FUNCTIONAL CONNECTIVITY OF THE POSTERIOR CINGULATE IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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DEDICATION

I would like to dedicate this dissertation to my parents for their belief in me and having only one expectation from me—that I choose to do what will make me happy. This also would not have been possible without the support and understanding of my daughter and the rest of my family through the times that I struggled (and the times I didn't). I'm truly blessed.

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Mild cognitive impairment (MCI) has been implicated as an early stage of Alzheimer's disease (AD) by some, while others argue this is not necessarily the case. While controversy around this issue continues, it is undisputed that MCI is a risk factor for AD. Finding a biomarker of AD would lead to early intervention that could potentially slow the progression of the disease and guide further research towards targets for a cure. Recent findings suggest that reduced connectivity between the posterior cingulate cortex (PCC) and associated brain regions may make an important contribution in this regard, as changes in the PCC/precuneus and entorhinal cortex are implicated as

early biomarkers for AD. The current study used functional connectivity magnetic resonance imaging (fcMRI) to examine the posterior cingulate's connectivity with other brain regions in subjects with AD (n=10), MCI (n=9), and age-matched elderly normal controls (NC; n=10). As hypothesized, results revealed that subjects with AD showed decreased connectivity in regions of the frontal lobe, temporal lobe, and cingulate gyrus when compared to NC, and in the frontal and temporal gyri when compared to MCI. When MCI was compared to NC, decreased connectivity was observed in the cingulate gyrus and parahippocampal gyrus while increased connectivity was found in prefrontal cortex and cerebellar regions. The latter finding of increased connectivity in the MCI group in the prefrontal cortex and cerebellum was interpreted as evidence of compensatory recruitment of alternate brain regions in the face of deficient processing in parahippocampal regions in the early stage of disease. It is possible that the connectivity between the PCC and cerebello-frontal structures in MCI may be helping to sustain episodic memory and executive functions that deteriorate in AD. This study showed that fcMRI may be sensitive enough to detect subtle changes in brain structure, and while it is premature to say that fcMRI might prove to be a biomarker of AD, these preliminary findings are encouraging and may serve as an impetus for further research.

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AD – Alzheimer's disease

ADC – Alzheimer's Disease Center

AFNI – Analysis of Functional NeuroImages

BA – Brodmann area

BNT – Boston Naming Test

BOLD – blood oxygenation level-dependent

CDR – Clinical Dementia Rating

CERAD – Consortium to Establish a Registry for Alzheimer's Disease

cm – centimeter(s)

CSF – cerebral spinal fluid

DLPFC – dorsolateral prefrontal cortex

DTI – diffusion tensor imaging

EPI – echo-planar image

ERC – entorhinal cortex

FA – fractional anisotropy

fcMRI – functional connectivity magnetic resonance imaging

FDG – fluorodeoxy-glucose

fMRI – functional magnetic resonance imaging

FOV – field of view

MCI – mild cognitive impairment

mm – millimeter(s)

MMSE – Mini-Mental State Examination

MP-RAGE – magnetization-prepared rapid gradient echo

MR – magnetic resonance

MRI – magnetic resonance imaging

NINDCDS/ADRDA – Neurological Disease and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association

PCC – posterior cingulate cortex

PET – positron emission tomography

PIB – Pittsburgh Compound B

ROI – region of interest

SD – standard deviation(s)

SNR – signal-to-noise ratio

SSGR – single-shot gradient-recalled

TE – echo time

TMT – Trailmaking Test (A and B)

TR – repetition time

WAIS-R – Wechsler Adult Intelligence Scale-Revised

WMS-R – Wechsler Memory Scale-Revised

CHAPTER ONE
Introduction

The proportion of elderly people in the United States is rapidly increasing. Based on estimates from the 2000 census, the population aged 65 and over is expected to double within the next 25 years (National Institute on Aging, 2006). An estimated 71 million people, or roughly 20% of the U.S. population, will be 65 or older by 2030 (Wan, Sengupta, Velkoff, DeBarrow, & U.S. Census Bureau, 2005). As the aging population increases, so too will the need for services aiding in the treatment and management of the elderly, creating a burden on not only patients and caregivers, but the health care system overall. Among older Americans, nearly 95% of health care expenditures is for chronic diseases (Hoffman, Rice, & Sung, 1996). In 2004, Alzheimer's disease was the 7th leading cause of death in the United States (Miniño, Heron, Murphy, Kochanek, & Division of Vital Statistics, 2007). Currently, more than five million Americans have Alzheimer's disease (AD) (Alzheimer's Association, 2007) and by mid-century it is estimated that this number will exceed 13.2 million (Hebert, Scherr, Bienias, Bennett, & Evans, 2003).

An area of study that has received a great amount of attention recently is mild cognitive impairment (MCI). It is well documented that MCI represents a significant risk factor for progression to dementia (Levey, Lah, Goldstein, Steenland, & Bliwise, 2006; Morris & Cummings, 2005; Petersen, 2001, 2004). There is no universally agreed-upon definition of MCI, but it is generally conceptualized as a condition in which cognitive functioning (usually memory) shows some impairment, but without significant disruption in the ability to perform daily activities (Petersen, 2004; Winblad et al., 2004). In

general, the construct of MCI was developed to represent a transitional stage of cognitive change that occurs between normal aging and early dementia (Petersen, 2007). While some consider most cases of MCI to be a prodrome of AD (Morris, 2006; Morris & Cummings, 2005; Whitehouse, 2007), others argue that there are different subtypes (i.e., single-domain amnestic, multiple-domain amnestic, single-domain nonamnestic, multiple domain nonamnestic) and etiologies of MCI (G. A. Jicha et al., 2006; Petersen, 2004; G. Smith & Rush, 2006; Whitwell et al., 2007) and caution that not all cases of MCI progress to AD even within a given subtype. There are disparate findings across studies with regard to rates of conversion from MCI to AD (Panza et al., 2005), which is likely a reflection of the inconsistency in defining and diagnosing MCI (Petersen, 2004). Reported rates of annual conversion range from 1% to 40% (Bischkopf, Busse, & Angermeyer, 2002; Devanand, Folz, Gorlyn, Moeller, & Stern, 1997; Flicker, Ferris, & Reisberg, 1991; Palmer, Fratiglioni, & Winblad, 2003; Petersen et al., 2001; Ritchie, Artero, & Touchon, 2001; Tierney et al., 1996), with 10% to 15% commonly reported, compared to 1% to 2% of the healthy aging population (Gauthier et al., 2006; Morris et al., 2001; Petersen et al., 1999). Over a six-year period, approximately 80% of 220 subjects in a Mayo Alzheimer's Disease Research study diagnosed with MCI progressed to AD (Petersen, 2004).

It is important to understand whether MCI and AD are separate entities or different stages of the same disease process because developing effective treatment will depend upon the etiology (or mixed etiologies). As already noted, not all cases of MCI progress to AD, and in fact some studies have shown that a substantial portion of persons (10% to 40%) meeting criteria for the amnestic subtype of MCI (i.e., memory being the

only domain affected) actually improve in cognitive functioning over time (Bickel, Mosch, Seigerschmidt, Siemen, & Forstl, 2006; Bondi et al., 2008b; Fisk & Rockwood, 2005; Ganguli, Dodge, Shen, & DeKosky, 2004; Larrieu et al., 2002; Petersen, 2004). Although there has been some success treating the symptoms and slowing the progression of AD with acetylcholinesterase inhibitors, antioxidants, anti-inflammatories, and nootropics (Samuels & Davis, 2006), to date, no clinical trials examining these agents have shown efficacy in preventing or delaying the progression of amnestic MCI to AD (Jelic, Kivipelto, & Winblad, 2006; Palmer & Fratiglioni, 2006).

Since even previously healthy individuals can develop AD, clearly there is no simple explanation for the disease process, and early detection may be equally as complex. Indeed, evidence from the Cognitive Function and Ageing Study (2001) revealed on autopsy that a third of people with no clinical signs of dementia had histopathological hallmarks of AD, underscoring the importance of finding biomarkers of preclinical AD so that these individuals may be targeted for intervention. Unfortunately, while AD can be clinically diagnosed with a high degree of accuracy (85% or greater) (McKhann et al., 1984), attempts at identifying definitive risk factors, predicting who will ultimately suffer from AD, and mapping out how the disease will progress after onset have been only mildly successful. Recent advances in understanding the mechanisms underlying AD have led to pharmacologic treatments that show potential for alleviating symptoms and/or delaying progression (Hayden & Sano, 2006; Samuels & Davis, 2006) in some individuals. However, as yet there are no methods of preventing or reversing the disease process. Research provides evidence that a number of health-related factors are associated with AD, for example, obesity (Barrett-Connor, 2007; Wolf et al., 2007), body

mass index (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007), increased systolic blood pressure and high cholesterol (Kivipelto, Helkala, Laakso et al., 2001), the metabolic syndrome (Yaffe, 2007), white-matter lesions (de Groot et al., 2001), and carrying the apolipoprotein e4 allele (Bookheimer et al., 2000). Similar to findings in AD, vascular risk factors for MCI have been identified (Bennett, Schneider, Bienias, Evans, & Wilson, 2005; Kivipelto, Helkala, Hanninen et al., 2001). A history of hypertension has been related to a higher risk of MCI, especially in the nonamnestic type of MCI in the elderly (Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007). In addition, in a study of community-dwelling older men, elevated midlife blood pressure, previously shown to predict increase in white matter hyperintensities (DeCarli et al., 1999), was found to be associated with as much of an increased risk for MCI as the apolipoprotein e4 allele (DeCarli et al., 2001).

Cognitive factors that predict the development of dementia in the normal population include impairments on tests of memory and executive function (Chen et al., 2001). The hallmark of AD is rapid forgetting, which can be observed on formal neuropsychological testing with list learning and related tasks (Salmon et al., 2002; K. Welsh, Butters, Hughes, Mohs, & Heyman, 1991). The memory impairment in AD is the result of neuropathology in the mediotemporal lobe (Bancher, Braak, Fischer, & Jellinger, 1993). It is possible that pathways from the entorhinal cortex (ERC) and hippocampus are disturbed and could lead to a disconnection from neocortical association areas. Recent studies have found functional interactions between the ERC and posterior cingulate cortex (PCC) at the very early stage of AD (Hirao et al., 2006). Furthermore,

neuroimaging research has demonstrated that the PCC is functionally compromised in individuals diagnosed with amnestic MCI (Ries et al., 2006).

In conclusion, a better understanding of the mechanisms underlying MCI and AD is needed to provide insight into the development of new treatment strategies as well as guide prevention strategies for potentially treatable risk factors. Furthermore, early identification of the disease could provide a window of opportunity for intervention that might delay cognitive and functional impairment.

Statement of the Problem

Due to the heterogeneity of MCI, studies have been inconclusive in determining its etiology and identifying which individuals will progress to AD. To this end, a better understanding of brain and behavioral changes in preclinical AD is needed.

Purpose of the Study

The question of whether MCI and AD are separate entities has been the subject of much debate. Some researchers suggest that most cases of MCI are in fact early AD (Morris, 2006; Morris & Cummings, 2005; Whitehouse, 2007). Others (e.g., G. Jicha et al., in press; Petersen, 2004) argue that since there appear to be different subtypes of MCI, and not everyone with MCI progresses to AD, it appears that not all MCI is an early phase in the course of the disease. Reliable predictors for the onset and progression of AD remain elusive, but imaging studies to date have implicated PCC, precuneus, and ERC involvement in MCI and prodromal AD. However, findings vary, and the underlying mechanisms and extent of involvement are not clear, especially with regard to what role these brain regions play before the manifestation of disease symptoms. The

proposed study seeks to help elucidate early functional contributions by examining functional connectivity of the PCC in MCI and AD.

CHAPTER TWO
Review of the Literature

Combining multiple methods of inquiry, such as the results from neuropsychological testing, neuroimaging, and pathophysiological studies, may increase their predictive value and aid in the early detection of AD. Kantarci and colleagues (2002) looked at the diagnostic accuracy of magnetic-resonance (MR) hippocampal volumetry and spectroscopy in patients with mild cognitive impairment, in normal older people, and in patients with Alzheimer's disease. Combinations of MR measures had superior diagnostic sensitivity compared with any single MR measurement for the AD vs. control and control vs. MCI comparisons. A systematic review of 91 studies of neuropsychological functioning, structural neuroimaging, or functional neuroimaging revealed that there are several cognitive and biochemical markers that precede the clinical manifestations of AD (Twamley, Ropacki, & Bondi, 2006), such as subtle deficits in attention, learning and memory, executive functioning, processing speed, and language, as well as volume loss and cerebral blood flow or metabolic changes.

NEUROCOGNITIVE FUNCTIONING

Normal Aging and Cognition

Normal aging involves a decline in abilities that were once stable, and individuals vary with regard to the extent that cognitive and functional abilities are affected. Individual variation in physiological and psychological function increases with age (Morse, 1993), and this, combined with factors such as life-long habits (e.g.,

smoking, exercise), educational attainment, occupational demands, and health status, make it challenging to compare what are considered to be normal cognitive abilities between individuals (Schaie & Willis, 1991). The rates of decline also vary according to the function being assessed as well as the study methodology (e.g., longitudinal vs. cross-sectional design, community-based samples vs. clinical samples, and differences in test batteries employed across studies). Notwithstanding these challenges, interpretation of test data shows that performance on neuropsychological measures still falls within the expected range when adjusted for changes typical for age. For example, overall intelligence has been assessed in the healthy aging population, and fluid intelligence (i.e., reasoning and problem-solving in novel situations) is believed to show a subtle decline from middle age through the early 60s, followed by a more rapid decline. In contrast, crystallized intelligence (i.e., acquired knowledge and overlearned skills) remains unchanged or shows gains into the 70s and 80s (Hochanadel & Kaplan, 1984; Kaufman, Reynolds, & McLean, 1989).

With respect to specific cognitive domains, despite methodological differences, a preponderance of studies has shown that many aspects of cognition decline as a function of normal aging, especially aspects of memory, perceptual speed and executive functioning (Backman, Small, & Wahlin, 2001). For example, there is some evidence to suggest that memory decline precedes loss of other cognitive abilities, with memory beginning to show a decline between the ages of 30 and 50 whereas verbal skills and reasoning abilities are maintained until the 60s or later (M. Albert, Duffy, & Naeser, 1987). In particular, episodic memory (i.e., memory for specific events that have occurred in a person's experience) decline has been noted in older adults, and encoding

deficiencies may be more salient than retrieval deficits in episodic memory decline (Friedman, Nessler, & Johnson, 2007), supporting the notion that typical cognitive aging involves a loss of efficiency in the acquisition of new information (LaRue, 1992; Petersen, Smith, Kokmen, Ivnik, & Tangalos, 1992). Another prominent sign of cognitive aging is a reduction in mental processing speed (Salthouse, 1996), as well as a reduction in the amount of information that can be processed at one time, and studies that have focused on processing speed, working memory, and inhibitory control have indeed found age-related cognitive decline (Park, 1999; Rozas, Juncos-Rabadan, & Gonzalez, 2008). Furthermore, as a consequence of reduced mental processing speed, performance in other domains of cognition is affected, including attention, language, memory, and executive functioning (Finkel, Reynolds, McArdle, & Pedersen, 2007; D. L. Fisher, Duffy, & Katskiopoulos, 2000; Keys & White, 2000; Levitt, Fugelsang, & Crossley, 2006; Parkin & Java, 2000; Salthouse, 1996, 2000; Sliwinski & Buschke, 1997; Zelinski & Lewis, 2003; Zimprich, 2002). In fact, some studies have reported that processing speed accounts for nearly all of the effects of age on performance in working memory tasks (Belleville, Rouleau, & Caza, 1998; McCabe & Hartman, 2003).

In summary, normal aging is associated with changes in nearly all domains of cognitive functioning. However, in particular, learning, processing speed, episodic memory, and executive functioning evidence the greatest declines.

Mild Cognitive Impairment and Cognition

Predementia syndromes have been described in numerous ways over the years, including benign senescent forgetfulness, age-associated memory impairment, age-

associated cognitive decline, age-related cognitive decline, mild neurocognitive disorder, and cognitive impairment no dementia (Panza et al., 2005; Petersen, 2007). The term "mild cognitive impairment" was originally proposed by Petersen et al. (1999) to describe a transitional state between normal cognitive aging and very early AD. According to these early criteria, MCI was characterized by a subjective memory complaint by the patient and/or an informant, impaired memory for age based on objective testing in the context of relatively preserved cognitive functioning in other domains, fairly intact activities of daily living, and no dementia. It has since become apparent that MCI encompasses other domains of functioning in addition to, and in some cases instead of, memory (Manly et al., 2005; Petersen et al., 2001; Tabert et al., 2006; Whitwell et al., 2007). Criteria have thus been revised to allow *any* subjective cognitive complaint (vs. memory only) and have been expanded to delineate different subtypes of MCI, including both amnestic and nonamnestic forms and accounting for whether a single or multiple cognitive domains are affected within these forms (Petersen, 2004; Winblad et al., 2004).

There are several challenges in making a diagnosis of MCI (Bondi et al., 2008b; Manly et al., 2005; Morris & Cummings, 2005; Petersen, 2004), which have contributed to inconsistent findings. Lending to these challenges is the element of subjectivity on the part of the clinician as well as the patient. Subjective judgments include the quality and degree of the memory/cognitive complaint, especially when it is based on self-report and not corroborated by an informant. The degree of functional change necessary to say that activities of daily living are no longer "largely intact" is also ill-defined. Lastly, what constitutes "essentially preserved" general cognitive functioning, particularly since no

specific assessment instruments or cutoffs are outlined for making this determination, is a subject in question. In this regard, a Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975)score of $\geq$24 and/or a Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993)score of 0.5 are conventionally used (DeCarli et al., 2001; Hirao et al., 2006; Zanetti et al., 2006). These instruments, however, are not without their limitations with regard to diagnostic utility (Petersen, 2004; Salmon et al., 2002).

In addition, objective neuropsychological impairment is variable and ill-defined (Portet et al., 2006), with no clear guidelines as to which cognitive domains should be assessed, which neuropsychological tests should be used, whether poor performance on one test vs. multiple is sufficient to confirm impairment, and what cutoff should be used to determine impairment (Bondi et al., 2008b). Typically, a score 1.5 standard deviations (SD) below the mean of age-matched normal elderly controls on neuropsychological tests (Petersen, 2004; Tuokko, Hadjistavropoulos, Miller, Horton, & Beattie, 1995) has been the cutoff used, although "impairment" varies, ranging from 1 to 1.96 SD (Bickel et al., 2006; Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006) below age-appropriate means. Interestingly, Smith et al. (2006) reported that in an analysis of nine neuropsychological measures, 23% of their MCI population had no cognitive performances that fell greater than 1.5 SD below the mean, while in the same analysis, 21% of the "normal" sample had at least one measure that fell more than 1.5 SD below age-appropriate means. Determining cutoffs is particularly important in the context of individuals of previously high intellect that now show average performance (indicating a relative decline for that individual) as well as those with a low education who have low

cognitive scores but are unchanged, and in these instances especially, clinical judgment must be exercised (Petersen, 2004). Finally, determining whether an individual is on a trajectory towards dementia presents another challenge, especially when changes are more subtle, as is often the case when distinguishing between normal aging and MCI and between MCI and AD.

As with normal aging, the cognitive profile of MCI can involve a wide range of cognitive domains (Backman, Jones, Berger, Laukka, & Small, 2005; Twamley et al., 2006), including attention, processing speed, executive function, language, and visuospatial function, as well as learning and memory. There has been some suggestion that lower performances on tests such as the MMSE (Johansson & Zarit, 1997; Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000) and other measures of global cognitive functioning (Aronson et al., 1990; Yoshitake et al., 1995) may be indicative of preclinical AD, although there has been debate as to whether the MMSE is adequately sensitive or reliable to detect very mild cognitive deficits (Benson, Slavin, Tran, Petrella, & Doraiswamy, 2005; Nasreddine et al., 2005; Salmon et al., 2002).

Studies that have focused on more specific patterns of cognitive decline in the absence of a diagnosis of MCI or AD have found that episodic memory decline is one of the most prominent features of a preclinical diagnosis (Bondi et al., 2008b; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Small, Mobly, Laukka, Jones, & Backman, 2003; Twamley et al., 2006), and often occurs several years before other changes (M. S. Albert, Moss, Tanzi, & Jones, 2001; Backman, Small, & Fratiglioni, 2001; Chen et al., 2000, 2001; Lange et al., 2002). When including individuals who have complaints of cognitive decline, Wang et al. (2002) showed that relative to normal aging, MCI subjects

demonstrated not only a significant decline in orientation, praxis, and language, but also in memory, and in particular, a greater decrement in encoding as compared to retrieval of episodic memory. It should be noted, however, that when compared to indices of delayed recall, immediate recall (i.e., encoding) may not be sensitive enough on its own to detect incipient dementia (G. Smith & Rush, 2006).

