CHARACTERIZATION AND DIFFERENCES BETWEEN POSSIBLE AND PROBABLE MILD COGNITIVE IMPAIRMENT IN AN ALZHEIMER'S DISEASE CENTER

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DEDICATION

I would like to thank my loving Mother, Stepdad, fiancé, and friends for their continued support and belief in me during pursuit of this degree.

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by

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THESIS

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Abstract

BACKGROUND: Mild cognitive impairment (MCI) is considered an intermediate state between normal aging and dementia. A subjective cognitive complaint (SCC) is a key component in the diagnosis of MCI. However, some individuals with SCCs do not show objective impairment on neuropsychological measures and there has been debate about the role of SCCs for the characterization of MCI. This study aimed to examine the differences in neurocognitive function and other risk factors between MCI subtypes and better understand the role of the SCC when objective cognitive impairment is not present.

SUBJECTS: This retrospective study includes 395 participants [age (M, SD) =67.5(7.2), education (M, SD)=15.10(2.7)], from the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center who were English speaking and between the ages of 50-90. Participants received a comprehensive clinical assessment including neuropsychological testing and diagnosis, which was made via multidisciplinary group consensus. This study consisted of participants classified at their baseline ADC visit as individuals with SCC but normal cognitive performance (possible MCI, n=83), individuals with SCC and abnormal cognitive performance (probable MCI, n=121), and normal controls (n=191).

METHOD: Differences in performance on neuropsychological measures among possible MCI, probable MCI, and normal control groups were examined using MANOVA. Differences in the frequency of selected cognitive and vascular risk factors, including APOE4, hypertension, high cholesterol, and diabetes mellitus, were examined using chi square test of independence. Demographic differences (age, education, gender, depression, and premorbid intelligence) across groups were compared using either ANOVA or chi square.

RESULTS: Normal controls performed significantly better than the probable MCI group on the MMSE, TMT-A, TMT-B, Block Design, WCST, FAS, Animal Fluency, and BNT ($p<.05$). On the CVLT, normal controls demonstrated fewer intrusion errors, higher total learning scores, and better long delay free recall than both the possible and probable MCI groups, and similarly, the possible MCI group performed significantly better than the probable MCI group. The frequency of APOE4 did not differ significantly among groups ($p>.05$). The probable MCI and possible MCI group had significantly higher rates of hypertension (58%, 59%) compared to the normal control group (46%). The probable MCI group had significantly higher rates of high cholesterol (66%) than the possible MCI group (18%). The probable MCI group had significantly more males, lower education, and higher GDS scores compared to NC groups ($p<.05$).

DISCUSSION: This study demonstrated that the probable MCI group differed from normal controls on measures of memory, executive function, and language, and had higher rates of hypertension and high cholesterol. Although statistically significant differences among all three groups on measures other than complex verbal memory were not seen; closer examination of the neurocognitive test scores showed that the possible MCI group performances were qualitatively more similar to that of the probable MCI group rather than the NC group. This may support the notion that individuals with a SCC but without overt impairment on testing do share commonalities with those with clear MCI, indicating that SCC do carry clinical significance and warrant evaluation and monitoring over time in older individuals.

Keywords: Mild cognitive impairment, subjective cognitive complaint, dementia, aging

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LIST OF ABBREVIATIONS

MCI	Mild Cognitive Impairment
SCC	Subjective Cognitive Complaint
AD	Alzheimer's Disease
aMCI	Amnestic mild cognitive impairment
naMCI	Non-amnestic mild cognitive impairment
sdMCI	Single-domain mild cognitive impairment
mdMCI	Multiple-domain mild cognitive impairment
VaD	Vascular dementia
ADL	Activities of daily living
MMSE	Mini Mental State Examination
APOE	Apolipoprotein E
CSF	Cerebrospinal fluid
Ab	Beta amyloid
PiB	Pittsburgh Compound B
ADC	Alzheimer's Disease Center

CHAPTER ONE

Introduction

Mild cognitive impairment (MCI) is a syndrome defined as cognitive decline greater than expected for an individual's age and education, but which does not significantly interfere with independence in functional abilities. It is estimated that as many as 10% to 20% of people over the age of 65 are living with MCI (Petersen, 2011) and approximately 70% of individuals with MCI will eventually progress to AD or another form of dementia at a rate of 7%-15% per year (Lopez et al., 2003). In contrast, normal aging individuals over the age of 65 have an annual conversion rate to dementia of 1%-2% (Ganguli, Dodge, Shen, & DeKosky, 2001). Subjective cognitive complaints (SCC) are a key component in the diagnosis of MCI and in some cases may be present before clinical detection of MCI is possible.

MCI is considered an intermediate state between normal aging and dementia and the term "mild cognitive impairment" was first used to describe someone who may be in the preclinical phase of dementia (Flicker, Steven & Reisberg, 1991). MCI is a heterogeneous entity, with possible trajectories including Alzheimer's disease (AD), other dementias, and even reversion to normal cognitive functioning. Petersen and colleagues were the first to outline diagnostic criteria for MCI, which included a memory complaint via self-report or reported by an informant (Petersen, 2011), in addition to objective cognitive dysfunction in one or more cognitive domains. The clinical presentation and progression in those who initially present with a subjective complaint but no objective cognitive impairment is unclear. The characteristics or risk factors this group may share with those with cognitive deficits are also not well understood. Given the importance of early identification of MCI and dementia, further investigation of

individuals with a subjective cognitive complaint but no significant impairment on formal testing is needed, as the clinical outcome of this group is unclear.

CHAPTER TWO

Review of the Literature

Mild cognitive impairment is a term used to reflect the cognitive state between normal aging and a diagnosis of dementia and identifies individuals with subtle cognitive impairment for their age but who remain functionally independent (Petersen et al., 2001). A formal diagnostic scheme for MCI has not been entirely agreed upon, but the most well-known criteria are the Peterson criteria (Peterson et al., 1995), defined by 1) the presence of a memory complaint 2) normal activities of daily living 3) normal global cognitive function, and 4) abnormal memory function compared to age and education corrected normative data (Peterson et al., 1999). However, MCI is understood to be a heterogeneous construct that can involve domains other than memory and can have varying outcomes. As such, distinct clinical subtypes of MCI have been identified based on the type and number of cognitive domains affected.

MCI Subtypes

Mild cognitive impairment is divided into four different types, amnestic versus non-amnestic, and single domain versus multiple domain. Amnestic MCI (aMCI) is defined by the following criteria: 1) memory complaints, preferably corroborated by an informant, 2) impaired memory function for age and education, 3) preserved general cognitive function, 4) intact activities of daily living, 5) not demented (Murayama et al., 2013). This type of MCI has received the bulk of attention in the literature. Mild cognitive impairment is classified as non-amnestic MCI (naMCI) when a domain other than memory is impaired, such as language or executive function (Murayama et al., 2013). Mild cognitive impairment subtypes were delineated with the expectation that aMCI is likely to be a transitional state between normal cognition and AD. Non-amnestic MCI may be more likely to progress to non-AD dementia, such as vascular

dementia (VaD) (Sachdev et al., 2011), Lewy body disease (Ferman, Smith, & Kantarci, 2013), or frontotemporal dementia (De Mendonca & Riberio, 2004).

Mild cognitive impairment can also be classified as single-domain or multi-domain depending on the number of cognitive domains with objective impairment (Sachdev et al., 2011). Individuals with multi-domain MCI (mdMCI) may present with memory impairment along with evidence of decline in other areas such as language, reasoning, or perceptual skills. Those with mdMCI are at greater risk of developing dementia than those with single-domain MCI (sdMCI) in which there is only one area of cognitive decline. In a study investigating the prognosis of MCI subtypes, 25% of patients with amnestic MCI, 37.5% of patients with single domain MCI, and 54% patients with multi-domain MCI progressed to dementia (follow up time 3.49 +/- 2.2 years) (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006). Individuals with sdMCI revert to normal cognitive functioning with greater frequency than those with mdMCI (Sachdev et al., 2011). This may actually reflect cases in which normal variability in cognitive test performance was misidentified as MCI.

Functional Status/Ability

A key distinction between MCI and dementia is that MCI is associated with a generally intact ability to perform activities of daily living (ADLs) (Perneczky et al., 2006), whereas impaired functional abilities are part of the definition of a dementia syndrome. Basic ADLs consist of bathing, eating, and getting dressed. Complex ADLs are dependent on a certain level of memory, executive function, and attention and include things such as organizing work, managing finances, and using public transportation. Complex ADLs are vulnerable to decline with even mild impairment in cognition. Supporting this idea, some deterioration of complex ADLs has been reported in patients with MCI, and these early limitations in activities before they

are clinically significant or interfere with independence have been referred to as preclinical disability (Perneczky et al., 2006).

Individuals with MCI obtain lower informant-based ratings of complex ADLs when compared with the cognitively normal peers, as measured by the Functional Capacities for Activities of Daily Living error-based measure (Glosser et al., 2002), and those with self-reported ADL impairment demonstrate more rapid functional decline (Jefferson & Byerly, 2008). A recent study of 157 older adults found that preclinical disability in certain ADLs (e.g., shopping and check-book balancing) discriminated between older adults with normal cognitive function (mean age 72.5) and those with MCI (mean age 75.5), supporting the idea that there may be early changes in performance of instrumental ADL evident in MCI. Although intact ADLs are considered part of the diagnostic criteria for MCI, subtle differences in the effort or adaptations required may be present and may improve diagnostic accuracy and perhaps earlier identification (Rodakowski et al., 2014).

Epidemiology of MCI

Epidemiological studies of MCI have shown considerable heterogeneity, due in large part to methodological differences including varying definitions, cognitive instruments, and diverse populations (Sosa-Ortiz et al., 2012). It is estimated that the prevalence of MCI among populations of community dwelling adults 71 and older is as high as 22%. Prevalence rates among older adults cared for in memory care practices are estimated at nearly 40% (Campbell, Unverzagt, LaMantia, Khan, & Moustani, 2013).

Age

Age is the most important risk factor for the development of MCI. In a population-based random sample examining the prevalence of MCI in an elderly population, MCI was more

prevalent in older subjects (Hanninen, Hallikainen, Tuomainen, Vanhanen & Soininen, 2002). Approximately 3%-5% of those over 60, and 15% of those over 75 are affected by MCI (Panza, 2005). In a longitudinal community-based study investigating risk factors for MCI, older age predicted greater declines in memory, attention/processing speed and global cognition (Sachdev et al., 2012). In a multicenter population study, participants with MCI were significantly older than the healthy, non-MCI population (Lopez et al, 2003).

