CHARACTERIZATION AND DIFFERENCES BETWEEN POSSIBLE AND PROBABLE MILD COGNITIVE IMPAIRMENT

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Dedicated in loving memory of

Loyce Elaine Denney

and in honor of

Fred and Rebecca Denney

CHARACTERIZATION AND DIFFERENCES BETWEEN POSSIBLE AND PROBABLE MILD COGNITIVE IMPAIRMENT

by

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ABSTRACT

Mild Cognitive Impairment (MCI) is the period of subtle cognitive decline that occurs between normal aging and clinical Alzheimer's Disease (AD). Patients' subjective memory complaints (SMCs) are essential to the diagnosis of MCI. In cases where memory complaints are not verifiable by objective measures, patients are left without a formal diagnosis of cognitive

impairment. The current proposal describes a study designed to compare the cognitive features and risk factors of AD in subgroups of patients with SMCs with (Probable MCI) and without (Possible MCI) objective memory deficits in relation to controls. It is predicted that the Probable MCI group will demonstrate lower performance and have a greater decline on neuropsychological measures than patients diagnosed with Possible MCI, who will demonstrate lower performance and have a greater decline on those measures than controls. Also, it is predicted that Probable MCI patients will have greater incidence of vascular risk factors and presence of the apolipoprotein element 4 (APOE-4) allele than the Possible MCI patients, who will have higher incidence of these variables than controls. There is also a demographic analysis designed to identify any differences in age, education, and gender between the groups. Implications of possible outcomes of the study are then discussed.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADC	Clinic for Alzheimer's and Related Diseases
APOE-4	Apolipoprotein element 4
a-MCI	Amnestic MCI
BNT	Boston Naming Test
CAD	Coronary artery disease
CDR	Clinical Dementia Rating Scale
COWAT	Controlled Oral Word Association Test
LDL	Low-density lipoprotein
MCI	Mild Cognitive Impairment
md-MCI	Multi domain MCI
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartic acid
SMC	Subjective memory complaints
tHcy	Homocysteine
WCST	Wisconsin Card Sorting Test

CHAPTER ONE
Introduction

As medical advances and other factors have lengthened the average life expectancy, progressive neurological diseases have become more prevalent, and, likewise, more research has been devoted to understanding these disorders. Alzheimer's Disease (AD) is the most commonly diagnosed form of dementia. Because of the irreversibility of the cognitive deficits it causes, scientists have increased efforts to identify the disease as soon as possible, as to try to minimize and slow its progression. Mild cognitive impairment (MCI) is the period of subtle cognitive decline that occurs between normal aging and clinical AD.

Essential to the diagnosis of MCI is the presence of patients' subjective memory complaints (SMCs) that is verifiable by objective measures. However, these deficits do not qualify for dementia. Some individuals with SMCs do not meet all criteria for MCI, due to a lack of clear impairment on neuropsychological measures. These individuals have been classified as having "possible MCI" at the UT Southwestern Alzheimer's Disease Research Center. It is unclear if these individuals will develop cognitive difficulties over time or if they are simply overly sensitive to cognitive lapses associated with aging. Numerous variables have been identified as risk factors for developing AD and MCI, including the presence of the apolipoprotein element 4 (APOE-4) allele, hypertension, high cholesterol, elevated homocysteine (tHcy) blood plasma levels, and diabetes mellitus. It is unknown if these factors may also be risk factors for possible MCI, and might ultimately contribute to progression to a more well defined disease process. Given the trend towards earlier identification of MCI and dementia, more study is needed in this group of individuals with memory complaints but minimal impairment on standardized testing.

CHAPTER TWO
Review of the Literature

Individuals with Alzheimer's Disease (AD) go through a subtle cognitive decline prior to reaching the clinical threshold for the diagnosis of probable AD. This period between normal aging and clinical AD is known as mild cognitive impairment (MCI; Petersen, Doody, et al., 2001). MCI is a term used to distinguish a clinical state in individuals with some form of cognitive impairment for their age but who function well enough in their daily lives as to not meet criteria for dementia (Petersen, Stevens, et al., 2001). While differences are sometimes subtle, individuals with MCI can be differentiated from healthy control subjects and those with very mild AD (Petersen, et al., 1999).

Diagnostic and research criteria for dementia are well documented, while there has been some debate in how to characterize the cognitive decline that occurs between normal aging and dementia, particularly when individuals are just beginning to become symptomatic. Patients with MCI demonstrate cognitive changes that are different from normal aging (Petersen, Doody, et al., 2001).

