PERFORMANCE ON THE TEXAS FUNCTIONAL LIVING SCALE (TFLS) IN MILD COGNITIVE IMPAIRMENT

APPROVED BY SUPERVISORY COMMITTEE

First Name Last Name, credentials

_____

_____

_____

_____

_____

_____

ACKNOWLEDGEMENTS

The people who see one through the entire dissertation process, and are still present on the other side, are saints. I would like to thank my entire dissertation committee, whose support and guidance not only navigated my progress, but also provided wisdom and invaluable life lessons along the way. Specifically, I would like to thank my chair, Dr. Munro Cullum, for mentoring me throughout graduate school and for providing unique academic and professional opportunities that will certainly continue to serve me in the years to come.

I am deeply appreciative of the guidance provided by Dr. Myron Weiner, whose many talents, insight, and unwavering serenity provided a rich learning environment and forever endeared him to me. Thank you to Dr. Laura Lacritz, who has been an invaluable source of knowledge and guidance and who never stopped challenging me to find my path. Dr. Hynan's willingness to guide and teach certainly made some of the more intimidating aspects of this dissertation possible. More importantly, however, I deeply appreciate her constant willingness to give her time, her dedication to this project, and her

friendship. Finally, I want to express my most sincere gratitude to Dr. Kathy Saine, whose door is always open no matter what the need and whose way with patients is a true inspiration. I never would have realized the truth of my direction without her.

Several people behind the scenes worked to make this study possible. I truly appreciate Kristin Martin-Cook, M.S., whose working knowledge of the database, and the patients whose stories it contains, was instrumental in my maintaining any kind of sanity. In addition, I would like to thank Dr. Monty Evans, Dr. Deanna Liss, Dr. Merrilee Anderson, Dr. Melanie Biggs, Dr. Randall Price, Dr. Ted Asay, Dr. Eric Smernoff, Dr. V.J. Lair, and Dr. Ray McNamara, who have been particularly helpful in my development as a psychologist.

Finally, I want to thank my friends and family for their love and support. Dr. Joseph Miller, mentor, instructor, supporter, friend-I simply would not be here without you. I do not know even where to begin. Thank you. My friends, in particular Shay, Suzie, Gavin, Traci, Eric, Shawn, and Matt, you have held me together when I felt like falling apart and you believed in me when I needed it most. I am sincerely blessed by a group of friends who all are amazing women (you know who you are); each of you have been, and always will be, an inspiration. In closure, I want thank my family. My mom is simply the light of my life, and her faith provided me with the most important gift a parent could impart-an understanding of, and a relationship with, God. My dad, who gave my sister and me a father, his name, and his home-I can never thank you enough. My sister is one of the most remarkable women I will ever know, and my best friend. She, her husband Andy, and my beautiful niece and nephew, Tess and Adam, hold a very

special place in my life and in my heart and have never stopped supporting me. My brother has been a source of inspiration in ways I never imagined. His never-ending love, unfathomable persistence, and his triumphant fight for life have played a significant part in the development of the person I have become. My grandma, Maxine Wiser, at age 85, continues to provide love, support, and faith. And in loving memory of my grandpa, Lelon Wiser-he spent his life serving God, his country, and his family. After a 14-year battle with Alzheimer's disease, the dearest man in my life has gone home.

PERFORMANCE ON THE TEXAS FUNCTIONAL LIVING SCALE (TFLS) IN MILD COGNITIVE IMPAIRMENT

by

DANI LYN BINEGAR

DISSERTATION

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

August 2007

Copyright

by

Dani Lyn Binegar, 2007

All Rights Reserved

PERFORMANCE ON THE TEXAS FUNCTIONAL LIVING SCALE (TFLS) IN MILD COGNITIVE IMPAIRMENT

Publication No. _____

Dani Lyn Binegar, Ph.D.

The University of Texas Southwestern Medical Center at Dallas, 2007

Supervising Professor: C. Munro Cullum, Ph.D., ABPP

Mild cognitive impairment (MCI) describes the transitional state between normal aging and dementia for many individuals, although debate continues over whether MCI represents an initial, separate condition, or if it is, in fact, the earliest presentation of dementia. One criterion for the diagnosis of MCI is an absence of impairment in activities of daily living; however, there is growing evidence that many individuals with MCI have difficulties with some instrumental activities of daily living (IADLs), such as managing finances and medications. The current study examined the performance of individuals diagnosed with MCI and normal control subjects (NC) on a brief, quantifiable

measure of IADLs, the Texas Functional Living Scale (TFLS). Additional goals of this study were to examine how the TFLS relates to standard neuropsychological measures of global cognitive function, memory, language, executive functioning, and attention, and to determine whether performance on the TFLS declines over time in MCI. As predicted, the MCI sample (n = 30) scored significantly lower than the NC group (n = 30) on the TFLS total score ($t(58) = 2.34$, $p = .011$) and on the TFLS Memory subscale ($t(58) = 3.29$, $p = .002$). Performance on the TFLS was significantly correlated with performance on the MMSE ($\rho = .26$) and The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD; $r = .37$). Scores on the TFLS Memory and Communication subscales were also correlated with the CERAD total score ($r = .45$ and .22, respectively). Across all subjects, the TFLS was associated with standard measures of memory and language (ρ's = .22 to .31). Although the difference did not reach statistical significance, subgroups of MCI and NC were followed over time, and 50% of individuals with MCI declined on the TFLS, compared with 29% of NC sample. These findings suggest that subtle changes in cognitive-related IADLs may be present in individuals with MCI, and that the TFLS is sensitive to such changes.

TABLE OF CONTENTS

PRIOR PUBLICATIONS

Chandler, 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(2).

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

CHAPTER ONE
Introduction

Many lay people still believe that cognitive decline is simply a product of getting older, while others argue that, in the absence of a disease process, there should be no decline in many aspects of mental functioning. Many workgroups, researchers, and clinicians have attempted to functionally define, "normal aging," and in 1986, Crook et al., as part of a mental health work group, proposed the concept of age-associated memory impairment (AAMI). AAMI is defined by a subjective report of memory impairment in tasks of everyday living, substantiated by evidence of such impairment on neuropsychological testing with adequate normative data, as applied to people over the age of 50. Based on a review of the literature that was available at that time, the group concluded that in the normal aging process, primary (immediate) memory and tertiary (remote) memory remain relatively intact, while secondary (recent) memory and processing speed show substantial age-related deficits when comparing older individuals to younger ones.

Petersen et al. (2001b) point out that because AAMI refers to increasing memory impairment in an elderly cohort as compared to younger normal adults, there is the inherent possibility that an overinclusion of elderly whom are neurologically normal for their age, but impaired when compared to people many years younger than they are. Another argument is that some individuals with undetected early dementia or other medical conditions that can affect memory performance may be erroneously classified as AAMI. One option to defining "normal aging" is to exclude those with any comorbid illness that may affect cognitive status from the normative sample; however, this appears

to result in a subgroup of elderly "supernormals" that may not be representative of the normal elderly population. Another alternative is to use age-specific norms (Heaton, 1992; Heaton, Grant, & Matthews, 1991), and many argue this is the most appropriate method (Derouesne, 1994; Ivnik, Malec, & Smith, 1992a, 1992b; O'Brien & Levy, 1992; Smith et al., 1992). More recently, Pioggiosi et al. (2006) applied several different sets of diagnostic criteria (AAMI, MCI, etc.) to a cohort of individuals over the age of 90 and determined that the AAMI criteria resulted in an overestimation of those with cognitive impairment. Additionally, they argued that AAMI criteria that excluded common cognitive risk factors were too restrictive, as many people aged 90 or older have comorbid medical disorders.

Other attempts have been made to classify the stage between normal cognitive functioning and dementia. Some of the proposed terminology includes "benign senescent forgetfulness," "prodromal AD," and "mild cognitive impairment." These terms are not interchangeable, however, as most researchers typically utilize the term 'benign senescent forgetfulness' to describe changes that occur during the normal aging process, while mild cognitive impairment and prodromal AD typically refer to a stage in which greater cognitive impairment than would be expected for age is observed. The latter stage is of particular interest, as it represents an abnormal process often leading to dementia.

Mild cognitive impairment (MCI) is a term most often used to describe the transitional state between normal aging and the early stages of dementia, in particular AD. Depending on the diagnostic criteria used, reported prevalence rates of MCI range anywhere from 3% - 22% in individuals aged 65 and older (Bischkopf, Busse, &

Angermeyer, 2002; Lopez et al., 2003). Ganguli et al. (2004) retroactively applied amnestic-type MCI criteria (Petersen et al., 2001a) to a random community sample of individuals who were nondemented at entry and who were assessed biannually over a period of 10 years. They found that 2.9%-4.0% of the cohort met MCI criteria, and of the 40 persons with MCI at the initial assessment, 27% developed dementia (primarily AD) over the next 10 years. An MCI prevalence rate of 32.4% was reported by Pioggiosi et al. (2006), although their community sample had a mean age of 96 years; thus, it is likely that this higher rate may be a reflection of the age-associated increased risk of developing MCI.

Original criteria developed by Petersen and colleagues required an individual diagnosed with MCI to have (a) memory complaint, (b) normal activities of daily living, (c) normal general cognitive function, (d) abnormal memory for age, and (e) absence of dementia (Petersen et al., 1995; Petersen et al., 1997; Petersen, Waring, Smith, Tangalos, & Thibodeau, 1996). In 1999, the group emphasized that the first criterion (memory complaint) would ideally be corroborated by an informant and added that the absence of impaired cognitive ability in a domain other than memory was required for the diagnosis of MCI (Petersen et al.). Grundman et al. (2004) insist that by accurately applying these criteria, MCI can be clearly distinguished from AD and normal elderly (NE). In a study of 234 normal elderly and 182 subjects with MCI, very mild AD, or mild AD, the group found that (a) the MCI group performed significantly worse than NE on immediate and delayed recall of a word list, (b) the area of greatest decline in MCI, over time, was performance on paragraph recall for both immediate and delayed recall trials, and (c)

hippocampal volumes in MCI subjects, as measured by magnetic resonance imaging (MRI), were greater than in AD, but less than in NE subjects. The term MCI, however, has continued to evolve.

Significant debate continues over whether MCI is an initial, separate stage from the actual onset of dementing illness, or if it is, in fact, the earliest presentation of AD. Certainly a large percentage of individuals with MCI go on to develop AD (Arnaiz et al., 2004; Dubois & Albert, 2004; Ganguli et al., 2004; Jicha et al., 2006; Petersen et al., 2001a), and many of these studies have demonstrated similarities between the two groups, both in clinical presentation and in neuropathologic outcome of the disease. Numerous studies have evaluated postmortem neuropathologic characteristics of MCI and concluded that many individuals diagnosed with MCI exhibit typical AD changes (Becker et al., 2006; Gauthier et al., 2006; Jicha et al., 2006; Morris, 2006; Petersen et al., 2006). Similarities between the two groups include whole brain and ventricle atrophy rates (Jack et al., 2005), hippocampal volumes/atrophy rates (Becker et al., 2006; Grundman et al., 2004; Jack et al., 2005; Winblad et al., 2004) and entorhinal cortex atrophy rates (Apostolova et al., 2006; Winblad et al., 2004). Additionally, regional involvement of neurofibrillary tangles has been found to correlate significantly with the degree of clinical impairment in MCI (Collie & Maruff, 2000; Petersen et al., 2006).

Prodromal AD is a term that has been to describe the stage in which an individual exhibits minor cognitive difficulties and/or impairments but does not meet criteria for dementia, though many believe that both of these concepts (prodromal AD and MCI) simply describe the earliest stages of the disease process. A prodrome is defined as “a

premonitory symptom of disease," or an early symptom of disease onset (Mish et al., 1993). Thus, as applied to AD, "prodromal" AD refers to an early symptom(s) indicating the onset of the disease, not necessarily a stage before the onset of AD. As early detection of AD is becoming increasingly important with the development of potential interventions, the view that MCI is simply early stage AD has significant implications. Primarily, it can be argued that the treatment of individuals who meet criteria for MCI should mirror, perhaps to a lesser degree, that of people who are diagnosed with AD, if MCI and AD are indeed one-and-the same. Perhaps even more salient to the "prodromal AD vs. separate diagnosis" debate, however, is the fact that not all patients diagnosed with MCI go on to develop AD or other types of dementia at all, with a subgroup of those individuals actually reverting to "normal" in some reports. Ganguli et al (2004) found that over a period of 2 years, 17.5% of the 27 individuals initially diagnosed with MCI remained MCI, while 30% reverted to "normal." In a study of 165 elderly outpatients who were diagnosed with MCI and followed for a period of three years, 67% remained stable, 4% reverted to normal, and 29% converted to dementia (Ravaglia et al., 2006); however, post hoc analyses also showed that converters, overall, had lower scores on the Mini-Mental Status Examination (MMSE), a test of global cognitive ability (Folstein, Folstein, & McHugh, 1975b). This raises the possibility that some "converters" may have actually been at the very early stages of AD, or were predisposed to developing dementia, simply based on their poorer baseline cognitive performance.

While not all cases of MCI progress to AD, some go on to develop other types of dementia, such as Parkinson's, frontotemporal, or vascular dementia (Winblad et al.,

2004). Jicha et al (2006) discovered that while 71% of MCI subjects (n = 34) went on to develop AD, the remaining 29% received other non-AD pathologic diagnoses such as hippocampal sclerosis, frontotemporal lobar degeneration, and progressive supranuclear palsy. The fact that many people who meet full diagnostic criteria for MCI, yet go on to develop another dementing disorder other than AD, implies that the diagnostic entity of MCI needs to be examined more closely if it is to be of use to clinicians and families regarding placement issues as well as treatment planning and recommendations. If the patient's diagnosis or the etiology of symptoms were unclear, subsequent treatment would be extremely difficult to determine. Some suggest that clinicians should not be diagnosing patients with MCI, but rather diagnosing "prodromal AD," or "incipient dementia," to more accurately identify the disease process, and therefore ensure the most appropriate treatment plan is implemented (Dubois, 2000). "As used today, MCI is a syndrome; to have full clinical usefulness, an aetiological understanding must follow" (Dubois & Albert, 2004).

Gauthier et al. (2006) suggested a diagnostic approach to MCI in which the clinician distinguishes between different types of MCI based on the most prominent feature upon presentation, whether that is amnestic, dysphoric, vascular, or associated with other medical disorders. Petersen et al. (2001a) discussed the ethical issues surrounding the concept of MCI, and agree that making an accurate diagnosis is a key element in the practice of medicine. They further noted that benefits of accurate diagnosis include appropriate treatment, as well as helping to provide information to the

patient and family regarding the nature of the illness and what they can expect as time progresses.

Dubois and Albert (2004) point out that the heterogeneity of the MCI group makes it more difficult to predict clinical progression for any patient diagnosed, and there has been a great response to the call for swifter and more accurate identification of individuals who meet criteria for MCI. As dissimilarities within the MCI group became more evident, some researchers began to examine these within-group differences and discovered that some people reported difficulties in only one cognitive domain (most often memory), while others reported cognitive difficulties in a variety of domains, such as language or executive functioning. Petersen (2004) reported that while individuals with MCI may or may not have deficits in memory, those who do not have a higher likelihood of progressing to non-AD types of dementia. Findings such as this not only stimulated studies aimed at examining potential differences between these groups, they inspired the concept of MCI subtypes that directly address the heterogeneity of MCI.

MCI Subtypes

Petersen has described 3 different types of MCI: amnestic, multiple-domain and single non-memory-domain (Petersen, 2003; Petersen et al., 2001a). Amnestic MCI (aMCI) is the most widely studied subtype, and involves primary impairment in learning and memory, with other cognitive domains being only slightly impaired, if at all. In multiple-domain MCI (mdMCI), individuals may have mild memory impairment in conjunction with mild impairment in at least one other domain, such as executive functioning or language. Individuals showing impairment in a single non-memory

domain, such as executive functioning, characterize the subtype of single non-memory-domain MCI. While subtyping MCI may not directly address Dubois's (2004) insistence that MCI is simply AD, and should be diagnosed as such, it paves the way for further research aimed at illustrating these differences and provides plausible explanations for why some individuals with MCI may progress to other types of dementia.

The concept of MCI subtypes is relatively new, and as such, the number of comparative studies is relatively small. In addition, consensus has not been reached regarding the differences between groups, their similarities to different types of dementia, or progression of impairment and disease process over time. For example, some studies suggest that aMCI, in particular, most closely resembles AD, both neuropathologically and clinically. Jicha et al (2006) followed a cohort of 34 subjects who were diagnosed with aMCI at study outset and who underwent subsequent postmortem brain examination. Variables considered included the duration of the diagnosis of MCI, final clinical outcome at time of autopsy, APOE genotyping, presence of Lewy Bodies, and various other neuropathologic elements. At final consensus, they discovered that 24 (71%) of the aMCI subjects met criteria for the diagnosis of AD; and in those, significant involvement of the medial temporal lobe was noted, a region that is also affected early in progressive AD (Braak & Braak, 1991). These findings may lend further support to the postulate that neuropathologically, individuals with aMCI resemble those with AD. In an MRI volumetric study of MCI subgroups compared to AD and normal elderly, Becker et al (2006) reported that the aMCI group showed significantly greater hippocampal atrophy

compared to mdMCI and NE, although the degree of atrophy was not significantly different from that seen in the AD sample.

