom-designed software, ILAB (Gitelman, 2002) running in the MATLAB environment (Mathworks, Natick, MA).

3.3.4 Analysis of Reaction Time Data

Trials with RTs shorter than 100 ms or longer than 1000 ms were discarded because they indicated that the subject was not paying attention. Fortunately, very few trials needed to be omitted. In order to evaluate the RT data, a multiple analysis of variance (MANOVA) was conducted on mean RTs to each of the trials in each of the 3 motivational conditions using 3 within-subject factors (cue type, motivational condition, and SOA) and one between-subject factor (group) design. Each of the three within-subject variables had three levels: cue type = valid, invalid, and non-directional; motivational condition = win, lose, and neutral; and SOA = 200, 400, and 800 msec. The between-subject variable also had three levels (PRAD, MCI and EC groups).

3.3.4.1 Cue Benefit Calculation

Valid cues have been shown to elicit faster target detection times in young subjects (Small et al., 2003; Small et al., 2005). Previous studies have measured the magnitude of this benefit derived from valid cues using the following equation:

$$\text{Cue Benefit Score} = 100 * \frac{\left(mean\left(\log_{10}\left(RTn_{ND(soa)}\right)\right)\right) - \log_{10}\left(RT(w,l,n)_{VAL(soa)}\right)}{mean\left(\log_{10}\left(RTn_{ND(soa)}\right)\right)}$$

The cue benefit equation was formulated to calculate the extent that the valid cue speeds response time. The data first undergoes log transformations in order to reduce skewness. Each

subject's mean RT per SOA for non-directionally cued trials ($RTn_{ND(soa)}$) during the neutral condition is used as a baseline comparison. This number is compared to each valid trial RT for that SOA separately in win, lose, and neutral ($RT(w,l,n)_{VAL(soa)}$). According to the formula, if the RT to a valid trial is faster than the mean RT of the non-directional neutral trials for the same SOA, the result is a positive CBs. In contrast, if the RT to a valid trial is slower than this mean, the result is a negative CBs. Once the mean CBs were calculated for each condition, they were entered into a MANOVA with condition and SOA as within group factors and group as the between group factor.

3.3.4.2 Cue Cost Calculation

In addition to CBs for valid trials, a cue cost score (CCs) was formulated for invalid trials to determine the degree to which the misleading invalid cue impaired performance.

$$\text{Cue Cost Score} = 100* \frac{\log_{10}\left(RT(w,l,n)_{INV(soa)}\right) - \left(mean\left(\log_{10}\left(RTn_{ND(soa)}\right)\right)\right)}{mean\left(\log_{10}\left(RTn_{ND(soa)}\right)\right)}$$

According to this formula, if the RT to an invalid trial is slower than the mean RT of the non-directional neutral trials for the same SOA, the result is a positive CCs. This indicates that the misleading cue 'cost time'. In contrast, if the RT to an invalid trial is faster than the mean, this indicates that the misleading cue did not 'cost time'. The mean CCs were then entered into a separate MANOVA with condition and SOA as within group factors and group as the between group factor.

3.3.5 Analysis of fMRI Data

One hundred and ninety images were acquired during each run and each subject performed 3 runs. The original DICOM images were converted into a readable format consisting

of header and image files. The fMRI data was then analyzed using SPM2 software (Wellcome Department of Cognitive Neurology, London) running under the Matlab environment (Mathworks, Inc, Natick, MA) (Friston, 1995; Worsley, 1995; Turner et al., 1998). For each subject, functional images were first realigned and unwarped. The realignment procedure was used to minimize the effects of a subject's head movements. This procedure created a mean image of all the functional volumes which was used to co-register with the anatomical T1 image. Unwarping helped reduce motion-related image distortion due to excessive head movements. A slice timing correction was administered to the images since the slices were acquired in an interleaved fashion throughout each TR of 2.1sec. The purpose of the interleaved order was to minimize "cross-talk" between slice pulses. For example, since slice 2 is partially excited when acquiring slice 1, slice 2 should not be measured right away because it may include artifacts from slice 1. The slice timing correction shifts the signal so that it is as if all the slices were acquired at the same time, at ½ TR. Next, coregistration was used to line up the functional and anatomical volumes by pulling the mean image created in the realign and unwarp procedure into the space of the anatomical T1. Then, normalization was used to warp the functional and anatomical volumes into the space of a template brain. The first process in normalization was to determine the parameters needed to warp the co-registered mean image to the template, in this case, the EPI template. Those parameters were then applied to warp the functionals and the anatomical. The final step was to smooth the functional volumes by a 10 mm Gaussian kernel. Smoothing was used to increase sensitivity of the images by averaging out uncorrelated noise across voxels.

After these preprocessing steps were complete, design matrices were created for each subject. The goal of the design matrix was to test for brain activity related to the degree of visual

spatial expectancy (as measured by validly cued trials and CBs) or degree of disengagement (as measured by invalidly cued trials and CCs). First, a vector of scan onset times (max 190) was generated for each of the trial types for each condition. The onset times of the cue were used for the valid and non-directional trials, while the onset times of the target were used for the invalid trials. The idea was that visual spatial expectancy occurred during the valid cues but visual spatial disengagement did not occur until the invalid targets. A hemodynamic response function (HRF) was used to create regressors for each event type by scaling the event onsets. The standard HRF model supplied with SPM2 was used to optimize detection of peaks. The cue benefit and cue cost scores for individual trials were analyzed as a parametric interaction with the event onset regressor. This was done by entering the CBs for each valid trial and multiplying by the event onset vector for the valid trials. The same was done for the CCs and each invalid trial. These interaction vectors were then convolved with the HRF and included in a separate design matrix with the event onset vector. Contrasts for the parametric effect relate to the cue benefit or cue cost scores and discount the main effect of the event onset itself.

The main effects of these correlations with cue benefit and cue cost were examined by applying the following contrast (WIN+LOSE+NEUTRAL). To isolate the effect of incentive in each subject, a comparison of the WIN and LOSE correlations to the NEUTRAL correlation was performed (WIN+LOSE-NEUTRAL). This comparison is equivalent to taking the average of the WIN and LOSE regressors versus the NEUTRAL regressor. Other contrasts were performed to isolate the effect of each incentive compared to no incentive (WIN–NEUTRAL and LOSE–NEUTRAL). Activations were searched for at a voxel threshold of $p<.005$ and a cluster threshold of >3 voxels.

3.4 Behavioral Results

3.4.1 Accuracy Data

As in the pilot study, accuracy is determined by the number of responses to the target X plus the number of non-responses to the foil + divided by the total number of trials, 152. Across all motivational conditions, the mean accuracy performance was 85% for the EC group, 83.7% for the MCI group, and 76.3% for the PRAD group. A single factor ANOVA revealed a main effect of group $\{F_{(2,4)}$ 9.05, p=.015$\}$, such that the EC (p=.013) and MCI (p=.023) groups responded significantly more accurately than the PRAD patient group, but no difference in accuracy was found between the EC and MCI groups (p=.25). Despite these group differences, there were no differences in accuracy between the three motive conditions $\{F_{(2,4)}$ .03, p = 0.97$\}$, with the mean at 82%.

3.4.2 Reaction Time Data

3.4.2.1 Main Effect of Group

The MANOVA of RT data revealed a main effect of group $\{F_{(2,28)}$ 3.3, p = 0.05$\}$. Planned comparisons using one-tailed t-tests revealed that EC was faster than PRAD (p=.008) and there was a trend for EC being faster than MCI (p=.08) and MCI being faster than PRAD (p=.1) (Figure 13).

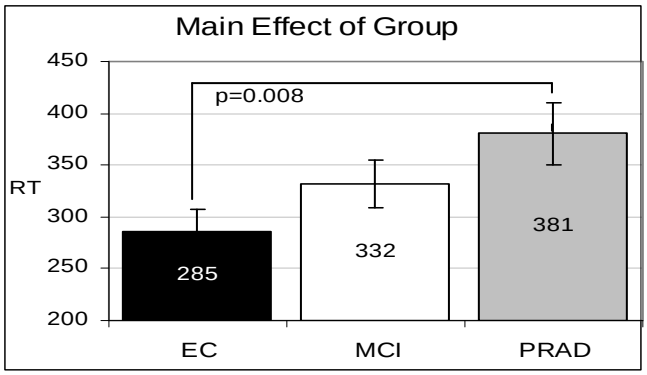

Figure 13. Main effect of group. The EC group responded significantly faster than the PRAD group (p=.008). Error bars represent standard errors of the mean.

3.4.2.2 Main Effect of Trial

There was also a main effect of trial $\{F_{(2,56)}\ 32.3,\ p = 4.6\times10^{-10}\}$ and planned comparisons revealed that this was due to all three groups responding fastest after the valid compared to the invalid ($p = 9.4\times10^{-7}$) and non-directional cues ($p = 6.5\times10^{-4}$) (Figure 14). Additionally, all three groups responded slower following the invalid cues compared to the non-directional cues ($p = 5.5\times10^{-6}$). Surprisingly, tests of within-subjects effects revealed no group by trial interaction $\{F_{(4,112)}\ 0.52,\ p = 0.7\}$. Thus all groups showed a validity and an invalidity effect, when collapsing across motivational conditions.

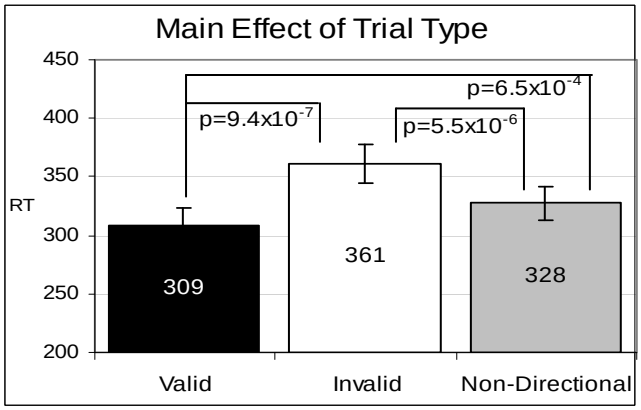

Figure 14. Main effect of trials. On average, all subjects responded faster to valid trials than invalid ($p=9.4\text{x}10^{-7}$) and non-directional trials ($p=6.5\text{x}10^{-4}$). Subjects also responded slower to invalid trials than non-directional ($p=5.5\text{x}10^{-6}$). Error bars represent standard errors of the mean.

3.4.2.3 Effects of SOA

Stimulus onset asynchrony (SOA), the time interval between cue onset and target onset, was another variable that caused significant differences in RT, resulting in a main effect of SOA {$F_{(2,56)}$ 7.96, p = 0.0009}. Planned comparisons between the three levels of SOA revealed that target detection was fastest at 800 msec compared to 400 msec (p = 0.012) and 200 msec (p = 0.0009) (Figure 15).

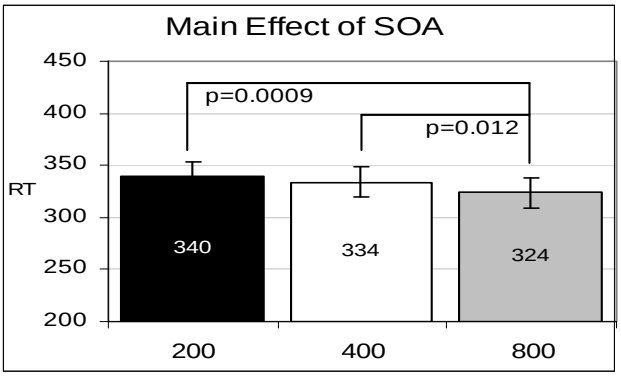

Figure 15. Main effect of SOA
On average, all subjects responded slower when the SOA was 800 ms compared to 200 ms (p=0.0009) and 400 ms (p=0.012). Error bars represent standard errors of the mean.

Besides the main effects of trial type and SOA, there was also an SOA by trial interaction in which SOA differentially influenced performance on the different trials {$F_{(4,112)}$ 10.5, p = 3×10^{-7}}. For example, performance did not differ between non-directional and invalid trials during the 200 msec SOA (p = 0.3), but differed significantly during the 400 (p = 9.4×10^{-8}) and 800 (p = 0.001) msec time intervals.

3.4.2.4 Group by Motive Interaction

There was a trend towards a group by motivation interaction {$F_{(4,84)}$ 1.72, p=.08 (one-tailed)}. Since the trend was in the predicted direction planned comparisons were performed and revealed that the EC group responded significantly faster during win compared to neutral (p = 0.04) and the MCI group showed a trend for responding faster during lose compared to neutral (p = 0.06) (Figure 15). There was no effect of motivation for the PRAD group (p > 0.2). That is,

they respond similarly whether they are winning, losing, or neither winning nor losing. Additionally, monetary incentives influenced group differences. When subjects could win money, EC performed significantly faster than PRAD ($p = 0.004$) and slightly faster than MCI ($p = 0.06$). When subjects could lose money, EC performed significantly faster than PRAD ($p = 0.03$) but not MCI ($p = 0.35$). When subjects could neither win nor lose money, all three groups performed similarly ($p > 0.1$).

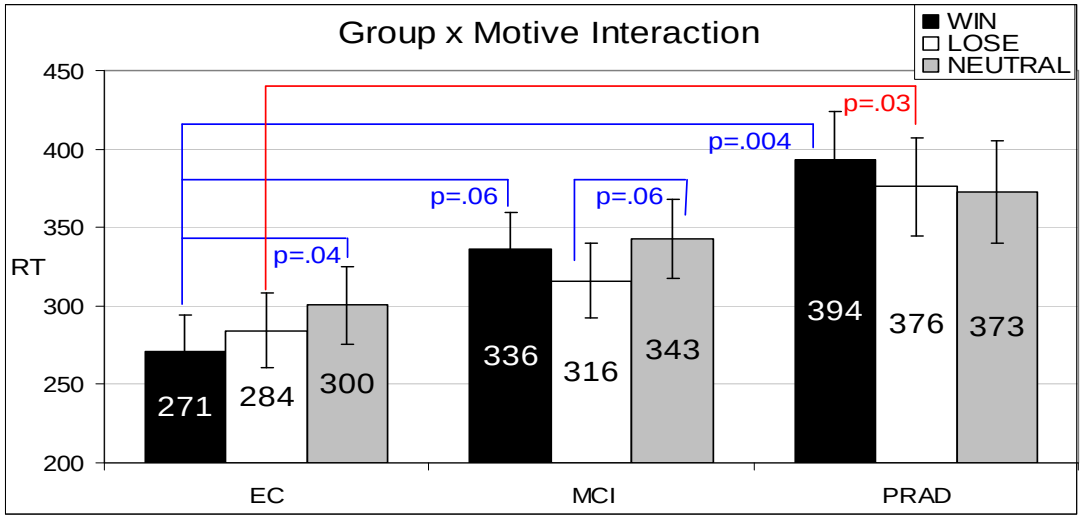

Figure 16. Group by motive interaction. The EC group responded faster during WIN than NEUTRAL ($p=0.04$). The MCI group responded slightly faster during LOSE than NEUTRAL ($p=0.06$). During WIN, the EC group responded significantly faster than the PRAD group ($p=0.004$) and slightly faster than the MCI group ($p=0.06$). During LOSE, the EC group responded faster than the PRAD group ($p=0.03$) but not the MCI group ($p=0.35$). Error bars represent standard errors of the mean.

3.4.3 Cue Benefit Scores

As mentioned previously cue benefit scores (CBs) were calculated to indicate the degree to which the valid cue speeded RT, presumably by biasing attention towards the cued spatial location. The mean CBs were entered into a repeated measures ANOVA with motive and SOA as within group factors and group as the between group factor. Planned comparisons revealed a tendency for a motive by group interaction $\{F_{(4,112)}\ 1.78, p = 0.07\}$ (Figure 17). During the WIN

condition, EC derived greater benefit from the valid cue than PRAD (p=0.02) and a tendency for greater benefit than MCI (p=0.09). During the LOSE condition, patients with MCI had greater CBs than patients with PRAD (0.035). Moreover, within the EC group, more cue benefit was generated during the validly cue trials in WIN than the validly cued trials in NEUTRAL (p=0.03). Within the MCI group, more cue benefit was generated during the LOSE condition than the NEUTRAL condition (p=0.05). In contrast, there was no effect of monetary incentive on CBs in the PRAD group (p=0.6).

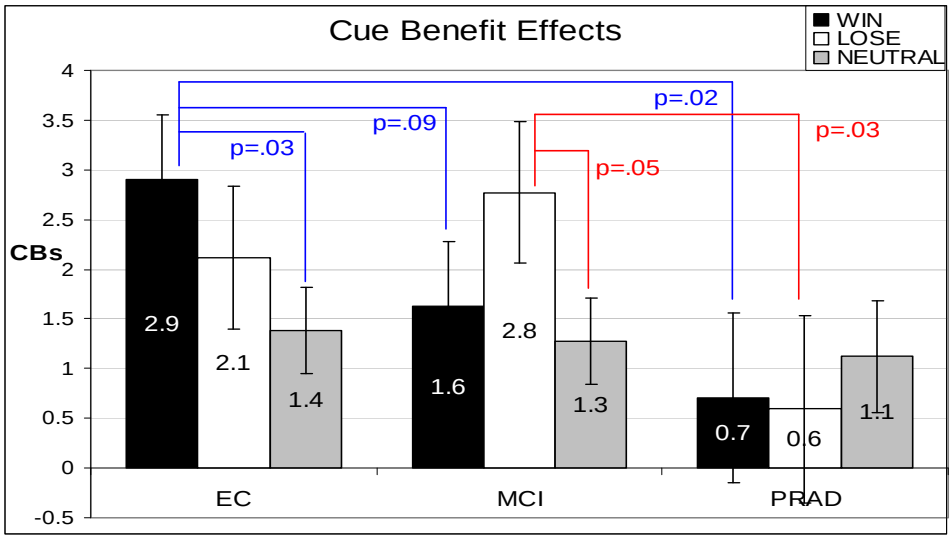

Figure 17. Cue Benefit Effects: Group by Motive Interaction. The EC group generated more CB during WIN than NEUTRAL (p=0.03). The MCI group generated more CB during LOSE than NEUTRAL (p=0.05). During WIN, the EC group generated more CB than the PRAD group (p=0.02) and slightly more than the MCI group (p=0.09). During LOSE, the MCI group generated more CB than the PRAD group (p=0.03). Error bars represent standard errors of the mean.