Much of the literature indicates that memory is the domain most typically affected in MCI (Petersen, 2004; Storandt, Grant, Miller, & Morris, 2006), and others report that multiple-domain MCI is even more common than that of single-domain amnestic MCI (Lopez et al., 2003). However, the latter finding is based on results from the Cardiovascular Heart Study Cognition Study (Lopez et al., 2003), where it was noted that most of the individuals had comorbid conditions that could affect cognition. Still others report that single-domain MCI is more frequent than multiple-domain MCI and that the nonamnestic MCI type is as frequent as the amnestic MCI type (Busse et al., 2006). According to this community-based sample of 980 dementia-free individuals aged 75 years or older, 9.3% of the sample was identified as single-domain amnestic MCI, 10.9% as multiple-domain amnestic MCI, 17.4% as single-domain nonamnestic MCI, and 3.9% as multiple-domain nonamnestic MCI. Discrepancies in research findings are likely a reflection of differences in defining MCI, the impairment cutoffs used, and the neuropsychological test batteries employed. Regardless, studies have demonstrated that patients with MCI show discrete nonamnestic impairments in other cognitive domains, such as confrontation naming, verbal fluency, executive dysfunction, and attention (Hanninen et al., 1997; Jacobs et al., 1995; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Petersen, 2004; Petersen et al., 1999; Twamley et al., 2006).

Challenges in diagnosing and classifying MCI have led to discrepancies in the literature. It appears that varying degrees of impairment are found in a range of cognitive domains, particularly episodic memory, executive functioning, and language/semantic memory, as well as attention, processing speed, and visuospatial functioning. For example, there is evidence that nonamnestic impairments contribute to progression from MCI to AD. Storandt et al. (2006) examined 32 individuals classified with MCI according to the original amnestic criteria (Petersen et al., 1999), 90 classified according to the new criteria that allowed impairment in domains other than memory (Petersen, 2004; Winblad et al., 2004), and 276 individuals who were too minimally impaired to meet MCI criteria, classified as pre-MCI. A general composite, as well as memory (Wechsler Adult Intelligence Scale [WAIS] Information, Wechsler Memory Scale [WMS] Logical Memory and Associative Learning, and the Boston Naming Test [BNT]), visuospatial (WAIS Block Design, Digit Symbol, and Trail Making Test [TMT] Part A), and executive (WMS Mental Control and Digit Span Forward, and Word Fluency for S and P) composites were utilized to aid in this classification. Both the amnestic MCI and revised-criteria MCI groups deteriorated more rapidly than the pre-MCI group on the general, memory, and visuospatial composites, but only the amnestic group declined more rapidly than the pre-MCI group on the executive composite. Median time to progress to a CDR score of 1 was approximately four years for the MCI groups but nearly double that for the pre-MCI group. Isolated memory deficits were observed in 30% of the individuals in the MCI group classified according to revised criteria and an additional 31% demonstrated deficits in memory plus one or two of the other domains assessed. Upon neuropathologic examination of those who died, all cases from the amnestic MCI

criteria group met diagnosis for AD, as did more than 90% of individuals in the revised MCI and pre-MCI groups. These authors thus concluded that MCI is usually early-stage AD.

MCI may be more accurately identified by examining performance across a range of tasks. Petersen et al. (1999) administered a variety of cognitive measures in 76 patients with MCI, 234 healthy controls, and 106 patients with mild AD every 12 to 18 months for four years. They found that the subjects with MCI performed more similarly to normal controls (NC) than AD on measures of general cognition and other non-memory indexes. That is, while the MCI subjects did not perform as well as NC, the differences were not significant and still fell within the normal range. In contrast, with regard to memory performance, the MCI patients were significantly more impaired on all measures of verbal and nonverbal learning and memory than the NC, and appeared more like the AD group in this respect. Patients with MCI also performed more similarly to those with AD on the BNT, ostensibly either due to early linguistic impairment (though the MCI group performed more like NC on the Controlled Oral Word Association Test) or because the BNT may actually be assessing semantic memory. These findings suggest that a decline in memory performance may differentiate MCI from normal aging, whereas impairment in other domains in addition to memory may be more helpful in differentiating MCI from AD.

Greenaway et al. (2006) sought to further delineate the episodic memory impairment observed in MCI. Similar to the findings of Petersen et al. (1999), in a study of 65 AD, 65 MCI, and 65 cognitively intact individuals, MCI subjects' performance on the California Verbal Learning Test (CVLT) fell between that of AD and controls. In

particular, they displayed a pattern of deficits closely resembling that of AD, including reduced learning, rapid forgetting, increased recency recall, elevated intrusion errors, and poor recognition discriminability with increased false-positives. It was also found that delayed recall and total learning were the most useful in differentiating MCI, AD, and normal aging controls.

In addition to memory impairment, understanding the nature of executive dysfunction in MCI is particularly important because some studies have indicated that executive impairments are predictive of later dementia (M. S. Albert et al., 2001; Tierney et al., 1996). However, findings are mixed with regard to executive functioning in MCI. For example, Mickes et al. (2007) retrospectively examined detailed neuropsychological test data collected over a three-year time period up to and including the year of first non-normal diagnosis (either MCI or AD) in 11 preclinical patients who eventually converted to AD. These data were compared to data from 11 control subjects matched on age (77 years), education (17 years), and years of participation in the same longitudinal data set. Data from neuropsychological tests administered 1 year and 2 years before a non-normal diagnosis were analyzed. Results showed that episodic memory and semantic knowledge were substantially more impaired than executive functioning in preclinical AD, suggesting that tests that rely on the integrity of the temporal lobes show greater deficits than those relying on frontal lobe integrity. Two years prior to first non-normal diagnosis, only one converter fell more than 1 SD below the mean of the controls on an executive functioning aggregate score (Wisconsin Card Sorting Test [WCST], letter fluency, TMT Parts A and B), whereas over half of the converters fell more than 1 SD below the mean of the controls on aggregate scores of episodic memory (free recall,

recognition, and cued recall of the CVLT) and semantic knowledge (BNT and category fluency).

In contrast, Storandt et al. (2006) reported that of 90 individuals with MCI who were assessed as noted above, 61% demonstrated deficits in memory or memory-plus domains, and additionally, 45% demonstrated deficits in executive or executive-plus functions as well as 44% in visuospatial or visuospatial-plus domains. This suggests that while memory appears to be the domain most impacted early on in the disease course, a substantial number of patients experience early declines in executive and visuospatial functions.

Chen et al. (2000, 2001) also presented evidence for executive dysfunction in addition to the episodic memory impairment observed in presymptomatic AD. In a 10-year prospective community-based study, performance in the presymptomatic state of 120 nondemented subjects who clinically manifested AD 1.5 years later was compared on 16 cognitive tests to 483 NC who remained nondemented over the 10 years. Among the 16 neuropsychological tests, Word List Delayed Recall from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, Word List Learning Trial 3, Word List Learning Trial 1, and TMT Part B (in that order) were the best at discriminating between cases and controls, and the combination of Word List Delayed Recall and TMT Part B showed the most optimal discriminating accuracy. Both Word List Delayed Recall and Word List Learning Trial 3 were significantly more accurate than the MMSE. The authors surmise that the predictive role of TMT Part B indicates that executive dysfunction is an early manifestation of incipient AD, along with memory dysfunction.

Recently, Nutter-Upham and colleagues (2008) conducted a study that compared verbal fluency performance between patients with amnestic MCI and older adults with cognitive complaints. They were administered five verbal fluency tasks: phonemic (letter), semantic (category), category switching (alternation between two categories), action naming fluency (things that people do), and supermarket (items found or bought in a supermarket). Results revealed an overall decline in verbal fluency in patients diagnosed with amnestic MCI compared to demographically matched normal controls, with the greatest effect size observed for switching and shifting, followed by category, letter, action, and then supermarket fluency. This suggests that semantic knowledge and effortful retrieval are compromised, and tasks that involve both components show the greatest effect sizes.

In summary, MCI subtypes may encompass various etiologies, and none of them are definitive of AD (Petersen, 2004; Petersen et al., 2001). Additionally, it has been noted that one etiology does not necessarily exclude the existence of another (Palmer & Fratiglioni, 2006).

Early Alzheimer's Disease and Cognition

AD is a progressive and degenerative brain disease that results in dementia, and it is the most common cause for late-life dementia (Hebert et al., 2003). It typically manifests after the age of 50, though it can present at earlier ages (Welsh-Bohmer & Warren, 2006). The illness is characterized by prominent memory impairment for recent events (K. Welsh et al., 1991) and eventual erosion of other cognitive domains, including language and semantic knowledge, executive functions, attention, and constructional and

visuospatial abilities (Bondi et al., 2008b; Salmon & Bondi, 1999). As general cognition declines, there is an increase in functional dependence and eventually death (Tschanz et al., 2004).

The hallmark feature of the memory impairment in AD is with the consolidation of new information from episodic memory tasks (e.g., list learning) into memory stores, evidenced by the lack of improvement in acquiring information over repeated learning trials (Buschke & Fuld, 1974; Hart, Kwentus, Harkins, & Taylor, 1988; Masur et al., 1989), heightened recency free recall (Delis et al., 1991; Massman, Delis, & Butters, 1993), inefficient or absence of encoding strategies (e.g., clustering) (Carlesimo et al., 1998; Knopman & Ryberg, 1989), and failure to benefit from a recognition versus free-recall format (Delis et al., 1991; Wilson, Bacon, Fox, & Kaszniak, 1983). Rapid forgetting is also observed (Salmon et al., 2002; Troster et al., 1993; K. Welsh et al., 1991), with little benefit from cueing (Tierney et al., 2001). In fact, it has been posited that delayed recall scores and percent retention after a delay, measures that reflect rapid forgetting, are important indicators of early AD, and have been shown to be highly effective in distinguishing between early AD and normal aging, even more so than measures of learning, confrontation naming, verbal fluency, abstract reasoning, and visuospatial and constructional ability (Flicker et al., 1991; Knopman & Ryberg, 1989; Troster et al., 1993; K. Welsh et al., 1991).

In addition to the episodic and semantic deficits described above, executive dysfunction has been found to occur in early AD (Lafleche & Albert, 1995; Salmon, Butters, Thal, & Jeste, 1998), if not one of the earliest domains to be affected (Welsh-Bohmer & Warren, 2006). Since working memory has both memory and executive

functioning demands (Baddeley, 1986), it is not surprising that working memory deficits are also observed in early AD (Becker, 1988). Consistent with this line of reasoning, global intelligence is affected in the early to middle stages of AD due to the executive components of abstraction, reasoning and judgment, and the ability to think flexibly and creatively (Welsh-Bohmer & Warren, 2006). Finally, other cognitive deficits often seen early in the course of the disease include those of attention (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Parasuraman, Greenwood, & Sunderland, 2002; Parasuraman & Haxby, 1993) and visuospatial (Benke, 1993; Rouleau, Salmon, & Butters, 1996) or praxis abilities (Nielson, Cummings, & Cotman, 1996). As AD progresses, cognitive deficits continue to decline, eventually resulting in pervasive cognitive impairment.

In summary, as is apparent from the cognitive profiles noted above, memory impairment, executive disturbances, and difficulties in expressive language/semantic knowledge that are characteristic of early AD are also features of MCI. Given the similarities in profiles, it can be difficult to distinguish between early AD and MCI, and between MCI and normal aging.

Detecting preclinical dementia, MCI, and AD is complex because the procedures are not always well defined. While a neuropsychological battery that includes measures of learning, delayed recall, attention, executive function, and semantic knowledge could provide valuable information in this endeavor, making an accurate diagnosis is not possible based on neuropsychological testing alone. One must consider all possible factors that influence neuropsychological test results, such as age, education, culture, and comorbid medical and psychiatric illnesses (Petersen et al., 2001), and one must also have an understanding of the overlap in neurobehavioral profiles and underlying

pathology. Multiple risk factors also need to be considered when making a diagnosis of AD (Collie & Maruff, 2000). Some clinicians and researchers believe that clinical judgment remains the best means of assessing MCI (Kelley & Petersen, 2007). This, in conjunction with a multidisciplinary approach, yields the greatest likelihood of detecting a neurodegenerative process and making a correct diagnosis.

NEUROPATHOLOGY

As originally proposed by Alois Alzheimer in 1907, AD is characterized by microscopic neuritic plaques and neurofibrillary tangle formations (Alzheimer, Stelzmann, Schnitzlein, & Murtagh, 1995) as well as extensive neuron death (Morrison & Hof, 2002) in the neocortex and hippocampus, resulting in memory impairment and cognitive dysfunction. Specifically, the ERC and the subiculum and CA1 field (i.e., the perforant pathway) of the hippocampus are severely involved early in AD, consistently displaying high neurofibrillary tangle densities, especially in layers II and V of the ERC (Hyman, Van Hoesen, Damasio, & Barnes, 1984).

A similar but more modest disruption in memory to that observed in AD is associated with normal aging, and it is believed that the same circuits involved in AD (i.e., connections between the ERC and the hippocampus, and between the corticocortical circuits and association regions) are vulnerable in normal aging. However, since primate studies of aging have shown a loss of spines rather than neuronal degeneration of pyramidal cells connecting prefrontal and temporal association cortices, it is postulated that age-related synaptic alterations in the hippocampus are the key to age-related

memory decline, but that the missing circuit is responsible for the memory decline in AD (Morrison & Hof, 2002). Thus, while senile plaques and neurofibrillary tangles are important markers of AD, the critical issue is the *degree* to which each of them reflects neuron or synapse loss that leads to circuit disruption and subsequent dementia (Morrison & Hof, 2002). This idea is supported by findings of Price and Morris (1999, 2004), who suggest that during aging, tangles and other neurofibrillary changes accumulate slowly in vulnerable limbic areas and that diffuse plaques begin to accumulate independently in the neocortex of many individuals. Later, during the stage of early AD, before clinical detection is possible, much more widespread deposition of plaques occurs in the neocortex, leading to an acceleration in neurofibrillary lesions, subsequent neuronal death, and clinical expression of AD. As the disease progresses, widespread neurofibrillary lesions and neuronal degeneration are produced throughout the cerebral cortex.

Other studies show that neuropathologic changes found in AD are also found in individuals without dementia or with mild cognitive impairment (Bennett et al., 2006; Knopman et al., 2003; Morris et al., 2001). For example, Tomlinson and colleagues (1968) observed moderate senile plaques and neurofibrillary tangles in the neocortex of brains of older individuals without dementia. Furthermore, Bennett et al. (2002) found that individuals with MCI had intermediate levels of AD pathology compared to those with dementia and those without cognitive impairment. The question remains as to whether cognitive change progresses on a continuum from normal aging to a transitional state (i.e., MCI) ultimately leading to dementia, and if so, what predisposes an individual to a diagnosis of AD. Indeed, age is the primary risk factor for the development of AD

(Bondi et al., 2008b). Bennett et al. (2006) suggest that cognitive reserve (defined by these authors as the efficiency and ability to respond to environmental challenges such as brain disease) permits a large number of older individuals to tolerate a significant amount of AD pathology without becoming demented. It may be that elderly individuals rely more on neocortical than hippocampal circuits for day-to-day memories, and while the presence of scarce neurofibrillary pathology in the ERC reflects normal aging with generally preserved cognition, it is only with the degeneration of presumed corticortical circuits within the neocortex that AD manifests (Morrison & Hof, 2002). Findings from studies such as those of Gomez-Isla et al. (1996) and West et al. (2000) suggest that neuronal loss in normal aging is distinct from that of AD and therefore not a process on a continuum.

The cortical areas that form the parahippocampal gyrus are vulnerable to pathological changes in AD, with its entorhinal and perirhinal subdivisions the most heavily damaged and hence a focus of disease onset (Van Hoesen, Augustinack, Dierking, Redman, & Thangavel, 2000). Postmortem studies have suggested that neurofibrillary pathology and neuronal loss are first observed in the ERC and later spread to other brain areas (Du et al., 2001; Frisoni et al., 1999; Gabrieli, Brewer, Desmond, & Glover, 1997; Killiany et al., 2002; Xu et al., 2000) and that the profound loss in layer II in very mild AD is distinguishable from nondemented aging (Gomez-Isla et al., 1996). A study examining differences in the total number of neurons in the five major subdivisions of the hippocampal regions of AD patients and normal age-matched controls revealed pronounced loss of CA1 neurons associated with AD (West et al., 2000), supporting the

conclusion that the neuropathologic mechanisms involved in the AD-related losses in CA1 are not related to normal aging.

PCC pathology is also involved early on in AD and includes alterations in neurochemistry (Procter et al., 1988; Rossor et al., 1982), glucose metabolism (Grady et al., 1990; Hirono et al., 1998; Minoshima, Foster, & Kuhl, 1994; Minoshima et al., 1997), neurodegeneration (Brun & Englund, 1981; Ishii et al., 2005; Mountjoy, Roth, Evans, & Evans, 1983), and senile plaques and neurofibrillary tangles (Braak & Braak, 1993). Metabolic reduction has also been shown in the PCC in asymptomatic individuals at genetic risk for the disease (Kennedy, Rossor, & Frackowiak, 1995; Reiman et al., 1996; G. W. Small et al., 2000). Interestingly, based on studies of laminar patterns and neuron densities in the PCC, Vogt et al. (1998; 1998) postulate that different patterns of cell loss are associated with different mechanisms and represent neuropathological subtypes within AD but are not the result of neurofibrillary tangle formation. Scahill et al. (2002) demonstrated the precuneus, a closely related region (discussed later) of the PCC, as well as the PCC, evidenced significant rates of atrophy in the earliest stages of AD. Due to the PCC's involvement in visuospatial and memory processing (Olson, Musil, & Goldberg, 1993, 1996; Paik et al., 1985), as well as parahippocampal and parietal cortical connections (Vogt & Pandya, 1987), it has been suggested that the functional impairments of AD may be related to disruption of integrative functions of the PCC (Vogt, Vogt et al., 1998). In particular, the cingulate is believed to link the motivational drives of the limbic system with attentional networks and memory function, as well as visceral and skeletal motor output (Mega & Cummings, 1997).

Neuropathological studies in MCI have been difficult, because individuals do not typically die with this diagnosis before AD or other dementia states set in. Some autopsy studies have examined the brains of individuals with a CDR score of 0.5 (indicative of very mild AD or MCI) (Morris et al., 2001; Price & Morris, 1999; Troncoso, Martin, Dal Forno, & Kawas, 1996). In a group of 16 patients with a diagnosis of MCI or AD, all demonstrated neurofibrillary tangles in the hippocampus and ERC, and seven had senile plaques in the neocortex (Troncoso et al., 1996). In another study (Price & Morris, 1999) of 39 patients with no dementia, 15 with a CDR of 0.5, and 8 with AD, all with a CDR of 0.5 showed evidence of AD pathology. A portion of the subjects without dementia also evidenced neocortical senile plaques and entorhinal tangles, which was interpreted as indicating a neuropathological presentation of AD that precedes MCI. More recently, autopsy tissue from 15 individuals who died while their clinical diagnosis was amnestic MCI was compared to that of 28 healthy individuals and 23 with AD (Petersen et al., 2006). It was found that the regional involvement of neurofibrillary tangles correlated best with the degree of clinical impairment, while the amyloid plaque burden was less discriminating. It was hypothesized that the transition to dementia occurs when neurofibrillary abnormalities spread outside the medial temporal lobe.

The Religious Orders Study (Bennett et al., 2005) was able to examine the brains of 37 individuals who died with a diagnosis of MCI and compare them to 60 without cognitive impairment and 83 with mild to moderate dementia. They found that nearly all of these 180 individuals had at least some AD pathology, with 60% meeting NIA-Reagan criteria for intermediate or high likelihood of AD at the time of death and the rest a low likelihood. Of those with dementia, 90% met pathologic criteria for AD and so did 40%

of those without cognitive impairment. However, while more than half of the individuals with MCI had a Braak stage of III/IV (i.e., neurofibrillary tangles in both transentorhinal region and proper entorhinal cortex), and more than half met CERAD neuropathologic criteria for probable or definite AD, less than half of them had intermediate likelihood of AD, with only four having a high likelihood. These findings argue against the notion that all MCI is early AD. Finally, the Mayo Clinic reported that findings from two of their studies (Petersen & Bennett, 2005) indicated that most individuals who die with a clinical diagnosis of amnestic-type MCI do not meet neuropathological criteria for AD, and that although 75% of those with amnestic MCI went on to develop AD, some progressed to other types of dementia.