Similarities between aMCI and AD are not limited to neuropathologic measurements, however. Dubois and Albert (2004) explored the similarities between aMCI and AD on neuropsychological tests by examining more closely the pattern of performance across memory tasks. Impaired free recall combined with limited benefit from cueing and the occurrence of many intrusions and false positives or recognition tasks is a pattern that is highly suggestive of AD (Greenaway et al., 2006) and was also seen in their aMCI group. In an attempt to describe the neuropsychological characteristics of MCI subgroups, Lopez et al. (2006) examined a group of subjects that included 10 aMCI, 28 mdMCI, and 374 normal elderly. The subjects were originally diagnosed with MCI and then sub-classified them as (a) MCI-AT—individuals who had impairments in delayed verbal or nonverbal recall which represented a decline from previous level of functioning and normal performance in other cognitive function, and (b) MCI-MCDT—individuals who had deterioration in at least one non-memory cognitive domain or who had at least one abnormal test score in at least two cognitive domains, one of which could be memory. The MCI-MCDT subjects were assessed as a whole, but also further divided, based on performance on memory tests (>1.5 SD), into those with and without memory impairment. The group conducted a large battery of tests designed to assess performance in a number of cognitive domains such as memory, language, attention, and executive functioning. As expected, individuals diagnosed with MCI-AT exhibited worse verbal and non-verbal memory performance than either MCI-MCDT or

NE groups. An additional finding was that individuals with MCI-MCDT performed worse than MCI-AT or NE on tests of language, psychomotor speed, fine motor control, and visuoconstructional functioning. After the MCI-MCDT subject scores were broken down by memory scores, the pattern of cognitive functioning changed somewhat. The group with memory disorders had more language deficits and fewer fine motor control deficits than the group without memory problems and the MCI-MCDT group without memory deficits had worse executive functions than normal controls and MCI-AT subjects, lending further support to the postulate that MCI may actually be a conglomerate of several different subtypes of mild cognitive impairment.

Ravaglia et al. (2006) enlisted a cohort of 165 elderly outpatients with MCI, further sub-classified them into aMCI, mdMCI, and non-memory mdMCI, and followed them for an average of 3 years. A variety of known risk factors for conversion to dementia were examined, while adjusting for demographic variables, and it was discovered that individuals with aMCI had a higher risk of developing dementia (hazard ratio = 2.84) than the other subtypes (mdMCI = 1.59%; non-amnestic MCI = 1.0). In contrast to these findings, however, are other studies that report mdMCI may actually have a higher risk of conversion to AD. Bozoki et al. (2001) examined a group of 48 non-demented persons with psychometric evidence of memory impairment (called M-), 17 of whom reported no other cognitive difficulties and whose neurological evaluation indicated normal scores in all other cognitive domains measured, including language, attention, motor visuospatial function, and verbal fluency (aMCI). The remaining 31 patients (called M+) had abnormal scores in at least one other domain in addition to

memory, and thus qualified as mdMCI. At the 2-year follow up, only 1 M- subject (6%) had progressed to AD, whereas 15 of the M+ group (48%) went on to develop AD. At the most recent follow up, an average of four years following enrollment, four (24%) of the M- group and 24 (77%) of M+ patients had progressed to AD, revealing a statistically significant difference ($p<.001$) in the rate of conversion from MCI to AD. While scores from several of the memory tests were not available, the WMS-Memory Quotient differed between groups (M- = 106.7 ± 14.2; M+ = 99.4 ± 12.7), although they were ultimately within normal limits in both groups. This difference in scores may indicate that the M+ group was more impaired than the M- group to begin with, or that their cognitive impairments were actually indicative of a different type of dementing disorder. Another consideration, given the significantly higher rate of conversion to AD that can be seen in mdMCI versus aMCI, is that individuals diagnosed with mdMCI may actually represent a different stage of progression to, or a different presentation of, AD than those with aMCI. Several other studies have shown that the number of cognitive domains affected in subjects with MCI predicts time to conversion to AD (Arnaiz et al., 2004), and increases the likelihood of converting to AD (Jicha et al., 2006; Sacuiu, Sjogren, Johansson, Gustafson, & Skoog, 2005). This highlights one of the major goals in studying the differences and similarities between MCI subgroups—i.e., to more accurately identify those who are at risk for converting to AD and other types of dementia.

Reported rates of conversion from MCI to AD vary widely from study to study. Petersen et al. (1999) reported a conversion rate of 12% over a period of four years in

their MCI sample (n = 76) compared to 1%-2% in their normal elderly sample (n = 234). Two years later, a Quality Standards Subcommittee of the American Academy of Neurology met to determine the utility of screening asymptomatic individuals for MCI. They performed an extensive search of existing literature that yielded conversion rates ranging from 6%-25% per year (Petersen et al., 2001b) and in a similar meta-analysis, Bischkopf , Busse & Angermeyer (2002) reported annual conversion rates ranging from 10% - 40% per year. The different estimates may reflect inconsistencies across diagnostic and conversion classifications, which represent some of the major obstacles in attempts to better understand what is normal aging and MCI, and risks of conversion from one state to another. Serious consideration should be given to the impact that individual inclusion, exclusion, and diagnostic criteria may have upon study results when reviewing and comparing the literature. For example, Arnaiz et al (2004) looked at two groups of subjects who were diagnosed as having MCI using either the Petersen criteria or a slightly modified version of those criteria, which was used at the Karolinska Institute. While they were very similar, the Karolinska group operationalized Petersen's 3rd-5th criteria to a decline in any cognitive domain as measured by neuropsychological testing that was 1.5 standard deviations (SD) below age-matched controls, as well as, "No reported social interference with daily life." They discovered that the Karolinska subjects were more cognitively impaired at baseline than were the Mayo Clinic subjects. In addition, the Mayo subjects with MCI were impaired primarily in the memory domain, with other cognitive domains predominantly intact. The Karolinska subjects were impaired slightly in multiple cognitive domains but the impairments were not significant

enough to constitute a diagnosis of dementia. This study illustrates that recruiting subjects using only slightly disparate diagnostic criteria can result in two populations who, while similar in age, education, and gender, differed significantly in the number of cognitive domains impacted and/or level of impairment.

Clearly, there are a variety of approaches that can be taken and variables that can be studied in order to better understand the characteristics of MCI and its subtypes and the ultimate risk of conversion to dementia. Most researchers and clinicians would agree, however, that the most accurate diagnosis can be made only after a comprehensive evaluation has been conducted and that predictive validity increases when several diagnostic methods are used (Albert, 1997; Albert, Moss, Tanzi, & Jones, 2001). Neuropsychological assessment, both of cognitive and everyday functioning, is an element of clinical evaluation that has proven extremely useful in diagnosing dementia and MCI (Albert et al., 2001; Bischkopf et al., 2002; Petersen, 2000, 2004; Sacuiu et al., 2005; Tierney, Szalai, Snow, & Fisher, 1996) and an element that some argue is a mandatory step in diagnosing these disorders (Portet et al., 2006). Delis et al (1991) showed that individuals with dementia tend to exhibit similar within-group neuropsychological profiles, and it would follow that MCI should show that same pattern of performance, albeit to a lesser degree. For example, their subjects with Huntington's disease showed substantially better recognition discriminability, lower false-positive rates, and higher difference scores between recognition discriminability and recall than those with cortical dementias, such as AD. Therefore, if MCI is a precursor to AD exclusively or even an early stage of AD, then MCI profiles on neuropsychological

testing and measures of global cognitive functioning should be qualitatively similar to those seen in AD.

Cognitive Functioning

Global cognitive functioning refers to overall functioning in the primary cognitive domains (memory, attention, language, executive functioning, and visuospatial abilities). Brief cognitive screening measures, such as the MMSE and more detailed neuropsychological measures, are valuable in determining "normal" versus "abnormal." These assessment tools utilize normative data to which individual performances can be compared, and in doing so, allow conclusions to be drawn about a person's overall cognitive functioning relative to others in his or her cohort. In addition, these normative values allow the classification of "abnormal" to be further clarified by also suggesting degree of impairment (i.e., mild, moderate, severe). While tests such as the MMSE or Clinical Dementia Rating Scale (CDR)(Morris, 1993) are adequate measures of global cognitive functioning, however, they are often not sensitive enough to detect mild impairment of cognitive functioning (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006; Collie & Maruff, 2000; Petersen, ; Petersen, 2000). This may be because measures designed to assess more global cognitive functioning (e.g., the MMSE) may not adequately target domains that can assist in the detection of a particular disorder (e.g., memory in AD). Boeve et al (2003) looked at aMCI in the "oldest old" (90- to 100-year-olds) and determined that while the MMSE was able to accurately distinguish AD from MCI and NE, it was not sensitive enough to clearly differentiate MCI from NE. As mentioned previously, neuropsychological testing of the major cognitive domains is

extremely helpful in the differential diagnosis of dementias. Dubois (2000) emphasized the need to not only examine performance in each cognitive domain, however, but also to evaluate the pattern of performance on these tests, particularly in the area of memory. This approach, in large part, is based on findings from numerous studies discussed previously regarding the "typical" performance on memory tasks that can be seen in AD patients and, to a lesser degree, in MCI.

In the typical AD patient, memory difficulties are the first symptom noted, and difficulties in other areas, such as language or executive functioning, appear to progress over time. Typically, simple attention remains relatively intact until later in the disease process. In terms of memory, both verbal and nonverbal memory can be affected. Common features of verbal learning profiles in AD include a flat learning curve, reduced semantic clustering, rapid forgetting, little-to-no benefit from semantic cuing, high number of extra-list intrusion errors, and poor performance on recognition testing with increased false-positive errors (Kaltreider et al., 2000; Lacritz, Cullum, Weiner, & Rosenberg, 2001). In individuals diagnosed with MCI, in particular aMCI, the profile is very similar, albeit with less impairment (Collie & Maruff, 2000; Greenaway et al., 2006; Tierney et al., 1996).

Memory is not the only domain that can be affected in early MCI, however, and most researchers agree that multiple-domain evaluations are required in order to increase diagnostic accuracy and consensus (Collie & Maruff, 2000; Gauthier et al., 2006; Petersen, 2000; Sacuiu et al., 2005). Recent studies have shown that even in MCI and early AD, deficits in executive functioning can be seen (Griffith et al., 2003; Lopez et al.,

2006). In examining tests that may discriminate between presymptomatic AD (i.e., MCI) and normal elderly who did not go on to develop AD, Chen et al (2000) reported that the optimal set of cognitive measures were measures of delayed recall and executive functioning. Royall, Chiodo and Polk (2004) argued that misclassification of MCI is likely because so many studies focus on memory impairment alone, while their research has shown that approximately 35% of "nondemented" memory-impaired subjects had equally severe executive impairments and an equal number have isolated executive dysfunction that memory assessment alone would not detect. They theorized that many individuals who are diagnosed with aMCI might actually qualify for the diagnosis of mdMCI, and thus over-inflate the number of subjects with aMCI who progress to AD. While this point is well made, it does not completely address the contribution of executive functions to performance on memory tasks, which Troyer, Graves & Cullum (1994) described in their study of executive functioning as a mediator of the relationship between age and episodic memory. They discovered that while initially age was a significant predictor of recall, after accounting for the effect of executive functioning on memory performance, this was no longer the case. In addition, the contribution of executive functioning accounted for 36% of the variance in subject's recall performance. The group speculated that this relationship was due to the executive demands of the particular memory tests used, theorizing that subjects who utilized higher-level organizational strategies on those tasks were more likely to use an effective framework from which to recall the material than those who used less efficient strategies. While not originally intended to be a measure of executive functioning, for example, the semantic

clustering index on the CVLT has been considered as a verbal measure of executive functions in that it reflects an individual's ability to organize effectively a list of words into categories. Theoretically, this allows more efficiency in accessing those items for recall at a later point. Along these lines, Simon and colleagues (1994) found that in their AD group, this ability to organize was severely impaired on this dimension, along with delayed recall of the words. Sacuiu et al (2005), in fact, suggested that low performance in both memory and executive functioning is required in order to be predictive of conversion to dementia. Regardless of varying perspectives on this issue, DSM-IV (APA, 2000) criteria require impairment in memory plus at least one other cognitive domain to be diagnosed with dementia; and, neuropsychological testing is the most efficient and accurate way of determining the presence and extent of these deficits (Albert et al., 2001; Chen et al., 2000; Collie & Maruff, 2000; Dubois, 2000; McKhann et al., 1984; Portet et al., 2006).

While measuring performance in multiple cognitive domains provides vital information diagnostically, neuropsychometric testing allows for only indirect inferences regarding patients' ability to function in everyday tasks (Franzen & Wilhelm, 1996). As discussed earlier, one criterion of MCI is a lack of impairment in everyday functional abilities; however, there is growing evidence that a relationship exists between overall cognitive functioning and activities of daily living (ADLs), and in particular, instrumental activities of daily living (IADLs) (Artero, Touchon, & Ritchie, 2001; Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Petersen et al., 2001b; Royall, Chiodo, & Polk, 2000). For example,

Bennett et al. (2006) evaluated 106 nondemented elderly aged 80-94 on three different occasions over a period of six years to determine the prevalence of functional incapacity in this group. They discovered that cognitive performance on neuropsychological tests was associated with functional status. While all subjects were independent in more basic ADLs such as bathing and dressing, some assistance from others was necessary for all IADLs measured. This is not the first study to report such findings, however, as Rapp et al. (2005) showed that executive functioning was associated with functional deficits in both community-dwelling older adults and nursing home residents and Royall, Chiodo and Polk (2000) identified an association between executive functioning and functional status in MCI. Longitudinal follow up of individuals with and without MCI (Artero et al., 2001) showed a significant relationship between loss of overall functional capacity and attentional ($p < 0.05$), language ($p < 0.001$), memory ($p < 0.05$), or visuospatial deficits ($p < 0.05$).

Grigsby et al. (1998) reported similar findings in community-dwelling older adults who were part of a larger study on health and aging. They examined 1158 individuals between the ages of 60 and 99 using self-report (structured interview) and an abbreviated version of a performance-based (Structured Assessment of Independent Living Skills; SAILS) measure of functioning. The Behavioral Dyscontrol Scale (BDS) evaluates the basic capacity to use an intention to regulate movement and has been validated as a measure of the ability to regulate purposeful, goal-directed behavior. Individual's BDS scores were found to account for a significant percentage of the variance on all 5 direct measures of functioning (SAILS), although the overall scores

were not significantly correlated (r=0.18-0.53). The ability to regulate behavior, as measured by the BDS, was a significant predictor of self-report IADL functioning but not ADL functioning, while the MMSE was not a significant predictor of self-reported ADLs or IADLs (model adjusted for age and education), although it contributed more significantly than did the BDS to the ability to handle medications. While the sample size was more than adequate, inclusion and exclusion criteria were not outlined and it is unknown if subjects had comorbid medical or psychiatric disorders that may have affected their cognitive and everyday functioning. Additionally, as the authors pointed out, the BDS measures a very specific executive ability involving initiation and monitoring of tasks without the assistance or supervision of others. There are many other executive abilities including planning, problem solving, working memory, and inhibition of inappropriate behavior, however, that the BDS is not designed to measure. Thus, results cannot be easily extrapolated to conclude that performance of ADLs and IADLs rely significantly on an individual's overall executive abilities. Given these more recent findings, however, there is a growing interest in identifying measures of ADLs/IADLs that may be sensitive enough to detect the more subtle changes in everyday functioning that can be seen in MCI.

Everyday Functioning and Activities of Daily Living

Activities of everyday functioning have been sorted into two groups: basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs). There lacks an overall consensus as to which activities belong in each of the two groups; however, in general, ADLs are thought to include more basic self-care skills such as

grooming, toileting and dressing, while IADL's typically include more complex activities such as housekeeping, driving, cooking, and management of finances and medications (Lawton & Brody, 1969; Nygard, 2003). Other definitions of IADLs include well-developed communication skills, such as knowing how to use the telephone or a phonebook. Some researchers further distinguish complex IADLs such as reading activity, active participation in a hobby, and involvement in social activities (Bennett et al., 2006). In normal aging, the majority of these skills are generally preserved, and to earn a diagnosis of dementia, impairment in one or more of these areas is required. According to the 1994 National Long-Term Care Survey, 2.3 million elderly persons in the US report one or more ADL impairments, while 4.4 million report one or more IADL impairments (Kassner & Jackson, 1998). These findings prompted Royall (2006) to speculate that one or more IADL impairments may serve as a better threshold for dementia case finding than would similar impairments in ADLs. In a community-based study (n=1145) that examined the role of executive abilities in everyday functioning, 830 persons reported no impairment in ADL's, while 157 reported difficulty with one, 50 reported difficulty with two, 45 had difficulty with three, and 63 persons reported difficulty with four or more ADLs. In contrast, only 667 persons reported no IADL impairment, while 249 reported difficulty with one, 86 reported difficulty with two, 51 reported difficulty with three, and 92 persons reported difficulty with four or more IADLs.

As previously stated, to meet criteria necessary to diagnose an individual with MCI, both ADLs and IADLs must be intact. It is known that IADLs are more complex

than basic ADLs and are therefore more likely to be vulnerable to the early effects of deterioration in cognitive functioning (Caltagirone, Perri, Carlesimo, & Fadda, 2001; Galasko et al., 1997). Additionally, some individuals who go on to develop dementia appear to experience subtle changes in IADLs several years before confirmation of a dementia diagnosis is made (Gustafson & Thulin, 1995). However, there is still significant debate about the existence and/or prevalence of ADL/IADL impairment in MCI.

Boeve et al (2003) sought to determine whether a relationship between functional status and performance on neuropsychological testing existed in a group of community dwelling residents aged 90-100 with and without MCI. They determined that functional capacity did not differ between MCI and normal elderly, and furthermore, that performance on several measures of global cognitive and executive functioning did not differ significantly between groups. In his meta-analysis of research studies looking at MCI as a diagnostic entity, Petersen (2004) determined that, consistent with diagnostic criteria, functional impairment in this group was slight, if present at all. Other researchers, however, have detected a variety of IADL impairments in MCI (Morris, 2006). As a part of a larger community study, Bennett et al (2006) reviewed the results of neuropsychological testing on 106 nondemented people, aged 80-94, who were evaluated three times over a period of six years. While all participants independently performed ADLs such as dressing, toileting and feeding, some level of dependency on IADLs, such as cooking, housework, and shopping, was noted. Of all subjects evaluated, 52% required at least some help with housework and 39% required assistance with

shopping; however, results also showed a significant association between motor functioning and shopping and thus, IADL difficulties may have partially been due to increased motor dysfunction in this older group.

