Longitudinal Trajectories and Predictors of Functional Impairment in Mild Cognitive Impairment, Alzheimer’s Disease, and Vascular Dementia

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LONGITUDINAL TRAJECTORIES AND PREDICTORS OF FUNCTIONAL IMPAIRMENT IN MILD COGNITIVE IMPAIRMENT, ALZHEIMER’S DISEASE, AND VASCULAR DEMENTIA

A Dissertation Presented

by

LAUREN ZERANSKI CHISHOLM

Submitted to the Graduate School of the University of Massachusetts Amherst in partial fulfillment of the requirements for the degree of

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Clinical Psychology
LONGITUDINAL TRAJECTORIES AND PREDICTORS OF FUNCTIONAL IMPAIRMENT IN MILD COGNITIVE IMPAIRMENT, ALZHEIMER’S DISEASE, AND VASCULAR DEMENTIA

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LAUREN ZERANSKI CHISHOLM

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ABSTRACT
LONGITUDINAL TRAJECTORIES AND PREDICTORS OF FUNCTIONAL IMPAIRMENT IN MILD COGNITIVE IMPAIRMENT, ALZHEIMER’S DISEASE, AND VASCULAR DEMENTIA
SEPTEMBER 2014
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Functional disability in older persons with cognitive impairment is associated with reduced quality of life and greater mortality, health care utilization, and caregiver burden. Episodic memory, executive function, apathy, depressive symptoms, and medical burden have been identified as cross-sectional predictors of functional disability but have received little longitudinal investigation in a way that explicates how changes in these variables relates to functional disability. Functional disability also drives the distinction between the diagnoses of Mild Cognitive Impairment (MCI) and dementia; however, little is known about the rates of functional decline in these groups over time. This study utilized multi-level modeling to determine the longitudinal associations between episodic memory, executive function, apathy, depressive symptoms, and medical burden and functional decline in older persons with MCI and two of the most prevalent types of dementia, Alzheimer’s disease and vascular dementia. Results provide support for the longitudinal associations between memory, executive function, and apathy symptoms and
instrumental activities of daily living (IADL) performance. Alzheimer’s disease was associated with a faster rate of function decline than normal aging and vascular dementia, but a rate not significantly different than seen in MCI. Longitudinal decline in IADLs was non-significant in both normal aging and vascular dementia.
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CHAPTER I
INTRODUCTION

Due to the aging of the Baby Boomer generation, the number of Americans aged 65 and older is projected to almost double to 72 million by 2030; the number of Americans aged 85 and older also is projected to increase to 19 million from 5.7 million by 2050 (Federal Interagency Forum on Aging-Related Statistics, 2010). While efforts are underway to develop treatments to prevent cognitive impairment in this population of older adults, prevention of premature disability and institutionalization in those who develop cognitive impairment remains an important goal. Central to this goal is an improved understanding of functional disablement in dementia. Functional disability is commonly described in terms of the ability to perform activities of daily living (ADLs). These include basic ADLs (BADLs), which are simple self-care activities such as eating, bathing, toileting, and dressing that are associated with motor functioning and basic visuospatial abilities (Boyle, Cohen, Paul, Moser, & Gordon, 2002; Herlitz, Hill, Fratiglioni & Backman, 1995). They also include instrumental ADLs (IADLs), which are more complex, adaptive activities that demand higher levels of function. IADLs include balancing a checkbook, preparing meals, driving, and using the telephone, and are tied to higher-order cognitive processes like organization, judgment, and sequencing of attention.

Impairments in ADLs are associated with a multitude of adverse outcomes for persons with dementia, including decreased autonomy and quality of life, increased mortality and health care utilization, and greater caregiver burden (Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sorensen, 2004; Covinsky, Newcomer, Fox, Wood,
Sands, & Dane et al., 2003; Hill, Fillit, Thomas, & Chang, 2006; Razani et al., 2007). Functional disability also is associated with increased expense. Greater functional dependence raises odds for institutionalization into nursing homes and other long-term care settings, at tremendous cost to families and the public welfare sector (Hill et al., 2006).

Much of the extant literature on functional disability in dementia has focused on cross-sectional relationships between single predictors or classes of predictors (e.g. neuropsychiatric or cognitive variables) and functional dependence. There is converging evidence for the power of cognition, neuropsychiatric symptoms, and, to a lesser extent, medical burden, in predicting functional disability in cognitively impaired older adults. Less attention has been directed towards modeling the power of these variables in combination and over time for predicting disability. The limited longitudinal research that is available has examined the strength of mostly cognitive predictors at baseline in determining later functional outcomes (Bennett et al., 2002; Royall, Palmer, Chiodo & Polk, 2004). Information on annual rates of change in functional dependence in MCI, Alzheimer’s disease, and vascular dementia also is limited. Only one study has used advanced statistical methods to estimate the level and annual rate of change in the ability to perform IADLs in persons with MCI and dementia (Tomaszewski Farias et al., 2009). This study assessed a small sample of participants and warrants replication.
CHAPTER II
LITERATURE REVIEW

Overview of Functional Disability in Mild Cognitive Impairment and Dementia

Pattern of Decline

Functional disablement in persons with dementia typically occurs in a progressive pattern whereby IADLs decline first, followed by BADLs; however, individual variability has been seen in both the rate of decline and the order in which activities become compromised (Arrighi, Gelines, McLaughlin, Buchanan & Gauthier, 2013). Performance of complex activities often begins to decline years prior to diagnosis. Indeed, transportation and telephone use, and management of finances and medications have been found to diverge significantly in predementia subjects from normal controls five and six years prior to dementia diagnosis (Amieva et al., 2008). Difficulties in driving also have been reported before detectable cognitive impairment in older adults (Fields et al., 2010). In contrast, deterioration of BADLs typically occurs in the later stages of dementia, when patients become dependent on others for care. After an individual becomes dependent in BADLs, he or she may lose the capacity for speech and posture (Desai, Grossberg, & Sheth, 2004).

Typical Levels of Impairment by Diagnosis

Little normative data exist regarding differences in the extent of functional disability in normal cognitive aging, MCI, and dementia subtypes (Rockwood, 2007). Historically, diagnostic criteria for MCI stipulated that persons must have essentially normal functional abilities; however, cross-sectional research suggests that individuals
with MCI demonstrate more functional impairments than persons with normal aging but fewer impairments than persons with dementia (Albert, Tabert, Dienstag, Pelton, & Devanand, 2002; Aretouli & Brandt, 2010; Brown, Devanand, Liu, & Caccappolo, 2011; Farias et al., 2006; Pereira, Yassuda, Oliviera, & Forlenza, 2008; Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008; Yeh et al., 2011). Based on this research, recent revisions to the MCI diagnostic criteria allow for mild difficulty in IADLs as well as some assistance in performing these activities (Morris, 2012). However, the field continues to lack consensus on how much functional dependence should be exhibited, and in what domains, before a diagnosis of dementia is warranted (Farias et al., 2006; Gold, 2012).

Data regarding differences in functional limitations by dementia subtype also is limited and conflicting. Cross-sectional research has described greater limitations in BADLs in persons with vascular dementia compared to those with Alzheimer’s disease, controlling for medical comorbidities and dementia severity, but no significant differences in IADLs (Gure, Kabeto, Plassman, Piette & Langa, 2010). A review of the literature on functional impairment in vascular dementia describes functional decline of a similar nature, but with a slower trajectory in vascular dementia, than that seen in Alzheimer’s disease (Boyle & Cahn-Weiner, 2004), a conclusion replicated recently by Gill et al. (2004). More longitudinal research is needed to better understand the course of functional decline in vascular dementia and how it compares to changes seen in normal aging, MCI, and Alzheimer’s disease, controlling for other predictors of disability.
Cognitive Impairments and Functional Disability

Overall Association Between Cognitive and Functional Impairments

Functional disability may result from impairments in memory, language, visuospatial abilities, planning, organization, and divided attention (Farias et al., 2006). Based on a comprehensive review of the literature of the relationship between cognition and functional status in older persons with cognitive impairment, Royall and colleagues (2007) found that cognitive variables account for a modest proportion (20%) of variance in functional outcomes. Global cognitive ability has consistently predicted functional outcomes in both cross-sectional and longitudinal research (Bennett et al., 2006; Royall et al., 2004). Tests of general cognition including the Mini Mental State Exam, the Dementia Rating Scale, the Mattis Dementia Rating Scale, and the Short Portable Mental Status Quotient are associated with functional status in dementia patients (Baird, Podell, Lovell, & McGinty, 2001; Royall et al., 2007; Tekin, Fairbanks, O’Connor, Rosenberg, & Cummings, 2001). This evidence is not surprising given that greater functional dependence typically accompanies greater disease severity. Associations between specific cognitive domains and functional disability have been studied and show that memory and executive functions consistently predict everyday functioning in cognitively impaired older adults.

Memory

Memory impairment is the hallmark symptom of dementia and of amnestic MCI, the most prevalent subtype of MCI that is chiefly characterized by memory decline. Episodic memory is memory for information that is personally experienced and is more impaired than memory for general information (i.e., semantic memory) in amnestic MCI.
Several studies demonstrated cross-sectional relationships between episodic memory and functional abilities. For example, in assisted living residents, a 10-point decline on a word-list verbal learning task predicted a 6-point decline on a functional impairment measure (Burdick et al., 2002). Another study of admissions to a geriatric inpatient unit determined that immediate recall performance on a verbal memory test (Logical Memory I, WMS-R; Wechsler, 1987) was significantly correlated with scores on a performance-based measure of ADLs, particularly in the domains of safety ($r = 0.30$), money management ($r = 0.30$), and medication management ($r = 0.44$; Richardson, Nadler, & Malloy, 1995). Verbal memory also has been shown to predict 23% of the variance in an informant-rated measure of everyday functioning in a large multicultural sample of community-dwelling older adults (Farias, Mungas, Reed, Haan, & Jagust, 2004).