3.4.4 Cue Cost Scores

Cue cost scores (CCs) were calculated as previously described and the means were entered into a repeated measures ANOVA with motive condition and SOA as within group factors and group as the between group factor. The only significant difference was observed

between SOA $\{F_{(2,56)}\ 4.44, p = 0.02\}$. More time was lost due to disengagement during invalidly cued trials when the SOA was 400 msec compared to 200 msec (p=0.003).

3.4.5 Maintenance of Fixation

As in the pilot experiments, eye-movements were recorded in the cognitive laboratory. Since this was the only eye movement data that was collected, we made sure to provide subjects with ample feedback to encourage them to maintain fixation. By reinforcing the importance of fixation in the cognitive laboratory, we hoped that subjects would make very few saccades while performing the task in the scanner. Eye data was successfully recorded from all 31 subjects during the initial session in the cognitive laboratory prior to being scanned. On average, the EC subjects maintained fixation 85% of the time, the MCI patients maintained fixation 84% of the time, and the PRAD patients maintained fixation 82% of the time. No group differences were found between the amount of time maintaining fixations $\{F_{(2,28)}\ 0.63, p=0.541\}$

3.4.6 Questionnaire Data

Once the participants were finished performing the modified Posner task with feedback in the scanner, they were asked to fill out a questionnaire regarding various features of the experiment (see Appendix G). All but one subject completed the questionnaire. The person who did not complete the questionnaire was a patient with PRAD who reported that he/she "just wanted to go home". The first question on the form was "where were you instructed to look on the screen?" All 12 EC subjects responded correctly with 'center diamond'. However, only 10 of 12 MCI patients and 4 of 6 PRAD patients responded correctly. All 30 subjects that completed the questionnaire answered the second question correctly "when did you press the button?" by writing down "when I saw an X". The third question was "could you tell the

difference between X and + ?". About half the subjects (4 EC, 4 MCI, 6 PRAD) answered "not really" and the other half answered "yes, but only after I already responded". The next question on the form was "could you win or lose money during the experiment. How much?". All subjects answered "yes", but only 7 EC and 8 MCI wrote down "$50". The last question asked them to identify the three feedback symbols. All of the EC and MCI subjects answered correctly by writing down "win money, lose money, neither", respectively. However, only 2 out of 6 PRAD subjects answered correctly. Three PRAD subjects wrote down "money" and the other two did not write a response. Thus, the questionnaire responses indicated that EC and MCI groups understood the task and were aware of the monetary contingencies. In contrast, only a subset of patients in the PRAD group had a sufficient grasp of the task. The reaction times of the PRAD subjects that did grasp the task were compared to the reaction times of the PRAD subjects that did not grasp the task, however, response times were not very different from each other (<100 msec difference between the PRAD subgroups).

After finishing the questionnaire, participants were paid their earnings. On average, the EC subjects earned $21.10 during WIN and $18.81 during LOSE, while MCI patients earned $20.30 during WIN and $18.66 during LOSE, and PRAD patients earned $14.07 during WIN and $13.13 during LOSE. A single factor ANOVA revealed a main effect for motive condition $\{F_{(1,28)}\ 13.0,\ p = 0.001\}$ and group $\{F_{(2,28)}\ 6.0,\ p = 0.007\}$, but no group by motive interaction $\{F_{(2,28)}\ 0.71,\ p = 0.5\}$. Across all subjects, more money was earned during WIN (mean=$18.49, SE=$0.72) than LOSE (mean=$16.87, SE=$0.87) (p=0.001). In addition, the EC (mean=$19.96, SE=$1.19) (p=0.003) and MCI subjects (mean=$19.48, SE=$1.19) (p=0.006) earned more money than the PRAD patients (mean=$13.60, SE=$1.56).

3.5 fMRI Results

For every subject, parameters were estimated for the comparisons of interest (referred to as contrasts). Contrasts were made to compare activity during the validly cued trials with non-directional trials and invalidly cued trials with non-directional trials. Regression analyses were conducted to identify regions where activity correlated with CBs (spatial expectancy) and CCs (disengagement). Contrasts were also made to examine the brain regions recruited when winning and losing money influenced these attentional processes (WIN+LOSE-NEUTRAL). These contrasts were then entered into a second-level analysis, a one-sample t-test, to assess within-group effects. This random effects analysis was conducted for the EC and MCI groups separately. Random effects analyses yield significant activation only if it is present in all subjects within the group (Holmes & Friston 1998; Penny & Holmes 2003). In contrast, a fixed effects analysis was conducted for the PRAD patient group due to the smaller number of subjects. This analysis gives the average activation from all subjects within the group. The imaging analyses were guided by the reaction time data. Contrasts were created to compare trial types and motive conditions that generated significantly different response times. In most cases, neural activity was in accordance with the behavioral effects. Predicted peaks were considered significant if they had a $p<.005$ uncorrected across the whole brain or a $p<.05$ corrected using 15 mm spherical small volume corrections (SVC) with the centroid defined from previous studies in young control subjects (Small et al., 2003,2005; Gitelman et al., 1999; Kim et al., 1999; Nobre et al., 1999; O'Doherty et al., 2001; Corbetta & Shulman, 2002). Predicted regions included the posterior parietal cortex, frontal eye fields, cingulate cortex, insula, thalamus and orbitofrontal cortex during visual spatial expectancy and the inferior parietal lobule near the tempero-parietal

junction, intraparietal sulcus, orbitofrontal cortex, and occipito-temporal cortex during visual spatial disengagement. Activity was also predicted in early visual cortical areas along the medial wall of the striate cortex (BA 18) and lateral part of the prestriate cortex (BA 19) during the top down modulation of spatial attention processes. Moreover, motivational incentives are predicted to influence performance via the cingulate cortex.

3.5.1 Healthy Elderly

3.5.1.1 Validity Effect

As a group, the healthy elderly subjects responded significantly faster to validly cued trials compared with non-directionally cued trials (p=.044). The faster responses suggest that a visual spatial bias was generated in response to the valid cues. This validity effect was evaluated by comparing activation evoked during validly cued trials with activation evoked during non-directionally cued trials. As predicted, activity was observed in the superior parietal lobule (SPL) {21,-60,66; Z=2.77, p=.003} and insula {-36,9,6; Z=2.79, p=.003} (see Figure 18). Both peaks were significant at p<.005 uncorrected across the entire brain.

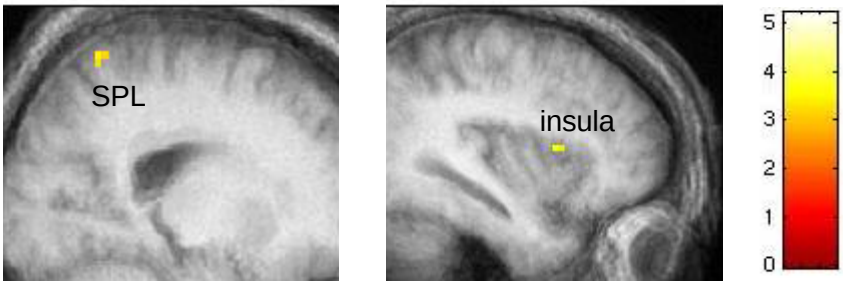

Figure 18. Sagittal sections showing activity in the superior parietal lobule (SPL) and insula during valid minus non-directionally cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 EC subjects. The images are thresholded at p < .005 and the color bar represents t-values.

3.5.1.1.1 Correlation with CBs

To test whether this area or other areas correlated with degree of expectancy, a regression analyses with the CBs was performed. The analysis takes into account the CBs associated with each valid trial as a parametric interaction and is done by regressing the CBs against the BOLD signal for all conditions (WIN+LOSE+NEUTRAL). As predicted, and consistent with results from the previous study in young subjects (Small et al., 2003; Small et al., 2005), activity was observed in the thalamus and the medial prefrontal cortex (MPFC) (see **Table 9**, Figure 19). These peaks were significant at p<.05 corrected using SVC.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(cor)}$ value
CBs Win+Lose+Neutral	Thalamus	18	-3	3	3.42	.003
	MPFC	-6	57	15	2.78	.04

Table 9. Brain regions linearly related to the degree of visual spatial expectancy generated across all conditions (WIN, LOSE, and NEUTRAL). MPFC=medial prefrontal cortex

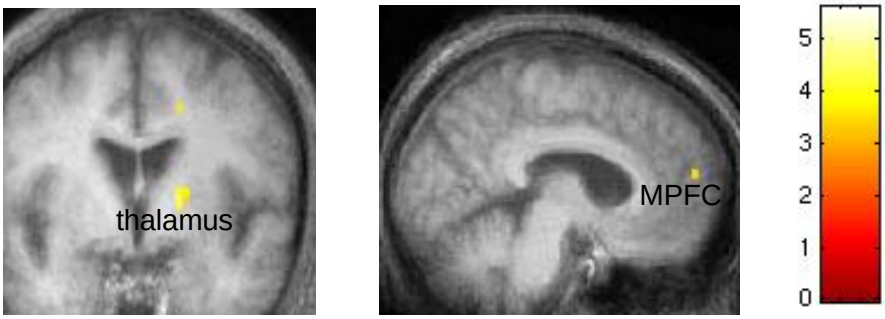

Figure 19. Correlation of cue benefit scores with validly cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 EC subjects. The coronal section shows the thalamus and sagittal section shows the medial prefrontal cortex (MPFC). The images are thresholded at p < .005 and the color bar represents t-values.

3.5.1.1.2 Interaction between motivation and validity effect

The RT data indicated that the EC subjects had a tendency to respond fastest to validly cued trials when there was a chance to win money compared to receiving no incentive (p=.067).

In order to identify brain regions underlying this interaction, neural activity during valid trials in WIN was compared to neutral (valid WIN - valid NEUTRAL). As predicted, activity was present in the posterior cingulate cortex (PCC) {3,-45,24; Z=2.58, $p_{(cor)}$=.05}, which was significant at p<.05 corrected using a SVC (see Figure 20).

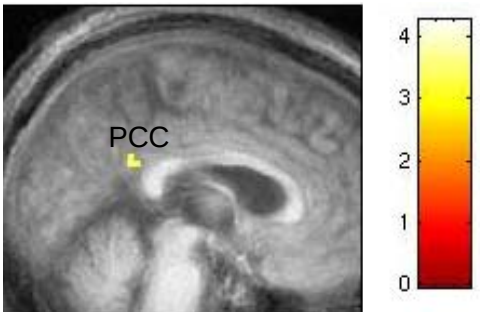

Figure 20. Sagittal section showing the posterior cingulate cortex (PCC) during validly cued trials in WIN-NEUTRAL. Data are from a one-sample t-test of the 12 EC subjects. The image is thresholded at p < .005 and the color bar represents t-value.

In addition to being faster at validly cued trials during WIN compared to NEUTRAL, more cue benefit was generated during WIN compared with NEUTRAL (p=.03). When these parametric effects were compared, activity was present in the orbitofrontal cortex (OFC) {-15,45,-18; Z=3.86, $p_{(cor)}$=.01}, a predicted region which was significant at p<.05 corrected using a SVC (see Figure 21).

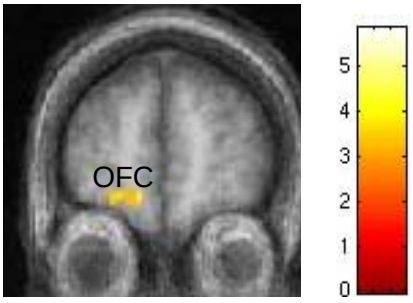

Figure 21. Coronal section showing the orbitofrontal cortex (OFC) in the correlation of cue benefit scores with validly cued trials in WIN-NEUTRAL. Data are from a one-sample t-test of the 12 EC subjects. The image is thresholded at p < .005 and the color bar represents t-value.

Unlike the cue benefit effect for WIN-NEUTRAL, analysis of the RT data from the EC group did not reveal greater cue benefit during LOSE compared with NEUTRAL (p=.33). When the parametric effects for LOSE and NEUTRAL were compared, neural activity was observed in the OFC, however the peak was not the same as reported above and did not reach significance.

3.5.1.2 Invalidity Effect

As a group, the healthy elderly individuals responded slower to invalidly cued trials compared with non-directionally cued trials (p=.009), suggesting that attention had to be disengaged. The main effects of disengaging attention from an invalidly cued location were examined by comparing neural activation during the invalidly cued trials with neural activation during the non-directionally cued trials. Activity was present in the visual cortex (area 19) {39,-87,9; Z=3.97, $p_{(cor)}$=.014} and the OFC {30,39,-21; Z=3.27, $p_{(cor)}$=.04}, predicted regions that were significant at p<.05 corrected using SVC (see Figure 22).

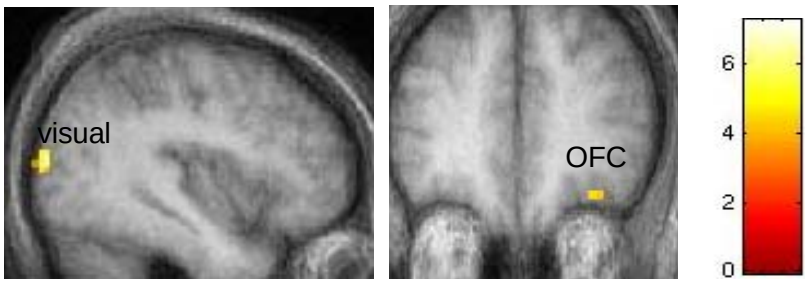

Figure 22. Brain responses during invalid minus non-directionally cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 EC subjects. The sagittal section shows activity in the visual cortex (BA 19) and the coronal section shows the orbitofrontal cortex (OFC) peak. The images are thresholded at p < .005 and the color bar represents t-value.

3.5.1.2.1 Correlation with CCs

To determine the regions that were correlated with the degree of disengagement, the CCs were regressed against the BOLD signal generated during invalidly cued trials. Activity in a separate region of visual cortex corresponding to area 19 {21,-93,3; Z=3.15, p=.001} was found to positively correlate with the degree of disengagement generated during the invalid trials (see Figure 23) and was significant at p<.005 uncorrected over the entire brain.

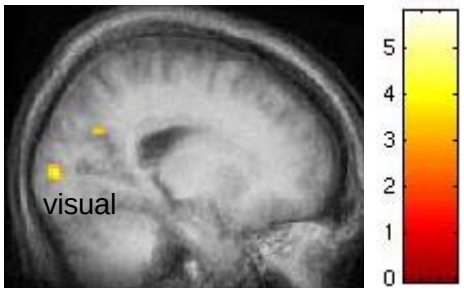

Figure 23. Correlation of cue cost scores with invalidly cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 EC subjects. The sagittal section shows the visual cortex (BA 19). The image is thresholded at $p < .005$ and the color bar represents t-value.

3.5.1.2.2 Interaction between motivation and invalidity effect

The healthy elderly subjects responded slowest to invalidly cued trials and were significantly slower on these trials during NEUTRAL compared to WIN (p=.041). To extract the brain areas that are important for the interaction between visual spatial disengagement and monetary reward, activity during the invalidly cued trials when subjects were winning money was compared to activity during invalidly cued trials when no monetary incentives were offered (i.e. NEUTRAL). This contrast resulted in activity in a separate region of the visual cortex near the fusiform gyrus {15,-54,-6; Z=2.82, p=.002} (see Figure 24), which was significant at p<.005 uncorrected over the entire brain.

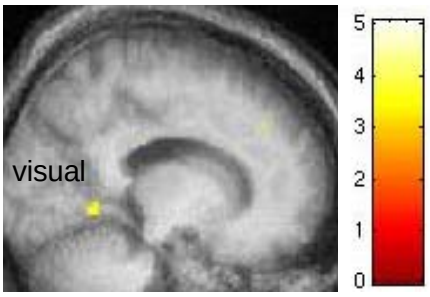

Figure 24. The visual cortex (fusiform gyrus) is active during invalidly cued trials when winning money was compared to neutral (WIN-NEUTRAL). Data are from a one-sample t-test of the 12 healthy elderly subjects. The image is thresholded at $p < .005$ and the color bar represents t-value.

Even though there was a difference in RTs during invalidly cued trials in WIN vs. NEUTRAL, there was no significant difference in CCs between the three conditions. Moreover, when the parametric effects of CCs were compared between WIN and NEUTRAL, no predicted regions showed a significant correlation with CCs.