Education

Education has been shown to be a protective factor against MCI and AD. MCI is more likely to be found in subjects with a lower level of education (Hanninen et al., 2002). Highly educated participants (>15 years) have a lower prevalence and incidence rate of AD than those who were less educated (Stern et al., 1994). However, there are longitudinal studies demonstrating a more rapid cognitive decline after diagnosis in highly educated AD patients (Stern, Albert, Tang & Tsai, 1999). The protective effect of education has been explained by the cognitive reserve theory, which states that the brain copes with pathology using premorbid cognitive or compensatory resources (Stern, 2006). Therefore, higher education may provide an abundance of cognitive reserve and contribute to the maintenance of cognitive functions or delay the presentation of dementia (Stern, 2006). High education (>15 years) was associated with an 85% reduced MCI/AD risk compared to low education (<10 years). Highly educated subjects had an MCI/AD risk that was 75% lower than the MCI/AD risk for subjects with a medium-level education (10-15 years) (Sattler & Toro, 2012).

Education also appears to have a role in progression of disease. Longitudinal studies have documented more rapid decline after diagnosis in highly educated AD patients compared to lesser-educated group (Stern et al., 1999). Education might alter progression depending on the

degree of impairment in MCI. For example, in a sample of 249 aMCI patients from 31 memory clinics, highly educated aMCI patients showed faster cognitive decline than less educated patients, similar to the pattern shown in patients with AD (Ye et al., 2013). This study also showed that early stage aMCI participants with a higher level of education demonstrated a slower decline, while those within the late stage of aMCI showed a more rapid progression. This suggests that cognitive reserve may override or mask pathology for some period of time, but eventually the protective effects of education succumb to disease progression (Ye et al., 2013).

Sex

The relationship between sex and MCI is less clear. A population-based study of 806 elderly subjects (aged 60-76) found no difference in the prevalence of MCI by sex (Hanninen, 2002). Some studies suggest a higher prevalence in males (Petersen et al., 2010), while others have found either a higher incidence in females (Di Carlo et al., 2007), or no sex difference in MCI (Kivipelto et al., 2001). In an epidemiological study investigating the role of sex in progression to MCI and other forms of dementia (n=2611), males (n=1061) had a higher risk of MCI, while females (n=1550) tended to be more affected by AD. This may be related to a survivor effect, given that females have more longevity than men (Sheshadri & Wolf, 1997).

Race

The relationship between race and MCI is complex; in part because of the well-known phenomenon of white adults generally obtaining higher mean scores on cognitive tests than African Americans after adjustment for age and education (Wood, Guiliano, Bignell & Pritham, 2006). Many of today's African American elders received their education in segregated schools; therefore, the quality of education may account for a considerable portion of racial differences observed in late life cognition (Sisco et al., 2013). Incidence of MCI and progression rates to AD

may differ among ethnically diverse individuals in part because the cognitive tests used to classify "objective" impairment have poor specificity in these groups (Manly & Jacobs, 2001). In a multicenter population-based longitudinal study over a four-year period, MCI risk factors and their role in development of MCI were investigated. There were significantly more African American participants in the MCI group than among the healthy participants. This study found an association between being African American and developing MCI, independent of other risk factors such as cerebrovascular risk factors and presence of the apolipoprotein 4 (APOE4) allele (Lopez et al., 2003).

Cognitive Characteristics of MCI

Neuropsychological assessment allows for the identification of cognitive impairment and assessment of degree and pattern of deficits in individuals with cognitive complaints or dementia. Scores that fall 1-1.5 standard deviations below the mean, based on appropriate normative data, are typically considered indicative of mild impairment (Chapman et al., 2011). Memory is the domain most commonly affected in MCI. Other domains can also be impaired, including executive function, language, visuospatial abilities, and attention.

Non-demented adults who later develop Alzheimer's disease frequently show a subtle decline in episodic memory prior to the emergence of the more obvious cognitive and behavioral changes required for a clinical diagnosis of dementia. A significant decline was found in episodic memory and executive functions in individuals with preclinical AD during the period from 1.5 years to 3.5 years before the diagnosis (Chen et al. 2001). Chen and colleagues (2001) found that 4 years before the onset of clinical symptoms, those with lower learning and retention scores were more likely to progress to Alzheimer's disease. Decline in episodic memory is evident

before the development of dementia and is correlated with the ensuing development of AD (Albert & Killiany, 2001).

In a study investigating the pattern of memory dysfunction in MCI, the California Verbal Learning Test, (CVLT) (Delis, Kramer, Kaplan & Ober, 1987), was examined across 3 groups, including 65 subjects with amnestic MCI, 65 with probable AD, and 65 normal controls. The pattern of deficits detected in the MCI sample was similar to the AD sample, with reduced learning, rapid forgetting, and poor recognition discriminability. MCI performance on this verbal memory measure was significantly worse than the normal controls and better than that of AD population (Greenaway et al., 2006). In this same study, CVLT delayed recall performance was one of the best predictors of conversion to AD, exceeding the predictive power of the APOE4 gene and a variety of neuroimaging variables.

Patients with naMCI often have trouble with attention items on the Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975), such as calculations, spelling WORLD backwards, and reciting the months of the year in backwards order (Budson & Solomon, 2011). Decline in executive function (EF) is often a feature of both MCI and Alzheimer's disease. EF has been associated with decline in activities of daily living and may play a role in predicting conversion from MCI to dementia; for example, a composite score of several executive function measures (e.g., Trails A and B, Category Fluency, and Clock Drawing) predicted conversion from MCI to AD in a sample of 390 longitudinally followed subjects (Gibbons, 2012). The presence of early memory impairment as the hallmark of MCI is widely accepted, but more research is necessary to examine the differences in other cognitive domains in MCI.

Risk Factors Associated with MCI

In addition to patterns of cognitive impairment, there are biological features commonly associated with MCI and/or AD. These biomarkers include hippocampal atrophy, changes in regional brain metabolites, the apolipoprotein E4 genotype, and CSF markers (Petersen et al.,1995). The identification of risk factors may help predict risk of progression from MCI to dementia and could have implications for delaying or preventing cognitive decline through interventions for modifiable risk factors.

APOE Genotype

According to the National Institutes of Health (2011), apolipoprotein E (APOE) is a type of plasma protein involved in transport of cholesterol. APOE is increased in various neurodegenerative diseases, including AD, in which APOE binds to senile plaques and neurofibrillary tangles. The APOE gene is found on Chromosome 19 and has three different isoforms: E2, E3, and E4. Those with the E4 genotype are at increased risk for developing late-onset Alzheimer's disease whereas people who possess the E2 genotype may be at a decreased risk. Those with the E4 gene are at an increased risk for displaying Alzheimer's disease at 4 times the rate of those without the E4 allele (Corder et al., 1993). Although those with the E4 genotype are at greater risk of developing dementia, once the disease process is underway E4 does not appear to lead to a more rapid deterioration (Bunce, Fratiglioni, Small, Winblad & Backman, 2004).

Individuals between ages 50-70 without dementia who carry the E4 allele performed more poorly on cognitive tasks than those without the E4 allele (Parasuraman, Greenwood & Sunderland, 2002). The E4 carriers also displayed subtle weaknesses in visual attention and working memory. A prospective observational study of 43 APOE 4 homozygote carriers, 59 APOE E4 heterozygotes, and 112 noncarriers showed that 40% of those who carried the E4

allele experienced cognitive decline that preceded the clinical diagnosis of MCI by the time the subjects reached their 60s. In addition, memory decline in the APOE E4 group was strongly predictive of future decline, suggesting that memory declines more rapidly with age in APOE E4 carriers (Caselli et al., 2007). Presymptomatic APOE E4 individuals may represent a population at risk for MCI syndromes (Caselli et al., 2007).

Hippocampal Atrophy

The importance of medial temporal lobe structures for learning and memory is well established. Hypoactivation of these areas and atrophy of the hippocampus have been shown in AD and MCI (Hampstead & Brown, 2013). For example, a recent meta-analysis revealed that hippocampal atrophy was characteristic of MCI and that there was greater atrophy in MCI relative to healthy older adults (Hampstead et al., 2013).

The most extensively studied predictor of progression from mild cognitive impairment to dementia is hippocampal atrophy measured by structural magnetic resonance imaging. For example, atrophy in these regions was a strong predictor of conversion from MCI to AD over a 2-year period (Hampstead et al., 2013). Those with aMCI with hippocampal volume at or below the 25th percentile for age and sex had 2 to 3 times the risk of progression to dementia over a 2-year period than those whose hippocampal volume was above the 75th percentile (Petersen, 2011). However, there is as yet no generally accepted specific threshold of hippocampal atrophy to distinguish “normal” from MCI or MCI from AD. Significant neuronal loss must have occurred prior to any volumetric changes, and cognitive reserve may allow individuals even with substantial atrophy to present as clinically normal. Therefore volumetric data must be interpreted within the context of other clinical and neuropsychological data (Hampstead et al., 2013).

Cerebrospinal Fluid Biomarkers

One of the earliest manifestations of the prodromal phase of dementia may be a change in levels of various CSF biomarkers (Moghekar et al., 2013). MCI has been associated with low levels of B-amyloid peptide 42 and elevated levels of tau protein in cerebrospinal fluid (Petersen, 2011). A study of 129 normal individuals (spanning from 21-100 years of age) reported an association between the ratio of CSF t-tau/A(beta)1-42 at baseline and progression toward MCI over a 3.5 year period (Li et al., 2007). Another study examining normal individuals aged 60-91 found that these ratios were associated with increased risk of progression to MCI over 1 to 8 years (Fagan et al., 2007). A longitudinal cohort (n=265) underwent clinical and cognitive evaluations, and baseline differences in CSF A(beta) 1-42 and p-tau, as well as the ratios of t-tau/A(beta)1-42 were predictive of cognitive outcome more than 5 years before symptom onset. Of this cohort, 53 participants developed MCI over a 5-year period (Moghekar et al., 2013).