Executive Function

Executive abilities also are a consistent predictor of functional disability. Executive function broadly relates to the regulation of multiple cognitive processes including the planning, coordination, and execution of a response, mental flexibility, response inhibition and self-monitoring. Due to its conceptualization as the brain’s central executive, impaired executive function can result in poor coordination of multiple cognitive functions (Cahn-Weiner et al., 2007) and thus impair performance on memory or attention tasks. Conversely, intact executive abilities may mediate the effect of impairment in other specific cognitive domains, such as memory, on functional status (Cahn-Weiner et al., 2007). For instance, the ability to coordinate mental functions, sequence attention, and plan and organize behaviors may allow an individual to
successfully utilize compensatory strategies, such as notes or to-do lists, and thereby reduce the effects of memory impairment on ADLs.

A review of cognitive predictors of functional status determined that tests of executive cognition predict an average of 6.5% of the variance in functional outcome measures (Royall et al., 2007). Problems with executive function have been significantly associated with IADL limitations in community-dwelling older adults with subclinical levels of cognitive impairment (Royall, Chiodo, & Polk, 2000), and baseline executive abilities, as measured by a composite scale, have predicted later change in everyday function in persons with a range of cognitive functioning, from normal cognitive aging to moderate dementia (Cahn-Weiner et al., 2007).

Working memory may be particularly useful in predicting functional disability (Aretouli & Brandt, 2009). Part B of the Trail-Making Test (TMT-B), a commonly used test of working memory and set shifting, has predicted everyday functioning in research with older adults with a range of cognitive impairment. Scores on the TMT-B accounted for 25% of the variance in BADLs and IADLs in a study of assisted living residents (Burdick et al., 2005). A similar relationship was found between TMT-B scores and performance on IADL items from the Disability Assessment in Dementia in persons with amnestic MCI ($r = 0.23$) and specifically with the planning, organization, and performance aspects of these tasks (Yeh et al., 2011). TMT-B scores were highly correlated with scores on the Independent Living Scales, an objective measure of ability to perform IADLs, in a study of community-dwelling elderly with and without dementia ($r = -0.71$; Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002).
Relative Associations of Memory and Executive Function with Functional Disability

Given the consistent associations between episodic memory and executive function and functional disability, recent research has attempted to determine their relative strengths in predicting everyday functioning in persons with cognitive impairment. In a longitudinal study of 106 older adults followed for an average of five and a half years, both memory and executive function were associated with baseline and longitudinal IADLs, such that poorer performance in both domains correlated with more impaired functional status as well as a faster rate of functional decline (Cahn-Weiner et al., 2007). However, when both memory and executive function were included in a model of longitudinal functional change, the relationship between memory and functional decline became non-significant and only executive function predicted functional decline over time (Cahn-Weiner et al., 2007). Likewise, a meta-analysis of studies about cognition and functional outcomes in older adults with cognitive impairment determined that executive function has a stronger association with functional disability than memory, and that the association between memory and functional status is attenuated by executive function and age, such that its independent contribution is basically non-significant (Royall et al., 2007).

Two studies that examined the longitudinal relationships between change in memory and executive function and change in functional abilities provide conflicting results. In one study, change in executive function but not memory was independently associated with IADL performance (Royall, Palmer, Chiodo, & Polk, 2005). In the other, changes in episodic memory and executive functions provided independent and additive
contributions to changes in IADLs (Tomaszewki Farias et al., 2009). Thus, it is presently unclear whether executive function is a stronger predictor of functional disability or whether, controlling for executive function, memory also plays a unique role.

**Neuropsychiatric Symptoms and Functional Disability**

**Prevalence of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Dementia**

As stated earlier, performance on cognitive testing predicts only a modest proportion of the variance in ADLs in persons with cognitive impairment, indicating that other variables also predict function (Fischer, Verhoeff, Churchill, & Schweizer, 2009; Royall et al., 2007). Empirical support has been provided for the contribution of neuropsychiatric, or behavioral, symptoms to functional limitations in MCI and dementia. Neuropsychiatric symptoms, as measured by the total score on the Neuropsychiatric Inventory (NPI), account for 30% of the variance in IADLs, suggesting that they may be as powerful as cognition in predicting functional status in dementia (Tekin et al., 2001).

Neuropsychiatric symptoms are prevalent in dementia and increase with disease severity (Okura et al., 2010). They appear to be equally prevalent among persons with Alzheimer’s disease and vascular dementia (Echávarri et al., 2013). A longitudinal study of persons with dementia reported five-year prevalence rates of 77% for depression, 71% for apathy, and 62% for anxiety, with greatest symptom severity in the apathy domain (Steinberg et al., 2008). Neuropsychiatric symptoms also are common in MCI but estimates of prevalence are widely variable. One longitudinal study documented a prevalence rate of 43% in persons with MCI, with symptoms reaching the level of clinical significance in approximately 29% of cases (Lyketsos et al., 2002). Another
longitudinal study found that as many as 75% of participants with MCI exhibited at least one neuropsychiatric symptom, and 37% endorsed four or more symptoms, with anxiety (39%) and depression (35%) the most common (Edwards, Spira, Barnes, & Yaffe, 2009). While some neuropsychiatric symptoms may be transient, several symptoms, including delusions, depression, apathy, and aberrant motor behavior are likely to persist across time (Steinberg et al., 2008).

**Associations with Functional Disability**

As compared to those with minimal symptoms, persons with MCI who have four or more neuropsychiatric symptoms evidence greater functional limitations and twice the risk for incipient dementia (Edwards et al., 2009). Similarly, the emergence of behavioral symptoms in individuals with Alzheimer’s disease has been associated with increasing functional limitations (Trachtenberg, Weiner, Patterson, Gamst, & Thal, 2002). The presence of three or more neuropsychiatric symptoms, and one clinically significant symptom, is associated with higher odds of functional disability in dementia patients (Okura et al., 2010). While several studies have analyzed the contribution of non-cognitive symptoms as a whole or as symptom clusters to functional outcomes, there is less research on the independent contributions of specific symptoms. An understanding of which neuropsychiatric symptoms are most strongly associated with functional disability may encourage health care providers and loved ones to vigilantly monitor for their presence and aggressively treat these symptoms to reduce their potentially modifiable effects on function. As reviewed below, among neuropsychiatric symptoms, apathy and depression are the most consistent cross-sectional predictors of functional disability in older adults with cognitive impairment.
Depressive Symptoms

Depressive symptoms are common in MCI and depressive symptoms are experienced by approximately 75% of persons with dementia (Edwards et al., 2009; Steffens & Potter, 2008). The nature of the relationship between depressive symptoms and functional disability remains unclear. It has been suggested that depressive symptoms are associated with increased disability due to distress resulting from awareness of one’s functional limitations or due to its associations with reduced motivation (Fitz & Teri, 1994). Alternatively, late life depression and dementia may be driven by the same underlying pathology. The pervasiveness of depressive symptoms in persons with cognitive impairment has led researchers to hypothesize that depression may be a risk factor for dementia, a prodromal stage before impairment, or a part of the same pathophysiological process (Barnes et al. 2012; Lyketsos, 2010).

Depression has independent effects on cognition, such that depressed older adults perform consistently worse than non-depressed peers on neuropsychological tests, most notably measures of processing speed, acquisition and retrieval of new information, and executive functions (Steffens & Potter, 2008). In this way, depressive symptoms can exacerbate existing functional impairments in persons with cognitive impairment (Hinton, Farias, & Wegelin, 2008). Depressive symptomatology also can provide unique contributions to functional disability in dementia. In a sample of persons with Alzheimer’s disease, with and without depression, the presence and severity of depressive symptoms predicted IADL performance, controlling for cognitive function. Not surprisingly, daily functioning was most compromised in participants with severe depression (Fitz & Teri, 1994). Similarly, a population-based study of older Italians with
very early dementia revealed that depressive symptoms tripled the risk for disability in IADLs compared to the diagnosis of early dementia alone (DeRonchi et al., 2005).

**Apathy**

Like depression, apathy is associated with functional disability. Apathy is characterized by loss of interest, social withdrawal, and generally decreased motivation, initiation, and persistence in the absence of low mood or depressive thought patterns (Fones, 1998; Ishii, Weintraub, & Mervis, 2009). In persons with cognitive impairment, apathy may be more common than depression, which is characterized by guilt, sad mood, hopelessness and poor self-concept (Landes, Sperry, & Strauss, 2005). Estimated prevalence rates for apathy in persons with MCI range from 3-60% (Ellison, Harper, Berlow, & Zeranski, 2008). It has been estimated to affect 55% of persons with AD and 70% of persons with mixed AD/vascular dementia in clinical practice (Mulin et al., 2011). Informant-rated apathy symptoms have been significantly associated with impairment in both BADLs and IADLs in dementia clinic outpatients (Clarke et al., 2008). In a study of persons with vascular dementia, apathy symptoms accounted for 36% of the variance in total ADL impairment (both BADLs and IADLs), controlling for dementia severity (Zawacki et al., 2002).

Due to the recognition that depression and apathy are not the same construct, there is a need to distinguish their independent contributions to daily functioning. Thus far, only a few cross-sectional studies addressed this question. In persons with probable or possible Alzheimer’s disease, apathy was found to be more common (59.5 %) than dysphoria (8.4%) and more strongly related to functional disability ($r = 0.57$) than dysphoria ($r = 0.21$) (Landes et al., 2005). Another study of 195 community-dwelling
Chinese elderly with questionable dementia (comprising MCI and very mild dementia) and 95 persons with Alzheimer’s disease found that apathy and depressive symptoms were differentially associated with functional abilities in the two groups. Apathy, depression, or the combination predicted poorer functional performance in participants with questionable dementia. Among participants with Alzheimer’s disease, apathy alone predicted poorer functional performance. Specifically, in persons with Alzheimer’s disease, apathy was associated with impairments in planning, initiating and executing IADLs, while depression only was associated with impaired initiation and planning (Lam, Tam, Chiu, & Lui, 2006). Similarly, apathy and not depression has been associated with greater functional disability in persons with amnestic MCI (Zahodne & Tremont, 2013). Additional research is needed to replicate these findings and determine whether depression and apathy independently predict functional loss.