Grundman et al (2004) compared individuals with MCI to both normal elderly and AD in attempts to describe and compare the baseline characteristics of these groups. To measure IADLs, they utilized the Alzheimer's Disease Cooperative Study Activities of Daily Living for patients with MCI (ADCS MCI-ADL), which was designed to be more sensitive to impairments in instrumental activities that may occur in this group and is scored correspondingly. Information required to complete the measure was collected from an informant, and results showed that patients with MCI had a significantly lower score on the MCI-ADL scale than controls. Detection of IADL impairments in MCI may be helpful in determining who, from this group, will go on to develop dementia. Purser et al. (2005) retrospectively applied MCI diagnostic criteria to 3,673, non-institutionalized, community residents aged 65 and older in attempts to estimate 10-year trajectories of incident disability. A total of 810 individuals met criteria for MCI, and approximately 196 of them reported (informant-reported) difficulties performing IADLs. For those who did not report IADL disability, the progression to disability (a prerequisite for the diagnosis of dementia) was similar to that of the cognitively intact group. For those who reported difficulties with IADLs at baseline, however, the median rate of change was equivalent to that of the severely impaired, indicating that reported IADL difficulties in MCI may be helpful in predicting who will go on to develop dementia. One criticism of this study, however, addresses the concern that caregiver-rated scales are

frequently biased by other issues such as caregiver depression (Pruchno, Burant, & Peters, 1997) and relationship issues (Lyons, Zarit, Sayer, & Whitlatch, 2002), particularly when relationship strain is perceived by the caregiver, but not the care recipient.

As mentioned previously, management of finances and investments and making medical and/or legal decisions are two more complex IADL skills. Earlier research has shown that some IADL activities, such as handling finances or taking care of medications, may be sensitive to early cognitive decline and thus may be useful as early indicators of a process that may lead to dementia (Nygard, 2003). In a study that used the Financial Capacity Instrument (Marson et al., 2000) to examine financial abilities in MCI (Griffith et al., 2003), results showed impairments in domains of conceptual knowledge, cash transactions, bank statement management, bill payment, and in overall financial capacity. Furthermore, controls performed significantly better than the MCI group on tasks of applying financial concepts, understanding and using a bank statement, understanding bills, and preparing bills for mailing. Royall, Cordes & Polk (1997) examined executive functioning in relation to comprehension of medical information in a group of randomly selected elderly and reported that impairment in this cognitive domain was strongly associated with impaired comprehension of medical information. In subsequent studies, these findings were replicated, prompting speculation that measures of executive functioning may be better cross-sectional and longitudinal correlates of IADLs than are measures of general cognition and memory (Royall, Palmer, Chiodo, & Polk, 2004, 2005).

There are many available measures of ADL/IADL impairments. Some were originally designed to use with specific populations, others to measure everyday functioning in general, regardless of diagnosis. Additionally, some measures rely on an individual's self-report of abilities, others require the assessment of the patient's abilities by a caregiver or someone who is well known to the patient, and still others utilize performance-based ratings on a variety of simulated tasks. Even in cohorts of nondemented older persons, studies have demonstrated that informant and performance-based ratings of functional capacity are most accurate, as people with MCI often underestimate their own level of functional impairment (Albert, Tabert, Dienstag, Pelton, & Devanand, 2002; Tabert et al., 2002). A review of recent literature reflected great consensus regarding the need for shorter, more comprehensive screening instruments with established norms (Gauthier et al., 2006; Petersen, 2004; Petersen et al., 2001b; Royall, 2006). Regardless of the type of measure used, the need to better understand ADL/IADL dysfunction in MCI is largely agreed upon throughout the literature (Petersen et al., 2001b; Winblad et al., 2004).

Measures of Activities of Daily Living

Galasko and colleagues (1997), as part of the Alzheimer's Disease Cooperative Study Instrument protocol, developed the ADCS-ADL inventory, an informant-based measure of activities of daily living designed specifically for clinical evaluation of patients with AD. The inventory is a set of 23 activities (e.g., preparing meals, using the phone) which are rated by the caregiver (identified as individuals who spent a minimum of two days per week with the patient) according to the amount of assistance the patient

requires to carry out each ADL. The ADCS-ADL exhibited moderate to very good test-retest reliability and correlated significantly with the extent of cognitive impairment in AD as measured by the MMSE. Findings regarding the correlation between the MMSE and the ADCS-ADL inventory were replicated in a study that looked at the relationship between changes in psychopathological, cognitive and activity of daily living instruments over time in persons with AD. Tractenberg et al (2005) found modest, positive correlations between changes in function (as measured by ADCS-ADL) and two different measures of global cognitive functioning (MMSE and CDR). While the ADCS-ADL has been utilized in numerous studies and has documented reliability and validity, there are several limitations to its use. First, it requires approximately 30-45 minutes to administer and thus, would not be appropriate for use as a brief screening instrument. Additionally, as it is an informant-based measure, the possibility of under- or over-estimation of abilities by the caregiver is substantial.

Lawton and Brody (1969) developed the Physical Self-Maintenance Scale (PSMS), which measures ADLs such as toileting, feeding, dressing and grooming, and the Instrumental Activities of Daily Living (IADL) scale, which measures activities such as ability to use the phone, shopping, housekeeping, and responsibility for one's own medications. In the literature, these measures are often referred to as Lawton and Brody's ADL/IADL scales, and it is important to note that these are one-and-the-same. Information required to complete the measures is collected from an informant. In the normative sample, informants included family, institutional employees, friends, the subject himself, or some combination of sources. Good interrater reliability was

established for the PSMS by comparing ratings of two licensed practical nurses and comparing two research assistant's ratings, for overall correlations of .87 and .91, respectively. An interrater reliability correlation of .85 was found between IADL total scores; however, only one social worker interviewed the informants while the other was present in the room but not participating; thus, more extensive testing of reliability may be appropriate in order to determine agreement between examiners. Strengths of the measures include ease of administration, as the authors purposefully excluded more technical language with the goal being that a variety of personnel could use them, including mental health workers, practical nurses, and social workers. In individuals with very early dementia (MMSE $\geq$ 23) alone, the IADL showed significant functional disability, with disability defined as the need for assistance in two or more activities (De Ronchi et al., 2005). The numerical size of this association tripled in subjects with very early dementia and symptoms of depression.

In a retrospective study of patients with the diagnosis of probable AD, Mok and colleagues (2004) looked at the role of non-cognitive symptoms (i.e., delusions, hallucinations, agitation), as predictive factors for functional outcome for functional outcome for AD. They determined that, while age and years of education were not significantly correlated with IADL scores, scores reflecting occurrence of hallucinations and aberrant motor acts were significantly and negatively correlated with IADL scores. However, multiple regression analysis went on to show that MMSE scores were the sole significant predictor for performance on the IADL.

A unique study examined the relationship between brain metabolism, as measured by positron emission tomography (PET), and performance on four dementia rating scales, including the IADL (Diaz et al., 2005). The IADL total score correlated significantly and negatively with regional brain metabolism in the right inferior parietal cortex and in the right inferior temporal cortex in individuals with AD, meaning that higher impairment in IADL corresponded to lower metabolism in the association cortices. The European Alzheimer's Disease Consortium (Diaz et al., 2005) examined typical evaluation protocols from 36 memory disorders clinics across 13 European countries. Of the six functional assessment scales utilized, 37.5% of the clinics used the ADL/IADL; however, to this author's knowledge there are no published studies of the IADL in subjects with MCI. Another limitation of this measure is that, like Galasko's ADL inventory, it is an informant-based measure and, thus, is also susceptible to caregiver bias. Finally, while each item on the rating scales has five different descriptors from which to choose in order to best describe the patient's performance for that activity, only 1 of the 5 results in a score of '1,' while the other four are scored as '0.' Essentially, this means that only complete independence on a given activity is positively scored, while varying degrees of dependence (i.e., needs to be reminded but can complete or cannot complete at all) result in the same outcome score of '0.' This limits the measure's ability to adequately reflect the full range of an individual's capabilities by restricting the range of possible scores and potentially decreasing sensitivity to more subtle changes in functioning.

The SAILS is a 50-item performance-based measure designed to assess everyday activities (i.e., using a telephone, zipping a jacket, telling time) that are often affected in

individuals with a dementia (Mahurin, DeBettignies, & Pirozzolo, 1991). Administration time is approximately 1 hour (DeBettignies, Mahurin, & Pirozzolo, 1993), and items are scored (scale of 0-3) in each of the 10 subdomains (i.e., Dressing Skills, Receptive Language), which yield composite Motor and Cognitive Scores, and an overall Total Score. One point is subtracted if task completion time is more than two standard deviations slower than the mean for controls; therefore, a subject may only receive two of three possible points if they are able to accurately carry out a task, but are significantly slower doing so. In individuals with difficulties in processing speed or motor programming and/or execution, however, this penalty may result in an underestimate of actual functional ability. Test-retest reliability (on control patients only; r = .81) and interrater reliability (on AD patients only; r = .99) were obtained, although there were only ten subjects in each group and neither sample included both AD and controls. AD patients showed significantly poorer performance than controls for Total Score, Motor Score, and Cognitive Score, and poorer performance across all 10 task domains. The pattern of impairments in the AD subjects revealed greater deficits particularly in the areas of Expressive & Receptive Language, Time and Orientation, Money-Related Skills, and Instrumental Activities. While correlations were reported for the AD group only, the most statistically significant relationships were found between the SAILS total score and tests of visuospatial construction, visual discrimination, visual memory and motor functioning (r = .50-.88), emphasizing the impact of visual and motor skills in AD on SAILS performance. High correlations were also obtained between the SAILS Total Score and tests of attention and language (r = .33-.88). Tasks of verbal memory, in

contrast, showed low correlations (r = .01) with the SAILS Total Score, underscoring several weaknesses of the measure including facts that the SAILS does not directly assess memory performance in everyday situations and does not include a subdomain or composite score for this domain. Additionally, inclusion of more basic ADL activities such as cutting with scissors and feeding skills may create a ceiling effect when looking at individuals with milder forms of cognitive impairment and the often less noticeable functional difficulties that can accompany them.

In a study that examined the use of a simulated environment (Easy Street; ES) to retrain independent living skills in elderly persons (n = 88), the SAILS was used as one of several outcome measures (as well as an initial stratification measure) of everyday functioning (Richardson, Law, Wishart, & Guyatt, 2000). Researchers omitted the social interaction domain as it yielded little, if any, incremental validity during a pilot study that was conducted, and subject diagnoses were varied (i.e., hemiplegia, Parkinson's disease, diabetes). While subjects in the simulated conditions performed slightly better than the traditional care group on overall SAILS scores (simulated SAILS mean = 103.1; traditional SAILS mean = 102.5) by the final testing point, no statistically significant treatment effects for the overall SAILS or any of the SAILS domains were found.

Espino et al. (2001) used a modified version of the SAILS as one of several performance-based measures of everyday functioning in a study designed to examine possible differences in correlates of the MMSE in older Mexican Americans (n=452) and European Americans (375) from three different neighborhood types (barrio, transitional, and suburb). Only timed tasks from the SAILS were utilized, however, with the outcome

measure being time to complete a given task. This score was consistently lower in the first group (MMSE < 24) than in the second group (MMSE > 23), regardless of ethnic group. They also reported that less education was associated with low MMSE scores in both groups. A statistically significant difference ($p < .001$) was noted between groups with close to 50% of Mexican American subjects (n=223) completing 8 or less years of education and only 4.5% of European Americans (n=17) falling into that same category. While Mexican Americans were 2.2 times more likely than European Americans to have MMSE scores < 24, no differences were noted between groups after adjusting for neighborhood type, in which European Americans only had subjects represented in two of the three neighborhoods.

The Texas Functional Living Scale (TFLS) is a 21-item performance-based measure of IADLs designed specifically for use with individuals with neurodegenerative brain disorders such as Alzheimer's disease (Cullum et al., 2001b). As the TFLS measures functional abilities on specific activities, however, it can be used with almost any demographic population. The measure takes approximately 15-20 minutes to administer, which makes it a convenient screening instrument, and includes five functional domains: Dressing, Time, Money-related skills, Communication, and Memory. The total maximum score possible is 52, and point values vary across tasks, ranging from 0-5 points. For example, on a task requiring patients to point to the date on a 1-year calendar, an accurate response would earn 3 points, with 2 points awarded if they point to the correct week but not the correct day, and 1 point if they point to the correct month only. This allows for a range of scores that may more adequately capture

the varying levels of functioning that can be seen in the dementia populations. Other activities assessed include telling time on a traditional clock (with hands), making change, paying a bill, using a phone and phonebook, managing medications, and making a snack. The TFLS was intended as a tool that may be helpful in diagnostic workups, treatment planning, deciding placement issues, and evaluating disease progression. Additionally, it is a measure that physicians, nurses, occupational therapists, and social workers can be trained to administer.

In a study of 22 patients with Alzheimer's disease and 21 healthy controls, the TFLS showed a significantly high correlation with the MMSE ($r = 0.89$, $p < 0.001$) in patients with AD, supporting the emphasis of the TFLS on cognitive aspects of functional daily skills. Test-retest reliability in the AD group was also strong, showing that baseline and 1-month scores correlated highly ($r = 0.93$, $p < 0.001$). Floor effects are common in IADL instruments; however, this is not seen with the TFLS until the more moderate stages of dementia. The TFLS has been used in pharmacologic studies to evaluate the impact of memory drugs on IADLs in patients with AD (Saine et al., 2002; Weiner, Womack, Martin-Cook, Svetlik, & Hynan, 2005) as well as in a caregiver skills training program in attempts to decrease the gap between caregivers' expectations and patients' actual functional abilities (Martin-Cook, Davis, Hynan, & Weiner, 2005). It is unknown, however, how individuals with MCI perform on the TFLS or if the measure is sensitive enough to detect the more subtle cognitive difficulties that can be seen in this population.

Individuals who are diagnosed with MCI are at increased risk for developing dementia, and in particular, AD. Early detection of AD onset is becoming particularly

important, as several medications have been shown to slow the progression of AD if given early in the disease, and knowledge of diagnosis can assist patients and caregivers with making plans for the future. While some individuals with MCI go on to develop AD, others remain in that stage between normal aging and AD, while others actually revert to normal. A lack of impairment in IADLs is necessary for the diagnosis of MCI, although more recent research has indicated that many individuals with MCI experience IADL difficulties. In addition, it appears that those with MCI who have IADL dysfunction may progress to dementia much more rapidly than those without. Many measures have been developed to assess performance on ADLs/IADLs, although many of them are lengthy and therefore not ideal as brief screening instruments. Additionally, it has been shown that performance-based measures of IADLs may be more accurate than informant-based measures, in which caregivers may over- or underestimate patients' actual abilities (Albert et al., 2002; Tabert et al., 2002). The TFLS is a performance-based measure of IADLs that takes approximately 15-20 minutes to administer and was designed for use in individuals with dementia. It focuses on activities that can be affected in MCI such as bill payment and overall financial capacity and management of medications, as well as activities designed to measure performance in specific cognitive domains, such as memory. The major purpose of this study was to examine how individuals with mild cognitive impairment perform on the TFLS relative to normals.

CHAPTER TWO
Goals and Hypotheses

Goals

1. Examine performance of normal controls (NC) and individuals diagnosed with MCI on a brief, quantifiable measure (TFLS) of everyday functional abilities.
2. Examine how performance on the TFLS relates to overall cognitive functioning in MCI and NC.
3. Examine TFLS scores as they relate to performance on standard neuropsychological measures of memory, language, executive functioning, and attention in MCI and NC.
4. Examine whether performance on the TFLS declines over time in MCI.

Hypotheses

H1: The mean TFLS total score will be significantly lower for subjects diagnosed with mild cognitive impairment (MCI) than for normal controls (NC).

H2: For all subjects combined (MCI and NC), the TFLS total score will be significantly correlated with overall cognitive functioning as measured by the CERAD total score.

H3: For all subjects (MCI and NC), the TFLS total score will correlate significantly with measures of memory and executive functioning and will not be significantly correlated with measures of language and attention.

H4: Annualized change scores on the TFLS will decline over time in MCI and will remain stable in NC.

Proposed Exploratory Analyses/Goals.

1. Examine the difference in TFLS subscale scores between NC and MCI to determine the areas in which they perform most differently (i.e., memory, time/orientation, etc).
2. Examine the relationship between the TFLS total score and the MMSE score in MCI and NC.
3. Examine the relationship between the TFLS total score and cognitive domain composite scores (memory, language, executive functioning) to determine if performance on the TFLS is related to performance on measures of these domains.
4. Examine TFLS total scores in both MCI and NC to determine the sensitivity and specificity of the TFLS in accurately classifying MCI and NC subjects.

CHAPTER THREE
Methodology

Participants

This was a retrospective study of data collected from 2003 to 2005 at the Clinic for Alzheimer's Disease and Related Disorders (ADC) at the University of Texas Southwestern Medical Center at Dallas. All subjects were participating in a larger study of dementia and normal aging and met the following basic inclusion criteria for the current study:

1. Age 48 years or older at initial visit
2. Able to fluently speak and comprehend English
3. Free of co-morbid conditions that could affect performance on cognitive tasks (i.e., major depression, alcoholism, delirium, systemic cancer, severe heart/pulmonary disease, stroke)
4. Had completed a comprehensive neuropsychological evaluation, including the TFLS

Normal controls had to be free of cognitive impairment as judged by the clinical assessment and received a CDR = 0.

The original goal of this investigation was to include only MCI subjects that met criteria for the amnestic subtype (subjects with aMCI exhibit deficits in memory, with relatively normal functioning in other cognitive domains) (Grundman et al., 2004); however, there were not enough participants who exhibited preserved cognitive functioning in all non-memory domains. Thus, subjects who met the general MCI criteria originally set forth by Petersen et al (1999) were included. In addition to the

basic inclusion criteria, additional criteria for the MCI cohort included the following, based upon patient report, performance on neuropsychological testing, and/or information obtained during clinical interview with the patient:

1. Presence of memory complaint
2. Normal general cognitive functioning
3. Abnormal memory for age on formal cognitive testing
4. Normal activities of daily living (as reported by the patient or informant)
5. No diagnosis of dementia

The original pool of 90 subjects consisted of 47 normal controls and 43 MCI. Ten subjects were labeled possible MCI, and as such, did not meet full criteria for the diagnosis of MCI. Subjects were followed longitudinally, and inclusion in this study required administration of the TFLS. Some subjects had progressed to probable AD by the visit at which the TFLS was administered; thus, each of these subjects' charts was reviewed with the diagnosing physician to ensure the accuracy of diagnosis. Because the current study was limited to evaluation of normal controls and individuals with MCI, any subject who was determined to have progressed to dementia by the time the TFLS was administered was excluded (i.e., many subjects were seen for several visits prior to the administration of the TFLS, and several of those progressed from the original diagnosis at their first visit to dementia by the visit at which the TFLS was given). This resulted in the loss of 12 subjects (1 normal control, 11 MCI). Original inclusion criteria required subjects to be at least 50 years of age; however, examination of the cohort revealed two normal controls aged 48 and 49, respectively, at the initial visit who met all other

inclusion/exclusion criteria, so the age range was expanded in order to increase the sample size and achieve more demographically similar matched groups.