3.5.1.3 Main Effect of Motivation

Irrespective of the task and hence attention processes (spatial expectancy or disengagement), the healthy elderly subjects responded faster when they were winning money compared to neutral (p=.036). To extract the neural activity responsible for this effect, I examined the neural response generated across all trials during WIN compared with all trials during NEUTRAL. Predicted activity was present in the anterior and posterior cingulate cortices as well as visual cortex area 18 (see **Table 10**, Figure 25). These peaks were significant at p<.05 corrected using SVC.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(cor)}$ value
Win - Neutral	ACC	0	51	15	3.09	.05
	PCC	-6	-57	33	2.60	.03
	Visual	-6	-54	6	2.77	.05

Table 10. Brain regions associated with winning money compared to neutral. ACC=anterior cingulate cortex, PCC=posterior cingulate cortex

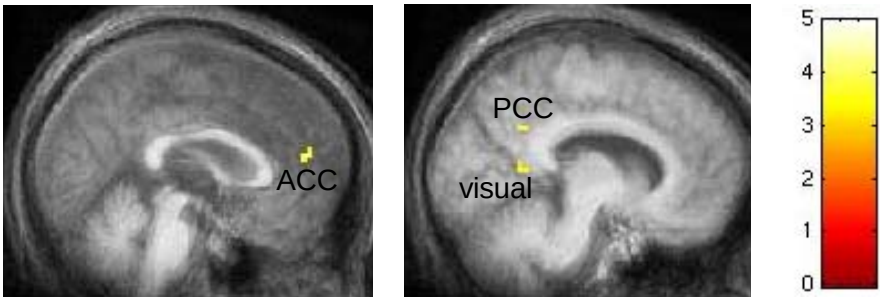

Figure 25. Brain response when winning money was compared to neutral, irrespective of attentional demand. Data are from a one-sample t-test of the 12 EC subjects. The sagittal sections show the anterior cingulate (ACC), posterior cingulate (PCC) and visual cortex (BA 18). The images are thresholded at p < .005 and the color bar represents t-values.

3.5.1.4 Discussion

Analysis of the RT data revealed that the healthy elderly subjects successfully used the valid cues to generate visual spatial expectancy. Specifically, targets following valid cues were

detected significantly faster compared to target detection following non-directional cues. This validity effect was associated with activity in the SPL and insula, which is in accordance with previous studies in young individuals that demonstrate activity in these regions during tasks of covert spatial attention (Gitelman et al., 1999; Kim et al., 1999). However, activity in neither the SPL nor insula correlated with the degree of visual spatial expectancy (as measured by CBs). Instead, a region of the MPFC and thalamus were found to be linearly related to expectancy. Since activity in these regions has previously been shown to correlate with visual spatial expectancy in healthy young subjects (Small et al., 2003; Small et al., 2005), these results suggests that both healthy young and elderly individuals recruit common neural circuits when they generate spatial biases.

I also found that the spatial biases were enhanced by monetary incentives. Specifically, the possibility of winning money was associated with faster target detection compared to target detection when offered no incentives. Like young controls (Small et al., 2005), EC subjects exhibited activity in the PCC when they saw valid cues during WIN compared to NEUTRAL. Taken together these results provide further evidence for the role of the PCC in top-down control of attention when motivational incentives are present. However, unlike young subjects, PCC activity did not increase linearly with the degree of spatial expectancy in the elderly subjects. Instead, activity in the OFC was found to correlate positively with the degree of expectancy when reward was offered. Since OFC activity was also reported in the previous study with young controls during this enhancement (Small et al., 2005), the OFC may be better at regulating the motivational influence on spatial expectancy. Moreover, the OFC region has been previously reported in studies investigating incentive behaviors and reward processing in humans (Gottfried

et al., 2003; McClure et al., 2004; Knutson et al., 2005). Taken together, these results suggest that the enhancement of attention by limbic regions differs between young and elder controls and may not be as effective in aging.

In this study, the elderly controls exhibited an invalidity effect since they responded significantly slower to invalidly cued trials than non-directionally cued trials. This effect was associated with activity in the OFC and visual cortex. These regions have been previously implicated in visual spatial disengagement in healthy young subjects (Nobre et al., 1999). However, the correlation analysis with CCs indicated that activity in neither of these regions was linearly related to disengagement. Rather a separate region of the visual cortex was the only predicted region found to correlate linearly with the degree of disengagement; activity increased with the degree to which the invalid cue induced disengagement. Yet another region of visual cortex was active when the possibility of winning money reduced the invalidity effect compared with receiving no incentives. These results suggest that the visual cortex plays an important role in modulating the influence of motivation on top down processes of spatial attention in healthy elderly individuals. Since activity in the visual cortex was specific to invalidly cued trials, this may be due to task difficulty or longer periods of attention needed for disengaging and reorienting to the target.

A main effect of motivational condition was also observed in the EC group. Across all trials, target detection was significantly faster when subjects were offered monetary reward compared with receiving no incentives. Improved performance was associated with activity in the cingulate and visual cortices. Previous studies have reported the anterior cingulate in tasks requiring target detection (Posner et al., 1990), conflict monitoring (Pardo et al., 1990; Paus et

al., 1993; Botvinick et al., 2004), and reward based decision making (Bush et al., 2002; Williams et al., 2004). In the current study, motivational incentives enhanced activity in both the anterior and posterior cingulate cortices. Further evidence for the role of the cingulate gyrus in motivationally influenced behavior comes from anatomical studies that illustrate its interconnections with core limbic areas such as the amygdala and frontoparietal neocortical areas (Mesulam, 1981; Mesulam, 2000).

3.5.2 MCI

3.5.2.1 Validity Effect

Patients with MCI showed a validity effect; they responded significantly faster to validly cued trials compared with non-directionally cued trials (p=.029). To extract the brain regions that were responsible for this validity effect, activity during the valid trials was compared with activity during the non-directional trials. As predicted, activity was present in the insula {-36,3,3; Z=3.51, $p_{(cor)}$=.039}, which was significant at p<.05 corrected using a SVC as described above (see Figure 26). This activation overlapped with the insular activity isolated by this contrast in the EC group analysis.

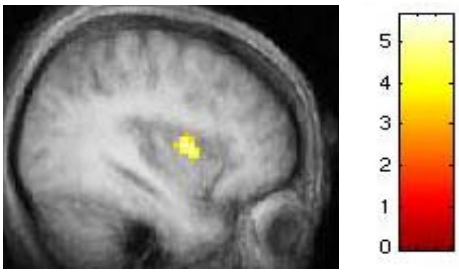

Figure 26. Insula activity during valid minus non-directionally cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 MCI subjects. The image is thresholded at p < .005 and the color bar represents t-values.

3.5.2.1.1 Correlation with CBs

To determine the regions that positively correlated with the degree of visual spatial expectancy generated during validly cued trials, CBs were regressed against the BOLD signal during validly cued trials collapsed across all three motive conditions. Activity was observed in the anterior cingulate (ACC) and posterior cingulate cortices (PCC), the precuneus, and the visual cortex corresponding to area 18 (see **Table 11**, Figure 27). The predicted peaks did not survive SVC, however, they were significant at p<.005 uncorrected over the entire brain.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(unc)}$ value
CBs Win+Lose+Neutral	Precuneus	9	-57	48	2.96	.002
	Visual	0	-51	15	2.74	.003
	ACC	-9	42	12	2.66	.004
	PCC	0	-57	30	2.61	.005

Table 11. Brain regions linearly related to the degree of visual spatial expectancy generated across all conditions (WIN, LOSE, and NEUTRAL). ACC=anterior cingulate cortex, PCC=posterior cingulate cortex

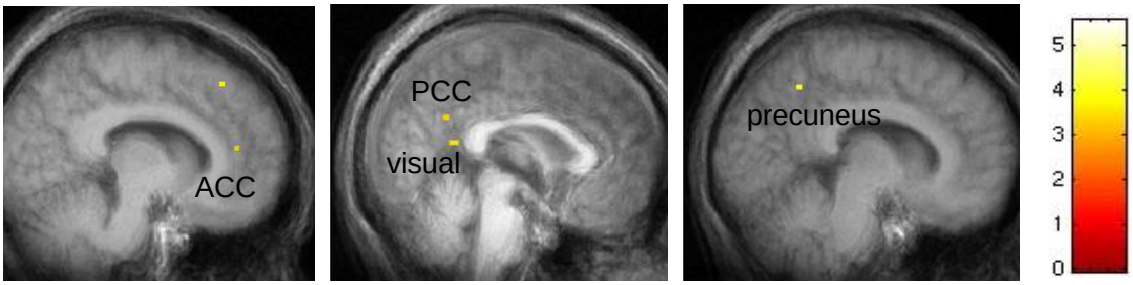

Figure 27. Correlation of cue benefit scores with validly cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 MCI subjects. The sagittal sections show the anterior cingulate (ACC) and posterior cingulate (PCC) cortices, the precuneus, and visual cortex (BA 18). The images are thresholded at $p < .005$ and the color bar represents t-value.

3.5.2.1.2 Interaction between motivation and validity effect

MCI patients responded fastest to validly cued trials when there was a possibility of losing money compared to receiving no incentive (p=.047). To examine the neural correlates of this behavioral effect we examined brain response during the validly cued trials in LOSE compared to NEUTRAL. A region of the posterior parietal cortex near the inferior parietal lobule (IPL) was the only region of the spatial attention network that was preferentially active during valid trials in LOSE-NEUTRAL {60,-45,36; Z=3.82, $p_{(unc)}$=.00007} (see Figure 28). This peak was significant at p<.005 uncorrected across the entire brain.

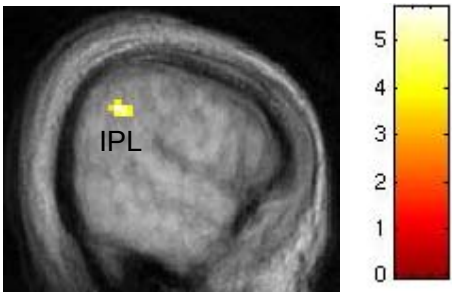

Figure 28. Sagittal section showing inferior parietal lobule (IPL) activity during validly cued trials in LOSE-NEUTRAL. Data are from a one-sample t-test of the 12 MCI subjects. The image is thresholded at $p < .005$ and the color bar represents t-value.

In addition to responding faster to validly cued trials during LOSE compared with NEUTRAL, more cue benefit was generated during LOSE compared with NEUTRAL, as evidenced by analysis of the CBs (p=.05). Regressing the CBs against BOLD signal in LOSE compared to NEUTRAL isolated responses in the left PCC {-15,-45,24; Z=3.15, $p_{(unc)}$=.001} and right precuneus {12,-51,51; Z=2.94, $p_{(unc)}$=.002} (see Figure 29). Both peaks were significant at p<.005 uncorrected over the entire brain.

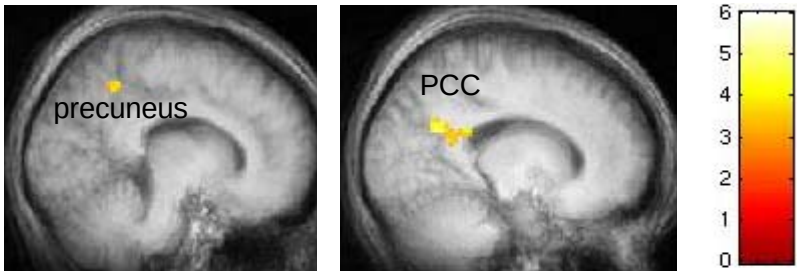

Figure 29. Correlation of cue benefit scores with validly cued trials in LOSE-NEUTRAL. Data are from a one-sample t-test of the 12 MCI subjects. The sagittal sections show the right precuneus and left posterior cingulate cortex (PCC). The images are thresholded at $p < .005$ and the color bar represents t-values.

3.5.2.2 Invalidity Effect

The MCI patients also showed an invalidity effect, responding slower to invalidly cued trials compared to the non-directionally cued trials (p=.002). To extract the regions associated with this invalidity effect, activity during the invalidly cued trials was compared with activity during the non-directionally cued trials collapsed across all three conditions

(WIN+LOSE+NEUTRAL). This produced activity in visual cortex corresponding to area 19 {-42,-81,15; Z=2.83, $p_{(unc)}$=.002} (Figure 30), which was significant at p<0.005 uncorrected over the entire brain.

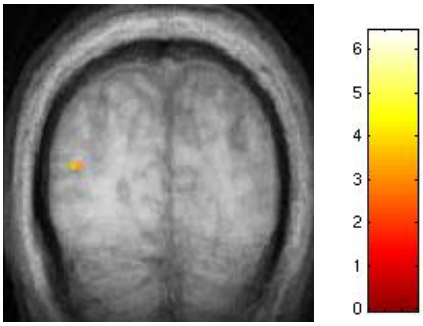

Figure 30. Coronal section showing visual cortex activity (BA 19) during invalid minus non-directionally cued trials collapsed across all conditions (WIN, LOSE and NEUTRAL). Data are from a one-sample t-test of the 12 MCI subjects. The image is thresholded at p < .005 and the color bar represents t-value.

To determine if activity in this or any other regions correlated with the degree of disengagement generated during the invalidly cued trials, the CCs were regressed against the BOLD signal generated during the invalidly cued trials collapsed across all three conditions (WIN+LOSE+NEUTRAL). Regions where activity correlated with the invalidity effect included the intraparietal sulcus (IPS) in both hemispheres (see **Table 12**, Figure 31). Both IPS peaks were significant at p<.005 uncorrected over the whole brain.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(unc)}$ value
CCs Win+Lose+Neutral	IPS	36	-63	54	3.12	.001
		-30	-48	63	3.19	.001

Table 12. Brain regions associated with the degree of disengagement generated across all conditions. IPS=intraparietal sulcus

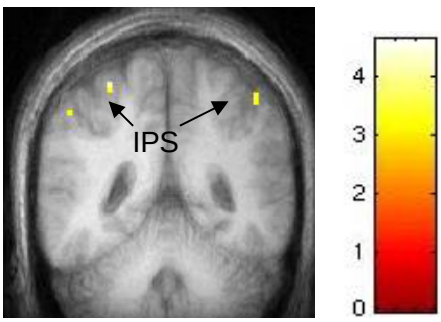

Figure 31. Correlation of cue cost scores with BOLD signal generated during invalidly cued trials collapsed across all conditions (WIN, LOSE, and NEUTRAL). Data are from a one-sample t-test of the 12 MCI subjects. The coronal section shows the intraparietal sulcus (IPS) on both sides. The image is thresholded at p < .005 and the color bar represents t-value.

3.5.2.2.1 Interaction between motivation and invalidity effect

The behavioral data indicated that there were no significant differences in RT to invalidly cued trials across the three motivational conditions. Likewise, the amount of disengagement generated during the invalidly cued trials (as measured by CCs) did not differ among the three conditions. Regardless of the lack of behavioral effects, brain responses were examined to determine if any regions were active during disengagement when incentives were offered. Unlike the EC group, no voxels survived a threshold of $p<.005$ in the MCI group analysis.

3.5.2.3 Main Effect of Motivation

As a group, patients with MCI tended to respond faster during LOSE compared to NEUTRAL across all trial types ($p=.06$). To determine the effect that losing money had on brain responses irrespective of attentional demand, activity during the LOSE condition was compared with NEUTRAL. This produced activity in the insula {-45,-9,12; $Z=4.01$, $p_{(unc)}=.00003$} and the visual cortex area 18 {12, -69,3; $Z=3.36$, $p_{(unc)}=.0004$} (Figure 32). Both peaks were significant at $p<.005$ uncorrected across the entire brain.

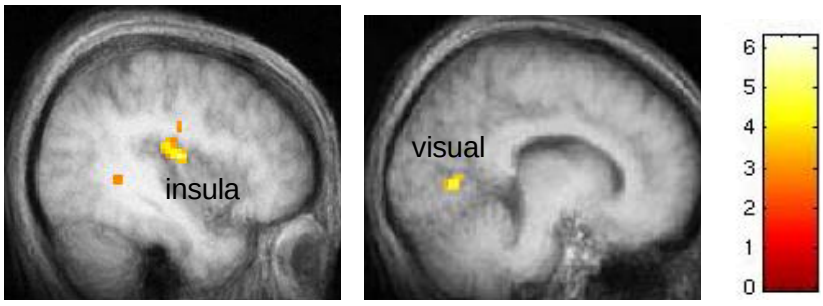

Figure 32. Brain responses when losing money was compared to neutral, irrespective of attentional demand. Data are from a one-sample t-test of the 12 MCI subjects. The sagittal sections show the insula and visual cortex (BA 18). The images are thresholded at $p < .005$ and the color bar represents t-value.

3.5.2.4 Discussion

Patients with MCI were capable of generating visual spatial expectancy; targets were detected faster following valid compared with non-directional cues. Similar to young and elderly controls, this validity effect was associated with activity in the insula (Gitelman et al., 1999; Kim et al., 1999). In contrast, when the fMRI signal was regressed against the degree of spatial expectancy, activity was present in the anterior and posterior cingulate cortices, the posterior parietal cortex, and the visual cortex. Activity in these regions increased as more spatial expectancy was generated, irrespective of motivational incentives. These peaks were in similar areas to those found in previous studies with young controls (Gitelman et al., 1999; Small et al., 2005), suggesting that patients with MCI recruit similar neural mechanisms as young controls when they generate spatial biases during valid cues.

Our results show that monetary incentives enhanced spatial expectancy; however, unlike elderly controls who exhibited improvements when they could win money, MCI patients demonstrated improvements when there was the possibility of losing money. These results are similar to those found in young controls (Small et al., 2005). Further, when MCI subjects were told that they would lose money for slow responses, the amount of spatial expectancy generated during the valid cues positively correlated with activity in the PCC and precuneus. Elderly and young controls (Small et al., 2005) also exhibit enhanced PCC activity when incentives influenced the allocation of spatial attention, suggesting that the role of the PCC in top down control of attention is preserved in aging and MCI.