Medical Burden and Functional Disability

Poor physical health is another established predictor of functional limitations in aging. Longitudinal investigations have found that cardiovascular risk factors, including hypertension, Type II diabetes, and obesity are associated with greater functional limitations in late life (Newman et al., 2009). Lower levels of disease burden are associated with recovery from functional limitations (Knoefel & Patrick, 2003; Miller et al., 2004). These conclusions largely have been reached through community-based studies, and information regarding the relationship between medical disease burden and functional abilities in persons with cognitive impairment is limited. One cross-sectional study of 143 clinic outpatients with probable or possible Alzheimer’s disease found no relationship between overall medical burden and IADL impairment (Tekin et al., 2001)
while another study using a larger sample (n= 999) of clinic outpatients and residents of assisted living facilities and nursing homes found significant associations between scores on a general rating of medical comorbidity and functional impairment (Lyketsos et al., 1999). In another study of 198 residents of assisted living facilities, the difference between excellent and fair health ratings had a comparable association with increased functional disability as a 7-point, or 23% drop in score on the Mini Mental State Exam, a commonly-used brief assessment of global cognitive impairment (Burdick et al., 2005). Clearly, more research is needed to clarify these discrepant findings and determine the relationship between medical illness burden and functional disability in persons with cognitive impairment. In addition, the relative strength of the relationship between medical burden compared to cognitive and neuropsychiatric predictors of disability remains an important question.

The Current Study

The proposed study expands our understanding of predictors of functional disability by examining longitudinal associations between cognitive, neuropsychiatric, and medical factors and functional disability in a large outpatient sample of persons aged 60+ with MCI, Alzheimer’s disease, and vascular dementia from the Massachusetts Alzheimer’s Disease Research Center’s Longitudinal Study on Memory and Aging. Specifically, the current study determined the longitudinal relationships between episodic memory, executive function, apathy, depression, and medical burden and IADLs. In addition, the current study provides precise estimation of average annual rates of functional change for persons with a given baseline diagnosis (MCI, Alzheimer’s disease, or vascular dementia) in comparison to older adult controls.
This study adds to the literature in several ways. First, it replicates and attempts to resolve contradictions posed by the few prior investigations of the longitudinal relationship between cognitive impairment and functional impairment in persons with MCI and dementia. Second, it extends these findings by considering other established cross-sectional predictors of functional disability in persons with cognitive impairment: the neuropsychiatric symptoms of depression and apathy, and general medical burden. In so doing, this study adds to our understanding of what factors contribute to functional disability in persons with cognitive impairment. Third, the current study measures the average level of functional impairment in MCI, Alzheimer’s disease, and vascular dementia, as well as the average annual rate of change in persons with these diagnoses. This information can help patients, caregivers, and health care providers plan future care needs.

Specific Aims

Aim 1

Determine the longitudinal associations between episodic memory, executive function, depression, apathy, and medical disease burden and IADLs in a sample of persons with baseline diagnoses of Mild Cognitive Impairment, mild to moderate Alzheimer’s disease, and vascular dementia.

Hypotheses

Episodic memory and executive function will predict everyday function such that greater impairments in memory and executive function will be associated with greater dependence in IADLs (Royall et al., 2005; Tomaszewski Farias, 2009). In addition to memory and executive function, longitudinal changes in depression, apathy, and medical
burden will be associated with longitudinal changes in function (Burdick et al., 2005; Clarke et al., 2008; De Ronchi et al., 2005; Fitz & Teri, 1994; Lyketsos et al., 1999; Zawacki et al., 2002). Increased depression, apathy, and medical burden will predict greater dependence in IADLs.

Aim 2

Determine the average level of dependence in IADLs in persons diagnosed at baseline with MCI, mild to moderate Alzheimer’s disease and vascular dementia, as compared to persons with normal cognitive aging.

Hypothesis

Persons with MCI will exhibit intermediate levels of IADL dependence, compared to persons with normal cognitive aging and persons with dementia, who will have the greatest levels of IADL dependence (Albert et al., 2002; Aretouli & Brandt, 2010; Brown, Devanand, Liu, & Caccappolo, 2011; Farias et al., 2006; Pereira, Yassuda, Oliveira, & Forlenza, 2008; Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008). Participants with Alzheimer’s disease and vascular dementia will exhibit comparable levels of IADL dependence (Boyle & Cahn-Weiner, 2004; Gure et al., 2010).

Aim 3

Determine how initial diagnostic status of MCI, Alzheimer’s disease, or vascular dementia relates to average annual rate of change in the ability to independently perform IADLs, in comparison to normal controls.

Hypotheses

Individuals with MCI will evidence slower rates of change in their ability to independently perform IADLs than persons with dementia but steeper declines than
CHAPTER III

METHOD

Participants

Data from 643 participants of the Massachusetts Alzheimer’s Disease Research Center’s (MADRC’s) "Longitudinal Cohort on Memory & Aging” project were used in this study. Participants were recruited in several ways. Approximately 10% of the cohort was recruited by the MADRC’s Education and Information Transfer Core, through a variety of outreach initiatives that include advertisements in minority-targeted newspapers and presentations at minority-focused events. Other participants were referred from affiliated clinics of the Massachusetts General Hospital (MGH): 18% from the MGH Memory Disorders Unit; 10% from the MGH Movement Disorders Unit; and approximately 1% from Brigham & Women's Hospital. Nine percent are spouses or other caregivers of patients with dementia, and approximately 18% were recruited from the MGH Department of Psychiatry's Gerontology Research Unit. Other sources of recruitment and enrollment include enrollees in the Nurses' Health study (approximately 4%) and individuals who participate in the MADRC's clinical trials or other studies.

Number of study visits ranged from 1-6 ($M = 2.4, SD = 1.3$). Approximately 35.8% had 1 visit, 25.8% had 2 visits, 20.2% had 3 visits, 12.8% had 4 visits, 4.2% had 5 visits, and 1.1% had 6 visits.

Of the total sample used for this study, at baseline, 271 persons exhibited normal cognitive aging (42%), 153 were diagnosed with MCI (24%), 188 were classified as having probable or possible Alzheimer’s disease cases (29%) and 31 were diagnosed with vascular dementia (4.8%). Mean baseline global CDR was significantly lower in persons
with normal cognitive aging than in persons with MCI, Alzheimer’s disease, and vascular dementia. Baseline global CDR scores in these latter groups did not significantly differ from each other (Table 2). Those classified as normal cognitive aging at baseline were significantly younger than persons diagnosed with MCI, Alzheimer’s disease, and vascular dementia (Table 2). There was a significant difference in the gender distribution of diagnostic groups: \( \chi^2 (3) = 24.47, p < 0.001 \). Thirty percent of persons with normal cognitive aging at baseline were male, compared to 45% of the MCI, 48% of the Alzheimer’s disease, and 68% of the vascular dementia groups. Participants had on average a college education and there was no significant difference in educational attainment between diagnostic groups. Across all diagnostic groups, participants were predominantly Caucasian, married or partnered, and living at home with a spouse/partner (Table 1).

Table 1

Descriptive Statistics for Participant Demographics at Baseline by Diagnostic Group

<table>
<thead>
<tr>
<th>Race</th>
<th>NCA (n = 271)</th>
<th>MCI (n = 153)</th>
<th>AD (n = 188)</th>
<th>VaD (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (%)</td>
<td>240 (89)</td>
<td>136 (89)</td>
<td>178 (95)</td>
<td>26 (84)</td>
</tr>
<tr>
<td>African American (%)</td>
<td>29 (11)</td>
<td>11 (7)</td>
<td>9 (5)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>2 (&lt;1)</td>
<td>6 (4)</td>
<td>1 (&lt;1)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hispanic* (%)</td>
<td>2 (&lt;1)</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Living Situation</th>
<th>NCA (n = 271)</th>
<th>MCI (n = 153)</th>
<th>AD (n = 188)</th>
<th>VaD (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lives alone (%)</td>
<td>71 (26)</td>
<td>44 (29)</td>
<td>34 (18)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>With spouse/partner (%)</td>
<td>179 (66)</td>
<td>96 (63)</td>
<td>139 (74)</td>
<td>23 (74)</td>
</tr>
<tr>
<td>With relative/friend (%)</td>
<td>16 (6)</td>
<td>9 (6)</td>
<td>11 (6)</td>
<td>—</td>
</tr>
<tr>
<td>With group (%)</td>
<td>1 (&lt;1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other/unknown (%)</td>
<td>4 (1.5)</td>
<td>4 (3)</td>
<td>4 (2)</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>NCA (n = 271)</th>
<th>MCI (n = 153)</th>
<th>AD (n = 188)</th>
<th>VaD (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married (%)</td>
<td>180 (66)</td>
<td>97 (63)</td>
<td>139 (74)</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Widowed (%)</td>
<td>35 (13)</td>
<td>36 (24)</td>
<td>27 (14)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Separated/divorced (%)</td>
<td>27 (10)</td>
<td>12 (8)</td>
<td>10 (5)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Never married (%)</td>
<td>20 (7)</td>
<td>4 (3)</td>
<td>10 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Living as married (%)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Other/unknown (%)</td>
<td>8 (3)</td>
<td>3 (2)</td>
<td>—</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

