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Awareness of Functional Difficulties in Mild Cognitive Impairment: Relation to Cognitive Variables and Mood

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AWARENESS OF FUNCTIONAL DIFFICULTIES IN MILD COGNITIVE IMPAIRMENT: RELATION TO COGNITIVE VARIABLES AND MOOD

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ABSTRACT

Self-report of functional abilities is weighted heavily in differential diagnostic decision making regarding mild cognitive impairment (MCI) and Alzheimer's disease (AD). However, it is unclear whether patients with MCI are fully aware of and provide reliable estimates of their functional status. Prior studies that examined accuracy of self-report of functional abilities in MCI have presented mixed findings. Common limitations of these studies include the use of informant report as the sole yardstick for ascertaining accuracy of patient self-report, and the failure to account for potential heterogeneity in awareness of functional difficulties in dementia. In this study, we examined accuracy of self-report in MCI across five functional domains by comparing patients' report of functioning to their performance on performance-based measures. We found that the discrepancy between self-report and objective performance was higher in MCI patients compared to controls only on the financial management domain. In multivariable regression analyses, discrepancy scores were correlated only with a composite measure of attention. We also found that MCI patients with greater depressive symptoms underestimated their financial abilities. The implications of these findings for case definition, risk of misdiagnosis, risk of financial exploitation, and family members' adjustment in MCI are discussed.

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of daily living
ADRC	Alzheimer's Disease Research Center
CDR	Clinical Dementia Rating scale
CDRS	Certified Driving Rehabilitation Specialist
CFCF	Current Financial Capacity Form
CLOX	Executive Clock Drawing Test
CPT	Conners' Continuous Performance Test
CTRAM	Center for Translational Research on Aging and Mobility
CVLT-II	California Verbal Learning Test, 2nd edition
DI	Discrepancy Index
DRS-2	Dementia Rating Scale, 2nd edition
FCI	Financial Capacity Instrument
GDS	Geriatric Depression Scale
IADL	Instrumental activities of daily living
MCI	Mild cognitive impairment
MILES	Measuring Independent Living in the Elderly Study
OTDL	Observed Tasks of Daily Living
TIADL	Time Instrumental Activities of Daily Living
WAIS-III	Wechsler Adult Intelligence Scale, 3rd edition
WMS-III	Wechsler Memory Scale, 3rd edition
WMS-R	Wechsler Memory Scale, revised edition

INTRODUCTION

The objectives of this dissertation are to assess awareness of limitations in the performance of various real world tasks necessary for independent functioning among persons with mild cognitive impairment (MCI) and to determine the cognitive and affective variables that are associated with reduced awareness of such difficulties. First, the concept of impaired awareness of deficits in the context of Alzheimer's disease (AD) is explicated, followed by a review of the extant literature on reduced awareness of functional difficulties among individuals with MCI. The next section focuses on the theoretical and practical relevance of awareness of functional difficulties among persons with MCI such as its implications for the diagnosis of MCI, treatment compliance and outcome, patient safety, and family caregiver adjustment. Then, the heterogeneity of awareness of deficits is explored, followed by a review of prior empirical attempts to map the neurocognitive mechanisms that mediate diminution in awareness. The next section addresses the theorized association between awareness of deficits and depression, followed by a discussion of the limitations of prior studies of awareness of functional difficulties in MCI. Finally, the specific aims and hypotheses of this dissertation are presented. Because studies of awareness in MCI have only recently begun, and as such there is not yet a well-established knowledge base in the area, the bulk of the material presented in this introductory section of the dissertation will be drawn from AD literature.

Impaired Awareness of Deficits in AD

AD is the most common neurodegenerative dementia and is characterized by gradual but progressive impairment in memory and other cognitive functions in addition to decline in the ability to perform both instrumental activities of daily living (IADLs,

such as medication management and driving) and basic activities of daily living (ADLs, such as bathing and feeding) (McKhann et al., 1984). AD patients also experience a spectrum of behavioral and psychiatric symptomatology such as anxiety, depression, irritability, confabulations, and delusions (Reisberg et al., 1987). Despite these salient and often debilitating symptoms that manifest over the course of the disease, many individuals with AD frequently minimize, fail to recognize, or entirely deny their cognitive, behavioral, and functional deficits (Ott et al., 1996; Vasterling, Seltzer, Foss, & Vanderbrook, 1995). Others may acknowledge these deficits but fail to appreciate their severity and their consequences in everyday life (Clare, 2003; Derouesne et al., 1999; Sevush, 1999).

This phenomenon has been variously described as anosognosia, lack of insight, unawareness of deficits, or imperception of disease and is a common feature of many neurological diseases (McGlynn & Schacter, 1989). Anosognosia is the most widely used term and was coined by Babinski (1914) to describe lack of knowledge, awareness, or recognition of a disease or aspects of it, especially in the context of hemiplegia. Although the term denial of illness/deficit has also been used to refer to this phenomenon, denial is generally thought to reflect a psychological defense/coping mechanism rather than an organic pathology. Anosognosia is also distinguished from lack of concern or indifference, since these may primarily index disordered affective response to a disease (anosodiaphoria) rather than mere unawareness of the disease (Clare, 2004b; Heilman, 1991). Anosognosia, lack of insight, and impaired awareness of deficits are used synonymously in this dissertation.

Several studies have reported that impaired awareness of deficits is observed even in the earliest stages of AD (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991; Sevush, 1999). Other studies have demonstrated that the degree of unawareness increases as the disease progresses. In a longitudinal assessment of patients diagnosed with probable AD, Vasterling and colleagues (1997) found significant patient-caregiver discrepancies across diverse cognitive and functional domains at baseline, and these discrepancies increased with the passage of time. In another longitudinal study (Starkstein et al., 1997), there was a significant increment in the number of AD patients with anosognosia as well as in the severity of anosognosia at follow-up relative to baseline. Other cross-sectional studies found that anosognosia was higher in later stages of illness (Harwood, Sultzer, & Wheatley, 2000), and remained significantly associated with longer duration of illness even when patients with and without anosognosia were matched for MMSE scores (Migliorelli et al., 1995).

Diminished Awareness of Functional Difficulties in MCI

The recognition that AD is an insidious disease with gradual onset has generated a great deal of clinical and research interest in identifying individuals who do not yet have AD but are at elevated risk of developing the disease relative to their peers (Petersen, Stevens et al., 2001). Such early detection, prior to significant declines in cognitive and functional abilities, will permit timely therapeutic intervention that could potentially delay the progression of the pathology (Petersen & Morris, 2005). In recent years, MCI has become widely accepted as the classification for this group of individuals in the transitional stage between normal aging and AD. Persons with MCI convert to AD at an

annual rate of 10% to 15% compared to the annual conversion rate of 1% to 2% among age- and education-matched peers (Petersen, Doody et al., 2001).

Until recently, criteria for MCI required subjective memory complaint preferably corroborated by an informant, objective memory impairment for age, preserved general cognitive function, normal activities of daily living, and the absence of a dementia diagnosis (Petersen, Doody et al., 2001; Petersen et al., 1999). However, the subjective complaint criterion has been modified to allow for either subjective memory complaint, informant report, or clinician's determination of memory difficulties (Kawas, 2003; Winblad et al., 2004). Furthermore, the requirement that performance of functional activities be normal has been modified to "largely intact functional activities" (Petersen, 2004). The modification was necessitated by convergent evidence from several studies (Griffith et al., 2003; Morris et al., 2001; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Touchon & Ritchie, 1999; Tuokko, Morris, & Ebert, 2005) indicating that individuals with MCI experience attenuation in functional abilities that is intermediate between the intact performance of age- and education-matched healthy adults and the frank impairment that is characteristic of AD, and that functional dependence is a predictor of subsequent progression to AD (Barberger-Gateau, Fabrigoule, Helmer, Rouch, & Dartigues, 1999; Daly et al., 2000; Tabert et al., 2002). Given that impairment in the performance of functional activities is considered an indication of (incipient) AD, the requirement that functional activities be largely intact is considered central to the diagnosis of MCI because once a considerable restriction in functional activities is observed, the diagnostic consideration shifts from MCI to AD (APA, 2000; McKhann et al., 1984; Petersen, 2004).