In conclusion, as pointed out by Gauthier et al. (2006), a combination of causal factors may be interacting in patients with MCI, including cholinergic dysfunction, white-matter lesions and cerebral infarctions, extracellular amyloid deposition, and intracellular neurofibrillary tangle formation. It appears that with respect to the underlying pathology, amnestic MCI versus other MCI subtypes represents an intermediate stage between normal aging and AD (Petersen, 2007). Furthermore, these studies help explain how the accrual of pathology during normal aging renders age a primary risk factor for AD.

REGIONS OF INTEREST

A growing body of evidence from imaging studies indicates that the PCC and the ERC are among the first brain regions to show change in preclinical AD and that episodic

memory decline is one of the first behavioral manifestations of the disease. Based on extant data, the PCC and ERC (limbic system structures), as well as the dorsolateral region of the prefrontal cortex (DLPFC) (implicated in attention, working memory, and episodic memory functions that erode early on), are areas of interest that are predicted to show reduced connectivity in the MCI and early AD subjects.

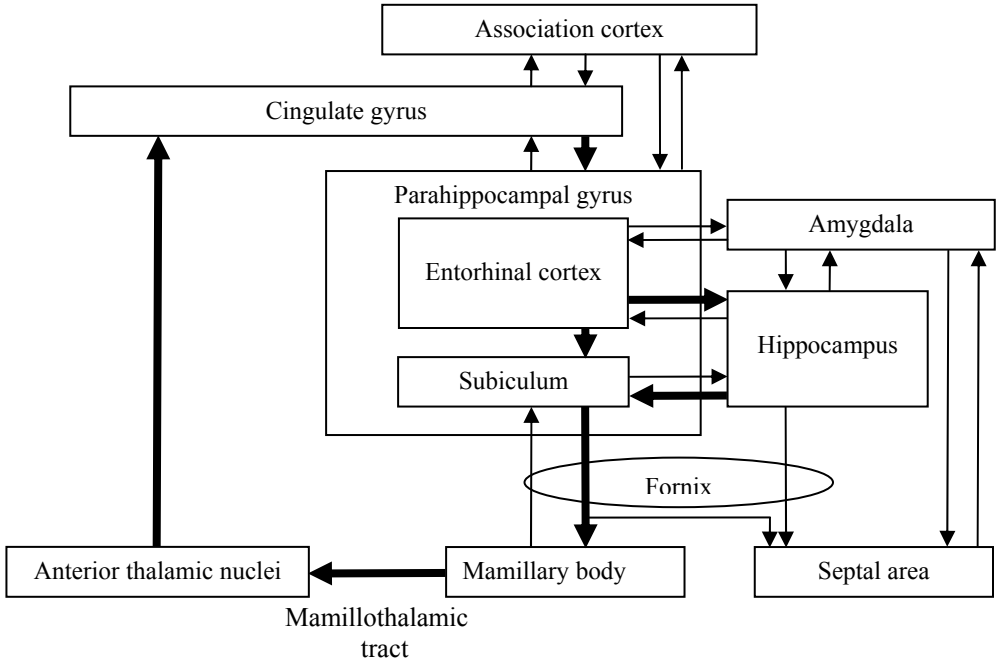
One can hardly discuss the limbic system without first mentioning the Papez circuit. The original circuit was proposed by James Papez in 1937 (Papez, 1995) to describe the mechanism of emotion and has subsequently led to increased understanding of the limbic system. The circuit consists of connections from the mammillothalamic tract that connect the medial mamillary nucleus to the anterior nucleus of the thalamus, thalamocortical fibers from the anterior nucleus of the cortex to the cingulate gyrus, and from the cingulate cortex, via the cingulum, to the entorhinal cortex as well as directly to the subiculum and hippocampus. From the subiculum, information is returned to the mamillary bodies via the fornix (see Figure 1, p. 28). Of primary significance to the current study is the fact that other areas of the cerebral cortex have functional associations with the Papez circuit, largely through connections of the cingulate gyrus (Chronister & Hardy, 1997), which not only receives input from premotor and prefrontal areas and from visual, auditory and somatosensory association cortices, but, in addition to its projections to the hippocampus, projects to most of the cortical regions from which it receives input.

Posterior Cingulate Cortex

Structure

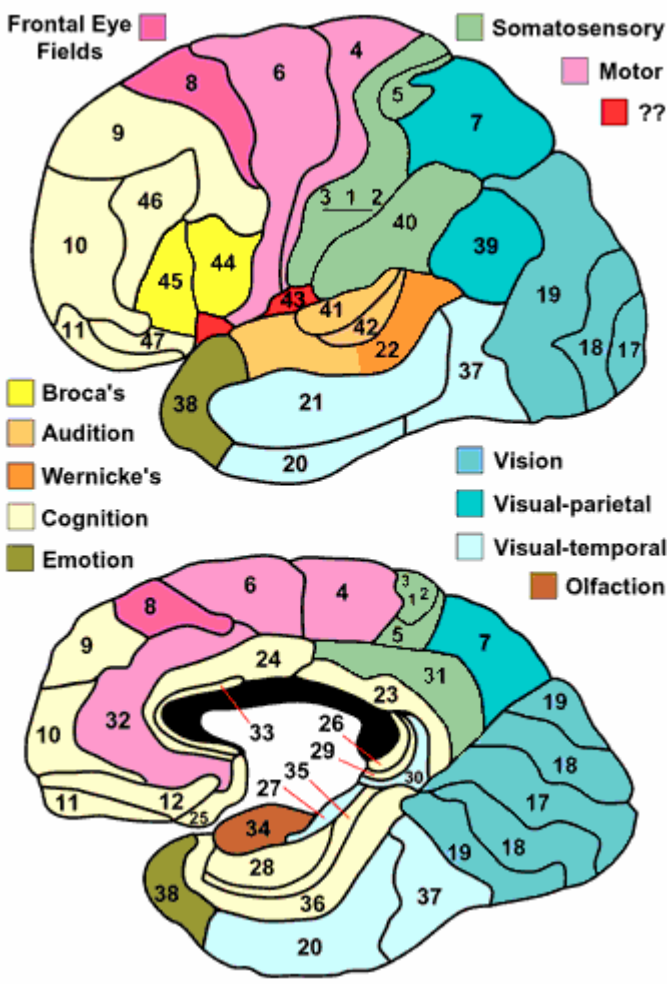
The posterior cingulate gyrus is roughly comprised of Brodmann areas (BA) 23, 26, 31, and the retrosplenial cortex areas 29 and 30 (Vogt, Vogt, Perl, & Hof, 2001). (See Figure 2, p. 29).

Figure 1. Major Neural Circuits of the Limbic System



Thick lines represent the circuit of Papez. The cingulate gyrus projects to the entorhinal cortex in the parahippocampal gyrus. Major efferent fibres projecting to the mamillary body via the fornix originate from the subiculum. Efferent fibres from the mamillary body project to the anterior thalamic nuclei via the mamillothalamic tract. The anterior thalamic nuclei connect to the cingulate gyrus. The hippocampal formation and the entorhinal cortex form an intrinsic circuit.

Figure 2. Brodmann Areas



With permission from Mark Dubin, University of Colorado
(http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html)

Reciprocal connections with the PCC include caudal parietal region (BA 7), frontal eye fields (BA 8), prefrontal region (BA 46), posterior parahippocampal region (BA 35 and 36), presubiculum, and the ventral caudal claustrum (see Mega & Cummings

for review1997). The reciprocal connections of the posterior parahippocampal and perirhinal areas 35 and 36, as well as the presubiculum, modulate multimodal efferents entering the entorhinal layer III cells that form the perforant pathway into the CA1 and subiculum. Direct hippocampal output from the CA1 and subicular sectors innervates and returns feedback to the PCC. Non-reciprocal afferents project from the occipital region (BA 19), hippocampal CA1/subicular sectors, anterior thalamus, medial pulvinar, and lateral dorsal and lateral posterior thalamus to the PCC (Mega & Cummings, 1997). Non-reciprocal efferents include projections to orbitofrontal (BA 11), posterior superior temporal (BA 22), and dorsal caudate areas from the PCC.

According to some authors (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997; Van Hoesen, Maddock, & Vogt, 1993), an adjacent cytoarchitectonic region, the precuneus (BA 7 and 31), is often considered part of the PCC since BA 31, positioned between the cingulate and splenial sulci, includes both posterior cingulate and precuneate cortices (Cavanna & Trimble, 2006). The precuneus has reciprocal corticocortical connections with adjacent areas of the posterior cingulate and retrosplenial cortices, in addition to extraparietal corticocortical connections with the frontal lobes, with connections concentrated at the level of BA 8, 9, and 46 (i.e., frontal eye fields and DLPFC).

Function

The PCC has been described as the "sensory processing region," whose primary function is to assist in visual attention and the processing of relevant environmental stimuli, spatial orientation, and memory (Dean, Crowley, & Platt, 2004; Mega &

Cummings, 1997; Vogt, Finch, & Olson, 1992). For example, Hampson et al. (2006) reported that better performance on a working memory task was positively correlated with the strength of functional connectivity between the ventromedial prefrontal cortex and the PCC, not only during the working memory task, but also at rest. In another study (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005), functional connectivity with the hippocampus was enhanced during successful memory formation in a distributed network of limbic cortical areas, including perirhinal, orbitofrontal, and retrosplenial/PCC. Functional imaging studies consistently report activation of the PCC during episodic memory encoding (Cabeza & Nyberg, 2000; Fletcher et al., 1995; Grasby, Frith, Friston, Frackowiak, & Dolan, 1993; Mega & Cummings, 1997; Shallice et al., 1994). Furthermore, PCC lesions in animal studies have indicated that the PCC interacts with the anterior thalamus and hippocampus during encoding and may also be important in the storage of long-term information (Sutherland & Hoesing, 1993).

In addition to its role in encoding and storage, the PCC appears to be involved in memory retrieval (Cabeza & Nyberg, 2000; Chetelat et al., 2003; Owen, Milner, Petrides, & Evans, 1996; Petrides, Alivisatos, & Evans, 1995). The exact mechanism whereby memories are retrieved is unclear, but it is postulated that changes in the PCC affect memory retrieval via a loss of afferent connections to the PCC from the CA1 and subiculum (Chetelat et al., 2003), with subsequent changes in connectivity and function of the PCC itself rather than the result of indirect effects of hippocampal pathology (Nestor, Fryer, Smielewski, & Hodges, 2003). The retrosplenial cortex area of the PCC is believed to play a critical role in episodic memory retrieval (Valenstein et al., 1987) and in accessing long-term memories (Vogt, Vogt, & Laureys, 2006). Using a

multitasking paradigm, Burgess et al. (2000) found that retrospective memory, prospective memory, and planning were important components of the task, and that the left anterior and posterior cingulate together play some part in the retrospective memory demands. Prospective memory and planning components relied on the left BA 8, 9 and 10 and the right DLPFC respectively. The role of the precuneus is not well understood, but appears to be involved in memory retrieval. For example, activation of this region has been observed during episodic memory retrieval (Desgranges, Baron, & Eustache, 1998), especially for image-related information (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1996; Kapur et al., 1995; Krause et al., 1999). Functional imaging studies have also implicated the precuneus in linking new information to prior knowledge (Maguire, Frith, & Morris, 1999) and in autobiographical memory retrieval (Maddock, Garrett, & Buonocore, 2001).

In summary, the PCC is involved in a complex network of connections that include the ERC and the DLPFC. Activation in these regions during episodic memory encoding and retrieval is consistently found in imaging studies. The PCC, via ERC and DLPFC connections, also appears to be involved in visual attention, spatial orientation, working memory, and retrospective memory storage and retrieval. Thus, it is conceivable that preclinical changes in the PCC structure and connectivity, supported by a wide body of research to precede even early changes in the ERC, would have a cascading effect on connected brain regions and a subsequent impact on functioning, especially episodic memory.

Entorhinal Cortex

Structure

The ERC (BA 28 and 34) is viewed by many as the gateway by which sensory information gains entrance into other fields in the hippocampal formation via the perforant pathway that projects primarily from layers II and III of the ERC (Morrison & Hof, 2002; Suzuki & Amaral, 1994). The perirhinal cortex, which receives information from somatosensory, auditory, and olfactory areas, as well as the postrhinal cortex, which receives input from visually related areas (Burwell & Amaral, 1998), are major sources of input to the ERC (Witter, Wouterlood, Naber, & Van Haeften, 2000). The ERC is divided into medial and lateral entorhinal areas (Kerr, Agster, Furtak, & Burwell, 2007) that project primarily to the dentate gyrus, the fields of the Ammon's horn (CA1-CA3), and the subiculum (Witter et al., 2000). In a hippocampal-cortical backward manner, projections originating from the CA1 and subiculum target the deep layers of the ERC as well as to the superficial layers of the ERC and then back out to cortical regions (Dolorfo & Amaral, 1998).

Function

Numerous studies have demonstrated that the ERC is essential for successful memory performance (Cabeza & Nyberg, 2000; Laakso et al., 1998; Langley & Madden, 2000; Squire & Zola, 1997; Vargha-Khadem et al., 1997), especially relative to encoding (Frisoni et al., 1999; Gabrieli et al., 1997; Xu et al., 2000) and recall of newly learned information (Moss, Albert, Butters, & Payne, 1986; K. A. Welsh, Butters, Hughes, Mohs,

& Heyman, 1992). The ERC appears to be involved in the pre-processing and selection of both spatial and nonspatial information directed to the hippocampus (Kerr et al., 2007). It is believed that the hippocampal-cortical backward projection (i.e., hippocampus back to the ERC and out to cortical regions) is the mechanism by which information processed by the hippocampus can be transferred to permanent storage sites in the neocortex, and therefore is maintained in an intermediate store before being transferred into a long-term store (Eichenbaum, Otto, & Cohen, 1994).

Dorsolateral Prefrontal Cortex

Structure

The topographical organization of the dorsolateral prefrontal cortex (DLPFC) includes BA 46 and part of BA 9. DLPFC areas are indirectly linked to parahippocampal areas through connections with the anterior and posterior cingulate and medial frontal area (Barbas, 2000). Sparse connections have also been identified between the DLPFC and entorhinal, presubicular, and caudal parahippocampal regions (Goldman-Rakic, Selemon, & Schwartz, 1984).

Function

The dorsolateral circuit subserves higher-level executive functioning (D'Esposito et al., 1998; Petrides et al., 1995), and damage to the dorsolateral frontal lobe or its circuits produces deficiencies in abilities such as complex problem-solving, monitoring and/or manipulating information, learning new information, systematically searching

memory, shifting and maintaining behavioral sets, and using verbal skills to guide behavior (Cummings, 1993). Deficits in sustained attention, working memory, and in the encoding and retrieval of episodic memory also occur with disruption to the DLPFC and are consistent with changes present in the preclinical or mild phase of AD (Cabeza & Nyberg, 2000; Small et al., 2003; Wheeler, Stuss, & Tulving, 1995). The parallel pathways between the DLPFC and hippocampus, represented by the connections noted above, are implicated in both verbal and spatial working memory (Goldman-Rakic, 1987, 1996). Successful long-term memory formation (i.e., encoding) may depend on intact DLPFC functioning. For example, Murray and colleagues (2007) suggest that the DLPFC may contribute to long-term memory through its role in active processing of relationships (e.g., word associations) during encoding. It is postulated that prefrontal activity patterns may differ preclinically with regard to encoding and retrieval in individuals at risk for AD. In a study comparing high-risk versus low-risk individuals on a cognitive screening battery (Elgh, Larsson, Eriksson, & Nyberg, 2003), during both encoding and retrieval, low-risk persons showed increased activity relative to a baseline condition in prefrontal brain regions, whereas high-risk persons did not significantly activate any prefrontal regions, but instead showed increased activity in visual occipitotemporal regions.

Imaging studies pertaining to semantic memory retrieval, frequently examined by way of categorization and word generation tasks, show activation in the DLPFC during these tasks (Cabeza & Nyberg, 2000), and it has been suggested that since fluency tasks require the monitoring of several items in working memory, perhaps these activations represent working memory rather than semantic memory per se. In fact, in an empirical

review of 275 imaging studies, Cabeza et al. (2000) found that most of the regions associated with semantic retrieval tasks were also associated with episodic memory encoding in the intact brains of healthy young adults. Lastly, clinically significant depression has been associated with hypometabolism in dorsolateral prefrontal regions (Holthoff et al., 2005).

In summary, the PCC is involved in a complex network of connections that include the ERC and the DLPFC. Activation in these regions during episodic memory encoding and retrieval is consistently found in imaging studies. The PCC, via ERC and DLPFC connections, also appears to be involved in visual attention, spatial orientation, working memory, and retrospective memory storage and retrieval. Thus, it is conceivable that preclinical changes in the PCC structure and connectivity, supported by a wide body of research to precede even early changes in the ERC, might affect connected brain regions and subsequently impact functioning, especially episodic memory.

POSTERIOR CINGULATE NEUROIMAGING

Functional Connectivity

Functional connectivity magnetic resonance imaging (fcMRI) is a fairly new investigative tool that can examine functional networks in the brain in a task-independent state. It is based on the premise that brain regions that are functionally related show correlated low frequency fluctuations of the MRI signal at rest (Biswal, Yetkin, Haughton, & Hyde, 1995; Lowe, Mock, & Sorenson, 1998), which may arise from fluctuations in blood oxygenation or flow. Moreover, evidence indicates that low

frequency correlations at rest correspond to activity in the same regions during task-dependent paradigms (Cordes et al., 2000; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000).

Numerous functional connectivity studies, at rest as well as during task performance, have implicated the posterior cingulate as a brain region showing disrupted connectivity in MCI and AD. It has thus been suggested that AD may represent a disconnection syndrome. De Lacoste and White (1993) review and expand on this model, which predicts that damage to the entorhinal cortex and/or subiculum results in the disconnection of the hippocampal formation and neocortex, and subsequent progression along cortico-cortical connections. Neuroimaging studies provide some support for this notion (Delbeuck, Van der Linden, & Collette, 2003; Greicius, Srivastava, Reiss, & Menon, 2004; K. Wang et al., 2007). Several recent fcMRI studies examining hippocampal connectivity with the rest of the brain have found disruptions that include the posterior cingulate and precuneus in early AD (Allen et al., 2007; Hirao et al., 2006; L. Wang et al., 2006) and MCI (Hirao et al., 2005). For example, Allen et al. (2007) investigated coherence in the magnetic resonance (MR) signal between the hippocampus and the rest of the brain in eight patients with probable AD and eight healthy volunteers. These investigators found that while the control subjects demonstrated significantly greater connectivity of the hippocampus diffusely throughout the cerebral cortex, limbic areas (including the PCC/retrosplenium and precuneus), subcortical regions, and cerebellum, the AD subjects demonstrated markedly reduced functional connectivity, and notably, an absence of hippocampal-frontal connectivity. This is in contrast to what has been reported by others (L. Wang et al., 2006). Indeed, in

this study of 13 patients with mild AD and 13 healthy age-matched controls, in addition to disrupted hippocampal connectivity with a set of regions that included the precuneus and PCC, increased functional connectivity between the left hippocampus and the right lateral prefrontal cortex was observed in AD patients. This finding was interpreted as recruitment of cognitive resources in prefrontal regions to compensate for losses of cognitive function.

A decrease in functional coherence has also been associated with AD progression. In a sample of 14 AD subjects and 14 age-matched controls, He et al. (2007) found significant regional coherence (i.e., within a voxel and a cluster made up of its nearest neighbors) decreases in the PCC/precuneus in the AD patients when compared with the normal controls. These findings were still significant even after controlling for PCC/precuneus atrophy, although a decrease in effect size suggests that reductions in coherence may be at least partially explained by regional atrophy. This study provides support that the pathophysiology of AD may be associated with changes in low-frequency blood oxygenation level-dependent fluctuations measured during a resting state. In addition, these authors found increased coherence in the bilateral cuneus, right lingual gyrus, and left fusiform gyrus in AD patients, suggesting recruitment of these brain regions as part of a compensatory process.

The focus of this study is not to define or provide support for a particular network of brain functioning per se. However, a brief discussion regarding the default mode network is warranted because it is commonly referenced in the literature as a conceptual framework, of which the PCC is a major component. The default mode hypothesis is based on the finding that certain brain regions consistently demonstrate

greater neural activity during a baseline state than during a task (Shulman et al., 1997). Raichle et al. (2001) identified brain regions (i.e., the PCC, bilateral inferior parietal cortices, left inferolateral temporal cortex, and ventral anterior cingulate cortex) that show decreased brain activity during performance of cognitive tasks. These authors posit that this response indicates a "default mode of brain function." However, given that there are other "resting state networks" in the brain that reside outside of the identified default mode network (Fransson, 2006) that show resting-state activation, there is debate regarding whether a default mode network actually exists.