* Hispanic ethnicity coded in addition to race.
Table 2

Descriptive Statistics for Model Variables at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>NCA (n = 271)</th>
<th>MCI (n = 153)</th>
<th>AD (n = 188)</th>
<th>VaD (n = 31)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR global&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.28 (0.42)</td>
<td>0.46 (0.58)</td>
<td>0.48 (0.54)</td>
<td>0.48 (0.56)</td>
<td>7.59 (3, 639)**</td>
</tr>
<tr>
<td>FAQ&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.01 (0.09)</td>
<td>0.30 (0.43)</td>
<td>0.98 (0.95)</td>
<td>0.66 (0.84)</td>
<td>104.52 (3,639)**</td>
</tr>
<tr>
<td>Number medications&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.87 (3.45)</td>
<td>6.09 (4.11)</td>
<td>6.14 (3.27)</td>
<td>7.06 (4.56)</td>
<td>7.63 (3, 639)*</td>
</tr>
<tr>
<td>Trail-Making Test B&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
<td>82.26 (64.81)</td>
<td>148.28 (121.30)</td>
<td>233.21 (264.83)</td>
<td>148.35 (176.84)</td>
<td>30.95 (3,639)**</td>
</tr>
<tr>
<td>WMS-R Logical Memory II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.41 (3.38)</td>
<td>8.22 (4.33)</td>
<td>6.16 (6.14)</td>
<td>10.58 (5.94)</td>
<td>97.29 (3,639)**</td>
</tr>
<tr>
<td>NPI-Q Depression&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.12 (0.37)</td>
<td>0.34 (0.65)</td>
<td>0.27 (0.56)</td>
<td>0.37 (0.62)</td>
<td>7.50 (3, 639)**</td>
</tr>
<tr>
<td>NPI-Q Apathy&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.03 (0.17)</td>
<td>0.14 (0.44)</td>
<td>0.39 (0.69)</td>
<td>0.23 (0.50)</td>
<td>23.34 (3,639)*</td>
</tr>
<tr>
<td>GDS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.94 (1.61)</td>
<td>1.97 (2.03)</td>
<td>1.78 (1.92)</td>
<td>2.07 (1.60)</td>
<td>14.60 (3,639)**</td>
</tr>
<tr>
<td>Age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72.73 (7.00)</td>
<td>77.49 (6.64)</td>
<td>77.63 (6.92)</td>
<td>77.45 (8.48)</td>
<td>25.08 (3,639)*</td>
</tr>
<tr>
<td>Education</td>
<td>16.31 (2.45)</td>
<td>15.73 (2.95)</td>
<td>15.96 (3.31)</td>
<td>16.29 (2.94)</td>
<td>1.5 (3,639)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>30</td>
<td>45</td>
<td>48</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> In posthoc tukey pairwise comparisons, NCA mean was significantly different from all other means (p < 0.001).
<sup>b</sup> In posthoc tukey pairwise comparisons, MCI mean was significantly different from AD mean (p < 0.001).
<sup>c</sup> In posthoc tukey pairwise comparisons, AD mean was significantly different from VaD mean (p = 0.01).
<sup>d</sup> In posthoc tukey pairwise comparisons, AD mean was significantly different from VaD mean (p = 0.01).

*p < .001. **p < .0001.
Measures

Functional Assessment

Functional disability was measured by the Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982; Appendix A). The FAQ is a 10-item questionnaire that assesses a patient’s independence in IADLs including paying bills, preparing a balanced meal, remembering appointments, etc. Questions can be scored from 0-3, with 0 = normal or intact abilities; 1= some difficulty but independent; 2 = requires assistance, and 3 = dependent. Higher scores indicate greater disability. The rater also can record which activities the patient never performed. To adjust for items that the participant never performed, the mean FAQ item score for each participant was used in the current study to represent IADL disability, rather than the sum of scores for all items. Thus, while total scores on the FAQ can range from 0-30, the possible range for the outcome variable in the current study is 0-3 (the score range for an individual item). The FAQ is clinician-rated based on informant report and has demonstrated high inter-rater reliability ($r = 0.80 - 0.97$; Pfeffer et al., 1982). The assessment has demonstrated adequate sensitivity (0.85) and specificity (0.81) in distinguishing cognitively normal and impaired older adults (Pfeffer et al., 1982). Previous analysis of data from the National Alzheimer’s Coordinating Centers (NACC) found that the FAQ distinguishes between persons with MCI and very mild Alzheimer’s disease with 80.3% sensitivity, 87% specificity, and 84.7% accuracy (Teng, Becker, Woo, Knopman, Cummings, & Lu, 2010). Cronbach’s alpha for the 10 FAQ items in the current study sample was 0.90, indicating excellent internal consistency.
Episodic Memory

Episodic memory was measured by the Logical Memory II test (Story A) from the Wechsler Memory Scale- Revised (WMS-R; Wechsler, 1987; Appendix D). The Logical Memory II test from the WMS-R (Wechsler, 1987) measures episodic memory via delayed recall of a short story that is read to the examinee. This test is routinely given to all MADRC study participants at each study visit. The delayed recall score of Logical Memory was chosen because it is considered a reliable measure of episodic memory that is highly convergent with other verbal learning tests (Lezak, Howieson, & Loring, 2004). Internal consistency reliability for WMS-R Logical Memory II has been estimated at \( r = 0.75 \), inter-rater reliability was estimated to be high \( (r = 0.97) \), and test-retest reliability for persons aged 65-74 was estimated to range from \( r = 0.78 - 0.85 \) (Wechsler, 1987). The WMS-R Logical Memory test demonstrated sensitivity in discriminating persons with neurological deficits from those without, including persons with dementia (Wechsler, 1987).

Executive Function

Executive function was represented by performance times on part B of the Trail-Making Test (TMT; Reitan & Wolfson, 1993; Appendix E). Part A (TMT-A) requires the examinee to rapidly connect numbers 1-25 in order and is a test of visual scanning and mental processing speed motor and visual processing speed. Part B (TMT-B) represents added complexity in that it is comprised of numbers and letters and requires the examinee to connect the numbers and letters in order from lowest number, to first letter, to the next number and the next letter (1-A-2-B-3-C) and so on. As such, part B is a test of sequencing, set-shifting, and mental flexibility (Arbuthnott & Frank, 2000; Reitan &
Wolfson, 1993). A review of the available literature suggests that the TMT has adequate test-retest reliability and high inter-rater reliability; TMT-B has demonstrated construct validity through convergence with several executive functions including executive control, cognitive flexibility, and set switching (Strauss, Sherman, & Spreen, 2006). Performance on the TMT-B has demonstrated ecological validity in predicting IADL performance in older adults and is sensitive to neurological deficits including dementia (Cahn-Weiner, Boyle, & Malloy, 2002; Bell- McGinty et al., 2002; Strauss, Sherman, & Spreen, 2006).

Neuropsychiatric Symptoms

Depression and apathy were measured by the NPI-Q (Kaufer et al., 2000; Appendix B), a brief questionnaire form of the Neuropsychiatric Inventory (NPI). The NPI-Q has high convergent validity ($r = 0.91$) with the NPI (Kaufer et al., 2000). The NPI-Q is designed to be self-administered to an informant, who is asked about the presence over the past four weeks of each of twelve neuropsychiatric symptoms: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime disturbances, and appetite/eating changes. If the informant endorses a symptom, he/she then rates whether the symptom is mild (1 point), moderate (2 points), or severe (3 points). NPI-Q item score can thus range from 0-3, and total score can range from 0-36, with higher numbers indicating greater presence of neuropsychiatric symptoms. Test-retest reliability for the NPI-Q symptom is adequate ($r = .80$; Kaufer et al., 2000). In order to examine the specific associations between depression and apathy
and functional disability, NPI-Q total score was not used in this study. Instead, scores on the apathy and depression items from the NPI-Q were extracted for analyses.

Self-reported depressive symptoms, as measured by the Geriatric Depression Scale (15-item version; Sheikh & Yesavage, 1986; Appendix C) also were included to determine whether informant-reported and self-reported depressive symptoms are differentially associated with functional disability. The GDS-15 is a 15-item measure intended for older adults that assesses self-reported depressive symptoms and is routinely administered to all MADRC participants as part of the UDS. Questions assess the presence of symptoms in the past week, and are answered in a dichotomous yes/no format. One point is given for each depressive symptom endorsed, for a total score range of 0-15. Analysis of the psychometric properties of the GDS-15 suggest that it has moderate internal consistency reliability, adequate criterion validity between depressed and non-depressed older persons, and acceptable construct validity with other indicators of depression including depressed mood, life satisfaction and suicidal ideation (Friedman, Heisel, & Delavan, 2005). Internal consistency and construct validity were similar for community-dwelling elders with high and low functional dependence (Friedman, Heisel, & Delavan, 2005). Cronbach’s alpha for the GDS-15 in this study sample was 0.73, indicating acceptable internal consistency.

Medical Burden

Medical burden was represented by the sum of prescription medications used at each visit. Over-the-counter medicines and vitamins/supplements were not included in the count. Simple medication counts reliably predict health care cost and utilization,
hospitalizations, and mortality in older adult outpatients, and compare favorably to other, more complex assessments of medical comorbidity (Perkins et al., 2004).

Procedure

Approval from the Partners Healthcare Institutional Review Board (IRB) was granted before analysis of de-identified patient data from the Massachusetts Alzheimer’s Disease Research Center (MADRC).

MADRC Data Collection

A Uniform Data Set (UDS), as required by the NIH/NIA for all federally funded Alzheimer's Disease Centers (ADCs), is collected from each participant, and data are stored locally in the ADRC database, as well as routinely submitted electronically to the National Alzheimer’s Coordinating Center (NACC) (www.alz.washington.edu) data repository. The UDS was first collected by all ADCs on September 1, 2005. Subjects are seen approximately every 12 months. The initial visit must be an in-person visit, but follow-up visits may be in-person (preferred) or via the telephone. Cognitive testing is not administered during telephone follow-up visits. Participants are strongly encouraged to bring an informant to the study visit. Each study visit may last from 1.5 to 2 or more hours. During each visit, both participants and informants are assessed/interviewed by the study doctor, and during in-person visits, the participant is also administered a series of neuropsychological tests by a trained research assistant. Some of the UDS forms are completed by the study doctor but other UDS forms are completed by the research assistant. During the initial study visit, the following data are collected: participant sex, age (derived from month & year of birth); race; education; living situation; marital status, health history and current medications. If an informant is present, he or she is asked about
his/her relationship to the participant. If the informant does not live with the participant, the frequency of the informant's visits/telephone calls to the participant is assessed. This data is updated at each visit as necessary/appropriate.