Hypotheses 1-3. From the remaining pool of 78 subjects (46 normal controls, 32 MCI), 2 subjects (MCI) were excluded because some of their follow-up testing (neuropsychological measures) was conducted more than 6 months after baseline, resulting in a total of 30 MCI subjects. Normal controls were selected to be as similar as possible in terms of age (± 7 years), gender (with the exception of 1 pair), and level of education (± 5 years).

Hypothesis 4. From the remaining pool of 78 subjects (46 normal controls, 32 MCI), 32 individuals (17 normal controls, 15 MCI) had been administered the TFLS at two different testing points, as hypothesis four required analysis of repeated measures (Time 1 and Time 2). Individuals for whom Time 1 and Time 2 (n = 3) were less than 9 months apart were excluded to reduce practice effects, resulting in a total of 29 (17 normal controls, 12 MCI) subjects. Change over time for Hypothesis 4 was calculated by subtracting Score 2 from Score 1 and dividing the difference by the time, in years, between Time 1 and Time 2. The formula is as follows: ([Score 2 – Score 1]/ ([Time 2 – Time 1]/365.25).

Measures

All subjects were administered a comprehensive neuropsychological evaluation that included the CERAD neuropsychological assessment battery (Morris et al., 1989) and the TFLS (Cullum et al., 2001b). A CERAD total score was calculated according to the method detailed by Chandler et al. (2005) so the relationship between the TFLS and a

standard measure of overall cognitive functioning could be investigated. From the comprehensive neuropsychological battery, specific measures were selected in order to tap the cognitive domains of memory, language, executive functioning, and attention. These measures, shown in the literature to be sensitive to change and progression in MCI, included the Trail Making Test (Parts A and B; TMTA, TMTB) (Reitan & Wolfson, 1993), Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtis, 1993), California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987), Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall (LMII), Wechsler Memory Scale-III LMII and Visual Reproduction Delayed Recall (VRII) subtests (Wechsler, 1987, 1997), the Rey-Osterrieth Complex Figure (Rey-O; Corwin & Bylsma, 1993), verbal fluency, the Modified Boston Naming Test (CERAD BNT) (Morris et al., 1989), and Digit Span Forwards (from the Wechsler Adult Intelligence Scale-Third Edition, Digit Span subtest; WAIS-III; Wechsler, 1997). Hypothesis 3 involved examining the relationship between the TFLS total score and several specific cognitive domains. The original goal was to have at least two measures of cognitive functioning within each domain, although there were not enough subjects who had received WAIS-III Digit Span ($\underline{n}$ = 22) to provide adequate data, and thus, this measure was excluded from the study. TMTA was the only measure of attention utilized. See Appendix A for descriptions of the individual measures.

Procedures

Each subject seen at the Clinic for Alzheimer's and Related Disorders at the University of Texas Southwestern Medical Center at Dallas was evaluated by a

neurologist or geriatric psychiatrist and a neuropsychologist, with diagnoses done via consensus. Each evaluation included a clinical interview, history and physical examination, routine labs, neuroimaging, and neuropsychological evaluation. All neurocognitive tests were administered and scored in standardized fashion by trained psychometrists/research coordinators.

Power Analysis

For Hypotheses 1 (Total TFLS), group sample sizes of 30 and 30 achieve 80% power to detect a significant difference of -1.7 between the null hypothesis that both group means equal 48.8 and the alternative hypothesis that the mean for the MCI group is 47.1 with estimated group standard deviations of 2.2 and 3.0, using a one-sided Mann-Whitney test with a significance level (alpha) of 0.05, and assuming that the actual distribution is uniform. For Hypothesis 4, group sample sizes of 17 and 12 achieve 43% power to detect a difference of 1.4 between the null hypothesis that both group means are 1.0 and the alternative hypothesis that the mean for the MCI group is -0.4 with estimated group standard deviations of 2.6 and 2.4, using a one-sided two-sample t-test with a significance level (alpha) of 0.05. To achieve 80% power with the given estimates, group sample sizes of 40 and 40 would be needed for Hypothesis 4.

Data Analyses

For normally distributed, continuous data, means and standard deviations were used to describe the demographic characteristics of the subjects. Groups were compared using an independent t-test. For categorical or dichotomous variables, percentages were

reported and Chi Square or Fisher's Exact Tests were performed for group comparisons. When Chi Square was used, continuity correction was performed.

All scaled scores and percentile scores were converted to T scores for ease of comparison. All raw scores on the CERAD verbal fluency task and the CERAD naming task were converted to T scores using the normative data derived by Welsh et al. (1994). Rey-O T scores were derived using the norms set forth by Meyers and Meyers (1995). Preliminary analyses were performed to ensure no violation of the assumptions of normality, equal variance, linearity, or homoscedasticity. In the event that these assumptions were not satisfied when relevant, appropriate non-parametric statistics were utilized and are noted in the description of the analyses (below).

In addition to analyzing the relationship between the TFLS total score and measures of memory, executive functioning, attention, and language, further exploratory analyses were performed to examine the relationship between the TFLS total score and domain composite scores (i.e., memory, executive function, etc.). Composite scores for memory (CVLT, WMS-R/WMS-III [Logical Memory II, Visual Reproduction II], Rey-O), executive functioning (WCST, TMTB), and language (CERAD naming and verbal fluency subtests) were calculated by adding T scores from each of the measures within a domain and dividing by the number of measures conducted to yield an overall mean composite score. As there was only one measure of attention (TMTA), this score was used as the score for the attention domain. Data were analyzed with the Statistical Package for the Social Sciences for Windows, version 14.0 (SPSS, 2005). The probability for significance was set at $p < .05$.

CHAPTER FOUR
Results

Demographic Characteristics

Hypotheses 1-3. Demographic information for the total group of 60 participants is provided in Table 1. The mean age at initial assessment was 73 years (Range = 49-87; SD = 7.34), and the sample was composed of equal numbers of men and women. The mean years of education for the sample as a whole was 15.07 (Range = 8-20; SD = 2.40). There was no significant difference between the groups in terms of age [$t(58) = .43$, $p = .670$], education [$t(58) = .64$, $p = .520$] or gender (NC M/F = 14/16; MCI M/F = 16/14; $\chi^2 (1, N = 60) = .07$, $p = .796$). Normal control subjects were selected to be as similar as possible in terms of age (± 7 years), gender (with the exception of 1 pair), and level of education (± 5 years).

Insert Table 1 here

Hypothesis 4. Demographic information for the 29 participants (12 MCI, 17 NC) who had received the TFLS at two different testing points is provided in Table 2. The mean age at initial assessment was 72 years (Range = 48-86; SD = 9.34), and the sample was composed of 11 men and 18 women. The mean years of education for the sample as a whole was 14.45 (Range = 8-18; SD = 2.50). There was no significant difference between the groups in terms of age [$t(27) = .50$, $p = .620$], education [$t(27) = 1.41$, $p =$

.160] or gender (NC M/F = 5/12; MCI M/F = 6/6; χ^2 (1, N = 29), p = .438). See Table 3 for group differences between the total sample and test-retest sample.

Insert Tables 2 and 3 here

Research Hypotheses

Hypothesis 1 stated that the mean TFLS total score would be significantly lower for subjects diagnosed with MCI than for normal controls. This hypothesis was supported (See Table 4). An independent-samples t-test revealed a significant difference between mean TFLS total scores for the NC group (M = 48.77, SD = 2.22) and the MCI group [M = 47.17, SD = 3.01; t (58) = 2.34, p = .012]. While the difference between groups in mean TFLS total score was statistically significant, it should be noted that the score discrepancy of 1.6 points is a small difference. To further explore group differences, TFLS subtest scores were compared between groups, revealing a significant difference only on the Memory subscale (NC M = 6.60, SD = 1.40; MCI M= 5.27, SD = 1.72; t (58) = 3.29, p = .002).

Insert Table 4 here

Hypothesis 2 stated that for all subjects (MCI and NC), the TFLS total score would be significantly correlated with overall cognitive functioning as measured by the CERAD total score. Using the Pearson product-moment correlation, this hypothesis was supported (see Table 5), as the TFLS was moderately correlated with the CERAD total score ($\underline{r} = .37$, $\underline{n} = 57$, $p = .003$). In further exploration of this hypothesis, the relationships between each of the TFLS subscale scores and the CERAD total score were examined. The CERAD total score and the TFLS Memory subscale score were moderately and positively correlated ($\underline{r} = .45$, $\underline{n} = 57$, $p < .001$), and there was a small, but significant, correlation between the CERAD total score and the TFLS Communication subscale ($\underline{r} = .22$, $\underline{n} = 57$, $p = .049$). However, the correlations between the CERAD total score and the other TFLS subscale scores were non-significant (r range = -0.01 to 0.07), and a correlation between the CERAD total score and the TFLS Dressing subscale score could not be computed because there was no variance on this score across subjects.

Insert Table 5 here

Hypothesis 3 stated that for all subjects (MCI and NC), the TFLS total score would be significantly correlated with measures of memory and executive functioning and would not correlate significantly to measures of language and attention. This hypothesis was partially supported (See Table 6). Pearson product-moment correlation coefficients could not be utilized because preliminary analyses revealed a violation of at

least one of the assumptions (normality, linearity, and homoscedasticity). Thus, the relationship among TFLS total score and several measures of memory (CVLT, Rey-O, WMS LMII and VRII), executive function (WCST, TMTB), language (fluency, CERAD BNT), and attention (TMTA) was investigated using Spearman's Rank Order Correlations. A significant correlation of medium strength was found between the TFLS total score and a measure of nonverbal memory (VRII Delayed Recall $\underline{\rho} = .31$, $\underline{n} = 56$, $p = .010$). The TFLS total score showed small, but significant correlations with two other individual measures of the cognitive domains explored (CVLT $\rho = .23$, $\underline{n} = 55$, $p = .049$; CERAD verbal fluency $\underline{\rho} = .22$, $\underline{n} = 57$, $p = .049$). A potential trend toward significance was noted in the relationship between the TFLS total score and TMTB ($\underline{\rho} = .20$, $\underline{n} = 57$, $p = .066$); however, the correlations between the TFLS total score and scores on the other cognitive measures were non-significant (range $\underline{\rho} = .08$ to .16; minimum p-value = .141). Therefore, as predicted, the TFLS total score correlated significantly with measures of memory (CVLT, VR2), and a potential trend toward significance was observed between the TFLS total score and a measure of executive functioning (TMTB). However, it was predicted that the TFLS total score would not correlate significantly with measures of language when, in fact, a small but significant correlation was found with the CERAD verbal fluency measure.

Insert Table 6 here

Hypothesis 4 stated that annualized change scores on the TFLS would decline over time in MCI and remain stable in NC. This hypothesis was supported, but not significantly. An independent-samples t-test was conducted to compare the mean annualized change scores of the two groups (MCI vs. NC) on the TFLS. There was no significant difference in TFLS change scores for the MCI group ($\underline{M}$ = -.42, $\underline{SD}$ = 2.36; t (27) = 1.48, $\underline{p}$ = .075) and the NC group ($\underline{M}$ = .98, $\underline{SD}$ = 2.60). It is noteworthy, however, that the mean TFLS total score increased, or improved, in the NC, but declined in MCI, with the mean changes going in opposite directions (See Figure 1). Furthermore, while only 29% of NC declined over time (41% improved and 29% remained stable) on the TFLS total score, 50% of MCI performed more poorly at their second testing point (33% improved; 17% remained stable). A decline referred to at least a one-point drop in TFLS total score from Time 1 to Time 2. Likewise, an improvement referred to at least a one-point gain in TFLS total score from Time 1 to Time 2, and a participant's score was determined to remain stable if there was no change in score.

Insert Figure 1 here

Exploratory Analyses

The relationship between the TFLS and MMSE total scores in each group (NC and MCI), as well as in both groups combined was investigated using Spearman rank order correlation coefficients (due to a violation of the assumption of homoscedasticity).

There was no significant relationship between the TFLS total score and MMSE total score in the MCI group ($\rho = .26$, $\underline{n} = 21$, $p = .253$) or the NC group ($\rho = .25$, $\underline{n} = 28$, $p = .198$). However, there was a moderate correlation between the TFLS and MMSE when the two subject groups were combined ($\rho = .34$, $\underline{n} = 49$, $p = .019$).

The relationship between the TFLS total score and the composite score for each cognitive domain was explored using Spearman Rank Order correlation coefficients (See Table 7). There was a small, but significant correlation between the TFLS total score and the language composite ($\rho = .25$, $\underline{n} = 57$, $p = .032$), but correlations with the executive function ($\rho = .12$, $\underline{n} = 54$, $p = .192$) and memory ($\rho = .19$, $\underline{n} = 42$, $p = .121$) composite scores were nonsignificant.

Insert Table 7 here

The relationship among the TFLS subscales and selected measures of cognition was also explored in both the NC and MCI groups using Spearman correlational analyses, and several significant relationships were observed (see Table 8). For instance, there was a moderate relationship between the TFLS Memory subscale and the CVLT total T-score ($\rho = .37$, $\underline{n} = 55$, $p = .003$), and the relationship between the TFLS Memory subscale and the VR2 delayed recall T-score ($\rho = .36$, $\underline{n} = 56$, $p = .004$) was also significant. Additionally, there was a moderate relationship between the TFLS Communication

subscale and LMII ($\rho = .35$, $\underline{n} = 46$, $p = .008$), and a small, but significant relationship between the TFLS Communication subscale and VRII ($\rho = .26$, $\underline{n} = 56$, $p = .026$)

Insert Table 8 here

Additional analyses were conducted to determine the sensitivity and specificity of the TFLS total score in predicting diagnosis. Sensitivity is the proportion of subjects with the diagnosis who have a positive test (true positives), and indicates how well the test can identify the individuals with the diagnosis. Specificity is the proportion of subjects without the disease who have a negative test and indicates how good the test is at identifying those who do not meet criteria for the diagnosis. The sensitivity and specificity for the observed range of TFLS total scores (40-52) distinguishing the MCIs from NC resulted in the area under the curve of 0.66 ($p = .031$, 95% CI: 0.52-0.80). A cut-off score of 48 was determined to represent the highest diagnostic accuracy (the highest combination of sensitivity, specificity, and percent correct). This cut-off score yields a sensitivity of 56.7% and a specificity of 63.3%, and percent accurate group classification of 60%.

CHAPTER FIVE
Discussion

Mild cognitive impairment (MCI) is a term that has been used to describe the stage between normal aging and the onset of Alzheimer's disease. One criterion for MCI requires the individual to exhibit impaired levels of functioning and normal activities of daily living; however, the findings in recent research suggest this is not necessarily the case (Artero et al., 2001a; Bell-McGinty et al., 2002b; Cahn-Weiner et al., 2000; Royall et al., 2000b; Tuokko, Morris, & Ebert, 2005). Such findings have compelled researchers in the field to examine functional status in MCI more closely, and assess the impact that it may have on overall assessment of cognitive functioning and prediction of conversion to dementia (Petersen et al., 2001c; Purser, Fillenbaum, Pieper, & Wallace, 2005a; Winblad et al., 2004b). As functional impairment becomes more evident in MCI, the need for detailed yet brief ADL/IADL screening instruments follows (Gauthier et al., 2006; Perneczky et al., 2006a; Petersen, 2004; Petersen et al., 2001c; Royall, 2006). As the controversy regarding functional impairment in MCI has only recently emerged, there are few, if any, assessment instruments that were designed to measure activities of daily living in this population. In addition, many of the general measures devised to evaluate performance on ADLs/IADLs are based on either self- or informant-report, which may not be as accurate as a performance-based measure in which the individual is scored on actual tasks performed during the evaluation.

The Texas Functional Living Scale (TFLS) is a quantitative performance-based measure of everyday functional abilities designed for use with the AD population, and as such, may be more sensitive to detecting the subtle changes in ADLs/IADLs that may be

seen in individuals with MCI. The overall purpose of the present study was to examine performance of the TFLS in MCI and to determine the relationships between the TFLS and other standard measures of cognitive functioning.

Specifically, the goals of this study were to examine: 1) performance of individuals diagnosed with MCI and healthy normal controls (NC) on a brief, quantifiable measure of everyday functional abilities (TFLS), 2) how performance on the TFLS relates to overall cognitive functioning in individuals diagnosed with MCI, 3) relationships between TFLS performance and standard neuropsychological measures of memory, language, executive functioning, and attention in MCI and NC, and 4) whether performance on the TFLS declines over time in MCI.

Proposed exploratory analyses included examination of: 1) TLFS subscale scores between MCI and NC groups to determine which subscale best distinguishes the groups (i.e., memory, time/orientation, etc), 2) the relationship between the TFLS total score and cognitive domain composite scores (memory, language, executive functioning), and 3) TFLS total scores in both MCI and NC to determine the sensitivity and specificity of the TFLS in accurately classifying MCI and NC.

Hypothesis 1 stated that the mean TFLS total score would be significantly lower for subjects diagnosed with MCI than for NC. Results supported this hypothesis, as the MCI group had a mean score of 47.17 compared with the mean of 48.77 in the NC group (See Table 4). Whereas the absolute difference in mean scores on the TFLS between groups was small (1.6 points), it is worth noting that global cognitive screening scores also showed relatively small differences (i.e., mean MCI MMSE = 27.43 vs. 29.21 in

NC). Results from this investigation parallel previous studies, which have consistently shown that individuals with MCI perform better than those with AD, but worse than NC, on the vast majority of neurocognitive tests. Similarly, MCI performance on the TFLS (M = 47.17) was much better than Cullum et al. (2001a) found in AD (M = 30.86), but worse than seen in this NC population (M = 48.77). Granted, there is a larger discrepancy in mean TFLS total scores between this MCI group and their AD group than between MCI and NC in this study; however, this is not at all surprising given that the diagnosis of MCI requires a *lack* of impairment in everyday functioning and because the TFLS was designed for use with the dementia population. The fact that this group showed lower scores on this measure at all may suggest that despite *perceived* normalcy in IADLs, individuals with MCI may experience greater difficulty with tasks of everyday functioning as measured by the TFLS, although their primary difficulties were on the Memory subscale.