Those who support the theory of a default mode network have noted that the PCC plays a central role therein (Greicius, Krasnow, Reiss, & Menon, 2003), and given that reduced PCC activity is among the most common findings in SPECT and PET studies of early AD (Matsuda, 2001; Minoshima et al., 1997), it is reasoned that the default mode network might be abnormal in AD (Greicius et al., 2004).

In a recent study combining structural and resting-state functional MRI techniques, Bai et al. (2008) examined default mode network activity in a sample of 20 normal aging individuals and 20 individuals with amnestic MCI. Like He et al. (2007), these authors found decreased coherence (i.e., disconnectivity) between the PCC/precuneus after controlling for regional atrophy. Other investigators who subscribe to the default mode network theory provide supportive evidence of PCC disconnectivity as well (Greicius et al., 2004; Sorg et al., 2007). Sorg et al. (2007) analyzed functional and structural MRI data from 16 healthy elderly individuals and 24 patients with amnestic MCI. The major finding was that functional connectivity between both hippocampi and the PCC was present in healthy controls but absent in patients. Evidence

from Greicius et al. (2004) was consistent with these findings when comparing 13 AD patients with 13 age-matched healthy controls.

Altered activity during a task has also been observed in the default mode network. Rombouts et al. (2005) examined deactivation (i.e., decreases in brain activity) during visual encoding and nonspatial working memory tasks in 18 AD, 28 MCI, and 41 NC individuals and found deactivation in the anterior frontal lobe, precuneus, and PCC. MCI patients showed less deactivation than NC, but more than AD. It was further noted that the response in the anterior frontal cortex significantly distinguished MCI from both NC and AD, while the response in the precuneus could only distinguish between patients and NC, not between MCI and AD.

Greicius et al. (2008) combined diffusion tensor imaging (DTI) with fcMRI to investigate connectivity within the default mode network. DTI tractography demonstrated that functional connectivity "reflects" structural connectivity. It is underscored that although functional connectivity implies structural connectivity, direct versus indirect connections cannot be delineated.

In summary, fcMRI is a noninvasive technique with promise for early detection of AD (Rombouts et al., 2005). Based on the previously cited findings, it is plausible that examination of the posterior cingulate/precuneus and entorhinal regions in particular might assist in this endeavor.

Other Supportive Imaging Findings

Despite the brain's plasticity, it has a limited ability to compensate in the face of neurodegenerative processes due to disease or injury, and functional connectivity

becomes disrupted with the deterioration of axonal connections (Quigley et al., 2001). The amount of axonal deterioration necessary before an appreciable decline in brain functioning manifests is difficult to determine, but the development of techniques such as DTI have been informative in this regard. DTI is a special form of imaging that allows the visualization and assessment of white matter tract integrity on a millimeter, multidimensional level not possible with standard MRI (Le Bihan et al., 2001). Three values commonly regarded as indices of white matter integrity are fractional anisotropy (FA), apparent diffusion coefficient (ADC), and relative anisotropy (RA). Essentially, higher FA and RA values indicate greater density of white matter tracts, whereas greater ADC indicates white matter degeneration.

DTI studies show that white matter changes are detectable before the onset of dementia, and in particular include changes in the posterior cingulate in MCI and AD patients (Medina et al., 2006; Zhang et al., 2007). Medina et al. (2006) examined FA in 14 patients with probable mild AD, 14 with MCI, and 21 elderly healthy control subjects. Significant reductions of FA were found in 12 brain regions in MCI patients as compared to NC and in 14 regions in AD patients when compared to NC, including reductions in the posterior cingulate bundle in both patient groups as compared to NC. In the Zhang et al. study (2007), FA was measured in 17 AD patients, 17 MCI patients, and 18 NC subjects. FA of the cingulum fibers (which connect the medial temporal lobe and posterior cingulate regions) was significantly reduced in MCI, and even more so in AD. Additionally, adding DTI to hippocampal volume significantly improved the accuracy in distinguishing MCI and AD from NC. Kantarci et al. (2001) examined MR images of 21 patients with AD, 19 patients with MCI, and 55 normally aging elderly control subjects

and found that hippocampal ADC was higher in MCI and AD patients than in NC and that ADC of the temporal stem and posterior cingulate, occipital, and parietal white matter was higher in AD patients than in NC.

Findings from these studies were corroborated by Stahl et al. (2007), who examined the ADC, FA, and RA values of several white matter regions in 15 patients with AD, 16 with MCI, and 19 NC subjects. FA and RA values were significantly decreased in the splenium of the corpus callosum in AD than MCI patients. Higher ADC values were found in the white matter of the temporal lobe in patients with AD than MCI and NC subjects, and in the parietal white matter in patients with MCI compared to NC. These findings suggest that diffusion tensor imaging can be used to confirm clinical manifestation of AD but may be less applicable in the detection of MCI.

A relationship between neuropsychological functioning and DTI indices in the PCC has also been found. For example, in a study using DTI to investigate the posterior cingulate's relationship to cognitive decline in AD, Yoshiura et al. (2002) found behavioral measures of mental status to be significantly correlated with diffusion values in 34 AD patients. Results from this study suggest that mean diffusivity (a.k.a. ADC), but not FA, reflects progression of AD-related histopathological changes in the posterior cingulate. Rose et al. (2006) also found a relationship between cognitive performance and DTI measurements. Diffusion images from 17 MCI subjects and 17 healthy elderly adults were obtained. Significantly raised ADC measurements were observed in the left and right entorhinal cortices, posterior occipital-parietal cortex, right parietal supramarginal gyrus, and right frontal precentral gyri in subjects with MCI. MCI subjects had significantly reduced FA in the limbic parahippocampal subgyral white

matter, right thalamus, and left posterior cingulate. Pearson's correlation coefficients calculated across all participants showed significant correlations between neuropsychological assessment scores and regional measurements of ADC and FA.

Overall, results from these studies suggest that DTI may offer a sensitive measure of detecting subtle changes associated with preclinical AD. In particular, decreased FA and increased ADC in the PCC in both AD and MCI indicate compromised white matter density, and are correlated with neuropsychological performance.

The precuneus and the posterior cingulate are purported to be among the first regions to show a disconnection of posterior temporal-parietal-occipital associative areas from the mesial temporal cortex in AD (Matsuda et al., 2002) and in MCI (Chetelat et al., 2003). These changes are thought to contribute to cognitive decline in verbal memory, constructional praxis, and visual sustained attention (Nobili et al., 2005), which have been found to be among the earliest signs of cognitive impairment in AD (N. J. Fisher, Rourke, & Bieliauskas, 1999; Tales, Muir, Jones, Bayer, & Snowden, 2004). Utilizing single photon emission computed tomography (SPECT) to correlate brain perfusion with neuropsychological functioning in these domains, Nobili et al. (2005) showed that the parietal precuneus was a common site of correlation. In another SPECT study, reduced relative blood flow of the posterior cingulate could be found at least two years before clinical diagnostic criteria of AD were met (Huang, Wahlund, Svensson, Winblad, & Julin, 2002). Furthermore, decreased baseline perfusion has been observed in individuals who have converted from MCI to AD (K. A. Johnson et al., 2007). Similarly, Borroni et al. (2006) evaluated the potential role of SPECT and memory scores in predicting conversion to AD in MCI subjects and found that pattern of hypoperfusion involving the

parietal and temporal lobes, precuneus, and posterior cingulate cortex and the severity of memory deficits predict the risk of progression to probable AD dementia in MCI subjects.

Positron emission tomography (PET) studies, too, provide supportive evidence of early posterior cingulate involvement. Valla et al. (2001) found that among brain regions affected in AD, the PCC showed the earliest and largest decrement in energy metabolism. Reiman et al. (1998) reported that PET measurements of decreased cerebral glucose metabolism precede memory decline, in contrast to MRI measurements of hippocampal volume, which begin to decrease in conjunction with memory decline in cognitively normal persons at risk for Alzheimer's disease. In a study that directly compared brain atrophy with hypometabolism (Mosconi et al., 2006) in seven individuals at risk for AD and seven matched healthy controls, all pre-AD subjects showed reduced glucose metabolism in the whole brain; bilateral inferior parietal lobe and superior temporal gyrus; and left ERC, PCC, and hippocampus. Furthermore, these widespread reductions occurred in the relative absence of structural brain atrophy. In a PET study examining cognition in MCI (Moulin et al., 2007), MCI subjects failed to show any different activation in a multi-trial learning task for encoding on the first and second trials, whereas the controls activated a region of the posterior cingulate. Others have also shown metabolic reduction in the PCC (Hirao et al., 2005; Minoshima et al., 1997), with associated impairments in learning and memory (Minoshima et al., 1997).

Consistent with SPECT and PET findings, a decrease in PCC activation during cognitive tasks has been noted. For example, when 14 MCI subjects and 14 age-matched controls were compared during an encoding and recognition task (S. C. Johnson et al.,

2006), it was found that the MCI subjects exhibited less activity in the PCC during recognition and in the right hippocampus during encoding. Ries et al. (2006) investigated fMRI activation in the PCC in individuals with MCI and matched controls across a visual episodic recognition task and an autobiographical self-appraisal task. Results revealed that while the PCC is commonly active during both tasks in the healthy older adults, MCI subjects showed PCC activation during self-appraisal, but not episodic retrieval. Results from these studies suggest that a change in function in the PCC may account, in part, for memory recollection failure in AD.

While posterior cingulate involvement may be an indicator of AD pathology, it does not necessarily predict disease progression. In a voxel-based morphometry study conducted by Shiino and colleagues (2006), posterior cingulate cortex atrophy was found in 16 of 40 AD patients and 8 of 20 MCI patients. In addition, there appeared to be two subgroups of AD patients with atrophy of the posterior cingulate cortex—one with disease progression and the other without. It was also noted that the subgroup that showed no progression of AD had characteristic features of early onset and no significant atrophy in the amygdala/anterior hippocampus.

N-Methyl-[11C]2-(4=-methylaminophenyl)-6-hydroxybenzothiazole ([11C]PIB) is a PET ligand that binds to amyloid plaques and has shown increased uptake in several brain regions in patients with AD versus healthy control subjects (Klunk et al., 2004). Kemppainen et al. (2007) used PIB to investigate whether 13 patients with amnestic MCI would show increased [(11)C]PIB uptake as compared to 14 control subjects. Analysis showed that patients with MCI had a widespread distribution of [(11)C]PIB uptake, significantly more so than NC subjects, and that this was most predominant in the frontal

cortex and PCC. In addition, an automated ROI analysis revealed that MCI patients showed the most increased [(11)C]PIB uptake in the frontal cortex and the posterior cingulate as compared to NC. In the frontal cortex and posterior cingulate, 8 of 13 patients with MCI had [(11)C]PIB uptake values above 2 SD from the control mean and about half of the MCI patients had [(11)C]PIB uptake in the AD range, suggestive of early AD process.

In a review examining the role of functional brain imaging techniques in the dementias, Devous (2002) reported that abnormalities of temporoparietal and posterior cingulate hypoperfusion or hypometabolism are common and appear to be present prior to symptom onset in AD. Based on this review, it was determined that greater predictive ability for progression to AD is obtained by combining measures of perfusion or metabolism with risk factors, tau protein levels, hippocampal N-Acetyl aspartate concentrations, or hippocampal volume measures.

PROGRESSION TO ALZHEIMER'S DISEASE

An increasing body of evidence indicates that subtle brain changes presage the clinical manifestation of AD (Wierenga & Bondi, 2007) by several years or even decades. Petersen et al. (1999) have demonstrated that patients with MCI convert to AD at a rate of about 12% a year versus 1% to 2% percent a year for healthy controls converting to MCI or AD. However, little is known about the factors that predict transition from MCI to AD. It is unclear which individuals will show a departure from

normal cognitive aging and progress to AD, and there have been attempts to facilitate prediction of such conversion.

The clinical, neuropathologic, and neuroimaging literature provides converging evidence that a large portion of individuals with MCI are likely at an intermediate stage between normal aging and very early AD, particularly those with the amnestic subtype of MCI. However, given that not all individuals with MCI have AD pathology, that some individuals diagnosed with MCI revert to normalcy (Busse et al., 2006), and that a substantial number of individuals with MCI have other contributing conditions and/or advance to other types of dementia, it appears that not all MCI is early AD. Despite the substantial body of literature identifying predictors that range from simple delayed recall to sophisticated radiological techniques (Modrego, 2006), an accurate and reliable marker has not yet been identified. As several investigators have pointed out, a multidisciplinary approach continues to be necessary for the early detection of the degenerative process, and recent findings suggest that reduced connectivity between the posterior cingulate and associated brain regions may be informative in this regard.

In summary, with early detection of AD, individuals at risk would potentially be afforded a delay in progression of disease and associated cognitive and functional impairments that compromise quality of life. Changes in the posterior cingulate, precuneus, and entorhinal cortex are implicated among the early biomarkers for AD, and as such, the relationship of functional connectivity of these regions, and by inference, associated neurobehavioral functioning, is the focus of this study.

CHAPTER THREE
Aim and Hypotheses

Aim

To measure functional connectivity of the posterior cingulate relative to all other brain regions in MCI and early AD.

Hypothesis I: Functional connectivity with the posterior cingulate will be decreased in the entorhinal cortex and prefrontal regions in AD and MCI.

Rationale I: MCI is purported to be an early stage of AD in most cases (i.e., amnestic variety of MCI), so it stands to reason that structures thought to be involved very early on in AD will show decreased connectivity

Hypothesis II: Groups will differ significantly from each other. It is expected that posterior cingulate connectivity will be reduced in MCI relative to normal controls and further reduced in AD.

Rationale II: The hallmark of AD is episodic memory decline, and in addition to hippocampal pathology, there is evidence that the entorhinal cortex and prefrontal regions are involved in episodic memory. Episodic memory decline has also been noted in MCI, although to a lesser degree. The posterior cingulate has been implicated in imaging studies that have examined MCI and AD, and fcMRI studies have shown reduced connectivity in these regions. It is thus reasoned that connectivity with the posterior cingulate and entorhinal and prefrontal regions will be reduced to the greatest degree in AD and to a lesser degree in MCI relative to NC.

CHAPTER FOUR
Methodology

PARTICIPANTS

Participants were recruited through the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center. Every year, patients and non-diseased individuals being followed there undergo a physical examination and a series of neuropsychological tests. Individuals from this longitudinal database were identified as potential participants by center personnel and invited to participate in the study. In addition to medical and neuropsychological data, imaging data were collected from 10 patients with AD, 9 patients with MCI, and 10 healthy control participants. Attempts were made to equate subject groups in terms of age and gender, as well as MCI subjects who were of the amnestic subtype.

Men or post-menopausal women (because memory problems have been associated with changes in estrogen concentration around menopause) of all races and ethnicities who were able to read, speak, and understand English and were between the ages of 55 and 85 were invited to participate in this study. The age range of those who completed the study was 56 to 85. Individuals unable to give informed consent or who had unstable medical conditions, other neurologic disease, or psychiatric illness other than depression were excluded. In addition, those with magnetic resonance imaging-related contradictions (e.g., metal in the eye, pacemaker, claustrophobia) were excluded. Five participants who consented to be in the study were excluded—two had a diagnosis

that could not be determined with a reasonable amount of certainty (i.e., AD vs. MCI), one had unidentified brain abnormalities, and two could not tolerate the scanner.

Healthy Control Sample

The healthy controls had a global CDR score of 0, an MMSE score $\geq$ 29, and no major memory complaints.

Patient Sample

A diagnosis of MCI was based on the following criteria (Petersen, 2004): (1) patient had a cognitive complaint, (2) cognitive functioning was abnormal for age, (3) no dementia was present, (4) current cognitive functioning represented a decline for the individual, and (5) the ability to carry out functional activities was deemed essentially normal. MCI participants were further classified into subtypes, i.e., amnestic single domain (memory impairment only), amnestic multiple domain (impairment in memory and one or more other domains), nonamnestic single domain (impairment in one non-memory domain), or nonamnestic multiple domain (impairment in multiple non-memory domains) based on objective tests of memory, language, attention, and executive functioning. Of the nine MCI participants, three were amnestic single domain, five were amnestic multiple domain, and one was nonamnestic multiple domain. Eight of the nine MCI participants had a CDR of 0.5 and the remaining one had a score of 0.

AD was diagnosed by a neurologist using the National Institute of Neurological Disease and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINDCDS/ADRDA) (McKhann et al., 1984) criteria. AD

patients had MMSE scores ranging from 21 to 27 and CDR scores of 0.5 or 1.0, with five of the subjects having a score of 0.5 and the other five a score of 1.0.

MATERIALS AND PROCEDURES

The complete experimental protocol was approved by the University of Texas Southwestern Medical Center's Institutional Review Board. Participants previously provided written, informed consent for participation in similar studies through the ADC, including medical evaluation and neuropsychological testing. Once potential participants were identified, the MRI component of the study was explained in detail, and if individuals indicated interest in completing this portion of the study, they were asked to sign an additional MRI-specific consent form. They were also asked to complete an MRI screening form required by the UT Southwestern Advanced Imaging Research Center to ensure there were no contraindications to the procedure. All participants were paid $50 upon completion of the 30-minute MRI procedure.

FcMRI Data Acquisition

Imaging data were acquired on a Philips 3.0 Tesla Achieva MR system using the standard Philips head coil. In order to avoid head motion, each participant's head was immobilized with tightly fitting foam padding, and cushioned ear plugs and head phones were placed to diminish noise from the scanner while enabling participants to hear the scanner operator.

A time series of 205 echo-planar image (EPI) volumes was acquired for full-brain coverage at 37 axial slice locations with the participant at rest (eyes closed but not sleeping). EPI images were acquired with a single-shot gradient-recalled pulse sequence in an interleaved fashion (repetition time [TR] = 2000 milliseconds [ms]; echo time [TE] = 30 ms; flip angle = 80 degrees; matrix = 64 x 64; field of view [FOV] = 22 centimeters [cm]; slice thickness = 4 millimeters [mm]). High-resolution anatomical images of the brain were acquired in the same scanning session using a magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence (TR = 8.1 ms; TE = 3.7 ms; flip angle = 12 degrees; matrix = 256 x 256; FOV = 16 cm; slice thickness = 1 mm).

FcMRI Data Pre-Processing

The MRI data were transferred to a workstation for pre-processing using Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software. Data were normalized to the Talairach grid (Talairach & Tournoux, 1988) in order to aid in anatomical localization and allow the combination of data across subjects and comparison between groups. Because images at the beginning of a high-speed functional imaging run are of a slightly different quality than the later images due to transient effects before the longitudinal magnetization settles into a steady state, the first five images were discarded from the analyses. To correct for the fact that within each TR, each slice is actually offset in time from the previous one, separate slices were shifted (i.e., phase corrected) to a common temporal origin using Fourier interpolation. To ensure that gross head motions did not corrupt the analyses or distort the results, the data were then motion corrected. Rotation and displacement parameters were inspected for motions greater than

what could reasonably be corrected by the motion correction algorithm (i.e., rotations of more than 2 degrees and displacements greater than approximately 1.5 mm). Next, the EPI data were co-registered to the high-resolution T1-weighted data (MP-RAGE) to correct for misalignment between the functional and structural images.