Vascular Risk Factors

Vascular risk factors such as hypertension, diabetes mellitus, and high cholesterol, among others, are associated with late-life cognitive decline and as such are thought to influence the development of MCI (Lopez, 2003). These health conditions are of interest as they represent potentially modifiable risk factors that may play a role in prevention of MCI and dementia. There is a very large body of literature examining the relationship between vascular risk factors and cognition, and often with conflicting findings, which often reflects varying methodology. A full review of this issue is beyond the scope of this project, but the relationship between each factor, MCI, and cognitive complaint is briefly outlined below.

Chronic hypertension is considered perhaps the most important vascular factor in terms of predisposition to cognitive impairment (Duron & Hanon, 2008). For example, a prospective longitudinal study over 2 years investigated the association between high blood pressure and

cognitive status in individuals with MCI. MCI participants with high BP (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) demonstrated significantly faster decline on neuropsychological measures of visual motor sequencing, set shifting, and naming than those who maintained normal blood pressure (Goldstein, Levey & Steenland, 2013).

Diabetes mellitus has been shown to be an independent risk factor for cognitive decline. Longer duration of diabetes, lack of antidiabetic medication, and a higher number of hypoglycemic episodes were also associated with an increased risk of cognitive decline (Etgen, 2011). Cross-sectional studies have shown that diabetes is related to impaired cognitive functioning in general. A review of 19 studies found that in 13 of these studies participants with type 2 diabetes showed significantly lower scores on at least one cognitive measure. Verbal memory and complex information processing were found to have the most significant relationship, with diabetes status supporting the effect of diabetes on cognition (Whitmer, 2007).

It is unclear whether dyslipidemia, an abnormal concentration of lipids in the body, is associated with MCI. A longitudinal cohort study explored lipid levels and risk of MCI, amnestic or non-amnestic, in the elderly. There were 324 cases of MCI, 153 cases of amnestic MCI and 171 cases of non-amnestic MCI. Baseline data were collected for 2 years and follow up was collected at sequential 18-month intervals. There was no relation between lipid levels and the risk of amnestic or non-amnestic MCI, and there was no effect of lipid-lowering treatment on MCI risk (Reitz, Tang, Manly, & Schupf, 2008). In contrast, in a sample of 449 subjects aged 65 to 79 years followed after 21 years, 6% of whom met criteria for MCI, elevated serum cholesterol (≥6.5 mmol/L) at midlife was a significant risk factor for MCI in late life (Kivipelto et al., 2001).

There has been limited investigation into the relationship between vascular risk factors and subjective cognitive complaints (SCC). In an Australian sample of 45,533 participants (aged 45 to 64) investigators examined the relationship between SCC and vascular risk factors. SCC was defined as 'fair' or 'poor' on a self-reported five-point Likert scale of memory function in relationship to obesity, diabetes, hypertension, hypercholesterolemia, and smoking. Twelve percent of respondents reported SCC, and SCC was strongly associated with the presence of diabetes. Two other risk factors, smoking and hypercholesterolemia, showed a small independent association with SCC. Two other studies observed a minimal association of vascular risk factors with SCC; however, these were cross-sectional samples of individuals who were not diagnosed with MCI or dementia. (Paradise, Glozier, Naismith, Davenport & Hickie, 2011). In an Afro-Caribbean population of 243 participants aged 55-75, diabetes, among other vascular risk factors, were not associated with memory complaints. (Stewart et al.,2001).

Depression

Depressive symptoms are commonly observed in older adults with MCI, (Hudon, Belleville, & Gauthier, 2008). In a population-based epidemiological study consisting of 320 participants with MCI, 138 (43%) demonstrated neuropsychiatric symptoms, with depression being the most common (20%) (Lyketsos et al., 2002). The role of depression as a risk factor for dementia has been well-established but a similar role for MCI risk is less clear (Dotson, Beydoun & Zonderman, 2010).

Depression has been shown to increase the likelihood of conversion from MCI to dementia. For example, in a prospective cohort study of 114 participants with aMCI, subjects were given baseline memory, verbal fluency, and depression measures. At 3-year follow-up, depressed participants developed dementia approximately 13 months earlier than the non-

depressed group. This study suggests that patients with both MCI and depression are at a greater risk of developing Alzheimer's related dementia and having these risk factors predicts a more rapid cognitive deterioration compared to those without depression (Modrego & Ferrandez, 2004).

The association between depression and cognitive complaints is an important consideration for understanding the clinical significance of SCC (Hannien et al., 1994). In a cross sectional analysis of 45,532 participants between 45 and 64 years of age, individuals who endorsed depressive symptoms were 7 times more likely to have SCC than those who were not experiencing psychological distress (Paradise et al, 2011). A community survey in 2546 participants ages 60-64 examined the role of memory complaints and their relationship to cognitive functioning (Jorm et al.,2004). They found that scores on self-report measures of depression were a substantial correlate of memory complaints. This study also asserted that a specific type of emotion-focused coping strategy, ruminative style, played an important role in a memory complaint. Ruminative style refers to a coping strategy involving a chronic focus on negative emotions and the meaning associated with those emotions. This suggests that some individuals are more prone to dwell on their memory failures and view themselves as having difficulty with memory (Jorm et al.,2004). The authors of this study concluded that SCC were most closely related to psychiatric symptoms, personality characteristics, and poor physical health. Individuals with depression may report more cognitive problems in daily life than non-depressed patients, but these complaints do not always correspond to impaired performance on neuropsychological tests (Jonker, Geerlings & Schmand, 2000). Depression is thus an additional factor to consider when attempting to explore the clinical utility of a SCC.

Role of Subjective Cognitive Complaint in MCI

Subjective cognitive complaint (SCC) can be conceptualized as personal knowledge and awareness of a change in cognitive ability. Common subjective complaints include forgetting where things are left, word finding difficulty, and slowed thinking. Cognitive complaints are a common occurrence in the elderly. For example, a large-scale community study of individuals without dementia (n=2537) ages 65-85 recruited from 30 general practitioners in Amsterdam, and using 3 memory questions, documented complaints in 34% of the sample (Jonker, Launer, Hooijer & Lindeboom, 1996). This perception of cognitive change may occur 15 years before diagnosis of MCI (Reisberg et al., 2008). However, there is debate about the clinical significance and diagnostic value of the subjective cognitive complaint (Jorm et al., 2004). For example, a community study of 3,079 participants over age 65 found that 56% of the sample had memory complaints but this did not predict later cognitive decline (Blazer, Hays, Fillenbaum, & Gold, 1997).

The utility of a cognitive complaint in predicting cognitive function is unclear, and methodologic differences in the evaluation of cognitive complaints may contribute to this variability (Jonker et al.,1996). There is evidence that SCC is important for MCI diagnosis for reasons other than it being part of Petersen's criteria. For example, in a study of Chinese subjects with MCI and early dementia, SCC were significantly correlated with objective performance on short term memory tasks, supporting the potential usefulness of SCC in the determination of cognitive impairment (Lam, Lui, Tam & Chiu, 2005). However, there is also evidence that SCC has modest diagnostic value and should not be a necessary criterion for MCI. In the Steel Valley study consisting of 1248 participants, 37% had a SCC but only 3.2% met criteria for MCI. When the MCI diagnostic requirement of SCC was dropped, 6.3% met criteria for MCI (Mitchell,

2008). The relationship between subjective and objective cognitive complaints may be uncertain; however, it may be possible to use SCC as a type of initial screening for detection of MCI (Mitchell, 2008).

A study investigating the nature and severity of the memory complaint in MCI found that complaints increased in parallel with global cognitive deficits (Clement, Belleville & Gauthier, 2008). The same study suggests that individuals with MCI report more memory complaints than healthy older controls. Similarly, in a community study of 157 volunteers, 80% of those with MCI had memory complaints (De Jager & Budge, 2005). In contrast, some individuals with MCI do not endorse a memory complaint even upon specific questioning. In a cross sectional study of 592 subjects age 75-76 years who underwent extensive neuropsychological testing, only 20.6% of subjects with broadly defined MCI complained about their memory (Lam, Lui, Tam & Chiu, 2005). MCI without SCC has been referred to as "asymptomatic MCI" and the clinical differences in presentation between MCI with and without SCC are debated (Mitchell, 2008). These findings illustrate the need for further exploration of the specific role SCC plays in the presentation of MCI.

The subjective cognitive complaint may also have implications for risk of conversion from MCI to dementia (Roberts, Clare & Woods, 2013). A longitudinal study of elderly residents in England (n=705), investigated the prevalence of subjective memory impairment and its value as a predictor of future depression or dementia, and found subjective memory impairment to be common, occurring in 25% of subjects. After a 2-year period, those with memory complaints had 4 times the risk of developing dementia (Tobiansky, Blizard, Livingston & Mann, 1995). SCC may then play a role in predicting risk of cognitive decline in those with MCI at baseline (Crowe, Andel, & Wadley, 2006). The finding that SCC is predictive of future cognitive decline was

replicated in a longitudinal study of normal subjects over the age of 50 (mean follow up time=8 years) (Glodzik-Sobanska et al., 2007).

However, others question the validity of SCC due to the prevalence among older adults and lack of specificity. Furthermore, the presence of an underlying neurodegenerative disorder could contribute to lack of insight and lead to an incorrect self-assessment (Gifford et al., 2014). A study investigating impaired awareness of cognitive deficits in patients with MCI and AD showed that both groups demonstrated impaired awareness and significant heterogeneity in clinical presentation of awareness (Vogel et al., 2004). These findings demonstrate that reduced insight is not only common in early AD but also present in MCI, which could limit the utility of a SCC especially without corroboration from an informant. Vogel and colleagues maintain that subjective memory complaints should not be a mandatory criterion when assessing MCI (Vogel et al., 2004).

In summary, MCI is a clinical state between normal aging and dementia. Subjective cognitive complaints are a key aspect of MCI; however, the role of SCC in the clinical presentation and progression of MCI remains somewhat ambiguous, and the relationship between subjective and objective cognitive impairment is complex. In addition, several biological risk factors are shared by MCI and AD. Individuals with SCC but normal cognitive function are of interest, as some may have very subtle cognitive changes that are not yet evident on formal testing while other individuals may have SCC related to depression or other reversible causes. This study examined a group with SCC and no objective cognitive deficit, classified as *possible MCI*, and a group that meets full MCI criteria (*probable MCI*), as well as healthy controls, in terms of neurocognitive test results, demographic variables, and selected associated dementia risk factors (e.g., APOE4).