It has been noted that the presence of functional impairment, in the absence of *endorsement* of these deficits during clinical interview, may actually be an early sign of pre-clinical dementia (Onor, Trevisiol, Negro, & Aguglia, 2006; Ries et al., 2007; Tierney, Szalai, Snow, & Fisher, 1996a). The literature has also revealed a lack of awareness of deficits in some individuals with AD, with many patients insisting that they have *no* difficulties with memory or other areas of cognitive functioning, despite their diagnosis (Kalbe et al., 2005; Onor et al., 2006; Vogel et al., 2004). The presence of functional impairment in MCI may either signify a lack of awareness of the deficits themselves, or at the very least, an underestimation of the impact of these deficits on

IADL performance. Either way, it is apparent that standard cognitive testing used in the diagnosis of MCI may not completely capture the functional skills of this group.

The difference in TFLS total scores between MCI and NC was largely attributable to the MCI group's performance on the Memory subscale, as scores were significantly lower in MCI than in NC. As with TFLS total scores, MCI performance on the Memory subscale (M = 5.27) fell in between that of NC (M = 6.60) and Cullum et al.'s (2001a) AD group (M = 1.96). Memory is the most commonly affected cognitive domain in AD, and impairment in this domain is required for an AD diagnosis. Although objective memory impairment on a psychometric test is no longer required for the diagnosis of MCI by some accounts (Morris et al., 2006; Winblad et al., 2004a), memory still appears to be the most commonly affected domain in this group (Arnaiz et al., 2004a; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001b; Collie & Maruff, 2000b; Farias et al., 2006; Grundman et al., 2004a; Loewenstein et al., 2006; Manly et al., 2005). This MCI cohort assessed with the TFLS mirrors those findings; of the 30 total MCI subjects included in this study, 14 were aMCI and only 2 of the 13 mdMCI scored in the normal range on standard memory testing. It was expected that performance on TFLS memory items would be impaired in such a group, and the results confirmed this expectation. Memory deficits may be one of the best predictors of progression to AD (Chen et al., 2000; Dubois, 2000b; Griffith et al., 2006), and as such, the TFLS's memory items may make it a useful tool in helping to identify those who may be at greatest risk for going on to develop AD.

Hypothesis 2 stated that for all subjects combined (MCI and NC), the TFLS total score would be significantly correlated with overall cognitive functioning as measured by the CERAD total score. This hypothesis was also supported. TFLS total scores were significantly and positively correlated with CERAD total scores ($r = .37$, $p = .003$), indicating a modest relationship between overall cognitive functioning and the TFLS. This is consistent with studies using other measures that have supported the relationship between cognitive and functional status (Barberger-Gateau et al., 1992; Barberger-Gateau, Fabrigoule, Rouch, Letenneur, & Dartigues, 1999; Li, Ng, Kua, & Ko, 2006; Sager, Hermann, La Rue, & Woodard, 2006; Steen, Sonn, Hanson, & Steen, 2001). Barberger-Gateau et al. (1999) examined the relationship between performance on neuropsychological testing and four instrumental activities of daily living that are considered sensitive to changes associated with an increased risk of dementia: telephone use, transportation use, medication management, and handling finances. They selected four items from Lawton's Scale of Instrumental Activities of Daily Living that they felt were specifically associated with cognitive performance and found that with increasing IADL dependency, performance on measures of verbal and nonverbal memory, language, verbal conceptualization, selective attention, processing speed, and visuospatial abilities declined. They also found that in the IADL-independent group, the means and standard deviations for each neuropsychological measure were strikingly similar, while in the IADL-dependent group, significant variability was observed, indicating that with functional disability comes varying degrees of cognitive disability.

Steen et al. (2001) evaluated the relationship between performance on cognitive testing (memory, attention, verbal and spatial abilities, and perceptual speed) and ADL/IADL dysfunction in 85- (n = 332) and 95-year-olds (n = 63). They utilized the Staircase of ADL (Sonn, 1996; Sonn & Asberg, 1991), which involved a registered nurse going to each patient's home and rating him or her on IADL and ADL performance. They discovered that the 85-year-olds who were ADL-independent performed significantly better on the majority of cognitive testing than those were ADL- or IADL-dependent. While these findings did not extend to the 95-year-old cohort, when they were examined the subjects by gender, the relationship between cognitive functioning and ADL performance persisted in females. They speculated that the reason this relationship was not seen in 95-year-old males (n = 17) was due to the limited number of subjects (and therefore, the limited range in scores) in this group. In general, however, for NC and for patients diagnosed with MCI and AD, the better the individual's overall cognitive functioning, the better they are able to effectively manage, and function in, their everyday lives.

The CERAD total score (Chandler et al., 2005) is comprised of six subtests that evaluate memory (immediate & delayed verbal recall and recognition for the verbal memory task), language abilities (verbal fluency and confrontation naming), and constructional abilities (figure copy), with memory (3 of 6 subtests) and language (2 of 6 subtests) being the primary loading factors. Given this bias in the CERAD total score formulation (loading heavily on memory items), it is not surprising that additional analyses revealed a moderate correlation (r = .45) between the TFLS Memory subtest

score and the CERAD total score, and a small but significant correlation (r = .22) between the TFLS Communication subtest score and the CERAD total score. These findings indicate some relationship between memory, as measured by cognitive testing, and memory as measured by the TFLS, and between performance on language testing and communication skills in everyday functioning.

The CERAD is a measure of global cognitive functioning, however, and because there is relatively little information in the literature regarding the relationship between performance on tests in various cognitive domains and IADL performance, it became necessary to evaluate, on a more domain-specific level, the relationship between cognitive and TFLS performance in MCI.

Hypothesis 3 stated that for all subjects (MCI and NC), the TFLS total score would be significantly correlated with measures of memory and executive functioning, but would not correlate significantly with measures of language and attention. This hypothesis was partially supported. The TFLS total score was moderately and significantly correlated with a measure of nonverbal memory, the WMS-III Visual Reproduction Delayed Recall subtest ($\rho = .31$, $p = .010$), and showed a small but significant correlation with a measure of verbal memory and learning, the CVLT ($\rho = .23$, $p = .049$), indicating a relationship between functional skills that the TFLS is measuring and standard measures of declarative memory. Ample research exists to support these findings (Atkinson et al., 2005; Cromwell, Eagar, & Poulos, 2003; Li et al., 2006; Steen et al., 2001), although the majority of reports highlight relationships between verbal declarative memory and IADL performance. Petersen's original MCI criteria included

'abnormal memory for age,' without specific criteria (Petersen et al., 1999b); however, Grundman et al. (2004a) suggested operational criteria that included cutoff scores for WMS-III Logical Memory II when qualifying 'abnormal memory,' and this focus on verbal memory has persisted throughout the literature (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006; Cunje, Molloy, Standish, & Lewis, 2007; Dierckx, Engelborghs, De Raedt, De Deyn, & Ponjaert-Kristoffersen, 2007; Fleisher et al., 2007; Greenaway et al., 2006a; Kircher et al., 2007; Ribeiro, Guerreiro, & De Mendonca, 2007; VonDras, Powless, Olson, Wheeler, & Snudden, 2005). Along these lines, several studies have suggested that deficits in verbal episodic memory may be one of the earliest and most sensitive precursors of conversion to AD (Collie & Maruff, 2000b; Devanand, Folz, Gorlyn, Moeller, & Stern, 1997; Dubois, 2000b; Reischies & Neu, 2000; Visser et al., 1999). The implementation of operational criteria by Grundman and colleagues and findings regarding verbal memory as a significant predictor of conversion to dementia are likely explanations for the continued emphasis on verbal memory deficits in MCI in research, although recent findings support the presence of nonverbal memory deficits in MCI as well (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006a; Bozoki et al., 2001b; Djordjevic, Jones-Gotman, De Sousa, & Chertkow, 2007; Griffith et al., 2006; Hort et al., 2007).

Memory impairment is required for the diagnosis of Alzheimer's disease and is a criterion for MCI. The TFLS was designed to detect deficits commonly seen in AD and thus, the inclusion of a Memory subscale was implicit. There are of course many different types, or aspects, of memory that can be measured with various tasks.

Declarative memory is the recollection of facts, while prospective memory is memory for appointments, tasks, and plans that are anticipated to occur in the future, and involves both declarative memory (by consciously recalling and following instructions) and executive functioning (Lezak, Howieson, & Loring, 2004; Loring, 1999). Incidental learning occurs without an individual's volitional effort, and is tested with tasks in which the person is unaware that memory recall will be assessed (Loring, 1999), such as priming tasks (Lezak et al., 2004). Declarative memory, incidental learning, and prospective memory contribute to performance on the TFLS Memory subscale. The first memory task gives instructions to remove three pills (represented by candies) from a bottle when a timer goes off after five minutes, and may measure both declarative and prospective memory. The other two memory tasks require the individual to recall information that was previously presented to them (the payee and amount paid on a simulated electricity bill); however, the individual is unaware that this information will be requested later. These tasks appear to tap into incidental learning/memory. This inclusion of a sundry of memory tasks may also help explain why the TFLS Memory subscale may be sensitive to the subtle memory deficits sometimes evidenced in MCI yet may fail to correlate more strongly with declarative memory tasks alone.

Upon examining the relationship between the TFLS and individual clinical memory tests more closely, it was discovered that the TFLS Memory subscale was moderately and significantly correlated with the CVLT and VRII (WMS-III), the same measures that correlated with the overall TFLS score. It was affirming to discover the relationships between the TFLS Memory subscale and a well-established measure of both

verbal and nonverbal memory; however, the results also showed relationships among performances on memory measures (LMII ρ = .35 & VRII ρ = .26) and on the TFLS Communication subscale. Possible explanations for the relatively low and/or lack of correlation between the TFLS Total Score and subscale scores and neuropsychological measures may be the limited range in scores and the overlap noted between MCI and NC on many of these variables. For example (see Table 9), ranges were within 2 points on the TFLS Total Score in MCI (40-52) and NC (42-52), within 1 point on the Time/Orientation and Money subscales, and equal on the Communication subscale (9-12). In addition, on LMII, a measure of verbal memory, MCI T-scores ranged from 43-66 while NC T-scores ranged from 40-73, again reflecting a limited range and significant overlap in scores (See Table 10). While broadly representative of the general MCI population in terms of age, education, and MMSE scores (Grundman et al., 2004a), many individuals with MCI obtained scores on neuropsychological testing that fell broadly within normal limits. In fact, T-scores of 40 or greater were discovered in the MCI population on each neuropsychological variable including the CVLT (15/25), LMII (18/18), VRII (18/26), Rey-O (14/19), WCST (22/25), TMTB (24/27), TMTA (22/27), CERAD BNT (24/28), and verbal fluency (24/28). The fact that the majority of scores on each task fell in the normal range in the MCI population may help explain the small and/or nonsignificant correlations found between the TFLS and these individual measures.

In order to further investigate the relationship between the TFLS Total Score and memory, a new memory composite score was calculated by adding the T scores of VRII

and the CVLT (the only verbal memory measure on which some MCI performed in the impaired range). The TFLS Total Score was moderately and significantly correlated with the modified memory composite score ($\rho = .325$, $\underline{n} = 54$, $p = .008$), substantiating a relationship between memory and everyday functional abilities as measured by the TFLS.

Insert Tables 9 and 10 here

Small but significant correlations were found between the TFLS total score and verbal fluency ($\rho = .22$, $p = .049$), and the TFLS total score and the language composite score ($\rho = .25$, $p = .032$), indicating a relationship between IADL performance and language skills. Language deficits, such as impaired naming or verbal fluency, have been noted in some individuals with MCI (Farias et al., 2006; Griffith et al., 2003; Grundman et al., 2004a; Loewenstein et al., 2006; Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007; Wang & Zhou, 2002). Fewer studies, however, have looked at the effects of language deficits on IADL performance in MCI. Farias et al. (2006) looked at everyday functioning in MCI using items from existing informant-based functional instruments that reflected everyday tasks and abilities related to memory, language, visual spatial abilities, planning, organization, and divided attention. Experts in the field of dementia (i.e., neurologists, neuropsychologists, social workers, nurses) generated additional items that they felt reflected functioning in these areas. While the Everyday Memory subscale (Farias et al., 2006) showed the most impairment, 4 of 14 (28%)

Everyday Language items were significantly more impaired in MCI than NC. Recent findings presented at the International Neuropsychological Society 2007 meeting (Griffith et al., 2007) revealed that MCI converters to dementia performed significantly worse than static MCI or NC on semantic fluency (animals), and that this same group also performed significantly worse on a measure of financial capacity. While this does not implicate causation, other studies have shown evidence of language and IADL impairment in MCI, and the current findings reflect a relationship between language abilities and performance on the TFLS.

While not anticipated, another finding of interest was the small, but significant, correlation between the TFLS Memory subscale and verbal fluency ($\rho = .30$). Verbal word generation requires access to stored words, thereby relying to some degree upon memory retrieval strategies. Furthermore, some of the information requested during the TFLS recall section was delivered via spoken command (to remove three pills from a prescription bottle when a timer beeps), requiring adequate receptive language skills. Information must be first be understood before being successfully encoded, and verbal defects tend to have more widespread cognitive consequences *because* task instructions, self-regulation, and ideational systems, even for nonverbal material, are usually verbal (Lezak et al., 2004; Luria, 1973). Other studies have shown a relationship between memory function and language abilities as well (Ribeiro et al., 2007; Taylor & Olichney, 2007; Vandenberghe, 2007; Wang & Zhou, 2002); thus, the correlation found between verbal fluency and the TFLS Memory subscale is not surprising.

While a trend towards significance was found between the TFLS total score and a measure of executive functioning (EF), TMTB, the hypothesized relationship between performance on the TFLS and executive functioning did not prove to be as strong as originally expected. Studies continue to show EF deficits in MCI (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Kounti, Tsolaki, & Kiosseoglou, 2006; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Perri et al., 2007; Royall et al., 2004a), although the extent of these deficits and their impact on functional abilities is less agreed-upon. Some findings have indicated that deficits in this cognitive domain may be an early indicator for those who will convert to dementia (Albert et al., 2007; Guarch, Marcos, Salamero, & Blesa, 2004; Perri et al., 2007), while others have shown a relationship between functional status and performance on EF measures (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002a; Burdick et al., 2005; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998b; Kounti et al., 2006; Okonkwo et al., 2006; Royall, Chiodo, & Polk, 2000a). While these results did not show a correlation between functional status, as measured by the TFLS, and performance on measures of executive functioning, there are many different dimensions of frontal/executive functioning (i.e., response inhibition, planning, problem-solving, behavioral regulation, etc), and no single cognitive measure taps into all of them. Even within the two EF measures utilized in this study, there are a number of variables that assess different aspects of executive functioning (i.e., Categories Completed, Perseverative Errors, and Losses of Set on the WCST; completion time and number of errors on TMTB). Ultimately, variables in this study were selected because they were most commonly used in the research when evaluating a particular domain (i.e.,

total perseverations is the most common of the WCST variables to be utilized when attempting to measure executive functioning).

Another factor that may have contributed to the lack of a significant finding between the TFLS and executive functioning is the several normal controls who performed in the impaired range on the WCST ($\underline{n}$ = 5 with T-scores < 40) and on TMTB ($\underline{n}$ = 2 with T-scores <40). These subjects were not eliminated from the study due to the small $\underline{n}$ and because their performance may simply represent scores at the lower end of the normal curve on that test. Nevertheless, retaining these outliers may have weakened the significance of the results. Original analyses revealed no significant difference between MCI and NC on either of these variables (WCST, TMTB); however, analyses rerun after eliminating all normal controls who scored in at least the mildly impaired range (T-score < 40) revealed a significant difference between groups on *both* variables (WCST MCI M = 53.96, NC M = 65.24, t (50) = 3.10, p = .003; TMTB MCI M = 48.74, NC M = 54.46, t (55) = 2.36, p = .022). The correlations between the TFLS total score and the WCST/TMTB, however, did not increase to significant levels.

Another goal of this study was to examine the relationship between performance on the TFLS and language, executive functioning, and declarative memory. To derive a composite score for the cognitive domain of language, the T-scores from the two language measures (BNT 15-item, verbal fluency) were summed and the total was divided by two. A small, but significant correlation emerged (ρ = .25, p = .032), indicating a relationship between performance on the TFLS and these tests. To derive a composite score for the executive functioning domain, the T-scores from the two

executive functioning measures (WCST perseverative errors, TMTB) were summed and the total divided by two. No significant relationship was found ($\rho = .12$, $p = .192$), even when the outliers discussed previously were removed from the analyses ($\rho = .17$, $\underline{n} = 48$, $p = .243$). To derive a composite score for the memory domain, T-scores from the four memory measures (CVLT total words learned, LMII, VRII, Rey-O Delayed Recall) were summed and the total divided by four. There was no significant relationship found with the TFLS ($\rho = .19$), although the distinct *lack* of correlation between the TFLS total score and the Rey-O/ LMII may have mediated the effects of the other two relationships noted. The Rey-O was the only memory variable that did not correlate with the TFLS total score or any of the subscales, so analyses were rerun between the TFLS total score and a memory composite score comprised of only LMII, VRII, and the CVLT. A small relationship was found, but it did not reach statistical significance ($\rho = .25$, $\underline{n} = 43$, $p = .055$). Another possible explanation for the small and/or lack of significant correlation between the TFLS total score and domain composite scores is the amount of overlap in neurocognitive scores between MCI and NC. For example, the mean scores for both groups on the majority of neuropsychological measures fell within normal limits, thereby restricting the overall range of scores (see Table 10).

Hypothesis 4 stated that annualized change scores on the TFLS would decline over time in MCI and remain stable in NC. "Decline" was defined as any change in the negative direction and "improvement" defined as any change in the positive direction. This hypothesis was supported, but not statistically. Fifty percent of MCI subjects showed an absolute decline in TFLS total scores from Time 1 to Time 2 (time interval

range = 10 months to 3 years), with 33% showing some improvement, and 17% remaining stable. In contrast, 41% of NCs improved on repeat testing, while only 29% declined and 30% remained stable across time. These findings may suggest an actual decline in IADL performance over time in MCI, although they may also reflect a stronger practice effect in NC than in MCI. It would make sense that individuals with decreased cognitive abilities (MCI) would show a smaller practice effect on repeat testing, signaling decreased efficiency in understanding, encoding, recalling, and applying the initially presented information at a later point. The fact worse performance on an IADL measure is seen in a group whose diagnostic criteria requires none, in addition to witnessing a greater decline in performance over time than seen in NC, is enough to validate the need for greater understanding of IADL performance in MCI.