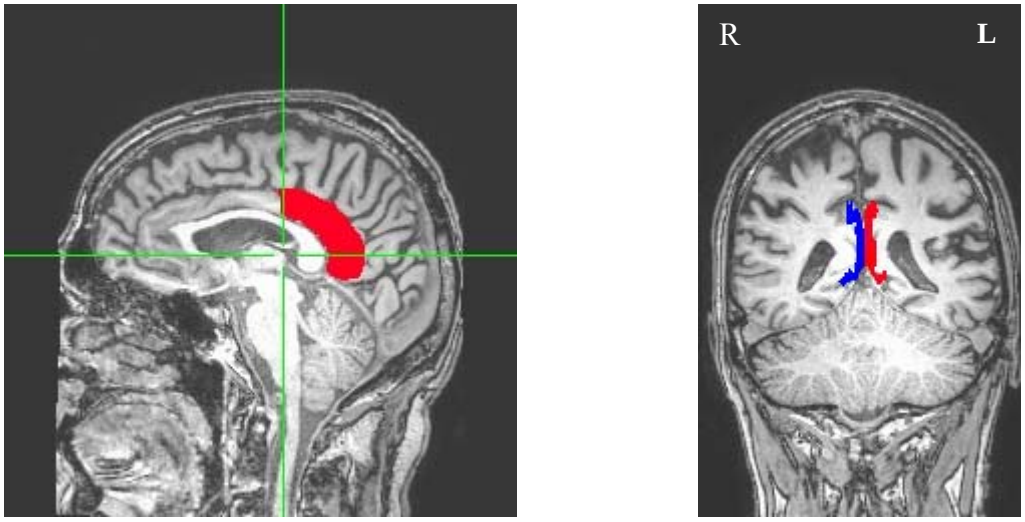
Since previous studies have shown that coherence in blood oxygenation level-dependent (BOLD) signal fluctuations occur at low frequencies (Biswal et al., 1995; Cordes et al., 2001; Lowe et al., 1998), a band-pass filter was applied to remove frequencies below 0.009 Hz and above 0.08 Hz. Head movement and whole brain, cerebral spinal fluid, and white matter signal fluctuations impact accurate signal detection and are sources of spurious variance, so these trends were extracted from the data following the regression procedure of Fox et al. (2005). Since individual brains vary, and activity is not represented precisely the same on a voxel-by-voxel basis in all brains, the data were spatially smoothed with a 3-dimensional Gaussian smoothing kernel set to 8 mm full width at half maximum. This process was implemented to increase the signal-to-noise ratio and decrease the possibility of losing significant signal that might have been obscured when voxels from multiple brains were compared.

Isolation of Seed Region

The posterior cingulate was drawn according to the guidelines delineated by Nestor et al. (2003), (see http://www.wbic.cam.ac.uk). First, the posterior commissure was identified in the coronal plane. On this slice, the PCC was defined and traced from superior to the corpus callosum to just superior to the cingulate sulcus and extended laterally to a depth that included all of the gray matter of the cingulate sulcus. Then, in the

sagittal plane, a radial trace of the posterior cingulate was made which attempted to maintain a similar depth from the corpus callosum as that set from the initial coronal tracing while excluding as much white matter as possible. The postero-inferior limit was the occipito-parietal fissure, the rostral limit the vertical line running through the posterior commissure. This region included the bulk of BA 23 as well as the small retrosplenial areas BA 29 and 30 (see Figure 3).

Figure 3. Posterior Cingulate Seed Region



Location was further verified with the assistance of brain atlases (Duvernoy, 1999; Mai, Assheuer, & Paxinos, 2004; Nolte & Angevine, 2000) and Talaraich coordinates (Talairach & Tournoux, 1988). To ensure that the quality of tracings was not affected by practice, the first 10 brains were redrawn. The investigator was blind to diagnosis.

Measurement of Functional Connectivity

In order to measure functional connectivity between the "seed" (PCC) and all other brain regions, temporally filtered time series magnetic resonance (MR) signal data were extracted from the voxels falling within the seed region. These data were then averaged to create a single MR signal time course for the seed in each subject. Cross-correlations of the seed signal with the measured time series from all other brain voxels were calculated. Correlations were transformed to z values using Fisher's r-to-z transformation. The *z*-transformed correlation coefficient at each voxel was used as the index of functional connectivity and entered into the group analysis. For this analysis, within-group *t*-tests were conducted separately for left and right PCC seeds to identify brain regions in the NC, MCI, and AD groups whose correlations with the PCC differed significantly from zero (see Figure 4 and Tables 8 through 13 at the end of this document). A between-group ANOVA with follow-up contrasts was used to identify brain regions that demonstrated significant group differences in PCC functional connectivity among the groups. The output from this group *t*-test was then thresholded using a voxel–cluster size method for the rejection of false-positive coherence.

First, all voxels whose *t* value did not exceed $\alpha = 0.001$ were excluded from further analysis. Next, the appropriate cluster size for the threshold was determined using the AFNI program AlphaSim. This program estimates the probability of a false-positive detection over an entire three-dimensional functional volume through Monte Carlo simulation of the processes of random image generation, spatial correlation of voxels, individual voxel intensity thresholding, and cluster identification. Spatial correlation estimates were derived from each participant's data using the AFNI program 3dFWHM.

By iterating these processes, the program generates an estimate of the overall significance level achieved for an individual voxel probability threshold combined with various cluster size thresholds. In other words, the program determines the probability of falsely detecting clusters of various sizes. AlphaSim reports the number of times out of 1000 iterations that a given cluster size is also the maximum cluster size in the random image. The goal for this study was an overall significance level of $\alpha < 0.01$. Cluster sizes that occur with a probability of less than 0.01 were identified, and clusters that met or exceeded this criterion in the group analysis were considered sites of significant functional coherence with the posterior cingulate.

Statistical Analyses

SPSS 15.0 software for Windows (SPSS, Chicago, IL) was used for analysis of demographic and clinical characteristic data. ANOVAs were used for between-group comparisons of age, education, and MMSE scores. Chi-square tests were used to examine group differences in gender and handedness. Imaging analyses were as described above. The AFNI program 3dANOVA was used to examine between-group differences in connectivity and 3dttest to examine within-group connectivity between the posterior cingulate and the rest of the brain.

CHAPTER FIVE
Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the subjects are shown in Table 1. No significant differences in age, gender, or handedness were found among the three groups. There was a significant difference in terms of education, $F_{(2,26)} = 6.6$, $p = .005$. Post hoc comparisons revealed that the MCI group's education level was significantly lower than the NC and AD groups. Main effects for MMSE, $F_{(2,26)} = 20.0$, $p < .001$; CDR total score, $F_{(2,26)} = 43.6$, $p < .001$; and CDR sum of boxes, $F_{(2,26)} = 33.8$, $p < .001$ were also observed, with group differences in the expected direction of scores in the AD group reduced compared to the MCI group, whose scores were reduced compared to the NC group.

Table 1. Demographic and Clinical Characteristics of Patients and Healthy Controls

	NC[a] *(n = 10)*	MCI[a] *(n = 9)*	AD[a] *(n = 10)*	P-value
Age (yrs.) at scan	74.1 ± 8.7	74.9 ± 6.6	70.4 ± 7.7	.395
Education (yrs.)	15.6 ± 2.2	11.89 ± 3.4	15.3 ± 1.4	.005[1]
Gender (χ^2)	5 female	5 female	6 female	.904
Handedness	7 right	9 right	8 right	.216
MMSE	29.6 ± 0.5	27.2 ± 0.6	24.7 ± 0.6	< .001[2]

NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.
[a]Data presented are means and standard deviations unless otherwise specified.
[1]MCI < AD p = .01; MCI < NC p = .008
[2]MCI < AD p = .01; MCI < NC p = .02; AD < NC p = < .001

Functional Connectivity Results

Within-Group Analyses

See Figure 4 on page 61 depicting peaks of PCC connectivity for within-group analyses.

Connectivity of the left posterior cingulate in normal controls (Table 8). Regions of connectivity with the left PCC included the left superior frontal gyrus; anterior and posterior cingulate and hippocampal regions; middle and superior temporal gyri; several regions of the parietal and occipital lobes, including the precuneus; regions in the cerebellum; and regions of the caudate, insula, and thalamus. Regions of left PCC connectivity with the right hemisphere included the medial and superior frontal gyri; anterior cingulate and parahippocampal gyrus; middle and superior temporal gyrus; only the postcentral gyrus, cuneus, and precuneus in parietal and occipital lobes; several areas of the cerebellum; and regions of the caudate, globus pallidus, and thalamus.

Connectivity of the right posterior cingulate in normal controls (Table 9). Regions of connectivity with the right PCC included the left superior frontal gyrus; anterior and posterior cingulate and parahippocampal gyrus; middle and superior temporal gyri; angular gyrus, middle temporal gyrus, and precuneus of the parietal and occipital lobes; regions of the cerebellum; and regions of the caudate, insula, and pulvinar. Regions of right PCC connectivity with the right hemisphere included the inferior frontal and precentral gyri; cingulate and parahippocampal gyri; middle and superior temporal gyri; postcentral gyrus and precuneus of the parietal and occipital lobes; six areas in the cerebellum; and regions of the caudate, putamen, and thalamus.

Connectivity of the left posterior cingulate in mild cognitive impairment (Table 10). Regions of connectivity with the left PCC included the left medial and middle frontal gyri; several areas of the cingulate gyrus; amygdala; fusiform and middle temporal gyri; the postcentral gyrus, inferior and superior parietal lobules, and the precuneus portion of the parietal lobe; lingual gyrus; a widespread area of the cerebellum; and regions of the caudate, insula, putamen, and thalamus. Regions of right hemisphere connectivity with the left PCC included the precentral, medial, middle, and superior frontal gyri; anterior and posterior cingulate; precuneus; middle, superior, and transverse temporal gyri; lingual, fusiform, and middle occipital gyri; a widespread region of the cerebellum; and regions of the claustrum, insula, globus pallidus, and thalamus.

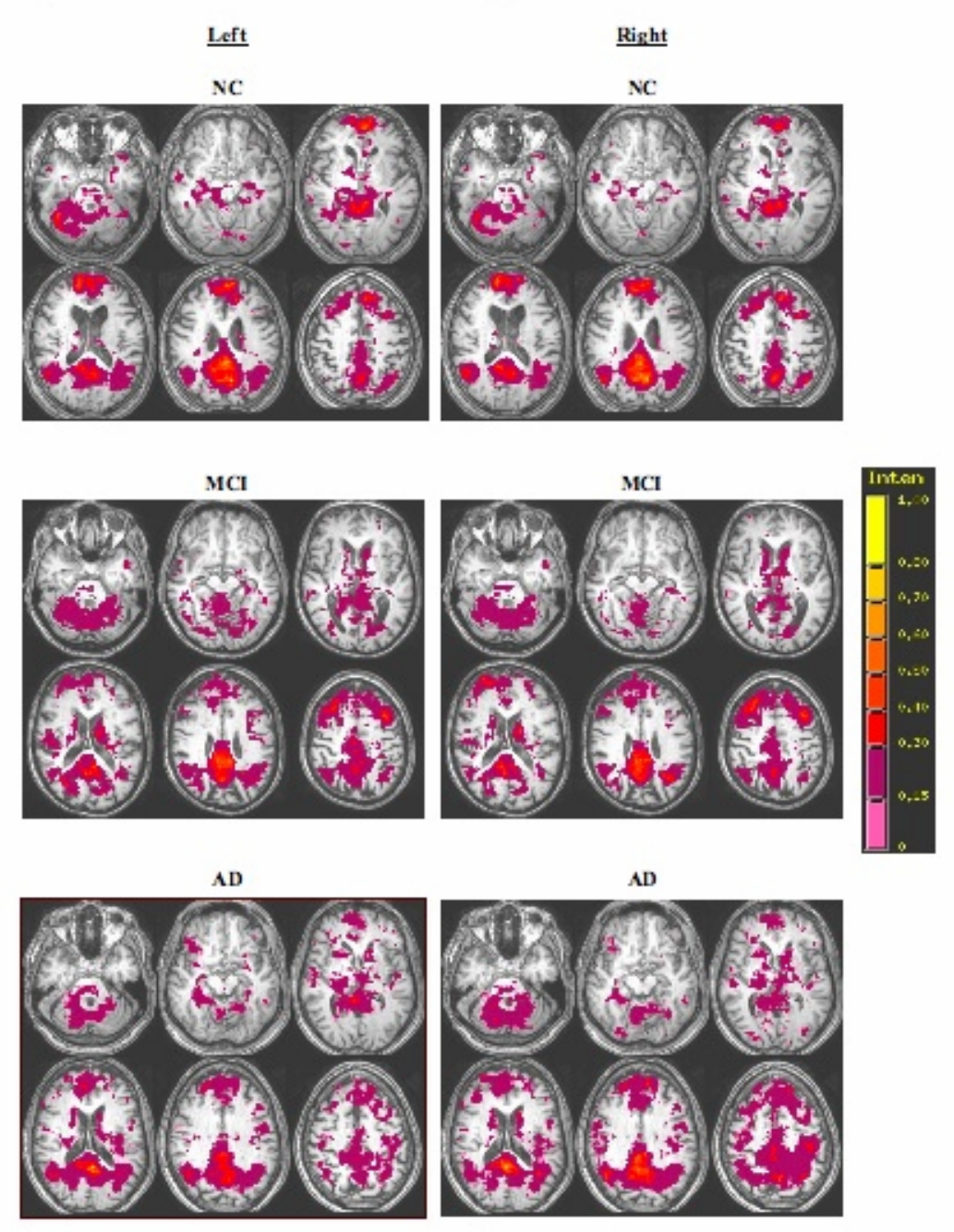
Connectivity of the right posterior cingulate in mild cognitive impairment (Table 11). Regions of right connectivity with the left hemisphere included the middle frontal gyrus; cingulate and parahippocampal gyri; fusiform and middle temporal gyri; inferior parietal lobule, postcentral gyrus, and precuneus; cuneus and lingual gyrus; a widespread region of the cerebellum; and regions of the caudate, insula, putamen, and thalamus. Regions of right hemisphere connectivity with the right PCC included the medial, middle, and superior frontal gyri; cingulate and parahippocampal gyri; middle and transverse temporal gyri; precuneus in the parietal and occipital lobes; cuneus; lingual and middle temporal gyri; a widespread region of the cerebellum; and regions of the insula, globus pallidus, and thalamus.

Connectivity of the left posterior cingulate in Alzheimer's disease (Table 12). Regions of left PCC connectivity included the left medial, middle, and precentral gyri; cingulate gyrus and parahippocampal gyrus; amygdala; middle and superior temporal

gyri; postcentral gyrus and precuneus of the parietal and occipital lobes; a large number of regions in the cerebellum; and regions of the caudate, insula, globus pallidus, and thalamus. Regions of left PCC connectivity with the right hemisphere included the medial frontal and precentral gyri; cingulate and parahippocampal gyri; superior temporal gyrus; precuneus of the parietal and occipital lobes; cuneus; a large number of areas in the cerebellum; and regions of the caudate, putamen, and thalamus.

Connectivity of the right posterior cingulate in Alzheimer's disease (Table 13). Regions of connectivity of the right PCC with the left hemisphere included the inferior, precentral, medial, and middle frontal gyri; cingulate gyrus; superior and transverse temporal gyri; postcentral gyrus, inferior and superior parietal lobules, and precuneus; lingual and middle temporal gyrus; a widespread region of the cerebellum; and regions of the caudate, globus pallidus, and thalamus. Regions of connectivity of the right PCC with the right hemisphere included the precentral, medial and middle frontal gyri; cingulate and parahippocampal gyri; angular and superior temporal gyri; inferior and superior parietal lobules and precuneus; cuneus; inferior and middle occipital gyri; a large number of regions in the cerebellum; and regions of the caudate, claustrum, and putamen.

Figure 4. Within-Group Peaks of Connectivity of the Posterior Cingulate



Between-Group Analyses

The overall 3dANOVA revealed significant group differences in functional coherence. Results of the post hoc tests are presented in Figures 2 through 7 and Tables 5 through 10 on pages 64 through 69.

Left posterior cingulate connectivity. When groups were compared, the MCI group showed decreased connectivity of the left PCC with the left cingulate gyrus and the right parahippocampal gyrus in comparison to the NC group (Figure 5, Table 2). In contrast, this same comparison revealed greater coherence in the MCI group in areas of the left middle frontal gyrus and the left cerebellum. When differences in left PCC connectivity were examined between the MCI and AD groups, the left cerebellum and the right middle frontal and temporal gyri showed decreased connectivity in the AD group (Figure 6, Table 3). No regions of increased connectivity were observed in the AD as compared to the MCI group. When the AD group was compared to the NC group, the largest areas of decreased connectivity in the AD group were in the left sub-gyral temporal lobe, cingulate gyrus, and superior frontal gyrus, as well as the right middle temporal gyrus and the cerebellum (Figure 7, Table 4). There were no areas of increased connectivity with the left PCC in the AD group compared to the NC group.

Right posterior cingulate connectivity. For the right PCC, small areas of coherence in the left and right cingulate gyri were decreased in the MCI group compared to the NC group, while an increase in connectivity with the left cerebellum was observed in the MCI group (Figure 8, Table 5). The AD group showed significantly less connectivity in a large portion of the left frontal middle gyrus as compared to the MCI group, and smaller areas of connectivity in the left cerebellum and right superior temporal

gyrus (Figure 9, Table 6). When right PCC connectivity in the AD group was compared to the NC group, multiple areas of decreased connectivity were observed in the AD group (Figure 10, Table 7). Large clusters were found in the left cingulate and middle temporal gyri, as well as somewhat smaller clusters in the left middle temporal gyrus and the left and right superior frontal gyri of the NC that were not observed in AD.

Figure 5. Left Posterior Cingulate Connectivity in NC vs. MCI

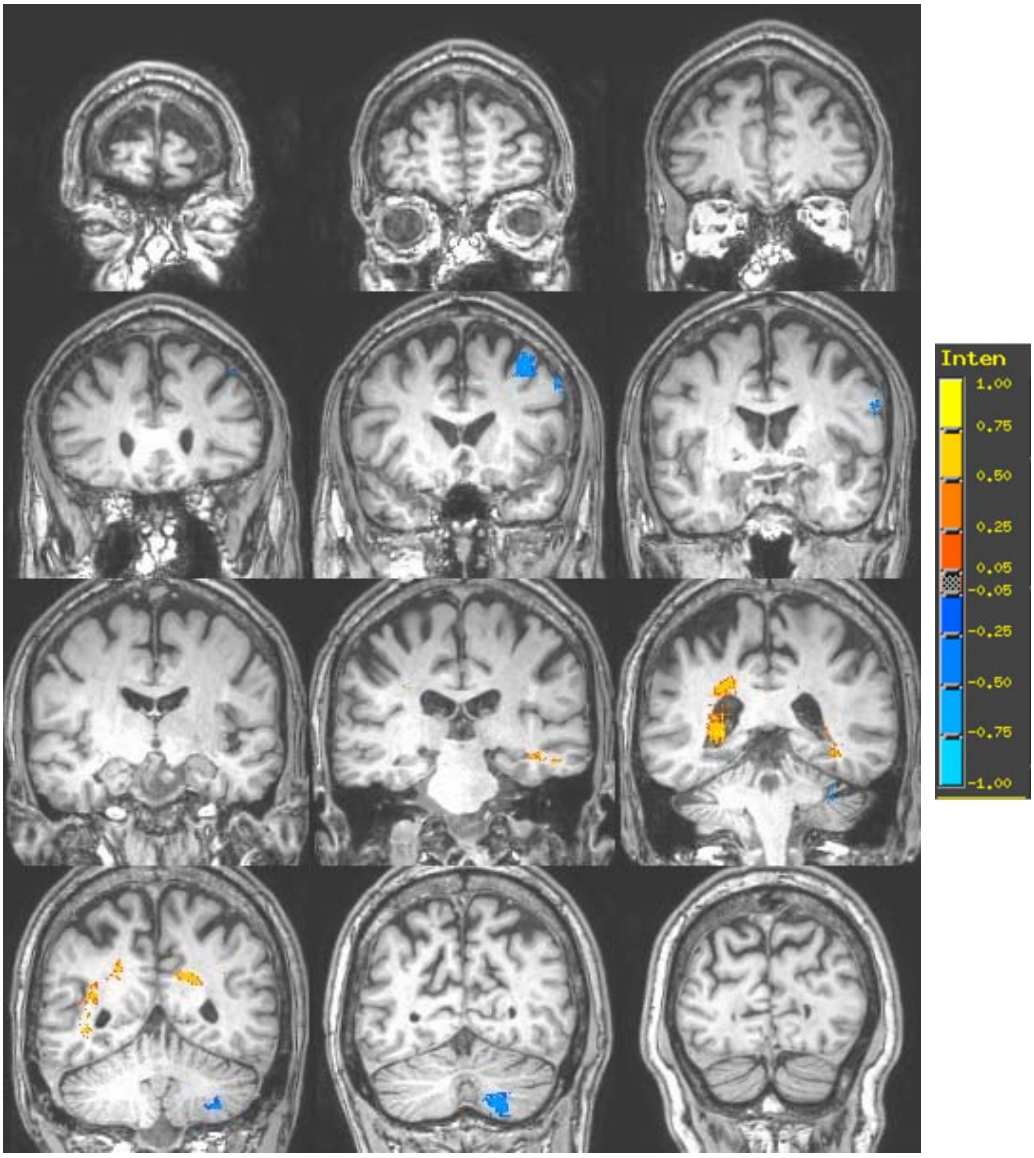


Table 2. Connectivity Differences of Left Posterior Cingulate in NC vs. MCI

NC > MCI	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)	Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Cingulate Gyrus	31	-14	-55	26	4.30	2077	Parahippocampal Gyrus	30	24	-37	3	5.44	3357