Like the elderly controls, patients with MCI showed evidence for an invalidity effect. Moreover, the mean difference between invalid and non-directional trials was similar in these

two groups ($p>.2$), indicating that disengaging attention was not further impaired in MCI compared with healthy aging. The IPS in both hemispheres was active when MCI subjects needed to disengage and reorient attention to the appropriate location. This activity is in accordance with a previous study using healthy young controls, however, unlike healthy young and elderly controls, the MCI group did not recruit the OFC during disengagement (Small et al., 2005). The OFC has also been implicated in previous studies examining economic value (Padoa-Schioppa et al., 2006) and control of goal-directed behavior (Wallis et al., 2003). These studies demonstrate that the OFC modulates reward processing. Together with the data from young controls, these results suggest that the OFC needs to be recruited for incentives to influence disengagement of spatial attention. The top-down mechanisms for these processes may therefore be different in healthy aging versus MCI.

3.5.3 EC vs. MCI

In order to show differential activations between the groups, one way ANOVAs were conducted for the contrasts of interest. Direct comparisons were only possible between the EC and MCI subjects because I did not have enough PRAD patients to perform a random effects analysis. The images were thresholded at $p<.005$ and predicted peaks were considered significant if they had a $p<.005$ uncorrected over the entire brain. Analysis of the RT data had indicated that overall RTs were somewhat slower for the MCI patients compared with the elderly controls, but the differences were not significant ($p=.16$). Therefore, differential RT is unlikely to play a dominant role in accounting for differential activations observed between the groups. Monetary incentives benefited performance in both groups by decreasing target response time. In healthy aging, winning money had a greater effect on spatial attention processes compared with receiving no incentives, whereas, in MCI, losing money had a larger effect on these processes compared with receiving no incentives. Based on the behavioral data, I was interested in examining the differential activation from each group when incentives influenced spatial attention processes. For example, I wanted to differentiate the regions that were associated with the interaction between spatial expectancy and reward in the EC group and spatial expectancy and punishment in the MCI group. I predicted that this modulation would be associated with differential PCC activity. Moreover, I was interested in examining the differential activity associated with disengagement when incentives influenced performance in these two groups. I predicted that this interaction would be associated with greater OFC activity in the EC group.

3.5.3.1 Validity Effect

Patients with MCI and age-matched controls exhibited a validity effect in that they both responded faster to validly cued trials compared with non-directionally cued trials. The magnitude of this effect was similar in both groups (mean difference: EC 15.7; MCI 17.1). However, winning money enhanced this effect in healthy aging, while losing money enhanced the effect in MCI. To determine the differential effects that monetary incentives had on visual spatial expectancy, neural activity generated during the validly cued trials in WIN-NEUTRAL was compared between the EC and MCI subjects. The EC subjects exhibited a larger response in a region of the PCC {0,-48,27; Z=3.91, $p_{(unc)}$=.00005} compared with the MCI subjects (see Figure 33A). No significant differences were observed in MCI > EC. On the other hand, when the validly cued trials for the contrast LOSE-NEUTRAL were compared between the EC and MCI subjects, the MCI group exhibited a larger response in a separate region of the PCC {18,-60,30; Z=3.07, $p_{(unc)}$=.001} (see Figure 33B). No significant differences were observed in EC > MCI and therefore suggests that the imaging data mirrors the behavioral data.

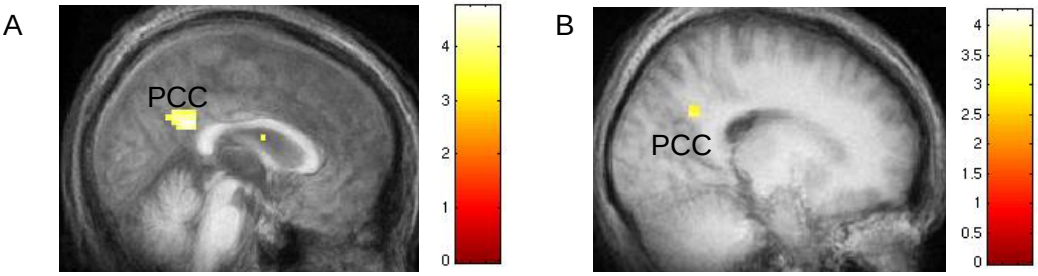

Figure 33. Sagittal sections showing PCC activity associated with the validly cued trials in A. WIN-NEUTRAL for the Elderly-MCI subjects and B. LOSE-NEUTRAL for the MCI-Elderly subjects. Data are from one-way ANOVAs of the 2 groups. The images are thresholded at $p < .005$ and the color bars represents t-values. PCC=posterior cingulate cortex

To determine if there were group differences between regions in which activity correlated positively with the degree of visual spatial expectancy, the contrasts from the regression analyses were compared across groups. For WIN-NEUTRAL, the elderly subjects did not exhibit a larger response in any predicted regions. However, for LOSE-NEUTRAL, the MCI subjects again revealed a larger response in the PCC {-18,-63,27; Z=3.34, $p_{(unc)}$=.0004} (see Figure 34).

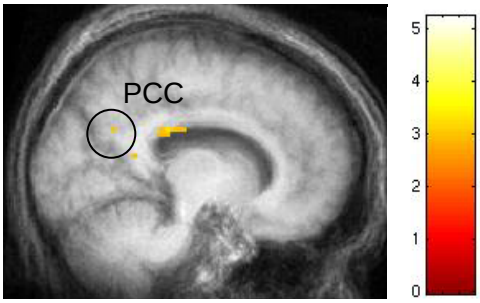

Figure 34. Sagittal section showing activity associated with the cue benefit scores in LOSE-NEUTRAL for MCI-Elderly subjects. Data are from a one-way ANOVA of the 2 groups. The image is thresholded at $p < .005$ and the color bars represents t-values. PCC=posterior cingulate cortex

3.5.3.2 Invalidity Effect

The elderly control and MCI patient groups both demonstrated an invalidity effect and the magnitude of the effect was similar in both groups (mean difference between invalid and non-directional trials: EC -26.7; MCI -31.1). Brain activity during these trials was compared between the two groups to probe for differential effects. The comparison revealed that the elderly subjects exhibited larger responses in the left and right orbitofrontal cortex (OFC) {33,39,-21; Z=3.03, $p_{(unc)}$=.001} {-33,33,-24; Z=2.86, $p_{(unc)}$=.002} (see Figure 35A), while the MCI subjects demonstrated larger responses in the anterior cingulate cortex (ACC) {-9,27,30; Z=3.39, $p_{(unc)}$=.0004} (see Figure 35B).

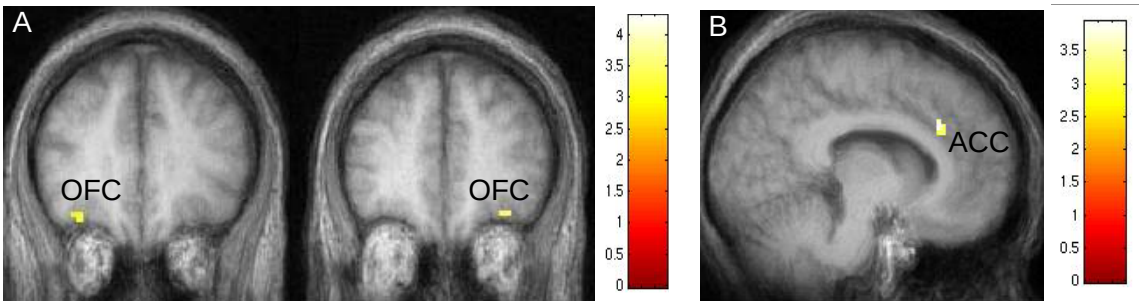

Figure 35. Coronal and sagittal sections showing activity associated with invalidly cued minus non-directionally cued trials collapsed across all conditions in A. Elderly-MCI subjects and B. MCI-Elderly subjects. Data are from a one-way ANOVA of the 2 groups. The images are thresholded at $p < .005$ and the color bars represents t-values. OFC=orbitofrontal cortex, ACC=anterior cingulate cortex

Motivational incentives, specifically winning money, enhanced the ability to disengage and reorient attention in the healthy elderly group. However, incentives had no effect on the ability to disengage attention in the MCI group. Accordingly, the contrast of EC compared to MCI showed differential responses in the OFC and visual cortex (see **Table 13**, Figure 36), whereas the reverse contrast did not yield significant differential response favoring MCI.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(unc)}$ value
EC-MCI Invalids WIN-NEUTRAL	OFC	24	30	-15	2.91	.002
	Visual	-9	-54	9	2.81	.002

Table 13. Differential brain responses during invalidly cued trials in WIN-NEUTRAL. OFC=orbitofrontal cortex

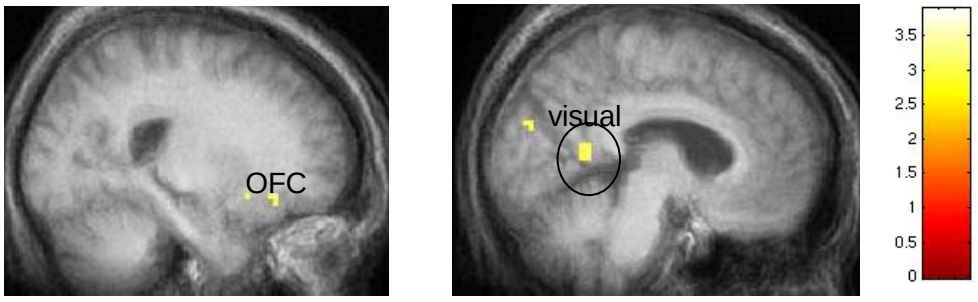

Figure 36. Sagittal sections showing activity associated with invalidly cued trials for WIN-NEUTRAL in the Elderly-MCI subjects. Data are from a one-way ANOVA of the 2 groups. The images are thresholded at $p < .005$ and the color bar represents t-values. OFC=orbitofrontal cortex

Across all trials, both groups demonstrated an effect of motivation; the healthy elderly group responded faster during WIN compared to NEUTRAL, while the MCI group responded faster during LOSE compared to NEUTRAL (see Figure 16). Differential activation for the contrast WIN-NEUTRAL in elderly controls included larger responses in the ACC {-6,30,0; Z=3.43, $p_{(unc)}$=.0003} and PCC {3,-48,27; Z=3.11, $p_{(unc)}$=.001} (see Figure 37A), while the MCI group did not exhibit larger responses in any predicted regions for this contrast. On the other hand, differential brain activity for the contrast LOSE-NEUTRAL in the MCI group resulted in a larger response in the PCC {18,-60,30; Z=2.93, $p_{(unc)}$=.002} (see Figure 37B), while the healthy elderly group did not reveal larger responses in any predicted regions for this contrast.

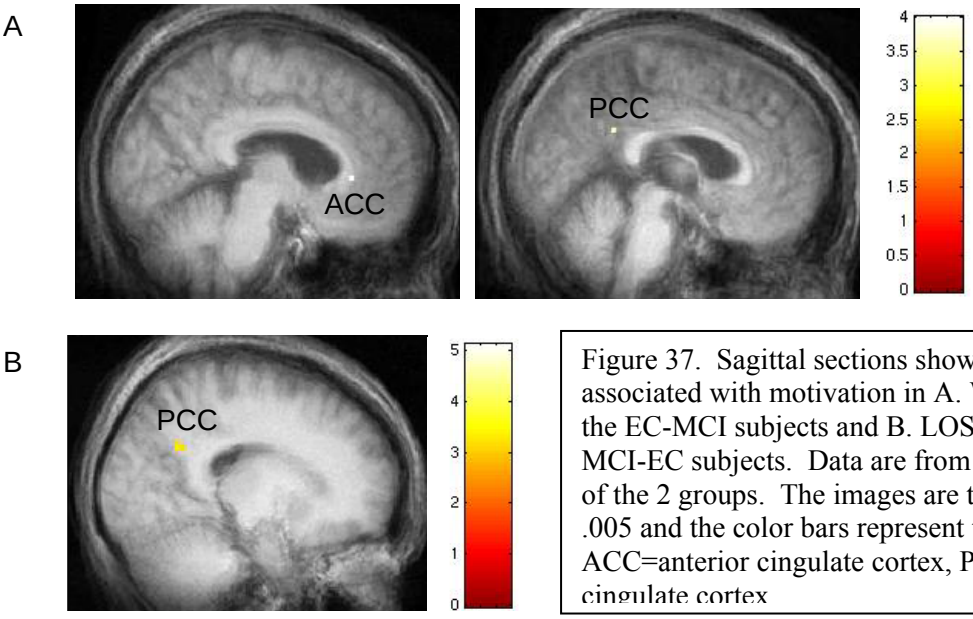

Figure 37. Sagittal sections showing activity associated with motivation in A. WIN-NEUTRAL for the EC-MCI subjects and B. LOSE-NEUTRAL for the MCI-EC subjects. Data are from one-way ANOVAs of the 2 groups. The images are thresholded at $p < .005$ and the color bars represent t-values. ACC=anterior cingulate cortex, PCC=posterior cingulate cortex

3.5.3.3 Discussion

Direct comparisons between brain response in EC and MCI were performed to test for potential differences in the neural mechanisms of motivational influence on top down control of spatial attention. Winning money compared with receiving no incentives enhanced the degree of visual spatial expectancy generated during the valid cues in the healthy elderly group, whereas,

losing money compared with receiving no incentives enhanced this expectancy in the MCI group. In both cases, larger responses were observed in the PCC when incentives speeded up target detection. Differential activity in the PCC was not observed in either group when incentives did not influence response times to valid targets. In young controls, the PCC has been shown to modulate the influence of motivation on top down control of spatial expectancy (Small et al., 2005). The results present in the current experiment demonstrate that the role of the PCC in mediating this influence on expectancy is preserved in healthy aging and MCI. These data also suggest that the MCI subjects tested in these experiments are more like the healthy aging subjects rather than the PRAD subjects.

The RT analyses revealed that disengaging attention is not more impaired in MCI compared with elderly controls. The absence of a greater impairment in disengaging attention in the MCI group provides further evidence for this group of subjects to be more similar to the elderly controls than to patients with PRAD. However, the ability of incentives to alleviate some of the deficits due to disengaging attention was evident in EC but not in MCI and this improvement in EC was associated with OFC activity. Therefore, disengagement may not be specifically impaired in the MCI population but incentives are not as effective in relieving the reaction time costs due to disengaging attention. The role of the OFC in disengaging attention has been demonstrated in a previous study with young controls (Nobre et al., 1999) and our results suggest that its function is preserved in healthy aging but not MCI. Winning money enhanced invalid target detection compared with receiving no incentives only in the elderly control group. When activity for this contrast was compared between the two groups, the healthy elderly group showed larger responses in the OFC and visual cortex, while the MCI

group did not exhibit larger responses in any predicted regions. A pathological study in patients who were diagnosed with PRAD revealed extensive neurofibrillary tangles in the OFC region (Van Hoesen et al., 2000). In the current experiment, the lack of OFC activity in the MCI group during disengagement provides further evidence for the OFC impairments present in early dementia.

When motivation was analyzed independently of spatial attention processes, the EC group responded faster when there was a possibility of winning money compared with receiving no incentives and the MCI group responded faster when there was a possibility of losing money compared with receiving no incentives. Larger responses were observed in the ACC and PCC in the EC group for WIN-NEUTRAL and in the PCC in the MCI group for LOSE-NEUTRAL. These data suggest that the role of the posterior cingulate gyrus in motivational influences on top-down control of spatial attention processes is not only preserved in the healthy aging population, but also in the MCI population. The differences that were observed between winning and losing money in the EC and MCI populations may be due to the apathetic behavior that occurs in early dementia. The MCI subjects may be more prone to negative affect and therefore demonstrate specificity for losing money.

3.5.4 PRAD

3.5.4.1 Validity Effect

Like the healthy elderly and MCI subjects, patients with PRAD responded significantly faster to validly cued trials than non-directionally cued trials (p=.03). To extract the neural regions responsible for this validity effect, activity during the validly cued trials was compared to activity during the non-directionally cued trials. This contrast produced activity in the medial prefrontal cortex (MPFC), thalamus, and visual cortex (see **Table 14**, Figure 38). These predicted areas were significant at p<.005 uncorrected over the entire brain.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(unc)}$ value
Valids – Non-Directionals	Visual	-15	-108	-3	3.35	.0004
	MPFC	-9	51	-9	2.85	.002
	Thalamus	-9	-12	-3	2.75	.003

Table 14. Brain regions associated with validly cued minus non-directionally cued trials collapsed across all conditions (WIN, LOSE, and NEUTRAL). MPFC=medial prefrontal cortex

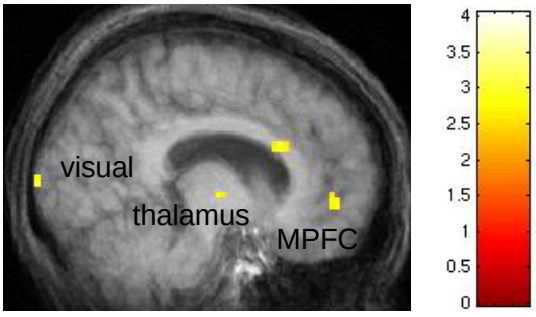

Figure 38. Brain response during valid minus non-directionally cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL). Data are from the 7 PRAD patients. The sagittal section shows visual, MPFC, and thalamic activity. The image is thresholded at p < .005 and the color bar represents t-values.

3.5.4.1.1 Correlation with CBs

To determine the regions that positively correlated with the degree of visual spatial expectancy generated during validly cued trials, CBs were regressed against the BOLD signal of validly cued trials collapsed across all three conditions (WIN+LOSE+NEUTRAL). A region of the primary visual cortex was found to correlate with the degree of spatial expectancy {-15,-48,3;

Z=3.12, $p_{(unc)}$=.001} and was significant at p<.005 uncorrected across the whole brain (see Figure 39).