MCI Diagnostic Criteria

Diagnosing MCI has been a source of controversy because it lacks a sound epidemiology (Ganguli, 2006). There is no consistent agreement in the field on a single set of criteria for MCI (Petersen, 2004). An international group formulated recommendations for criteria that include: (1) the individual is neither normal nor demented; (2) there is evidence of cognitive deterioration, shown by either objectively measured decline over time or subjective report of decline by self or an informant in conjunction with objective cognitive deficits; and (3) activities of daily life (ADLs) are preserved and complex instrumental functions are either intact or

minimally impaired (Winblad, et al., 2004). The Mayo Alzheimer's Disease Research Center developed criteria focused on memory impairment while other cognitive domains are preserved. These criteria include: (1) memory complaint, preferably corroborated by an informant, (2) objective memory impairment for age, (3) relatively preserved general cognition for age, (4) essentially intact activities of daily living, and (5) not demented (Petersen, et al., 1999). The cognitive functioning criteria require that the impairment be greater than 1.5 standard deviations below age-adjusted norms (Tabert et al., 2006).

MCI is thought to be a pathological disorder that is heterogeneous in nature (DeCarli, et al., 2001; Portet, at al., 2006). Not all individuals who present with symptoms of MCI will progress to the same fate. Some develop AD while others may develop a different dementia or not progress at all (Petersen, Doody, et al., 2001). Because of this heterogeneity, subsets of MCI have been identified. Individuals with Amnestic MCI present with complaints of memory loss that is preferably confirmed by an informant and have objective memory impairment when compared to education and age corrected norms; however, they perform reasonably well on tasks of general cognitive function and have mostly intact daily living activities (Petersen, Doody, et al., 2001).

While most research has focused on the amnestic type of MCI (a-MCI), other MCI subtypes have been described, though minimally, and the limited literature devoted to these descriptions are mostly theoretical in nature. One alternate type of MCI, labeled multi domain MCI (md-MCI), involves impairment in multiple cognitive domains including language, executive function, and/or visuospatial skills with or without a memory impairment. Those in this group with a memory impairment are labeled as md-MCI + a. Those without are labeled md-

MCI – a. The third, least common type of MCI is single nonmemory domain MCI in which an impairment in a nonmemory cognitive domain such as language, executive function or visuospatial skills is present. These individuals most likely have an outcome different from those with memory impairment that could include primary progressive aphasia, frontotemporal dementia, or vascular dementia (Petersen, et al., 1999; Petersen, Doody, et al., 2001). The majority of research to date has focused on amnestic MCI, and there is relatively little data at this point on the other MCI subgroups and how similar/different they are from a-MCI in terms of demographic information, course, and progression.

Neuropsychological assessment is routinely used to quantify cognitive impairment in patients with memory complaints and/or dementia and can help identify cases of AD at early stages. Neuropsychological tests may also help identify persons with a high propensity to convert to MCI or AD before they meet diagnostic criteria (Petersen, Doody, et al., 2001). Poor performance on executive function and delayed recall tests point to high risk of progression to dementia (Flicker, Ferris, Reisberg, 1991; Chen, et al., 2000; Ritchie, Artero, Touchon, 2001). However, some patients with memory complaints are unaccompanied by deficits on formal testing. Saykin, et al. (2006) used magnetic resonance imaging (MRI) neuroimaging to test the validity of these individuals' complaints and found that gray matter loss was seen in individuals who had memory complaints with normal neuropsychological test performance as well as in individuals with a-MCI. They asserted that the cognitive complaint group may represent a stage of impairment prior to MCI, and thus, may provide an earlier opportunity for therapeutic intervention.

MCI: Progression to Dementia

Some patients with MCI remain stable or return to normal over time, but more than half develop dementia within 5 years (Petersen, 2004). Individuals rarely deviate from a cognitively normal state to dementia without first going through early signs of impairment. MCI may therefore be regarded as a risk factor for dementia. Longitudinal studies indicate that patients with MCI are likely to develop AD at a faster rate than in the normal elderly population (Petersen, et al., 1999; Petersen, Doody, et al., 2001; Ganguli, 2006). However, there is some variation in the rates of progression, in part due to differences in criteria for MCI. According to Petersen, Stevens, et al. (2001) progression to AD ranges from 0.2% in the 65 to 69 age range to 3.9% in the 85 to 89 year range for subjects in the general population while rates of progression from MCI to AD range from 6% to 25% per year. Individuals with MCI progress most commonly to Alzheimer's type dementia (Kluger, Ferris, Golomg, Mittelman, Reisberg, 1999). One year follow up evaluations over a 6-year period of time revealed that subjects in the Mayo Clinic studies progressed from MCI to dementia at a rate of approximately 12% per year (Petersen, Morris, et al., 2003). After 6 years, approximately 80% of the MCI subjects had converted to dementia (Petersen, 2004). Incidence rates from the same community document a progression from normal aging to dementia at a rate of 1% to 2% per year.

