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Hippocampal and Anterior Cingulate Cortex Volumes in Amnestic and Non-Amnestic Mild Cognitive Impairment

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LOYOLA UNIVERSITY CHICAGO

HIPPOCAMPAL AND ANTERIOR CINGULATE CORTEX VOLUMES IN
AMNESTIC AND NON-AMNESTIC MILD COGNITIVE IMPAIRMENT

A THESIS SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
MASTER OF ARTS

PROGRAM IN CLINICAL PSYCHOLOGY

BY

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CHICAGO, IL

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ABSTRACT

Mild Cognitive Impairment (MCI) is a syndrome thought to fall between cognitively normal aging and dementia. Although much research has investigated the structural neuroimaging correlates of amnesic MCI, little research has been done on the imaging correlates of non-amnesic MCI. Even less research has examined the anterior cingulate cortex (ACC), a region important in executive functions (EFs), in these patients. This study attempted to address this gap by examining hippocampal and ACC volumes among amnesic and non-amnesic MCI patients and cognitively normal controls. Those with amnesic MCI were expected to have smaller hippocampal volumes than controls and those with non-amnesic MCI, while those with non-amnesic MCI were expected to have smaller ACC volumes than controls or those with amnesic MCI. Fifty-seven participants, 21 cognitively normal controls, 20 with amnesic MCI, and 16 with non-amnesic MCI, were recruited. Contrary to hypotheses, mixed-model analyses of variance revealed no significant differences among the diagnostic groups in ACC or hippocampal volumes. These results suggest that the ACC is not involved in MCI or that it is affected only in later disease stages. The executive dysfunction seen in some cases of non-amnesic MCI may be due to atrophy in other brain regions associated with EF or may be due to white matter changes in these regions. However, the study's small, highly educated sample and the possibility that amnesic MCI patients also exhibited executive

dysfunction may also have impacted results. Future research should longitudinally examine MCI patients with and without executive dysfunction to determine the role of the ACC and other brain regions involved in EF and should also investigate the correlation between neuropsychological test scores and volumes in these brain regions.

CHAPTER ONE

INTRODUCTION

Mild Cognitive Impairment (MCI) is a concept initially created to identify patients who were experiencing cognitive impairments consistent with, but not fully qualifying for, a diagnosis of dementia (Petersen & Morris, 2005). Although functioning fairly well, these patients were often found to be at increased risk of developing dementia, particularly Alzheimer's disease (AD) (Davis & Rockwood, 2004; Petersen & Morris, 2005; Petersen & O'Brien, 2006). The development of the concept of MCI allowed researchers the opportunity to identify possible AD patients before they became demented (Davis & Rockwood, 2004; Petersen & O'Brien, 2006; Winblad et al., 2004). Because of its close link with AD, MCI was characterized as primarily amnesic, involving memory loss not accounted for by simple aging, while functional skills and general cognitive abilities remain intact (Davis & Rockwood, 2004; Rosenberg & Lyketsos, 2008; Winblad et al., 2004).

Over the years, the concept of MCI has evolved to include cognitive deficits beyond the memory domain, including executive dysfunction, language, and visuospatial impairments (Petersen, 2004; Winblad et al., 2004). The expansion of the concept of MCI to include these non-amnesic categories allowed clinicians and researchers to

identify a wider range of at-risk patients. In fact, research has shown that some patients who eventually go on to develop AD may initially experience non-memory deficits in the absence of memory loss (Storandt, Grant, Miller, & Morris, 2006). In addition, some researchers have posited that the non-amnesic category of MCI may include prodromes of other forms of dementia, including Frontotemporal Dementia (FTD), dementia with Lewy Bodies, and Vascular dementia (Busse, Hensel, Hugne, Angermeyer, & Riedel-Heller, 2006; Petersen, 2004; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006).

Since the revision of the diagnostic criteria for MCI, much research has attempted to elucidate the relationship between the amnesic and non-amnesic categories as well as their relation to different forms of dementia. Studies have overwhelmingly supported the link between amnesic MCI and Alzheimer's disease, finding that amnesic MCI patients may convert to AD at a rate of 16-41% per year (Gauthier et al., 2006). This is in stark comparison to the much smaller conversion rate of 1-2% per year in the general population (Petersen et al., 2001). In contrast, studies on non-amnesic MCI have been less clear-cut. Some have found no difference from amnesic MCI in the rate of conversion to AD (e.g., Fischer et al., 2007; Loewenstein et al., 2006), while others have found that patients with non-amnesic MCI are more likely to convert to other forms of dementia than their amnesic counterparts (e.g., Busse et al., 2006; Yaffe et al., 2006).

Moreover, research comparing the two subtypes has found several differentiating factors beyond domains of impairment. As previously mentioned, some studies have found the two subtypes to convert to different types of dementia at varying rates (Busse et al., 2006; Yaffe et al., 2006). Studies on biological markers have also found that those

with the amnesic type are more likely to have the APOE ϵ 4 allele, a variant of a gene consistently associated with an increased risk for the development of AD (Manly, Bell-McGinty, Tangy, Schupf, Stern, & Mayeux, 2005). Additionally, the rate of reversion back to “normal” cognition and, as a result, the stability of the diagnostic category, has been found to vary by subtype (Busse et al., 2006; Jak et al., 2009; Loewenstein, Acevedo, Agron, & Duara, 2007). Jak et al. (2009), in a study comparing clinical outcomes of populations identified by different sets of diagnostic criteria for MCI, found that the non-amnesic subtype was the most unstable diagnosis, with more patients reverting back to normal than in any other category. Despite the abundance of research on amnesic and non-amnesic MCI, it is still unclear whether these subtypes preferentially lead to different forms of dementia, and what causes some to revert to normal, remain cognitively stable, or convert to dementia.

In an attempt to address some of these inconsistencies in the literature, researchers have frequently used structural and functional neuroimaging to explore the anatomical and functional substrates of the subtypes of MCI. Not surprisingly, structural MRI studies have frequently found that patients with amnesic MCI exhibit atrophy in medial temporal lobe regions, primarily the hippocampus and entorhinal cortex (e.g., Becker et al., 2006; Bell-McGinty et al., 2005; Caffarra, Ghetti, Concari, & Venneri, 2008; Jack et al., 2004; Pa et al., 2009; Pennanen et al., 2005; Stoub et al., 2006; Whitwell et al., 2007). These brain areas belong to the limbic system, and are known to be one of the main processing sites for memory encoding within the brain.

Importantly, hippocampal and entorhinal cortex atrophy are characteristically associated with AD progression. In fact, medial temporal lobe structures are the first to experience cell death in AD, presumably through the effects of neurofibrillary tangles and amyloid plaques (Mesulam, 2000). These neuropathologies, which are required for a definitive diagnosis of AD, form within and around neurons and disrupt their functioning, leading to disruptions in cell-cell communication and eventual neuron death. Consequently, hippocampal atrophy has been shown to be a harbinger of cognitive decline in those with AD as well as MCI (Bell-McGinty et al., 2005; Jack et al., 2004; Karas et al., 2008).

Functional neuroimaging studies have supported the conclusions reached through structural imaging. Several researchers, using functional MRI, have found those with amnesic MCI to exhibit reduced activity in hippocampal and entorhinal regions (Johnson, 2004; Johnson et al., 2006; Machulda et al., 2003; Petrella et al., 2006; Small et al., 1999). Such reduction in activity presumably indicates a decrease in neuronal functioning within the affected regions compared to cognitively normal controls. This decrease is most likely due to the neuronal damage and death caused by AD-related neuropathologies. In support, functional imaging studies have found similar activity reductions in medial temporal lobe regions in patients with AD. However, other research has indicated that patients with MCI may actually exhibit increased activation than controls in medial temporal lobe areas, including the hippocampus (see Pihlajamaki, Jauhiainen, & Soininen, 2009, and Ries et al., 2008 for reviews). Researchers have conceptualized these discrepant findings as evidence for a compensatory response, in

which patients with MCI recruit more brain areas in order to counteract the effects of early memory loss (Ries et al., 2008).

Imaging studies with non-amnesic MCI patients are not as common as those with amnesic patients. However, of those that have been completed, the non-amnesic subtype has frequently been found to be associated with atrophy and reduced metabolism in several frontal and temporal lobe regions, including the anterior cingulate and hippocampus (Caffarra et al., 2008; Jauhiainen et al., 2008; Johnson, Vogt, Kim, Cotman, & Head, 2004; Machulda et al., 2009; Nobili et al., 2008; Pa et al., 2009; Whitwell et al., 2007). Frontal lobe regions of the brain have been found to be associated with executive functions, including the ability to plan, organize, direct and sustain attention, inhibit unwanted behavior, and mentally shift between mindsets. The involvement of these regions in patients with non-amnesic MCI is presumably associated with their functional deficits. For non-amnesic patients suffering from executive dysfunction, for example, the executive skills in which they are impaired are also those that are subserved by frontal lobe regions.

The anterior cingulate cortex (ACC) in particular, a structure located in the medial prefrontal cortex, is believed to be generally involved in executive functioning (Carter, 2000; Koo et al., 2008; Mesulam, 2000; Rosen et al., 2005). The ACC has commonly been subdivided into subcallosal, rostral, and dorsal subregions, each with its own specialization. Studies have found the subcallosal region to be involved in mood (Koo et al., 2008) while the rostral region is implicated in affective regulation (Bush, 2000) and the dorsal region in attention and executive control (Koo et al., 2008). Despite its

relevance, very few studies have investigated the ACC in MCI patients. Of those that did pursue this line of research, they found evidence of atrophy or reduced metabolism in this region in patients with non-amnesic MCI, coinciding with the patients' cognitive deficits (Caffarra et al., 2008; Jauhiainen et al., 2008; Johnson, et al., 2004).

Although studies have independently examined the neuroanatomical substrates of amnesic and non-amnesic MCI, few studies have attempted to compare the regional volumes of patients with each subtype. Those that have examined this question have reported discrepant findings. Moreover, despite its relevance due to the impairments associated with each subtype, no study to date has compared ACC and hippocampal volumes in amnesic and non-amnesic MCI patients. The purpose of this study is to address this gap in the literature by comparing the volumes of two manually outlined regions of interest (ROIs), the ACC, divided into rostral and dorsal subregions, and the hippocampus, among amnesic and non-amnesic MCI patients and cognitively normal controls.

CHAPTER TWO

REVIEW OF RELATED LITERATURE

Historical Perspectives on MCI

Original Conceptualization and Diagnostic Criteria

The concept of Mild Cognitive Impairment (MCI) was first created in the 1980's by Petersen and colleagues (Petersen & Morris, 2005). MCI is a syndrome originally conceptualized as a risk factor for the later development of Alzheimer's disease (AD) (Davis & Rockwood, 2004). Alzheimer's disease is a progressive disease that is usually first diagnosed in those age 65 and above (Mesulam, 2000). The hallmark symptom of AD is memory loss, which usually begins as a decline in short-term episodic memory, with relative preservation of remote episodic memories and semantic memory (Mesulam, 2000). As the disease progresses, however, even remote memories are prone to decay, and the ability to create new memories is severely impaired (Mesulam, 2000). Other cognitive domains, including language and visuospatial abilities, are also affected in later stages of the illness (Mesulam, 2000). As a large percentage of the population reaches older ages, it becomes important to identify AD as early as possible, in order to implement treatments in initial stages of the illness. Thus, if MCI truly is a prodromal stage of AD, MCI patients may represent a useful target population for preventative

treatments for AD. This aspect of MCI has made it one of the most widely studied models of cognitive decline.

Following its close ties to AD, MCI was historically thought of as an amnesic syndrome, characterized by progressive memory loss in the absence of functional impairments or general cognitive decline. Petersen (e.g., Petersen, Smith, & Waring, 1999) first proposed formal diagnostic criteria for MCI, which required a subjective memory complaint usually elicited during a clinical interview, along with intact general cognitive functioning. This has been operationalized in several different ways, most commonly as a score greater than 24 on the Mini Mental State Exam (MMSE) (Storandt et al., 2006). In addition to a subjective memory complaint, objective memory impairment must also be observed through neuropsychological testing. Although varied in the literature, this is usually operationalized as a score greater than 1.5 standard deviations below age and education-based norms on a test of delayed recall (Storandt et al., 2006). Despite memory deficits, to be diagnosed with MCI according to Petersen's criteria a person must exhibit preserved ability to perform activities of daily living, usually defined as scores less than 1 on all 6 domains of the Clinical Dementia Rating Scale (CDR) (Storandt et al., 2006). Finally, a person with MCI cannot also be diagnosed with dementia. To ensure this, MCI patients are usually required to achieve a Global CDR score less than one (Storandt et al., 2006).