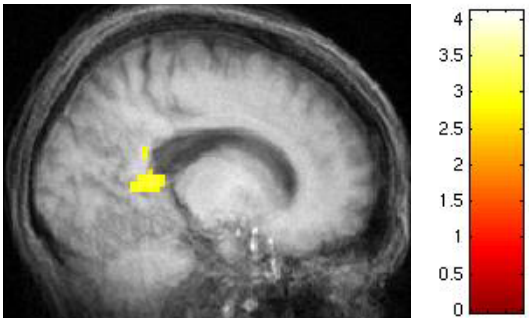

Figure 39. Correlation of cue benefit scores with validly cued trials collapsed across all three conditions (WIN, LOSE, and NEUTRAL) gives primary visual cortex activity. Data are from the 7 PRAD patients. The image is thresholded at p<.005 and the color bar represents t-value.

Since the PRAD subjects did not show a motivational effect when monetary incentives were offered, it was not surprising to see that this contrast did not generate neural activity in any predicted regions.

3.5.4.2 Invalidity Effect

Like the healthy elderly and MCI subjects, patients with PRAD responded slower to invalidly cued trials compared with non-directionally cued trials (p=.002). The reaction time costs due to disengaging and reorienting attention were greater in the PRAD group than in the EC and MCI groups (mean difference between invalid and non-directional trials: EC -25.9, MCI -31.7, PRAD -42.5), providing further evidence for the specific impairment of disengagement in the PRAD population. To determine the brain regions that were responsible for this effect, activity during the invalidly cued trials was compared with the non-directionally cued trials. This comparison revealed activity in regions of the tempero-occipital junction in both hemispheres (see **Table 15**, Figure 40). These regions were predicted from a previous neuroimaging study in young subjects (Gitelman et a., 1999) and significant at p<.005 uncorrected over the whole brain.

	Region	X (mm)	Y (mm)	Z (mm)	Z value	$p_{(unc)}$ value
Invalids – Non-Directionals	TOJ	-57	-69	0	2.79	.003
		39	-66	-3	2.60	.005

Table 15. Brain regions associated with invalidly cued minus non-directionally cued trials collapsed across all conditions (WIN, LOSE, and NEUTRAL). TOJ=tempero-occipital junction

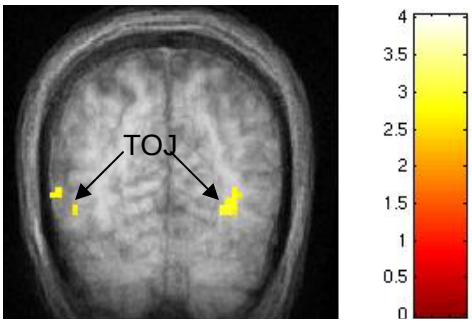

Figure 40. Coronal section showing activity in the tempero-occipital junction (TOJ) in both hemispheres during invalid minus non-directionally cued trials collapsed across all conditions (WIN, LOSE and NEUTRAL). Data are from the 7 patients with PRAD. The image is thresholded at $p < .005$ and the color bar represents t-values.

3.5.4.2.1 Correlation with CCs

When the cue cost scores for the invalidly cued trials were examined across all three conditions, activity was present in the primary visual cortex {-15,-63,-9; Z=3.20, $p_{(unc)}$=.001} (see Figure 41).

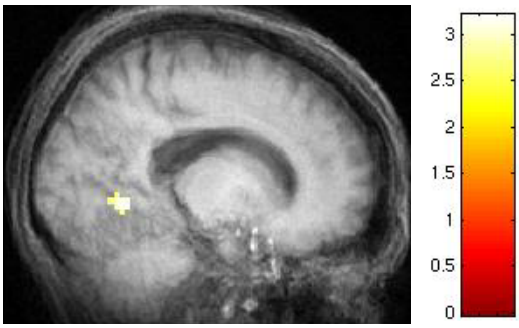

Figure 41. Correlation of cue cost scores with BOLD signal generated during invalidly cued trials collapsed across all conditions (WIN, LOSE, and NEUTRAL). Data are from the 7 PRAD patients. The sagittal section shows primary visual cortex activity. The image is thresholded at $p < .005$ and the color bar represents t-value.

Like the validly cued trials, PRAD patients did not show a motivational effect for the invalidly cued trials among the monetary incentive conditions. In accordance with the behavioral data, no predicted or unpredicted regions were active when the cue cost scores during WIN and LOSE were compared to NEUTRAL.

3.5.4.3 Discussion

Patients with PRAD showed a validity effect; they detected targets significantly faster following valid compared with non-directional cues. These results provide further evidence for the idea that attentional focusing remains intact in the early stages of Alzheimer's disease (Parasuraman et al., 1992). Moreover, the neural mechanisms involved in orienting are similar to those reported in young controls in previous studies (Gitelman et al., 1999; Small et al., 2005) and the elder controls reported above. Activity was observed in regions of the MPFC, thalamus and visual cortex when spatial expectancy was generated. However, unlike young and elderly controls, no activity was observed in the posterior parietal region. These findings provide further evidence for the parietal dysfunction commonly reported in PRAD subjects (Buck et al., 1997; Prvulovic et al., 2002).

Even though patients with PRAD used the valid cue to detect targets faster than non-directional cues, they did not respond quicker to the valid targets when incentives were present compared with no incentives. Whether or not incentives were present, PRAD patients exhibited an increase in visual cortical activity that positively correlated with the degree of spatial expectancy generated during the valid cues. Taken together, these results strengthen the theory that parietal dysfunction in mild AD is compensated by recruitment of the ventral visual pathway (Prvulovic et al., 2002). A motivational influence is not observed in this population and may be due to them simply forgetting the incentive conditions.

Patients with PRAD also exhibited an invalidity effect like the MCI and age-matched controls. However, the effect of disengaging attention from an invalid location to the target location was greater in PRAD patients compared with EC and MCI subjects. Since the PRAD

patient group took longer to disengage and reorient attention, this confirms their specific impairment in disengagement of visual spatial attention (Parasuraman et al., 1992). In other words all groups demonstrated an invalidity effect but it was most pronounced in PRAD.

In PRAD the invalidity effect was associated with activity in the occipito-temporal cortex. A significant positive correlation was also found between activity in the visual cortex and the degree of disengagement (cue cost). These results provide further evidence for the role of the ventral visual pathway in tasks of spatial attention (Prvulovic et al., 2002). In the PRAD patient group, motivational incentives provided no behavioral enhancement during disengagement. Accordingly, no differential neural responses were observed as a function of motivational condition.

3.6 Voxel Based Morphometry

3.6.1 Introduction

Voxel based morphometry (VBM) is a technique used for comparing the concentrations of grey matter between groups of subjects and, therefore, is a direct measurement of atrophy or loss of brain volume. Before the advent of VBM, positron emission tomography (PET) was used to assess metabolic decline in the parietal and temporal cortices in patients with PRAD (Foster et al., 1983). In fact, the decline has even been shown to precede cognitive deficits in this population (Haxby et al., 1986). More recent PET studies have confirmed this finding and have also shown metabolic reductions in the posterior cingulate cortex (PCC) in patients with mild dementia (Minoshima et al., 1997) and in adults that are carriers of the ε4 allele but do not show any cognitive impairments (Small et al., 2000; Alexander et al., 2002; Reiman et al., 2004). Moreover, the severity of AD symptoms has been shown to correlate with hypo-activity in the

PCC better than in temporal regions, suggesting that metabolic decline in the PCC may be an early indicator in the progression of AD (Ishii et al., 1997). PET studies are useful for detecting early cortical changes; however, the low resolution of the images makes it difficult to detect subcortical changes in the hippocampal region. Since the hippocampus shows the earliest and largest amount of atrophy in AD at autopsy (Braak et al., 1991), it is important to investigate this region in vivo. Magnetic resonance imaging (MRI) was used to examine the hippocampal volume changes in patients with PRAD and found that this region is susceptible to atrophy (Reiman et al., 1998). However, this technique was subject to inherent bias because the hippocampus was defined and measured manually in each subject. In order to investigate other areas of atrophy using this method, a priori hypotheses regarding "normal" size would need to be made. Fortunately, an automated method for investigating regional atrophy was introduced in 2000 based on statistical parametric mapping (SPM) of MRI data, defined as VBM (Ashburner et al., 2000). This procedure was important for locating brain regions that differed in size and volume between two different population groups.

Examination of the hippocampus with VBM revealed that the amount of atrophy correlated with memory impairments in PRAD subjects (Busatto et al., 2003), however, MCI subjects that did not have memory impairments did not show hippocampal atrophy and were less likely to convert to PRAD (Chetelat et al., 2005). VBM studies have also reported atrophy in early AD in parietal, temporal, and frontal association areas as well as PCC (Frisoni et al., 2002) which replicates the earlier PET studies (Minoshima et al., 1997). A functional neuroimaging study that compared PRAD patients with normal age-matched controls found that the controls showed greater activity in the superior parietal lobe, while PRAD subjects showed greater

activity in the occipito-temporal region (Prvulovic et al., 2002). The researchers explain this dichotomy by suggesting that the AD patients recruited the ventral visual pathway to compensate for the dysfunction in the dorsal pathway, specifically the parietal lobe. These results demonstrate that association cortices are more susceptible to damage than primary sensory cortices and may explain the cognitive deficits associated with AD. Based on the previous VBM studies, I predicted that the hippocampus and the posterior parietal cortex would show the greatest amount of atrophy in the PRAD group compared with the EC group and these regions may even reveal a loss of gray matter volume in the MCI group compared with the EC group.

3.6.2 Procedure

VBM is based on separating gray and white matter voxels and analyzing them individually while taking the total brain volume into account (Ashburner et al., 2000). The structural magnetic resonance images acquired from each of the 31 subjects during the scanning procedure were used. First, templates of grey matter, white matter, and CSF were made from the 12 EC subjects' structural scans. These templates were used for normalizing the images to the same stereotaxic space. Prior to normalization, however, all the original structural images were segmented into grey and white matter, and then underwent an automated procedure to remove scalp tissue, skull, and unconnected non-brain voxels. These segmented grey/white matter images (in native space) were normalized to the grey/white matter templates (in stereotaxic space). The normalization parameters from the grey matter image were reapplied to the original structural image, and again segmented into grey/white matter images. These images then underwent modulation, which preserved the volume of a particular tissue (grey or white matter) within a voxel. Using modulated data for analysis is important because it tests for regional

differences in the absolute volume of grey matter, rather than the concentration of grey matter per unit volume. Finally, these images were smoothed with a 12 mm FWHM kernel. To extract the regions that showed grey matter loss in patients with MCI or PRAD compared with elderly controls, an analysis of covariance (ANCOVA) was performed. The total intracranial volume was included as a covariate in order to factor out the variance due to whole brain volume.

3.6.3 Results

3.6.3.1 EC > PRAD

The grey matter images from the EC and PRAD subjects were compared to determine the neural regions that had a larger response in the elderly group than the PRAD group. These regions were significant at $p<.005$ corrected across the whole brain. Regions in the right {25,-13,-19; Z=5.78, $p_{(FDR\text{-}cor)}=.0002$} and left {-26,-10,-21; Z=4.28, $p_{(FDR\text{-}cor)}=.002$} hippocampus were found to have significantly smaller responses in the PRAD patient group compared with the EC subject group (see Figure 42). Several studies have demonstrated that the hippocampus is one of the first regions to become atrophied in patients with mild to moderate dementia (Braak et al., 1991; Reiman et al., 1998). The anatomical measurements which show hippocampal reduction in PRAD patients gives validity to this data.

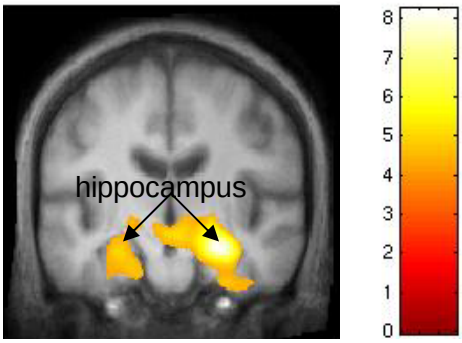

Figure 42. Coronal section shows the left and right hippocampus have significantly smaller responses in PRAD subjects compared to elderly subjects. Data are from a one-way ANCOVA of the 3 groups. The image is thresholded at corrected $p_{(FDR\text{-}cor)} < .005$ and the color bar represents t-values.

In addition to the hippocampus, a region of the right inferior parietal lobule (IPL) near the intraparietal sulcus (IPS) {34,-68,54; Z=4.53, $p_{(FDR\text{-}cor)}$=.002} revealed less activity in the PRAD patients compared with the EC subjects (see Figure 43). These findings are in accordance with previous VBM studies that report gray matter loss in the IPL region (Karas et al., 2004). This region has also been show to play an important role during disengagement (Corbetta et al., 2002). Reduced activity in this area may explain why PRAD patients have a harder time disengaging and reorienting attention to an invalidly cued location.

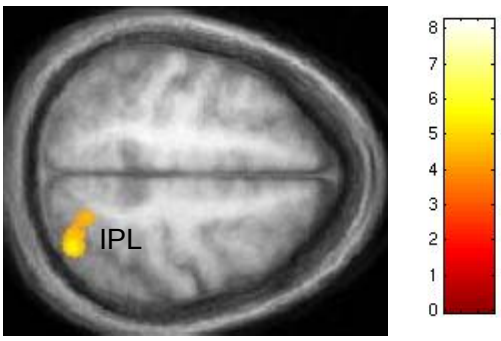

Figure 43. Horizontal section shows a region of the IPL has a significantly smaller response in PRAD subjects compared to elderly subjects. Data are from a one-way ANCOVA of the 3 groups. The image is thresholded at corrected $p_{(FDR\text{-}cor)} < .005$ and the color bar represents t-values. IPL=inferior parietal lobule

3.6.3.2 EC > MCI

Unlike the comparison between the EC and PRAD subjects, the VBM comparison between the EC and MCI subjects did not reveal any neural regions with a significantly smaller response in MCI compared with EC subjects when corrected across the whole brain. However, when the threshold was dropped to uncorrected p<.005, an area of the medial temporal lobe (MTL) {34,3,-37; Z=3.69, $p_{(unc)}$=.0001} showed reduced activity in the MCI subjects compared to the EC subjects (see Figure 44). Since the MTL is thought to play an important role in memory, the loss of gray matter voxels in this area provides evidence for the memory impairments present in MCI patients.

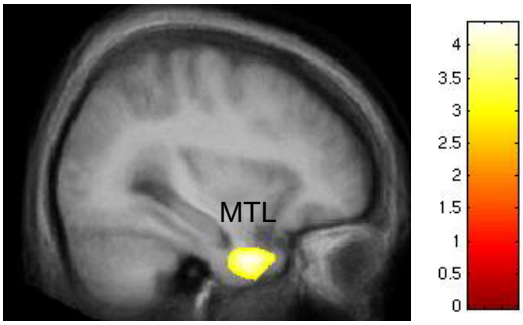

Figure 44. Sagittal section shows a region of the MTL has a significantly smaller response in MCI subjects compared to elderly subjects. Data are from a one-way ANCOVA of the 3 groups. The image is thresholded at $p_{(unc)}<.005$ and the color bar represents t-values. MTL=medial temporal lobe

3.6.4 Discussion

The VBM study was performed in order to extract the neural regions that showed significant gray matter loss between the healthy aging and PRAD groups and between the healthy aging and MCI groups. The greatest loss of volume between the PRAD and EC groups was in the hippocampus bilaterally. The hippocampus is known to be involved in memory functions and is one of the first areas to be affected in dementia. The results from this study are in accordance with previous VBM studies which report hippocampal atrophy in patients with AD (Busatto et al., 2003). Other VBM studies have reported atrophy in posterior parietal regions in early dementia and suggest that parietal loss may contribute to the spatial attention deficits common in this population (Karas et al., 2003). The reduction of gray matter voxels in the inferior parietal lobule of the PRAD patient group is consistent with these previous findings.

The difference in cortical volume between the healthy aging and MCI subjects revealed loss of gray matter in the medial temporal lobe of the MCI subjects. Atrophy in this area is consistent with previous VBM studies which suggest that the MTL is the only region that reliably shows atrophy in the MCI population (Pennanen et al., 2005). In summary, the results from this volumetric study are consistent with the results found in previous VBM studies which examined and compared cortical atrophy between healthy aging, MCI, and PRAD subjects.

CHAPTER 4: GENERAL DISCUSSION

The purpose of the studies conducted in this dissertation was to examine the influence of motivational incentives on visual spatial attention in healthy aging, MCI, and PRAD patients. Specifically, I compared the ability of monetary incentives to influence behavioral and neural performance on a covert visual spatial attention task while participants were scanned using functional magnetic resonance imaging (fMRI). A volumetric MRI study was also conducted to test for potential group differences in brain atrophy. The results from the experiments presented in this dissertation reveal that: 1) motivational incentives can influence top-down modulation of visual spatial expectancy in EC and MCI, but not PRAD; 2) the enhancement of spatial expectancy by incentives is regulated by the PCC in the EC and MCI subject groups; 3) disengaging attention is specifically impaired in the PRAD population; 4) EC, but not MCI or PRAD subjects can disengage and reorient attention quicker when incentives are present; 5) the OFC controls the influence of motivation on disengagement; and 6) hippocampal atrophy and the associated memory impairments in the PRAD group may account for the inability of incentives to enhance spatial attention in this population. I conclude that monetary incentives are effective in motivating elder controls and MCI subjects to enhance visual spatial attention processes and that the PCC and OFC areas responsible for this enhancement are the same as those in young adults.