Hippocampal atrophy has been reported in amnestic MCI compared with cognitively intact controls, and can predict the rate of conversion from MCI to AD (Jack, Petersen, Xu, et al., 1999). Hippocampal atrophy seen in MCI is correlated with atrophy and neuronal loss seen at autopsy (Bobinski, de Leon, Tarnawaski, et al., 1998). Rates of hippocampal atrophy for individuals who convert from control subjects to MCI or from MCI to AD are comparable,

supporting MCI as a transition to early AD (Jack, Petersen, Xu, et al., 2000). Neuroimaging studies support the view that MCI, especially amnestic MCI, shares features with AD, such as hippocampal atrophy, so that the presence or development of atrophy is an additional risk factor for conversion to clinical AD (Petersen, Doody, et al., 2001).

Risk Factors for AD and MCI

The memory loss and neurodegenerative changes associated with AD are essentially permanent. Clinical research has, therefore, increased emphasis on early diagnosis of the disease as well as identifying risk factors that can be modified at early stages before symptoms become severe. Identifying the presence of MCI could lead to secondary prevention by controlling cognitive risk factors. Mayo Clinic investigators identified a number of variables that are thought to predict a more rapid progression to dementia. Among these include apolipoprotein element 4 (APOE-4) allele carriers, poor performance on a cued memory task, and neuroimaging findings such as decreased hippocampal volumetric measurements (Petersen, 2004).

APOE is a plasma protein involved in the transport of cholesterol (Mahley, 1988). It is produced and secreted in the central nervous system by astrocytes (Ignatius, Gebicke-Harter, Skene, Schilling, Weisgraber, Mahley, & Shooter, 1986; Boyles, Pitas, Wilson, Mahley, & Taylor, 1985; Pitas, Boyles, Lee, Foss, & Mahley, 1987). APOE synthesis is increased after injury and is implicated in the growth and repair of the nervous system during development or after injury (Strittmatter, Saunders, Schmechel, Pericak-Vance, Enghild, Salvesen, & Roses, 1993). APOE is also increased in some chronic neurodegenerative diseases, including AD. In AD, APOE binds to extracellular senile plaques, intracellular neurofibrillary tangles, and at sites of cerebral vessel congophilic angiopathy (Namba, Tomonaga, Kawasaki, Otomo, & Ikeda,

1991). The APOE gene is located on chromosome 19 and has three major alleles: element 2, element 3, and element 4 (Mahley, 1988). The element 2 allele has a protective role, decreasing the risk of AD and delaying the onset of dementia (Corder, Saunders, Risch, et al., 1994). The element 4 allele, however, is harmful and increases the risk of AD, hastening the onset of dementia (Corder, Saunders, Strittmatter, et al., 1993; Roses, Strittmatter, Pericak-Vance, Corder, Saunders, & Schmechel, 1994). Individuals homozygous for the element 4 allele are at greatest risk for AD (Corder, Saunders, Strittmatter, Schmechel, Gaskell, Small, Roses, Haines, & Pericak-Vance, 1993).

Other risk factors have been identified that relate to cognitive deficits. Elevated plasma homocysteine (tHcy) concentrations, potentially caused by insufficient amounts of B vitamins and folic acid, are reportedly associated with a higher prevalence of cognitive deficits, dementia, and AD (Clarke, Smith, Jobst, Refsum, Sutton, & Ueland, 1998; Gottfires, Lehmann, & Regland, 1998; Morris, Jacques, Rosenberg, & Selhub, 2001; Prins, den Heijer, Hofman et al., 2002). Consistent with this, AD patients are more likely than control subjects to have elevated plasma tHcy levels (McCaddon, Davies, Hudson, Tandy, & Cattell, 1998). Also, it has been reported that a low-normal plasma tHcy level reduces the risk of progression of MCI to AD (Annerbo, Wahlund, & Lokk, 2005). Elevated tHcy levels have been observed in 39% of patients with late-onset AD and 58% of patients with vascular dementia but only 10% of nondemented patients (Clark, Smith, Jobst, et al., 1998). It has been observed that a tHcy level >14 mmol/L almost doubles the risk for AD (Budge, de Jager, Hogervorst, et al., 2002). Homocysteine's definitive mechanism of harm is not known; though tHcy is understood to be a neurotoxic amino acid. At mildly elevated concentrations, tHcy acts as an N-methyl-D-aspartic acid (NMDA) receptor

agonist (Lipton, Kim, Choi, et al., 1997). The NMDA hyperstimulation results in excessive calcium ion influx and neural toxicity (Lafon-Cazal, Pietri, Culcasi, et al., 1993).