Aims

Overall Aim: To examine the cognitive and risk features of MCI subgroups to better understand the role of subjective cognitive complaints.

Aim 1: To examine differences on selected neuropsychological measures among possible MCI, probable MCI, and normal control groups.

Hypothesis 1: Individuals with probable MCI will have significantly lower performance on select measures of executive function and language than those with possible MCI, who will demonstrate lower performances than normal control subjects.

Aim 2: To examine differences in selected MCI and AD risk factors among the possible MCI, probable MCI, and normal control subjects.

Hypothesis 2: Individuals with possible MCI will have a lower prevalence of APOE4 than those with probable MCI, and control subjects will have a lower APOE4 prevalence than either MCI group.

Hypothesis 3: Rates of vascular risk factors (hypertension, high cholesterol, diabetes mellitus) will be greater in the probable MCI group than possible MCI group, and controls will have lower rates than either MCI group.

Exploratory Aim: To examine the demographic differences between possible MCI and probable MCI groups (age, education, gender, depression, premorbid intelligence).

CHAPTER THREE

Methods

Participants

This project is a retrospective study of data collected from the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center. The ADC collects neurocognitive and clinical data of individuals with Alzheimer's Disease as well as other known or suspected neurodegenerative disorders, and healthy aging persons at regular intervals. All participants received a comprehensive clinical assessment including neuropsychological testing, and diagnosis was made via a multidisciplinary clinical group consensus. This study consisted of those participants diagnosed as Possible MCI, Probable MCI, (including both amnestic and non-amnestic subtypes, see Appendix 1 for criteria), and Normal Controls according to the criteria below at their baseline ADC visit. Inclusion criteria included being English speaking and between the ages of 50-90. Groups were classified by the following criteria:

Probable MCI (n=121)

1) presence of a cognitive complaint

2) objective evidence of cognitive impairment on one or more cognitive tests (standard deviation or more below the mean)

3) normal activities of daily living

4) Clinical Dementia Rating Scale (CDR) global score of 0.5 (see Appendix 2 for CDR description)

5) does not meet criteria for dementia

6) absence of neurologic disorder or psychological disorder that could account for symptoms

Possible MCI: (n=83)

1) presence of a cognitive complaint

2) absence of cognitive impairment on neuropsychological tests

3) CDR global score of 0.5

4) normal activities of daily living

5) does not meet criteria for dementia

6) absence of neurologic disorder or psychological disorder that could account for symptoms

Normal Control Subjects (n=191)

1) absence of cognitive complaints

2) CDR global score of 0

3) normal cognitive testing

4) absence of degenerative neurologic disorder or psychological disorder

Measures

Examination of ADC participants includes a clinical history obtained by trained personnel, neurological examination, administration of the CDR, interview of informant, and formal neuropsychological testing. The following tests were selected for this study to sample performance in multiple cognitive domains from a larger battery administered as part of the baseline study visit.

The *Mini Mental State Examination* (Folstein et al., 1975) is a brief cognitive measure utilized to quantify cognitive function and screen for dementia. It investigates several domains including orientation, attention, recall, language and visuospatial skills. This study utilized the raw score from the MMSE, with a total possible score of 30.

The *American version of the National Adult Reading Test (AMNART*; Grober & Sliwinski, 1991*)* is a measure of premorbid intelligence for older adults (Grober & Sliwinski, 1991). This test consists of 50 orthographically irregular English words. Participants are instructed to pronounce each word out loud, beginning at the top of the list and continuing through the end. The AMNART is considered a better premorbid estimate than demographic variables (Pavlik, Doody, Massman, & Chan, 2006). The AMNART total error score was converted to a standard score.

The *Wisconsin Card Sorting Test (WCST*; Heaton, Chelune, Talley, Kay & Curtiss, 1993) is a measure of abstract reasoning and problem solving. The WCST consists of four stimulus cards and 128 response cards that depict figures of varying forms, colors, and number. The client is asked to match the response card to one of the four stimulus cards (Heaton, Chelune, Talley, Kay & Curtiss, 1993). This study utilized Heaton normative data for number of perseverations (T score) as well as categories completed (6 possible categories).

The *Trail Making Test (TMT*; Reitan, 1955) is a test of motor speed, visual attention, and mental flexibility. The TMT consists of two parts, Part A and B. In Part A, the task is to draw lines on a page connecting 25 consecutive numbers, while in Part B the subject is instructed to draw the lines alternating between numbers and letters (Reitan, 1955). This study utilized raw and Heaton T scores for TMT A and B.

The *Boston Naming Test (BNT*; Kaplan, Goodglass &Weintraub, 1983) is a confrontation naming measure. The BNT consists of 60 items and assesses visual naming ability by presenting black and white line drawings. The BNT is useful for detecting relatively mild word finding difficulty (LaBarge, Edwards & Knesevich, 2004). This study utilized a 30-item version of the BNT (the odd numbered items from the original). The BNT raw score was utilized for this study.

The *Controlled Oral Word Association Test (COWAT)* (Benton & Hamsher, 1976) is a phonemic fluency task in which the participant produces as many words beginning with that letter as possible in one minute. There are three 60 second trials with 3 different letters (F, A, S). This study utilized the total number of words from all 3 trials. The *Animal fluency* task was utilized as a measure of semantic fluency. This task allows a 60 second trial to name as many animal names as possible. This study utilized the total number of words from the animal fluency and FAS tasks.

The *California Verbal Learning Test (CVLT)* (Delis, Kramer, Kaplan & Ober, 1987) is a measure of verbal learning and memory. The CVLT measures recall and recognition of a word list over multiple trials of immediate and delayed recall. CVLT Total Learning (raw and T-score), Long Delay Free Recall (raw and Z scores), and total number of intrusions were utilized in statistical analyses.

Block Design is a subtest on the Weschler Adult Intelligence Scale Revised (WAIS-R) (Weschler, 1981). Block design is a timed subtest designed to measure nonverbal abstract problem solving and visuospatial skills. This study utilized the raw scores and age corrected scaled scores.

The *Geriatric Depression Scale (GDS Short Form*; Yesavage et al., 1983) is a self-report measure of depression in older adults. Subjects respond in a "yes/no" format. The items listed pertain to depressive symptoms that have been validated in previous studies (Yesavage et al., 1983). The long form consists of 30 items and the short form consists of 15 items. The short form was utilized for this study. On the short form, total scores of 0-4 are considered normal, 5-8 are indicative of mild depression, 9-11 indicate moderate depression, while 12-15 indicate severe

depression. Subjects are asked to respond according to how they have felt over the past week. This study utilized the total number of items endorsed as an indicator of depression.

The Alzheimer's Disease Center is part of the National Alzheimer Coordinating Center Uniform Data Set, which provided participant demographic and health information. This study included diabetes, hypercholesterolemia, hypertension, and Apolipoprotein E genotyping, which involved DNA amplification and extraction from blood samples. Vascular risk factors were classified as either present or absent.

Procedures

This study employed the database of the Alzheimer's Disease Center (ADC) at the University of Texas Southwestern Medical Center in Dallas, TX. All persons whose data reside in this database have provided signed informed consent on forms approved by the UT Southwestern Institutional Review Board for use of their de-identified clinical data for clinical research. ADC participants were examined on an annual basis under standardized procedures and trained personnel administered the neuropsychological tests. The tests were scored and double scored by trained staff. After statistical assumptions for all analyses were examined to ensure the appropriateness of each statistic, descriptive data were generated for categorical variables and continuous measures. Alpha was set at $p < 0.05$. Statistical analyses were conducted using Statistical Package for Social Sciences version 23.0.

CHAPTER FOUR

Results

Five hundred cases from the ADC met diagnostic inclusion criteria. Of these, 103 participants were excluded as they were missing more than half of the cognitive test variables of interest and 2 participants were excluded due to missing demographic information, resulting in an available 395 participants. Of these 395 cases, 191 met criteria for normal controls, 83 met criteria for possible MCI, and 121 met criteria for probable MCI. Demographic characteristics of the sample are presented in Table 1. Seven individuals had a history of stroke; they were included in the sample as results did not differ when they were removed.

Hypothesis 1: Individuals with probable MCI will have significantly lower performance on select neuropsychological measures of executive function and language than those with possible MCI, who will demonstrate lower performances than normal control subjects.

Descriptive statistics for group performance on the selected cognitive measures are shown in Table 2. In order to determine whether groups differed in terms of cognitive performance, scores on the selected measures were compared using Multivariate Analysis of Variance (MANOVA) with three levels of the independent variable followed by Bonferroni post hoc analysis. Of the 395 participants in this study, 343 had all of the necessary neuropsychological data to be included in Hypothesis 1: possible MCI (n=70), probable MCI (n=97), normal controls (n=176). Statistically significant differences in neuropsychological scores were found across groups [$F(2,340)=24.452$, $p=.001$; partial $\eta^2=.126$] as discussed below.

Significant differences on several neuropsychological measures were noted between the normal control and probable MCI group, with the control group obtaining higher overall scores. The normal control (NC) group demonstrated significantly higher Mini Mental State

Examination (MMSE) scores than the probable MCI group [F(18, 323)=17.0, *p*=.001]. Although the mean score for the possible MCI group was not significantly different from the other groups, the possible MCI group demonstrated a lower overall MMSE score (M=27.91) than the NC group (M=28.91) and was generally comparable to the probable MCI group (M=27.74). The NC group also had significantly higher Trail Making Test B (TMT-B) raw scores [F(18, 323)=8.117, *p*=.001] and Trail Making Test B T scores [F(18, 323)=.452, *p*=.001] compared to the probable MCI group. Although not statistically significant, a subtle trend also was seen with the possible MCI group demonstrating a TMT performance (M=47.14) that was qualitatively more similar to the probable MCI group (M=48.05) than the NC group (M=53.00). A similar pattern in which the NC group performed significantly better than the probable MCI group and the possible and probable MCI groups displayed qualitatively similar scores was observed for the Boston Naming Test [F(18, 323)=14.187, *p*=.001], Animal fluency [F(18, 323)=.394, *p*=.001], FAS [F(18, 323)=1.674, *p*=.001], Trail Making Test A raw [F(18, 323)=2.732, *p*=.001], Trail Making Test A T score [F(18, 323)=.704, *p*=.016], Block Design raw [F(18, 323)=2.280, *p*=.001], and BD scaled score [F(18, 323)=.410, *p*=.001]. Normal controls made fewer perseverative errors on the Wisconsin Card Sorting Test [F (18,323)=21.35, *p*=.001], and completed more categories [F(18,323)=19.36, *p*=.001] compared to both MCI groups but the difference was only significant between the NC and probable MCI groups. Significant differences among all 3 groups were observed in aspects of CVLT performance including number of intrusions, [F(18,323)=8.84, *p*=.001], CVLT total learning raw score, [F(18, 323)=.205, *p*=.001], CVLT total learning T score, [F(18,323)=.041, *p*=.001], long delay free recall raw score [F(18, 323)=.391, *p*=.001] and long delay free recall Z score [F(18,323)=.309, *p*=.001]. The normal controls demonstrated fewer intrusion errors, higher total learning scores (raw and T scores), and better long delay free recall

(raw and Z scores) than both the possible and probable MCI groups, and, the possible MCI group performed significantly better than the probable MCI group.