Although the clinical interview is frequently used in making an MCI diagnosis, clinicians and researchers also utilize alternative methods to supplement clinician judgment when assessing for possible MCI (Gauthier et al., 2006; Petersen et al., 2001).

Neuropsychological testing is a valuable tool for diagnosis, as its sensitivity allows the clinician to detect possible cases of MCI before behavioral or functional deficits are apparent (Petersen et al., 2001). However, because of individual differences in cognitive performance and MCI presentation, a diagnosis cannot be based upon testing information alone, and clinical judgment including consideration of the patient's history and symptomatology is always necessary (Petersen et al., 2001).

Structural and functional neuroimaging may also be used to assist the clinician in detecting cases of MCI. Structural magnetic resonance imaging (MRI) has shown that atrophy in the hippocampus, a structure located in the limbic area of the brain and integral for memory (Mesulam, 2000), can predict progression from cognitively intact to a diagnosis of MCI, and from MCI to AD (Bell-McGinty et al., 2005; Jack et al., 2004; Karas et al., 2008; Petersen et al., 2001). In addition, studies have found that atrophy in the entorhinal cortex, which is adjacent to and extensively interconnected with the hippocampus (Mesulam, 2000), can predict conversion of MCI to AD, perhaps beyond the ability of hippocampal atrophy to do so (de Toldedo-Morrell et al., 2004; Petersen et al., 2001; Stoub et al., 2005). The utility of assessing entorhinal cortical atrophy is still under debate, however, as other studies have not found any additional diagnostic sensitivity contributed by entorhinal cortex imaging beyond that gained from measuring hippocampal volumes (Jack et al., 2005; Stoub et al., 2006).

Similarly, functional neuroimaging may be useful for the diagnosis of MCI. Research has shown that those with this diagnosis exhibit reduced activation in the posterior cingulate and temporoparietal regions of the brain (Petersen et al., 2001). Yet,

as with the use of neuropsychological test batteries, a diagnosis of MCI cannot be made with neuroimaging data alone, particularly because the atrophy and activity reductions associated with MCI may also be found in other cognitive disorders (Petersen et al., 2001).

Initially, some researchers questioned whether MCI was not equivalent to a single score on a clinical rating scale like the CDR. Some did indeed propose that MCI was synonymous with a CDR score of 0.5, which represents questionable dementia. However, research has shown that MCI diagnostic criteria and the criteria to reach a score of 0.5 on the CDR identify different patient populations (Petersen et al., 2001). Similarly, although a score of two on the Global Deterioration Scale (GDS) represents a person who is cognitively normal but with subjective memory complaints, a description that may fit well with MCI diagnostic criteria, research has shown that MCI patients are not reliably identified by this category, and may receive GDS scores of 2 or 3, representing mild dementia (Petersen et al., 2001). Such research has shown that, although clinical rating scales are important tools for gauging a person's cognitive abilities, there is no direct agreement between a person's score and an MCI diagnosis.

Early Research

MCI is thought to be a pathological process distinct from normal aging (Knopman, Boeve, & Petersen, 2003; Petersen, 2006; Petersen et al., 2001). In support, patients who die with a diagnosis of MCI, when autopsied, have been found to manifest neuropathologies associated with dementia, such as neurofibrillary tangles and amyloid plaques in the medial temporal lobe (Geda et al., 2006; Petersen, 2006; Petersen et al.,

2001). Although these pathologies may also be found in normal aging, the degree to which they occur in MCI patients is more extensive than that due to age-related changes.

Furthermore, studies on normal aging have indicated that, although slight cognitive decline may occur with aging, this decline is a result of physiological aging instead of a pathological disease process (Petersen et al., 2001). In fact, some research has shown that once those with incipient dementia are removed from a sample of those experiencing normal aging, the remainder of the sample does not exhibit cognitive decline in areas such as delayed recall (Knopman et al., 2003). Despite this finding, much research has suggested that aging is associated with some cognitive decline, and that the memory loss most commonly associated with aging is in rote, short term recall, of the kind assessed by a test of Digit Span (Knopman et al., 2003). This is similar to the pattern of memory loss experienced in patients with MCI. However, as opposed to MCI patients, when allowed sufficient time to learn the material, older adults have been found to be just as capable of recalling the learned material as their younger counterparts (Knopman et al., 2003).

Research has also indicated that, even among elderly experiencing age-related cognitive decline, the progression to AD is no different than in the older adult population without cognitive deficits (Petersen et al., 2001). In contrast, those with MCI have been shown to progress to AD at elevated rates compared to the general population as well as those who are normally aging while suffering from cognitive deficits (Petersen et al., 2001). However, other research has suggested that older adults with age-related cognitive decline may in fact progress to dementia at a higher rate than in healthy, cognitively

intact populations (Petersen et al., 2001). It is therefore unclear whether cognitive decline, including the development of memory impairment, is intrinsic to aging. Despite this, research has generally supported the assertion that MCI is not an extension of normal aging, and is instead a distinct, pathological process.

Early research on MCI determined that those with this diagnosis progressed to AD at rates of 10-15% per year, much higher than the 1-2% annual progression rate in the general population (Petersen et al., 2001). Moreover, research by the Mayo Alzheimer's Disease Research Center in Rochester, MN, reported that 80% of a sample of patients with MCI converted to AD over a 6-year period (Petersen et al., 2001). Conversely, later studies indicated that not all patients diagnosed with MCI exhibited the same trajectory of decline, and many converted to dementias other than that of the Alzheimer type (Petersen et al., 2001).

Discoveries such as these have led researchers to acknowledge MCI as a highly heterogeneous category; some with the diagnosis convert to AD, some to other forms of dementia, while others remain stable or actually improve (Busse et al., 2006; Jak et al., 2009; Knopman et al., 2003; Loewenstein et al., 2006; Petersen et al., 2001; Winblad et al., 2004). Although differences in research methodology and diagnostic criteria likely contribute to this heterogeneity, it also appears that MCI may constitute a population of individuals with diverse pathologies (Petersen et al., 2001). In fact, studies have shown that, despite the exclusive emphasis on memory impairment in early conceptualizations of MCI, MCI patients with isolated memory impairments are rare. It is much more common to see patients with multiple domains of impairment (Nordlund et al., 2005).

Current Perspectives on MCI and Revision of Diagnostic Criteria

Despite earlier conceptualizations of MCI emphasizing memory loss and association with AD, later research has revealed not only that other non-memory cognitive domains may be impaired in MCI, but also that the clinical outcome of MCI was heterogeneous and included dementias beyond AD. Spurred by such research and in order to clarify the construct of MCI, the International Working Group on Mild Cognitive Impairment convened and modified the diagnostic criteria for MCI (Petersen, 2004; Winblad et al., 2004).

The working group acknowledged that MCI represented a heterogeneous category, particularly in symptomatology (Winblad et al., 2004). Research has found that symptoms of MCI may extend beyond memory into other cognitive domains and that a person may have more than one type of impairment. Thus, the construct of MCI could include either a primary memory impairment, a memory impairment accompanied by non-memory impairments, or decline in a non-memory domain, such as executive functioning, language, or visuospatial skills. The working group also noted the findings of recent studies suggesting etiological heterogeneity of the MCI population. Based on such findings, the working group concluded that the symptoms associated with MCI may be due to AD, but may also be due to other neurodegenerative disorders such as Parkinson's disease or Frontotemporal Dementia. Additionally, MCI could be due to other problems, such as vascular disease or psychiatric disorders (Winblad et al., 2004).

In the context of these advances in the knowledge concerning MCI, the working group proposed several recommendations, including the need to adapt the diagnostic criteria of MCI to address current research findings. The proposed criteria allowed for four specific diagnoses within the MCI population: amnesic, single domain; amnesic, multiple domain; non-amnesic, single domain; and non-amnesic, multiple domain. Such revisions would allow prodromal AD patients with non-amnesic impairments to be identified, as well as patients suffering from the early stages of a non-AD dementia (Winblad et al., 2004).

The working group's recommendation for the revised general criteria for a diagnosis of MCI required that the patient not be cognitively normal. This should be decided through the use of clinical judgment on the part of the clinician, along with evidence of cognitive abnormality from the MMSE. However, despite cognitive abnormality, the patient cannot meet DSM-IV or ICD-10 criteria for dementia. Additionally, there must be evidence of cognitive decline; a person with longstanding cognitive deficits, such as those with Mental Retardation or Traumatic Brain Injury, would therefore not qualify for a diagnosis of MCI. Whatever cognitive deficits the patient experiences should be a decline from a higher level of previous functioning. This should be gathered from a detailed history taken from the patient, and preferably corroborated by another source. Cognitive decline, as well as significant impairment in one or more cognitive domains as compared to age-adjusted norms, should also be supported by objective neuropsychological assessment. Furthermore, the revised criteria required that the patient not exhibit significant functional impairment in activities of daily

living. However, as opposed to early criteria which did not allow evidence of any functional deficits, the working group's revised criteria recognized that those with MCI may show minor impairment in complex tasks (Winblad et al., 2004). In fact, recent research has shown that patients with well-defined MCI exhibited slight impairment in complex tasks requiring memory and executive functions, although they still maintained the ability to function independently (Rosenberg & Lyketsos, 2008).

Once the probable diagnosis of MCI has been determined, the specific MCI subtype of the patient should be assessed through neuropsychological testing. Although no specific assessments have been recommended for MCI subtype diagnosis, at least one form of delayed recall is commonly used to assess for memory impairment (Jak et al., 2009). Neuropsychological testing would also be used to assess other cognitive domains, such as visuospatial, executive function, and language domains. Although no universally accepted cut-off exists (Jak et al., 2009), performance 1.5-2.0 standard deviations below age- and education-adjusted norms is commonly required for a determination of the "significant" impairment required for a diagnosis of MCI. If the patient is only impaired in the memory domain, they would be diagnosed with amnesic MCI, single domain, while a patient with a primary impairment in memory as well as deficits in other domains would receive the diagnosis of amnesic MCI, multiple domain. Similarly, a patient exhibiting impairment in a non-memory domain alone would be diagnosed with non-amnesic MCI, single domain, while a patient impaired in multiple non-amnesic domains would be diagnosed with non-amnesic MCI, multiple domain.

Several studies have examined the implications of the revised diagnostic criteria for identification of patient populations. Storandt et al. (2006) conducted a study examining differences in clinical outcome among patients diagnosed according to the original criteria, which identified patients with amnesic MCI, the revised criteria, which identified those with memory deficits as well as non-memory impairments, and patients that did not yet meet criteria for MCI (termed pre-MCI) (Storandt et al., 2006). All patients had a CDR rating of 0.5 at the beginning of the study, and all patients, along with a collateral source, were given a semi-structured interview. The original MCI criteria operationalized an objective memory impairment by requiring patients to score at least 1.5 standard deviations below the mean for the reference group on the Logical Memory subtest of the Wechsler Memory Scale (WMS). In contrast, the revised criteria assessed objective cognitive deficits in three areas. Memory was assessed using the Information subscale from the Wechsler Adult Intelligence Scale (WAIS), the Associate Learning and Logical Memory subscales from the WMS, and the Boston Naming Test. Visuospatial abilities were assessed using the Block Design and Digit Symbol subscales from the WAIS and Trailmaking Test A. Executive functions were measured using the Mental Control and Digit Span Forward subscales of the WMS and Word Fluency using the letters S and P. Similar to the cut-off scores used with the original criteria, objective impairment was defined as performance of at least 1.5 standard deviations below the performance of an age-adjusted reference group. Finally, the pre-MCI group was identified primarily by clinician judgment using the interview. The group had a CDR score of 0.5, but did not meet either set of criteria for MCI (Storandt et al., 2006).

As expected, the two sets of diagnostic criteria identified dissimilar MCI populations. The original criteria identified 32 patients from the sample as having MCI, while the revised criteria identified 90 patients from the same sample as having MCI. Despite differences in the size of the identified populations, both the samples declined at comparable, elevated rates compared to those with pre-MCI. The patients identified by the original criteria had elevated decline on measures of general cognitive functioning, memory, visuospatial abilities, and executive functions. Interestingly, the group diagnosed according to the revised criteria declined at an elevated rate for all the above measures except executive functions, for which there was no difference between the MCI and pre-MCI groups. Moreover, the time for both groups to advance to a CDR rating of 1 was comparable, and both of the groups took nearly half the time to advance to this point as the pre-MCI group (Storandt et al., 2006).