A question that has not been satisfactorily addressed relates to the degree of awareness that MCI patients have concerning their functional difficulties. This is especially critical for a number of reasons. First, MCI is considered a prodromal stage of AD and several studies have demonstrated that reduced awareness of deficits is present even in the earliest stages of AD (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991; Sevush, 1999). Secondly, other studies have reported that diminished awareness of functional difficulties strongly predicts progression from MCI to AD (Albert, Tabert, Dienstag, Pelton, & Devanand, 2002; Tabert et al., 2002). Thirdly, despite recent modifications in MCI classification criteria, self-report of difficulties is still weighted heavily in clinical decision making regarding MCI classification (Gauthier & Touchon, 2005; Petersen & Morris, 2005). Therefore, ascertaining the reliability and validity of such self-report of functioning has strong clinical and research relevance.

A few studies have examined awareness of functional difficulties in MCI but the evidence from these studies is inconsistent. We briefly review the findings from these studies here but reserve the discussion of their limitations for a later section. In the earliest investigation of this issue, Albert and colleagues (1999) studied two groups of individuals with MCI, operationalized as obtaining a Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993) score of 0 (minimal impairment, non demented) or 0.5 (questionable dementia), respectively. They found that both MCI groups reported significantly poorer functional abilities than cognitively intact control participants. Although the MCI groups did not differ in the degree of self-reported functional difficulties, comparison of self-reported functional status to informant reports of patient's functional status revealed a significant discrepancy in the CDR 0.5 patient-

informant dyads. Informants reported that patients displayed a significantly greater number of difficulties compared to patients' self-report. The self-informant disparity was greatest for those CDR 0.5 patients with the lowest modified Mini-Mental State Exam (mMMSE; Stern, Sano, Paulson, & Mayeux, 1987) scores. The authors considered this an indication that MCI patients in the CDR 0.5 group might be losing insight into the true extent of their functional limitations.

In a prospective study, Tabert and colleagues (2002) examined the predictive utility of self- and informant-reported functional difficulties in MCI for progression to AD within a 2-year period. They found that at baseline, MCI patients had more self-reported difficulties than normal controls. Also, baseline self- and informant-reported functional difficulties were significantly greater for MCI individuals who later progressed to AD than for nonconverters. Furthermore, those who subsequently developed AD self-reported significantly fewer functional difficulties at baseline relative to informant reports whereas nonconverters manifested the opposite pattern. In direct tests of the predictive power of self-report, informant-report, and a discrepancy index (informant report minus patient report), they found that informant-report and, to a greater extent, the discrepancy index were the significant predictors of conversion to AD. These results suggest that not only do MCI patients experience functional difficulties, but they may also lack awareness of the scope of their difficulties, relative to family informants, which in turn predicts progression to AD.

A more recent study (Farias, Mungas, & Jagust, 2005) investigated the degree of discrepancy between self- and informant-reported everyday functioning in a sample consisting of healthy older adults and individuals diagnosed with amnestic MCI,

nonamnestic MCI, and dementia. Groups were matched on age, gender, ethnicity, and education. A difference score was calculated by subtracting the patient's average self-reported functioning from the average functioning reported by an informant. Whereas patient-reported functional abilities did not differ among the four groups, informant-reported everyday functioning was significantly different across the groups with the exception of nonamnestic MCI versus normals. Difference scores were significantly higher in the dementia group, indicating greater loss of awareness, compared to normal controls and MCI groups. However, difference scores for the MCI groups were not significantly different than those for the healthy controls. This was considered an indication that persons with MCI do not under-report their functional difficulties.

The Relevance of Assessing Awareness of Difficulties in MCI

The assessment of diminished awareness of difficulties among MCI patients is important for theoretical reasons, especially regarding MCI case definition, and for practical considerations. Criteria for MCI require self-report, informant report, or clinician judgment of memory difficulties as well as intact performance of activities of daily living, which also is typically assessed by self-report. These requirements are predicated upon the assumption that the patient is generally capable of providing accurate estimates of cognitive and functional abilities, an assumption that largely awaits empirical substantiation. Assessment of awareness of functional difficulties is also germane to the growing clinical and research focus on early detection of AD because diminished awareness of difficulties has been shown to strongly predict progression from MCI to AD (Albert, Tabert, Dienstag, Pelton, & Devanand, 2002; Tabert et al., 2002). Timely detection of diminished awareness, if followed by appropriate therapeutic

intervention, may impede the progression of AD pathology while offering the prospect of considerable reduction in the individual and societal cost of the disease (Burns & Zaudig, 2002; Petersen & Morris, 2005).

From a practical clinical perspective, assessment of awareness is directly relevant to diverse areas of patient care and management. The relationship between awareness of illness and treatment compliance is well-recognized (Mullen, Howard, David, & Levy, 1996). Patients who lack awareness of their impairments frequently resist rehabilitative and therapeutic interventions either because they do not acknowledge these deficits or because they do not fully appreciate their severity and their impact on their daily life (Aalten, van Valen, Clare, Kenny, & Verhey, 2005). In addition, increased morbidity often results from delayed self-identification to healthcare professionals (Carr, Gray, Baty, & Morris, 2000). Exploratory studies indicate that the degree of awareness manifested by a patient is also relevant in deciding the form of patient-caregiver intervention to implement, such as reality reorientation therapy (which seeks to reorient the patient to person, place, time, or abilities) or validation therapy (which emphasizes acceptance of the reality and personal truth of the patient's experiences) (Morton & Bleathman, 1991).

Loss of awareness in the context of AD has implications for patients' safety because it is a predictor of the likelihood that they might engage in behaviors that pose significant risk of harm to themselves or others because they fail to judge situations adequately. For example, they might persist in driving when it is no longer safe to continue doing so (Cotrell & Wild, 1999). Bergman, Proctor, and Prudham (1979) also reported that level of awareness discriminated community-dwelling dementia patients

(more intact awareness) from hospitalized ones (less awareness) and suggested that patients with preserved awareness knew when tasks were too difficult or dangerous for them and appropriately asked for or willingly received help. There is also indication that diminished awareness of functional difficulties exposes older adults in general to different forms of financial exploitation and renders them vulnerable to unintentional self-impoverishment, conservatorship proceedings, and overall loss of personal and financial autonomy (Marson, 2001; Van Wielingen, Tuokko, Cramer, Mateer, & Hultsch, 2004).

A series of studies has implicated level of awareness as a determinant of treatment outcome. Koltai, Welsh-Bohmer, and Schmechel (2001) investigated the effects of a memory intervention and coping program designed to help patients with mild to moderate dementia better adjust to diminution in their cognitive abilities. Control versus treatment group comparisons across various cognitive and affective variables at the end of treatment revealed a trend, which did not attain statistical significance, towards improvement in the treatment group. However, when they performed subgroup analyses within the treatment group, they found that participants with preserved awareness reported significantly improved memory functioning compared to those without awareness. Clare and colleagues (2004) assessed the relationship between awareness of deficits and outcome of a cognitive rehabilitation intervention in patients with early-stage AD. Post-intervention analyses showed that a higher level of awareness was related to better learning performance on intervention-related variables. Because MCI is considered a target population for various cognitive and functional interventions, it is pertinent that the level of awareness of individuals with MCI be adequately assessed and documented.

Lack of awareness also affects the psychological functioning of caregivers and family members. Seltzer and associates (1997) demonstrated that as patient underestimation of memory deficits increased, so did the level of burden reported by caregivers, independent of disease stage, dementia severity, amount of outside assistance received by the caregiver in caring for the patient, and whether or not the caregiver resided with the patient. Another study (DeBettignies, Mahurin, & Pirozzolo, 1990) also showed that the degree of burden experienced by caregivers was directly related to the amount of discrepancy between caregiver and patient reports of functioning, with greater discrepancy being associated with higher burden. Indeed, it is easy to understand how discrepant perceptions of patient functioning by patient and caregiver might, in itself, be a source of stress to both patient and caregiver. These findings are noteworthy because other studies (Harwood, Sultzer, & Wheatley, 2000) have suggested that chronic conflict between patient and caregiver increases the likelihood of premature institutionalization of the patient.

The burden and negative affect that caregivers experience are partially explained by the attributions they make regarding the patient's deficits. Attributing the patient's deficits to lack of effort or to personality characteristics rather than to the disease process is likely to result in less sympathy toward the patient, more blame, and less willingness to help the patient (Wadley & Haley, 2001; Weiner, 1986). Determining the presence and degree of unawareness of functional difficulties in MCI should provide material for educating caregivers of MCI patients concerning the reasons for the functional difficulties and diminished insight they might observe in their care recipients. This would help modify the attributions caregivers make, empower them to cope adaptively with the

patient's difficulties, and also protect the patient from undue embarrassment and self-blame.