Participants receive a brief physical exam at each study visit, are rated on the Unified Parkinson’s Disease Rating Scale - Motor Exam, and are assigned a value on the Hachinski Ischemic Score scale, a measure of vascular disease risk. In addition, the following information is collected at each visit: participant score on the Clinical Dementia Rating Scale (CDR); score on the Geriatric Depression Scale (GDS), informant-reported score on the Neuropsychiatric Inventory Questionnaire (NPI-Q); and score on the Functional Activities Questionnaire (FAQ). In addition, the following cognitive tests are administered as part of the UDS: Mini Mental State Exam (MMSE); Logical Memory I & II, Story A from the Wechsler Memory Scales, Revised Edition (WMS-R, 1987); Digit Span Forward and Backward; Trail-Making Test A and B; Digit-Symbol Coding from the Wechsler Adult Intelligence Scale, Revised edition (WAIS-R); Category Fluency (Animals); and 30 odd-numbered items from the Boston Naming Test (BNT). Based on the clinical interview, the study doctor assigns a diagnosis to each participant at each visit. Diagnoses related to Alzheimer’s disease are made according to criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). Diagnoses of vascular dementia are arrived at according to criteria established by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN; Roman et al., 1993).
Analyses

Construction of Hierarchical Linear Models

Trajectories of longitudinal change were estimated using Hierarchical Linear Modeling (HLM; Bryk & Raudenbush, 1987), a multi-level modeling technique that predicts change over time within individuals as well as the variability in individual trajectories over time. Longitudinal analysis in HLM is conceptualized as a two-level model, wherein each participant’s development is modeled as an individual growth trajectory plus random error at level 1 (within person change over time) and level 2 represents a between–person model that represents inter-individual differences in change. Dependence in IADLs over time, as measured by mean FAQ item score, was the primary outcome variable. Memory, executive function, depression, apathy, and medical burden were treated as time-varying covariates and entered at level 1. Baseline diagnosis of normal cognitive aging, MCI, Alzheimer’s disease or vascular dementia was considered a time-invariant covariate at level 2. Because they are known to be associated with functional impairment, age (Benke et al., 2013; Millán- Calenti, 2010), gender (Benke et al., 2013; Maddox & Clark, 1992; Millán- Calenti, 2010), and level of education (Maddox & Clark, 1992), were included as time-invariant controls and also entered at level 2.

Model building began with an unconditional growth model to determine if there was significant change in functional disability in IADLs over time, whether change in IADLs was linear or curvilinear, and whether there was significant variability in that change across individuals. This model served as a baseline model against which subsequent models were compared. Level 1 of the model represents an individual’s (j’s)
repeated measures of mean FAQ item score (y) across study visits (VISITNUM; from 1 to i). The intercept $\beta_{0j}$ represents person j’s expected value of y at study entry or baseline, and slope $\beta_{1j}$ represents the expected linear rate of change in person j’s mean FAQ item score as a function of time. Level 2 of the model estimates the average growth trajectory across individuals, and indicates whether there is individual variation in trajectory intercepts ($\beta_{0j}$) and slopes ($\beta_{1j}$) where $\gamma$ represents the average intercept ($\gamma_{00}$) and slope ($\gamma_{10}$) and $\mu$ represents the individual j’s deviations from the average intercept ($\mu_{0j}$) and average slope ($\mu_{1j}$).

Unconditional Model

Level 1

$$FAQ_{ij} = \beta_{0j} + \beta_{1j} \times VISITNUM_{ij} + r_{ij}$$

Level 2

$$\beta_{0j} = \gamma_{00} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

Model Conditioned on Cognitive, Neuropsychiatric, and Medical Predictors

Next, five models were built, one each to include five other level 1 predictors that were expected to themselves change across time and explain variation in mean FAQ item scores over time. These predictors (i.e., episodic memory, executive function, depression, apathy, and medical burden) were treated as time-varying covariates. Each predictor was grand-mean centered and entered individually into the unconditional level 1 model to determine its relationship with mean FAQ item score over time. After these five separate models were run, one for each time-varying covariate, variables that showed a significant relationship with mean FAQ item score over time were included together at level one in a
final, conditional level 1 model. The conditional level 1 model allowed for random
effects to capture between-person variability in mean FAQ item score and apathy and
depressive symptom scores. It did not allow for random effects in memory and executive
function scores because univariate testing did not provide evidence for significant
variability across groups in the longitudinal relationships between these variables and
mean FAQ item score. This conditional level 1 model also served as the basis for
checking the HLM assumptions of homoscedasticity, linearity, independence, and
normality.

**Model Conditioned on Baseline Diagnostic Status**

A third model was built to determine the average level of functional disability by
initial diagnostic status (normal cognitive aging, MCI, Alzheimer’s disease, and vascular
dementia; diagnosis was treated as a time-invariant predictor at level 2), as well as the
average annual rate of change in mean FAQ item score for each group. Models allowed
for random effects to capture between-person variability in baseline and longitudinal
mean FAQ item scores. Persons with MCI, Alzheimer’s disease, and vascular dementia
were compared to the reference group of persons with normal cognitive aging.
Hypothesis tests were then performed to separately compare persons with MCI,
Alzheimer’s disease, and vascular dementia to each other, e.g., MCI to vascular
dementia, vascular dementia to Alzheimer’s disease, etc. Additional time-invariant
predictors including age, gender, and level of education were entered at level 2, one at a
time into this model to determine whether they should be included as control variables; a
variable that did not explain significant variability in mean FAQ item score was omitted
from the final model.
CHAPTER IV

RESULTS

Descriptive Statistics

Descriptive analyses revealed significant differences in diagnostic groups on baseline measures (Table 2). Persons with normal cognitive aging took fewer prescription medications than persons with MCI. Performance on Part B of the Trail-Making test was significantly faster in persons with normal cognitive aging compared to those with MCI, indicating that they were less taxed by this complex task. Persons with Alzheimer’s disease performed significantly slower on Part B of the Trail-Making test than all other groups. Persons with normal cognitive aging performed significantly better on the memory test than persons with MCI, who themselves performed better than persons with Alzheimer’s disease. Persons with vascular dementia also performed better on the memory test than persons with Alzheimer’s disease.

Similar patterns were seen in baseline measures of neuropsychiatric symptoms. Persons with normal cognitive aging evidenced significantly fewer depressive symptoms than persons with MCI on the NPI-Q and the GDS. They also exhibited significantly less apathy than persons with MCI, who as a group exhibited significantly less apathy at baseline than persons with Alzheimer’s disease. Both informant and self-reported neuropsychiatric symptoms were minimal across all diagnostic groups.

Most of the study variables at the baseline visit were significantly inter-correlated (Table 3). Higher mean FAQ item scores were associated with poorer performance on cognitive tests and higher ratings for depressive symptoms and apathy. Contrary to prediction, number of prescription medications, an indicator of medical burden, only
shared significant correlations with scores with depressive symptoms (both GDS and NPI-Q) and executive functions, not with daily functioning. A small but significant correlation was found between mean baseline FAQ item score and age ($r = 0.22, p = 0.01$).

Table 3

Correlation Matrix for Model Variables

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FAQ</td>
<td>—</td>
<td>.57**</td>
<td>−.63**</td>
<td>−.63**</td>
<td>.52**</td>
<td>.11*</td>
<td>.09</td>
</tr>
<tr>
<td>2. Trail Making Test B</td>
<td>—</td>
<td>−.44**</td>
<td>.11**</td>
<td>.25**</td>
<td>.10*</td>
<td>.29**</td>
<td></td>
</tr>
<tr>
<td>3. WMS-R Logical Memory II</td>
<td>—</td>
<td>−.14**</td>
<td>−.37**</td>
<td>−.02</td>
<td>−.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. NPI-Q Depression</td>
<td>—</td>
<td>.34**</td>
<td>.09**</td>
<td>.21*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. NPI-Q Depression</td>
<td>—</td>
<td>.14**</td>
<td>.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Number Medications</td>
<td>—</td>
<td>.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. GDS</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**$p < .01$. *$p < .05$.**

Results of Hierarchical Linear Models

Longitudinal Change in Functional Disability

Results of the unconditional model, which included all diagnostic groups and no predictors other than time, yielded a significant linear effect of time, indicating that on average, participants’ mean FAQ item scores increased by 0.06 from one year to the next, $p < 0.001$ (Table 4). That is, overall functional abilities significantly declined over time. This model also revealed significant individual variability in the linear rate of change in functional disability, $\chi^2(422) = 978.49, p < 0.001$, which suggests that some participants declined faster than others. Indeed, some persons may have experienced no change in their level of functional dependence and some may have become less dependent over time (see Figure 1 for an illustration of the mean trajectories of change for each
diagnostic group). This individual variability provides support for further examination of predictors of variation in trajectories of functional disability.

Table 4

Model of Change in Functional Disability (Unconditional model)

<table>
<thead>
<tr>
<th>Fixed effect</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean initial status</td>
<td>0.03</td>
<td>0.02</td>
<td>11.22</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean growth rate</td>
<td>0.06</td>
<td>0.01</td>
<td>5.65</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effect</th>
<th>SD</th>
<th>Variance component</th>
<th>df</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial status</td>
<td>0.55</td>
<td>0.30</td>
<td>422</td>
<td>993.83</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Growth rate</td>
<td>0.16</td>
<td>0.03</td>
<td>422</td>
<td>978.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Level-1, e</td>
<td>0.25</td>
<td>0.06</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Figure 1. Mean longitudinal trajectories in mean FAQ item score by baseline diagnosis.

Variation by Cognitive Function, Neuropsychiatric Symptoms, and Medical Burden

Episodic memory, executive function, and depressive and apathy symptom scales from the NPI-Q significantly improved the fit of the unconditional model and
significantly predicted functional disability over time\(^1\) (Table 5). Inclusion of the number of prescription medications taken by participants did not improve the model fit and therefore was not included in the final conditional level 1 model. Self-reported depression symptomatology, as measured by the GDS, was not included for the same reasons. When these four variables were included together in the final conditional level 1 model, depressive symptoms (as measured by the NPI) no longer significantly predicted functional disability over time.