Type 2 diabetes mellitus has been identified to increase risk for progression to MCI and AD (Luchsinger, Tang, Stern, Shea, & Meayeux, 2001; Luchsinger & Mayeux, 2004; Luchsinger, Reitz, Patel, Tang, Manly, & Mayeux, 2007). The association between diabetes and AD is presumably related to the effects of peripheral hyperinsulinemia on the clearance of brain beta amyloid (Farris, Mansourian, Chang, et al., 2003; Qiu, Walsh, Ye, et al., 1998), which is one of the main culprits in the pathogenesis of AD (Selkoe, 2000). Other mechanisms have also been implicated, such as advanced products of glycosylation. These are byproducts of a pathogenic mechanism that result from an accumulation of metabolites seen in cells that are unable to reduce glucose intake. Ultimately, they cause a wide array of damage, as they have been implicated in numerous age- and diabetes-related chronic diseases, such as atherosclerosis, asthma, arthritis, myocardial infarction, nephropathy, and neuropathy (Smith, Sayre, & Perry, 1996).

High cholesterol and coronary artery disease (CAD), among other vascular diseases, have also been implicated as risk factors for AD (Sparks, Hunsaker, Scheff, Kryscio, Hanson, & Marksbery, 1990). A history of previous hypercholesterolemia was associated with a greater than 3-fold increase in risk for AD, independent of age and presence of the APOE-4 allele in a Finnish population-based study (Notkola, Sulkava, Pekkan, et al., 1998). In a different Finnish study, individuals with raised systolic blood pressure ($\geq$160 mm Hg) or high serum total cholesterol concentration ($\geq$6.5 mmol/L, or $\geq$250 mg/L) in midlife had a significantly higher risk of AD and MCI in later life than those with normal blood pressure or serum cholesterol levels

(Kivipelto, Helkala, Laakso, et al., 2001). Having both hypertension and hypercholesterolemia in midlife significantly increased those subjects' risk of developing AD compared to subjects with either risk factor alone. In another study, total and low-density lipoprotein (LDL) cholesterol was examined in a group of patients with a clinical diagnosis of dementia who had a brain autopsy after death. In patients with AD, both total and LDL cholesterol were significantly higher than in patients with other dementias (Lesser, Kandiah, Libow, et al., 2001). The cholesterol-AD relationship is not well understood. Some experts hypothesize that increased cholesterol augments cellular membrane rigidity that results in intracellular aggregation and neuronal death (Howland, Tusko, Savage, et al., 1998).

Hypertension has been associated with cognitive decline. Both high systolic blood pressure and diastolic blood pressure were found to be more prevalent in patients with AD in a 15-year follow up study (Skoog, Lernfelt, Landahl, et al., 1996). In a neuropathology study, elevated midlife systolic blood pressure was associated with more senile plaques in both the neocortex and hippocampus, while high diastolic blood pressure was associated with more neurofibrillary tangles in the hippocampus (Rosendorff, Beeri, & Silverman, 2007).

Patients' subjective memory complaints (SMC) have been identified as a potential risk factor for cognitive decline (Schmand, Jonker, Geerlings, & Lindeboom, 1997; Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; Jorm, Christensen, Korten, Jacomb, & Hendersen, 2001; Glodzik-Sobanska, Reisberg, De Santi, Babb, Pirraglia, Rich, Brys, & de Leon, 2007). Several studies have shown that presence of SMC at baseline was associated with future decline to MCI or dementia (Risberg, Ferris, de Leon, Torossian, Kadiayala, & Zhu, 2005; Gauthier, Reisberg, Zaudig, et al., 2006; Glodzik-Sobanska, Reisberg, De Santi, Babb, Pirraglia, Rich,

Brys, & de Leon, 2007). Measured by two questionnaires, SMCs showed a significant association with verbal memory performance in an amnestic MCI (aMCI) group but did not in a no-MCI group. Subjects were age 65 years and older and were put into groups of aMCI and no-MCI. The aMCI subjects met criteria for diagnosis for MCI. The no-MCI were normal controls, and did not present with SMCs. The SMC group's association with poorer verbal memory than the no-MCI group suggests that the aMCI patients have legitimate insight into their memory deficits (Cook & Marsiske, 2006). In another study, multiple regression analysis showed that over a two-year follow up period, endorsement of a one-item memory complaint at baseline predicted future decline in memory (Crowe, Andel, Wadley, et al., 2006).

Age affects the odds that a person will transition to a form of MCI, as does the presence of the aforementioned APOE-4 allele (Petersen, Smith, Ivnik, et al., 1995; Lopez, Jagust, Dulberg, et al., 2003). Education has also shown to affect transitions into MCI. Having 12 – 15 years of education, compared to 16 years, increases the risk of transitioning into a variant of MCI (Kryscio, Schmitt, Salazar, Mendiondo, & Markesbery, 2006).