Hypothesis 2: Individuals with possible MCI will have a lower prevalence of APOE4 than those with probable MCI, and normal control subjects will have a lower APOE4 prevalence than either MCI group.

A chi square test of independence with post hoc analysis with Bonferonni corrections was utilized to identify differences in the prevalence of APOE4 in the possible MCI, probable MCI, and normal control groups. One NC participant did not have APOE4 data. A total of 394 participants were included in the analysis. The frequency of APOE4 did not significantly differ among groups, X^2 (2)=7.891, p=.096, as shown in Figure 1. The majority of the overall sample (62%) did not have an APOE4 allele (66% of the normal control group, 61% of the possible MCI group, and 58% of the probable MCI group). There were 129 participants (33%) with one E4 allele. Thirty-one percent of the normal control group, 36% of the possible MCI group, and 33% of the probable MCI group had one E4 allele. A small number of participants (5%) had two E4 alleles. The probable MCI group had the largest number of participants with 2 E4 alleles (9%), followed by the normal controls (3%), and the possible MCI group (2%), though these differences were not statistically significant.

Hypothesis 3: Incidence of vascular risk factors (hypertension, high cholesterol, diabetes mellitus) will be greater in the probable MCI group than possible MCI group, and the normal controls will have lower rates than either MCI group.

A chi square test of independence with post hoc analyses with Bonferroni corrections was utilized to examine the prevalence of vascular risk factors (hypertension, high cholesterol, and diabetes mellitus) among the three groups. The frequency of high cholesterol varied significantly

among groups, X^2 (2)=12.79, *p*=.012, with the probable MCI group including a greater number of participants with high cholesterol (66%) than the possible MCI group (49%) and normal controls (53%). The probable MCI and possible MCI group had a significantly higher occurrence of hypertension (59% and 58%, respectively) than the normal control group (46%), (X^2 (2)=6.48, *p*=.039). The frequency of diabetes mellitus did not differ among groups (X^2 (2)=3.8, *p*=.150).

Exploratory Aim: To examine the demographic differences between the normal control, possible MCI, and probable MCI groups (age, education, gender, level of depression, and premorbid intelligence).

A chi square test of independence was utilized to determine whether groups varied by gender, and analysis of variance (ANOVA) and post hoc analyses with Bonferonni corrections were conducted to determine group differences in the continuous variables of age, education, level of depression, and premorbid intellect. There was a significant difference in gender between NC and probable MCI groups, X^2=10.652, *p*=.005. There were more females in the normal control group (65%), and possible MCI group (55%), while there were more males in probable MCI group (54%). Groups did not differ significantly in terms of age (F(2, 390)=2.108, *p*=.074, partial η^2=.011). Education differed by diagnosis, [F(2,390)=4.919, *p*=.007, partial η^2=.025], with a higher level of education observed in the normal control group (M=15.55) compared with the probable MCI group (M=14.65). There was a statistically significant difference between the probable MCI group and normal controls in level of depression, as measured by the GDS, (F(2,390)=17.259, *p*=.001, partial η^2=.081). The probable MCI group endorsed the most depressive symptoms (M=2.16) followed by the possible MCI group (M=1.27), and the normal controls endorsed the least number of depressive symptoms (M=0.95).

With regard to estimated premorbid intellect, the NC group demonstrated high average AMNART scores and the possible and probable MCI groups demonstrated average AMNART scores, with no significant difference found (F (2,69)=.599, p=.391, partial n^2=.017).

CHAPTER FIVE

Discussion

The present study examined differences in cognitive performance, vascular risk factors, and demographic factors among normal controls, a group with possible MCI, and a group with probable MCI. The first hypothesis was that participants with probable MCI would demonstrate lower performance on selected neuropsychological measures compared to participants with possible MCI, who in turn would perform more poorly than normal controls. The expected trend was observed on the MMSE, TMT-A, TMT-B, Animal Fluency, FAS, BNT, WCST, and BD although only differences between the probable MCI group and normal control group rose to statistical significance. These tasks tap into global cognitive status (MMSE), executive function (WCST, TMT), and language (BNT, Animal Fluency, FAS), all areas that are commonly linked to early cognitive decline in AD (Chapman et al., 2011; Chen et al., 2001). The only test that showed significant differences among all three groups was the CVLT, a finding that is not surprising given that CVLT performance was taken into consideration when participants were given a consensus diagnostic classification in the ADC and given that the majority of MCI participants were amnestic MCI subtype. This may also help explain differences in performance by group. As expected, normal controls demonstrated the strongest performance and the probable MCI group showed the lowest level of learning and recall as well as a higher number of intrusions. The only area in which possible MCI differed from normal controls was in verbal memory, a domain that has been shown to be a key indicator of prodromal dementia stages, particularly for aMCI (De Jager & Budge, 2005). The CVLT in particular has repeatedly been shown to be sensitive to early changes associated with MCI and Alzheimer's disease (Pozueta et al., 2011; Rabin et al., 2009) and it is well established that verbal list learning tasks can aide in

characterizing the severity of memory impairment in the early stages of dementia (Rabin et al., 2009). An increase in number of intrusions on the CVLT is consistent with previous studies of memory patterns in MCI (Greenaway et al., 2006). This finding is consistent with the idea that individuals with a subjective cognitive complaint but no objective impairment on testing may represent a very early MCI group. These individuals may be alert to insidious changes that are not overtly demonstrated on formal testing, consistent with prior work showing discrepancies between subjective complaints and performance on formal testing (Lenehan, 2012), and thus may be an important group to follow over time in order to better understand the trajectory of cognitive decline. These findings may also suggest that individuals with SCC who show lower performance in memory as well as aspects of executive function and language, such as seen in the probable MCI group, are further along in the course of MCI and potentially at greater risk of converting to a dementia, though a longitudinal study of these groups would be required to fully address this possibility.

A secondary aim of this study was to examine differences in common risk factors for MCI and AD among the probable and possible MCI groups and normal controls. It was hypothesized that the probable MCI group would have a higher prevalence of the APOE4 allele than the possible MCI group, who in turn would have the allele in higher numbers than the NCs. Interestingly, there was no statistically significant difference in APOE4 prevalence among groups, although there was a trend suggesting the expected pattern of probable MCI demonstrating a greater prevalence of APOE4 than possible MCI and normal control groups. This could suggest that these individuals are perhaps at less risk for progression to dementia. Alternatively, these results could suggest that although APOE4 is a powerful risk factor for AD

(Caselli et al., 2007), perhaps it is less so for MCI populations (Bunce et al., 2003) that are heterogeneous in nature.

The third hypothesis was that the probable MCI group would have higher rates of vascular risk factors (hypertension, high cholesterol, and diabetes) compared to those with possible MCI, who were expected to have higher rates of these factors than NCs. There was a significantly higher prevalence of hypertension in both the possible and probable MCI groups compared to normal controls. There was a significantly higher rate of high cholesterol in the probable MCI group compared to the possible MCI group. The rate of diabetes did not differ among groups. The presence of hypertension and high cholesterol in individuals with a SCC could convey a higher risk of incipient cognitive decline even in the absence of objective impairment on formal testing. However, the mechanisms for this may not necessarily be neurodegenerative, as hypertension and other vascular issues can obviously exert detrimental effects on cognition through independent processes (Gorelick et al., 2011; Venkat, Chopp & Chen, 2015).

A final aim of this study was to explore differences in demographic variables among possible MCI, probable MCI, and normal controls, including age, education, gender, depression, and premorbid intellect. This type of epidemiologic information can provide clinicians and researchers with more information about which demographic factors are more associated with these respective diagnoses and perhaps help gauge the likelihood of either the presence or risk of cognitive impairment. This study found a significantly higher prevalence of males in the probable MCI group, while a higher prevalence of females was seen in the possible MCI and normal control groups. This pattern is supported by previous literature showing the variable rates of MCI across gender groups (DiCarlo et al., 2007; Hannien, 2002; Kivipelto et al., 2001;

Petersen et al., 2010). There was also a significant difference in the level of education between normal controls and those with probable MCI, with the probable MCI group obtaining fewer years of education. This is consistent with existing literature showing a protective effect of education (Hanninen et al., 2002; Stern et al., 1994), although it should be noted that this was a well-educated sample overall (mean years = 15.10) and the difference was essentially 1 year of education which may be of limited clinical significance. The level of depressive symptoms endorsed on a screening measure differed between the probable MCI and normal control groups. It should be noted that this was not a depressed sample as evidenced by the very low level of item endorsement on the GDS (M=2.2). However, findings could suggest that perhaps even very low levels of depressive symptoms may have some association with SCC and MCI. Finally, it has been posited that individuals of higher intelligence may present with SCCs that are not substantiated on formal testing as a function of cognitive reserve; however, this study examined a measure of premorbid intellect (AMNART) and no differences were seen.