Table 5

Conditional Model of Change in Functional Disability

<table>
<thead>
<tr>
<th>Fixed effect</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean initial status</td>
<td>0.31</td>
<td>0.22</td>
<td>13.72</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean growth rate</td>
<td>0.033</td>
<td>&lt;0.01</td>
<td>3.70</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Memory slope</td>
<td>−0.04</td>
<td>&lt;0.01</td>
<td>−15.47</td>
<td>1518</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Executive function slope</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>13.40</td>
<td>1518</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apathy slope*</td>
<td>0.31</td>
<td>0.04</td>
<td>7.63</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effect</th>
<th>SD</th>
<th>Variance component</th>
<th>df</th>
<th>$\chi^2$</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Initial status</td>
<td>0.37</td>
<td>0.13</td>
<td>11</td>
<td>28.37</td>
<td>&lt;.010</td>
</tr>
<tr>
<td>Growth rate</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>11</td>
<td>49.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apathy slope</td>
<td>0.32</td>
<td>0.10</td>
<td>11</td>
<td>32.94</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Level-1</td>
<td>0.28</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. This model did not allow for random effects for memory or executive function.

Results from the final conditional level 1 model indicate that, controlling for executive function and apathy symptoms, there was a 0.04 increase in mean FAQ item score for every one-unit decrease in memory test performance. This suggests that episodic memory performance is inversely related to functional disability; for the average

\(^1\) When the ratio of performance times on Trails A divided by Trails B was used to represent executive function, the ratio did not significantly predict functional disability.
participant, worse memory performance predicts greater functional disability. There was a significant positive relationship between executive function and functional disability, such that mean FAQ item score increased by less than 0.001 for every one second increase in completion time on part B of the Trail-Making test, controlling for memory test scores and apathy symptoms. There also was a significant positive relationship between apathy symptoms and functional disability; controlling for memory and executive function, mean FAQ item score increased by 0.31 for every one unit increase on the apathy scale of the NPI-Q. Thus, greater apathy and executive dysfunction were associated with greater functional impairment.

Univariate models indicated that there was no significant individual variation in the slopes of the associations between longitudinal episodic memory and executive function performance and functional disability, indicating that the association between these variables and functional disability is similar for all participants. Estimation of variance components from the final conditional level 1 model reveals significant variability in the slope of the relationship between longitudinal apathy symptoms and functional disability. Therefore, controlling for memory and executive function, the relationship between apathy symptoms and everyday functioning is different across participants.

Examination of Baseline Age, Gender, and Level of Education

Participant age at study entry, gender, and level of education were added to the model at level 2 to see whether they were associated with participants’ baseline and longitudinal levels of functional disability. Gender was entered as an un-centered variable and age and education were grand mean centered. Education did not significantly predict
disability or improve the model fit and was excluded from the model. Baseline age and gender emerged as significant predictors of disability, improved the model fit, and were retained in the final model. However, in the conditional model that included age, gender, and baseline diagnostic groups, gender no longer significantly predicted mean FAQ item score at baseline; $t(635) = 1.28, p = 0.20$. Gender also no longer predicted longitudinal rate of change in functional disability; $t(635) = -0.54, p = 0.59$. Age continued to predict both mean FAQ item score at baseline [$t(635) = 2.73, p < 0.01$] and longitudinal trajectories of functional decline [$t(635) = -2.39, p = 0.02$].

Baseline Levels of Functional Disability by Diagnostic Status

Baseline mean FAQ item score for the entire sample ranged from 0-3, with a mean of 0.40 ($SD = 0.73$). Mean FAQ item score at baseline was significantly different between diagnostic groups: $F(3,639) = 104.502, p < 0.0001$ (Table 2).

Functional disability at the baseline study visit was estimated for each diagnostic group using the intercept for each group from the level 2 model (Table 6). The values for persons with MCI, Alzheimer’s disease and vascular dementia represent the difference in their baseline scores from the intercept for persons with normal cognitive aging, who were selected as the reference group. Participant gender and age at baseline were controlled. After controlling for gender and age, mean baseline FAQ item score for a person with normal cognitive aging was 0.04, suggesting no appreciable functional disability in this group at baseline (Table 6). As expected, persons with MCI exhibited a baseline level of functional disability significantly greater than persons with normal aging. Mean FAQ item scores were significantly higher at baseline for persons with Alzheimer’s disease and vascular dementia than for normal controls.
Table 6
Baseline Levels of and Rates of Change in Functional Disability by Baseline Diagnosis

<table>
<thead>
<tr>
<th>Fixed effect</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>Approx. df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline levels normal aging</td>
<td>0.04</td>
<td>0.04</td>
<td>1.01</td>
<td>635</td>
<td>.31</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>0.13</td>
<td>0.06</td>
<td>2.09</td>
<td>635</td>
<td>.04</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>0.68</td>
<td>0.06</td>
<td>11.22</td>
<td>635</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>0.42</td>
<td>0.12</td>
<td>3.34</td>
<td>635</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Rates of change

<table>
<thead>
<tr>
<th>Fixed effect</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>Approx. df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal aging</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.18</td>
<td>635</td>
<td>.86</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>0.10</td>
<td>0.03</td>
<td>3.68</td>
<td>635</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>0.14</td>
<td>0.03</td>
<td>5.36</td>
<td>635</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>0.09</td>
<td>0.06</td>
<td>1.41</td>
<td>635</td>
<td>.16</td>
</tr>
</tbody>
</table>

Note. All means are adjusted for age.

Participants with baseline diagnoses of MCI, AD, and vascular dementia also were compared to each other through hypothesis testing in HLM. Mean baseline FAQ item score for persons with MCI was significantly different from that for persons with vascular dementia; $\chi^2(1) = 4.65, p = 0.03$. Baseline diagnosis of AD also was associated with a significantly higher mean FAQ item score than for MCI, $\chi^2(1) = 61.86, p < 0.001$. A baseline diagnosis of AD also was associated with a significantly higher mean baseline FAQ item score than a diagnosis of vascular dementia; $\chi^2(1) = 4.26, p = 0.04$. Residuals for the level 1 and level 2 data files were checked and indicated that the data do not violate the assumptions of linearity, homoscedasticity, independence and normality (see Figures 2 and 3).

Longitudinal Trajectories of Functional Disability by Baseline Diagnostic Status

The ability to perform IADLs did not change significantly over the course of the study in persons with baseline status of normal cognitive aging, controlling for baseline age and gender (Table 6). Longitudinal trajectories of functional disability did not differ
Figure 2. Level 1 residual plot.

Figure 3. Level 2 residual plot.
significantly between persons with normal aging and persons diagnosed with vascular dementia. Trajectories of functional decline also did not significantly differ in persons with vascular dementia and MCI; $\chi^2(1) = 0.07, p > 0.50$. Compared to persons with baseline status of normal cognitive aging, persons with baseline diagnoses of MCI and Alzheimer’s disease experienced significantly greater impairment in function over time. FAQ score increased by 0.10 annually for persons with MCI and 0.14 for persons with Alzheimer’s disease, controlling for baseline age and gender. Change in functional disability over time was not significantly greater in persons with Alzheimer’s disease compared to persons with MCI; $\chi^2(1) = 1.63, p = 0.20$. Trajectories of functional change also were not significantly steeper in persons with Alzheimer’s disease compared to those with vascular dementia; $\chi^2(1) = 0.84, p > 0.50$.

Summary of Results

In summary, episodic memory, executive function, and apathy symptoms independently predicted longitudinal decline in complex activities of daily living, consistent with a priori hypotheses. Contrary to expectations, depressive symptoms and medical burden did not predict longitudinal disability. Persons with a baseline diagnosis of MCI exhibited a baseline level of functional disability that was intermediate to persons with baseline classifications of normal aging and dementia, as expected. Also expected were the significantly steeper trajectories of longitudinal functional decline in MCI and Alzheimer’s disease compared to those seen in persons with normal aging at baseline. The lack of significant difference in longitudinal rates of functional change in MCI and Alzheimer’s disease was an unexpected finding. In the current study, persons with Alzheimer’s disease exhibited significantly greater baseline functional disability than
persons with vascular dementia, a finding that ran counter to expectations. Longitudinal trajectories of disability in vascular dementia also were significantly flatter than in Alzheimer’s disease. While a slower rate of decline in vascular dementia compared to Alzheimer’s disease was expected, it was not expected that longitudinal decline of functional abilities in persons with vascular dementia would not differ significantly from persons with baseline classification of normal aging.
CHAPTER V
DISCUSSION

This is the first study to simultaneously model the longitudinal relationships between cognitive, neuropsychiatric, and medical predictors and functional disability. This study also adds to the literature by separately comparing longitudinal rates of functional decline in normal aging, MCI, and the two most common types of dementia, Alzheimer’s disease and vascular dementia. Results from this study suggest that memory and executive function independently predict change in complex activities of daily living over time. Results also suggest that symptoms of apathy but not depression predict longitudinal functional decline. Further, this study reveals that complex activities of daily living decline faster in MCI and Alzheimer’s disease than in normal aging and vascular dementia, and that these groups exhibit comparable rates of decline. A surprising finding was the lack of significant longitudinal functional decline in vascular dementia.

Baseline Levels of Functional Disability by Diagnostic Group

Comparisons of baseline and longitudinal levels of functional disability between persons with normal cognitive aging and those diagnosed with MCI, Alzheimer’s disease, and vascular dementia partially support prior research. Normal cognitive aging was associated with a minimal level of dependence at baseline and no significant change over the course of the study, as expected. Persons with MCI demonstrated a level of baseline disability that was greater than persons with normal aging and less than dementia, consistent with previous findings and conforming to diagnostic conventions (Albert et al., 2002; Aretouli & Brandt, 2010; Brown, Devanand, Liu, & Caccappolo, 2011; Farias et
Contrary to expectations, dementia groups did not exhibit comparable levels of functional disability at baseline. Diagnosis of Alzheimer’s disease was associated with the greatest level of dependence at baseline. The finding that vascular dementia was associated with less functional dependence than Alzheimer’s disease is surprising, given prior research documenting comparable levels of dependence in these groups (Boyle & Cahn-Weiner, 2004; Gure et al., 2010). In this study, persons with vascular dementia performed better on tests of memory and executive function than persons with Alzheimer’s disease, indicating less impairment on key predictors of everyday functioning. Memory and executive function in persons with vascular dementia were more similar to persons with MCI in this study, and perhaps commensurately, so was their performance on complex ADLs. In addition to their stronger cognitive testing performance, methodological reasons may underlie the significantly lower level of baseline functional disability in vascular dementia compared to Alzheimer’s disease. It is possible that the small size of the vascular dementia sample did not allow for optimal estimation of disability levels in this group, particularly considering the variability seen in their FAQ scores and the heterogeneous nature of the diagnosis itself.