Awareness of Deficits as a Heterogeneous Construct

Earlier studies of awareness of deficit in AD approached awareness from a global, all-or-nothing perspective and focused mainly on awareness of memory deficits without considering the possibility that patients may have varying levels of awareness for distinct cognitive, behavioral, and functional deficits (Aalten, van Valen, Clare, Kenny, & Verhey, 2005). Preliminary evidence for dissociations in awareness across functional domains among AD patients was provided by Green and associates (1993) and Kotler-Cope and Camp (1995). In the former study, varying levels of awareness across domains were demonstrated by greater patient-informant report discrepancies in recent memory and everyday activities relative to remote memory and attention. In the latter study, AD patients' ratings of their own functional status diverged from ratings by family members on domains of apraxia, memory, dementia, 'higher cognitive' deficits, and language but not on domains of need for routine, disorientation, agitation, and depression. Although these studies drew attention to the need to relate unawareness of deficits to specific domains of functioning, they were limited by small sample sizes (Ns = 20 and 13, respectively) and restricted range of dementia severity among study participants.

Vasterling and colleagues (1995) were the first to systematically investigate domain-specific differences in awareness of deficit. They examined patient-informant disparities across six domains of functioning – memory, general health, self-care, anxiety, depression, and irritability. They found that the discrepancy between patient and caregiver reports of functioning was greatest for memory, followed by self-care, anxiety,

and irritability in that order. There were no significant patient-caregiver discrepancies in the areas of general health and depression. The authors viewed the observed hierarchy of discrepancies as suggesting that AD patients were less aware of their deficits in skills requiring higher-order information processing and integration (that is, memory and self-care) compared to domains of emotional disturbance and general health, which do not require such higher-order processing. Their findings indicate that awareness does not function as a global or unitary construct but differs across areas of impairment.

Another study (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996) considered the existence of distinct domains of anosognosia by performing factor analysis on a questionnaire instrument that inquired into different cognitive deficits and behavioral problems. Two factors emerged – "cognitive unawareness" and "behavioral unawareness." Stepwise forward regression to identify psychiatric correlates of the unawareness factors revealed that cognitive unawareness was associated with greater delusions and apathy, but less depression. On the other hand, behavioral unawareness had significant associations with increased mania and pathological laughing. Another stepwise forward regression to identify neuropsychological correlates of the unawareness factors identified verbal comprehension and delayed recall as correlates of the cognitive unawareness factor. There were no significant neuropsychological correlates of the behavioral unawareness factor. The authors also found that impaired awareness of behavioral symptoms was more prominent in the earlier stages of AD whereas unawareness of cognitive deficits appeared in the later stages. They considered their results as pointers to two discrete dimensions of anosognosia that are differentially related to psychiatric and cognitive variables.

Kalbe and colleagues (2005) also reported that AD patients manifested varying levels of awareness of deficits across different cognitive domains. In their study, AD patients' report of cognitive dysfunction differed significantly from caregivers' report on domains of executive function, abstract thinking, orientation to space, and calculation but not for memory, attention, verbal abilities, orientation to time, and praxis. In a longitudinal assessment of impaired awareness among AD patients, Vasterling, Seltzer, and Watrous (1997) measured the degree of discordance between patient and caregiver ratings of memory functioning, health status, self-care, anxiety, depression, and irritability. They found that irrespective of time of assessment, patient-caregiver discrepancies were most pronounced for ratings of memory and self-care, followed by health and depression. These discrepancies increased with the passage of time although there were no domain-specific differences in the longitudinal progression of discordance between functional ratings by patients and caregivers.

Taken together, these studies provide convergent evidence that contrary to prior conceptualizations, unawareness of deficits is not a unitary construct. Rather it is a heterogeneous phenomenon that dissociates across diverse cognitive and functional domains. This finding is central to the main thrust of this dissertation – the examination of awareness of functional difficulties across a spectrum of real world tasks among individuals with MCI in order to clearly distinguish the domains of independent functioning in which they may already be experiencing decreased awareness of difficulties from the domains wherein they currently retain awareness of deficits.

Neuropsychological Correlates of Anosognosia

An investigation of the neurocognitive variables associated with impaired awareness of deficits is pertinent to our understanding of the relationship between cognitive dysfunction and behavioral disturbance. Specific associations between awareness and circumscribed neuropsychological deficits may signify dysfunction of discrete neural structures or pathways, thereby explicating the neural basis of this distinct neuropsychiatric symptom (Seltzer, Vasterling, Mathias, & Brennan, 2001). Such an investigation also provides an opportunity to explore key theoretical issues relevant to the conceptualization of awareness such as the degree to which unawareness can be considered a primary disorder in the absence of generalized cognitive impairment (Agnew & Morris, 1998). Furthermore, given that awareness of deficits is compromised quite early on in AD (Sevush, 1999), and that diminished awareness is a predictor of conversion from MCI to AD (Tabert et al., 2002), the current focus on early identification and treatment of at-risk MCI cases can only benefit from the delineation of neurocognitive markers of reduced awareness across various functional areas.

One proposal that has been put forward is that impaired awareness is mediated by the severity of dementia as indexed by measures of global cognitive impairment such as the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Using this measure, Vasterling and colleagues (1995) found that although specific correlates of awareness varied across the domains assessed, the overall finding was that AD patients with greater cognitive impairment (low MMSE scores) had more impaired awareness of deficits. Other studies (Harwood, Sultzer, & Wheatley, 2000; Seltzer, Vasterling, Hale, & Khurana, 1995; Sevush, 1999; Smith, Henderson, McCleary, Murdock, & Buckwalter,

2000) have also reported an association between high patient-caregiver discrepancies and low scores on the MMSE. When Migliorelli and associates (1995) matched patients with and without anosognosia on MMSE scores, they found that the anosognosic group showed significantly longer duration of illness, suggesting that anosognosia may mark slower progression of AD rather than mere dementia severity.

Episodic and/or semantic memory failures have also been adduced as the neurocognitive underpinnings of impaired awareness of deficits in AD – the patient with impaired episodic memory constantly forgets they have this impairment whereas the patient with semantic memory problems never experiences amnestic difficulties, despite their occurrence, and so disputes their existence (Agnew & Morris, 1998). Feher and colleagues (1991) found that memory impairment had a stronger association with patient-caregiver discrepancy on a measure of everyday memory than dementia severity. In another study that examined the specific neuropsychological correlates of anosognosia (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996), only a measure of long term memory and another measure of verbal comprehension had significant associations with a cognitive unawareness factor. Migliorelli and colleagues (1995) also reported that a test of delayed recall was the only neuropsychological measure to correlate significantly with impaired awareness.

The memory dysfunction theory of anosognosia is intuitively compelling because memory deficit resulting from cytoskeletal alterations in the mesiotemporal region is a hallmark of AD pathology; and it is reasonable to expect that the more severe a person's memory deficit is, the less likely they are to remember that they have one (Whitlock, 1981). However, studies of anosognosia in amnestic syndromes suggest that amnesia and

awareness of deficit are independent events (Shimamura & Squire, 1986). Therefore, although memory impairment might play a role in maintaining anosognosia, it is not the factor responsible for it (Agnew & Morris, 1998).

Executive dysfunction and frontal lobe pathology have also been proposed as the neurocognitive bases of anosognosia. Initial evidence for this came from the finding that executive functions of self-monitoring, mental flexibility, behavioral inhibition, and problem solving were largely instantiated in the frontal lobes (Fuster, 1997). This proposal gained wider currency when other studies revealed that amnesiacs with co-morbid frontal lobe injury were more likely to have anosognosia than those without frontal involvement (Agnew & Morris, 1998).

Researchers, using both behavioral and neuroimaging techniques, have directly investigated the involvement of executive functions and the frontal lobes in anosognosia in AD. One of the earliest studies was from Michon and colleagues (1994). They demonstrated that anosognosia scores were highly correlated with a "frontal score" but not with any of the other neuropsychological measures in their battery, including measures of memory and global cognitive impairment. Van Wielingen and associates (2004) showed that higher scores on the Frontal Behavioral Inventory (FBI; Kertesz, Davidson, & Fox, 1997) were associated with unawareness of difficulties with financial abilities in a sample of demented persons. Other studies (Dalla Barba, Parlato, Iavarones, & Boller, 1995; Ott et al., 1996) have also demonstrated relationships between poor performance on neuropsychological measures of executive function and impaired awareness.