Limitations

The sample was primarily Caucasian and fairly well educated; therefore, whether the patterns observed in this study would be replicated in different sociodemographic groups is not known. In addition, as in all clinical research, there is an inherent selection bias, as participants were seen through a memory disorders research clinic and thus more likely to have SCC. It is unclear if similar patterns would be seen in individuals recruited from the general population or other type of clinical setting. In addition, this study utilized a moderate sample size, which could have limited our ability to detect group differences. Similarly, this study was not able to separately analyze amnestic and non-amnestic MCI in the possible and probable MCI groups due to limited sample size, and it may well be that these distinctions are important for understanding

the relationships between SCCs and patterns of cognitive performance. In this study, the range of data obtained on the GDS was limited. This limited range reduced the possible power of demonstrating the relationship between depression and MCI status. Another limitation is that there are a number of other factors that could relate to the presence of a subjective cognitive complaint aside from those examined in this study. For example, other aspects of mood such as anxiety, potential medication effects, and other health issues are potential variables that could relate to cognitive complaints and have little to do with actual cognitive dysfunction or brain pathology. Finally, this study was a retrospective, cross-sectional design examining differences in cognition and risk factors based on the presence of a SCC at baseline. It may be that SCCs have implications for change over time that would not be evident until a follow-up evaluation.

Future Directions

It would be useful to replicate this study in a larger and more diverse sample to help examine patterns of neurocognitive test performance and risk factors across groups with a subjective cognitive complaint. It would be helpful to monitor these individuals longitudinally in order to determine if there is a relationship between a SCC and later outcomes. Also, future studies should include measures of other neurocognitive domains, such as attention. Similarly, other risk factors associated with MCI and AD would be of interest to examine, such as patterns of hippocampal atrophy, particularly given that verbal memory was the primary area of difference among groups in this study.

Conclusions

SCCs are common in the general population and part of the diagnostic paradigms for MCI. However, the current diagnostic criteria of MCI have recently attracted criticism, particularly in relation to the role of the subjective cognitive complaint. It is unclear whether the

SCCs are a necessary criterion for the diagnosis of MCI or enhance the detection of MCI. This study aimed to better understand the cognitive characteristics and risk factors of a group of normal controls, individuals with SCC but normal cognitive performance (possible MCI), and individuals with SCC and abnormal cognitive performance (probable MCI) in an attempt to better understand the utility or importance of a cognitive complaint.

This study demonstrated that the probable MCI group differed from normal controls on measures of memory, executive function, and language, and had higher rates of hypertension and high cholesterol. Although statistically significant differences among all three groups on measures other than complex verbal memory were not seen, closer examination of the neurocognitive test scores showed that the possible MCI group performances were qualitatively more similar to that of the probable MCI group rather than the NC group. This suggests that the possible MCI classification may represent a population with more cognitive difficulties than observed in healthy individuals in a similar age group. This may support the notion that individuals with a subjective cognitive complaint but without overt impairment on testing do share commonalities with those with clear MCI.

Overall, this study did not demonstrate a consistent relationship between isolated SCC and general cognitive impairment. Presence of a cognitive complaint may relate to early decrements in complex verbal learning and memory and could be indicative of an individual at risk for cognitive decline, and thus may warrant monitoring over time to aid in early detection of MCI or AD. Specific vascular risk factors (hypertension and high cholesterol) were more prevalent in the probable MCI group, which is a valuable, though not novel finding that supports treatment and early intervention of these potentially modifiable risk factors. This study contributes to the current debate of the inclusion of the SCC in the diagnostic criteria for MCI,

indicating that subjective cognitive concerns do carry clinical significance and warrant further evaluation and monitoring over time in older individuals.

References

Albert, M.S. & Killiany, KJ. (2001). *Age-related cognitive change and brain-behavior relationships.* Handbook of the Clinical Psychology of Ageing. J .E. Birren & KW. Schaie (Eds.),161-85.San Diego, CA: Wiley.

Alexopoulos, P., Grimmer, T., Perneczky, R., Domes, G., & Kurz, A. (2006). Progression to dementia in clinical subtypes of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 22*(1), 27-34. doi: 10.1159/000093101

Benton, A.L., & Hamsher, K. (1976). Multilingual Aphasia Examination. University of Iowa, Iowa City, IA

Blazer, D. G., Hays, J. C., Fillenbaum, G. G., & Gold, D. T. (1997). Memory complaint as a predictor of cognitive decline: a comparison of African American and White elders. *Journal of Aging and Health, 9*(2), 171-184.

Budson, A., & Solomon, P.R. (2011). Memory Loss: A Practical Guide for Clinicians. Geriatric Research Education Clinical Center &Neurology Service. Philadelphia: Elsevier Inc.

Bunce, D., Fratiglioni, L., Small, B.J., Winblad, B., & Backman, L. (2004). APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. *Neurology*, *63*(5), 816-821

Campbell, N. L., Unverzagt, F., LaMantia, M. A., Khan, B. A., & Boustani, M. A. (2013). Risk factors for the progression of mild cognitive impairment to dementia. *Clinics in Geriatric Medicine, 29*(4), 873-893. doi: 10.1016/j.cger.2013.07.009

Chapman, R.M., Mapstone, M., McCrary, J.W., Gardner, M.N., Porsteinsson, A., Sandoval, T.C.,…Reilly, L.A. (2011). Predicting conversion from mild cognitive impairment to

Alzheimer's disease using neuropsychological tests and multivariate methods. *Journal of Clinical and Experimental Neuropsychology, 33*(2), 187-199.

Chen, P., Ratcliff, G., Belle S.H., Cauley, J.A., DeKosky, S.T., Ganguli, M. (2001). Patterns of Cognitive Decline in Presymptomatic Alzheimer Disease: A Prospective Community Study. *Archives of General Psychiatry*, *58*(9), 853-858. doi:10.1001/archpsyc.58.9.853.

Clement, F., Belleville, S., Gauthier, S. (2008). Cognitive complaints in mild cognitive impairment and Alzheimer's disease. *Journal of the International Neuropsychology Society, 14*(2), 222-232.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W.,…Pericak-Vance, M.A. (1993). Gene dose of aploipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, *261*(5123), 921-923.

Crowe, M., Andel, R., Wadley, V., (2006). Self-reported severe memory problems as a screen for cognitive impairment and dementia. *Dementia, 4*(4): 539-551.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A. (1987). California Verbal Learning Test. San Antonio, TX: The Psychological Corporation.

De Jager, C.A., Budge, M.M. (2005). Stability and predictability of the classification of mild cognitive impairment as assessed by episodic memory test performance over time. *Neurocase 11*(1), 72-79.

De Mendonca, A., & Riberio, F. (2004). Frontotemporal mild cognitive impairment. *Journal of Alzheimer's Disease, 6*(1), 1-9.

Di Carlo, A., Lamassa, M., Baldereschi, M., Inzitari, M., Scafato, E., Farchi, G., & Inzitari, D. (2007). CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology, 68*(22),1909-1916.

Dotson, V. M., Beydoun, M. A., & Zonderman, A. B. (2010). Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology, 75*(1), 27-34. doi: 10.1212/WNL.0b013e3181e62124

Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. Journal of *Vascular Health and Risk Management, 4*(2), 363-381.

Fagan, A.M., Roe, C.M., Xiong, C., Mintun, M.A., Morris, J.C., Holtzman, D.M. (2007). Cerebrospinal fluid tau/beta amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Archives of Neurology,* 64,343-349.

Ferman, T., Smith, G., & Kantarci, K. (2013). Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. *Neurology, 81*(23), 2032-2038.

Flicker, C., Steven F.H., and Reisberg, B. (1991). Mild cognitive impairment in the elderly predictors of dementia. *Neurology, 41*(7),1006-1006.

Folstein, M. F., Folstein, S. E., & Fanjiang, G. (2001). *Mini-mental state examination: clinical guide*. Lutz, FL: Psychological Assessment Resources.

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

Ganguli, M., Dodge H.H., Shen, C., & DeKosky, S.T. (2004). Mild cognitive impairment, amnestic type. An epidemiologic study. *Neurology,* 63, 115-121.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R.C., Ritchie, K., Broich, K.,…Winblad, B. (2006). Mild cognitive impairment. *Lancet*, 367, 1262–1270.

Gibbons, L. E., Carle, A. C., Mackin, R. S., Harvey, D., Mukherjee, S, Insel, P….,Curtis, S.M. (2012). A composite score for executive functioning, validated in Alzheimer's Disease

Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behavior, 6*(4), 517-527. doi: 10.1007/s11682-012-9176-1

Gifford, K.A., Liu, D., Lu, Z., Tripodis, Y., Cantwell, N.G., Palmisano, J.,…Jefferson, A.L. (2014). The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults. *Alzheimer's & Dementia*, 10, 319-327.

Glodzik-Sobanska L., Reisberg B., De Santi S., Babb J.S., Pirraglia E., Rich K.E.,...de Leon, M.J. (2007). Subjective memory complaints: presence, severity and future outcome in normal older subjects. *Dementia and Geriatric Cognitive Disorders*, 24, 177–84.

Glosser, G., Gallo, J., Duda, N., de Vries, J. J., Clark, C. M., & Grossman, M. (2002). Visual perceptual functions predict instrumental activities of daily living in patients with dementia. *Neuropsychiatry Neuropsychology, and Behavioral Neurology, 15*(3), 198-206.

Greenaway, M.J., Lacritz, L.H., Binegar, D., Weiner, M.F., Lipton, A., & Cullum, C.M. (2006). Patterns of verbal memory performance in mild cognitive impairment, Alzheimer's disease, and normal aging. *Cognitive and Behavioral Neurology*, 19, 79-84.

Goldstein, F. C., Levey, A. I., & Steenland, N. K. (2013). High Blood Pressure and Cognitive Decline in Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *61*(1), 67–73. doi:10.1111/jgs.12067

Gómez-Tortosa, E., Mahillo-Fernández, I., Guerrero, R., Montoya, J., Alonso, A., & José Sainz, M. (2012). Outcome of mild cognitive impairment comparing early memory profiles. *The American Journal of Geriatric Psychiatry, 20* (10), 827-835.

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., . . .Sellke, F.W. (2011). Vascular contributions to cognitive impairment and dementia: a statement

for healthcare professionals from the american heart association/american stroke association. *Stroke, 42*(9), 2672-2713. doi: 10.1161/STR.0b013e3182299496

Grober, E., & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology*, *13*(6), 933–949.

Hampstead, B.M., & Brown, G.S. (2013). Using neuroimaging to inform clinical practice for the diagnosis and treatment of mild cognitive impairment. *Clinics in Geriatric Medicine,* 29, 829-845.

Hanninen, T., Hallikainen, M., Tuomainen, S., Vanhanen, M., & Soininen, H. (2002). Prevalence of mild cognitive impairment: A population-based study in elderly subjects. *Acta Neurologica Scandinavica,* 148-154.