Longitudinal Trajectories of Functional Disability by Diagnostic Group

Longitudinal trajectories of change in functional disability were different between groups. As expected, functional disability in persons with MCI progressed at a faster rate than in persons with baseline classification of normal aging. Surprisingly, longitudinal rates of change in functional disability were not significantly different in MCI and
Alzheimer’s disease. In this study, the average score on an item of the FAQ for persons with MCI increased by one tenth of one point annually, controlling for age. This measurement represents the annual rate of change in any surveyed IADL for the average person with MCI.

The comparable rate of functional decline in MCI and Alzheimer’s disease contradicts results from one prior longitudinal study that measured intermediate rates of functional decline in persons with MCI compared to persons with normal aging and dementia (Tomaszewski Farias et al., 2009). There are several possible explanations for this discrepancy. The current sample is comprised of persons from both clinic and community sources compared to Tomaszewski Farias’s (2009) clinic-based sample and indeed participants in this study were less functionally impaired at baseline than participants in the other. Further, it is arguable that IADL items from the Blessed Roth Dementia Rating Scale, the measure of functional disability used by Tomaszewski Farias (2009), are less complex than IADLs included in the FAQ and therefore less sensitive to annual change in less impaired persons, such as those with MCI. For example, IADL items on the Blessed Roth include “tendency to dwell in past” and “find way about indoors” and “interpret surroundings” whereas IADLs included on the FAQ include “playing a game of skill” and “writing checks, paying bills, or balancing a checkbook.” Viewed in this way, it is understandable how rates of functional change measured by the FAQ in persons with MCI in the current study might be more similar to persons with dementia than rates of change measured by the Blessed Roth.

Alternatively, it is possible that longitudinal rates of functional decline did not significantly differ in persons with baseline diagnoses of MCI and Alzheimer’s disease
because the majority of persons with Alzheimer’s disease in this study were in the mild stages of disease. While baseline FAQ scores were significantly different in MCI versus Alzheimer’s disease, baseline CDR scores were not significantly different in these diagnostic groups. Mean baseline CDR scores for the Alzheimer’s disease group represents a very mild stage of disease that may not be qualitatively different from MCI.

Another surprising finding was the lack of significant longitudinal functional decline in vascular dementia compared to persons with normal aging. As stated previously, the small size of the vascular dementia sample may have limited statistical power to detect group differences. It also is possible that the time course of the study was insufficient to detect functional decline in vascular dementia. Past research indicates that functional decline in vascular dementia progresses at a slower rate than in Alzheimer’s disease (Boyle & Cahn-Weiner, 2004; Gill et al., 2013). In addition, vascular dementia caused by large infarcts, as opposed to cumulative small vessel disease, may progress in a step-wise function and as such, significant changes in everyday function may not be visible over the short-term (Boyle & Cahn-Weiner, 2004); unfortunately, more data about subtypes of vascular dementia for participants in this study were not available.

**Longitudinal Predictors of Functional Disability**

Examination of the longitudinal relationships between cognitive, neuropsychiatric and medical variables and everyday functioning revealed that cognitive performance and apathy symptoms, and not depression or medical comorbidities, predict functional decline over time. Performance on tests of memory and executive function, as well as informant-reported apathy symptoms, predicted functional disability in a combined longitudinal model, indicating that they confer independent effects on daily functioning.
Memory

Declines in episodic memory performance predicted declines in performance of complex activities of daily living. On the one hand, this finding is not surprising given prior evidence of episodic memory’s cross-sectional associations with everyday functioning (e.g., Burdick et al., 2002; Farias et al., 2004, Richardson, Nadler, & Malloy, 1995). The current results also align with those of Tomaszewski Farias et al. (2009), showing a significant relationship between changes in episodic memory and changes in IADL performance over time. The current finding that longitudinal episodic memory performance independently predicts longitudinal functional decline is discrepant from some prior research indicating that changes in episodic memory either are not significantly related to functional change (Royall et al., 2005) or that the relationship between memory and everyday functioning is moderated by executive functioning (Cahn-Weiner et al., 2007; Royall et al., 2005; Royall et al., 2007). Differences in the way episodic memory was measured may explain these discrepancies. Episodic memory in the current study was represented by participant scores on a delayed free recall trial of a verbal learning test. Royall et al. (2005) used learning curve on a verbal list learning test to represent episodic memory, which represents encoding but not necessarily the storage/retrieval aspect of memory that is captured by delayed recall trials. Both Cahn-Weiner and colleagues (2007) and Tomaszewski- Farias et al. (2009) used composite measures of memory performance in their studies; in the former, the composite comprised scores from encoding and short delay recall trials of a list learning task, and the latter used scores from encoding and long delay recall trials. Thus, significant independent longitudinal relationships between episodic memory and IADL performance
may be more likely when using delayed recall rather than encoding or immediate recall scores: Scores on delayed recall trials may be a better indicator of memory decline than encoding or free recall performance.

It is easy to understand how memory abilities predict IADL performance because many of the items on the FAQ require memory skills both prospectively (e.g., remembering items that need to be purchased on a shopping trip, remembering appointments, remembering the need to pay bills and what needs to be accomplished when assembling paperwork) as well as during the execution of tasks (e.g. keeping track of current events or the content of TV shows, movies, books and magazines).

Interestingly, the longitudinal relationship between memory and functional disability did not vary across study participants. This suggests that declines in memory predict increased functional disability regardless of diagnosis or the magnitude of pre-existing cognitive or functional impairment: A change in memory does not precipitate steeper functional declines in dementia than it does in MCI or in normal aging.

Executive Function

This study also provided evidence for a longitudinal association between executive functions and functional abilities, consistent with results from prior research showing that executive function longitudinally predicts everyday functioning (Royall et al., 2005; Tomaszewski Farias et al., 2009). This finding was expected given that several IADLs included in the FAQ seem to require the ability to plan, sequence, and organize one’s behavior (preparing a balanced meal, playing a game of skill, traveling, etc.). Results from this study further provide additional evidence for the power of Part B of the
Trail-Making Test specifically in predicting IADL performance in older adults with and without dementia (Bell-McGinty et al., 2002; Burdick et al., 2005; Yeh et al., 2011).

As with memory, the relationship between executive function and everyday functioning did not vary significantly between participants, indicating that declines in executive function are associated with similar declines in functional abilities regardless of diagnosis. It is possible that the same physiological processes that underline declines in executive abilities also drive functional disability. Decreased volume in the orbitofrontal cortex, the site of reward and decision-making behaviors, is associated with functional impairments in older adults, independent of total brain volume (Taylor et al., 2003). Recent research also indicates that hypoperfusion in the right precuneus, part of the associative cortex, is associated with declines in performance on both a set-shifting task and the FAQ (Chao et al., 2010).

Neuropsychiatric Symptoms

Apathy and not depressive symptoms predicted longitudinal declines in daily functioning. Longitudinal associations between depressive symptoms and functional decline were expected, given prior research documenting relationships between depression and poorer daily functioning in persons with cognitive impairment (DeRonchi et al., 2005; Fitz & Teri, 1994). One possible reason that depressive symptoms were not associated with function in this study is the paucity of depressive symptoms reported for participants; informant reports of depressive symptoms were extremely low for all study groups, and participants themselves endorsed minimal depressive symptoms. Limited variability in depression scores may have made it difficult to discern relationships with functional disability. Further, such a low frequency and severity of neuropsychiatric
symptoms is unusual for persons with cognitive impairment (Edwards et al., 2009; Lyketsos et al., 2002; Steinberg et al., 2008) and also may explain differences from other studies.

This study revealed a significant longitudinal relationship between greater apathy and decline in complex activities of daily living despite minimal informant-reported apathy symptoms, providing support for the association between this syndrome and functional impairment. The current results align with prior research documenting stronger associations between apathy and functional disability compared to depression in persons with dementia (Clarke et al., 2008; Zawacki et al., 2002) and in amnestic MCI (Zahodne & Tremont, 2013).

Key symptoms of apathy include decreased motivation, initiation, and persistence (Ishii et al., 2009), behavioral components that are necessary for task performance. Apathy has been related in Alzheimer’s disease patients to impairments in planning, initiating and executing IADLs, in contrast to depression, which relates only with impaired initiation and planning (Lam et al., 2006). Therefore, it may be that reduced desire/drive to persist in and complete tasks accounts for apathy’s particularly negative impact on daily functioning.

Medical Burden

Results from this study did not support the hypothesis that greater medical burden would predict greater functional disability, which suggests that physical health does not factor into the performance of complex activities of daily living. These results contradict prior findings of significant relationships between poor health and functional disability in nursing home and assisted living residents (Burdick et al., 2005; Lyketsos et al., 1999)
but align with results from a study of IADL performance in an outpatient Alzheimer’s disease sample (Tekin et al., 2001). Methodological differences may underlie these contrasting results. First, it is possible that there is greater variability in both physical health and functional dependence in persons living in professional facilities than in outpatients, which may increase the likelihood of finding a significant relationship between medical burden and daily functioning in facility samples. Second, there are many ways to operationalize medical burden. This study utilized total medication count to represent burden, which has compared favorably to other, more complex assessments of medical comorbidity (Perkins et al., 2004). However, medication counts may be less sensitive than the health surveys used in other studies that include specific medical conditions, such as arthritis, back pain, or a physical disability, that may not require medication but that nevertheless impact daily functioning. Third, ADL assessments differ across studies. Medical burden may have a stronger association with certain ADLs (i.e., traveling out of the neighborhood, grooming and personal hygiene) and less so with others (i.e., keeping track of current events), depending on the nature of the task. Functional disability questionnaires that include both BADLs and IADLs of the type used by Burdick et al. (2005), or that include more IADLs with a physical component, may share stronger relationships with medical burden than those that do not.