Of those patients who could be examined for neuropathological evidence of dementia at autopsy, 100% of the patients in the original criteria group had neuropathological AD. In contrast, 90% of the revised criteria group had confirmed AD, with one patient having hippocampal sclerosis without AD, and another having vascular dementia and Lewy Body disease without AD. Ninety-one percent of those from the pre-MCI group had AD, while three were neuropathologically normal, and one had corticobasal degeneration (Storandt et al., 2006).

Thus, this study provides evidence that although slight differences may exist between samples identified by the original and revised MCI criteria, several similarities between the groups are also prominent. In addition, this study revealed that AD can begin

with deficits in non-memory domains, as several of those with non-amnesic MCI were found to have confirmed AD upon autopsy. This finding supports the revision of diagnostic criteria to allow for non-amnesic subtypes, which may allow identification of those with prodromal AD who do not initially present with the typical array of memory deficits. Finally, because more patients in the sample identified by the revised criteria converted to non-AD pathologies than those identified by the original, amnesic MCI criteria, it may be that non-amnesic subtypes can also represent prodromal stages for non-Alzheimer's dementias (Storandt et al., 2006).

However, the findings of Storandt et al. (2006) may have been affected by several factors related to criteria operationalization known to affect the outcome of MCI samples. Indeed, despite the recommendation of the working group for a reconstruction of MCI diagnostic criteria, much variability still exists in the operationalization of the criteria in research on MCI (Jak et al., 2009; Petersen & Morris, 2005). A universally accepted cut-off score necessary for an MCI diagnosis has not been agreed upon, and research protocols have used cut-points ranging from 1.0-2.0 standard deviations below age-adjusted norms (Jak et al., 2009). Petersen and Morris (2005) noted that this inconsistency in the use of cut-off scores as well as the emphasis on cut-offs instead of the use of clinical judgment may have contributed to the instability occasionally found with the MCI diagnosis (Petersen & Morris, 2005).

Additionally, the number and type of neuropsychological assessments used for objective corroboration of cognitive decline have varied considerably in the literature (Jak et al., 2009; Petersen & Morris, 2005). Not only do such inconsistencies prevent

clear comparisons from being drawn across research studies, but research has also shown that the use of different criteria leads to the identification of patient populations that differ in size and clinical outcome (Jak et al., 2009). These factors may have influenced the results of the study by Storandt et al. (2006), which used a strict cut-off score of 1.5 standard deviations and required only one abnormal score for diagnosis.

Jak et al. (2009) further explored the effect of varied diagnostic criteria on the composition and outcome of MCI samples, taking into account the use of different cut-off scores and number and type of assessments required for diagnosis. The study compared the clinical outcomes of populations identified by different sets of MCI criteria and provided evidence for the importance of using multiple neuropsychological measures when assessing for MCI.

Several sets of diagnostic criteria were compared. The “historical criteria” set identified patients as having amnesic MCI if they performed 1.5 standard deviations below age-based norms on the Logical Memory subtest of the WMS-R. The “typical criteria” set identified those with MCI who scored more than 1.5 standard deviations below age-based norms in any cognitive domain, including memory. The “comprehensive criteria” diagnosed with MCI those who scored more than one standard deviation below age-based norms on two or more subtests assessing a single cognitive domain. The “liberal criteria” identified MCI in those who scored more than one standard deviation below age-based norms on a single test per cognitive domain. Finally, the “conservative criteria” diagnosed with MCI those who performed more than 1.5 standard

deviations below age-based norms on two or more tests within one cognitive domain (Jak et al., 2009).

Similar to the findings of Storandt et al (2006), the size of patient samples identified by the different criteria sets varied greatly; 10-74% of the entire sample was diagnosed with MCI depending on the criteria used. Prevalence rates of single-domain amnesic MCI in the sample varied from 8.9-12.2%, rates for non-amnesic single domain MCI varied from 2.2-31.1%, rates for multiple domain amnesic MCI ranged from 1.1-23.3%, and those for multiple-domain non-amnesic MCI varied from 0-10%. Moreover, agreement in diagnosis across the criteria sets ranged from 36-94% of the patient sample (Jak et al., 2009).

The stability of patients' diagnoses also depended on which criteria were used. Seventy to ninety-eight percent of the identified samples maintained their diagnosis over an average of 17 months. While the historical criteria exhibited the most diagnostic stability, the comprehensive criteria exhibited the least stability. Although conversion from normal to MCI contributed to this instability, many patients also reverted from an MCI diagnosis to normal (Jak et al., 2009).

Additionally, although assessment for memory impairment has been typically confined to verbal memory, Jak et al. (2009) demonstrated the importance of assessing other forms of memory, such as visual memory, as well. This provided a more sensitive assessment for MCI than a measurement of verbal memory alone. Indeed, the historical criteria, which used only a measure of verbal memory, was found to overlook patients who qualified for the diagnosis due to visual memory impairments in the absence of

deficits in verbal memory. Other studies have also found that the inclusion of visual memory measures allowed the diagnosis of patients with MCI who would have been missed had only verbal memory measures been used (Petersen, 2004).

In addition, in both memory and non-memory domains, the sensitivity and specificity of the MCI diagnosis was improved if impairment in two assessments within one cognitive domain was required for diagnosis. The use of this requirement also increased diagnostic stability over time. This supports assertions by Petersen and O'Brien (2006) and Petersen and Morris (2005) that studies' use of a diagnostic criterion which requires impairment on only one assessment for diagnosis may have contributed to the elevated rates of reversion to normalcy observed in the literature.

These findings suggest that operationalization of criteria is an important consideration for both researchers and clinicians, in that it strongly influences the sensitivity of the diagnosis as well as its stability over time. Importantly, Jak et al. (2009) also demonstrated that the revised diagnostic criteria for MCI, which included non-memory domains, allowed for the identification of a larger number of patients at risk for the development of MCI.

Subtypes of MCI

Amnesic MCI

Amnesic MCI is a syndrome characterized by a memory performance below that expected for one's age and education. The prevalence of amnesic MCI, including both multiple and single domains, has been found to range from 3 to 6% (Rosenberg & Lyketsos, 2008). More specifically, in a sample of adults age 75 and older, single domain

amnesic MCI was found in 4.5% of the sample, while multiple domain amnesic MCI was found in 5.5% of the sample (Busse et al., 2006). Although reversion to normal has been found to occur in all MCI subtypes, the rate of reversion has been found to be lowest in amnesic MCI, while the rate of conversion to AD has been found to be the highest among those with this subtype (Rosenberg & Lyketsos, 2008). Those with amnesic MCI have been found to convert to AD at rates ranging from 16-41% per year (Gauthier et al., 2006).

Several factors have been found to predict conversion to dementia, including being a carrier for the $\epsilon 4$ allele of the gene coding for apolipoprotein E, poor performance on verbal-based delayed recall tasks and executive functioning tasks, particularly when the patient is unaware of such deficits, poor baseline verbal memory, informant reports of cognitive decline, psychiatric symptoms, such as depression, and the presence of functional impairment (Gauthier et al., 2006; Petersen & O'Brien, 2006; Rosenberg & Lyketsos, 2008).

Studies have shown the APOE $\epsilon 4$ allele to be more often found in those with amnesic MCI than in other MCI subtypes (Manly et al., 2005). Because the $\epsilon 4$ allele is known to be a risk factor for AD, its prevalence in those with amnesic MCI suggests that this, more than other MCI subtypes, may be an early stage of Alzheimer's disease. To investigate this possibility, neuropathological studies of amnesic MCI have compared the amount and type of brain abnormalities in those with amnesic MCI and AD.

AD is associated with certain neuropathological features termed neurofibrillary tangles (NFTs) and amyloid plaques. Neurofibrillary tangles consist of intra-neuronal

aggregations of a phosphorylated form of tau, a protein involved in the cytoskeletal functioning of the neuron. Amyloid plaques occur when β -amyloid, a peptide involved in neuronal functioning, aggregates outside of neurons (Mesulam, 2000). Both of these neuropathologies disrupt neuronal functioning and eventually lead to cell death. Although initially focused in the medial temporal lobes of the brain, an area integral for memory function, these abnormalities eventually spread throughout the brain, with the exception of a few areas associated with motor and sensory function (Mesulam, 2000).

Studies have found that, upon autopsy, most of those with amnesic MCI did not meet neuropathological criteria for AD (Petersen et al., 2006). However, compared to those who died with a diagnosis of probable AD and those who died while cognitively normal, those with MCI had an intermediate amount of brain abnormalities, including NFTs and amyloid plaques. This was particularly salient in the medial temporal lobes (Petersen et al., 2006). This suggests that, although those with amnesic MCI do not yet meet neuropathological criteria for AD, they are also not neuropathologically equivalent to their cognitively normal peers.

Non-amnesic MCI

Non-Amnesic MCI consists of a primary deficit in a cognitive domain other than memory, such as language, executive functioning, or visuospatial functioning. The prevalence of non-amnesic MCI, including both single and multiple domains, has been found to range from 9% to 15% in a sample of adults age 75 and older (Busse et al., 2006; Jungwirth, Weissgram, Zehetmayer, Tragl, & Fischer, 2005) and to occur in 17% of an ethnically diverse sample aged 65 and older (Manly et al., 2005). The non-amnesic

subtype of MCI has been found to be either more prevalent than or equally as prevalent as amnesic MCI (Busse et al., 2006). Furthermore, multiple domain non-amnesic MCI, which was found in 2% of a sample of older adults, is much less common than the single domain non-amnesic version, which was found in 7% of the same sample (Busse et al., 2006).

According to Busse and colleagues (2006), 34% of their sample of single domain non-amnesic MCI patients and 21% of their multiple domain patients converted to some form of dementia by the end of a four-year follow-up period. Similar to other studies in this area (e.g., Fischer et al., 2007), this rate of conversion was lower than that found for patients with amnesic MCI. Of the non-amnesic patients that did convert, 60% of the single domain non-amnesic patients and 50% of the multiple domain patients converted to AD. The remainder of the single domain non-amnesic sample converted either to vascular dementia (VD) (15%) or another form of dementia (25%). The remaining 50% of the multiple domain non-amnesic sample converted to another form of dementia, other than AD or VD. Interestingly, AD was the most common form of dementia which patients converted to, except for those with multiple domain non-amnesic MCI. In this case, these patients were just as likely to convert to a different form of dementia as they were to AD (Busse et al., 2006).

These results support the hypothesis that, in the same way that amnesic MCI may be a prodromal form of AD, non-amnesic forms of MCI may be prodromal periods for other dementias, such as VD or frontotemporal dementia (FTD) (Busse et al., 2006; Yaffe et al., 2006). However, this hypothesis is still controversial and has not been

unequivocally supported (e.g., Fischer, 2007; Loewenstein, 2006). For instance, in a study examining those with MCI who converted to AD or VD, there were no differences found in the memory, language, visuospatial, or executive functioning of the two groups (Loewenstein, 2006). In other words, no neuropsychological criteria could differentiate those who later converted to AD or VD.

Although those with amnesic MCI may exhibit slight deficits in executive functioning (e.g., Rabin, 2006), executive function deficits are of particular interest in those with non-amnesic MCI (Petersen, 2004; Winblad et al., 2004). Executive functions (EFs) refer to a diverse set of higher order functions typically localized in prefrontal brain regions (Denckla, 1996). EFs have historically been thought to include planning, decision-making, judgment, and self-regulation, although the precise nature of EFs is still under debate (Han, 2008). More specifically, EFs are thought to be manifested in the ability to inhibit an unwanted response, such that one is able to consider all alternative solutions to a problem instead of impulsively acting (Han, 2008). Once a suitable decision is settled upon, EFs allow one to initiate and maintain behavior to reach a goal or solve a problem (Han, 2008). Furthermore, EFs involve the ability to generate and maintain a set of “rules” pertaining to one’s current activity in order to successfully complete a task, as well as the ability to flexibly switch between cognitive sets in response to changes in one’s goals or the demands of the environment (Han, 2008). Finally, EFs allow one to plan and organize behaviors in order to better reach goals and also to monitor oneself to determine whether proper goal-oriented behaviors are being performed (Han, 2008).

Patients with a dysexecutive form of non-amnesic MCI will exhibit impairments in executive functions. Executive impairments can have a varied presentation, reflecting the diverse nature of executive functions. In general, executive functioning impairments may include difficulties monitoring oneself, difficulties focusing attention or switching attentional focus, and difficulties in decision making.