Exploratory analyses were conducted to determine the sensitivity and specificity of the TFLS total score in predicting diagnosis. It was not anticipated that the TFLS would be efficacious in doing so, because, as pointed out previously, in order to receive the diagnosis of MCI, individuals must report a *lack* of impairment in ADLs/IADLs. Various cut-off scores were examined for sensitivity and specificity, and a cut-off score of 48 accurately identified 56.7% of those with MCI and yielded a specificity of 63.3%, which were the highest values achieved among the various cut-points that were set. In the original TFLS validity paper, Cullum et al. (2001a) found that a TFLS total cut-off score of 45 yielded a sensitivity of 96% and a specificity of 71% in differentiating NC from AD. The fact that these rates are so much better in AD vs. NC than in MCI vs. NC no doubt reflects the fact that the AD group was much more cognitively impaired and

thus, scored much lower than NC's on the TFLS. Furthermore, the restricted ranges and overlap of TFLS scores among NC and MCI subjects likely played a role in the instrument's lack of sensitivity in this regard (See Table 9). It should be kept in mind, however, that the TFLS was developed for use with demented individuals and to avoid ceiling as well as floor effects in that population; as a result, subjects with no or minimal cognitive dysfunction would not be expected to lose many points on the test.

The MMSE is the most widely used screening measure of global cognitive functioning, and Cullum et al. (2001a) found a strong correlation ($\underline{r} = .89$) between this test and the TFLS—results that were supported but not replicated in this study. In the MCI/NC sample there was only a moderate correlation ($\rho = .34$) between the TFLS and the MMSE, and while this relationship is not as strong as that found among NC and AD subjects, the range of scores on the MMSE was restricted in MCI (21-30) when compared to AD (6-29), and TFLS scores were also more restricted, which likely reduced the strength of the relationship. There was little absolute difference between groups on the MMSE total score (6.37%) and even less on the TFLS Total Score (3.08%), which also may have reduced the strength of the relationship. Additionally, while it has shown to adequately differentiate between NC and AD, and between MCI and AD, the MMSE's ability to differentiate between NC and MCI is also less robust (Alladi et al., 2006a; Collie & Maruff, 2000b; Petersen, 2000; Petersen et al., 1997b). For example, Perneczky et al. (2006b) mapped MMSE scores onto CDR categories to determine how well the MMSE performed as a surrogate of the CDR, as the MMSE takes considerably less time to administer. They discovered that while the MMSE was effective at differentiating

between CDR stages 0.5, 1, 2, and 3, it performed poorly at discriminating between stages zero (NC) and 0.5 (MCI), findings mirroring those of the current study of the TFLS.

It is known that IADLs are more complex than basic ADLs, and are therefore more likely to be vulnerable to the early effects of deterioration in cognitive functioning (Caltagirone, Perri, Carlesimo, & Fadda, 2001b; Galasko et al., 1997b; Nygard, 2003a). Recent findings indicate that individuals with MCI plus IADL impairment may have a greater likelihood of progressing to dementia than those without IADL dysfunction (Grundman et al., 2004a; Purser et al., 2005a). This is in no way to suggest the substitution of the TFLS for measures designed to detect general cognitive impairment, such as the MMSE. However, in light of recent research indicating the limited utility of the MMSE in detecting MCI (Devanand et al., 2007; Li et al., 2006; Sager et al., 2006), as well as the noted importance of early identification of those with increased risk of developing dementia, the *addition* of the TFLS may prove to be of value in terms of diagnosis, family feedback, and treatment planning.

Limitations of the Current Study

While the findings of this study are encouraging, it is not without its limitations. It is established that the smaller the sample size, the more difficult it is to conclusively establish a general relationship between two variables (Anastasi, 1988); thus, it is possible that the number of subjects in each group and on each measure limited the strength of the primary results. Another factor that may have affected the results of this study is the selection of the MCI population itself. As generally accepted diagnostic

criteria for MCI continue to evolve (Petersen, 2007; Petersen et al., 2001a; Petersen et al., 1999b; Portet et al., 2006b), researchers and clinicians struggle to maintain consistency and to identify them appropriately. The data collected for this study spanned several years, during which clinical MCI diagnostic criteria fluctuated. For example, original criteria required normal cognitive functioning in all non-memory domains. However, it was soon discovered that many individuals with MCI who went on to develop AD often experienced cognitive difficulty in non-memory domains prior to meeting criteria for dementia, thus leading to the concept of MCI subtypes. In fact, some studies suggest that the greater the number of cognitive domains affected, the greater the risk for conversion to dementia (Arnaiz et al., 2004a; Backman, Jones, Berger, Laukka, & Small, 2005; Bozoki et al., 2001b). Consequently, due to the limited number of pure aMCI cases available, the MCI population in this study was made up of a variety of subtypes including aMCI (verbal, $\underline{n} = 2$; nonverbal, $\underline{n} = 7$; and mixed, $\underline{n} = 5$), mdMCI ($\underline{n} = 13$), and single non-memory domain MCI ($\underline{n} = 2$). The heterogeneity of this group may be a confounding factor, as one recent study has shown that individuals with aMCI may exhibit greater functional deficits than MCI without memory impairment (Farias, Mungas, & Jagust, 2005). If that is the case, then an even greater contrast may be expected in TFLS performance between MCI and NC if this MCI population was limited to the memory-impaired only. Closer examination of the data indeed revealed more variance in TFLS total scores in the MCI group than in the NC group, indicating greater variation in the ability to perform IADLs in individuals with MCI. Garand et al. (2005) and Tuokko et al. (2005) reported similar variability in IADL dysfunction in the general

MCI population. This may be a function of combining the various subtypes of MCI into one group; however, due to small subtype sample sizes, separate analyses would not yield respectable results. Little research has been done examining IADL impairment in aMCI versus non-memory impaired MCI. At this point, however, results of this study can be extrapolated only to the MCI population in general. Even then, it would be a stretch to propose that this sample of thirty MCI of mixed subtypes, recruited from a memory disorders clinic, is representative of the overall MCI population.

In evaluating the relationships among the TFLS total and subscale scores, and individual measures of neuropsychological functioning, multiple correlations were computed, which inflates the probability of experiment-wise error. Since MCI performance on the TFLS has not been examined previously, and because Bonferroni corrections are highly conservative, and it was decided that more traditional significance values would be used in this initial investigation of the TFLS in MCI. The findings, however, must be interpreted with due caution in light of this.

Another issue with MCI diagnostic criteria that may have affected the study's outcome is the concept of subjectivity. Two criteria for MCI require a self-report of functioning—the subject must endorse memory difficulties and he/she must deny any impairment in ADLs, with IADLs only slightly impacted, if at all. This is a hotly debated topic as well, as it poses the potential problem of under-reporting or over-reporting symptoms. For example, if individuals with MCI tend to underreport memory dysfunction, as suggested by Purser et al. (2006) and Jungwirth et al. (2004; 2005), then those individuals may not receive the diagnosis of MCI. Likewise, if individuals tend to

over-report their functional disabilities, they may no longer qualify for the diagnosis of MCI. If subjective memory complaint was not a criterion of MCI and individuals without complaint but with objective memory impairment were included, IADL disability may have been more prevalent. Purser et al. (2006) looked at large group (n = 3,673) of community-dwelling elderly and diagnosed individuals with MCI if they met each of the required criteria except for the presence of a subjective memory complaint. They then evaluated the "complainers" versus the "noncomplainers" and discovered that MCI participants without subjective memory complaint constituted a larger proportion of the overall sample (14% vs. 8.9%) AND of persons objectively classified as having MCI (61% vs. 39%), than those with subjective memory complaint. These findings would suggest that a large number of individuals *with* cognitive impairment, not sufficient to warrant the diagnosis of dementia, are being excluded from the MCI group. As the relationship between overall cognitive functioning and activities of daily living, and in particular, instrumental activities of daily living has been well established (Aguero-Torres, von Strauss, Viitanen, Winblad, & Fratiglioni, 2001; Artero, Touchon, & Ritchie, 2001b; Bennett et al., 2006a; Franzen & Wilhelm, 1996), it would follow that individuals with objective memory impairment, regardless of subjective report, will likely have greater functional impairment as well.

In addition to diagnostic issues, item validity on the TFLS within these populations may be a limitation. First, it is apparent that some of the items on the test, particularly the dressing exercises, are far too easy for most individuals with MCI. The TFLS only requires a person to button a coat and tie a shoe correctly to score perfectly on

the Dressing subscale, which is intended to measure motor activity and avoid floor effects on the TFLS among those with more severe dementia. While some individuals with MCI may have physical limitations that affect these abilities, as a group, they typically function normally when it comes to this domain. The current findings certainly support this postulate, as only one of 30 individuals with MCI scored less than perfect on the Dressing subscale (4/5 possible points), and none of the NC obtained a score less than five. The concept of mobility dysfunction in MCI was examined in a study by Tuokko et al. (2005), who discovered that many individuals diagnosed with MCI/CIND had difficulty with walking and bathing in particular, but with the other ADL skills relatively intact. They speculated that walking and bathing involve coordinated use of both upper and lower extremity strength, which may be affected earlier in the dementing process, while dressing, feeding, toileting, and transferring may only rely on upper *or* lower extremity strength only, which appears to remain relatively intact until mid- to late-stage dementia. Regardless of the reasons, it is clear that the Dressing subscale contains items that most individuals with MCI, at least in this sample, can perform without difficulty.

This raises the ultimate question, "Is the TFLS, overall, sensitive enough to detect the more subtle deficits that are seen in MCI?" Certainly these data have shown significant differences between MCI and NC on the TFLS; however, these positive results translate into only a 1.6 point absolute difference in TFLS total score, a disparity that simply may not reflect much of a difference in ability to carry out IADLs. Examination of the ranges, means, and standard deviations reveals little difference, and significant overlap, in MCI/NC TFLS total scores and subscale scores (See Table 9), with

the MCI group demonstrating significantly lower scores on the TFLS total and Memory subscale only. If the discrepancy between MCI and NC on the Memory subscale is all that accounts for the difference seen in mean total scores, could these two groups just as easily be distinguished utilizing the TFLS memory items or a more commonly used measure of memory, such as Logical Memory or the CVLT? While this may be the case, the primary goal of administering a measure of ADLs/IADLs is to gain a better understanding of how individuals *function* in their everyday environment. While it cannot be said that the TFLS does this explicitly, we may be able to glean more practical information about IADL performance (such as the ability to make change or utilize a phonebook) by administering the TFLS than by simply using a measure of memory. Considering that IADL dysfunction may be an early indicator of conversion to dementia, discovering which IADL tasks are most sensitive in detecting the more subtle changes that can be seen in MCI becomes critical. Some items on the TFLS have shown the ability to differentiate between MCI and NC; however, they are primarily memory items. In fact, the only two items on the TFLS that showed a significant difference between groups were the two incidental memory items on the TFLS Memory subscale (recalling the payee and amount on a simulated check). While this would be expected of a measure designed for use with the dementia population (and in particular, AD), it begs the question of the measure's incremental validity in identifying those at risk for conversion. On the other hand, a subject's poor performance on a given memory task may not necessarily map to difficulties remembering appointments, medications, etc., in their everyday life. The TFLS has shown sensitivity in detecting some of the subtle changes

that can be seen in those with increased likelihood of conversion to dementia. Further exploration of IADL impairment in MCI might allow for the development of a modified TFLS that may be of more practical use in this population.

Conclusions and Future Directions

The primary goal of the current study was to examine performance on the TFLS in MCI and NC. It was predicted that subjects with MCI would perform significantly worse than NC on the TFLS total score. It was also expected that performance on the TFLS would correlate significantly with a measure of global cognitive functioning (CERAD battery Total Score) and standard measures of memory and executive functioning, but not with measures of language or attention. Last, performance on the TFLS was hypothesized to decrease over time in MCI, but to remain stable in NC.

Overall, MCIs performed significantly worse than NCs on the TFLS, although the 1.6-point (out of 52 possible) absolute difference was relatively small. While the hypothesized difference prevailed, findings may indicate that the TFLS may not be sensitive enough to detect many of the subtle cognitive difficulties that are sometimes seen in MCI. While the TFLS yielded a sensitivity of 96% and a specificity of 71% in differentiating NC from AD (Cullum et al., 2001a), it performed less than adequately in differentiating MCI from NC (57% sensitivity, 63% specificity). This may reflect the expression of the MCI criterion requiring essentially normal activities of daily living, or it may indicate that while some individuals with MCI may experience difficulties with IADLs, the TFLS's design as a measure for dementia does not contain enough items that are sensitive to more subtle deficits. Future studies could perform an item analysis of

each TFLS task to determine which of them best differentiates between MCI and NC. These results could be combined with findings from other studies of IADL performance in MCI to develop a modified version of the TFLS for use in the MCI population. Tasks that have shown to be particularly sensitive to differentiating MCI from NC are items such as management of public transportation, food preparation, and management of finances and medications. While the TFLS includes some of these tasks, they may be too easy for the MCI population. For example, the current version of the electricity bill only contains a couple of lines of the imperative information. Another performance-based measure of IADLs, the UCSD Performance Based Skills Assessment (UPSA) contains a similar task; however, the stimulus contains much more detailed information for the subject to discern. Other useful tasks on the UPSA include management of transportation (a series of bus schedules used to plot a route from Point A to Point B) and comprehension of basic medical information and instructions (a simulated letter from a doctor's office containing appointment time and instructions that must be understood and recalled by the subject). These types of tasks may be useful to examine in patients with MCI.

Poorer performance on the TFLS total score was associated with impairment on a measure of global cognitive functioning and on individual measures of verbal and nonverbal memory. Relationships were also discovered between the TFLS Communication and Memory subscale scores and performance on standard clinical measures of verbal and nonverbal memory and language. Unfortunately, several of the subjects in this study lacked scores for some of the measures, which is an issue with

retrospective studies. For example, while both the 30-item BNT and the CERAD BNT were generally administered, the number of subjects who received the 30-item version was too small to be of use. Future studies could reevaluate the relationships discovered in this study using larger numbers of subjects with complete test data.

One-half of all MCI subjects showed a decline in performance on the TFLS over time, compared with only 29% of NC, although this difference did not reach statistical significance. Because the number of subjects with repeat testing data available was limited, it would be interesting to rerun these analyses in larger samples. One concept that is not explicitly included in current MCI diagnostic criteria is change over time. While an individual's score on a given measure can indicate the presence of or lack of impairment, it does not take into consideration each person's premorbid or earlier level of functioning. A measure of premorbid level of functioning, such as the Wechsler Test of Adult Reading (WTAR), could be included to provide an estimated baseline level of functioning, and change scores over time could be examined with respect to diagnostic sensitivity. Examination of the preliminary test-retest RCI results furthermore suggests that serial evaluations with the TFLS over time may be useful in identifying not only patients with MCI, but perhaps those who may become demented more quickly, as most controls showed no change or improvement in performance over times, while those with MCI more often showed a decline.

The implications of the current study suggest that some individuals with MCI may experience difficulties with more complex activities of daily living, at least those affected by memory difficulties, although the subtlety of these difficulties can make them more

difficult to detect. In individuals with MCI and NC, performance on this test is related to global cognitive functioning and memory and language abilities, with a trend association noted between TFLS performance and measures of executive functioning. In order to explore these findings more extensively, future studies should consider using larger sample sizes, different MCI subtypes, and a longitudinal design to assess MCI performance on the TFLS over time. Ultimately, results from the current research support incorporating the TFLS into the framework of MCI and AD assessment and diagnosis.