MCI > NC	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)	Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Middle Frontal Gyrus	6	-33	11	46	-4.80	1771							
Inferior Semi-Lunar Lobule	*	-20	-62	-42	-4.47	1767							

Figure 6. Left Posterior Cingulate Connectivity in MCI vs. AD

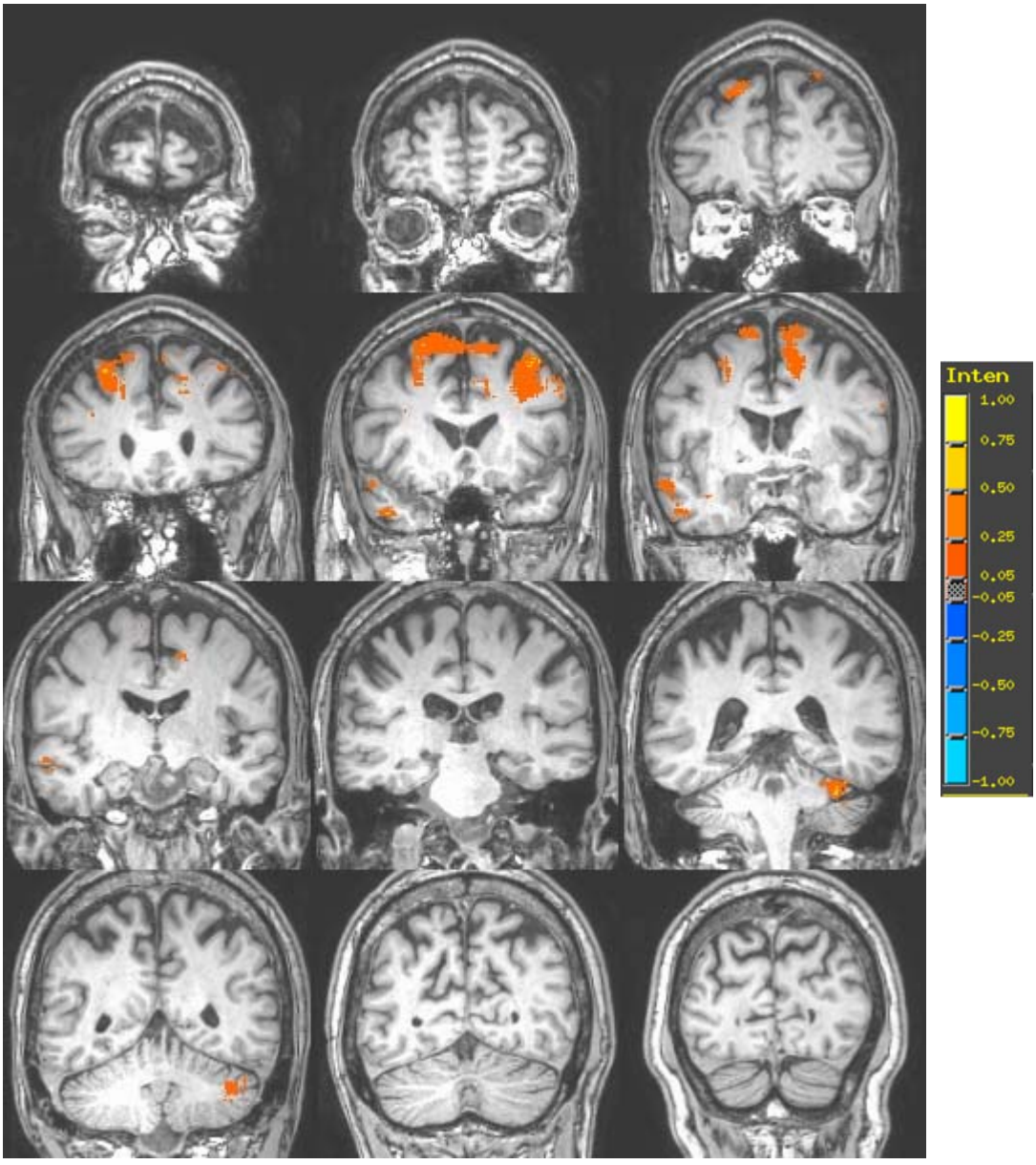


Table 3. Connectivity Differences of Left Posterior Cingulate in MCI vs. AD

	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)		Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Cerebellum - Culmen	*	-34	-34	-21	8.85	1998		Middle Frontal Gyrus	6	22	18	57	6.63	15758
								Middle Temporal Gyrus	21	53	5	-18	5.65	2208

Figure 7. Left Posterior Cingulate Connectivity in NC vs. AD

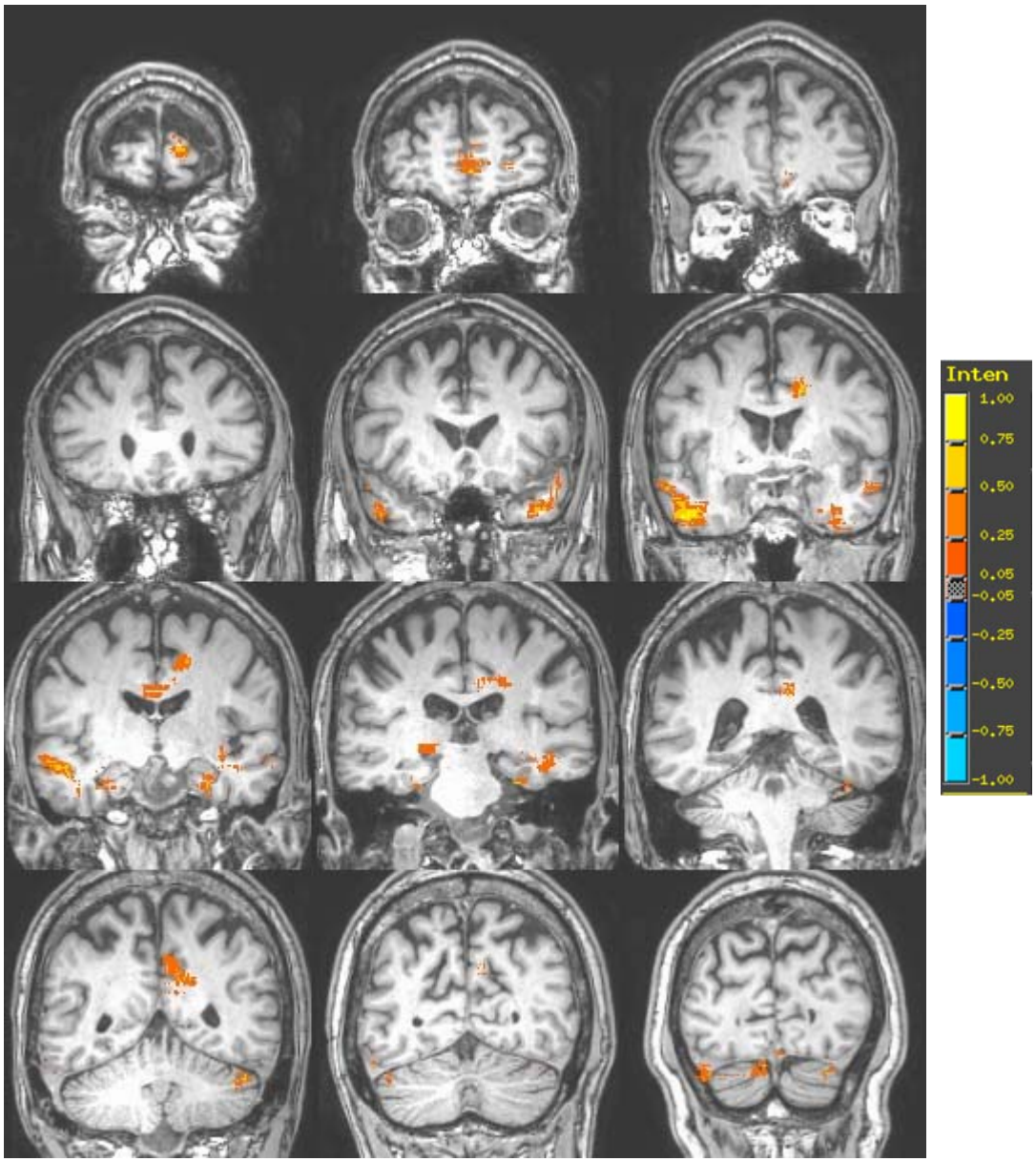


Table 4. Connectivity Differences of Left Posterior Cingulate in NC vs. AD

	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)		Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Sub-Gyral Temporal Lobe	38	-32	4	-30	6.07	6397		Middle Temporal Gyrus	21	43	-1	-32	6.98	5501
Cingulate Gyrus	24	-16	-1	36	5.70	4505		Cerebellum - Declive	*	39	-69	-19	5.94	1855
Superior Frontal Gyrus	10	-15	64	8	5.55	3011								

Figure 8. Right Posterior Cingulate Connectivity in NC vs. MCI

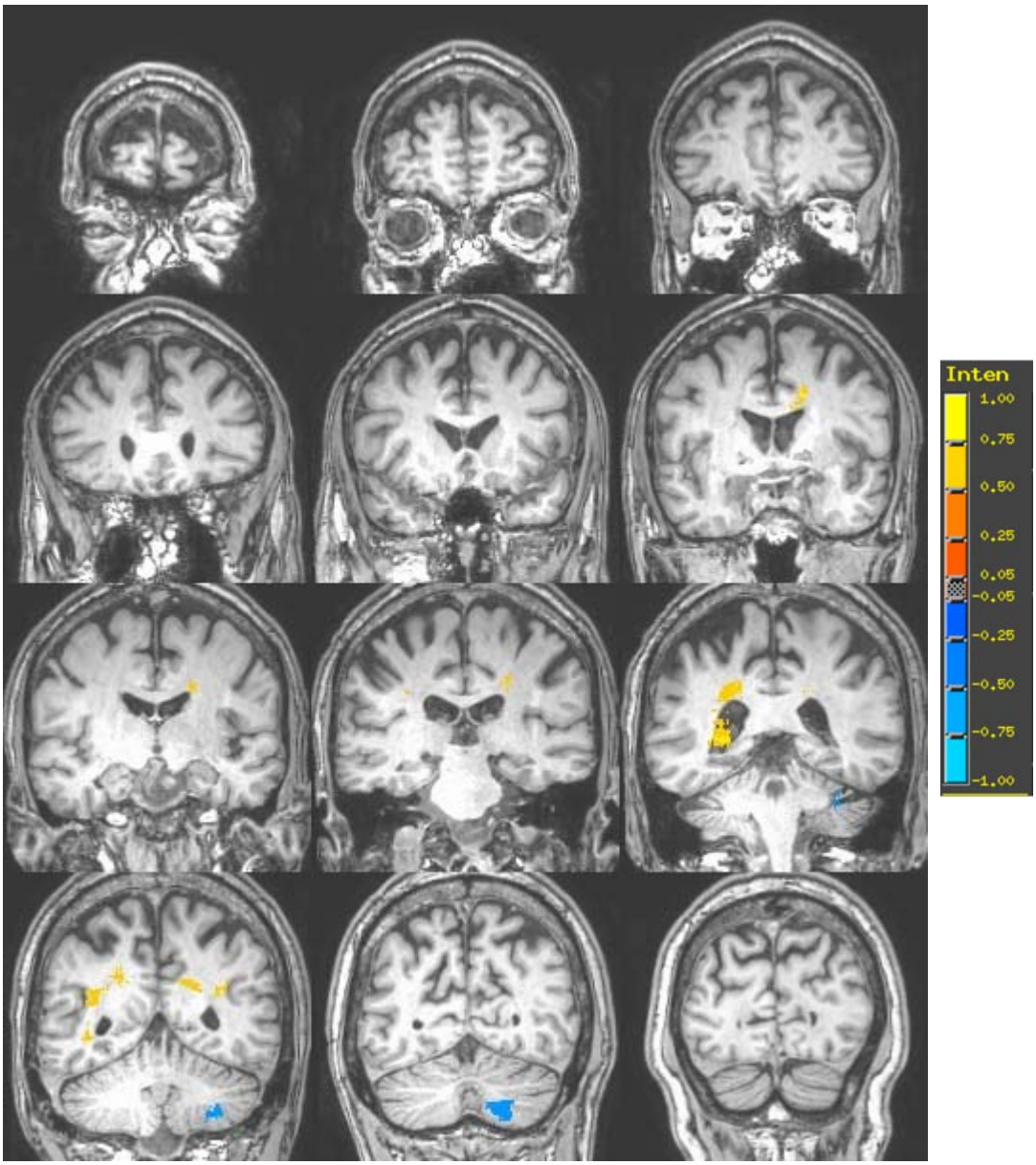


Table 5. Connectivity Differences of Right Posterior Cingulate in NC vs. MCI

NC > MCI	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)	Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Cingulate Gyrus	24	-15	2	33	4.79	1993	Cingulate Gyrus	31	17	-46	28	4.71	3486

MCI > NC	Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)	Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Cerebellar Tonsil	*	-33	-51	-42	-4.14	2171							

Figure 9. Right Posterior Cingulate Connectivity in MCI vs. AD

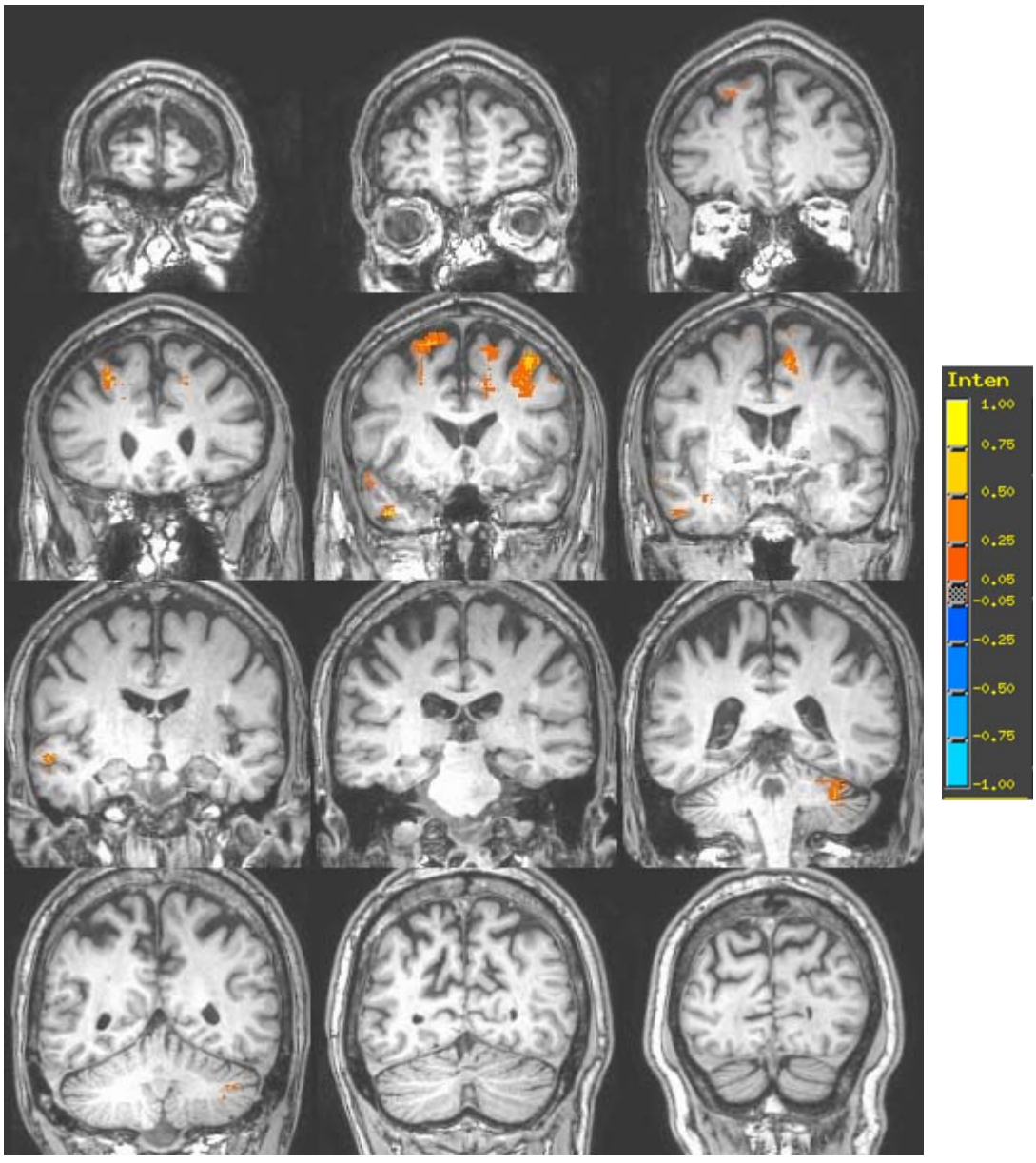


Table 6. Connectivity Differences of Right Posterior Cingulate in MCI vs. AD

	Left							Right						
Region	BA	x	y	z	score	(mm3)		Region	BA	x	y	z	score	(mm3)
Middle Frontal Gyrus	6	-35	12	47	6.88	8269		Superior Temporal Gyrus	38	50	12	-13	4.98	1524
Cerebellum - Culmen	*	-34	-35	-21	6.93	1674								

Figure 10. Right Posterior Cingulate Connectivity in NC vs. AD

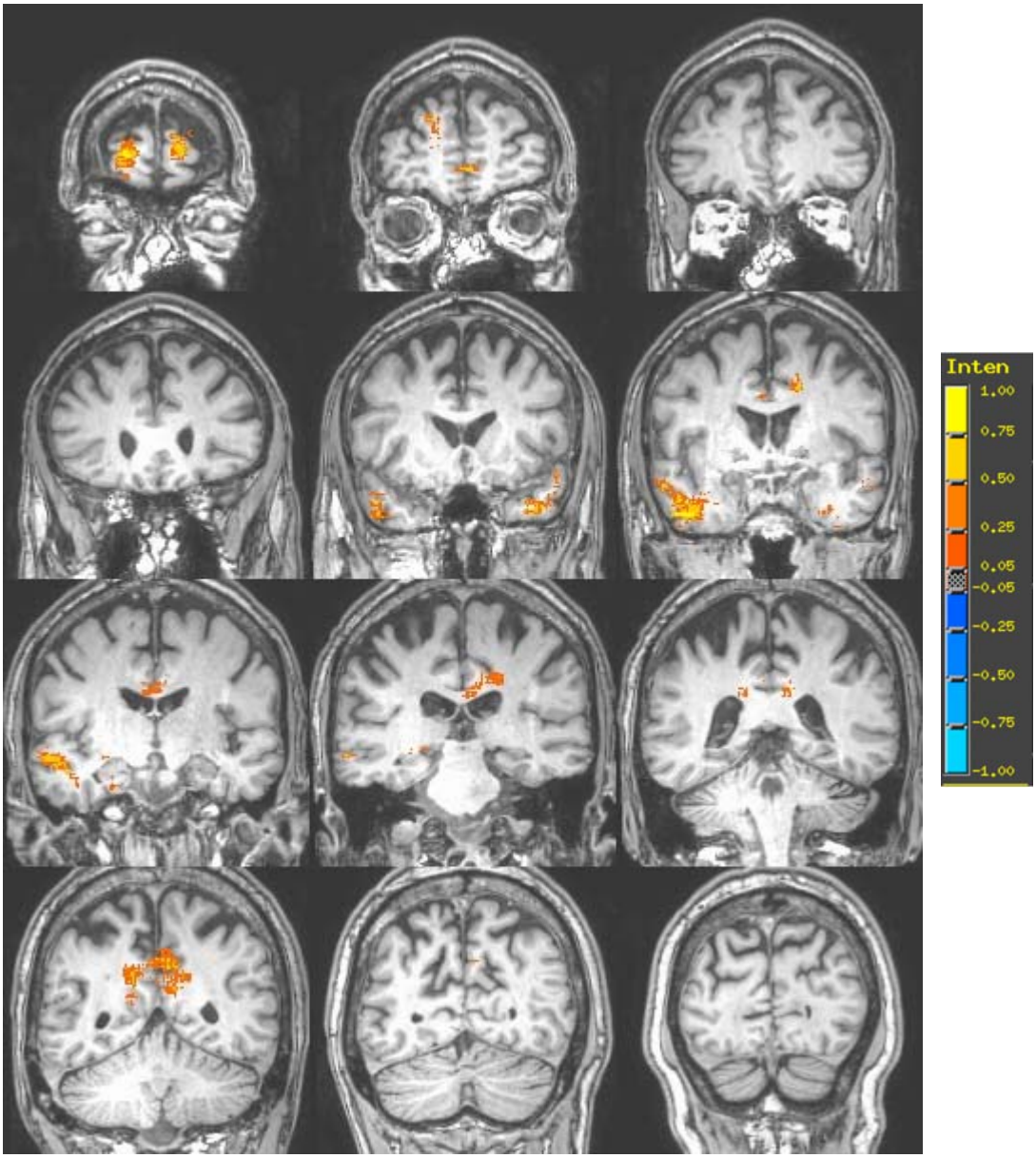


Table 7. Connectivity Differences of Right Posterior Cingulate in NC vs. AD

		Left							Right						
Region	BA	x	y	z	Peak *t* score	Volume (mm3)		Region	BA	x	y	z	Peak *t* score	Volume (mm3)
Cingulate Gyrus	24	-15	3	37	5.21	6147		Middle Temporal Gyrus	21	43	-0	-32	6.59	5250
Superior Frontal Gyrus	10	-15	64	8	5.09	1981		Superior Frontal Gyrus	10	17	65	6	6.17	1656
Middle Temporal Gyrus	21	-52	6	-17	4.64	1709								

CHAPTER SIX
Discussion

Alzheimer's disease, a neurodegenerative disease that is characterized by progressive impairment in memory and other cognitive abilities as well as a decline in daily functioning, is a growing concern in our rapidly aging population, both from economic and quality-of-life standpoints. *Mild cognitive impairment* involves complaints in cognitive functioning, which can be memory or non-memory related, in the context of relatively intact daily functioning. MCI has been implicated as an early stage of AD by some (Morris, 2006), while others opine that although it may be a risk factor, it is not always preclinical AD (Petersen, 2004). Finding a biomarker of early AD could potentially lead to early intervention that might slow the progression of the disease and guide further research towards targets for a cure.