Neuroimaging in MCI Subtypes

Amnesic MCI

Because those with amnesic MCI exhibit significant impairments in episodic memory, the hippocampus, a brain structure integral to memory functioning, has been frequently studied in these patients. This structure is shown below in Figure 1. Among other things, the hippocampus is critical for the formation of episodic memories, or the personal memories one forms throughout life (Mesulam, 2000). The hippocampus is found in the limbic system in the temporal lobes of the brain and receives inputs from brain regions associated with all sensory modalities as well as from other subcortical regions (Mesulam, 2000).

Although older memories are typically accessed through other brain regions beyond the hippocampus, the activity of the hippocampus is critical for new memories to be learned and their connections with previously learned information strengthened (Mesulam, 2000). Evidence from patients with amnesia has also suggested the importance of the hippocampus for the retrieval of previously stored memories (Mesulam, 2000). When hippocampal volume is lost, new information is not encoded as effectively nor are memories retrieved as easily (Mesulam, 2000). These findings may

help explain the difficulties patients with amnesic MCI have in learning new information and remembering recent life events.

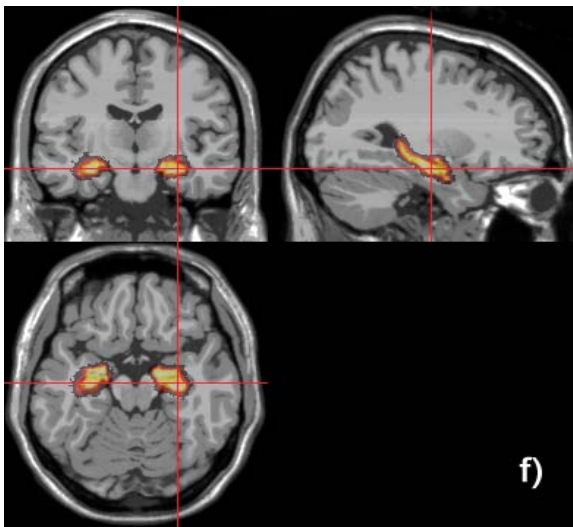


Figure 1. Coronal, sagittal, and axial views of the hippocampus (Collins, Zijdenbos, & Evans, 1998).

Magnetic Resonance Imaging (MRI) research has supported the connection between amnesic MCI and hippocampal atrophy (see Pihlajamaki et al., 2009 and Ries et al., 2008, for reviews). Several studies have indicated that patients with amnesic MCI display smaller hippocampal volumes than cognitively normal controls (e.g., Bai et al., 2009; Becker et al., 2006; Bell-McGinty et al., 2005; Schmidt-Wilcke, Poljansk, Hierlmeier, Hausner, & Ibach, 2009; Shi, Liu, Zhou, Yu, & Jiang, 2009; Stoub et al., 2006; Whitwell et al., 2007). In a meta-analytic review of 14 studies comparing hippocampal atrophy in patients with MCI, AD, and cognitively normal controls, MCI patients were found to exhibit significant hippocampal atrophy in both hemispheres as compared to controls (Shi et al., 2009). In fact, volumetric reductions between MCI

patients and controls averaged 12.9% for left hippocampi and 11.1% for right hippocampi (Shi et al., 2009). In comparison, patients with AD exhibited hippocampal volume reductions compared to controls of 24.2% and 23.1% for left and right hippocampi, respectively (Shi et al., 2009).

Becker and colleagues (2006) compared manually traced hippocampal volumes obtained through three-dimensional structural MRI in those with AD, amnesic MCI, and cognitively normal controls. Patients with both AD and amnesic MCI were found to have smaller hippocampi than controls. Moreover, the hippocampal volumes of those with AD and amnesic MCI did not differ. In a similar study by Stoub and associates (2006), hippocampal volumes of patients with amnesic MCI and cognitively normal controls were obtained using both whole brain, voxel-based morphometry and manual tracing of the hippocampus in structural MRI images. MCI patients exhibited significantly more hippocampal atrophy than controls; in addition, hippocampal atrophy was associated with decreased memory performance (Stoub et al., 2006). Bell-McGinty et al. (2005) also compared volumes of several brain regions, including the hippocampus, among two subtypes of MCI and cognitively normal controls using voxel-based morphometry. As expected, those with amnesic MCI had significantly smaller hippocampi than controls (Bell-McGinty et al., 2005). Whitwell and colleagues (2007) also used voxel-based morphometry to compare the four subtypes of MCI with cognitively normal controls; those with the amnesic variant, both single and multiple domains, were found to have smaller hippocampal volumes than controls.

Because hippocampal atrophy is a continuous, degenerative process, it is critical to consider the association between hippocampal volume and diagnosis over time. Jack and colleagues (2004) reported the results of a longitudinal study of the relationship between manually traced hippocampal volumes and conversion to MCI and AD using structural MRI. The authors found that hippocampal volumes were smaller in cognitively normal adults who later converted to MCI than in those whose diagnosis remained stable, a finding also reported in other studies (e.g., Martin, Smith, Collins, Schmitt, & Gold, 2010). Similarly, Jack et al. (2004) found that the hippocampi of patients with MCI who later converted to AD were smaller than that of MCI patients' who did not convert to AD. In addition, hippocampal atrophy was commonly visible when no significant neuropsychological or functional deficits were apparent (Jack et al., 2004). Wang, Liu, Lirng, Lin, & Wu (2009) also investigated the association of hippocampal atrophy and diagnosis over time. Their findings, similar to those of Jack et al. (2004), indicated that patients with amnesic MCI who later converted to AD had the highest hippocampal atrophy rates compared to both controls and MCI patients who remained stable. Furthermore, MCI patients whose diagnosis remained stable exhibited a rate of hippocampal atrophy intermediate of that found in controls and progressive MCI patients (Wang et al., 2009).

In a similar study using voxel-based morphometry (Karas et al., 2008), amnesic MCI patients who had converted to AD by a three-year follow-up had smaller hippocampi than MCI patients who remained stable. After controlling for demographic variables, total brain volume, and time of neuropsychological assessment, this difference

was only significant for the left hippocampus (Karas et al., 2008). Devanand and colleagues (2007) also compared hippocampal volumes among controls, MCI patients who later converted to AD, and MCI patients whose diagnosis remained stable. The authors found that hippocampal volumes of stable MCI patients were intermediate between controls and MCI patients who later converted to AD. As expected, MCI patients who converted to AD exhibited the smallest hippocampal volumes of all the groups studied (Devanand et al., 2007).

Measurement of hippocampal atrophy has also been suggested for use in the diagnosis of amnesic MCI. One study examined the diagnostic utility of manually traced hippocampal volumes in comparison to and in addition to the Mini Mental Status Exam (MMSE) for amnesic MCI patients (Slavin, Sandstrom, Tran, Doraiswamy, & Petrella, 2007). The left hippocampus was found to be more accurate in diagnosing amnesic MCI than the right hemisphere, although there were no differences between the efficacy of diagnosis with hippocampal volumes and use of the MMSE. Importantly, however, the diagnostic efficacy produced by addition of the left hippocampal volumes to MMSE scores was significantly greater than that from the MMSE alone (Slavin et al., 2007). However, in a study by Fleisher and associates (2008), hippocampal atrophy was found to predict conversion of amnesic MCI to AD with only 60% accuracy. In contrast, prediction using neuropsychological measures fared much better, with nearly 79% predictive accuracy (Fleisher et al., 2008). Thus, although hippocampal atrophy may be able to be used in a diagnostic capacity, this practice is still under scrutiny (Slavin et al., 2007).

Amnestic and Non-amnestic MCI Compared

Due to the recent development of the non-amnestic MCI subgroup, all neuroimaging studies involving non-amnestic MCI patients have compared them with amnestic MCI patients. Patients with non-amnestic MCI have typically been found to exhibit atrophy in the frontal cortex as compared with controls and amnestic MCI patients. Pa et al. (2008) used voxel-based morphometry to compare amnestic and non-amnestic MCI patients and cognitively normal controls. Those with amnestic MCI were found to have smaller hippocampal volumes than controls, while non-amnestic MCI patients were found to have smaller volumes in dorsolateral and dorsomedial prefrontal cortices than controls. However, when the two MCI subtypes were compared with one another, these differences were not maintained (Pa et al., 2008).

The findings of functional studies have generally echoed those using structural imaging. A study using SPECT reported that amnestic MCI patients exhibited reduced metabolism in the hippocampus when compared to controls; in contrast, those with non-amnestic MCI had reduced metabolism in the right frontal cortex (Nobili et al., 2008). Machulda and colleagues (2009) asked amnestic and non-amnestic patients to perform encoding and recognition memory tasks which required them to remember a complex scene while undergoing functional Magnetic Resonance Imaging (fMRI). During the recognition portion of the task, non-amnestic MCI patients were found to exhibit less activity in frontal brain regions than cognitively normal controls (Machulda et al., 2009).

Although the effect of MCI diagnosis on atrophy in several different brain regions has been examined, the anterior cingulate cortex is of particular interest in relation to executive functioning. The anterior cingulate cortex (ACC) is located in the medial frontal region of the brain and receives most of its subcortical connections from the amygdala (Mesulam, 2000). This structure is shown below in Figure 2 and includes the pink, blue, and yellow areas. The anterior cingulate cortex is involved in several executive functions, including emotional regulation, general attention and engagement with the environment (Mesulam, 2000), as well as the prevention of errors through detecting incompatibilities between one's behavior and other response tendencies (Carter, 2000). In fact, Rosen and colleagues (2005) demonstrated that ACC atrophy is associated with several deficits in executive functions, including apathy and disinhibition.

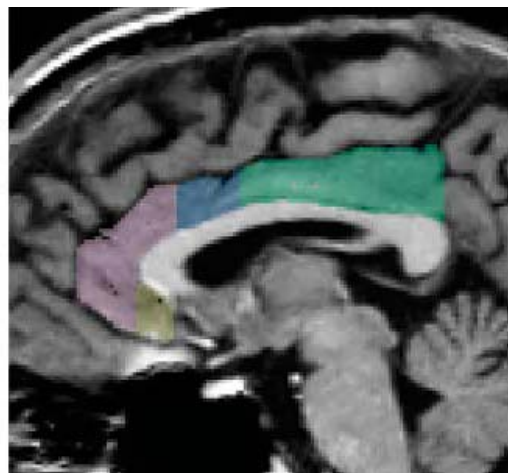


Figure 2. Saggital view of the brain illustrating ACC divisions. Rostral ACC is shown in pink, dorsal ACC in blue, and subcallosal ACC in yellow (Koo et al., 2008).

The ACC can be divided into rostral, dorsal, and subcallosal regions. The rostral ACC, colored pink in Figure 2, receives most of its input from limbic and paralimbic regions such as the nucleus accumbens, amygdala, insula, hippocampus, and orbitofrontal cortex, many of which are involved in affective regulation. As such, the rostral ACC is associated with assessing the relevance of emotional and motivational cues in the environment in order to regulate emotional responses (Bush, 2000). The dorsal ACC, which is blue in Figure 2, is interconnected with several cortical areas, including the lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas (Koo et al., 2008). This region is involved in attention, executive functions, detection of errors, and memory (Koo et al., 2008). The subcallosal region, colored yellow in Figure 2, is highly connected with subcortical regions associated with mood (Koo et al., 2008).

In one study using voxel-based morphometry with MCI patients and cognitively normal controls, a section of the left anterior cingulate gyrus was found to be smaller in those with MCI than controls (Pennanen et al., 2005). In addition, MCI patients also exhibited atrophy in the medial temporal lobe, which includes the hippocampus, in the right hemisphere. Unfortunately, however, the authors did not discriminate between different subtypes of MCI. It is therefore unclear from the results of this study alone whether ACC atrophy is associated with MCI patients in general or non-amnesic MCI patients in particular.