In summary, MCI is a clinical state of cognitive impairment that falls between normal functioning and dementia. It is marked by complaints of memory impairment that are verifiable by objective measures while ADLs remain relatively intact. Because SMCs are a key element of MCI, individuals with memory complaints that do not show up in testing are also of interest as they may represent a very early form of MCI. Given that those with SMCs do not meet full criteria for MCI, they will be classified as possible MCI in the current study. Also, several biological risk factors have been identified for AD and MCI. The proposed study will focus on how individuals with Possible MCI differ from those that meet full MCI criteria (Probable MCI)

as well as controls across neuropsychological results, risk factor variables, and demographic variables. Further examining MCI and associated risk factors may aid in earlier identification of individuals at risk of developing AD and other forms of dementia. Earlier identification of these progressive disorders can help patients minimize the progression and offer important clinical information to aid researchers and practitioners in providing the best care to these individuals.

CHAPTER THREE
Hypotheses

Overall Goal: To compare the cognitive features and risk factors of AD in subgroups of MCI.

Specific Aim One: To examine differences in neuropsychological functioning other than memory among the Probable MCI, Possible MCI, and control groups.

Hypothesis 1: Patients diagnosed with Probable MCI will demonstrate lower performance on select nonmemory neuropsychological measures (i.e., 2 measures of executive function and 2 language measures) than patients diagnosed with Possible MCI who will perform lower than control subjects.

Hypothesis 2: Patients diagnosed with Probable MCI will demonstrate a greater decline in performance on one or more cognitive measures after one year than patients diagnosed with Possible MCI, who will show changes greater than those seen in control subjects.

Specific Aim Two: To examine differences in risk factors of AD and MCI among the Probable MCI, Possible MCI, and control groups.

Hypothesis 3: Incidence of vascular risk factors (hypertension, high cholesterol, elevated tHcy blood plasma levels, and diabetes mellitus) in Probable MCI will be greater than Possible MCI, which will be greater than controls.

Hypothesis 4: The APOE-4 allele will be more prevalent in patients diagnosed with Probable MCI than those diagnosed with Possible MCI, who will have a higher prevalence than control subjects.

Exploratory analyses: Examine demographic variables in patients diagnosed with probable and possible MCI to identify differences in age, education, and gender, if any.

CHAPTER FOUR
Method

Participants

Patients will be chosen from those evaluated at the Clinic for Alzheimer's and Related Diseases (ADC) and diagnosed via clinical group consensus, consisting of neurologists, psychiatrists and neuropsychologists. All patients received a comprehensive assessment including medical history, neurological examination, and neuropsychological testing. The current study will include 30 patients diagnosed with Probable MCI according to the criteria below, 30 patients diagnosed with Possible MCI according to the criteria below, and 30 control subjects. All subjects will have had a cranial MRI to rule out intracranial abnormalities that could account for their symptoms.

Inclusion Criteria

All subjects are English speaking and between the ages of 50 and 90 years old. Subjects will be assigned to each group according to the following inclusion criteria:

Probable MCI

1. Presence of memory complaint
2. Memory impairment on one or more tests (standard deviation or more below the mean
3. A Clinical Dementia Rating (CDR) Scale score of 0.5
4. Does not meet criteria for dementia
5. Generally normal activities of daily life (ADLs)
6. Absence of other neurological or psychological disorder that could account for deficits

Possible MCI

1. Presence of memory complaint
2. Absence of memory impairment as measured on neuropsychological tests
3. A CDR Scale score of 0.5
4. Does not meet criteria for dementia
5. Generally normal ADLs
6. Absence of neurological or psychological disorder that could account for symptoms

Control Subjects

1. Absence of cognitive complaints
2. A CDR Scale score of 0
3. Absence of major neurological or psychological disorder

Measures

Information about psychological and daily functioning will be taken from information obtained during initial evaluation at the ADC. This data is gathered from a pre-visit telephone interview with a caregiver or family member regarding the patient's past and current daily functioning (Dementia/Clinical History), and by interview and examination of subjects that includes the administration of a CDR, as well as an interview of informants by a study coordinator. The initial dementia/clinical history is obtained at the ADC by trained personnel and consists of questions regarding memory problems, onset of symptoms, personality changes, behavioral changes, depression, drug use and numerous questions regarding physical health.

Neuropsychological Battery

The following tests were chosen for analysis from a larger battery of tests administered to all subjects as part of their regular baseline study visit.