Disparate findings in the MCI literature are in part a result of differing methods of diagnosis (Bondi et al., 2008a; Morris & Cummings, 2005), making it difficult to draw definitive conclusions. As noted in the literature review, cognitive profiles of aging, MCI, and AD show some overlap (e.g., memory impairment, executive disturbances, and difficulties in expressive language/semantic knowledge), and it can be difficult to distinguish among them. It has been suggested that brain imaging, in combination with other methods such as neuropsychological testing, may be more helpful in distinguishing between MCI and AD. Furthermore, recent findings suggest that reduced connectivity between the posterior cingulate and associated brain regions may make an important contribution in this regard, as changes in the posterior cingulate, precuneus, and entorhinal cortex are among the brain regions affected earliest in the course of AD.

To briefly review, the posterior cingulate gyrus is roughly comprised of BA 23, 26, 31 (the precuneus), and the retrosplenial cortex areas 29 and 30. A complex network of connections to and from these regions has been noted, including BA 7, 8, 9, 11, 19, 22, 35, 36, and 46. These areas represent the somatosensory association cortex, frontal eye fields, DLPFC (BA 9/46), a portion of the orbitofrontal area, associative visual cortex, superior temporal gyrus, and perirhinal and parahippocampal cortices in the parahippocampal gyrus (BA 35/36). The ERC (BA 28/34) receives projections from the PCC via the parahippocampal gyrus. This circuit allows the PCC to carry out its primary function, which are to assist in visual attention and the processing of relevant environmental stimuli, spatial orientation, and memory. Imaging studies have shown that the PCC is involved in a complex network of connections that include the ERC and the DLPFC. Specifically, co-activation of the ERC and DLPFC during episodic memory encoding and retrieval is consistently found in task-dependent functional imaging studies. The parallel pathways between the DLPFC and hippocampus, represented by the connections noted above, are implicated in both verbal and spatial working memory (Goldman-Rakic, 1987, 1996). Furthermore, abnormalities within the PCC have been associated with pathologic changes in the ERC and the hippocampal cortices. From a cognitive standpoint, studies in search of methods to discriminate normal aging, MCI, and AD have found that measures of attention, working memory, and executive functioning (in addition to tests of memory) have been sensitive to cognitive decline in these groups. It was therefore rationalized that a putatively intact PCC in the NC group would show significantly greater connectivity with other brain regions, whereas the

patient groups with less intact PCCs would show decreased connectivity, particularly in regions such as the ERC and DLPFC.

The primary objective of this investigation was to examine functional connectivity of the posterior cingulate with all other brain regions in MCI and early AD. This study is unique in that functional connectivity studies in MCI and AD to date have focused on the hippocampus as a "seed" region of interest in order to examine its connectivity with other brain regions. Imaging findings in the literature provide evidence that the posterior cingulate is a brain region affected early on in the course of AD, even before clinical signs are evident. It was thus hypothesized that functional connectivity would be reduced in both AD and MCI relative to NC, with AD showing the largest reduction in overall brain connectivity.

Within-Group Analyses

As hypothesized, the NC group showed widespread connectivity bilaterally throughout the frontal, limbic, temporal, parietal, and occipital lobes, as well as the cerebellum and subcortical regions. Left PCC connectivity appeared to be more extensive than right PCC connectivity. PCC connectivity to brain regions within normal elderly control subjects has not been reported, but Wang et al. (2006) reported results from a hippocampal connectivity study in which rightward asymmetry of connected brain regions within normal controls was observed. The difference between this finding and the apparent left-sided asymmetry observed in the current study may be explained by the fact that several MRI-based measurement studies have found rightward asymmetry in hippocampal volume in normal adults, thus contributing to greater right-sided

connectivity. It is possible that there may be asymmetry in the posterior cingulate as well, with left-sided volumes greater than the right, but this remains to be examined. While connectivity between the left PCC and a portion of the right DLPFC (BA 9) was observed, other peaks in the DLPFC or in the ERC were absent, contrary to what might be expected given the circuitry of the PCC (Mega & Cummings, 1997). However, the DLPFC is a large and highly convoluted cortical region that varies in exact location in individual brain anatomy, and there are differing opinions as to what actually constitutes the DLPFC (Al-Hakim, Fallon, Nain, Melonakos, & Tannenbaum, 2006). This could make it difficult to interpret findings in the DLPFC with any specificity. The lack of peak connectivity in BA 46 may be an artifact of how this area is defined within the Talairach coordinate system. Regardless, this is not a major concern given that BA 9 is also a prominent region of the DLPFC. Regarding the ERC, the absence of connectivity with the PCC in the current study may be related to the high degree of signal dropout in the ERC (i.e., 12 of 39 subjects). Consequently, the restricted signal-to-noise ratio in those subjects could decrease the signal time course, making it weak and undetectable.

The MCI group similarly showed regions of connectivity that involved all lobes of the brain bilaterally, most notably in the frontal lobe and cerebellum. There was connectivity between the left PCC and BA 9, but again regions of the ERC did not show significant connectivity with the PCC. Peaks of connectivity were present between the left PCC and left amygdala as well as the right PCC and right parahippocampal gyri (BA 19/30). It is interesting to note the extent of connectivity between the PCC and the frontal and cerebellar regions is observable to the greatest degree in left PCC connectivity with left brain regions (vs. connectivity with right brain regions), especially since

episodic memory encoding is typically thought to occur in the left prefrontal cortex (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Evidence for the role of the cerebellum in cognition is mounting, and in particular, connectivity between the dentate of the cerebellum and prefrontal regions has been demonstrated (Allen et al., 2005). Findings from that study suggest that connectivity between the cerebellum and the prefrontal cortex may play a role in episodic memory encoding that is observable in MCI.

Similar to findings within the MCI group, the greatest amount of PCC connectivity in the AD group was in the frontal lobe and cerebellum. Again, BA 46 did not show connectivity, but the medial frontal gyrus (BA 9/10/14) did. In addition to BA 9 and BA 46, imaging studies have consistently shown that BA 10 is involved in verbal and nonverbal episodic memory retrieval as well as working memory tasks (Grady, 1999; Grasby et al., 1993; Petrides, Alivisatos, Meyer, & Evans, 1993; Tulving, Markowitsch, Craik, Habib, & Houle, 1996). Furthermore, the left PCC showed connectivity with the left amygdala and ERC (BA 34), and the right parahippocampal gyrus (BA 36). Connectivity of the right PCC with the right limbic lobe included the right parahippocampal gyrus (BA 11), which is a surprising finding. It was postulated at the conception of this study, based on imaging studies showing *decreased* connectivity between the hippocampus and the PCC complex (Allen et al., 2007; Hirao et al., 2006; L. Wang et al., 2006), that connectivity between the PCC and the ERC would be diminished. While a clear interpretation of this awaits future study, it is possible that the connectivity between the PCC and cerebello-frontal structures may be supporting connectivity in the parahippocampal regions in this early stage of the disease.

Between-Group Analyses

Decreased Connectivity

Comparisons between the NC and MCI groups revealed that left PCC connectivity with the cingulate gyrus (BA 31) and the parahippocampal gyrus (BA 30) was reduced on the left in the MCI group. Right PCC connectivity was decreased in the MCI group for the cingulate gyrus bilaterally (BA 24/31) compared to NC. No other significant decreases were found in the MCI group relative to the NC group. The regions showing decreased connectivity in the MCI group have been associated with AD pathology (i.e., parahippocampal gyrus and posterior cingulate). This suggests that functional changes present in these MCI subjects might represent an early stage of AD.

The AD group's left PCC connectivity was decreased compared to NC in the left temporopolar area (BA 38), cingulate gyrus (BA 24), and superior frontal gyrus (BA 10), as well as the right temporal gyrus (BA 21) and the cerebellum. With respect to the right PCC, reduced connectivity was seen in the middle temporal gyrus (BA 21) and the superior frontal gyrus (BA 10). The decreases in connectivity observed are consistent with brain regions affected in AD. For instance, decreased connectivity in the anterior prefrontal cortex (BA 10) could contribute to the verbal and nonverbal episodic memory retrieval problems that are a hallmark of the disease. Decreased connectivity in this region in conjunction with reductions in the middle temporal gyrus may also account for working memory deficits frequently observed, as functional connectivity between prefrontal and hippocampal regions during working memory tasks in older adults has been noted (Grady, 1999; Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001). Additionally, BA 21 is involved in auditory processing and language. As noted

previously, in addition to the episodic memory difficulties that are a feature of AD, language and semantic knowledge are affected by the disease process (Bondi et al., 2008a; Salmon & Bondi, 1999).

When the AD group was compared with the MCI sample, AD subjects showed decreased connectivity of the left PCC with the left cerebellum and the right middle frontal (BA 6) and temporal (BA 21) gyri. The right PCC showed reduced connectivity with the left middle frontal gyrus and the culmen of the cerebellum and the superior temporal gyrus on the right (BA 38). The intermediate extent of decreased connectivity in MCI versus NC compared to a greater extent of decreased connectivity in AD in these regions is consistent with what was hypothesized, and the areas of involvement support the episodic memory retrieval deficit often observed in amnestic MCI. One of the primary areas affected in the MCI group was an area of the cingulate gyrus (BA 31), which is part of the precuneus. PET activation of this region has been observed during episodic memory retrieval (Desgranges et al., 1998), and disrupted connectivity between this region and the PCC is consistent with the cognitive deficits in MCI. Other studies, as well, have shown that deficits in working memory and in the encoding and retrieval of episodic memory occur with disruption to the DLPFC in the preclinical or mild phase of AD (Cabeza & Nyberg, 2000; Small et al., 2003; Wheeler et al., 1995).

Increased Connectivity

Following pair-wise comparisons between the groups, an interesting finding was *increased* coherence between the PCC and the left middle frontal gyrus and the cerebellum in the MCI group relative to the NC group. As indicated earlier, the

cerebellum appears to play a role in various aspects of cognitive functioning. For example, the lateral posterior lobes of the cerebellum have been implicated in aspects of memory, learning, executive function, and language (Exner, Weniger, & Irle, 2004; Kalashnikova, Zueva, Pugacheva, & Korsakova, 2005; Schmahmann & Sherman, 1998). Studies have shown that the cerebellum receives input from nearly all levels of the central nervous system, including the frontal lobe (Salman, 2002), and efferent fibers deliver information from the cerebellum to the frontal lobes (Middleton & Strick, 1994). A functional connectivity study by Allen et al. (2005) found connectivity between the dentate and areas of the superior, medial, and middle frontal gyri. In addition, connections with the cingulate gyrus were also found, including the posterior cingulate and precuneus. Based on these connections and the finding of an *increase* in functional connectivity, accompanied by a *decrease* in the parahippocampal gyrus in MCI relative to NC, it is plausible that the cerebellum is acting in a compensatory fashion to maintain function in the face of deficient processing of the parahippocampal region in the earliest stage of disease. Activation increases in frontal regions have frequently been observed in PET and fMRI aging studies (Buckner, 2004), with increased recruitment observed in older nondemented individuals (Park et al., 2003), individuals with AD (Grady et al., 2003), nondemented individuals at risk for AD (Bookheimer et al., 2000), and stroke recovery patients (Rosen et al., 2000). From this evidence, it appears that compensation may be a general brain response that occurs across a spectrum of conditions, from normal aging to brain injury or degeneration. Therefore, the utility of this knowledge may lie not in observation of regions of increased activation or connectivity, but rather, in regions of simultaneous decrease.

There may also be an alternative explanation to the notion that the MCI group was recruiting other brain regions to compensate for reductions in connectivity in the cingulate and parahippocampal gyri, two regions expected to show early change in AD. The fact that the AD group failed to show similar recruitment may be explained by this group having reached a plateau in recruitment of alternate brain regions, followed by a subsequent decline, perhaps in a manner described by Smith et al. (2007). These investigators analyzed neuropsychological test data from 199 individuals that eventually received a diagnosis of clinically probable AD after being followed for as much as 10 years and found that a plateau in memory decline that lasted about four years on average ended with a final abrupt decline that resulted in a diagnosis of AD. This finding was explained by a compensatory hypothesis that may involve the recruitment of other neural networks. For example, as the medial temporal lobe structures required for memory begin to degenerate and are no longer able to handle the burden of processing information, other neocortical areas are recruited. Compensatory brain recruitment has been reported in other imaging studies as well. Grady et al. (2003) also found that early AD patients appeared to recruit prefrontal cortices when performing semantic and episodic memory tasks. Yetkin et al. (2006) observed increased activation in a wide distribution of regions in AD and MCI groups relative to NC during a working memory task and interpreted this as a sign of recruitment of other brain regions as a form of compensation. Wang et al. (2006), too, attributed a finding of disrupted connectivity between the right hippocampus and other brain regions in AD with a relative increase in connectivity between the left hippocampus and the prefrontal cortex.

Changes in the posterior temporal-parietal-occipital associative areas from the mesial temporal cortex in AD (Matsuda et al., 2002) and in MCI (Chetelat et al., 2003) are thought to contribute to cognitive decline in verbal memory, one of the earliest signs of cognitive impairment in AD. Decreased connectivity in these regions important for memory, language, and executive functioning was observed in the present study while other regions showed increases in connectivity believed to support compensatory functioning, i.e., prefrontal cortices and the cerebellum.

Limitations

This study had several limitations. The sample sizes were small, which likely affected the power to detect more significant findings, especially in light of potential variability. On visual inspection, there appeared to be a large amount of variability within the subjects of each group in terms of brain anatomy, an observation inherent in small samples. This may have affected the number of voxels included in the PCC and hence the extent of connectivity since cluster size is an important component of determining significant coherence.

Handedness may also have been a factor, as differences in brain anatomy in individuals who are left-handed as compared to right-handed individuals have been shown in some studies (Hertz-Pannier et al., 1997). However, a voxel-based morphometry study found no significant effect of handedness on brain structure in 465 normal healthy adults (Good et al., 2001). The effect of handedness in fcMRI studies has not been reported. All of the MCI subjects in this study were right-handed, as well as seven of the ten NC and eight of the ten AD subjects. Regardless of potential brain

differences, since the groups in this study did not differ with regard to handedness, it is not felt that putative handedness-related brain structural changes had a significant effect on the findings.

Another limitation was that the groups were heterogenous in that they differed in education; specifically, the MCI group's education was significantly below that of the NC and AD groups. While a high education does not necessarily decrease the risk of AD, a low education may increase the risk for developing MCI (Stachura, 2006). Studies to date have been inconclusive in this regard. With regard to functional imaging studies, however, potential effects of education have not been systematically explored. Upon visual inspection, subjects in the MCI sample with lower education did not show less connectivity than higher-educated subjects. It is therefore felt that education did not impact the findings from this study.

One might argue that findings might be influenced by a mixed MCI group in terms of cognitive dysfunction. Eight of the nine MCI subjects had memory impairment while one subject was nonamnestic MCI. It is not felt that the results would have been different had the nonamnestic subject been removed from the study since the remaining MCI subjects had varying degrees of memory impairment, from negligible to mild. In light of this, it was felt that the issue of power was more important to consider than diagnostic subtype, so this individual was included in all analyses.

Lastly, signal drop-out in the ERC was observed in a large percentage of subjects (i.e., five AD patients, four MCI patients, and three NC), and this undoubtedly restricted findings in this region. One disadvantage to fMRI techniques is that ventral frontal and temporal brain regions are susceptible to artifact from bone and air underlying brain

tissue. The field inhomogeneity in these regions can produce signal dropout such as that which was observed in this study(Zald & Pardo, 2000). One way to get around this would have been to exclude all subjects with signal dropout. It was felt that losing this number of subjects, although it would have been similar across groups, would have limited findings in other brain regions.

Conclusions and Future Directions

Reliable predictors for the onset and progression of AD remain elusive, but imaging studies to date have implicated PCC, precuneus, and ERC involvement in MCI and preclinical AD. The underlying mechanisms and extent of involvement are still not clear, especially with regard to what role these brain regions play before the manifestation of disease symptoms. This study sought to help elucidate early contributions by examining functional connectivity of the PCC in MCI and AD. Overall, findings from the current study's small sample of NC, MCI, and AD patients indicate that there are early changes in PCC connectivity in the MCI group that are detectable with fcMRI. Specifically, when compared to NC, increased connectivity was observed in MCI (but not AD) in the frontal and cerebellar region *in conjunction with* decreased connectivity in parahippocampal and cingulate regions previously shown to be affected in AD. It appears that this unique combination of increased and decreased connectivity in these regions could serve as a biomarker of incipient dementia. Yet, however enticing it might be to think that the PCC-prefrontal-cerebellar findings represent compensatory mechanisms at work and are indicative of preclinical AD, other conditions such as normal aging and stroke also provide evidence for compensation in the face of altered

brain structure. It would thus be premature to draw this conclusion. Functional connectivity studies comparing brain conditions that have been shown to display compensatory mechanisms at work would be informative in this regard.

An interesting avenue to explore would be connectivity between the PCC and specific brain areas in the prefrontal cortex (e.g., BA 9 and 10), regions known to be involved in verbal and nonverbal episodic memory retrieval as well as working memory tasks (Grady, 1999), and the cerebellum. Specifically, evidence shows that other structures in addition to the hippocampus are activated during episodic memory tasks, such as preferentially left-sided activation of the association temporal and posterior cingulate areas in encoding tasks and preferentially right-sided activation of the association parietal cortex, cerebellum, and posterior cingulate in retrieval tasks (Desgranges et al., 1998). One might speculate that a pattern of coherence with these regions and the PCC may emerge across groups if directly examined and add evidence for compensatory mechanisms during degenerative processes.

Combining diffusion tensor imaging studies with fcMRI also holds promise for the detection of white matter changes before the onset of dementia. Early changes in the posterior cingulate in MCI and AD patients have already been shown (Medina et al., 2006; Zhang et al., 2007). For example, Medina et al. (2006) found significant reductions of fractional anisotropy (FA; an index of white matter tract integrity, with the higher the value, the greater the integrity) in the posterior cingulate bundle in MCI and AD patients as compared to NC. Zhang et al. (2007) found that FA of the cingulum fibers (which connect the medial temporal lobe and posterior cingulate regions) was significantly reduced in MCI, and even more so in AD. Greicius et al. (2008) employed

DTI and fcMRI and found that resting-state functional connectivity reflected underlying structural connectivity. No studies to date have reported similar methodology or findings in AD and MCI, and doing so might confirm PCC connectivity in these conditions.