More recent studies in this area, which differentiate between subtypes of MCI, allow more definitive interpretations of results to be drawn. Caffarra and colleagues (2008) reported results from a study of regional cerebral blood flow measured with

SPECT. Although blood flow does not directly indicate regional volume, smaller volumes can be inferred from lower blood flow in the region (e.g., Schaller, 2008). The authors compared those with amnesic MCI to those with dysexecutive, non-amnesic MCI (i.e., those with executive functioning deficits). Whereas amnesic MCI patients had lower levels of blood flow than controls in the hippocampus, dysexecutive MCI patients had lower levels of blood flow in the anterior cingulate cortex (Caffarra et al., 2008). In addition, Johnson, Vogt, Kim, Cotman, & Head (2004) reported the results of an autopsy performed with a patient who exhibited primary executive functioning deficits, as assessed by the Trail Making Test parts A and B. The autopsy revealed neuropathies, including NFTs and amyloid plaques, dispersed throughout the brain. However, the density of A β 42, the primary component of amyloid plaques, was greatest in the ACC, particularly around the genu of the corpus callosum (Johnson et al., 2004).

Finally, Jauhiainen et al. (2008) performed structural MRI and Positron Emission Tomography (PET) with a sample of patients with amnesic MCI, non-amnesic MCI, and cognitively normal controls. While the amnesic MCI patients did not differ from controls in the volumes of any brain regions, non-amnesic patients had smaller volumes in several frontal areas, including the anterior cingulate cortex, than controls. Furthermore, non-amnesic patients had smaller volumes in several frontal regions than amnesic MCI patients (Jauhiainen et al., 2008). In contrast, results with the PET scans indicated that amnesic patients exhibited hypometabolism in medial temporal lobe areas including the hippocampus as compared to both controls and non-amnesic MCI patients. However, no differences in the metabolism in frontal lobe regions were found between

the non-amnestic patients and either amnestic patients or controls (Jauhiainen et al., 2008).

Current Study

Description and Purpose

Research on patients with MCI has grown in frequency due in part to the possibility of preventing the development of MCI and various forms of dementia, particularly AD, in the future. Although those with amnestic MCI and non-amnestic MCI differ in numerous respects, research comparing these two subtypes is only in its nascent stages. Particularly because different types of dementia have distinct patterns of brain atrophy, it is important to research structural imaging correlates in subtypes of MCI. Not only will this enhance the current knowledge regarding differences between amnestic and non-amnestic MCI populations, but such research will also begin to elucidate the etiology underlying the subtypes of MCI.

In accordance with these goals, this study examined the structural imaging correlates of amnestic and non-amnestic MCI as compared to cognitively normal controls. Using a manual tracing procedure, hippocampal and rostral, dorsal, and subcallosal anterior cingulate cortex volumes were delineated. Hippocampal and whole ACC volumes as well as rostral and dorsal ACC volumes were compared among all three diagnostic groups. Subcallosal ACC volumes were not individually analyzed due to the subregion's limited relevance for executive functioning. Although a small number of studies have reported findings with the anterior cingulate in MCI patients, no study to date has specifically examined manually traced ACC volumes in both amnestic and non-

amnesic populations, despite the relevance of the ACC to non-amnesic patients, particularly those with executive dysfunction.

Hypotheses

This study examined hippocampal and ACC regional volumes among amnesic MCI, non-amnesic MCI, and cognitively normal patients.

Hypothesis: There will be a significant interaction between brain region and diagnostic group, indicating that the brain region volumes differ depending on diagnosis. Specifically, it is predicted that amnesic MCI patients will have smaller hippocampi than controls and non-amnesic patients, while having larger ACC volumes than non-amnesic MCI patients. It is also predicted that non-amnesic MCI patients will have smaller ACC volumes than amnesic MCI patients and controls, while having larger hippocampi than amnesic MCI patients.

Post-hoc Hypotheses (to be investigated if brain region x diagnosis interaction is significant):

Post hoc Hypothesis 1: Patients with amnesic MCI will have smaller hippocampi than cognitively normal controls.

Post-hoc Hypothesis 2: Patients with amnesic MCI will have smaller hippocampi than those with non-amnesic MCI.

Post-hoc Hypothesis 3: Patients with non-amnesic MCI will have smaller whole anterior cingulate cortex volumes, as well as smaller volumes in dorsal and rostral subregions, than cognitively normal controls.

Post-hoc Hypothesis 4: Patients with non-amnestic MCI will have smaller whole anterior cingulate cortex volumes, as well as smaller volumes in dorsal and rostral subregions, than those with amnestic MCI.

CHAPTER THREE

METHODS

Participants

Fifty-seven right-handed participants, including 21 cognitively normal controls, 20 with amnesic MCI, and 16 with non-amnesic MCI, were drawn from a sample of community dwelling older adults recruited at the University of California San Diego (UCSD) for a longitudinal study investigating normal aging. The sample was composed of 44% men ($n = 25$) and 56% women ($n = 32$). Within each diagnostic group, the control sample was composed of 33% men ($n = 7$) and 67% women ($n = 14$). The sample with amnesic MCI was 50% men ($n = 10$) and 50% women ($n = 10$). The sample with non-amnesic MCI was also 50% men ($n = 8$) and 50% women ($n = 8$). Ninety-five percent of the sample was white ($n = 54$) and 1.8% of the sample was Asian-American ($n = 1$). Ethnicity data was not available for two participants. The overall sample had an average age of 76.12 ($SD = 7.26$), an average educational level of 16.04 ($SD = 2.25$), an average estimated verbal IQ (from the ANART) of 119.89 ($SD = 6.16$), and an average dementia rating of 52.89 ($SD = 5.79$). These demographic factors, broken down by diagnostic group, are shown below in Table 1.

Participants were drawn from a sample of community dwelling older adults recruited at the University of California San Diego (UCSD) for a longitudinal study

investigating normal aging. The participants for this study were selected by UCSD researchers on the basis of their having received an MRI and a comprehensive neuropsychological assessment prior to recruitment. Furthermore, only non-demented participants were included in this study's sample. UCSD researchers assessed the presence of dementia by examining participants' level of functional impairment using the Independent Living Scales (ILS; Loeb, 1996) as well as participants' level of global cognitive functioning using the Dementia Rating Scale (DRS; Mattis, 1988). Only those participants with normal global cognitive functioning and without functional impairment were included in the sample. Additional exclusion criteria included history of neurological or severe psychiatric illness, learning disability, or a history of drug or alcohol abuse. All participants gave written informed consent prior to participation in the study.

Table 1. Mean Values for Demographic Variables by Diagnostic Group

Diagnostic Group	Age	Education	DRS	ANART ¹
Controls	76.22 (5.55)	15.94 (2.24)	56.56 (3.24)	122.89 (4.10)
Amnesic MCI	74.15 (7.40)	16.30 (2.43)	49.60 (6.37)	117.70 (6.41)
Non-amnesic MCI	78.44 (8.16)	15.56 (2.22)	52.07 (4.79)	118.36 (6.81)

Note. Standard deviations are in parentheses. ¹ANART used as an estimate of verbal IQ.

Demographics

Participant demographics were collected by a UCSD researcher prior to participation. Such demographics included the participant's age, education, and gender. UCSD researchers ascertained participants' general cognitive functioning through the American National Adult Reading Test (ANART). The ANART requires participants to read a list of 45 irregularly spelled words. Because the words are relatively short and have irregular spelling (e.g., bouquet, depot), the test does not require participants to process complex visual stimuli and does not allow the use of phonetics to deduce the pronunciation of the words (Strauss, Sherman, & Spreen, 2006). As a result, a person's performance on the ANART is thought to reflect past knowledge (i.e., familiarity with each irregularly spelled word) instead of current cognitive functioning (Strauss et al., 2006). Thus, participants' scores on the ANART were used as a proxy for full-scale IQ. Finally, participants' scores on the Dementia Rating Scale (DRS) were used to determine their dementia stage. The DRS assesses five cognitive areas which are most likely to show decline in early Alzheimer's disease: attention, initiation and perseveration, construction, conceptual abilities, and memory. As described in the results section, all participant groups were compared on each of the above demographic variables to determine equivalency. Any variable which significantly differed by diagnostic group was controlled for in all subsequent analyses.

Neuropsychological Assessment

All participants were given a comprehensive neuropsychological evaluation by a UCSD researcher prior to recruitment for the larger, longitudinal study from which this

study's participants were selected. This study focused only on those neuropsychological tests assessing five relevant cognitive domains, including memory, executive functioning, language, attention, and visuospatial function. Each of these domains is represented by at least three neuropsychological tests within the larger battery. These tests were selected for use in diagnosis in this study based on their common use with older adult populations and their psychometric properties.

Memory Assessments

Three measures were used by UCSD researchers to assess participants' memory. Selected tests include the immediate and delayed recall portions from the Logical Memory subtest of the *Wechsler Memory Scale – Revised* (*WMS-R*; Wechsler, 1987) and the Visual Reproduction subtest of the *WMS-R*, as well as Trials 1-5 total recall and long delay free recall from the *California Verbal Learning Test* (*CVLT*; Delis et al., 1987).

Executive Functioning Assessments

Four tests were used by UCSD researchers to assess participants' executive functioning. Selected tests include the modified, 48-card version of the *Wisconsin Card Sorting Test* (*WCST*; Lineweaver, Bondi, Thomas, & Salmon, 1999) specifically focusing on categories achieved and perseverative errors, the *Trail Making Test, Part B* (Reitan & Wolfson, 1985a), the inhibition and inhibition/switching conditions of the *Delis-Kaplan Executive Function Scale* (*D-KEFS*; Delis, Kaplan, & Kramer, 2001a) Color-Word Interference Test, and the switching condition of the design and verbal fluency tasks of the *D-KEFS*.

Language Assessments

Three tests were used by UCSD researchers to assess participants' language abilities. The selected tests include the *Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 1983), letter fluency, and category fluency (Gladsjo et al., 1999).

Attention Assessments

Three measures were used by UCSD researchers to assess participants' level of attention. Selected tests include the attention subscale of the *DRS* (Mattis, 1988), the Digit Span subtest of the *WAIS-R* (Wechsler, 1981), and the *Trail Making Test, Part A* (Reitan & Wolfson, 1985a).

Visuospatial Assessments

Five measures were used by UCSD researchers to assess participants' visuospatial functioning. Selected tests include the Block Design subtest of the *Wechsler Intelligence Scale for Children-Revised (WISC-R)*; Wechsler, 1974), the Visual Scanning condition of the D-KEFS Trail Making Test, the empty and filled dot conditions of the D-KEFS Design Fluency Test, *DRS* construction (Mattis, 1988), and draw-a-clock.

MCI Diagnosis

A UCSD researcher assessed participants for the presence of MCI using a comprehensive set of diagnostic criteria developed by Jak et al. (2009). The criteria allow a diagnosis of either amnesic MCI, single domain, if only the memory domain is impaired, amnesic MCI, multiple domain, if the memory domain plus additional cognitive domains are impaired, non-amnesic MCI, single domain, if one non-memory

domain is impaired, and non-amnesic MCI, multiple domain, if more than one non-memory domains are impaired. In order for a domain to be classified as impaired, the person must score at least 1 SD below age-adjusted norms on at least two assessments within the domain (Jak et al., 2009). This differs from the criteria historically used to diagnose MCI (Storandt et al., 2006), which required impairment of at least 1.5 SD below age-adjusted norms on only one assessment per cognitive domain.

The comprehensive diagnostic criteria were selected based on results indicating that such criteria provided the best balance between sensitivity and specificity in detecting cases of MCI and stability of the diagnostic categories (Jak et al., 2009). Thus, although historical or conservative criteria provide above average diagnostic stability, it is likely such criteria have a high false negative rate, missing many cases of MCI (Jak et al., 2009). Likewise, although more liberal criteria detect more cases of MCI, they also likely have a higher false positive rate and therefore increased diagnostic instability (Jak et al., 2009). The comprehensive criteria which were used in this study strike a balance between detecting cases of MCI while preserving the stability of the diagnostic categories (Jak et al., 2009).

Structural Magnetic Resonance Imaging Acquisition and Image Analysis

Participants were scanned by a UCSD researcher using either a 3.0 Tesla General Electric (GE) Medical Systems EXCITE whole body imager or a 1.5-Tesla GE Signa imager (General Electric Medical Systems, Milwaukee, WI, USA). The images were stripped of all skull material and segment them into gray matter, white matter, and cerebrospinal fluid compartments. Residual non-brain material was manually removed

when necessary. Whole-brain volume was determined and used in normalizing the region of interest volumes (Bigler & Tate, 2001).