An initial report from Reed, Jagust, and Coulter (1993) demonstrated an association between anosognosia for memory impairment and hypoperfusion of the right dorsolateral frontal lobe in AD patients. Since then, other studies have reported significant correlations between the severity of unawareness and diminished cerebral perfusion involving the frontal lobes (Derouesne et al., 1999; Harwood et al., 2005; Starkstein et al., 1995). These studies provide confirmatory support for the neuropsychological findings described above and further bolster the putative link between impaired awareness and frontal (executive) functions. In addition, Agnew and Morris (1998) and Heilman (1991) developed separate cognitive neuropsychological models of anosognosia in which anosognosia is hypothesized to result from a malfunctioning of a monitoring or comparator system.

To date, only one MCI study has examined the neuropsychological correlates of unawareness of functional difficulties. Farias, Mungas, and Jagust (2005) obtained differences scores by subtracting patients' average self-reported functioning from the average functioning reported by informants, and computed Pearson correlations between these scores and cognitive measures of object naming, verbal attention span, verbal comprehension, spatial localization, verbal memory, and nonverbal memory. After applying Bonferroni correction, no cognitive measure was significantly correlated with the difference scores. However, they noted that there was a trend toward significance for verbal memory.

In this dissertation, we will be directly testing these accounts of anosognosia among persons with MCI by examining the relative contributions of distinct

neurocognitive domains, particularly global cognition, memory, and executive function to diminished awareness of difficulties across a diverse array of real world functional tasks.

Awareness of Deficits and Depression

The co-occurrence of awareness of deficits and depression in AD is a complex but well-recognized phenomenon, and has been specifically addressed in many studies. However, whereas several of these studies reported a strong association between increased awareness of deficits and prominent depressed or dysthymic mood (Clare, Wilson, Carter, Roth, & Hodges, 2004; Harwood, Sultzer, & Wheatley, 2000; Migliorelli et al., 1995; Sevush & Leve, 1993), other studies only found a trend in that direction (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991), and others yet failed to find such a relationship (Ott et al., 1996; Reed, Jagust, & Coulter, 1993; Verhey, Rozendaal, Ponds, & Jolles, 1993). The heterogeneous findings might be partly due to variability of study samples in terms of dementia severity and sample size or to the adoption of discrepant methodologies for assessing awareness and depression (Aalten, van Valen, Clare, Kenny, & Verhey, 2005).

Furthermore, among the studies that found strong positive correlations between awareness and depression, the interpretation of this finding remains controversial. The predominant hypothesis is that depression is a psychological reaction, an emotional response to the perceived decline in cognitive and functional abilities (Harwood, Sultzer, & Wheatley, 2000; Seltzer, Vasterling, & Buswell, 1995; Sevush & Leve, 1993); however others have contended that dysthymia is arguably a psychological reaction whereas major depression is an endogenous mood disorder (Starkstein et al., 1997; Zubenko, Moossy, & Kopp 1990). Another interpretation is that depression in dementia

is due to the neurochemical and neuropathological changes concomitant with dementia (Ballard, Bannister, & Oyebode, 1996; Verhey, Rozendaal, Ponds, & Jolles, 1993; Zubenko & Moossy, 1988). A third view is that the association between depressed mood and self-report of poor functioning is not specific to AD because non-demented depressed patients also tend to report poor functioning (Migliorelli et al., 1995; Mullen, Howard, David, & Levy, 1996; Smith, Henderson, McCleary, Murdock, & Buckwalter, 2000).

The differing positions on (and interpretations of) the association between awareness of deficits and depression notwithstanding, depression occurring in the context of a dementing disorder deserves clinical and empirical attention for several reasons. Co-morbid depression is quite treatable (Reifler, Larson, Teri, & Poulsen, 1986). However, if unrecognized and untreated, it can become a source of distress to both patients and their family caregivers (Garand, Dew, Eazor, DeKosky, & Reynolds, 2005; Garand et al., 2007; Rabins, Mace, & Lucas, 1982), negatively affect cognitive (Chodosh, Kado, Seeman, & Karlamangla, 2007; Greenwald et al., 1989) and functional (Alexopoulos et al., 2002; Fitz & Teri, 1994) abilities, compromise quality of life, and may result in reduced life expectancy (Burns, Lewis, Jacoby, & Levy, 1991; Steffens et al., 2006).

These adverse effects of depression on the physical, cognitive and emotional well-being of AD patients and their caregivers is directly relevant to the current focus on the early identification and treatment of MCI patients who, by the very nature of their disorder, are at risk of further cognitive and functional decline. To date, no study has explicitly examined the relationship between awareness of functional difficulties and depression in MCI. This dissertation proposes to investigate this question. If the association between depression and awareness of deficits among AD patients is found to

be also present in MCI, the knowledge will position clinicians and family members to intervene in a timely fashion to prevent further compromise of the patient's condition. For example, psychotherapy (Teri & Gallagher-Thompson, 1991) and antidepressant medication (Lyketsos et al., 2000) have been shown to be efficacious in AD and should help ameliorate depression in the MCI population as well.

Diminished Awareness of Functional Difficulties in MCI Revisited

Although the aforementioned studies of awareness of functional difficulties in MCI are important for providing preliminary evidence of reduced awareness of difficulties in this population, they had some limitations that may have biased their findings.

A major shortcoming of these studies is the use of the discrepancy between self and informant reports as the sole index of unawareness. This methodology assumes that the caregiver's evaluation of the patient's functional abilities is objective and accurate such that any discrepancy is due to the patient's misrepresentation of abilities. However, several studies have shown that caregivers' reports are subject to a variety of estimation biases such as their personality, mood, relationship to patient (e.g., spouse versus adult child), and perceived burden of care giving (Argüelles, Loewenstein, Eisdorfer, & Argüelles, 2001; DeBettignies, Mahurin, & Pirozzolo, 1990; Loewenstein et al., 2001; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). Furthermore, some functional difficulties may go undetected by both patients and caregivers (Wadley, Griffith, & Marson, 2002; Wadley, Harrell, & Marson, 2003).

Another shortcoming in prior studies is their use of the CDR (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993) as the principal instrument for

classifying patients as normal, MCI, or AD. Although the CDR is a useful instrument for describing individuals at various levels of cognitive and functional status, the validity of this diagnostic methodology has been called into question. A CDR score of 0.5 is not necessarily co-extensive with the clinical condition of MCI because patients with probable AD have also been assigned similar CDR scores. Indeed, the same patient may progress from MCI to AD and still remain at a CDR of 0.5 (Petersen, 2000; Petersen, Doody et al., 2001).

Furthermore, these studies (e.g., Albert et al., 1999; Tabert et al., 2002) used convenient samples of elderly adults presenting for clinical services at a memory disorders clinic rather than a random sample recruited from the community. Such sampling methodology is a potential source of bias (Petersen, 2004; Tuokko & Frerichs, 2000) and therefore limits the generalizability of their study findings to the wider population of individuals with MCI in the community. This dissertation will seek to address the above limitations by (1) using a sample of older adults recruited from both clinical and community sources, who are carefully characterized by means of neurologic evaluation, comprehensive neuropsychological examination, and consensus clinical judgment and (2) by comparing their self-report of functional status to their actual performance on objective measures of functional ability.

Studies of awareness of deficits in persons with AD have demonstrated that awareness is a heterogeneous phenomenon that dissociates across domains (Markova & Berrios, 2001; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996; Vasterling, Seltzer, Foss, & Vanderbrook, 1995; Vasterling, Seltzer, & Watrous, 1997). The initial studies of awareness of functional difficulties in MCI mentioned above did not

adequately account for this domain-specific character of awareness. Rather, they assessed awareness globally as though it were a unitary construct. Thus, there is need for a more thorough investigation of awareness with an eye to ascertaining its stability, or lack thereof, across different domains. This dissertation plans to accomplish this by examining awareness of functional difficulties across several cognitively demanding IADLs that are critical to autonomous functioning in the community. Such multi-component inquiry will permit the discrimination of the domains of higher order functional activities in which persons with MCI, as a group, demonstrate diminished awareness of difficulties from the domains where they still evidence intact awareness.

Of the three studies that investigated awareness of functional difficulties in MCI, only one (Farias, Mungas, & Jagust, 2005) probed the neuropsychological correlates of impaired awareness. However, this study did not include tests of executive function among its cognitive measures. This is a substantial omission given the evidence in the literature that MCI patients show impairments in executive function (Hanninen et al., 1997; Morris et al., 2001) and that executive dysfunction is one of the hypothesized substrates of unawareness of deficits (Harwood et al., 2005; Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Michon, Deweer, Pillon, Agid, & Dubois, 1994). Based on extant theories on the neurocognitive correlates of awareness, this dissertation will examine the relative contributions of distinct neurocognitive domains, particularly global cognitive status, memory, and executive function to impaired awareness of functional difficulties in MCI.