4.1 Validity Effect

These experiments revealed that, independent of the nature or presence of the monetary incentives, all three groups of subjects were able to use the valid cue to generate spatial

expectancy as indicated by reduced time to target detection for validly cued trials. Accordingly, cue benefit scores in all three groups were correlated with activity in the medial prefrontal cortex (MPFC). This is an important finding because the same region has been shown to underlie visual spatial expectancy in young subjects (Small et al., 2000). Therefore, the results indicate that visual spatial expectancy is preserved at the behavioral and neurological levels in healthy aging, MCI, and PRAD.

4.1.1 Motivational Enhancement of Expectancy

In order to examine the behavioral and neural influences of motivation on top-down control of spatial expectancy monetary incentives were offered during the win and lose conditions but not the neutral condition. In the EC group, larger spatial biases were generated when the subjects could win money, whereas in the MCI group, more expectancy was generated when the subjects could lose money. In the PRAD group, no effect of motivation was seen; the degree of spatial expectancy generated during the valid cues did not increase when monetary incentives were offered.

The imaging results mirrored the reaction time data in that significant activations were only seen when the subjects demonstrated a behavioral effect. Since the PCC has been shown to play a role in the interaction of motivation and spatial attention processes in young controls (Small et al., 2000) this was the primary region of interest. In the EC group the PCC was isolated in the comparison between the validly cued trials in WIN compared to NEUTRAL. Patients with MCI also revealed PCC activity that correlated with the degree of visual spatial expectancy generated during the validly cued trials; however, this correlation was demonstrated when MCI subjects were losing money compared to NEUTRAL. While the EC subjects showed

more PCC activity during the valid trials in WIN compared to the valid trials in NEUTRAL, the MCI subjects demonstrated a correlation between PCC activity and spatial expectancy such that PCC activity increased as more spatial expectancy was generated during the valid cues in LOSE compared to the valid cues in NEUTRAL. The lack of a correlation in the EC group may suggest that positive motivation associated with winning money does not enhance attentional biases as strongly as the negative motivation associated with losing money. MCI subjects may also experience more apathetic symptoms than EC subjects and therefore be more sensitive to the negative motivation. In either case, these results reinforce the idea that activity in the PCC is associated with greater spatial biases when motivational incentives are present. The imaging and behavioral results are in accordance with each other and demonstrate that top-down modulation of visual spatial expectancy is preserved in the healthy aging and MCI populations.

In contrast to the EC and MCI groups there was no evidence for motivational enhancement of attention at the neural or behavioral level in the PRAD subject group. This may be due to their apathetic symptoms (Benoit et al., 2004) and suggests that the ability to use motivational enhancement to improve performance is lost in this population. However, the results from the questionnaire suggest that it is more likely that the PRAD group simply forgot about the incentives. In this case the explicit feedback was meaningless and the lack of influence of monetary incentives should be attributed to memory deficits rather than an inability to enhance attention by motivation. The VBM analysis, which revealed more hippocampal atrophy in PRAD vs. EC, is consistent with this possibility and with the well documented memory impairments that are observed in PRAD patients (Busatto et al., 2003).

Although I was unable to find evidence for a deficit in motivation to influence attention, previous studies have demonstrated that explicit emotional stimuli, in the form of facial expressions, can enhance spatial attention processes in PRAD patients; however, this increase was specific to negative emotions (LaBar et al., 2000). The possibility of a selective influence of aversive stimuli may explain why MCI patients were more affected by losing money rather than winning money. Since positive motivation from winning money enhanced spatial biases in the EC group, winning and losing money could differentially influence spatial expectancy in these two groups. In either case, the PCC was selectively activated when incentives enhanced the amount of spatial bias generated during the valid cues.

4.2 Invalidity Effect

In order to detect the target after an invalid cue attention must be disengaged from the incorrect location and then reoriented to the correct location. Thus invalidly cued trials are associated with slower target detection (Posner, 1980). All the subjects that were studied in these experiments demonstrated an invalidity effect, such that target detection was significantly slower following invalid cues compared with valid and non-directional cues. Parasuraman and colleagues have reported that patients with early dementia show a marked deficit in disengagement (Parasuraman et al., 1992). In accordance with these findings, the PRAD subjects in this study showed a greater deficit in disengagement compared with the EC subjects ($p=.015$). On the other hand, the MCI subjects were just as effective at detecting invalidly cued targets as EC subjects, suggesting that the ability to disengage and reorient attention is preserved in MCI but not PRAD.

The imaging data accord with these behavioral deficits and preservations. The PRAD subjects showed activity in the tempero-occipital junction (TOJ) during invalidly cued trials. The TOJ is located at the point where the superior temporal gyrus meets the occipital cortex and is part of the ventral visual processing stream. This region has been shown to be recruited for visuospatial processing in PRAD as a compensatory mechanism for parietal atrophy (Prvulovic et al., 2002). The authors concluded that inactivity in the parietal visual processing stream is offset by processing in the ventral visual pathway. The engagement of a different processing stream for reorienting attention may explain the disengagement deficits observed in the PRAD population.

The MCI subjects were just as efficient as EC subjects at disengaging and reorienting attention to invalidly cued targets; however, each group used different neural mechanisms to accomplish this task. While the EC group recruited the OFC to process invalidly cued trials, similar to young controls (Small et al., 2005), the MCI group recruited the IPS during these trials.

4.2.1 Motivational Enhancement of Disengagement

Monetary incentives have been shown to be effective in motivating young controls to enhance detection of invalidly cued targets and this is thought to be achieved via top-down influences on visual sensory cortex from parietal and frontal regions (Small et al., 2005). The experiments conducted in this dissertation revealed that incentives were only effective in the EC subject group for recovering some of the reaction time costs due to disengaging attention. In contrast, the MCI and PRAD subject groups did not exhibit a motivational enhancement during the invalidly cued trials; in these subjects incentives did not influence the amount of time needed

for disengaging and reorienting the attentional focus. The EC group analysis revealed activity in the visual cortex during the interaction between motivation and disengagement; however, the differential comparison of neural responses between the EC and MCI groups revealed greater activity in the OFC of EC subjects when disengagement was influenced by incentives. Differential OFC activity during invalidly cued trials when subjects were winning money compared to neutral may illustrate why EC subjects are able to use top-down motivational incentives to influence disengagement. These results replicate a previous neuroimaging study that reported OFC activity during trials with invalid spatial and temporal cues (Nobre et al., 1999). The OFC role during the disruption of expectation is preserved in the healthy aging, but not the MCI population, suggesting that its involvement begins to deteriorate in early dementia. VBM studies that report a greater amount of OFC atrophy in patients with mild dementia confirm these findings (Callen 2001). Moreover, metabolic activity in the ventral prefrontal region has been shown to decline during response inhibition tasks that require subjects to inhibit the allocation of spatial attention to irrelevant stimuli and reorient their attention to relevant stimuli (Slavin et al., 2002). Previous studies have also demonstrated that the OFC participates in reward-related behaviors (Elliott et al., 2000; Knutson et al., 2005) and hypo-perfusion in this area is associated with apathy (Benoit et al., 2004). The lack of a motivational effect and OFC activity in the MCI subjects tested in our fMRI experiment provides further evidence for the OFC involvement in reward-related behaviors.

4.3 Limitations and Future Directions

One important limitation is that too few PRAD subjects were tested in the fMRI experiment and a group analysis could not be performed. The same random effects analysis as

was used in the EC and MCI groups would also be useful for making direct comparisons and examining differential neural responses between the PRAD and EC or MCI groups. Another limitation may have been that not enough null events were used to properly deconvolve the hemodynamic response function for each of the trial types. Null events include the task display without any cues or targets and do not require a response. They are considered as an implicit baseline and allow the blood flow to return to a baseline level. In order to extract a response for a particular trial type, it is important that the response not be contaminated by activity from another trial type. Therefore, a null event after each trial would be ideal to allow enough time for the response to return to baseline and not influence the next trial. Another procedure to minimize cross-talk between events of interest is to model the design matrix with all the covariates that may be present in the task even if they are not of interest. In this way, any variance that is not specific to the event of interest will be accounted for in the design matrix and will not cross-contaminate the important event.

Monetary incentives were used in this study to examine the influence of motivation on top-down control of attention via endogenous mechanisms. The motivational salience of these endogenous factors may have been lost in the PRAD population due to their high memory demands. To overcome this, exogenous factors such as fearful faces which have greater emotional content and no memory requirements may better influence spatial attention. In addition, primary motivational factors, such as food reward, may have a more direct effect on visual spatial attention processes in patients with early dementia.

4.4 Conclusion

Generating visual spatial biases during valid cues in preserved in the healthy aging, MCI and PRAD populations. Monetary incentives influence the top-down modulation of visual spatial attention processes in healthy aging and patients with MCI, but not PRAD. The motivational enhancement of spatial expectancy is regulated by the posterior cingulate cortex and is preserved in aging and MCI. Disengaging and reorienting attention is required during invalidly cued trials and is specifically impaired in the PRAD population. Incentives did not improve invalid target detection for PRADs or MCIs but did reduce reaction times in elder controls and this enhancement was associated with OFC activity. These results suggest that the OFC becomes impaired earlier in dementia than the PCC and may underlie the disengagement deficits and apathetic behavior observed in the PRAD population. These findings may help to develop treatments for the attention deficits and apathetic symptoms that are common in the PRAD population.

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APPENDICES

Appendix A: MINI-MENTAL STATE EXAMINATION

"I am going to ask you some questions to check your memory and concentration. Some of them may be easy and some of them may be hard."

QUESTIONS: SCORE: CORRECT = 1, ERROR = 0

1. What year is it now? _____ _____
2. What is the season of the year? _____ _____
3. What is the date? _____ _____
4. What is the day of the week?_____ _____
5. What is the month?_____ _____
6. Can you tell me where we are? _____ _____
   (for instance, what state are we in)
7. What county are we in?_____ _____
8. What city/town are we in?_____ _____
9. What floor of the building are we on?_____ _____
10. What is the name or address of this place?_____ _____
11. I am going to name three objects. After I have said all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. Please repeat the names for me:

    (Score 1st try. Repeat objects for 3 trials only)
    Apple _____
    Table _____
    Penny _____

12. Now I am going to give you a word and ask you to spell it forwards and backwards. The word is WORLD. First, can you spell it forwards? Now spell it backwards.

    Response: _____ _____ _____ _____ _____
    (score number of letters given in correct order, max = 5) _____

What were the three objects I asked you to remember? (record responses)

13. _____ (Apple) _____

14. _____ (Table) _____

15. _____ (Penny) _____

16. (Show wrist watch) What is this called?_____ _____

17. (Show pencil) What is this called?_____ _____

18. I would like you to repeat a phrase after me. The phrase is:
(one trial allowed) "NO IF'S, AND'S OR BUT'S" _____

19. Read the words on this paper then do what it says.
(the paper reads) "CLOSE YOUR EYES" _____
Code correct if subject closes eyes.

20. I'm going to give you a piece of paper. When I do, take the paper in your right hand, fold the paper in half with both hands, and put the paper down on your lap. (read full statement, THEN hand over paper.
Do not repeat instructions or coach)

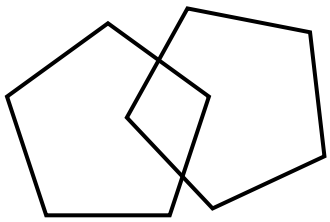
Right hand _____

Fold _____

In lap _____

21. Write any complete sentence on that piece of paper for me. _____

22. Here is a drawing. Please copy the drawing on the same paper.
(Score correct if the two five-sided figures intersect to form a four-sided figure and if all angles in the five-sided figure are preserved.) _____



TOTAL SCORE	

(maximum = 30)

Appendix B: CLINICAL DEMENTIA RATING SCALE

CDR	Type	Memory	Orientation	Judgment and Problem Solving	Community Affairs	Home and Hobbies	Self Care
0	Healthy	No memory loss or slight inconstant forgetfulness	Fully oriented	Solves everyday problems well; judgment good in relation to past performance	Independent function as usual level in job, shopping, business, financial affairs, volunteer and social groups.	Life at home, hobbies, intellectual interests well maintained	Fully capable of self care
0.5	Question-able dementia	Mild consistent forgetfulness ; partial recollection of events; benign forgetfulness	Fully oriented	Only doubtful impairment in solving problems, similarities, differences	Only doubtful or mild impairment, if any, in these activities	Life at home, hobbies, intellectual interests well maintained or only slightly impaired	Fully capable of self care
1	Mild dementia	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Some difficulty with time relationships; orient for place and person, may have geography disorientatio n	Moderate difficulty in handling complex problems; social judgment usually maintained	Unable to function independently these activities though may still be engaged in some; may still appear normal	Mild but definite impair. of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Needs occasional prompting
2	Moderate dementia	Severe memory loss; only highly learned material retained; new material rapidly lost	Usually disoriented in time; often to place	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	No pretense of independent functioning outside the home.	Only simple chores preserved; very restricted interests, poorly sustained	Requires assistance in dressing, hygiene, keeping of personal effects
3	Severe dementia	Severe memory loss; only fragments remain	Oriented to person only	Unable to make judgments or solve problems	No pretense of independent functioning outside the home.	No significant function in home outside of own room	Requires much help with personal care; often incontinent

Appendix C: ACTIVITIES OF DAILY LIVING QUESTIONNAIRE

"Please rate the patient on each of the activities compared to how he/she was functioning before the onset of any symptoms. DO NOT rate the patient in comparison to the most recent examination."

Relationship to patient:_____

Circle one number for each item according to instructions provided by the examiner.

1. SELF CARE ACTIVITIES

A. Eating

0 = No problem
1 = Independent, but slow or some spills
2 = Needs help to cut or pour; spills often
3 = Must be fed most foods
9 = Don't know

B. Dressing

0 = No problem
1 = Independent, but slow or clumsy
2 = Wrong sequence, forgets items
3 = Needs help with dressing
9 = Don't know

C. Bathing

0 = No problem
1 = Bathes self, but needs to be reminded
2 = Bathes self with assistance
3 = Must be bathed by others
9 = Don't know

D. Elimination

0 = Goes to the bathroom independently
1 = Goes to the bathroom when reminded; some accidents
2 = Needs assistance for elimination
3 = Has no control over either bowel or bladder
9 = Don't know

E. Taking Pills or Medicine

0 = Remembers without help
1 = Remembers if does is kept in a special place
2 = Needs spoken or written reminders
3 = Must be given medicine by others
9 = Does not take regular pills or medicine OR Don't know

F. Interest in Personal Appearance

0 = Same as always
1 = Interested if going out, but not at home
2 = Allows self to be groomed, or does so on request only
3 = Resists efforts of caretaker to clean and groom
9 = Don't know

2. HOUSEHOLD CARE

A. Preparing Meals, Cooking

0 = Plans and prepares meals without difficulty
1 = Some cooking, but less than usual, or less variety
2 = Gets food only if it has already been prepared
3 = Does nothing to prepare meals
9 = Never did this activity OR don't know

B. Setting the Table

0 = No problem
1 = Independent, but slow or clumsy
2 = Forgets items or puts them in the wrong place
3 = No longer does this activity
9 = Never did this activity OR don't know

C. Housekeeping

0 = Keeps house as usual
1 = Does at least half of his/her job
2 = Occasional dusting or small jobs
3 = No longer keeps house
9 = Never did this activity OR don't know

D. Home Maintenance

0 = Does all tasks usual for him/her
1 = Does at least half of usual tasks
2 = Occasionally rakes or some other minor job
3 = No longer does any maintenance
9 = Never did this activity OR don't know

E. Home Repairs

0 = Does all the usual repairs
1 = Does at least half of usual repairs
2 = Occasionally does minor repairs
3 = No longer does any repairs
9 = Never did this activity OR don't know

F. Laundry

0 = Does laundry as usual (same schedule, routine)
1 = Does laundry less frequently
2 = Does laundry only if reminded; leaves out detergent, steps
3 = No longer does laundry
9 = Never did this activity OR don't know

3. EMPLOYMENT AND RECREATION

A. Employment

0 = Continues to work as usual
1 = Some mild problems with routine responsibilities
2 = Works at an easier job or part-time; threatened with loss of job
3 = No longer works
9 = Never worked OR retired before illness OR don't know

B. Recreation

0 = Same as usual
1 = Engages in recreational activities less frequently
2 = Has lost some skills necessary for recreational activities (e.g., bridge, golfing); needs coaxing to participate
3 = No longer pursues recreational activities
9 = Never engaged in recreational activities OR don't know

C. Organizations

0 = Attends meetings, takes responsibilities as usual
1 = Attends less frequently
2 = Attends occasionally; has no major responsibilities
3 = No longer attends
9 = Never participated in organizations OR don't know

D. Travel

0 = Same as usual
1 = Gets out if someone else drives
2 = Gets out in wheelchair
3 = Home - or hospital - bound
9 = Don't know

4. SHOPPING AND MONEY

A. Food Shopping

0 = No problem
1 = Forgets items or buys unnecessary items
2 = Needs to be accompanied while shopping
3 = No longer does the shopping
9 = Never had responsibility in this activity OR don't know

B. Handling Cash

0 = No problem
1 = Has difficulty paying proper amount, counting
2 = Loses or misplaces money
3 = No longer handles money
9 = Never had responsibility for this activity OR don't know

C. Managing Finances

0 = No problem paying bills, banking
1 = Pays bills late; some trouble writing checks
2 = Forgets to pay bills; has trouble balancing checkbook; needs help from others
3 = No longer manages finances
9 = Never had responsibility in this activity OR don't know

5. TRAVEL

A. Public Transportation

0 = Uses public transportation as usual
1 = Uses public transportation less frequently
2 = Has gotten lost using public transportation
3 = No longer uses public transportation
9 = Never used public transportation regularly OR don't know

B. Driving

0 = Drives as usual
1 = Drives more cautiously
2 = Drives less carefully; has gotten lost while driving
3 = No longer drives
9 = Never drove OR don't know

C. Mobility Around the Neighborhood

0 = Same as usual
1 = Goes out less frequently
2 = Has gotten lost in the immediate neighborhood
3 = No longer goes out unaccompanied
9 = This activity has been restricted in the past OR don't know

D. Travel Outside Familiar Environment

0 = Same as usual
1 = Occasionally gets disoriented in strange surroundings
2 = Gets very disoriented but is able to manage if accompanied
3 = No longer able to travel
9 = Never did this activity OR don't know

6. COMMUNICATION

A. Using the Telephone

0 = Same as usual
1 = Calls a few familiar numbers
2 = Will only answer telephone (won't make calls)
3 = Does not use the telephone at all
9 = Never had a telephone OR don't know

B. Talking

0 = Same as usual
1 = Less talkative; has trouble thinking of words or names
2 = Makes occasional errors in speech
3 = Speech is almost unintelligible
9 = Don't know

C. Understanding

0 = Understands everything that is said as usual
1 = Asks for repetition
2 = Has trouble understanding conversations or specific words occasionally
3 = Does not understand what people are saying most of the time
9 = Don't know

D. Reading

0 = Same as usual
1 = Reads less frequently
2 = Has trouble understanding or remembering what he/she has read
3 = Has given up reading
9 = Never read much OR don't know

E. Writing

0 = Same as usual
1 = Writes less often; makes occasional spelling errors
2 = Signs name but no other writing
3 = Never writes
9 = Never wrote much OR don't know

SCORING:

ADL SCALE:

For each section (e.g., self care, household care, etc.) count the total number of questions answered (i.e., questions that are NOT rated as "9" - don't know).