Regions of Interest Manual Tracing Protocol

Volumes for the anterior cingulate and hippocampus were obtained bilaterally through manual tracing in the coronal plane using Analysis of Functional NeuroImages (AFNI) software. Prior to tracing, the images were realigned so as to be perpendicular to the anterior-posterior commissure line. However, images were not transformed into standard space coordinates. Interrater reliability for the delineation of the regions of interest was required to exceed .85 using a separate set of images not analyzed in this study. More specifically, Dr. Amy Jak, a researcher from UCSD who is reliable on tracing the ACC regions, as well as the student researcher, independently traced the ACC regions in five brains not included in this study. The whole ACC, rostral, and dorsal ACC volumes delineated by the tracings were compared between Dr. Jak and the student using intra-class correlation to determine whether an acceptable tracing reliability had been reached. The interrater reliability between Dr. Jak and the student researcher for tracing the whole ACC was .94, and the interrater reliabilities for tracing the left and right rostral and dorsal ACCs ranged from .94 to .99. Once reliability was established, the student researcher completed manual tracing of the ACC regions of interest for all participants included in the study, while being blind to participant identity and group.

The procedure for tracing the anterior cingulate cortex was adapted from a previously published methodology (Fornito et al., 2006). A more detailed manual describing the boundaries and tracing procedures was obtained from the authors. This

particular methodology was chosen due to the clarity with which it describes the boundaries used in delineation, increasing the ease with which the boundaries can be reliably reproduced. In addition, several other structural imaging studies have used this methodology as well.

The anterior cingulate cortex, divided into rostral, dorsal, and subcallosal portions, was traced bilaterally in the coronal plane. Although subcallosal volumes were not individually analyzed, this region was still individually delineated in order to identify the rostral and dorsal subregions of the ACC. Prior to tracing, three boundaries were established for the regions of interest. The midline, identified in the sagittal plane and defined as the slice in which the septum pellucidum is most visible, was masked out to prevent regions of interest from containing gray matter belonging to the other hemisphere. The posterior boundary for the anterior cingulate cortex was identified in the coronal plane and was defined as the first slice in which the anterior commissure no longer crosses the midline of the brain. The boundary dividing the rostral and dorsal portions of the anterior cingulate, termed Plane A, was also identified in the coronal plane and was defined as the first slice in which the white matter of the corpus callosum can be seen crossing the midline of the brain.

Before the regions of interest are delineated, the sulci of each brain were examined according to the tracing methodology and an additional protocol (Fornito et al., 2006; Yucel et al., 2001) to determine whether the brain contained a paracingulate sulcus. The presence or absence of a paracingulate sulcus affects the way in which the regions of interest are delineated. The paracingulate sulcus was deemed present if a sulcus is present

dorsal to the cingulate sulcus and if parallel portions of the sulci overlap for at least 20 mm before reaching the posterior boundary of the anterior cingulate. Furthermore, this overlap should continue for at least three slices laterally for the presence of the paracingulate sulcus to be counted. The origin of the paracingulate sulcus was defined as the point at which the sulcus arches away from a vertical line. Should two sulci overlap for less than 20 mm, this was counted as a segmented cingulate sulcus. The tracing of such a sulcus is described below. Although the Yucel et al. (2001) protocol requires that the inferior sulcus originate anterior to the corpus callosum to be considered the cingulate sulcus, following the recommendation of Fornito et al. (2006), any overlap of sulci greater than 20 mm was counted as the presence of a paracingulate sulcus, regardless of the origin of the inferior sulcus.

Should a paracingulate sulcus be present, the gray matter dorsal to the cingulate sulcus was not included in the regions of interest and was instead counted as part of the paracingulate cortex. Should the sulcal pattern represent a segmented cingulate sulcus in which there is less than 20 mm of overlap, the area of overlap between the sulci were included in the region of interest. In the case where two parallel sulci overlap for more than 20 mm but there is an additional sulcus more dorsally, the area of overlap was counted in the region of interest if it lies under the more dorsal sulcus. However, if the area of overlap does not lie under the more dorsal sulcus, it was not included in the region of interest and was counted as part of the paracingulate cortex.

Once the presence or absence of a paracingulate sulcus was established, each region of interest was traced bilaterally in the coronal plane. All regions of interest were traced in one hemisphere and then the other. In general, boundaries for regions of interest were traced in the center of the relevant sulcus. Boundaries for each region of interest are given below.

The rostral anterior cingulate cortex was bordered posteriorly by Plane A. The anterior, dorsal, and inferior boundaries were the cingulate sulcus. In cases where the cingulate sulcus is continuous with another sulcus, such as the superior rostral sulcus, the boundary was traced along the joined portion to the posterior boundary. If the cingulate sulcus is separate from other sulci but does not reach to Plane A, a line following the imagined path of the cingulate sulcus was traced back to Plane A. The dorsal anterior cingulate was bounded dorsally by the cingulate sulcus and posteriorly by the posterior border. The anterior boundary was Plane A, while the inferior boundary was the corpus callosum. The subcallosal anterior cingulate was bounded dorsally by the corpus callosum, anteriorly by Plane A, and inferiorly by the cingulate sulcus. The posterior boundary was the first slice in which the internal capsule clearly separates the caudate and putamen.

Examples of tracings of the ACC done for this study are shown below in Figures 3, 4, and 5. Figure 3 depicts the tracing of the ACC of a cognitively normal control participant, Figure 4 depicts the tracing of the ACC of a patient with amnesic MCI, and Figure 5 depicts the tracing of the ACC of a patient with non-amnesic MCI. In all

Figures, the rostral ACC is in green, the dorsal ACC is in yellow, and the subcallosal ACC is in orange.

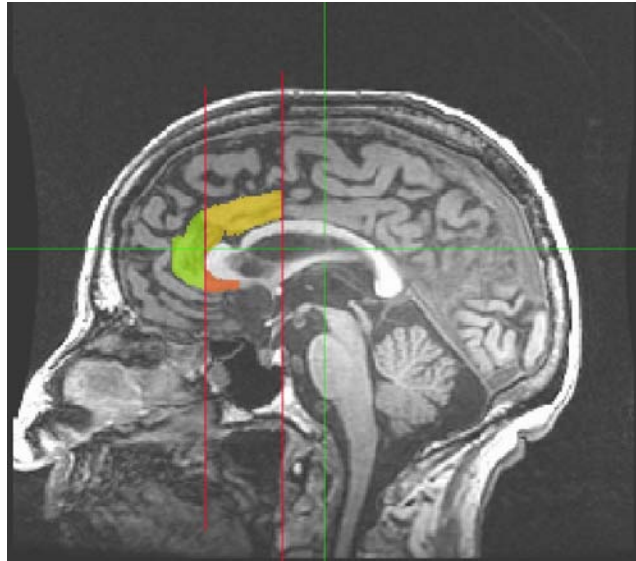


Figure 3. Tracing of the ACC of a cognitively normal control participant completed for the current study. Rostral ACC is in green, dorsal ACC is in yellow, and subcallosal ACC is in orange.

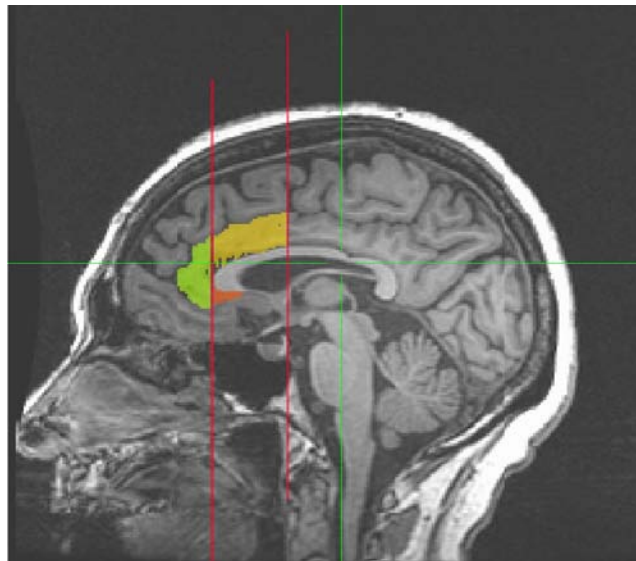


Figure 4. Tracing of the ACC of a patient with amnesic MCI completed for the current study. Rostral ACC is in green, dorsal ACC is in yellow, and subcallosal ACC is in orange.

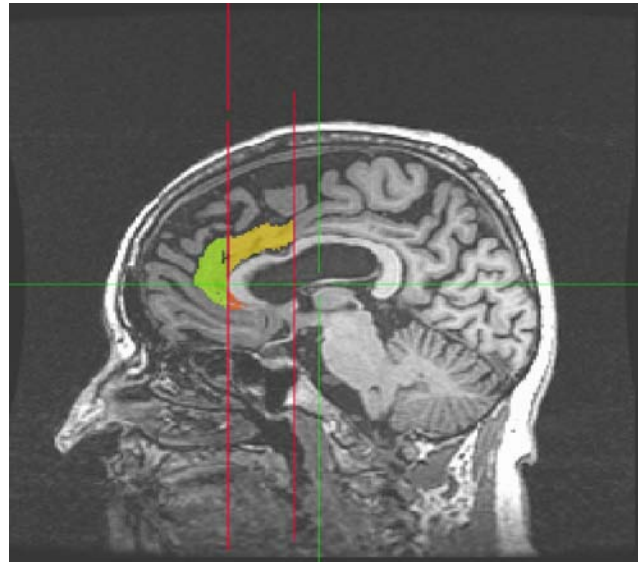


Figure 5. Tracing of the ACC of a patient with non-amnesic MCI completed for the current study. Rostral ACC is in green, dorsal ACC is in yellow, and subcallosal ACC is in orange.

Hippocampal regions of interest were traced by UCSD researchers according to a previously published protocol (Jak et al., 2007). The anterior boundary was the slice through the fullest part of the mammillary bodies, while the posterior boundary was the last slice in which the superior colliculi are still fully visible.

Procedure

Prior to participation, participants provided written informed consent for a larger, ongoing longitudinal study at UCSD. Participants were then screened for dementia by UCSD researchers using the ILS and DRS scales. Only those participants who were free of functional impairment and who displayed normal cognitive functioning were included. UCSD researchers then gave participants a comprehensive neuropsychological battery, which was used to determine whether a diagnosis of MCI would be appropriate. Participants were deemed cognitively normal or diagnosed with either amnesic MCI or

non-amnesic MCI, according to the diagnostic criteria outlined above. Finally, participants also underwent a structural MRI at UCSD.

Data Analysis

Participants in each group, cognitively normal controls, those with amnesic MCI, and those with non-amnesic MCI, were compared on all relevant demographic variables, including age, education, gender, IQ, as measured by the ANART, and dementia stage, as measured by the DRS. Four between-subjects analyses of variance (ANOVAs) were used to compare the groups on age, education, IQ, and dementia stage. When significant differences were found, these variables were controlled for in subsequent analyses. Chi-square analyses were also performed to determine the existence of group differences on gender.

Prior to analysis, all ROI volumes were converted to percentages for each participant. This was done by dividing the ROI volume by the participant's whole brain volume and multiplying by 100. In this way, differences in whole brain volume, which may vary between participants, was controlled for. Brain volumes were analyzed using two mixed-model analyses of variance (ANOVA). The first ANOVA consisted of the between-subjects variable Diagnosis (amnesic MCI, non-amnesic MCI, cognitively normal) and within-subjects variable Region of Interest (left and right hippocampus, left and right whole ACC) The second ANOVA consisted of the between subjects variable Diagnosis (amnesic MCI, non-amnesic MCI, cognitively normal) and within subjects variable Region of Interest (left and right hippocampus, left and right dorsal ACC, left and right rostral ACC). Of particular interest in this study was whether a significant

interaction between diagnosis and brain region was found, indicating that brain region volumes differ depending on diagnosis.

CHAPTER FOUR

RESULTS

The diagnostic groups were compared on age, education, Dementia Rating Scale (DRS) score, and estimated verbal IQ using one-way analysis of variance (ANOVA). Groups were compared on gender using Pearson's chi-square analysis. The groups were not found to differ in terms of gender, $\chi^2(2, N = 57) = 1.50, p = .47$. There were no significant differences among the diagnostic groups in terms of age, $F(2, 51) = 1.63, p = .21$. Similarly, the diagnostic groups did not differ in terms of education, $F(2, 51) = 0.46, p = .64$. The diagnostic groups were found to differ significantly on estimated verbal IQ, $F(2, 51) = 4.23, p = .02$, and DRS score, $F(2, 51) = 9.17, p < .001$. Because the diagnostic groups differed on estimated verbal IQ and DRS score, these variables were used as covariates in subsequent mixed-model ANOVAs.