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay & Curtiss, 1993). The WCST is a measure of abstract reasoning and problem solving. In this test, four stimulus cards are placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses, and the fourth with four blue circles. The subject is presented with two identical decks of 64 cards, with designs similar to those on the stimulus cards, and is instructed to match each of the cards to one of the four stimulus cards. Each card varies in shape (triangles, circles, stars, and crosses), number of figures on the card (one to four), and color (red, blue, green, and yellow). The cards can be matched in one of three ways: color, form, or number. Subjects must match the cards to each of the specific sorting principles (i.e., color, form, and number) for a series of ten consecutive trials, but he or she is not told how to match the cards or in what order. The subject is told each time whether the match is correct or incorrect, but no other help is given. The test is completed when the subject successfully completes each category twice in the designated order. The test can be discontinued after the first deck of 64 cards if the subject has not completed a single set. Performance is based on number of categories completed, the number of errors made, and the number of perseverations made. For this study, the normative data proved by Heaton, Grant, and Matthews (1991) will be used. Inter-rater reliability has been reported at r = .93 for perseverative responses (Axelrod, Goldman, & Woodard, 1992; as cited in Heaton, Chelune, Talley, Kay & Curtiss, 1993). In terms of construct validity, Paolo, Troster, Axelrod, and Koller (1995; as cited in Spreen & Strauss, 1998) factor

analyzed the performance of a sample of healthy elderly on the WCST and found that the number of perseverations and categories completed loaded highly on an overall conceptualization and problem-solving factor. This study will utilize both categories completed and perseverations to measure executive function.

Trail Making Test A & B (Partington & Leiter, 1949): This measure is a timed test in which individuals connect either encircled numbers or alternate between numbers and letters. Overall, this test is considered to examine speeded attention and sequencing and mental flexibility. Scores are based on time of completion and the number of errors made. Reliability coefficients have been found to range from .80-.90 in populations of neurological impairment, and as low as .60 for non-neurological aged populations (Spreen & Strauss, 1998). The Trail Making Test B (Partington & Leiter, 1949) is a timed test in which individuals connect encircled letters and numbers. In Trails B, the goal of the task is to connect 25 encircled numbers alternating with encircled letters in sequential order. Overall, this test is considered to examine speeded attention, sequencing and mental flexibility. Specifically, Trails B examines logical analysis plus flexibility for sequential processing. Scores are based on time of completion and the number of errors made. Reliability coefficients have been found to range from .80-.90 in populations of neurological impairment, and as low as .60 for non-neurological aged populations (Spreen & Strauss, 1998). This study will utilize time to complete Trails B as a measure of executive function.

Controlled Oral Word Association Test: (COWAT, Benton, 1968): This test requires the generation of as many words as possible when given a specific letter of the alphabet within one minute, usually F-A-S. Restrictions include not naming people, places or numbers. Skills

involved are free reproduction of words (verbal fluency) and monitoring of previous responses. Therefore, this test not only requires multiple response generation, but also maintenance of complex task set and inhibition. Test-retest reliability has been reported at .88 for adults, with a slight decline in estimates for older adults at .70 (Snow, Tierney, Zorzitto, Fisher, & Reid, 1988, as cited in Spreen & Strauss, 1998). Construct validity tests in adult populations have found that this test loads mainly on a verbal knowledge factor. It has been reported to have high sensitivity to frontal lobe damage regardless of laterality (Bruyer & Tuyumbu, 1980, as cited in Spreen & Strauss, 1998). This study will utilize the total number of words generated as a measure of language function.

Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983). The BNT is a measure of confrontation naming ability. This test includes 60 black and white drawings that are presented one at a time, ranging from simple, high-frequency words (e.g., tree) to words of increasing complexity (e.g., abacus), and is required to name each object pictured. If an item is not correctly named within 20 seconds, and it is unclear if the subject comprehends what image represents, the examiner provides the subject with a semantic cue (e.g., "something to eat" for mushroom). Another 20 seconds is provided for the subject's response. If he or she does not provide the correct response after semantic cuing, a phonemic cue and additional 20 seconds are given for responding (e.g., "starts with the sound 'ca'" for cactus). A semantic cue is not given if the subject clearly demonstrates that he or she understands what the drawing is meant to represent. Instead the examiner proceeds directly to the phonemic cue. One point is given for each spontaneous, correct response and for each correct response following semantic cuing. For this study, a shortened 30 item version will be used that takes the odd numbered items from the

original (Lansing, Ivnik, Cullum, & Randolph, 1999). On the 60 item version, the mean score for normal controls equals 52.4 (Kaplan, et al., 1983), while the 30 item, odd number version equals 25.4 (Williams, et al., 1989). When prorated (doubled), the 30 item version mean would equal approximately 52. In Alzheimer's patients, the 60 item mean equals 39.9 (Kaplan, et al., 1983). This population's mean equals 19.1 for the 30 item version, which, again, when prorated is very near the 60 item version (Williams, et al., 1989). Prorated age-, gender-, and education-corrected scores for the BNT will be obtained from the Heaton, Grant, and Matthews (1991) normative sample. Williams, Mack, and Henderson (1989) reported that the BNT is a sensitive measure for detecting differences in naming ability among AD patients and healthy, elderly controls. This study will utilize the total number of items correctly named without a phonemic cue for a measure of language function.