Hanninen T., Reinikainen K.J., Helkala, E.L., Koivisto, K., Mykkanen, L., Pyorala, K.,…Riekkinen, P.J. (1994). Subjective memory complaints and personality traits in normal elderly subjects. *Journal of American Geriatrics Society*, 42, 1–4.

Heaton, S. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). Wisconsin Card Sorting Test manual: Revised and expanded. Odessa, FL: Psychological Assessment Resources.

Jefferson, A.L., & Byerly, L.K. (2008). Characterization of activities of daily living in individuals with mild cognitive impairment. *American Journal of Geriatric Psychiatry, 16*(5), 375-383.Jonker, C., Geerlings, M.I., Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population based studies. *International Journal of Geriatric Psychiatry*, 15, 983–991.

Jonker, C., Launer L.J., Hooijer, C., & Lindeboom, J. (1996). Memory complaints and memory impairment in older individuals. *Journal of American Geriatrics Society, 44*(1), 44-49.

Jorm, A., Butterworth, P., Anstey, K., Christensen, H., Easteal, S., Maller, J., & Sachdev, P. (2004). Memory complaints in a community sample aged 60–64 years: Associations with cognitive functioning, psychiatric symptoms, medical conditions, APOE genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. *Psychological Medicine, 34*(8),1495-1506.

Kaplan, E., Goodglass, H., Weintraub., S. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

Kivipelto M., Helkala, E.L., Hanninen, T., Laakso, M.P., Hallikainen, M., Alhainen, K., …Nissinen, A. (2001). Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology, 56*(12),1683-1689.

LaBarge, E., Edwards, D., & Knesevich, J. W. (1986). Performance of normal elderly on the Boston Naming Test. Brain and Language, 27, 380-384.

Lam, L.C., Lui, V.W., Tam, C.W., Chiu, H.F. (2005) Subjective memory complaints in Chinese subjects with mild cognitive impairment and early Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 20, 876-882.

Langa, K. M., & Levine, D. A. (2014). The diagnosis and management of mild cognitive impairment: a clinical review. *Journal of the American Medical Association, 312*(23), 2551-2561. doi: 10.1001/jama.2014.13806Lenehan, M.E., Klekociuk, S.Z., Summers, M.J. (2012). Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): Is it time to abandon

subjective memory complaint as an MCI diagnostic criterion? *International Psychogeriatrics*, *24*(9),1505-14. doi 10.1017/S1041610212000695

Li G., Sokal I., Quinn J.F., Leverenz, J.B., Brodey, M., Schellenber, G.D.,…Montine, T.J. (2007). CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology*, 69:631-639

Lopez, O.L., Jagust, W.J., DeKosky, S.T., Becker, J.T., Fitzpatrick, A., Dulberg, C.,…Kuller, L.H. (2003). Risk factors for mild cognitive impairment in the cardiovascular health study cognition study. *Archives of Neurology, 60* (10), 1394-1399.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *Journal of American Medical Association, 288*(12), 1475-1483.

Manly J.J., & Jacobs D.M. (2001). Future directions in neuropsychological assessment with African Americans. In F.R. Ferraro (Ed*.) Minority and cross-cultural aspects of neuropsychological assessment*, 79–96. Lisse, The Netherlands: Swets & Zeitlinger Pubilshers.

Manly, J. J., Tang, M.X., Schupf, N., Stern, Y., Vonsattel, J.P. G., & Mayeux, R. (2008). Frequency and Course of Mild Cognitive Impairment in a Multiethnic Community. *Annals of Neurology*, *63*(4), 494–506. doi:10.1002/ana.21326

Mielke, M. M., Vemuri, P., & Rocca, W. A. (2014). Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clinical Epidemiology*, *6*, 37–48. doi:10.2147/CLEP.S37929

Mitchell, A. J. (2008). The clinical significance of subjective memory complaints in the diagnosis of mild cognitive impairment and dementia: a meta-analysis. *International Journal of Geriatric Psychiatry*, *23*, 1191-1202. doi: 10.1002/gps.2053

Modrego, P. J., & Ferrandez, J. (2004). Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Archives of Neurology, 61*(8), 1290-1293. doi: 10.1001/archneur.61.8.1290

Moghekar, A., Li, S., Lu, Y., Li, M., Wang, M., Albert, M., & O'Brien, R. (2013). CSF biomarker changes precede symptom onset of mild cognitive impairment. *Neurology, 81*, 1753-1758.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–2414.Murayama, N., Tagaya, H., Ota, K., Fujishiro, H., Manabe, Y., Sato, K & Isek, E. (2013). Neuropsychological detection of the early stage of amnestic mild cognitive impairment without objective memory impairment. *Dementia and Geriatric Cognitive Disorders,* 35, 98-105.

Paradise, M., Glozier, N., Naismith, S., Davenport, T., & Hickie, I. (2011). Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: A cross-sectional study. *Biomedical Central Psychiatry*, *11*(108). doi:10.1186/1471-244X-11-108

Parasuraman, R., Greenwood P.M., & Sunderland, T. (2002). The apolipoprotein E gene, attention, and brain function. *Neuropsychology, 16* (2), 254.

Pavlik, V.N., Doody, R.S., Massman, P.J., & Chan,W. (2006). Influence of premorbid IQ and education on progression of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 22*(4), 367–377.

Perneczky, R., Pohl, C., Sorg, C., Hartman, J., Komossa, K., Alexopoulos, P.,…Kurz, A. (2006). Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. *Age and Aging*, 35, 240-245.

Petersen, R.C., (2011). Mild cognitive impairment. *The New England Journal of Medicine*, 364, 2227-34.

Petersen, R. C., Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S., … Rocca, W. A. (2010). Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging(CME) *Neurology*, *75*(10), 889–897. doi:10.1212/WNL.0b013e3181f11d85

Petersen R.C., Smith G.E., Ivnik R.J., Tangalos, E.G., Schaid, D.J., Thibodeau, S.N.,…Kurland, L.T.(1995). Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *Journal of the American Medical Association, 273*(16),1274-1278.

Petersen, R., Smith, G., Waring, S., Ivnik, R., Tangalos, E., & Kokmen, E. (1999). Mild Cognitive Impairment: Clinical Characterization and Outcome. *Archives of Neurology, 56*(3), 303-308.

Petersen, R.C., Stevens, J.C., Ganguli, M.,Tangalos, E.G., Cummings, J.L., & DeKosky, S.T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *American Academy of Neurology, 56*(9), 1133-1142.

Pozueta, A., Rodriguez-Rodriguez, E., Vazquez-Higuera, J. L., Mateo, I., Sanchez-Juan, P., Gonzalez-Perez, S., . . . Combarros, O. (2011). Detection of early Alzheimer's disease in

MCI patients by the combination of MMSE and an episodic memory test. *Biomedical Central Neurology, 11*, 78. doi: 10.1186/1471-2377-11-78

Rabin, L. A., Pare, N., Saykin, A. J., Brown, M. J., Wishart, H. A., Flashman, L. A., & Santulli, R. B. (2009). Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. *Neuropsychology, Development, and Cognition. Section B, Aging Neuropsychology and Cognition, 16*(3), 357-376. doi: 10.1080/13825580902825220

Reisberg, B., Ferris, S.H., Kluger, A., Franssen, E., Wegiel, J., & De Leon, Mony J. (2008). Mild cognitive impairment (MCI): a historical perspective. *International psychogeriatrics, 20*(1), 18-31.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting Psychology*

Reitz, C., Tang, M., Manly, J., & Schupf, J. (2008). Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 25*(3), 232-237.

Roberts, J. L., Clare, L., & Woods, R. T. (2009). Subjective memory complaints and awareness of memory functioning in mild cognitive impairment: A systematic review. *Dementia and Geriatric Cognitive Disorders*, *28*(2), 95-109.

Rodakowski, J., Skidmore, E.R., Reynolds, C.F., Dew, M.A., Butters, M.A., Holm, M.B.,…Rogers, J.C. (2014). Can performance of daily activities discriminate between older adults with normal cognitive function and those with Mild Cognitive Impairment? *Journal of American Geriatric Society*, *62*(7), 1347-1352.Sachdev P.S., Lipnicki, D.M., Crawford, J., Reppermund, S., Kochan, N.A., Trollor, J.N.,…Brodaty, H. (2012). Risk

Profiles for Mild Cognitive Impairment Vary by Age and Sex: The Sydney Memory and Ageing Study. *American Journal of Geriatric Psychiatry*, 20, 854–865. doi: 10.1111/j.1532-5415.2011.03774.

Sattler, C., & Toro, P. (2012). Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatry Research, 196*, 90-95.

Sheshadri, S., & Wolf, P. (1997). Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. *Neurology, 49*(6), 1498-1504.

Sisco, S., Gross, A.L., Shih, R.A., Sachs, B.C., Maria Glymour, M., Bangen, K.J.,… Manly, J.J. (2013). The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. *Journals of Gerontology, Series B*: Psychological Sciences and Social Sciences, doi: 10.1093/geronb/gbt133

Sosa-Ortiz, A.L., Acosta-Castillo, I., & Prince, M.J. (2012) Epidemiology of Dementias and Alzheimer's Disease. *Archives of Medical Research*, 43, 600-608.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *20*(Suppl 2), S69–74.

Stern Y., Albert S., Tang M.X., Tsai W.Y.(1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology*, 53, 1942-1947.

Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M., Wilder, D., Mayeux, R. (1994) Influence of Education and Occupation on the Incidence of Alzheimer's Disease. *Journal of American Medical Association, 271*(13), 1004-1010. Stewart, R., Russ, C., Richards, M., Brayne, C., Lovestone, S., & Mann, A. (2001). Depression, APOE genotype and subjective

memory impairment: A cross sectional study in African-Caribbean population. *Psychological Medicine, 31*, 431-440.

Tobiansky R., Blizard R., Livingston G., Mann A. (1995). The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychological Medicine, 25*(4), 779-86.

Venkat, P., Chopp, M., & Chen, J. (2015). Models and mechanisms of vascular dementia. *Experimental Neurology*. doi: 10.1016/j.expneurol.2015.05.006

Vogel, A., Stokholm, J., Gade, A., Andersen, B. B., Hejl, A. M., & Waldemar, G. (2004). Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? *Dementia and Geriatric Cognitive Disorders, 17*(3), 181-187. doi: 10.1159/000076354

Wechsler D. (1981). WAIS-R manual: Wechsler Adult Intelligence Scale-Revised. New York: Jovanovich HB. Psychological Corporation.