To the best of our knowledge, no prior study has investigated the relationship between awareness of functional difficulties and depression in MCI. This is an area in

need of research due to the above-mentioned association between awareness of deficits and depression in AD, as well as the negative physical, cognitive, and psychosocial effects of depression on both patients and caregivers. This need is further reinforced by the current focus on the early identification of MCI patients who are at risk of further decline because, as discussed above, depression in the context of a dementing disorder makes one vulnerable to further cognitive and functional deterioration, and vitiates overall quality of life.

Aims and Hypotheses

The purpose of this dissertation is to contribute to the growing body of literature examining diminished awareness of functional difficulties among individuals with MCI. We build on, and extend, prior research by examining the following aims and hypotheses.

Aim 1: To assess awareness of functional difficulties in MCI patients by comparing their self-report of higher order functional abilities—driving, financial management, medication management, grocery shopping, and telephone use—to their performance on objective measures of these abilities.

Hypothesis: MCI patients will show significantly greater discrepancy between self-report and objective performance relative to normal controls. This discrepancy will be more pronounced on the financial management and driving domains relative to other functional domains, because of the comparatively greater cognitive demands of these functional domains, thus demonstrating heterogeneity in awareness of functional difficulties among MCI patients. Preliminary analyses will examine group differences on objective measure of these functional domains in order to establish that MCI patients do indeed experience functional difficulties.

Aim 2: To examine the neuropsychological predictors of diminished awareness of functional difficulties in MCI in those functional domains in which reduced awareness of functional difficulties was demonstrated.

Hypothesis: Measures of executive function will explain a significantly greater portion of the variance in reduced awareness of functional difficulties relative to measures of other neurocognitive domains.

Aim 3: To examine the relationship between awareness of functional difficulties and depression in MCI

Hypothesis: MCI patients with preserved awareness of their functional difficulties will endorse significantly more symptoms of depression compared to MCI patients with diminished awareness (i.e. depression is conceptualized as resulting from one's awareness of functional difficulties).

METHODS

Participants

The initial sample for this study consisted of 138 older adults. Seventy-five of them had a putative diagnosis (i.e, pre Alzheimer's Disease Research Center (ADRC) diagnostic consensus conference) of *cognitively normal older adult* whereas 63 persons were putatively characterized as patients with MCI. They were recruited through the community (via talks and fliers) and through presentation to the UAB Memory Disorders Clinic for participation in UAB's ADRC and subsequently enrolled in the ADRC's Measuring Independent Living in the Elderly Study (MILES), a longitudinal study conducted at UAB's Center for Translational Research on Aging and Mobility (CTRAM). Because the measures specific to this dissertation were added to the MILES study battery after its inception, the analyses reported in this dissertation are based on

data acquired at either participants' baseline or first annual visit. Furthermore, the analyses are cross-sectional, not longitudinal.

Of the 75 persons presumptively characterized as cognitively normal older adults, four withdrew from the ADRC prior to their first annual visit, one is scheduled to have his ADRC first annual visit later this year, and two are yet to be formally diagnosed at the ADRC consensus conference. Of the 63 persons with initial diagnosis of MCI, three withdrew from the ADRC prior to their first annual visit, two persons' cognitive difficulties were determined to not be due to MCI, and one was diagnosed with mild AD at the ADRC consensus conference. These "exclusions" resulted in a final sample that consisted of 68 cognitively normal control participants and 57 persons with MCI. The sample is demographically representative of metropolitan Birmingham, Alabama (see Table 1) (US Census Bureau, 2002).

Diagnosis of MCI versus cognitively normal control was made by the ADRC consensus conference based upon neurological evaluation, neuroradiological data, and neuropsychological testing using Petersen/Mayo criteria for MCI (Petersen, Doody et al., 2001). Petersen/Mayo criteria was operationalized as follows: (1) memory complaint by patient and/or collateral source, as reported in interview with our clinical neurologists, (2) objective memory impairment on neuropsychological testing, operationalized as one or more memory test scores falling beyond 1.5 SD below older adult norms; (3) overall preserved general cognitive function, as reflected in a majority of other cognitive test scores falling above 1.5 SD below older adult norms; (4) generally intact functional activities, as measured by clinical interview information, CDR score, and collateral

source ratings on a functional capacity form developed at the UAB ADRC (Forsyth Functional Capacity Form); and (5) an absence of a dementia diagnosis.

Informed consent was obtained from all participants. The UAB Institutional Review Board approved all procedures (see Appendix A3 – A5).

Measures

Neuropsychological Assessment

An extensive neuropsychological battery was administered to each participant as part of their baseline or annual ADRC evaluations. This battery consisted of measures representing the following clinically-relevant neurocognitive domains:

Global Cognition: Total score on the Dementia Rating Scale, 2nd edition (DRS-2) (Jurica et al., 2001).

Attention: Attention subscale of the DRS-2, the Digit Span subtest of the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler, 1997b), the Spatial Span subtest of the Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 1997a), and Omission errors, Commission errors, and Hit Reaction Time on the Conners' Continuous Performance Test (CPT) (Conners, 1992).

Language: Boston Naming Test (Kaplan et al., 1983) and a semantic fluency composite (animals, fruits/vegetables, clothing) (Spreen & Strauss, 1991).

Memory: Memory subscale of the DRS-2, the Logical Memory subtest of the Wechsler Memory Scale, revised edition (WMS-R) (Wechsler, 1987), the Visual Reproduction subtest of WMS-III, the California Verbal Learning Test, second edition (CVLT-II) (Delis et al., 2000), and the10/36 Spatial Recall Test (Boringa et al., 2001).

Visuospatial Abilities: Construction subscale of the DRS-2 and the copy portion of the Executive Clock Drawing Task (CLOX 2) (Royall et al., 1998).

Abstraction: Conceptualization subscale of the DRS-2 and the Verbal Reasoning subtest of the Cognitive Competency Test (Wang & Ennis, 1986).

Executive Function: Initiation/Perseveration subscale of the DRS-2, Trails A and Trails B (Reitan & Wolfson, 1993), Trails C (Okonkwo et al., 2008), Perseveration errors on the CPT, spontaneous generation portion of the Executive Clock Drawing Task (CLOX 1), and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler, 1997b).

Depressive Symptoms: Geriatric Depression Scale (GDS) (Yesavage, 1988).

Functional Assessment

Whereas participants underwent neuropsychological assessments during their ADRC visit, the functional assessments described in this dissertation were conducted during their MILES study visit. The only exception involved participants who were concurrently enrolled in MILES and in another ADRC study of functional change in MCI — the Cognitive Observations in Seniors (COINS) study. In those cases, their assessment on the Financial Capacity Instrument (FCI, see below) occurred during their COINS visit. The principal investigators of both studies came to this arrangement as a way to ensure that the FCI data of these participants were not affected by practice effect, a possibility if participants were administered the FCI at both their MILES and COINS visits. The functional assessment data utilized in this dissertation are from the following measures (for a listing of the specific items used, see Appendix A2):

Objective performance

Financial Capacity Instrument (FCI; Marson et al., 2000): The FCI is a standardized psychometric instrument that directly assesses nine domains of financial ability. Only four of the nine domains – Financial Conceptual Knowledge, Cash Transactions, Bank Statement Management, and Bill Payment – were administered to participants because they were the domains that best discriminate between MCI participants and controls (Griffith et al., 2003). The FCI's domains have internal consistency reliabilities ranging from 0.85 to 0.92, test-retest reliabilities ranging from 0.85 to 0.98, and inter-rater agreement ranging from 86.4% to 99.7% (Marson et al., 2000).

Observed Tasks of Daily Living (OTDL; Diehl et al., 2005; Diehl, Willis, & Schaie, 1995): This validated instrument requires participants to perform actions required to solve everyday tasks in three domains - medication use, telephone use, and financial management. Only a subset of items from the medication use and telephone use domains was used in the present analyses. All OTDL tasks make use of actual everyday objects (e.g., medical history forms, telephone, coins and currency) using standardized administration procedures. On the OTDL, participants who either do not engage tasks within fifteen seconds of presentation or say "I do not know" are provided prompts to assist them with task completion. Performance is scored using a correct(0)-incorrect(1) format. The OTDL has a reliability (Kuder-Richardson 20) of 0.82 (Diehl et al., 2005).