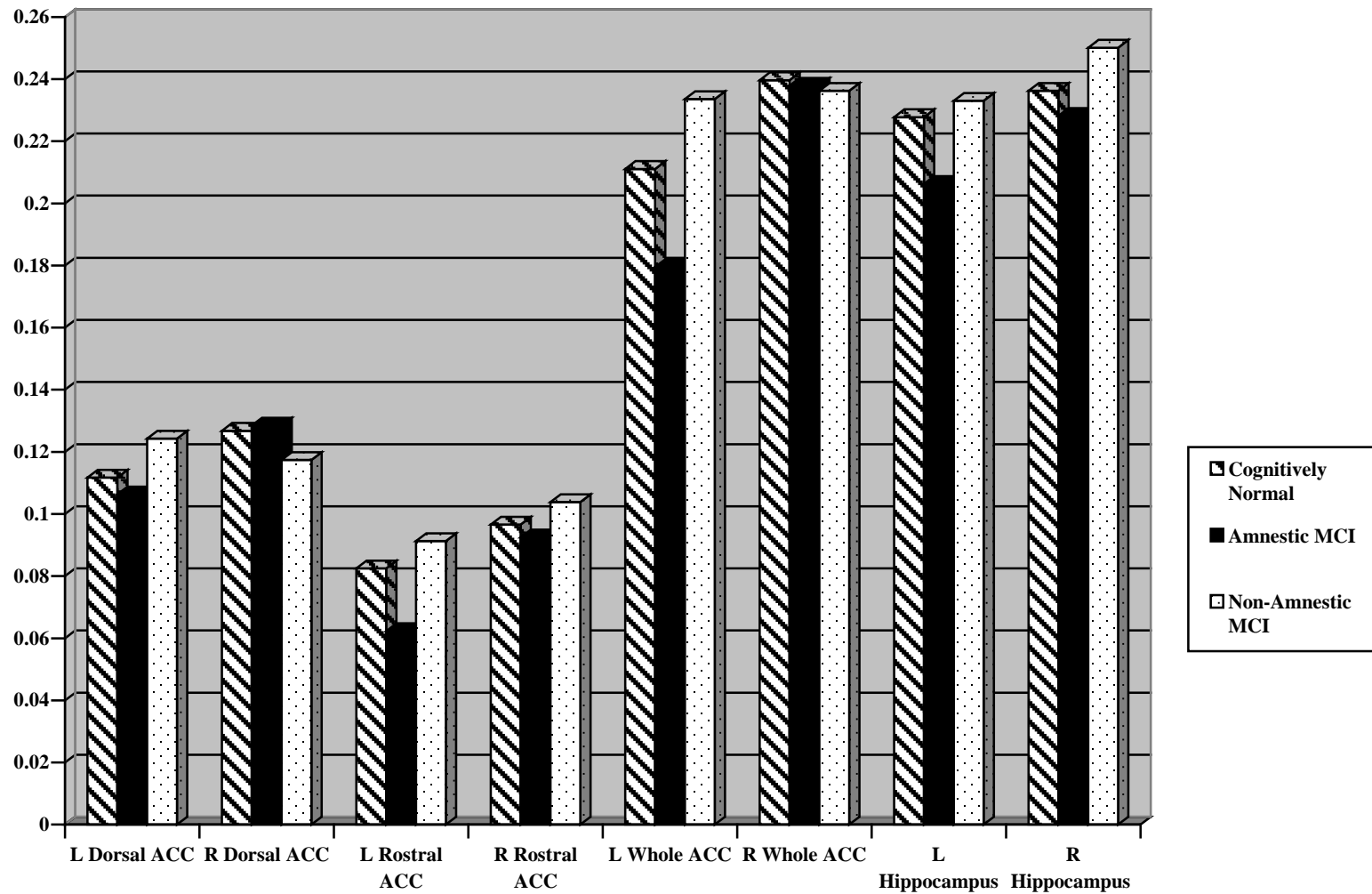
Hippocampal and ACC volumes were compared across the three diagnostic groups (cognitively normal, amnesic MCI, non-amnesic MCI) using two mixed-model analyses of variance. In the first model, the within-subjects variable was Region of Interest (left and right hippocampal volumes and left and right whole ACC volumes), while the between-subjects variable was Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI). In the second model, the within-subjects variable was Region of Interest (left and right hippocampal volumes and left and right rostral and dorsal ACC

volumes), while the between subjects variable was Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI). Mean ROI volumes for each diagnostic group are presented in Figure 6.

The first mixed-model ANOVA included ROI (left and right hippocampal volumes and left and right whole ACC volumes) as the within-subjects variable and Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI) as the between-subjects variable. It was hypothesized that the interaction between Region of Interest and Diagnosis would be significant, indicating that brain region volume differed by diagnostic group. This prediction was not supported; the interaction of Region of Interest and Diagnosis was not significant, $F(6, 156) = 0.68, p = .67$. This implies that left and right hippocampal and whole ACC volumes did not differ across diagnostic groups. The interaction between estimated verbal IQ and ROI was also not significant, $F(3, 156) = 2.15, p = .10$, indicating that ROI volumes did not differ by estimated verbal IQ. Furthermore, the interaction between ROI and DRS score was not significant, $F(3, 156) = 1.42, p = .24$, which suggests that ROI volumes did not vary with dementia severity.

In examining results of the main effects, it was found that the main effect of Diagnosis was not significant, $F(2, 52) = 1.20, p = .31$. Thus, it appears that, across all Regions of Interest, brain volumes did not differ by diagnostic group. The main effects of estimated verbal IQ ($F(1, 52) = 0.01, p = .91$) and DRS score ($F(1, 52) = .44, p = .51$) were also not significant, suggesting that ROI volume across diagnostic group did not differ by estimated verbal IQ or dementia severity. Finally, the main effect of ROI was also not significant, $F(3, 156) = 1.01, p = .39$, suggesting that hippocampal and whole

Figure 6. Mean Percentage of Whole Brain Volume for each Region of Interest by Diagnostic Group



ACC brain region volumes did not significantly differ from one another. Because significant results were not found, post-hoc analyses were not performed.

The second mixed-model ANOVA included Region of Interest (left and right hippocampus and left and right rostral and dorsal ACC) as the within-subjects variable and Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI) as the between-subjects variable. It was hypothesized that the interaction between Region of Interest and Diagnosis would be significant, indicating that region of interest volumes differed across diagnostic groups. This hypothesis was not supported, as the interaction between Region of Interest and Diagnosis was not significant, $F(10, 260) = 1.00, p = .44$. Thus, it appears that left and right hippocampal and rostral and dorsal ACC volumes did not differ across diagnostic groups. Furthermore, the interaction between ROI and estimated verbal IQ was not significant, $F(5, 260) = 1.88, p = .10$, indicating that ROI volumes did not vary according to estimated verbal IQ. The interaction between ROI and DRS score was also not significant, $F(5, 260) = 2.06, p = .07$, which suggests that ROI volumes did not differ by dementia severity.

In terms of main effects, the main effect for Diagnosis was not significant, $F(2, 52) = 1.21, p = .31$. Thus, it appears that, across all ROIs, brain volumes did not differ based on a person's diagnostic category. The main effect of estimated verbal IQ was also not significant, $F(1, 52) = 0.001, p = .98$, suggesting that ROI volume did not differ by estimated verbal IQ. Finally, the main effect of DRS score was not significant, $F(1, 52) = .66, p = .42$, which indicates that ROI volume was not associated with dementia rating. Because no significant results were found, post-hoc analyses were not performed.

CHAPTER FIVE

DISCUSSION

The purpose of the current study was to determine whether hippocampal and Anterior Cingulate Cortex volumes differed across patients with amnesic MCI, non-amnesic MCI, and cognitively normal controls. Much research has examined hippocampal volumes in MCI subtypes, particularly the amnesic variant (see Pihlajamaki et al., 2009; Ries et al., 2008; and Shi et al., 2009, for reviews). As expected, their findings indicate that amnesic MCI is associated with hippocampal atrophy when compared with cognitively normal controls (e.g., Bai et al., 2009; Becker et al., 2006; Bell-McGinty et al., 2005; Schmidt-Wilcke et al., 2009; Shi, et al. 2009; Stoub et al., 2006; Whitwell et al., 2007). Such atrophy is strongly related to their concomitant memory deficits and is consistent with the more severe hippocampal tissue loss characteristic of AD (e.g., Shi et al., 2009).

However, because the non-amnesic MCI variant was only recently created by the International Working Group on Mild Cognitive Impairment in 2004 (Winblad et al., 2004), research on the neuroimaging correlates of this subtype is lacking. What research has been done suggests that patients with non-amnesic MCI exhibit atrophy in frontal regions associated with executive functions, such as the dorsolateral and dorsomedial

prefrontal cortices (Pa et al., 2008). Functional imaging studies have also found evidence of frontal involvement in patients with non-amnesic MCI. A study using SPECT (Nobili et al., 2008) reported lower levels of blood flow in non-amnesic MCI patients in the right frontal cortex, while a study using fMRI (Machulda et al., 2009) found less activity in frontal regions in non-amnesic MCI patients when performing a memory task.

Despite its involvement in executive functioning, the ACC has rarely been included in such research. The ACC, composed of rostral, dorsal, and subcallosal subregions, is thought to be involved in emotion regulation, attention, and error detection, all skills necessary for optimal executive functioning (Carter, 2000; Koo et al., 2008; Mesulam, 2000). What research has examined the ACC in relation to non-amnesic MCI has found that non-amnesic MCI patients, particularly those with EF deficits, may exhibit lower levels of blood flow in the ACC (Caffarra et al., 2008), smaller ACC volumes (Jauhiainen et al., 2008), and a concentration of neuropathologies in the ACC upon autopsy (Johnson et al., 2004). Yet, the ACC has not been examined in these populations using manual tracing procedures, which many consider to be more accurate delineations of an ROI than automated methods (Tisserand et al., 2002). Nor have ACC volumes been examined in relation to hippocampal volumes in both amnesic and non-amnesic MCI variants. This study aimed to address these oversights in the literature by comparing manually traced hippocampal and ACC volumes across patients with amnesic MCI, non-amnesic MCI, and cognitively normal controls.

It was hypothesized that patients with amnesic MCI would have smaller hippocampi when compared to both cognitively normal controls and those with non-

amnesic MCI, while patients with non-amnesic MCI were hypothesized to have smaller ACCs than cognitively normal controls and amnesic MCI patients. To test these hypotheses, two mixed-model analyses of variance (ANOVAs) were conducted. The first mixed-model ANOVA included ROI (left and right hippocampal volumes and left and right whole ACC volumes) as the within-subjects variable and Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI) as the between-subjects variable. The second mixed-model ANOVA included Region of Interest (left and right hippocampus and left and right rostral and dorsal ACC) as the within-subjects variable and Diagnosis (cognitively normal, amnesic MCI, non-amnesic MCI) as the between-subjects variable.

In both of these analyses, of particular interest was the Region of Interest x Diagnosis interaction, which would indicate that the ROI volumes differed according to diagnosis. Contrary to predictions, this interaction was not significant in either analysis, preventing follow-up post-hoc tests from being conducted to assess the study's specific hypotheses. This lack of significance implies that left and right hippocampal and left and right whole, rostral, and dorsal ACC volumes did not vary by a patient's diagnosis.

Some studies have also failed to find significant differences in hippocampal and ACC volumes between MCI patients and controls. One study examining amnesic MCI patients whose diagnosis remained stable and patients who later converted to AD found no hippocampal volume differences from controls for those patients who remained stable (Whitwell et al., 2008). A second study examined hippocampal volumes in cognitively normal controls and in patients with amnesic MCI or AD (Hua et al., 2008). While patients with AD exhibited significant levels of hippocampal atrophy compared to

controls, patients with MCI showed no differences in hippocampal volume (Hua et al., 2008).