Limitations

The current study has several limitations. First, the study sample overall was high-functioning. Mean total FAQ score for all groups at baseline was 2.56 out of a possible 30. There was a floor effect in the FAQ for normal controls and persons with MCI. While the dementia groups included persons with a range of cognitive impairment, persons with
Alzheimer’s disease and vascular dementia were on average at very mild stages of
disease based on analysis of baseline CDR scores. As stated previously, minimal levels of
depressive and apathy symptoms were endorsed by informants for all groups. In addition
to these generally high levels of emotional and behavioral functioning, the majority of
study participants were Caucasian, married, and living at home with a spouse or partner.
They had on average a college education, and many participants had Master’s,
professional, and doctoral degrees, which could indicate solid cognitive reserve that
might moderate the outward manifestation of brain pathology (Stern, 2012). For the
above reasons, results from this study may not generalize to the greater population of
persons with MCI, Alzheimer’s disease, and vascular dementia. Finally, functional
performance was measured using a scale that assessed IADLs only and did not include
BADLs. Therefore, estimates of longitudinal change in daily functioning based on
memory and executive function performance, and rates of change by baseline diagnosis,
apply only to higher-level activities and not to basic activities of daily living such as
eating, bathing, and dressing.

Conclusions

Results from this study, while based in an overall high-functioning sample,
provide evidence that longitudinal memory and executive function performance, as well
as apathy symptoms independently predict daily functioning. Thus, in terms of cognitive
abilities, clinicians and caregivers should expect that changes in both memory and
executive function will correspond with subtle changes in the performance of everyday
activities. Interestingly, the nature of the relationship between memory and executive
function declines and functional disability appears to be similar for persons with normal
cognitive aging, MCI, and dementia. Therefore, providers should not expect more rapid functional decline given a change in cognitive performance in dementia than in MCI. With regard to neuropsychiatric symptoms, results indicate that apathy is a potentially modifiable predictor of longitudinal functional decline. Future research should address whether aggressive psychological and pharmacological treatment can palliate its adverse effects on complex daily living activities. Clinicians and caregivers also should expect significant and progressive functional decline in persons with MCI and Alzheimer’s disease. However, this study suggests that disablement is gradual even in persons with Alzheimer’s disease, which may offer some hope to patients and their caregivers.
NACC Uniform Data Set (UDS)
Follow-up Form B7: Functional Assessment – Functional Assessment Questionnaire (FAQ)³

Center: __________________________ ADC Subject ID: __________________________ Form Date: __/__/_____ ADC Visit #: __________ Examiner’s initials: __________

NOTE: This form is to be completed by the clinician or other trained health professional, based on information provided by informant. For additional clarification and examples, see UDS Coding Guidebook for Follow-up Visit Packet, Form B7. Indicate the level of performance for each activity by circling the appropriate response.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not applicable (e.g., never did)</th>
<th>Normal</th>
<th>Has difficulty, but does by self</th>
<th>Requires assistance</th>
<th>Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing checks, paying bills, or balancing a checkbook.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Assembling tax records, business affairs, or other papers.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Shopping alone for clothes, household necessities, or groceries.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Playing a game of skill such as bridge or chess, working on a hobby.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Heating water, making a cup of coffee, turning off the stove.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Preparing a balanced meal.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Keeping track of current events.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Paying attention to and understanding a TV program, book, or magazine.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Remembering appointments, family occasions, holidays, medications.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Traveling out of the neighborhood, driving, or arranging to take public transportation.</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>


(version 2.0, February 2008)
## APPENDIX B

### NACC UNIFORM DATA SET

#### FOLLOW-UP FORM B5:Behavioral Assessment – Neuropsychiatric Inventory Questionnaire (NPI-Q)\(^1\)

Center: __________________ ADC Subject ID: ______________ Form Date: __/__/____ ADC Visit #: ______________

**NOTE:** This form is to be completed by the clinician or other trained health professional per informant interview, as described by the training video. (This is **not** to be completed by the subject as a paper-and-pencil self-report.) For information regarding NPI-Q Interviewer Certification, see UDS Coding Guidebook for Follow-up Visit Packet, Form B5. Check only one box for each category of response.

Examiner’s initials: ______________

Please ask the following questions based upon changes. Indicate ‘yes’ only if the symptom has been present in the past month; otherwise, indicate ‘no’.

For each item marked “yes”, rate the **SEVERITY** of the symptom (how it affects the patient): 1 = Mild (noticeable, but not a significant change) 2 = Moderate (significant, but not a dramatic change) 3 = Severe (very marked or prominent; a dramatic change)

<table>
<thead>
<tr>
<th>1. NPI informant: □ 1 Spouse □ 2 Child □ 3 Other (specify):</th>
<th>Yes</th>
<th>No</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. DELUSIONS: Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?</td>
<td>2a. □ 1 □ 0</td>
<td>2b. □ 1 □ 2 □ 3</td>
<td></td>
</tr>
<tr>
<td>3. HALLUCINATIONS: Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?</td>
<td>3a. □ 1 □ 0</td>
<td>3b. □ 1 □ 2 □ 3</td>
<td></td>
</tr>
<tr>
<td>4. AGITATION OR AGGRESSION: Is the patient stubborn and resistive to help from others?</td>
<td>4a. □ 1 □ 0</td>
<td>4b. □ 1 □ 2 □ 3</td>
<td></td>
</tr>
<tr>
<td>5. DEPRESSION OR DYSPIORIA: Does the patient act as if he or she is sad or in low spirits? Does he or she cry?</td>
<td>5a. □ 1 □ 0</td>
<td>5b. □ 1 □ 2 □ 3</td>
<td></td>
</tr>
<tr>
<td>6. ANXIETY: Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?</td>
<td>6a. □ 1 □ 0</td>
<td>6b. □ 1 □ 2 □ 3</td>
<td></td>
</tr>
</tbody>
</table>

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(version 2.0, February 2008)
**APPENDIX C**

**NACC UNIFORM DATA SET FOLLOW-UP FORM B6**

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**NACC Uniform Data Set (UDS)**

**Follow-up Form B6: Behavioral Assessment – Geriatric Depression Scale (GDS)**

Center: __________ ADC Subject ID: __________ Form Date: __/__/____

*NOTE: This form is to be completed by the clinician or other trained health professional, based on subject response. For additional clarification and examples, see UDS Coding Guidebook for Follow-up Visit Packet, Form B6. Circle only one number per question. Examiner’s initials: ____________*

- **□ Check this box and enter “88” below for the Total GDS Score if and only if the subject: 1) does not attempt the GDS, or 2) answers fewer than twelve questions.**

**Instruct the subject:** “In the next part of this interview, I will ask you questions about your feelings. Some of the questions I will ask may not apply, and some may make you feel uncomfortable. For each question, please answer “yes” or “no,” depending on how you have been feeling in the past week, including today.”

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you basically satisfied with your life?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Have you dropped many of your activities and interests?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3. Do you feel that your life is empty?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4. Do you often feel bored?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5. Are you in good spirits most of the time?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6. Are you afraid that something bad is going to happen to you?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7. Do you feel happy most of the time?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8. Do you often feel helpless?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9. Do you prefer to stay at home, rather than going out and doing new things?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10. Do you feel you have more problems with memory than most?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11. Do you think it is wonderful to be alive now?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12. Do you feel pretty worthless the way you are now?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13. Do you feel full of energy?</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14. Do you feel that your situation is hopeless?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15. Do you think that most people are better off than you are?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>16. Sum all circled answers for a Total GDS Score (maximum score = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(did not complete = 88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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APPENDIX D

WORKSHEET FOR LOGICAL MEMORY IIA-DELAYED

Worksheet for LOGICAL MEMORY IIA–DELAYED

Administer this test approximately **20 minutes** after Logical Memory IIA – Immediate.
(Note: If 20 minutes have not elapsed, do not add other tests to fill the interval. Administer Logical Memory IIA – Delayed and enter the actual time elapsed.)

Read the instructions:

[SAY]: “I read you a little story a few minutes ago. Now I want you to tell me the story again. It was about a woman who was robbed. Tell me everything that you can remember about that story.”

Record the subject’s response on the Worksheet for Logical Memory IIA–Delayed. Make sure that your written record is legible before proceeding. If the subject asks a question about the story or for repetition of some or all of it, say “Please tell me as much as you can remember about the story.”

Scoring is deferred until after the examination. The examiner may prefer to tape record the subject’s response and then transcribe the results after the session; this is acceptable if appropriate consent has been obtained.

<table>
<thead>
<tr>
<th>Story A – Delayed</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anna / Thompson / of South / Boston /, employed / as a cook /</td>
<td>(0–6)</td>
</tr>
<tr>
<td>in a school / cafeteria /, reported / at the City Hall / Station /</td>
<td>(0–5)</td>
</tr>
<tr>
<td>that she had been held up / on State Street / the night before /</td>
<td>(0–3)</td>
</tr>
<tr>
<td>and robbed / of fifty-six dollars /, She had four /</td>
<td>(0–3)</td>
</tr>
<tr>
<td>small children /, the rent was due /, and they had not eaten /</td>
<td>(0–3)</td>
</tr>
<tr>
<td>for two days /, The police /, touched by the woman’s story /,</td>
<td>(0–3)</td>
</tr>
<tr>
<td>took up a collection / for her /,</td>
<td>(0–2)</td>
</tr>
</tbody>
</table>

**Total number of story units recalled:** __ __

**Time elapsed since Logical Memory IIA – Immediate:** __ __ (minutes)
APPENDIX E
TRAIL-MAKING TEST PART B

[Diagram of Trail-Making Test Part B with numbers and letters arranged in a specific sequence]
REFERENCES