Overall, results from these studies suggest that a combination of fcMRI, DTI, and neuropsychological testing may offer a sensitive measure of detecting subtle changes associated with preclinical AD. There are many questions remaining to be answered that future studies should address. While single time-point studies such as the current one provide useful information, they cannot answer the question regarding who might progress to AD. Extending this study by examining within-group and between-group differences over time, scanning at several time points to gauge change in relation to brain structure, function, and cognition, could make a valuable contribution to our knowledge. In order to increase our understanding of MCI and AD, because of the nature of compensatory brain recruitment, it would be interesting and enlightening to include samples of other types of brain injury and degenerative disease. Ideally, combining fcMRI, DTI, and neuropsychological data from larger samples drawn from a community-based population that would permit stratification by age, education, gender, disease/condition, and level of cognitive deficit would be optimal.

From a clinical standpoint, fcMRI could eventually be used to investigate early memory complaints, in conjunction with neurocognitive testing. This would require a large normative reference sample in order to make a comparison, but once a comparison has been made, should compensatory recruitment appear to be present, one might then follow up with other lab tests and neuropsychological testing to support or refute abnormal findings. Another avenue would be to complete an fcMRI scan at the earliest

sign of decline and follow over time, with the subject serving as his or her own control. FcMRI is non-invasive, can be completed in a relatively short amount of time (less than 10 minutes), and does not require a task. While it is premature to say that fcMRI might prove to be a biomarker of AD, these preliminary findings are encouraging and may serve as an impetus for further research.

Table 8. Connectivity of the Left Posterior Cingulate in Normal Controls

Left						Right					
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
Frontal Lobe											
Superior Frontal Gyrus	6	-5	9	52	7.24	Medial Frontal Gyrus	9	2	39	27	8.03
						Superior Frontal Gyrus	6	17	-12	68	7.52
Limbic Lobe											
Anterior Cingulate	24	-3	34	4	9.14	Anterior Cingulate	32	2	44	8	8.57
Cingulate Gyrus	31	-1	-38	28	25.83	Parahippocampal Gyrus	27	14	-37	2	11.56
Hippocampus	*	-24	-11	-20	9.30						
Posterior Cingulate	30	-2	-55	7	23.61						
Temporal Lobe											
Middle Temporal Gyrus	21	-45	6	-23	5.86	Middle Temporal Gyrus	39	48	-63	29	10.77
Superior Temporal Gyrus	38	-34	19	-25	8.95	Superior Temporal Gyrus	38	39	9	-27	7.63

Note: BA = Brodmann Area

Table 8 (continued). Connectivity of the Left Posterior Cingulate in Normal Controls

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Parietal Lobe						
Angular Gyrus	39	-40	-60	36	11.95	Postcentral Gyrus	3	22	-32	67	8.10
Inferior Parietal Lobule	40	-38	-46	52	7.34	Precuneus	7	3	-64	49	10.98
Postcentral Gyrus	5	-3	-45	66	10.79						
Precuneus	7	-3	-61	37	29.15						
Superior Parietal Lobule	7	-31	-54	49	7.11						
					Occipital Lobe						
Fusiform Gyrus	19	-21	-81	-12	9.56	Cuneus	18	5	-74	24	6.31
Lingual Gyrus	18	-14	-54	3	5.68	Precuneus	31	8	-61	28	27.09
Middle Occipital Gyrus	19	-30	-78	18	4.97						
Precuneus	31	-21	-77	29	5.93						

Note: BA = Brodmann Area

Table 8 (continued). Connectivity of the Left Posterior Cingulate in Normal Controls

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Cerebellum						
Culmen	*	-20	-32	-17	9.43	Culmen	*	38	-46	-29	25.96
Fastigium	*	-4	-55	-21	8.89	Cerebellar Tonsil	*	18	-41	-37	4.90
Cerebellar Tonsil	*	-27	-41	-35	5.12	Declive	*	38	-68	-22	13.44
Declive	*	-37	-68	-15	5.15	Pyramis	*	5	-72	-25	6.74
Uvula	*	-34	-68	-25	6.62	Uvula	*	17	-75	-23	9.30
					Sub-Lobar						
Caudate Head	*	-7	11	-2	7.41	Caudate Body	*	16	13	11	5.67
Insula	13	-37	-20	15	5.94	Medial Globus Pallidus	*	12	0	1	11.84
Pulvinar	*	-17	-27	3	12.34	Pulvinar	*	12	-25	5	11.56

Note: BA = Brodmann Area

Table 9. Connectivity of the Right Posterior Cingulate in Normal Controls

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Frontal Lobe						
Superior Frontal Gyrus	6	-14	-13	65	5.12	Inferior Frontal Gyrus	47	39	30	-8	8.28
						Precentral Gyrus	6	11	-16	68	5.51
					Limbic Lobe						
Anterior Cingulate	32	-5	44	-5	5.20	Cingulate Gyrus	31	3	-54	27	25.01
Cingulate Gyrus	32	-11	20	41	9.98	Parahippocampal Gyrus	27	14	-37	2	11.74
Parahippocampal Gyrus	36	-30	-34	-12	8.74						
Posterior Cingulate	30	-4	-54	7	15.58						
					Temporal Lobe						
Middle Temporal Gyrus	21	-44	5	-28	5.13	Middle Temporal Gyrus	22	62	-33	3	9.53
Superior Temporal Gyrus	38	-37	17	-23	9.61	Superior Temporal Gyrus	22	60	-10	0	9.59

Note: BA = Brodmann Area

Table 9 (continued). Connectivity of the Right Posterior Cingulate in Normal Controls

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
Parietal Lobe											
Angular Gyrus	39	-40	-61	36	13.49	Inferior Parietal Lobule	40	36	-52	43	4.89
Inferior Parietal Lobule	7	-34	-59	47	7.16	Postcentral Gyrus	5	7	-45	66	6.90
Precuneus	7	-3	-50	36	20.67	Precuneus	7	4	-61	38	32.17
Occipital Lobe											
Middle Temporal Gyrus	19	-37	-57	17	12.08	Lingual Gyrus	17	18	-91	0	7.02
Precuneus	31	-21	-77	29	5.00	Precuneus	7	14	-67	31	6.76
Sub-Lobar											
Caudate Head	*	-7	9	-1	7.91	Caudate Body	*	16	13	11	6.23
Insula	13	-39	-23	5	4.81	Putamen	*	19	4	-3	5.09
Pulvinar	*	-17	-27	3	11.04	Pulvinar	*	12	-25	5	10.82

Note: BA = Brodmann Area

Table 9 (continued). Connectivity of the Right Posterior Cingulate in Normal Controls

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Cerebellum						
Culmen	*	-24	-31	-24	9.50	Culmen	*	42	-54	-25	17.48
Fastigium	*	-4	-55	-21	8.26	Cerebellar Tonsil	*	19	-41	-39	4.99
Cerebellar Tonsil	*	-34	-54	-33	5.22	Declive	*	38	-68	-22	12.55
Uvula	*	-34	-68	-25	7.73	Declive of Vermis	*	0	-76	-15	6.06
						Pyramis	*	5	-72	-25	6.95
						Uvula	*	17	-75	-23	8.07

Note: BA = Brodmann Area

Table 10. Connectivity of the Left Posterior Cingulate in Mild Cognitive Impairment

Left						Right					
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
Frontal Lobe											
Cingulate Gyrus	32	-12	25	34	5.89	Medial Frontal Gyrus	9	16	37	22	5.16
Medial Frontal Gyrus	6	-17	9	48	7.19	Middle Frontal Gyrus	6	29	-9	58	5.69
Middle Frontal Gyrus	8	-27	14	39	12.29	Precentral Gyrus	6	50	-2	31	5.45
Paracentral Lobule	5	-4	-44	58	7.69	Superior Frontal Gyrus	6	11	-13	63	6.66
Precentral Gyrus	4	-18	-23	65	6.06						
Limbic Lobe											
Anterior Cingulate	32	-5	37	24	10.17	Anterior Cingulate	32	5	35	20	7.27
Cingulate Gyrus	31	-1	-31	35	17.31	Cingulate Gyrus	32	2	24	41	7.07
Amygdala	*	-19	-6	-11	9.72	Posterior Cingulate	31	3	-67	15	5.89
						Precuneus	31	6	-60	26	20.66

Note: BA = Brodmann Area

Table 10 (continued). Connectivity of the Left Posterior Cingulate in Mild Cognitive Impairment

Left						Right					
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
						Temporal Lobe					
Fusiform Gyrus	37	-43	-63	-11	6.53	Middle Temporal Gyrus	20	53	-42	-13	6.42
Middle Temporal Gyrus	21	-45	6	-26	9.17	Superior Temporal Gyrus	41	41	-35	16	10.62
						Transverse Temporal Gyrus	41	34	-26	10	11.81
						Parietal Lobe					
Inferior Parietal Lobule	7	-35	-59	45	8.14	Precuneus	7	8	-63	43	8.40
Postcentral Gyrus	5	-6	-40	67	7.83	Superior Parietal Lobule	7	7	-63	57	6.64
Precuneus	31	-12	-67	24	8.46						
Superior Parietal Lobule	7	-10	-62	55	7.65						

Note: BA = Brodmann Area

Table 10 (continued). Connectivity of the Left Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Occipital Lobe						
Lingual Gyrus	18	-16	-81	-14	8.12	Lingual Gyrus	18	5	-62	3	8.25
						Cuneus	17	15	-78	13	6.09
						Fusiform Gyrus	*	23	-57	-10	5.52
						Middle Occipital Gyrus	18	29	-85	0	5.94
						Middle Temporal Gyrus	19	43	-60	14	8.27
					Sub-Lobar						
Caudate Head	*	-9	15	2	14.33	Claustrum	*	29	17	0	5.65
Insula	13	-36	-19	16	7.26	Insula	13	43	-12	9	15.05
Putamen	*	-24	-7	6	5.08	Lateral Globus Pallidus	*	15	0	2	8.58
Medial Dorsal Nucleus	*	-11	-20	13	13.56	Medial Dorsal Nucleus	*	8	-16	12	7.20

Note: BA = Brodmann Area

Table 10 (continued). Connectivity of the Left Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Cerebellum						
Culmen	*	-40	-45	-20	7.49	Culmen	*	19	-42	-13	9.44
Culmen of Vermis	*	-4	-61	-2	6.90	Fastigium	*	7	-49	-19	12.64
Fastigium	*	-9	-53	-19	10.39	Dentate	*	15	-61	-19	11.07
Cerebellar Tonsil	*	-13	-60	-35	13.11	Cerebellar Tonsil	*	15	-49	-42	6.69
Declive	*	-24	-58	-17	8.90	Declive	*	14	-79	-16	10.15
Declive of Vermis	*	-2	-76	-18	13.79	Inferior Semi-Lunar Lobule	*	16	-64	-42	9.49
Pyramis	*	-24	-70	-31	8.96	Pyramis	*	20	-70	-30	8.73
Tuber	*	-36	-57	-29	10.63	Tuber	*	43	-59	-23	9.33

Note: BA = Brodmann Area

Table 11. Connectivity of the Right Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Frontal Lobe						
Middle Frontal Gyrus	8	-27	14	39	13.98	Medial Frontal Gyrus	6	15	-12	49	6.55
Paracentral Lobule	5	-4	-44	58	7.34	Middle Frontal Gyrus	6	26	-9	59	5.07
						Superior Frontal Gyrus	6	11	-13	63	8.62
					Limbic Lobe						
Anterior Cingulate	32	-5	37	24	8.81	Cingulate Gyrus	31	7	-58	28	25.68
Cingulate Gyrus	31	-3	-58	28	12.41	Parahippocampal Gyrus	19	35	-45	-5	10.12
Parahippocampal Gyrus	30	-16	-37	3	9.79	Posterior Cingulate	23	4	-56	15	22.47
					Temporal Lobe						
Fusiform Gyrus	37	-40	-50	-18	6.86	Middle Temporal Gyrus	20	53	-42	-13	7.24
Middle Temporal Gyrus	21	-45	6	-26	9.77	Transverse Temporal Gyrus	41	34	-26	10	9.40

Note: BA = Brodmann Area

Table 11 (continued). Connectivity of the Right Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Parietal Lobe						
Inferior Parietal Lobule	40	-43	-49	39	6.12	Precuneus	7	8	-61	43	9.56
Postcentral Gyrus	3	-18	-29	60	5.48						
Precuneus	7	-10	-60	56	8.51						
					Occipital Lobe						
Cuneus	*	0	-79	24	6.52	Cuneus	18	12	-76	24	5.25
Lingual Gyrus	18	-16	-81	-14	7.16	Lingual Gyrus	18	2	-80	5	5.07
						Middle Temporal Gyrus	19	47	-60	15	8.07
						Precuneus	31	14	-66	18	7.08

Note: BA = Brodmann Area

Table 11 (continued). Connectivity of the Right Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Cerebellum						
Culmen	*	-33	-35	-20	9.82	Dentate	*	16	-60	-20	9.78
Fastigium	*	-9	-53	-19	9.83	Culmen	*	10	-35	-18	14.61
Cerebellar Tonsil	*	-22	-57	-40	15.01	Cerebellar Tonsil	*	22	-43	-32	15.88
Declive	*	-24	-58	-18	8.71	Declive	*	7	-67	-14	10.80
Declive of Vermis	*	-2	-76	-18	12.19	Inferior Semi-Lunar Lobule	*	24	-71	-39	5.57
Inferior Semi-Lunar Lobule	*	-13	-63	-35	9.81	Uvula	*	4	-66	-31	10.10
Pyramis	*	-24	-70	-31	10.39						

Note: BA = Brodmann Area

Table 11 (continued). Connectivity of the Right Posterior Cingulate in Mild Cognitive Impairment

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Sub-Lobar						
Caudate Head	*	-9	15	2	12.10	Insula	13	45	-19	16	9.00
Insula	13	-36	-19	16	8.17	Lateral Globus Pallidus	*	25	-10	-2	5.19
Putamen	*	-31	-18	-5	6.69	Thalamus	*	5	-14	5	18.10
Thalamus	*	-10	-8	15	19.34						

Note: BA = Brodmann Area

Table 12. Connectivity of the Left Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
Frontal Lobe											
Medial Frontal Gyrus	9	0	33	32	7.69	Medial Frontal Gyrus	10	17	41	13	8.26
Middle Frontal Gyrus	6	-28	-11	46	4.81	Precentral Gyrus	6	49	-8	9	11.91
Paracentral Lobule	31	0	-20	44	7.48						
Precentral Gyrus	4	-36	-24	54	6.55						
Limbic Lobe											
Anterior Cingulate	32	-5	46	5	7.76	Anterior Cingulate	32	4	39	20	15.74
Cingulate Gyrus	24	-10	-7	40	7.07	Cingulate Gyrus	9	13	26	33	6.86
Parahippocampal Gyrus	34	-30	3	-16	8.87	Parahippocampal Gyrus	36	30	-34	-14	11.25
Posterior Cingulate	31	-10	-55	23	32.7						
Amygdala	*	-23	-2	-22	5.66						

Note: BA = Brodmann Area

Table 12 (continued). Connectivity of the Left Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Temporal Lobe						
Middle Temporal Gyrus	20	-51	-41	-11	7.96	Superior Temporal Gyrus	39	46	-60	20	18.13
Superior Temporal Gyrus	22	-46	-13	1	10.78						
					Parietal Lobe						
Inferior Parietal Lobule	40	-41	-37	45	6.7	Precuneus	39	40	-64	34	14.61
Postcentral Gyrus	3	-33	-20	44	9.07	Superior Parietal Lobule	7	37	-65	45	5.71
Precuneus	19	-33	-63	42	11.33						
					Occipital Lobe						
Precuneus	31	-22	-81	29	5.52	Cuneus	19	4	-78	30	8.33
						Precuneus	31	15	-61	28	17.11

Note: BA = Brodmann Area

Table 12 (continued). Connectivity of the Left Posterior Cingulate in Alzheimer's Disease

Region	Left BA	x	y	z	Peak *t* score	Region	Right BA	x	y	z	Peak *t* score
						Cerebellum					
Culmen	*	-15	-43	-17	9.43	Culmen	*	18	-41	-14	11.89
Fastigium	*	-9	-58	-20	7.65	Cerebellar Tonsil	*	10	-52	-31	8.21
Declive	*	-24	-60	-11	4.88	Declive	*	3	-59	-14	6.57
Inferior Semi-Lunar Lobule	*	-8	-64	-39	4.87	Inferior Semi-Lunar Lobule	*	10	-75	-37	7.46
Pyramis	*	-30	-67	-34	6.03	Pyramis	*	34	-72	-32	6.76
Tuber	*	-28	-74	-27	5.62	Uvula	*	12	-65	-29	10.13
Uvula	*	-11	-65	-28	8.22						

Note: BA = Brodmann Area

Table 12 (continued). Connectivity of the Left Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Sub-Lobar						
Caudate Body	*	-10	11	16	10.58	Caudate Head	*	13	15	3	7.34
Insula	13	-34	-32	21	9.83	Putamen	*	20	2	12	8.86
Lateral Globus Pallidus	*	-24	-17	5	8.21	Thalamus	*	3	-8	5	12.15
Thalamus	*	-7	-9	9	11.73						

Note: BA = Brodmann Area

Table 13. Connectivity of the Right Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Frontal Lobe						
Inferior Frontal Gyrus	9	-47	0	25	7.74	Cingulate Gyrus	32	2	13	35	6.15
Medial Frontal Gyrus	*	-5	-11	56	6.00	Medial Frontal Gyrus	6	14	-11	51	6.20
Middle Frontal Gyrus	6	-17	-4	58	7.72	Middle Frontal Gyrus	6	31	-9	58	7.35
Precentral Gyrus	4	-46	-15	39	8.61	Precentral Gyrus	6	41	-7	37	7.83
					Limbic Lobe						
Anterior Cingulate	32	-5	36	10	6.49	Anterior Cingulate	32	4	35	22	16.16
Cingulate Gyrus	23	-4	-34	28	21.66	Cingulate Gyrus	31	4	-27	38	15.63
						Parahippocampal Gyrus	30	11	-49	3	8.16
						Posterior Cingulate	23	2	-55	14	32.70

Note: BA = Brodmann Area

Table 13 (continued). Connectivity of the Right Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Temporal Lobe						
Superior Temporal Gyrus	39	-47	-56	23	7.72	Angular Gyrus	39	38	-75	30	7.47
Transverse Temporal Gyrus	41	-43	-24	10	6.92	Fusiform Gyrus	*	37	-45	-17	6.56
						Superior Temporal Gyrus	*	58	-1	-6	5.19
					Parietal Lobe						
Inferior Parietal Lobule	40	-57	-31	24	8.19	Inferior Parietal Lobule	40	51	-29	31	6.88
Postcentral Gyrus	3	-31	-21	47	16.40	Precuneus	31	4	-49	33	22.87
Precuneus	19	-32	-63	42	16.20	Superior Parietal Lobule	7	39	-55	49	6.94
Superior Parietal Lobule	7	-33	-48	51	7.42						

Note: BA = Brodmann Area

Table 13 (continued). Connectivity of the Right Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Occipital Lobe						
Lingual Gyrus	17	-14	-92	-2	6.76	Cuneus	19	5	-78	30	10.15
Middle Temporal Gyrus	19	-36	-57	16	16.34	Inferior Occipital Gyrus	18	36	-82	-6	4.83
						Middle Occipital Gyrus	18	22	-85	-8	8.13
					Sub-Lobar						
Caudate Body	*	-13	12	16	12.03	Caudate Body	*	17	17	7	8.31
Lateral Globus Pallidus	*	-24	-17	5	10.53	Claustrum	*	34	-7	-4	5.08
Thalamus	*	-7	-9	9	14.30	Putamen	*	24	11	-1	9.95

Note: BA = Brodmann Area

Table 13 (continued). Connectivity of the Right Posterior Cingulate in Alzheimer's Disease

	Left						Right				
Region	BA	x	y	z	Peak *t* score	Region	BA	x	y	z	Peak *t* score
					Cerebellum						
Culmen	*	-13	-42	-18	11.27	Culmen	*	18	-44	-15	12.55
Cerebellar Tonsil	*	-34	-58	-39	5.34	Cerebellar Tonsil	*	34	-62	-31	10.51
Declive	*	-34	-58	-16	6.94	Declive	*	28	-60	-22	7.00
Inferior Semi-Lunar Lobule	*	-16	-74	-36	9.63	Declive of Vermis	*	2	-73	-12	7.11
Pyramis	*	-27	-71	-32	8.29	Inferior Semi-Lunar Lobule	*	10	-73	-37	8.76
Tuber	*	-40	-64	-27	5.49	Pyramis	*	14	-65	-29	12.06
Uvula	*	-11	-66	-31	11.08	Uvula	*	24	-73	-25	6.54
Uvula of Vermis	*	0	-66	-32	6.84						

Note: BA = Brodmann Area

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