Some studies assessing ACC involvement across diagnostic groups have also failed to find significant results. Importantly, most of these studies examined functional instead of structural differences in the ACC and most did not differentiate between subtypes of MCI. An fMRI study of patients with MCI found no differences between patients and controls in ACC activation during an attentional control task (Rosano et al., 2005). A study examining regional cerebral blood flow in MCI and AD patients found no significant differences in blood flow in the ACC between MCI patients and controls, and AD patients actually had increased regional blood flow in the ACC compared to controls (Dai, Lopez, Carmichael, Becker, Kuller, & Gach, 2009). The authors conceptualized this finding as evidence for a compensatory response in the ACC in patients with cognitive decline (Dai et al., 2009). This was also suggested by two studies examining neuropathologies in the brains of patients who met post-mortem criteria for AD but were asymptomatic (Iacono et al., 2008; Ruidavets et al., 2007). The authors found hypertrophy in the ACC in these patients compared with control and MCI patients and suggested that this may act to offset cognitive decline (Iacono et al., 2008; Ruidavets et al., 2007). Also in support of a compensatory response in the ACC, an additional study examining MCI patients over time using SPECT found that those who converted to AD had higher levels of perfusion in the rostral anterior cingulate than non-converters and controls (Johnson, Moran, Becker, Blacker, Fischman, & Albert, 2007). In contrast, no differences were found between controls and non-converters in ACC perfusion. This

study also found converters to have lower levels of perfusion in caudal regions of the anterior cingulate and posterior cingulate (Johnson et al., 2007).

Following from these results, it may be that ACC pathology found in MCI and AD is limited to caudal ACC regions, with rostral regions of the ACC showing a compensatory response. Another explanation may be that ACC pathology begins caudally, closer to the posterior cingulate, and moves anteriorly, while the rostral ACC initially shows a compensatory response. Indeed, many studies have reported posterior cingulate involvement early on in the AD disease course (e.g., Twamley, Ropacki, & Bondi, 2006). Importantly, ACC boundaries vary across studies which examine it. It is possible that conflicting results regarding the involvement of the ACC in MCI may be due to the use of different boundaries to delineate the ACC. However, in comparing the delineation methods of studies that found ACC atrophy in MCI subtypes (e.g., Caffarra et al., 2008; Jauhiainen et al., 2008) with those that did not (e.g., Dai et al., 2009; Rosano et al., 2005), no clear pattern emerges. Studies reporting ACC atrophy in MCI and those finding no atrophy both utilized similar delineation methods; all used either automated delineation or histological methods. However, it may be that the boundaries in the current study excluded posterior portions of the ACC, which Johnson et al. (2007) found to be affected in MCI patients who convert to AD, causing significant group differences in posterior ACC regions to be missed.

Yet, the current study's findings contrast with several studies that have reported smaller hippocampal volumes among amnesic MCI patients than cognitively normal controls (e.g., Bai et al., 2009; Becker et al., 2006; Bell-McGinty et al., 2005; Schmidt-

Wilcke et al., 2009; Shi et al., 2009; Stoub et al., 2006; Whitwell et al., 2007).

Furthermore, although only a few studies have explored ACC volumes in MCI patients, some of these studies reported significant differences between MCI patients and controls (e.g., Jauhiainen et al., 2008; Pennanen et al., 2005).

The discrepancy between the findings of this study and those of other studies in this area may be due to several factors. First, it may be that the ACC is not involved in the degenerative processes associated with MCI. It is possible that the ACC only becomes affected farther along in the course of dementia. This would suggest that ACC differences might only be found in comparing different forms of dementia (e.g., AD vs. FTD) or in comparing MCI patients whose deficits are fairly advanced. If this is indeed the case, the exclusion of patients with dementia from the present study may have prevented the detection of significant differences in brain region volumes. In addition, while one variant of non-amnesic MCI involves executive dysfunction, such dysfunction need not be due to ACC involvement at all but may instead be associated with other frontal regions involved in EF, such as the dorsolateral prefrontal cortex (dLPFC; Lezak, Howieson, & Loring, 2004; Pa et al., 2008). One study examining the dLPFC in MCI patients using fMRI and an attentional control task found that MCI patients had higher levels of activity in the dLPFC compared to controls (Rosano et al., 2005). With increasing task difficulty, however, the controls preferentially recruited the dLPFC and the ACC, while MCI patients recruited the posterior cingulate. The authors suggested that the dLPFC may be affected early on in the course of MCI and suggest that changes in

neural networks underlying EF may precede other symptoms in AD development (Rosano et al., 2005).

Additionally, it may be that the executive dysfunction found in some cases of non-amnesic MCI is due to damage in other brain regions with relative sparing of the frontal lobes. For instance, intact basic attentional abilities, among other things, are necessary for optimal performance on executive functioning tasks. According to the dual-attentional theory, attention is subserved by a fronto-parietal network which includes the dorsal and ventral posterior parietal cortex (PPC; e.g., Behrmann et al., 2004; Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). It may be that non-amnesic MCI patients with executive dysfunction are impaired in the parietal brain regions underlying basic attention, such as the PPC. While much research has examined the involvement of parietal areas in memory impairment in MCI and AD (see Uncapher & Wagner, 2009, for a review), more research is needed to examine the involvement of parietal areas in executive dysfunction found in these populations as well.

An additional possibility regarding hippocampal volumes is that white matter instead of gray matter changes may account for memory impairment in MCI. Some studies have reported that the memory deficits found in amnesic MCI are due to a disruption of white matter tracts found in the parahippocampal gyrus, including the perforant path (e.g., Huang, Friedland, & Auchus, 2007; Stoub et al., 2006). It is possible that the amnesic MCI patients in the current study suffered from changes in the parahippocampal white matter, which would negatively impact memory performance, in the absence of significant hippocampal atrophy. Other studies using diffusion-tensor

imaging have found white matter changes in the fibers which connect the medial temporal lobe, including the hippocampus, to the cingulate (e.g., Zhang et al., 2007). In sum, these studies suggest that white matter changes are also important to consider in MCI, and may be present in the absence of gray matter changes.

Also, studies of atrophy in amnesic MCI have frequently reported atrophy in the entorhinal cortex (EC), a structure intimately related to the hippocampus and important for memory (Mesulam, 2000). Some studies have suggested that changes in the EC precede those in the hippocampus (e.g., de Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2008; Mesulam, 2000; Ries et al., 2008). Thus, the amnesic MCI patients in the current study may have exhibited atrophy in the EC with sparing of the hippocampus, particularly if the patients were early in their disease course.

However, because of the large body of evidence finding hippocampal involvement in amnesic MCI, it is likely that the current study's null findings are also attributable to methodological issues. It is possible that this study's relatively small sample size may have reduced the power to detect significant effects. Additionally, as is typical of samples collected through medical centers affiliated with educational institutions, this study's sample was generally a highly educated group. Education has been found to be a protective factor against cognitive decline (see Stern, 2009, for a review). Such associations between education and lower risk for cognitive decline have been attributed to the possibility that those receiving more years of education may have more cognitive reserve (Stern, 2009). Cognitive reserve is thought to allow a person to maintain cognitive performance despite increases in neuropathology, and is hypothesized

to operate through two processes (Stern, 2009). The first is neural reserve, which represents individual differences in the “efficiency, capacity, or flexibility” (Stern, 2009, p. 2016) of neural networks which mediate performance on a certain cognitive task (Stern, 2009). The second process is neural compensation, which refers to the ability of someone with more cognitive reserve to recruit additional brain regions or networks during task performance to off-set decline (Stern, 2009). Thus, individuals with high cognitive reserve can off-set potential cognitive decline from increasing neuropathology by employing neural reserve and compensation (Stern, 2009). Based upon this theory of cognitive reserve, an older adult with high cognitive reserve is expected to have more neuropathology than an older adult with the same level of cognitive functioning who has less cognitive reserve (Stern, 2009). Following this prediction, it is possible that the control subjects in the current study, who had high educational attainment (a proxy for cognitive reserve), actually exhibited atrophy in the hippocampus and ACC but did not meet criteria for MCI through the action of cognitive reserve. If control subjects did in fact exhibit brain atrophy, this contamination of the cognitively intact sample would prevent the detection of differences in ROI volumes between cognitively intact and MCI groups.

It is also possible that the MCI patients in this study’s sample were less severe cases of MCI than in other studies. Because severity has been found to be positively correlated with brain atrophy in MCI and dementia patients (e.g., Iacono et al., 2008; Ruidavets et al., 2007; Whitwell et al., 2008), it may be that a less severe sample would not yet display the brain atrophy seen in more advanced cases of MCI, leading to null

findings. In fact, one longitudinal study examined patients with amnesic MCI whose diagnosis remained stable and amnesic MCI patients who later converted to AD. While the patients who converted to AD showed significantly smaller volumes in several brain regions than controls, MCI patients who remained stable showed no gray matter differences when compared to controls (Whitwell et al., 2008). Several other studies have also reported hippocampal atrophy to be predictive of conversion from MCI to AD (e.g., DeCarli et al., 2007; Fleisher et al., 2008; Karas et al., 2008). Thus, if this study's participants were less severe or were less likely to convert to dementia, differences in hippocampal volumes between these patients and cognitively normal controls would be negligible.

Finally, another possible explanation for the lack of significant findings in this study lies in the division of patients into amnesic and non-amnesic MCI categories. As discussed earlier, MCI patients can be impaired in either one cognitive domain or multiple cognitive domains. Memory impairment trumps impairment in all other domains; thus, if a person is impaired in memory in addition to non-memory domains, they are automatically categorized as an amnesic MCI patient. This means that multiple-domain amnesic MCI patients may in fact also be impaired in executive functioning. The presence of patients with executive dysfunction in this study's amnesic MCI sample would dilute any differences in ACC volumes between amnesic and non-amnesic MCI groups. Similarly, patients with non-amnesic MCI may be impaired in domains other than executive functioning, such as language or visuospatial processing. Such lack of

homogeneity in the non-amnesic MCI sample may again dilute any ACC volume differences between amnesic, non-amnesic, and cognitively normal controls.

Future research can address these limitations by examining ACC and hippocampal volumes in amnesic and non-amnesic MCI patients with and without executive dysfunction. Moreover, the inclusion of neuropsychological test scores would allow an investigation of the relationship between cognitive functioning and ROI volume. In this way, the relationship between performance on EF measures and ACC volume, for example, can be directly assessed in this population. It may also be beneficial to include an analysis of the EC as well as to examine white matter changes in parahippocampal regions. Additionally, studies in this area should examine other frontal regions in addition to the ACC, such as the dorsolateral prefrontal cortex. Functional imaging may be an even more sensitive indicator of brain abnormalities than volumetric studies, as certain ROIs may begin to function abnormally prior to any tissue loss. For instance, in a study of amnesic and non-amnesic MCI patients using both structural MRI and PET, no significant volumetric differences were found between amnesic MCI patients and controls, yet PET imaging revealed significant hypoperfusion in medial temporal lobe structures, including the hippocampus, in amnesic MCI patients compared to controls (Jauhiainen et al., 2008). It may also be worthwhile to investigate the relative contribution of frontal versus parietal involvement in MCI patients with executive impairment. As discussed above, it may be that dysexecutive MCI is characterized not by damage in frontal areas but rather damage in other areas which indirectly affect executive functioning, such as the PPC (e.g., Behrmann et al., 2004; Corbetta & Shulman, 2002;

Corbetta et al., 2008). Ultimately, longitudinal research is essential for determining whether the atrophy rate in various ROIs differs across MCI subtypes and whether these differences predict the type of dementia MCI patients eventually convert to.

Bearing in mind the limitations of this study, it nonetheless has several implications for research on MCI. This study suggests that the ACC may not be involved in non-amnesic MCI, although additional studies are needed to fully examine this possibility. Should this finding be replicated by future work, it suggests that EF deficits found in MCI occur through damage to a different area in the neural network underlying EF, either within or beyond the frontal lobes. Because the lack of findings in this study also leaves open the possibility that no specific brain region differentiates the subtypes of MCI, it begs the question whether MCI subtypes are truly distinct. The nature of the subtypes of MCI, and in particular whether they are pathways to the same or different forms of dementia, has been a point of contention in the literature. While the current study does not provide an answer to this debate, it does imply that the subtypes of MCI may be more similar than previously believed.

In summary, the present study examined differences in hippocampal and ACC volumes in cognitively intact patients and those with amnesic and non-amnesic MCI. After controlling for the effects of premorbid IQ, education, and dementia severity, no significant differences were found among participants in either ROI. While the interpretation of these results is limited by a small, highly educated sample and the possibility of executive dysfunction being present in patients in both amnesic and non-amnesic groups, these findings still have important implications for the field. This study

suggests that the ACC is not involved in non-amnesic MCI and that other areas in the EF-neural network may instead be compromised. Furthermore, it is possible that no brain regions exist that consistently differentiate the subtypes of MCI, which suggests the possibility that the distinction between amnesic and non-amnesic MCI is invalid. Future research in this area is necessary to further elucidate the nature of the subtypes of MCI and their relationship to one another. Once a full understanding of MCI is achieved, effective interventions targeting the cognitive decline seen in MCI and dementia can be designed.

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