Figure 1

TFLS Test-Retest Results in MCI and NC

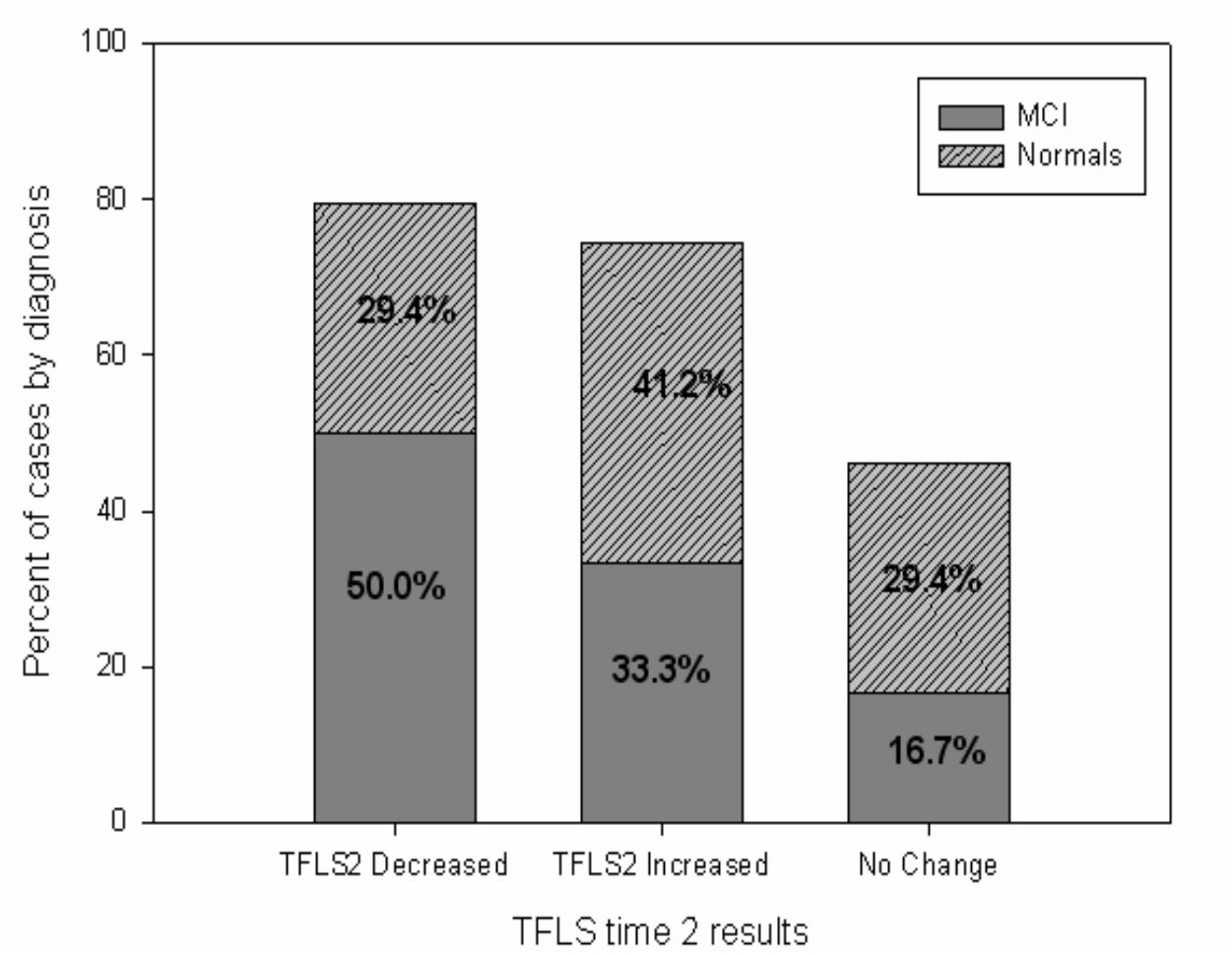

Table 1

Demographic Results for MCI, Normal Controls, and Total Sample (Hypotheses 1-3)

	MCI (n = 30)	NC (n = 30)	Total Sample (n = 60)
Age M (SD)	72.84 (7.88)	73.65 (6.87)	73.24 (7.34)
Education M (SD)	14.87 (2.76)	15.27 (2.00)	15.07 (2.40)
Gender M/F (%Male)	16/14 (53)	14/16 (47)	15/15 (50)

Note. No significant differences were found between MCI and NC in terms of age, education, or gender

Table 2

Demographic Results from Test-Retest Data for MCI, Normal Controls, and Total Subsample (Hypothesis 4)

	MCI (n = 12)	NC (n = 17)	Total Sample (n = 29)
Age M (SD)	71.13 (6.73)	72.92 (10.96)	72.18 (9.34)
Education M (SD)	13.67 (3.06)	15.00 (1.94)	14.45 (2.50)
Gender M/F (%Male)	6/6 (50)	5/12 (29)	11/18 (38)

Note. MCI and NC subjects matched to be similar in terms of age, education, and gender and no significant differences between groups for these variables were seen.

Table 3

TFLS Scores in MCI and NC Between Total Sample and Test-Retest Subsample

	Total Sample (n=60) M (SD)	Test-Rest Sample (n=29) M (SD)
TFLS Total Score	48.33 (2.57)	48.24 (2.80)
Dressing	4.98 (0.14)	4.97 (0.19)
Time	14.69 (0.89)	14.62 (1.05)
Money Skills	11.15 (0.92)	11.17 (1.04)
Communication	11.30 (0.90)	11.34 (1.01)
Memory	6.22 (.86)	6.14 (1.81)

Note. No significant differences between groups for these variables were seen.

Table 4

TFLS Total and Subtest Scores in MCI and NC Groups

	MCI (n=30) M (SD)	NC (n=30) M (SD)	t-test (df = 58)	p-value (1-tailed)
TFLS Total Score	47.17 (3.01)	48.77 (2.22)	2.34	.023
Dressing	4.97 (0.18)	5.00 (0.00)	N/A	N/A
Time	14.73 (0.74)	14.63 (1.00)	-.44	.661
Money Skills	11.10 (0.89)	11.17 (0.95)	.28	.779
Communication	11.10 (1.00)	11.37 (0.85)	1.12	.269
Memory	5.27 (1.72)	6.60 (1.40)	3.29	.002

Note. N/A Cannot be computed

Table 5

Pearson Product Moment Correlations Between TFLS Total Score and Subtest Scores and CERAD Total Score (n = 57)

	CERAD Total Score	
	r	p-value (1-tailed)
TFLS Total Score	.37*	.003
Dressing	N/A	N/A
Time	-.01	.921
Money Skills	.07	.627
Communication	.22	.097
Memory	.45*	<.001

Note. N/A Cannot be computed because Dressing Subscale Total = 5 for all subjects

*Correlation is significant at the 0.01 level

Table 6

Spearman Rank Order Correlations Between TFLS Total Score and Individual Measures of Memory, Executive Functioning, Attention, and Language

	n	TFLS Total Score	
CVLT	55	.23*	.049
LM II	46	.16	.148
VR II	56	.31*	.010
Rey-O	46	.08	.307
WCST	55	.12	.187
TMTB	57	.20	.066
TMTA	57	.15	.141
BNT	58	.11	.206
Fluency	57	.22*	.049

Note. (CVLT = California Verbal Learning Test Total Score; LM II & VR II = WMS-R/WMS-III Logical Memory Delayed Recall and Visual Reproduction Delayed Recall; Rey-O = Rey-Osterrieth Complex Figure; WCST = Wisconsin Card Sorting Task Total Perseverations; TMTA/TMTB = Trail-Making Test Parts A & B; BNT = CERAD 15-item Boston Naming Test; Fluency = Animal Fluency)

*Correlation is significant at the 0.05 level

Table 7
Memory, Language, and Executive Function Composite Scores in MCI and NC

	MCI M (SD)	NC M (SD)	t-test Z	p-value (1-tailed)
Memory Composite (n = 42)	47.4 (2.2)	59.3 (8.1)	-3.78	<.001
Language Composite (n = 57)	47.1 (7.6)	54.6 (8.5)	-3.55	<.001
Executive Function Composite (n = 54)	51.7 (7.3)	56.2 (12.4)	-1.86	.064

Note. (Memory composite score includes California Verbal Learning Test Total Score, WMS-R/WMS-III Logical Memory Delayed Recall and Visual Reproduction Delayed Recall, and Rey-Osterrieth Complex Figure; Language composite score includes CERAD 15-item Boston Naming Test and Animal Fluency; Executive Function composite score contains Wisconsin Card Sorting Task Total Perseverations and Trail-Making Test Part B)

Table 8

Spearman Rank Order Correlations Between TFLS Subscale Scores and Individual Measures of Memory, Executive Functioning, Attention, and Language

	n	Dressing	Time	Money Skills	Communication	Memory
CVLT	55	.20	-.13	.02	.10	.37**
LM II	46	N/A	-.24	-.06	.35**	.21
VR II	56	.14	-.15	.09	.26*	.36**
Rey-O	46	-.19	-.05	.19	.10	.06
WCST	55	.12	.07	.15	.13	-.04
TMTB	57	N/A	.11	.10	.02	.15
TMTA	57	N/A	-.03	.08	.04	.18
BNT	58	N/A	-.03	.02	.20	.12
Fluency	57	N/A	-.13	.04	.14	.30*

Note. (CVLT = California Verbal Learning Test Total Score; LM II & VR II = WMS-R/WMS-III Logical Memory Delayed Recall and Visual Reproduction Delayed Recall; Rey-O = Rey-Osterrieth Complex Figure; WCST = Wisconsin Card Sorting Task Total Perseverations; TMTA/TMTB = Trail-Making Test Parts A & B; BNT = CERAD 15-item Boston Naming Test; Fluency = Animal Fluency)

*$p < 0.05$ (1-tailed)

** $p < 0.01$ (1-tailed)

Table 9

Means, Standard Deviations, and Ranges for TFLS Total Score, TFLS Subscale Scores, CERAD, and MMSE in MCI and NC

	MCI			NC				
	Mean	SD	Range	Mean	SD	Range	t-test	p-value (1-tailed)
TFLS Total Score	47.17	3.01	40-52	48.77	2.22	42-52	2.34	.023
Dressing	4.97	0.18	4-5	5.00	0.00	n/a	N/A	N/A
Time/Orientation	14.73	0.74	12-15	14.63	1.00	11-15	-.44	.661
Money	11.10	0.89	9-12	11.17	0.95	8-12	.28	.779
Communication	11.10	1.00	9-12	11.37	0.85	9-12	1.12	.269
Memory	5.27	1.72	1-8	6.60	1.40	3-8	3.29	.002
CERAD Total Score	84.61	7.95	69-100	96.90	7.79	79-109	5.89	<.001
MMSE	27.30	2.15	21-30	29.21	0.96	27-30	3.54	.002

Table 10

Individual Neuropsychological Test Results s (T scores) by Group

		MCI			NC		
	n	Mean	SD	Range	Mean	SD	Range
CVLT	55	44.60	8.47	32-64	55.97	10.21	39-72
LM II	46	54.56	7.91	43-66	63.04	8.70	40-73
VRII	56	43.62	10.92	29-73	57.77	10.71	36-73
Rey-O	46	48.16	17.12	10-90	60.44	14.83	27-90
WCST	55	53.96	13.15	30-87	59.33	18.37	6-93
TMTB	57	48.74	7.21	30-62	52.97	11.54	32-81
TMTA	57	49.11	8.72	32-61	53.67	9.00	34-71
Boston	58	48.42	12.43	13-57	52.19	8.63	27-57
Fluency	57	45.74	9.22	30.63	56.74	12.25	34-80

APPENDIX A

Neuropsychological Measures

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery (Morris et al., 1989)

The neuropsychological tests developed and utilized by the CERAD are designed to measure cognitive impairment in individuals with AD and to assist with diagnosis. The battery is comprised of six subtests that measure memory, language, and praxis, as well as a slightly modified version of the original MMSE. Normative data for the battery has been published (Welsh et al., 1994), and was utilized in this study to derive age- and education-corrected T-scores for both language measures used (verbal fluency, naming; see below). The CERAD takes approximately 20-30 minutes to administer and has high interrater consensus (0.92 to 1.0) and high test-retest reliability (Morris et al., 1989). This study computed a CERAD total score as described by Chandler et al. (2005) by summing the raw scores of the following CERAD subtests: Verbal Fluency, CERAD BNT, Constructional Praxis, and Word List Recall, Recognition, and Discriminability. Recognition Discriminability is calculated by subtracting the number of false positives from the number of true negatives.

Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975a)

The MMSE is a brief, cognitive rating scale that was developed to assess level of functioning in several cognitive domains. The MMSE contains 22 items that assess orientation, memory, concentration, language, and praxis, and takes approximately 5 to 10 minutes to administer and score. Instead of the using the serial seven subtraction item

from the original measure developed by Folstein et al. (1975a), the MMSE used in the CERAD battery requires the subject to spell the word "world" backwards. Additionally, the subject is required to answer questions that assess orientation and memory, follow verbal and written commands, generate an original sentence, and copy a design.

California Verbal Learning Test (CVLT) (Delis et al., 1987)

The CVLT is a 16-item list-learning task that includes 5 learning trials and assesses numerous aspects of memory including immediate and delayed free recall, semantically cued recall, and recognition. The initial list ("Monday" list) contains 4 words in each of the following categories: clothing, tools, fruits, and spices and herbs. After 5 trials of the "Monday" list, an interference list ("Tuesday" list) of 16 words is presented once, followed by a free recall and semantically cued recall of the "Monday" list. Later, following a 20-minute delay, a free recall, cued recall, and recognition of the "Monday" list occurs.

Rey-Osterrieth Complex Figure (Rey-O)

The Rey-O measures spatial organizational skills, visuoperceptual skills, and visual memory (Mitrushina, Boone, Razani, & D'Elia, 2005). The subject is required to copy a complex geometric design, then to draw it immediately from memory. Following a 15-minute delay, subjects are asked to redraw the figure again and then to recognize it from a group of similar figures. The subject unaware that the immediate or delayed recall of the figure will take place. A scoring system was developed by Loring, Martin, Meador, and Lee (1990) that awards zero to two points for each of the 18 figure elements, depending on accuracy and placement of the element. All points awarded for each

component are summed separately for each of the 3 trials to determine a score. Normative data derived by (put the article in endnote to reference properly!!) then converts the raw scores into percentile scores, which were then converted to T-scores for ease of comparison.

Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall (LMII) and Wechsler Memory Scale-III (WMS-III) Logical Memory Delayed Recall (LMII) and Visual Reproduction Delayed Recall (VRII)

The Wechsler Memory Scale was originally developed in 1945 and was one of first standardized memory batteries available. Revisions were published in 1987 (WMS-R) and 1997 (WMS-III). The Logical Memory subtest of both revisions involves reading a short story to the subject, which they are then required to recall immediately and after a 30-minute delay (LMII). Scoring criteria allow credit to be given for each story detail (or general gist of the detail) and norms that accompany the WMS provide percentile scores and scaled scores, stratified by age. In the Visual Reproduction subtest, the subject is shown 5 consecutive pages of simple designs for 10 seconds each, then is required to recall the design immediately after it is shown. Following a 30-minute delay, the subject is asked to redraw the designs from memory. For both LM and VR, the subject is notified that they will be required to recall the information at a later point.

Trail Making Test (TMT) (Reitan & Wolfson, 1993)

The Trail Making Test measures attention, visual scanning and processing, motor speed, and mental sequencing and flexibility (Spreen & Strauss, 1998). TMT Part A requires the subject to draw a continuous line connecting numbers one to 25 (scattered in

circles) as quickly as possible. TMT Part B assesses mental flexibility, requiring the subject to alternate between numbers 1-13 and letters A-L within circles. The subject is scored according to the amount of time it takes to complete the task. Errors are corrected during the task and are calculated at the end; however, they do not contribute directly to the scores, which are age-, gender-, and education-corrected (Heaton et al., 1991).

Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993)

The WCST is believed to assess several executive functions including problem solving, abstract reasoning, organization, and mental flexibility (Mitrushina et al., 2005), and requires that the subject sort 2 decks of 64 cards to 4 stimulus cards. There are 3 sorting principles (color, form, number); however, these are not revealed to the subject. The subject is told "right" or "wrong" by the examiner after each card sort and must determine, given this feedback, what principle he or she is to use. After 10 consecutive correct trials, the sorting principle changes and the subject must adapt accordingly. The task ends when the subject completes each category twice in the correct order or when all 128 cards have been sorted. If the subject does not sort any categories in the first 64 cards, the task can be discontinued. The WCST yields several useful outcome measures including perseverative errors, losses of set, and categories completed. This study examined perseverative errors, which occur when the subject continuously sorts to the same wrong response, despite negative feedback. Axelrod, Goldman, and Woodard (1992) report good interrater reliability of $r = .88$ to $r = .93$ for the WCST. Age-, gender-, and education-corrected scores for perseverative errors were obtained from the Heaton et al. (1991) norms.

Verbal Fluency

Verbal fluency is a categorical semantic fluency task. The subject is asked to name as many items in a given category ("animals" is used) as they can in one minute. The total score is derived by summing the number of words produced for the category. Perseverative errors (repetition of the same word) and losses of set (generation of words that do not fit into the category) do not count toward the total score. The raw score is then converted into a T-score using the normative data derived by Welsh et al. (1994).

CERAD 15-Item Boston Naming Test (BNT)

The CERAD 15-Item BNT is one of many versions of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). It is a confrontation naming task that includes 15 drawn objects presented one-at-a-time. The subject is allowed 10 seconds to name the picture presented before moving on to the next item. The CERAD BNT is comprised of 3 groups of words that occur with high, medium, and low frequency in the English language (Morris et al., 1989).

References

Albert, M. (1997). Preclinical Predictors of Alzheimer's Disease. *Brain and Cognition, 35*, 284-426.

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *J Int Neuropsychol Soc, 7*(5), 631-639.

Albert, S. M., Tabert, M. H., Dienstag, A., Pelton, G., & Devanand, D. (2002). The impact of mild cognitive impairment on functional abilities in the elderly. *Curr Psychiatry Rep, 4*(1), 64-68.

Alladi, S., Arnold, R., Mitchell, J., Nestor, P. J., & Hodges, J. R. (2006). Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychol Med, 36*(4), 507-515.

APA. (2000). *Diagnostic and statistical manual of mental disorders (4th ed. Text Revision)* (IV-TR ed.). Washington: American Psychiatric Association.

Apostolova, L. G., Dutton, R. A., Dinov, I. D., Hayashi, K. M., Toga, A. W., Cummings, J. L., et al. (2006). Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. *Arch Neurol, 63*(5), 693-699.

Arnaiz, E., Almkvist, O., Ivnik, R. J., Tangalos, E. G., Wahlund, L. O., Winblad, B., et al. (2004). Mild cognitive impairment: a cross-national comparison. *J Neurol Neurosurg Psychiatry, 75*(9), 1275-1280.

Artero, S., Touchon, J., & Ritchie, K. (2001). Disability and mild cognitive impairment: a longitudinal population-based study. *Int J Geriatr Psychiatry, 16*(11), 1092-1097.

Axelrod, B. N., Goldman, B. S., & Woodard, J. L. (1992). Interrater reliability in scoring the Wisconsin Card Sorting Test. *The Clinical Neuropsychologist, 6*, 143-155.

Becker, J. T., Davis, S. W., Hayashi, K. M., Meltzer, C. C., Toga, A. W., Lopez, O. L., et al. (2006). Three-dimensional patterns of hippocampal atrophy in mild cognitive impairment. *Arch Neurol, 63*(1), 97-101.

Bell-McGinty, S., Podell, K., Franzen, M., Baird, A. D., & Williams, M. J. (2002). Standard measures of executive function in predicting instrumental activities of daily living in older adults. *Int J Geriatr Psychiatry, 17*(9), 828-834.

Bennett, H. P., Piguet, O., Grayson, D. A., Creasey, H., Waite, L. M., Lye, T., et al. (2006). Cognitive, extrapyramidal, and magnetic resonance imaging predictors of functional impairment in nondemented older community dwellers: the Sydney Older Person Study. *J Am Geriatr Soc, 54*(1), 3-10.

Bischkopf, J., Busse, A., & Angermeyer, M. C. (2002). Mild cognitive impairment--a review of prevalence, incidence and outcome according to current approaches. *Acta Psychiatr Scand, 106*(6), 403-414.