Multiply the total number of questions answered by 3. This equals the total points possible for that section.

Add up the total score (i.e., the sum of the responses) for that section and divide by the total points possible. Multiple by 100 to get the percent impairment.

EXAMPLE:
If the questions were answered as follows in section 1:
A. 0
B. 2
C. 9
D. 0
E. 1
F. 9

The total number of questions answered would be 4 (A, B, D, and E), total points possible is 12.

The total score for that section is 3 and the percent impairment is 3 / 12 or .25 times 100 = 25%.

Repeat this procedure for each section and sum up the total to get a percent impairment score for the whole test.

0 - 33% = mild impairment
34 - 66% = moderate impairment
67 + % = severe impairment.

Appendix D: EDINBURGH HANDEDNESS INVENTORY

1. Which of the following do you consider yourself to be? (circle):

right-handed left-handed ambidextrous

2. Please indicate for each of the activities below whether you always use your left hand, usually use your left hand, have no preference, usually use your right hand, or always use your right hand. Please be sure to answer every item and only leave a blank if you have no experience at all for the object or task.

ITEM	Always left (-10)	Usually left (-5)	No preference (0)	Usually right (+5)	Always right (+10)
Writing					
Drawing					
Throwing					
Scissors					
Toothbrush					
Holding a knife to cut meat					
Spoon					
Broom (upper hand)					
Striking a match					
Opening box (lid)					

Laterality Quotient:	

Appendix E: MRI SAFETY QUESTIONNAIRE

MAGNETIC RESONANCE (MR) PROCEDURE SCREENING FORM FOR PATIENTS

Date _____/_____/_____ Patient Number _____

Name _____ Age _____ Height _____ Weight _____
Last name First name Middle Initial

Date of Birth ____/____/_____ Male ☐ Female ☐ Body Part to be Examined _____
month day year

Address _____ Telephone (home) (_____) _____-_____

City _____ Telephone (work) (_____) _____-_____

State _____ Zip Code _____

Reason for MRI and/or Symptoms _____

Referring Physician _____ Telephone (_____) _____-_____

1. Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind? ☐ No ☐ Yes
   If yes, please indicate the date and type of surgery:
   Date _____/_____/_____ Type of surgery _____
   Date _____/_____/_____ Type of surgery _____
2. Have you had a prior diagnostic imaging study or examination (MRI, CT, Ultrasound, X-ray, etc.)? ☐No ☐ Yes
   If yes, please list:

	Body part	Date	Facility
MRI	_____	____/____/____	_____
CT/CAT Scan	_____	____/____/____	_____
X-Ray	_____	____/____/____	_____
Ultrasound	_____	____/____/____	_____
Nuclear Medicine	_____	____/____/____	_____
Other_____	_____	____/____/____	_____

3. Have you experienced any problem related to a previous MRI examination or MR procedure? ☐ No ☐ Yes
   If yes, please describe: _____
4. Have you had an injury to the eye involving a metallic object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)? ☐ No ☐ Yes
   If yes, please describe: _____
5. Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)? ☐ No ☐ Yes
   If yes, please describe: _____
6. Are you currently taking or have you recently taken any medication or drug? ☐ No ☐ Yes
   If yes, please list:_____
7. Are you allergic to any medication? ☐ No ☐ Yes
   If yes, please list:_____
8. Do you have a history of asthma, allergic reaction, respiratory disease, or reaction to a contrast medium or dye used for an MRI, CT, or X-ray examination? ☐ No ☐ Yes
9. Do you have anemia or any disease(s) that affects your blood, a history of renal (kidney) disease, or seizures? ☐ No ☐ Yes
   If yes, please describe: _____

For female patients:

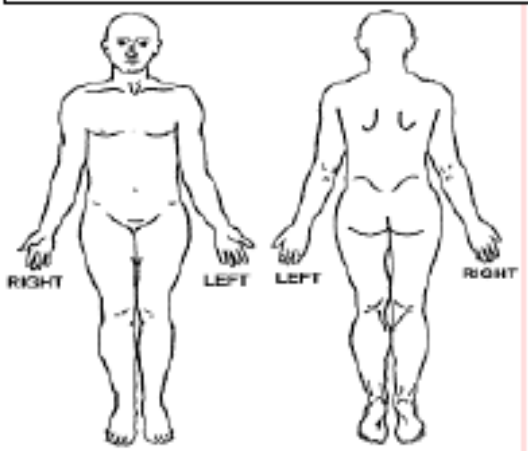
10. Date of last menstrual period:_____/_____/_____ Post menopausal? ☐ No ☐ Yes
11. Are you pregnant or experiencing a late menstrual period? ☐ No ☐ Yes
12. Are you taking oral contraceptives or receiving hormonal treatment? ☐ No ☐ Yes
13. Are you taking any type of fertility medication or having fertility treatments? ☐ No ☐ Yes
    If yes, please describe: _____
14. Are you currently breastfeeding? ☐ No ☐ Yes

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the MRI Technologist or Radiologist BEFORE entering the MR system room. The MR system magnet is ALWAYS on.

Please indicate if you have any of the following:

- ❑ Yes ❑ No Aneurysm clip(s)
- ❑ Yes ❑ No Cardiac pacemaker
- ❑ Yes ❑ No Implanted cardioverter defibrillator (ICD)
- ❑ Yes ❑ No Electronic implant or device
- ❑ Yes ❑ No Magnetically-activated implant or device
- ❑ Yes ❑ No Neurostimulation system
- ❑ Yes ❑ No Spinal cord stimulator
- ❑ Yes ❑ No Internal electrodes or wires
- ❑ Yes ❑ No Bone growth/bone fusion stimulator
- ❑ Yes ❑ No Cochlear, otologic, or other ear implant
- ❑ Yes ❑ No Insulin or other infusion pump
- ❑ Yes ❑ No Implanted drug infusion device
- ❑ Yes ❑ No Any type of prosthesis (eye, penile, etc.)
- ❑ Yes ❑ No Heart valve prosthesis
- ❑ Yes ❑ No Eyelid spring or wire
- ❑ Yes ❑ No Artificial or prosthetic limb
- ❑ Yes ❑ No Metallic stent, filter, or coil
- ❑ Yes ❑ No Shunt (spinal or intraventricular)
- ❑ Yes ❑ No Vascular access port and/or catheter
- ❑ Yes ❑ No Radiation seeds or implants
- ❑ Yes ❑ No Swan-Ganz or thermodilution catheter
- ❑ Yes ❑ No Medication patch (Nicotine, Nitroglycerine)
- ❑ Yes ❑ No Any metallic fragment or foreign body
- ❑ Yes ❑ No Wire mesh implant
- ❑ Yes ❑ No Tissue expander (e.g., breast)
- ❑ Yes ❑ No Surgical staples, clips, or metallic sutures
- ❑ Yes ❑ No Joint replacement (hip, knee, etc.)
- ❑ Yes ❑ No Bone/joint pin, screw, nail, wire, plate, etc.
- ❑ Yes ❑ No IUD, diaphragm, or pessary
- ❑ Yes ❑ No Dentures or partial plates
- ❑ Yes ❑ No Tattoo or permanent makeup
- ❑ Yes ❑ No Body piercing jewelry
- ❑ Yes ❑ No Hearing aid
  (Remove before entering MR system room)
- ❑ Yes ❑ No Other implant _____
- ❑ Yes ❑ No Breathing problem or motion disorder
- ❑ Yes ❑ No Claustrophobia

Please mark on the figure(s) below the location of any implant or metal inside of or on your body.



IMPORTANT INSTRUCTIONS

Before entering the MR environment or MR system room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, & clothing with metallic threads.

Please consult the MRI Technologist or Radiologist if you have any question or concern BEFORE you enter the MR system room.

NOTE: You may be advised or required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic noise.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: _____ Date _____/_____/_____
Signature

Form Completed By: ❑ Patient ❑ Relative ❑ Nurse _____ _____
Print name Relationship to patient

Form Information Reviewed By: _____ _____
Print name Signature

❑ MRI Technologist ❑ Nurse ❑ Radiologist ❑ Other_____

Appendix F: INFORMED CONSENT

Northwestern University Medical School
CONSENT FORM

PROJECT TITLE: Neural correlates of the interaction between motivation and visual spatial attention in Alzheimer's Disease, Mild Cognitive Impairment and Healthy Aging

PRINCIPAL INVESTIGATOR: Dana M. Small, PhD

CO-INVESTIGATORS: Lisa Bagurdes and Marsel M. Mesulam

FUNDING: Northwestern University

Introduction/Purpose

You are being asked to participate in a research study of attention and motivation. Your participation in this study will involve one 30-minute training session and one 90-minute session using functional magnetic resonance imaging (fMRI). The purpose of this study is to 1) learn how motivation can influence attention in healthy aging, in people with isolated memory impairment and in people diagnosed with Alzheimer's disease; and 2) learn what parts of the brain play a role in possible influences of motivation upon attention. Sixty subjects will be recruited into this study.

Procedures

If you agree to participate, you will undergo the following 30-minute training session in the Cognitive Laboratory. You will be seated facing a TV screen and be asked to press a button as fast as you can when you see an X appear on the screen. Each run lasts approximately 7 minutes. Following a short practice session, you will perform the task two times to ensure you are performing the task correctly and to measure your average response time. During these trials an instrument will be recording the reflection of a beam of light from one eye. This beam gives us information about where your eyes are looking. This session will take approximately 30 minutes.

The functional Magnetic Resonance Imaging (fMRI) study will take place later that same day. Functional MRI is a type of brain scan that uses magnetic fields and radio waves to record changes in blood flow in your brain while you perform certain tasks. This tells us about the parts of your brain that are active during the task. This session will take approximately 90 minutes, although you will be in the scanner for only 50 of the 90 minutes. While you are in the scanner you will be asked to perform the same task that you performed in the training session. There are three 7-minute conditions in the fMRI study. In one condition you will have the opportunity to win 18 cents for fast responses and may earn up to an extra $24.84. At the beginning of another condition you will begin with $24.84 and will lose 18 cents for slow responses. In the third condition you will not win or lose money, but you should still respond to the X as fast as you can.

In order to make sure that MRI procedure will be safe, you will first be asked to fill out a screening form prior to participating in this study. This will take no more than five minutes. It is important that you tell the experimenters in this study if you have any history of:

- Metal fragments in your eyes or face.
- Implantation of any electronic devices such as (but not limited to) cardiac pacemakers, cardiac defibrillators, cochlea implants or nerve stimulators.
- Surgery on the blood vessels of your brain of the valves of the heart
- Claustrophobia (fear of enclosed places)
- Tattoos or piercings

You will be given instructions outside the MRI scanner about the scanning. Next you will be asked to lie still on the MRI patient table and your head will be placed in a special head holder, enabling us to record the imaging signal. The front of this head-holder will be open, permitting you to look through a special mirror and to observe pictures presented to you on a projection screen. You will be asked to hold your head as still as possible and to respond to the pictures by pushing a button or thinking quietly to yourself. Your head will be cushioned by a firm foam pillow. The table will then slide into the enclosed space of the MRI scanner. A camera, located at the back of the scanning room will be adjusted to record the reflection of a beam of infrared light aimed at one of your eyes. You will not be able to see this light beam. You will also be asked to look at different positions on the computer screen so that the position of your eyes can be measured precisely.

Some people feel fatigued, uncomfortable or claustrophobic in the MRI scanner. The MRI scanning session will take approximately 50 minutes to complete once you are in the scanner. The information obtained from the MRI scanner is only useful if you are able to complete the entire imaging session, and hold your head very still the entire time. Therefore you will be encouraged to hold as still as possible, and to let the investigators know if you are uncomfortable in any way as soon as possible after the imaging session begins.

The MRI scanner makes loud banging noises while performing a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise. The experimenters will be in communication with you through an intercom system to inform you of the progress of the study. The earplugs or headphones should not interfere with your communication with the experimenters or your performance in the study.

The MRI pictures obtained in this study will not be in a form readable by either you or your physician. Therefore a copy of the MRI pictures or the results of your individual study will not be routinely given either to you or your physician. While the MRI pictures in this study are not formally reviewed by a radiologist, if in the course of processing the images we notice any abnormality that would be potentially relevant to your health we will notify you and a physician you designate.

Risks There are no known risks associated with the infrared reflection system for measuring eye movements. Illumination is no more that 1 milliwatt per cm^2, which is less than $1/10^{th}$ the amount that has been shown to be safe for adults and children. Near-infrared light makes up a large part of ordinary sunlight. If you experience tiredness or restlessness during testing you can always ask for a break.

There are no known risks associated with the fMRI procedure, although some subjects experience discomfort from trying to keep still during the study, and some subjects feel anxious or claustrophobic in the scanner.

Benefits There may be no direct benefits to you for participating in this study. However, the results may be of benefit to others by contributing to our understanding of how different areas of the brain help us pay attention to our surroundings.

Alternatives You may choose not to participate in the study.

Confidentiality Participation in this research study may result in a loss of privacy, since persons other than the investigators might view your study results. Unless required by law, only the study investigator, members of the investigator's staff, and the Northwestern University Institutional Review Board will have authority to review your study records. They are required to maintain confidentiality regarding your identity. Records of your ongoing participation in this study will be kept confidential at the Cognitive Neurology and Alzheimer's Disease Center located at 320 East Superior, Searle 11-465, Chicago IL. Your research materials (behavioral and fMRI data) will not be directly linked to your identity. The MRI scan data will be kept indefinitely. The results of this study may be published or presented at scientific meetings; however, participants will be identified in these reports by number and not by name.

Financial Information Participation in this research study is at no medical cost to you. You will not have to pay for any of the procedures in which you participate as part of this research project, including the MRI scan. You will receive $20 in cash for your participation in the study. Additionally, you will have the opportunity to win an additional $24.84 during the fMRI portion. Your winnings earned during the fMRI study will be calculated and you will receive $20 - $44.84 in cash following completion of today's study. If you do not complete the fMRI portion for any reason, you will be paid $20 for your participation. You will receive a parking sticker for parking related to your participation in this project.

Subject's Rights Participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, and you may discontinue participation at any time without any penalty or loss of benefits. Your participation in this study may be discontinued by the investigator without your consent if technical problems with the scanner arise. If this occurs, you will be paid $20 and have the option to reschedule. If you choose not to reschedule you will still be paid $20 for partial completion of the fMRI portion of the study.

Contact Persons

Any questions you may have about this study may be directed to Lisa Bagurdes at (312) 908-9488. Questions about your rights as a research subject may be directed to the Office for the Protection of Research Subjects of Northwestern University, at telephone number (312) 503-9338. If problems arise evenings or weekends, you may call (224) 430-0965.

CONSENT

"I have read this form and the research study has been explained to me. I have been given the opportunity to ask questions and my questions have been answered to my satisfaction. If I have additional questions, I have been told who to contact. I agree to participate in the research study described above and will receive a copy of this consent form. I will receive a copy of this consent form after I sign it."

_____ _____

Subject's Name (printed) and Signature Date

_____ _____

Name (printed) and Signature of Legally Authorized Individual or next of kin (*if necessary*) Date

_____ _____

Name (printed) and Signature of Person Obtaining Consent Date

_____ _____

Investigator's Signature Date

Appendix G: EXPLICIT MEMORY QUESTIONNAIRE

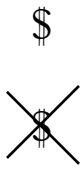
1. Where were you instructed to look on the screen?

2. When did you press the button on the button box?

3. Could you tell the difference between the “X” and “+”?

4. Could you win or lose money during the experiment. How much?

5. What did these three symbols represent?



Appendix H: CERAD WORD LIST

Initial Instructions: "I am going to show you ten printed words one at a time. Read each word out loud as I show it to you. Later, I will ask you to recall all ten words." (Correct them if they mispronounce the word; one reminder per trial is permissible.).--- "Now tell me all the words that you can remember in any order."