Timed Instrumental Activities of Daily Living (TIADL; Owsley, McGwin, Sloane, Stalvey, & Wells, 2001; Owsley, Sloane, McGwin, & Ball, 2002): This test is a validated measure of everyday instrumental activities. It evaluates speed and accuracy of task completion within five domains of everyday functioning – telephone use, nutrition

evaluation, financial abilities, grocery shopping, and medication management. Tasks from the financial abilities domain were not used in this dissertation. Like the OTDL, the TIADL also makes use of actual everyday objects (e.g., telephone book, canned food) and all tasks are administrated using standardized procedures. During task execution, the examiner assigns participants an error code reflecting whether the task was: (1) completed correctly within the time limit with no errors, (2) completed within the time limit with minor errors, or (3) not completed in the time limit or completed with major errors. Because hardly any participant received error scores of 3, error categories were recoded as follows: (0) task was completed correctly within the time limit with no errors, or (1) task was completed with some error or was not completed within the time limit. This rescoring procedure, which provides a safeguard against sparseness of data, was successfully adopted in a prior report (Wadley, Okonkwo, Crowe, & Ross, in press). The TIADL has a test-retest reliability of 0.85 (Owsley, Sloane, McGwin, & Ball, 2002).

On-Road Driving Evaluation: The driving skills of each licensed currently driving participant were assessed during the MILES study visit, in collaboration with the UAB Driving Assessment Clinic. Under clear weather conditions, the assessment was performed during the study visit. Under rainy or inclement weather conditions the evaluation was postponed and conducted in fair weather within two weeks of the study visit. Each participant drove an instrumented vehicle with dual controls under the supervision and evaluation of a Certified Driving Rehabilitation Specialist (CDRS) who was also a licensed occupational therapist (OTR/L). The CDRS was blind to participants' group status (i.e., MCI or cognitively normal). At multiple pre-established points during the drive, the CDRS coded each participant's performance on specific

driving skills using a 5-point Likert scale: 1 = CDRS took control of car and ended road test; 2 = skill performed in an unsafe manner and/or CDRS verbally intervened; 3 = skill performed in an unsatisfactory manner and/or would have been unsafe if another vehicle was approaching; 4 = skill performed in a less than optimal manner; and 5 = skill performed in an optimal manner. For this study, the specific driving skills analyzed include parking, lane control, turning, and exiting highways and interstates (see Appendix A2). They were selected *a priori* on the basis of their importance to the proper and safe operation of a motor vehicle. Because the vast majority of participants received ratings of either 5 or 4, we recoded ratings on the driving variables as follows: 0 (optimal execution of skill), or 1 (less than optimal execution of skill). This approach was satisfactorily adopted in an earlier study (Wadley et al., in press).

Self-Report

Current Financial Capacity Form (CFCF; Marson et al., 2000): This is a parallel self-report version of the FCI. It elicits participants' judgment about their current level of functioning across the same financial tasks evaluated on the FCI. This study only included CFCF domain-level judgments corresponding to the four FCI domains being evaluated. Response categories are (0) cannot do, (1) can do but need help, or (2) can do without help. These categories were recoded as (0) can do without help, or (1) can do but need help because only about one percent of cases rated themselves as "cannot do" on any CFCF domain. The CFCF has a test-retest reliability of 0.98 (Wadley, Harrell, & Marson, 2003).

MILES Self-Report Questionnaire (see Appendix A1): This is a new self-report measure that inquires into the amount of difficulty experienced in performing various

tasks required for independent living in the areas of driving, medication/health care management, grocery shopping, and telephone use. The items on this questionnaire were developed to closely parallel the functional skills assessed on the OTDL, the TIADL, and the on-road driving evaluation. Responses were made on a 4-point Likert scale: 1 = not difficult; 2 = a little difficult; 3 = moderately difficult; and 4 = very difficult. The vast majority of participants rated themselves as either having no difficulty or a little difficulty. Therefore, these ratings were recoded as (0) no difficulty or (1) some difficulty. Within the sample used in this study, this questionnaire has an internal consistency reliability of 0.84 and a test-retest reliability of 0.72.

Statistical Analysis

A variety of abilities were objectively assessed within each functional domain, resulting in numerous indices of behavior that were not necessarily independent observations and therefore did not warrant individual examination. For example, the MILES Self-Report Questionnaire item D2 that asks *How difficult is it for you to drive safely around a sharp curve to the right?* maps onto five skills assessed at different time points during the on-road evaluation. To limit multiplicity, it was necessary to implement some data reduction. This was accomplished in a 2-step process. First, participants' scores on all objective test items that map onto a single MILES Self-Report Questionnaire item were averaged to form a composite variable. For example, the MILES Self-Report Questionnaire item G2 that asks *How difficult is it for you to find and read the ingredients on cans of food?* is related to three distinct tasks on the TIADL in which participants are asked to find and read the ingredients on a can of food. Therefore, participants' scores on these three TIADL tasks were averaged to form a composite

variable. This step of the data reduction process resulted in 15 objective-measure composite variables in addition to the four FCI domain-level variables. If a participant was missing scores on any component item, their composite score was calculated as the average of their scores on the non-missing component items.

Because 19 variables were still deemed an inordinate number of (non-independent) comparisons to make, and because the thrust of this study is to examine domain-specificity in awareness of functional difficulties, a second data reduction was effected. Composites for each functional domain were formed by averaging participants' scores on the composite variables derived from the just-described data reduction process. This resulted in 5 functional-domain-level objective measure composites – driving, financial management, medication management, grocery shopping, and telephone use. This second data reduction was also performed for ratings on the MILES Self-Report Questionnaire and on the CFCF in order to have the self-report analogues of the objective measure composites. For example, participants' self-ratings on items M1 through M5 on the MILES Self-Report Questionnaire were averaged to obtain a composite self-report measure of medication/health care management abilities. With the exception of scores on the FCI, which were on an interval scale, all other composite variables (self-report and objective) were dichotomous: (0) can do without difficulty, or (1) experiences some difficulty.

Demographic and clinical variables: Group differences in age, education, DRS-2 Total scores, and depressive symptoms were analyzed with independent samples t-tests. Differences in gender and racial distributions across groups were examined using Pearson's $\chi 2$ tests of independence.

Aim 1: To assess awareness of functional difficulties in MCI patients by comparing their self-report of higher order functional abilities to their performance on objective measures of these abilities.

Hypothesis: MCI patients will show significantly greater discrepancy between self report and objective performance relative to normal controls. This discrepancy will be more pronounced on the financial management and driving domains relative to other functional domains, because of the comparatively greater cognitive demands of these functional domains, thus demonstrating heterogeneity in awareness of functional difficulties among MCI patients. Preliminary analyses will examine group differences on objective measure of these functional domains in order to establish that MCI patients do indeed experience functional difficulties.

Analysis: The preliminary examination of group differences on objective measures of functional ability was executed with a series of $\chi 2$ analyses. These $\chi 2$ analyses examine the proportion of MCI versus control participants who perform the objective tasks with "no difficulty" versus "some difficulty." Hypothesis 1 proper was tested with five binary logistic regression analyses, one for each functional domain. For each analysis, self-report was modeled as a function of objective outcome *(no difficulty vs. some difficulty)*, group membership *(MCI vs. control)*, and a group*objective outcome interaction. The interaction was the substantive term of interest because it would reveal whether the association between self-report and objective outcome was comparable across control participants and persons with MCI. Consistent with our hypothesis, we expected to find a significant group*objective outcome interaction indicating that the association between self-report and objective outcome was stronger for controls relative to patients with MCI.

Aim 2: To examine the neuropsychological predictors of diminished awareness of functional difficulties in MCI in those functional domains in which reduced awareness of functional difficulties was demonstrated.

Hypothesis: Measures of executive function will explain a significantly greater portion of the variance in reduced awareness of functional difficulties relative to measures of other neurocognitive domains.

Analysis: To examine this hypothesis, we first calculated Discrepancy Index (DI) scores using the formula [(self-rating minus objective test outcome) (-1)][‡] (Barrett, Eslinger, Ballentine, & Heilman, 2005; Farias, Mungas, & Jagust, 2005; Tabert et al., 2002). To derive objective test outcomes for the FCI, a *can do without difficulty* (0) outcome was defined as a score better than 1.5 SD below the control group mean (33.13) on the FCI composite variable whereas an *experiences some difficulty* (1) outcome was defined as a score falling at or worse than 1.5 SD below the control group mean on the FCI composite variable. This psychometric approach to assigning capacity outcomes has been successfully employed in prior studies (Marson et al., 2000; Okonkwo et al., 2007; Okonkwo et al., in press; Wadley et al., 2007). The DI scores ranged from -1 to +1. They were 0 when a participant accurately estimated his/her functional ability relative to his/her objective test outcome; +1 when he/she overestimated his/her ability relative to his/her objective outcome; and -1 when he/she underestimated his/her ability relative to his/her objective outcome.