Boeve, B., McCormick, J., Smith, G., Ferman, T., Rummans, T., Carpenter, T., et al. (2003). Mild cognitive impairment in the oldest old. *Neurology, 60*(3), 477-480.

Bozoki, A., Giordani, B., Heidebrink, J. L., Berent, S., & Foster, N. L. (2001). Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol, 58*(3), 411-416.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl), 82*(4), 239-259.

Cahn-Weiner, D. A., Malloy, P. F., Boyle, P. A., Marran, M., & Salloway, S. (2000). Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *Clin Neuropsychol, 14*(2), 187-195.

Caltagirone, C., Perri, R., Carlesimo, G. A., & Fadda, L. (2001). Early detection and diagnosis of dementia. *Arch Gerontol Geriatr Suppl, 7*, 67-75.

Chandler, M. J., Lacritz, L. H., Hynan, L. S., Barnard, H. D., Allen, G., Deschner, M., et al. (2005). A total score for the CERAD neuropsychological battery. *Neurology, 65*(1), 102-106.

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2000). Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology, 55*(12), 1847-1853.

Collie, A., & Maruff, P. (2000). The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neurosci Biobehav Rev, 24*(3), 365-374.

Crook, T., Bartus, R., Ferris, S. H., Whitehouse, P., Cohen, G., & Gershon, S. (1986). Age-Associated Memory Impairment: Proposed Diagnostic Criteria and Measures of Clinical Change-Report of a National Institute of Mental Health Work Group. *Developmental Neuropsychology, 2*(4), 261-276.

Cullum, C. M., Saine, K., Chan, L. D., Martin-Cook, K., Gray, K. F., & Weiner, M. F. (2001a). Performance-Based instrument to assess functional capacity in dementia: The Texas Functional Living Scale. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 14*(2), 103-108.

Cullum, C. M., Saine, K., Chan, L. D., Martin-Cook, K., Gray, K. F., & Weiner, M. F. (2001b). Performance-Based instrument to assess functional capacity in dementia: The Texas Functional Living Scale. *Neuropsychiatry Neuropsychol Behav Neurol, 14*(2), 103-108.

De Ronchi, D., Bellini, F., Berardi, D., Serretti, A., Ferrari, B., & Dalmonte, E. (2005). Cognitive status, depressive symptoms, and health status as predictors of functional disability among elderly persons with low-to-moderate education: The Faenza Community Aging Study. *Am J Geriatr Psychiatry, 13*(8), 672-685.

DeBettignies, B. H., Mahurin, R. K., & Pirozzolo, F. J. (1993). Functional Status in Alzheimer's Disease and Mulit-Infarct Dementia: A Comparison of Patient Performance and Caregiver Report. *Clinical Gerontologist, 12*(4), 31-49.

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

Delis, D. C., Massman, P. J., Butters, N., & Salmon, D. P. (1991). Profiles of Demented and Amnesic Patients on the California Verbal Learning Test: Implications for the Assessment of Memory Disorders. *Psychological Assessment: A Journal of Consulting and Clinical Psychology, 3*(1), 19-26.

Derouesne, C. (1994). [Complaints of memory loss in the elderly]. *Rev Prat, 44*(11), 1432-1435.

Diaz, P. R. S., Gregorio, P. G., Casado, M. R. J., Reynish, E., Jean Ousset, P., Vellas, B., et al. (2005). The need for a consensus in the use of assessment tools for

Alzheimer's disease: the Feasibility Study (assessment tools for dementia in Alzheimer Centres across Europe), a European Alzheimer's Disease Consortium's (EADC) survey. *International Journal of Geriatric Psychiatry, 20*(8), 744-748.

Dubois, B. (2000). 'Prodromal Alzheimer's disease': a more useful concept than mild cognitive impairment? *Curr Opin Neurol, 13*(4), 367-369.

Dubois, B., & Albert, M. L. (2004). Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurol, 3*(4), 246-248.

Espino, D. V., Lichtenstein, M. J., Palmer, R. F., & Hazuda, H. P. (2001). Ethnic differences in mini-mental state examination (MMSE) scores: where you live makes a difference. *J Am Geriatr Soc, 49*(5), 538-548.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975a). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975b). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Franzen, M., & Wilhelm, K. (1996). Conceptual foundations of ecological validity in neuropsychological assessment. . In R. Sbordone & C. Long (Eds.), *Ecological validity of neuropsychological testing* (pp. 91-112 of 513). Delray Beach: Gr Press/St Lucie Press, Inc.

Galasko, D., Bennett, D., Sano, M., Ernesto, C., Thomas, R., Grundman, M., et al. (1997). An inventory to assess activities of daily living for clinical trials in

Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord, 11 Suppl 2*, S33-39.

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology, 63*(1), 115-121.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., et al. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270.

Greenaway, M. C., Lacritz, L. H., Binegar, D., Weiner, M. F., Lipton, A., & Munro Cullum, C. (2006). Patterns of Verbal Memory Performance in Mild Cognitive Impairment, Alzheimer Disease, and Normal Aging. *Cogn Behav Neurol, 19*(2), 79-84.

Griffith, H. R., Belue, K., Sicola, A., Krzywanski, S., Zamrini, E., Harrell, L., et al. (2003). Impaired financial abilities in mild cognitive impairment: a direct assessment approach. *Neurology, 60*(3), 449-457.

Grigsby, J., Kaye, K., Baxter, J., Shetterly, S. M., & Hamman, R. F. (1998). Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. *J Am Geriatr Soc, 46*(5), 590-596.

Grundman, M., Petersen, R. C., Ferris, S. H., Thomas, R. G., Aisen, P. S., Bennett, D. A., et al. (2004). Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol, 61*(1), 59-66.

Gustafson, L., & Thulin, A. K. (1995). [A care program for dementia. Increased cooperation between health care and social service]. *Lakartidningen, 92*(25), 2574, 2577.

Heaton, R. (1992). *Comprehensive norms for an expanded Halstead-Reitan Battery: A supplement for the WAIS-R*. Odessa: Psychological Assessment Resources.

Heaton, R., Grant, I., & Matthews, C. (1991). *Comprehensive norms for an expanded Halstead-Reitan Battery: Demographic corrections, research findings, and clinical applications*. Odessa: Psychological Assessment Resources.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtis, G. (1993). *Wisconsin Card Sorting Test Manual Revised and Expanded*. Odessa, FL: Psychological Resources, Inc.

Ivnik, R. J., Malec, J. F., & Smith, G. E. (1992a). Mayo's Older Americans Normative Studies: WAIS-R Norms for Ages 56-97. *The Clinical Neuropsychologist, 6*(Supplement), 1-30.

Ivnik, R. J., Malec, J. F., & Smith, G. E. (1992b). Mayo's Older Americans Normative Studies: WMS-R Norms for Ages 56 to 94. *The Clinical Neuropsychologist, 6*(Supplement), 49-82.

Jack, C. R., Jr., Shiung, M. M., Weigand, S. D., O'Brien, P. C., Gunter, J. L., Boeve, B. F., et al. (2005). Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. *Neurology, 65*(8), 1227-1231.

Jicha, G. A., Parisi, J. E., Dickson, D. W., Johnson, K., Cha, R., Ivnik, R. J., et al. (2006). Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol, 63*(5), 674-681.

Kaltreider, L. B., Cicerello, A. R., Lacritz, L. H., Honig, L. S., Rosenberg, R. N., & Cullum, M. C. (2000). Comparison of the CERAD and CVLT list-learning tasks in Alzheimer's disease. *Clin Neuropsychol, 14*(3), 269-274.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test* (2nd ed.). Philadelphia: Lea & Febiger.

Kassner, E., & Jackson, B. (1998). Determining comparable levels of functional disability. *Issue Brief (Public Policy Inst (Am Assoc Retired Pers))*(IB32), 1-10.

Lacritz, L. H., Cullum, C. M., Weiner, M. F., & Rosenberg, R. N. (2001). Comparison of the hopkins verbal learning test-revised to the California verbal learning test in Alzheimer's disease. *Appl Neuropsychol, 8*(3), 180-184.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist, 9*(3), 179-186.

Lopez, O. L., Becker, J. T., Jagust, W. J., Fitzpatrick, A., Carlson, M. C., DeKosky, S. T., et al. (2006). Neuropsychological characteristics of mild cognitive impairment subgroups. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*(2), 159-165.

Lopez, O. L., Jagust, W. J., DeKosky, S. T., Becker, J. T., Fitzpatrick, A., Dulberg, C., et al. (2003). Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol, 60*(10), 1385-1389.

Lyons, K. S., Zarit, S. H., Sayer, A. G., & Whitlatch, C. J. (2002). Caregiving as a dyadic process: perspectives from caregiver and receiver. *J Gerontol B Psychol Sci Soc Sci, 57*(3), P195-204.

Mahurin, R. K., DeBettignies, B. H., & Pirozzolo, F. J. (1991). Structured assessment of independent living skills: preliminary report of a performance measure of functional abilities in dementia. *J Gerontol, 46*(2), P58-66.

Marson, D. C., Sawrie, S. M., Snyder, S., McInturff, B., Stalvey, T., Boothe, A., et al. (2000). Assessing financial capacity in patients with Alzheimer disease: A conceptual model and prototype instrument. *Arch Neurol, 57*(6), 877-884.

Martin-Cook, K., Davis, B. A., Hynan, L. S., & Weiner, M. F. (2005). A randomized, controlled study of an Alzheimer's caregiver skills training program. *Am J Alzheimers Dis Other Demen, 20*(4), 204-210.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-944.

Meyers, J. E., & Meyers, K. R. (1995). *Rey Complex Figure Test and Recognition Trial*. Odessa, Florida: Psychological Assessment Resources.

Mish, F., Morse, J., Novak, M., Copeland, R., Lowe, J., Pease, R., et al. (Eds.). (1993). *Merriam-Webster's Collegiate Dictionary 10th ed.* (10th ed.). Springfield: Merriam-Webster, Incorporated.

Mitrushina, M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of Normative Data for Neuropsychological Assessment* (2nd ed.). New York, NY: Oxford University Press.

Mok, W. Y., Chu, L. W., Chung, C. P., Chan, N. Y., & Hui, S. L. (2004). The relationship between non-cognitive symptoms and functional impairment in Alzheimer's disease. *Int J Geriatr Psychiatry, 19*(11), 1040-1046.

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology, 43*(11), 2412-2414.

Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer disease: time to revise diagnostic criteria. *Arch Neurol, 63*(1), 15-16.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., et al. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology, 39*(9), 1159-1165.

Nygard, L. (2003). Instrumental activities of daily living: a stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurol Scand Suppl, 179*, 42-46.

O'Brien, J. T., & Levy, R. (1992). Age associated memory impairment. *Bmj, 304*(6818), 5-6.

Petersen, R., Smith, G., Waring, S., Ivnik, R., Tangalos, E., & Kokmen, E. (1999). Mild Cognitive Impairment. *Archives of Neurology, 56*(March), 303-308.

Petersen, R. C. (2000). Mild cognitive impairment: transition between aging and Alzheimer's disease. *Neurologia, 15*(3), 93-101.

Petersen, R. C. (2003). Mild cognitive impairment clinical trials. *Nat Rev Drug Discov, 2*(8), 646-653.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J Intern Med, 256*(3), 183-194.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001a). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F., et al. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Arch Neurol, 63*(5), 665-672.

Petersen, R. C., Smith, G. E., Ivnik, R. J., Tangalos, E. G., Schaid, D. J., Thibodeau, S. N., et al. (1995). Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *Jama, 273*(16), 1274-1278.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Kokmen, E., & Tangelos, E. G. (1997). Aging, memory, and mild cognitive impairment. *Int Psychogeriatr, 9 Suppl 1*, 65-69.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001b). 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. *Neurology, 56*(9), 1133-1142.

Petersen, R. C., Waring, S. C., Smith, G. E., Tangalos, E. G., & Thibodeau, S. N. (1996). Predictive value of APOE genotyping in incipient Alzheimer's disease. *Ann N Y Acad Sci, 802*, 58-69.

Pioggiosi, P. P., Berardi, D., Ferrari, B., Quartesan, R., & De Ronchi, D. (2006). Occurrence of cognitive impairment after age 90: MCI and other broadly used concepts. *Brain Res Bull, 68*(4), 227-232.

Portet, F., Ousset, P. J., Visser, P. J., Frisoni, G. B., Nobili, F., Scheltens, P., et al. (2006). Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *J Neurol Neurosurg Psychiatry, 77*(6), 714-718.

Pruchno, R. A., Burant, C. J., & Peters, N. D. (1997). Typologies of caregiving families: family congruence and individual well-being. *Gerontologist, 37*(2), 157-167.

Purser, J. L., Fillenbaum, G. G., Pieper, C. F., & Wallace, R. B. (2005). Mild cognitive impairment and 10-year trajectories of disability in the Iowa Established Populations for Epidemiologic Studies of the Elderly cohort. *J Am Geriatr Soc, 53*(11), 1966-1972.

Rapp, M. A., Schnaider Beeri, M., Schmeidler, J., Sano, M., Silverman, J. M., & Haroutunian, V. (2005). Relationship of neuropsychological performance to functional status in nursing home residents and community-dwelling older adults. *Am J Geriatr Psychiatry, 13*(6), 450-459.

Ravaglia, G., Forti, P., Maioli, F., Martelli, M., Servadei, L., Brunetti, N., et al. (2006). Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. *Dement Geriatr Cogn Disord, 21*(1), 51-58.

Reitan, R., & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation* (2nd ed.). Tucson, AZ: Neuropsychology Press.

Richardson, J., Law, M., Wishart, L., & Guyatt, G. (2000). The use of a simulated environment (easy street) to retrain independent living skills in elderly persons: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci, 55*(10), M578-584.

Royall, D. R. (2006). Mild cognitive impairment and functional status. *J Am Geriatr Soc, 54*(1), 163-165.

Royall, D. R., Chiodo, L. K., & Polk, M. J. (2000). Correlates of disability among elderly retirees with "subclinical" cognitive impairment. *J Gerontol A Biol Sci Med Sci, 55*(9), M541-546.

Royall, D. R., Chiodo, L. K., & Polk, M. J. (2004). Misclassification is likely in the assessment of mild cognitive impairment. *Neuroepidemiology, 23*(4), 185-191.

Royall, D. R., Cordes, J., & Polk, M. (1997). Executive control and the comprehension of medical information by elderly retirees. *Exp Aging Res, 23*(4), 301-313.

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2004). Declining executive control in normal aging predicts change in functional status: the Freedom House Study. *J Am Geriatr Soc, 52*(3), 346-352.

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2005). Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House Study. *J Am Geriatr Soc, 53*(1), 11-17.

Sacuiu, S., Sjogren, M., Johansson, B., Gustafson, D., & Skoog, I. (2005). Prodromal cognitive signs of dementia in 85-year-olds using four sources of information. *Neurology, 65*(12), 1894-1900.

Saine, K., Cullum, C. M., Martin-Cook, K., Hynan, L., Svetlik, D. A., & Weiner, M. F. (2002). Comparison of functional and cognitive donepezil effects in Alzheimer's disease. *Int Psychogeriatr, 14*(2), 181-185.

Simon, E., Leach, L., Winocur, G., & Moscovitch, M. (1994). Intact primary memory in mild to moderate Alzheimer disease: indices from the California Verbal Learning Test. *Journal of Clinical And Experimental Neuropsychology, 16*(3), 414-422.

Smith, G. E., Ivnik, R. J., Malec, J. F., Kokmen, E., Tangalos, E., & Kurland, L. T. (1992). Mayo's Older Americans Normative Studies (MOANS): Factor Structure of a Core Battery. *Psychological Assessment, 4*(3), 382-390.

Spreen, O., & Strauss, E. (1998). *A Compendium of Neuropsychological Tests: Second Edition*. New York: Oxford University Press.

SPSS. (2005). SPSS for Windows, Rel. 14.0.0. 2005. Chicago: SPSS Inc. (Version 14). Chicago.

Tabert, M. H., Albert, S. M., Borukhova-Milov, L., Camacho, Y., Pelton, G., Liu, X., et al. (2002). Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology, 58*(5), 758-764.

Tierney, M. C., Szalai, J. P., Snow, W. G., & Fisher, R. H. (1996). The prediction of Alzheimer disease. The role of patient and informant perceptions of cognitive deficits. *Arch Neurol, 53*(5), 423-427.

Tractenberg, R. E., Singer, C. M., & Kaye, J. A. (2005). Symptoms of sleep disturbance in persons with Alzheimer's disease and normal elderly. *J Sleep Res, 14*(2), 177-185.

Troyer, A. K., Graves, R. E., & Cullum, C. M. (1994). Executive Functioning as a Mediator of the Relationship between Age and Episodic Memory In Healthy Aging. *Aging and Cognition, 1*(1), 45-53.

Wechsler, D. (1987). Wechsler Memory Scale-Revised (WMS-R). San Antonio: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Memory Scale--Third Edition (WMS-III)*. San Antonio: Psychological Corporation.

Weiner, M. F., Womack, K. B., Martin-Cook, K., Svetlik, D. A., & Hynan, L. S. (2005). Levetiracetam for agitated Alzheimer's disease patients. *Int Psychogeriatr, 17*(2), 327-328.

Welsh, K. A., Butters, N., Mohs, R. C., Beekly, D., Edland, S., Fillenbaum, G., et al. (1994). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology, 44*(4), 609-614.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*(3), 240-246.

Vitae

Dani Lyn Pearson was born in Lansing, Michigan, on July 19, 1973, the daughter of Carol Lee Pearson and Theodore Bruce Pearson and raised Dani Lyn Binegar by mother, Carol Lee Binegar, and father, James F. Binegar, Jr. She completed her work at Taft High School, San Antonio, Texas in 1991, and entered Texas Tech University in 1995. She received the degree of Bachelor of Arts with a major in psychology from Texas Tech University, 1999. During the first year she was employed as a social work assistant at Queen's Medical Center, Honolulu, Hawaii. In August, 2001 she entered a Master's program in Cell & Neurobiology at the University of Southern California and worked as a teaching assistant for Joseph Miller, Ph.D. In August, 2002 she entered the Graduate School of Biomedical Sciences at the University of Texas Health Science Center at Dallas. She was awarded the degree of Doctor of Philosophy, August 3, 2007.

Permanent Address: 2 Townsend St. #2-1301
San Francisco, CA 94107