Procedures

All patients were evaluated at the ADC. Neuropsychological tests were administered by trained technicians using standardized procedures, but the order of presentation may vary to meet the needs of each subject. All subjects or their legal representatives gave clinical consent prior to evaluation for participation in the ADC, and had no knowledge of the present study. Subjects are followed on a yearly basis for repeat evaluations to assess for changes in their functioning. Those with one year follow up data will be analyzed to assess for changes over time. After all data is collected, patient's names will be removed from the database to ensure confidentiality.

CHAPTER FIVE
Data Analysis

Neuropsychological Variables

Hypothesis 1: Patients diagnosed with Probable MCI will demonstrate lower performance on select nonmemory neuropsychological measures (i.e., 2 measures of executive function and 2 language measures) than patients diagnosed with Possible MCI who will perform lower than control subjects.

To identify differences in neuropsychological functioning among subjects in the probable MCI, possible MCI, and control groups, performance on neuropsychological variables will be compared across groups using a series of one-way analyses of variance (ANOVA) if all assumptions are met. For all variables, Tukey Honest Significant Difference (HSD) post hoc tests will be used to assess any significant findings. If all assumptions needed to use ANOVA are not met, then the appropriate non-parametric test will be utilized.

Hypothesis 2: Patients diagnosed with Probable MCI will demonstrate a decline in performance on one or more cognitive measures after one year than patients diagnosed with Possible MCI, who will show changes greater than those seen in control subjects.

To examine differences in cognitive measures over time in the Probable MCI, Possible MCI, and control groups, performance on neuropsychological variables of executive function and language will be compared across groups using a series of one-way repeated measures ANOVA (time x group). For all variables, Tukey HSD post hoc tests will be used to assess any significant findings.

Vascular Risk Factors

Hypothesis 3: Incidence of vascular risk factors (hypertension, high cholesterol, elevated tHcy blood plasma levels, and diabetes mellitus) in Probable MCI will be greater than Possible MCI, which will be greater than controls.

To examine differences in prevalence of vascular risk factors in the probable MCI, possible MCI, and control groups, four vascular risk factors (hypertension, high cholesterol, diabetes mellitus, and elevated tHcy blood plasma levels) will be compared across groups. Hypertension and high cholesterol will be identified based on the subjects' past history or current treatment of such conditions. Diabetes mellitus will be identified by a physician's diagnosis in available medical records. Homocysteine levels will be labeled as elevated or not elevated. This distinction will be made based on whether levels are currently or have been (before treatment) >14 mmol/L, as such levels are previously noted to double the risk of AD (Budge, de Jager, Hogervorst, et al., 2002). Differences in all variables will be examined using chi-square tests of independence as 3 X 2 chi square contingency tables will be used to investigate significant findings from chi-square tests of independence. Also, a logistic regression model will be used to examine whether these same vascular risk factors (present or absent), each as a single factor, predict group membership.

APOE-4 Allele

Hypothesis 4: The APOE-4 allele will be more prevalent in patients diagnosed with Probable MCI than those diagnosed with Possible MCI, who will have a higher prevalence than control subjects.

Differences in presence of the APOE-4 allele in the probable MCI, possible MCI, and control groups will be examined across groups using chi-square tests of independence, and 3 X 2 chi square contingency tables will be used to investigate significant findings from chi-square tests of independence.

Demographic Variables

Exploratory Analyses: Demographic variables will be examined in patients diagnosed with probable and possible MCI to identify differences in age, education, and gender, if any.

To identify differences in demographic variables among subjects in the probable MCI, possible MCI, and control groups, three demographic variables (age, education level, and gender) will be compared across groups. Differences in age and education will be investigated using ANOVA. Differences in gender will be examined using chi-square tests of independence. For all variables, Tukey HSD post hoc tests will be used to assess any significant findings on one-way ANOVAs, and 3 X 2 chi square contingency tables will be used to investigate significant findings from chi-square tests of independence.