[‡] The valence of -1 was invoked to enhance the "face validity" of the DI scores. Without it, those who overestimated would have negative DI scores (i.e., self rating of 0 minus objective outcome of 1 = -1) and those who underestimated would have positive DI scores (i.e., self rating of 1 minus objective outcome of 0 = 1).

Next, participants' scores on the measures constituting each neurocognitive domain were converted to z scores and averaged to form a composite variable representing the construct (Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Sheline et al., 2006). This resulted in seven cognitive composites: global cognition, attention, language, memory, visuospatial abilities, abstraction, and executive function. If a participant was missing scores on any component neurocognitive variable, their composite score was calculated as the average of their scores on the non-missing component variables. The neurocognitive composites were then entered into a series of stepwise multinomial logistic regression predicting DI scores on each functional domain. For these analyses, the "accurate" subgroup was the reference group. Therefore parameter estimates were developed for the "underestimation" and "overestimation" subgroups.

Aim 3: To examine the relationship between awareness of functional difficulties and depression in MCI.

Hypothesis: MCI patients with preserved awareness of their functional difficulties will endorse significantly more symptoms of depression compared to MCI patients with diminished awareness (i.e., depression is conceptualized as resulting from one's awareness of functional difficulties).

Analysis: This hypothesis was examined by testing mean differences in depressive symptoms among the "accurate," "underestimation," and "overestimation" subgroups, using one-way analysis of variance.

All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). Only findings with a 2-tailed p value $\leq .05$ were considered significant.

RESULTS

Demographic and clinical variables

Table 1 shows the result of group comparisons on demographic and clinical variables. As expected by virtue of diagnosis, patients with MCI differed significantly from the control group on DRS-2 Total scores. The two groups did not differ from each other in age, years of education, depressive symptoms, or in gender or racial distributions. Table 2 presents group means and standard deviations on the measures that constituted each neurocognitive domain.

Aim 1: Awareness of functional difficulties in MCI

The preliminary examination of group differences in performance measures of functional ability revealed that, compared to control participants, MCI patients were significantly more likely to evince "some difficulty" on the functional domains of financial management [χ^2 (1) = 19.57, p < .001; OR (95% CI) = 9.87 (3.14, 31.01)], driving [χ^2 (1) = 4.61, p = .032; OR (95% CI) = 2.36 (1.07, 5.19)], and telephone use, [χ^2 (1) = 7.01, p = .008; OR (95% CI) = 3.42 (1.33, 8.75)]. There were no significant group differences on the other functional domains. However, proportionately more MCI patients evinced "some difficulty" on these domains relative to controls. These results are displayed on Table 3.

The logistic regression models for examining the association between self-report and objective test outcome failed to converge to an admissible solution. This lack of convergence was due to quasi-separation in the dataset as a result of (i) cells with 0 counts, (ii) suboptimal overlap in the distribution of self-report ratings across study groups on some functional domains, and (iii) high correlation between the covariates (group and objective test outcome) on some functional domains (Hosmer & Lemeshow,

2000). This convergence failure led to a revision of the analytical strategy for Aim 1. The revised analytic plan involved analyses of group differences on the DI scores described above, using likelihood ratio G^2 tests. Likelihood ratio G^2 tests are based on maximum likelihood estimation, just as logistic regression is, and examine the hypothesis of no association between rows (group membership) and columns (DI scores) in a contingency table (Agresti, 1996). A similar procedure was successfully used in a prior study of awareness of difficulties in financial abilities in MCI (Okonkwo et al., in press).

Table 4 presents the results from the G^2 analyses. The discrepancy between self-report and objective test outcome was significantly greater for patients with MCI compared to controls only on the financial management domain, $\underline{G}^2$ (2) = 14.02, $\underline{p} < .001$. On this functional domain, 6.3% of controls versus 7.1% of MCI patients underestimated their abilities; 89.1% of controls versus 64.3% of MCI patients accurately estimated their abilities; and 4.7% of controls versus 28.6% of MCI patients overestimated their abilities.

Aim 2: Neuropsychological predictors of awareness of functional difficulties in MCI

Within the MCI group, counts on the DI for financial management indicated that 4 persons underestimated their financial abilities relative to their objective test outcome, 36 persons accurately estimated their financial abilities relative to their objective test outcome, and 16 persons overestimated their financial abilities. Because an n of 4 was deemed inadequate for developing reliable neurocognitive models, the 4 persons who underestimated their financial abilities were excluded from further neurocognitive analyses. This yielded two subgroups: persons who accurately estimated their financial abilities relative to their objective test outcome (n = 36) and persons who overestimate

their financial abilities relative to their objective test outcome (n = 16).With only two groups, the originally-planned multinomial logistic regression was reduced to a binary logistic regression. The event modeled was the probability of being in the accurate subgroup.

A series of preliminary univariate analyses was executed to identify the bivariate associations between each neurocognitive domain and accuracy of self-report on the financial management domain. These analyses revealed that: (i) the attention domain was significantly associated with accuracy of self-report, $\beta = 1.18$, $\chi^2(1) = 7.08$, $p = .008$, OR(95% CI) = 3.25 (1.37, 7.73). In essence, among MCI patients, each standard deviation increment on the attention composite was associated with about three-fold increase in the odds of accurately estimating one's financial abilities relative to one's objective test outcome on the FCI. This model had satisfactory calibration (Hosmer and Lemeshow test, $\chi^2(8) = 5.83$, $p = .667$) and discrimination (overall classification accuracy = 75.0%). (ii) The language domain was significantly associated with accuracy of self-report, $\beta = 1.43$, $\chi^2(1) = 6.15$, $p = .013$, OR(95% CI) = 4.17 (1.35, 12.87). In essence, among MCI patients, each standard deviation increment on the language composite was associated with about four-fold increase in the odds of accurately estimating one's financial abilities relative to one's objective test outcome on the FCI. This model had satisfactory calibration (Hosmer and Lemeshow test, $\chi^2(8) = 7.78$, $p = .455$) and discrimination (overall classification accuracy = 71.2%). (iii) The abstraction domain was significantly associated with accuracy of self-report, $\beta = 0.87$, $\chi^2(1) = 4.76$, $p = .029$, OR(95% CI) = 2.39 (1.09, 5.24). In essence, among MCI patients, each standard deviation increment on the abstraction composite was associated with about two-fold

increase in the odds of accurately estimating one's financial abilities relative to one's objective test outcome on the FCI. This model had satisfactory calibration (Hosmer and Lemeshow test, $\chi^2(8) = 8.19$, $p = .415$) and discrimination (overall classification accuracy = 74.5%). Finally, (iv) the executive function domain was significantly associated with accuracy of self-report, $\beta = 0.86$, $\chi^2(1) = 3.91$, $p = .048$, OR(95% CI) = 2.35 (1.01, 5.49). In essence, among MCI patients, each standard deviation increment on the executive function composite was associated with about two-fold increase in the odds of accurately estimating one's financial abilities relative to one's objective test outcome on the FCI. This model had satisfactory calibration (Hosmer and Lemeshow test, $\chi^2(8) = 6.59$, $p = .582$) and discrimination (overall classification accuracy = 71.2%).

There were trends towards statistical significance for the global cognition [$\beta = 0.58$, $\chi^2(1) = 3.30$, $p = .069$, OR(95% CI) = 1.79 (0.96, 3.35)] and memory [$\beta = 0.85$, $\chi^2(1) = 3.43$, $p = .064$, OR(95% CI) = 2.35 (0.95, 5.78)] composites. Both models calibrated adequately (Hosmer and Lemeshow test, $\chi^2(8) = 7.49$, $p = .484$ and $\chi^2(8) = 6.15$, $p = .630$, respectively) and discriminated fairly well (overall classification accuracy = 68.6% and 70.6%, respectively).

Next, all the neurocognitive composites were entered into a stepwise logistic regression in order to parsimoniously identify the non-overlapping contribution of each composite to accuracy of self-report of financial abilities. This analysis revealed that only the attention domain was significantly associated with accuracy of self-report, $\beta = 1.25$, $\chi^2(1) = 7.48$, $p = .006$, OR(95% CI) = 3.48 (1.42, 8.50). These results suggest that a standard deviation increment on the attention composite is associated with about three-and-half times increased odds of accurately estimating one's financial abilities relative to

one's objective test outcome on the FCI. This model had satisfactory calibration (Hosmer and Lemeshow test, $\chi^2(8) = 3.02$, $p = .933$) and discrimination (overall classification accuracy = 72.5%). This finding was contrary to our expectation that the executive function composite would be the most potent correlate of awareness of difficulties among MCI patients.