Whitmer, R. (2007). Type 2 Diabetes and risk of cognitive impairment and dementia. *Current Neurology and Neuroscience Reports, 7*, 373-380.

Wood, R.Y., Giuliano, K.K. Bignell, C.U., & Pritham, W.W. (2006). Assessing cognitive ability in research: use of MMSE with minority populations and elderly adults with low education levels. *Journal of Gerontological Nursing, 32*(4), 45-54.

Ye, B.S., Seo, S.W., Cho, H., Kim, S.Y., Lee, J.S., Lee, Y.,…Na, D.L. (2013). Effects of education on the progression of early versus late-stage mild cognitive impairment *International Psychogeriatrics*, *25*(4), 597–606. http://dx.doi.org/10.1017/S1041610212002001

Ye, B.S., Seo, S.W., Lee,Y., Kim, S.Y., Choi, S.H., Lee, Y.M.,…Kim, E.J. (2012). Neuropsychological performance and conversion to Alzheimer's disease in early- compared to late-onset amnestic mild cognitive impairment: CREDOS study.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17*, 37-49.

Table 1. Demographics of Diagnostic Groups

	Normal Controls	Possible MCI	Probable MCI	Overall Sample
	n=191	n=83	n=121	n=395
Age M(SD)	66.74 (7.59)	68.06 (6.01)	68.31 (7.12)	67.50 (7.16)
Education M(SD) *	15.55 (2.49)	14.74 (2.76)	14.65 (2.49)	15.10 (2.74)
Sex (n,% Female)*	124 (65)	46 (55)	56 (46)	226 (57)
Ethnicity (%Caucasian)	41	11	23	298 (75)
AMNART M(SD)	116 (12.84)	106 (15.05)	106 (15.20)	110.29 (14.63)
GDS M(SD) *	0.95 (1.40)	1.27 (1.81)	2.16 (2.23)	1.39 (1.84)
Hypertension (n,%)□	87 (46)	49 (59)	70 (58)	206 (52)
Diabetes (n,%)	16 (8)	7 (8)	18 (15)	41 (10)
High Cholesterol (n,%)□	101 (53)	41 (49)	80 (66)	222 (56)

Note. MCI-Mild Cognitive Impairment, AMNART-American Version of the National Adult Reading Test
GDS-Geriatric Depression Scale

*p<.05- significant difference between normal controls and probable MCI group

□*p*<.05 significant difference between possible MCI and probable MCI group

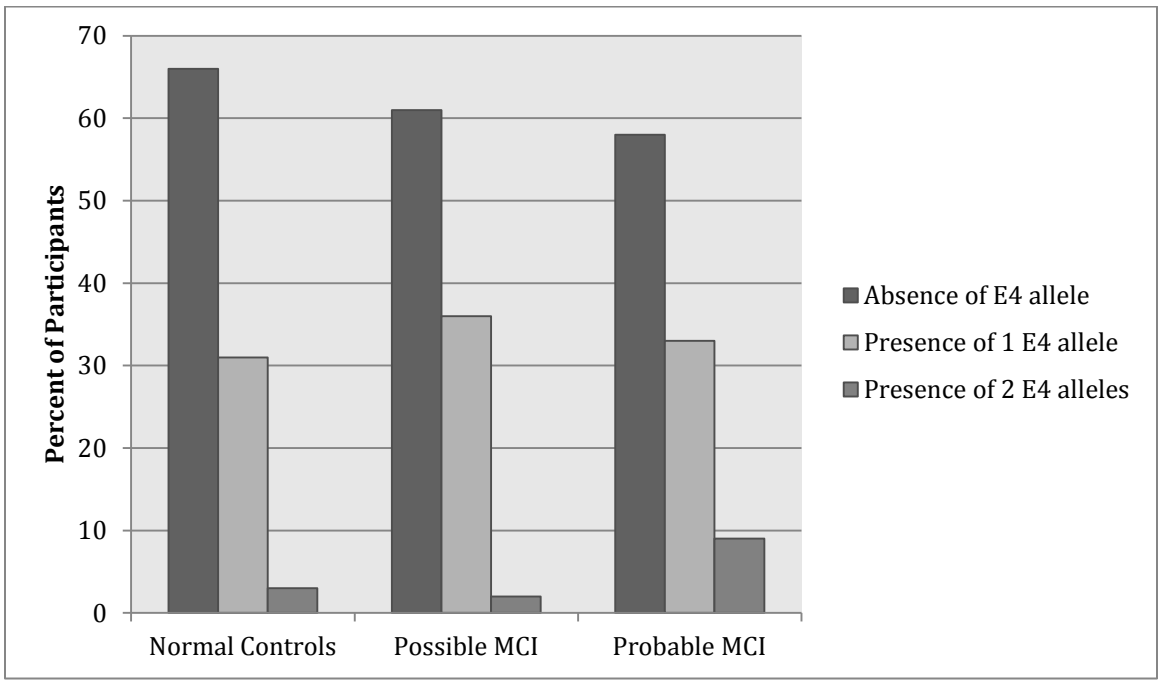
□*p*<.05 significant difference between normal controls and both MCI groups

Table 2. Performance on Neuropsychological Measures by Group

	NC	Possible MCI	Probable MCI	*p*	Effect Size
	M(SD)	M(SD)	M(SD)		
MMSE*	28.91(1.06)	27.91(1.72)	27.74(1.85)	.001	.126
Animals Raw*	21.20(5.51)	18.47(4.61)	18.45(5.60)	.001	.062
BNT Raw*	27.48(2.33)	25.46(3.61)	25.79(4.13)	.016	.077
FAS Raw*	40.48(10.70)	36.49(11.28)	35.26(11.87)	.001	.044
CVLT Total Raw**	52.34(8.61)	44.09(9.26)	40.04(9.09)	.001	.277
CVLT Total T-score **	52.28(9.25)	44.76(9.46)	41.14(9.59)	.001	.220
CVLT LD Raw**	11.27(2.91)	8.97(2.97)	7.21(3.21)	.001	.258
CVLT LD Z score**	.35(1.03)	-.24(1.07)	-.82(1.07)	.001	.192
CVLT Intrusions**	4.52(5.60)	6.01(5.15)	9.03(8.47)	.001	.082
TMT-A Raw*	29.09(11.16)	33.46(12.14)	34.3(13.1)	.001	.041
TMT-A T-score*	55.65(9.80)	53.14(10.69)	52.30(9.13)	.001	.024
TMT-B Raw*	75.99(34.93)	103.99(42.22)	103.37(49.45)	.001	.103
TMT-B T-score*	53.00(9.32)	47.14(9.62)	48.05(8.69)	.001	.079
WCST Psv T-score*	54.54(13.53)	44.44(14.09)	44.85(17.12)	.001	.134
WCST Cat*	5.03(1.59)	3.74(1.97)	3.38(2.31)	.001	.139
Block Design Raw *	27.21(8.94)	20.39(10.99)	22.26(10.27)	.001	.079
Block Design SS*	8.72(2.38)	7.17(2.67)	7.46(2.51)	.001	.073

Note. MMSE-Mini Mental State Examination, Animals-Animal Fluency, BNT-Boston Naming Test, FAS-Phonemic Fluency, CVLT-California Verbal Learning Test Total Score, CVLT-California Verbal Learning Test Z Score LD-Long Delay Free Recall, TMTA-Trail

Making Test A, TMTA-T-Trail Making Test A (T score), TMTB-Trail Making Test B, TMTB-T-Trail Making Test B (T score), WCST Psv -Wisconsin Card Sorting Test Perseverative Errors, WCST Cat - Wisconsin Card Sorting Test Categories Completed, SS-Scaled Score. *p<.05 significant difference between normal controls and probable MCI groups. **p<.05 significant difference between all three groups.



Note. No statistically significant differences among groups.

Figure 1. APOE4 frequency among probable MCI, possible MCI, and normal controls

Appendix 1

This sub classification was not available for all participants included in this study, below is available sample size:

Amnestic MCI (n=89)

1) evidence of subjective and objective memory impairment (with or without deficits in other cognitive domains).
2) memory complaints, preferably corroborated by an informant
3) impaired memory function for age and education
4) preserved general cognitive function
5) intact activities of daily living
6) not demented

Non-Amnestic MCI (n=15)

1) evidence of subjective and objective cognitive impairment
2) impairment is in a domain other than memory, such as language or processing speed
3) preserved general cognitive function
4) intact activities of daily living
5) not demented

Appendix 2

Clinical Dementia Rating Scale (CDR). The Washington University Clinical Dementia Rating Scale (Morris, 1993) was developed to clinically denote the presence of dementia of Alzheimer's type and stage its severity. The CDR utilizes a semi structured interview protocol with patient and informant. The CDR assesses cognitive functioning in six domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. The Global CDR is derived from these domains and is made up of five cognitive impairment staging groups: CDR-0 = normal, CDR-0.5 = very mild dementia, CDR-1 = mild, CDR-2 = moderate, CDR-3 = severe.

BIOGRAPHICAL SKETCH

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Texas Christian University	B.S.	2011	Psychology Child Development
The University of Texas Southwestern Medical Center School of Health Professions	M.R.C.	2015	Clinical Rehabilitation Counseling

Positions and Employment

Oklahoma Health Science Center 2011-2012

INTEGRIS Caregiver Support Group May 2015-present

INTEGRIS Jim Thorpe Rehabilitation September 2014-present

Clinical Experience

HealthSouth Rehabilitation Hospital January 2010-March 2010

Neuropsychology Intern August 2013- February 2014

UT Southwestern Neuropsychology Clinic February 2014- August 2014

UT Southwestern University Rehabilitation Service August 2013-August 2014

Brain Injury Caregiver Support Group February 2014-August 2014

Presentations and Publications

Matthews, R.N., **Weaver, V.A**., Elliot, B.R. (2015, March). A presentation given to Jim Thorpe Rehabilitation Network, Oklahoma City, Oklahoma.

Weaver, V.A. (2015, February) *Profession of Rehabilitation Counseling*. Guest lecture given to the Rehabilitation Counseling class in the Master's of Counseling and Rehabilitation Counseling program at East Central University, Ada, Oklahoma.