CHAPTER SIX
Implications

Analysis of Hypotheses

The first aim of this study is to examine differences in neuropsychological functioning other than memory between the Probable MCI, Possible MCI, and control groups. Specifically Hypothesis 1 predicts that patients diagnosed with probable MCI will demonstrate poorer performance on selected executive functioning and language measures than patients diagnosed with possible MCI, who will perform more poorly than control subjects. If analyses indicate that the Possible MCI group does indeed perform worse on these measures than control subjects, then that will give credence to the possibility that they are a very early MCI group. It is important to better understand the significance of memory complaints in a population where deficits do not show on testing. Are these individuals worried well or over sensitive, or are they picking up early changes that cannot be identified on tests? Finding that Possible MCI subjects perform worse than control subjects would validate the importance in following these individuals in order to identify potential disorders as soon as possible. If this hypothesis were not supported, then possible MCI subjects may be too early in the stage of the disease for language and executive function to be quantifiably deficient, or they may be unlikely to progress (i.e., worried well). Another possibility is that those individuals with higher IQs may be capable of better compensating for memory loss, resulting in greater report of symptoms than can be seen on formal testing.

Hypothesis 2 predicts that patients diagnosed with Probable MCI are more likely to demonstrate a decline in performance on one or more cognitive measures after one year than patients diagnosed with Possible MCI, who will show more decline than control subjects. If

Possible MCI patients are found to decline more than control subjects on these measures, then the Possible MCI patients' SMCs may serve as a very early risk factor for advancement into dementia that would justify following these patients more closely. It is worth noting that though deficits may be minimal at baseline on testing, some decline in performance over time would be expected if these individuals suffered from an early form of MCI.

The second aim of this study is to examine differences in risk factors of AD and MCI among the Probable MCI, Possible MCI, and control groups. Hypothesis 3 predicts that patients diagnosed with Probable MCI will have a higher incidence of vascular risk factors (hypertension, high cholesterol, elevated tHcy blood plasma levels, and diabetes mellitus) than patients diagnosed with Possible MCI, who will have higher incidence than control subjects. If Possible MCI patients were shown to have more of these vascular risk factors than controls, then they would share these risk factors with MCI and AD. This would, again, argue a case for Possible MCI's prospective distinction as a precursor to these diseases. In this event, the ability to manage these vascular issues would become a means to minimize the likelihood of progression to a more advanced disorder of cognitive impairment. If Possible MCI had a greater number of vascular risk factors than the Probable MCI group, this might implicate an independent effect that could explain cognitive changes in this group.

The fourth hypothesis predicts that the APOE-4 allele will be more prevalent in patients diagnosed with Probable MCI than patients diagnosed with Possible MCI, who will have the allele in higher numbers than control subjects. If analyses support this prediction, then Possible MCI would share a biological risk factor known for MCI and AD. If this hypothesis is not supported, then patients diagnosed with Possible MCI may be less likely to progress to MCI or

dementia and other reasons for subjective memory complaints should be explored in this population.

The fifth analysis examines demographic variables in patients diagnosed with probable and possible MCI to identify any differences in age, education, and gender. Having this information will provide patients and practitioners with more information regarding the likelihood and nature of the respective diagnoses. Knowing which demographic variables are more prevalent in these diagnoses could help predict further someone's risk for developing advanced cognitive impairment, and thus potentially provide more information in serving as additional risk factors with further analysis. Ultimately, it will be important to investigate the relevance of following Possible MCI if these individuals look like controls in every way.

Limitations to the Current Study

One limitation of this study is the potential fallibility of using subjects' self report of memory impairment. Most notably in the possible MCI group (whose complaints do not have to be verified by neuropsychological test scores), subjects may be hypersensitive to the cognitive decline observed with aging. Their professed memory impairment could be the result of any number of extraneous factors that have little relevance to actual brain dysfunction. In hypothesis two, one year follow up data are used to examine differences in cognitive decline between the possible MCI and probable MCI groups. Here, the time allowed to examine such differences is relatively short and may not capture actual cognitive decline that would be apparent over time. More time between examinations and/or multiple follow up evaluations would give more confidence in identifying any trends. Also, MCI patients sometimes show variability in testing performance because of medication, mood, etc. until they convert to a dementia, if they do

convert. This variability could lead to inaccurate and/or inconsistent findings when looking only at one year follow up data. Another limitation to this study is that a small number of subjects are being used, especially given that the Possible MCI group may be more heterogeneous. This would reduce the likelihood of finding consistent differences if they exist.

Future Research and Study

Probable MCI and possible MCI are new terms that the ADC uses to identify patients with the aforementioned criteria. These labels may prove to be useful to help synchronize the language researchers use when looking at these populations. Other variables are worth investigating in determining risk factors in these populations as well as differences in ethnicity. Also, other neuropsychological abilities should be investigated to identify any trends in those areas. Potential areas of interest include visuospatial and attentional abilities. Finally, as mentioned previously under limitations, additional time analyses should be done that employ longer periods of time between testing to identify cognitive trends.

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