Subsequent Instructions: "I am going to show you the same ten words again but in a different order. Read each word out loud and try to recall as many as you can."----- "Now tell me all the words that you can remember in any order."

(Exposure time: 1 word every 2 seconds; Recall time: 90 seconds per trial maximum)

Check each word as it is recalled
After each trial say "Can you think of anymore" only once.

can't read	TRIAL 1		TRIAL 2		TRIAL 3	
	Butter		Ticket		Queen	
	Arm		Cabin		Grass	
	Shore		Butter		Arm	
	Letter		Shore		Cabin	
	Queen		Engine		Pole	
	Cabin		Arm		Shore	
	Pole		Queen		Butter	
	Ticket		Letter		Engine	
	Grass		Pole		Ticket	
	Engine		Grass		Letter	
	INTRUSIONS		INTRUSIONS		INTRUSIONS	

TOTALS:

Correct ____ Correct ____ Correct ____

Intrusions ____ Intrusions ____ Intrusions ____

TOTAL CORRECT ALL TRIALS_____

Appendix I: CERAD WORD LIST RECALL

"A few minutes ago I asked you to learn a list of 10 words which you read one at a time out of a book. Now I want you to try to recall as many of those 10 words as you can. Tell me as many of those 10 words as you can remember." (maximum time: 90 seconds)

Check each word as it is recalled
After recall say "Can you think of anymore?" only once.

Butter	
Arm	
Shore	
Letter	
Queen	
Cabin	
Pole	
Ticket	
Grass	
Engine	

INTRUSIONS

TOTALS:

CORRECT	
INTRUSIONS	

Appendix J: CERAD WORD LIST RECOGNITION

"Now I am going to show you more words in this book. Some of the words are from the list you saw earlier and some of the words I haven't shown you before. I want you to say YES if the word I show you is one you saw earlier and NO if it not."

	YES	NO
Church		
Coffee		
Butter		
Dollar		
Arm		
Shore		
Five		
Letter		
Hotel		
Mountain		
Queen		
Cabin		
Slipper		
Pole		
Village		
String		
Ticket		
Troops		
Grass		
Engine		

Targets correct		
Foils correct		

10 - foils correct = False positives

Appendix K: CERAD SEMANTIC FLUENCY

CERAD - VERBAL FLUENCY CATEGORIES

TIME: 0 to 15 seconds

TOTAL

TIME: 16 to 30 seconds

TOTAL

TIME: 31 to 45 seconds

TOTAL

TIME: 46 to 60 seconds

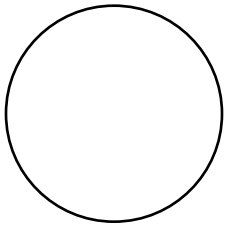
TOTAL

TOTAL WORDS (0-60 sec):

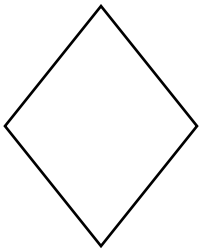
Appendix L: CERAD CONSTRUCTIONAL PRAXIS

Instructions: "I'd like you to copy this figure in the space below. Can you draw one that looks just like this one? Copy these as neatly as you can" (Have subject use a pen and do not allow him or her to sketch, examiner can cross out errors, subject can draw figure a maximum of two times.)

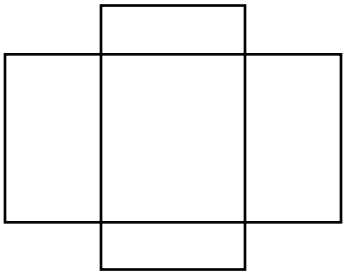
1. Circle	Error	Correct
closed circle		
circular shape		



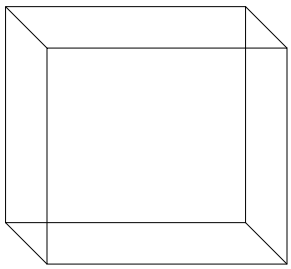
2. Diamond	Error	Correct
draws 4 sides		
closes all 4 angles of figure (within 1/8")		
sides of approximately equal length		



3. Rectangles	Error	Correct
both figures are four-sided		
overlap resembles original		



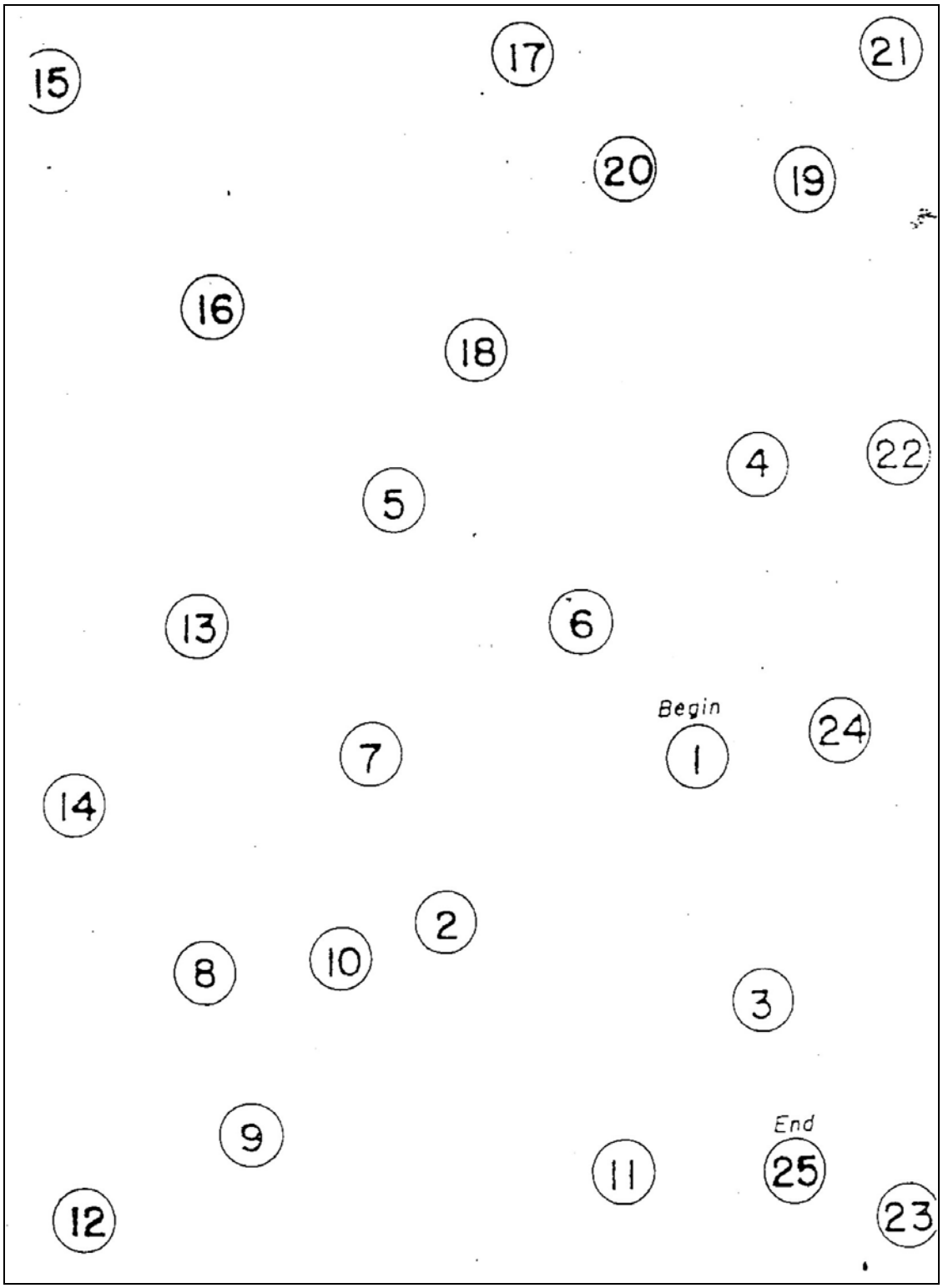
4. Cube	Error	Correct
figure is 3-dimensional		
frontal face correctly oriented (may be right or left oriented)		
internal lines correctly drawn		
opposite sides are parallel (within 10^{o})		



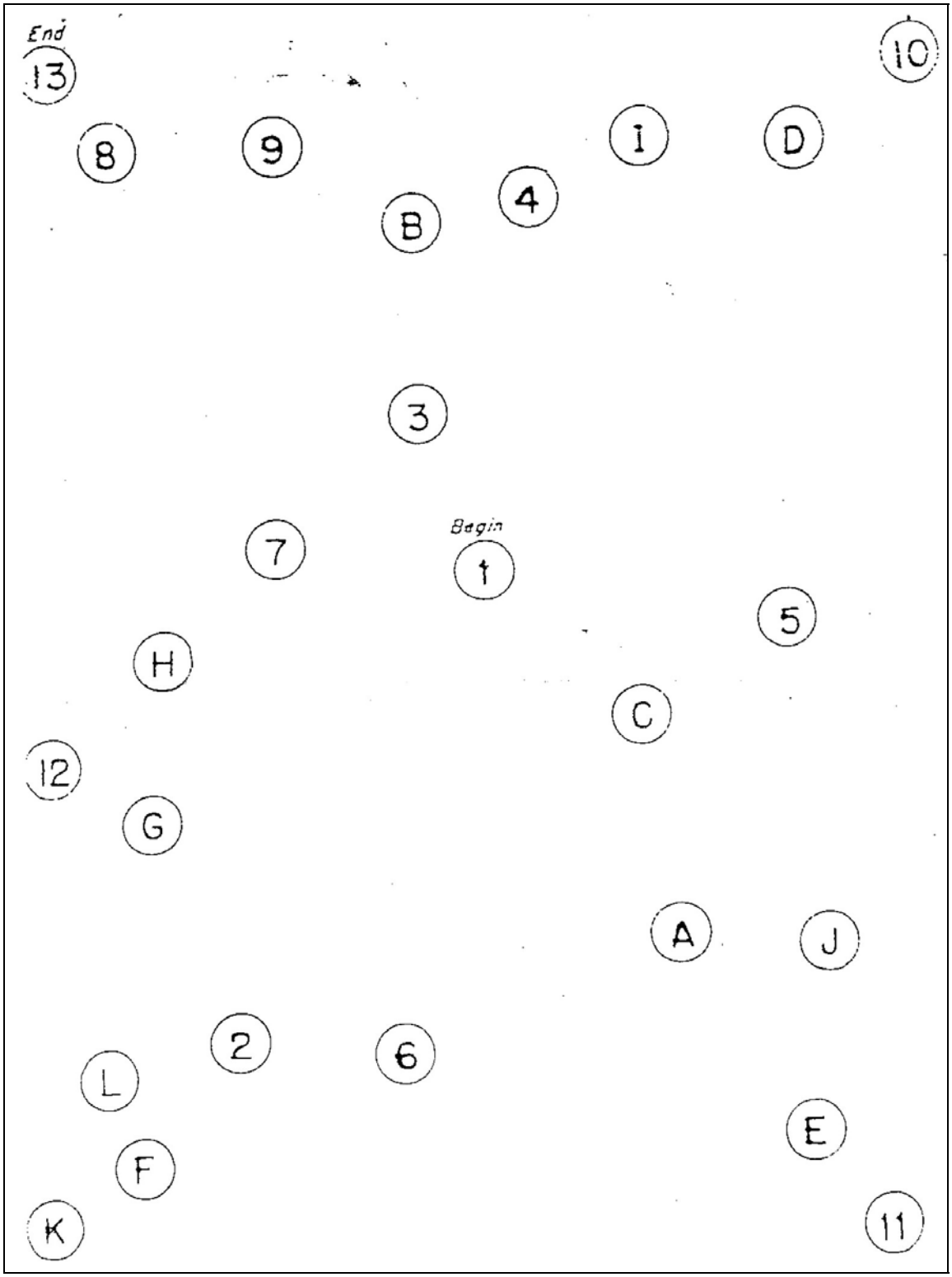
	TOTAL
Item #1	
Item #2	
Item #3	
Item #4	

TOTAL SCORE: | |

Appendix M: TRAIL MAKING TEST PART A



Appendix N: TRAIL MAKING TEST PART B



Appendix O: GERIATRIC DEPRESSION SCALE

Ask patient to answer each question based on how he/she has felt OVER THE PAST WEEK, including TODAY.

1.	Are you basically satisfied with your life?	YES	NO
2.	Have you dropped many of your activities and interests?	YES	NO
3.	Do you feel that your life is empty?	YES	NO
4.	Do you often get bored?	YES	NO
5.	Are you hopeful about the future?	YES	NO
6.	Are you bothered by thoughts that you can't get out of your head?	YES	NO
7.	Are you in good spirits most of the time?	YES	NO
8.	Are you afraid that something bad is going to happen to you?	YES	NO
9.	Do you feel happy most of the time?	YES	NO
10.	Do you often feel helpless?	YES	NO
11.	Do you often get restless and fidgety?	YES	NO
12.	Do you prefer to stay at home rather than going out and doing new things?	YES	NO
13.	Do you frequently worry about the future?	YES	NO
14.	Do you feel you have more problems with memory than most?	YES	NO
15.	Do you think it is wonderful to be alive now?	YES	NO
16.	Do you often feel downhearted and blue?	YES	NO
17.	Do you feel pretty worthless the way you are now?	YES	NO
18.	Do you worry a lot about the past?	YES	NO
19.	Do you find life very exciting?	YES	NO
20.	Is it hard for you to get started on new projects?	YES	NO
21.	Do you feel full of energy?	YES	NO
22.	Do you feel that your situation is hopeless?	YES	NO
23.	Do you think that most people are better off than you are?	YES	NO
24.	Do you frequently get upset over little things?	YES	NO
25.	Do you frequently feel like crying?	YES	NO
26.	Do you have trouble concentrating?	YES	NO
27.	Do you enjoy getting up in the morning?	YES	NO
28.	Do you prefer to avoid social gatherings?	YES	NO
29.	Is it easy for you to make decisions?	YES	NO
30.	Is your mind as clear as it used to be?	YES	NO

TOTAL SCORE: [ ] (maximum score = 30)

Appendix P: 3T SUBJECT DATA

Subject	Age	Sex	Classification	CDR	MMSE	Race	Handedness	Education (years)	Memory (CERAD Word List: 1-3)	Memory (Delayed Recall)	Memory (Target (Recognition)	Attention (CERAD-Semantic Fluency)	Visual Perceptual Constructions	Trail Making Test Part A	Trail Making Test Part B	Logical Memory II WMS-R	Geriatric Depression Score
SY	63	F	EC	0	29	Cauc	85	17	26	10	10	23	11	29	61	41	4
LC	77	F	EC	0	29	Cauc	100	16	24	8	10	21	9	40	100	28	2
MD	70	F	EC	0	29	Cauc	100	13	23	9	10	26	10	37	71	29	5
CH	70	F	EC	0	30	Cauc	85	18	30	10	10	32	10	23	50	42	8
ELA	91	F	EC	0	29	Cauc	100	16	21	6	10	20	11	74	226	20	3
RP	68	F	EC	0	27	Afr	100	13	24	7	10	20	9	28	77	10	1
AG	79	M	EC	0	30	Cauc	100	17	18	4	10	14	8	33	70	22	1
BR	65	F	EC	0	30	Cauc	100	16	24	8	10	16	10	23	74	20	0
MR	72	F	EC	0	29	Cauc	100	14	23	8	10	20	11	33	106	28	2
MaS	74	M	EC	0	30	Cauc	85	15	25	8	10	15	11	32	60	30	0
RS	73	M	EC	0	29	Afr	95	19	23	9	10	19	11	40	70	24	6
MS	77	F	EC	0	29	Cauc	100	18	22	6	10	13	10	22	58	29	0
WR	70	F	MCI	0	29	Afr	80	12	28	9	9	17	9	25	220	21	3
PR	65	M	MCI	0.5	30	Cauc	100	12	22	8	10	15	10	30	62	30	0
EM	68	F	MCI	0	28	Afr	100	15	20	9	9	20	7	31	70	17	2
MP	83	F	MCI	0	26	Cauc	100	13	19	3	10	11	8	63	141	9	9
EL	74	F	MCI	0	30	Cauc	100	19	27	10	10	17	10	46	102	35	4
BK	69	F	MCI	0	30	Cauc	90	15	23	7	10	18	11	22	57	21	10
EF	73	F	MCI	0.5	29	Cauc	100	12	19	5	9	28	11	49	74	14	6
WD	65	M	MCI	0.5	27	Cauc	100	16	28	10	10	23	11	34	72	23	4
LA	74	F	MCI	0	30	Cauc	100	18	23	5	10	23	11	29	236	21	6
LD	73	F	MCI	0	30	Cauc	100	16	22	9	10	21	9	31	66	16	5
AA	69	F	MCI	0	28	Afr	100	14	24	7	9	21	10	57	157	21	0
EB	70	F	MCI	0.5	30	Afr	100	20	18	4	10	19	11	55	95	16	0
MC	61	F	PRAD	1	29	Cauc	80	12	2	4	5	15	8	31	300	5	0
LS	73	F	PRAD	0.5	28	Afr	100	11	15	3	10	14	10	26	300	8	4
CK	86	F	PRAD	1	24	Cauc	100	13	20	3	9	11	10	67	117	6	8
JK	67	F	PRAD	0.5	27	Cauc	100	20	18	1	9	13	10	34	102	9	0
GH	83	F	PRAD	0.5	28	Cauc	100	14	12	0	10	12	9	57	289	0	2
BG	78	M	PRAD	1	25	Cauc	100	13	11	0	10	10	9	54	300	1	2
AC	80	F	PRAD	1	24	Cauc	95	13	16	3	10	11	8	41	135	3	0