Across the univariate and multivariable regression models tested, the neurocognitive composites were consistently much better at classifying the MCI patients who accurately estimate their financial abilities than they were at classifying the patients who inaccurately estimated their financial abilities. The foregoing results are summarized on Table 4.

An exploratory stepwise logistic regression analysis was performed to identify the component attention variable that best discriminates the "accurate" and "overestimated" subgroups. None of the six attention variables was selected for entry at the .05 alpha level. The closest trend was for CPT Commissions (a measure of response inhibition), $\beta = 0.89$, $\chi^2(1) = 1.83$, $p = .176$, OR(95% CI) = 2.45 (0.67, 8.96).

Aim 3: Relationship between awareness of functional difficulties and depression in MCI

Contrary to our hypothesis, MCI patients who accurately estimated their financial abilities relative to objective performance did not report significantly greater depressive symptoms compared to those patients who overestimated their financial abilities (see Table 5).

To further explore this null finding, the MCI group was partitioned into four subgroups: (i) those who *accurately reported that they had no difficulties with financial*

management (i.e., those for whom self-report = 0 and objective outcome = 0), n = 30; (ii) those who *accurately reported that they had some difficulties with financial management* (i.e., those for whom self-report = 1 and objective outcome = 1), n = 6; (iii) those who *overestimated their financial abilities relative to their objective outcome* (i.e., those for whom self-report = 0 and objective outcome = 1), (n = 16); and (iv) those who *underestimated their financial abilities relative to their objective outcome* (i.e., those for whom self-report = 1 and objective outcome = 0), (n = 4).

Single-degree of freedom t-tests of subgroup differences on depressive symptoms, corrected for unequal variance across groups, revealed that MCI patients who underestimated their financial abilities reported significantly higher depressive symptoms (mean = 9.00, SD = 9.49) compared to those who accurately reported that they had no difficulties with financial management [mean = 4.07, SD = 3.67; t (52) = 2.13, p = .038] or those who overestimated their abilities (mean = 4.00, SD = 4.03; t (52) = 2.05, p = .045]). There were no other subgroup differences on depressive symptoms. The mean (SD) depressive symptom reported by those who accurately reported that they had some difficulties with financial management was 5.00 (4.05).

DISCUSSION

Awareness of functional difficulties in MCI

Assessment of functional abilities in MCI is an important clinical and diagnostic endeavor as it is essential to differentiating MCI from AD (Petersen, Stevens et al., 2001). Indeed, proceedings from a recent international expert conference on MCI noted that "a structured assessment of functional capacities will become increasingly important in determining the point at which people with mild cognitive impairment progress to

dementia"(Gauthier et al., 2006). However, the reliability and validity of the information obtained from clinical assessment of functional abilities, especially when the assessment is entirely report-based, is dependent on the accuracy of the reporter. Investigating the accuracy of self-report of functional abilities is therefore a critical scientific and clinical undertaking.

In this study, we used a multi-domain approach to examine accuracy of self-report of functional abilities in MCI by comparing patients' self-report of functioning to their performance on objective measures. This represents a novel approach as prior investigations of awareness of functional difficulties in MCI have only compared patients' self-report to informant report (Albert et al., 1999; Farias, Mungas, & Jagust, 2005; Tabert et al., 2002), notwithstanding the methodological limitations of this approach (Loewenstein et al., 2001; Okonkwo et al., in press; Wadley, Harrell, & Marson, 2003; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). In addition, these studies examined awareness of difficulties as though it were a unitary, all-or-nothing phenomenon despite evidence from prior reports suggesting that such an approach may be overly reductionist (Aalten, van Valen, Clare, Kenny, & Verhey, 2005; Kotler-Cope & Camp, 1995; Vasterling, Seltzer, & Watrous, 1997).

Although several studies have shown that patients with MCI experience difficulties in the performance of everyday tasks(Griffith et al., 2003; Morris et al., 2001; Okonkwo et al., 2007), we sought to replicate those findings in this study as a logical precondition for examining awareness of the said functional difficulties. We found that MCI patients were significantly more likely than controls to exhibit some difficulty in the performance of tasks assessing financial abilities, driving, and telephone use. Similar

findings have been observed in several prior studies (Artero, Touchon, & Ritchie, 2001; Daly et al., 2000; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Peres et al., 2006; Tuokko, Morris, & Ebert, 2005; Wadley et al., in press).

When self-report of functional abilities was referenced against objective test performance across several functional domains, we found that relative to control participants, patients with MCI demonstrated lower accuracy in their estimation of ability only on the financial management domain. Specifically, patients with MCI tended to overestimate their abilities on this domain. This finding immediately highlights two important points. First, it provides evidence that the degree of concordance between self-report of functional abilities and objective performance is generally comparable across persons with MCI and healthy older adults. Therefore, reliance on self-report in this patient population may, overall, not be any more problematic than among healthy older adults. Some studies have found that self-report of cognitive function is related to objective cognitive function and future cognitive decline among MCI patients (e.g., Cook & Marsiske, 2006; Crowe et al., 2006). Secondly, this finding supports the notion that awareness of functional difficulties is a heterogeneous phenomenon that is preserved in some domains and diminished in others (Aalten, van Valen, Clare, Kenny, & Verhey, 2005; Derouesne et al., 1999; Vasterling, Seltzer, & Watrous, 1997).We originally expected that MCI patients would also demonstrate significantly greater self-objective discrepancy, relative to control participants, on the driving domain. This hypothesis was not supported by the data although MCI patients were also less accurate and exhibited greater overestimation of abilities on this domain relative to the cognitively normal older adults.

Financial management and driving share two important commonalities – they are cognitively intensive and have greater bearing on an individual's personal autonomy relative to the other functional domains assessed. Our findings, therefore, suggest that when patients with MCI are asked to rate their present ability on relatively complex functional abilities that have implications for their personal autonomy, they may tend to erroneously (and/or defensively) reference their prior ability levels as veritable indices of their present ability, resulting in an overestimation of present abilities for some patients. On the other hand, if they are asked to rate their present ability on functional abilities that are comparatively less "coveted," they may become less guarded, leading to an underestimation of present abilities for some patients as was the case on the grocery shopping domain. However, this interpretation is speculative.

A competing reason for the exclusive between-group differences on the Discrepancy Index scores for financial abilities relates to the manner in which "objective difficulty" was defined on this domain. As noted earlier, "objective difficulty" was defined in reference to the control group's performance. All participants received an outcome rating of 0 *(can do without difficulty)* if their FCI composite score was better than 1.5 SD below the control group mean on the FCI composite. If their composite score was at or worse than 1.5 SD below the control mean, they received a rating of 1 *(experiences some difficulty).* This procedure differs from that adopted on other functional domains where participants received an outcome rating of 0 or 1 based on successful completion of the tasks subsumed under the domain. Because the control group served as the reference for "objective difficulty," their base rate of *some difficulty*

was, ipso facto, quite low on this domain (see Table 3). This low base rate, in turn, meant that control participants had little room to overestimate their financial abilities.

Even so, the initial interpretation of the data is supported by evidence from the only prior study, to date, that has examined agreement between self-report of functional abilities and objective performance in MCI (Okonkwo et al., in press). In that study, the authors focused on the agreement between self-report of financial abilities and performance on an objective test of financial skills among a group of patients with MCI. They found that patients with MCI exhibited overestimation of abilities on financial capacity domains of checkbook management, bank statement management, and bill payment, but not on any other domains. Relative to the other financial capacity domains tested, these three domains are arguably more complex and perhaps more relevant to an older adult's financial autonomy. On the other hand, MCI patients committed underestimation errors on the financial capacity domain of investment decision making, a financial skill likely to be less commonly exercised and, therefore, less essential for fiscal autonomy. An earlier investigation that compared self-report of financial abilities to objective test performance in an AD sample (Wadley, Harrell, & Marson, 2003) also found that, compared to healthy controls, patients with mild AD overestimated their financial skills on several financial capacity domains.

The present study's finding that some MCI patients may not be fully aware of the difficulties they experience with regards to financial abilities raises a number of important considerations. Financial capacity is a higher order functional ability that is critical to personal autonomy and independent functioning in the community (Marson et al., 2000). Accordingly, reduced awareness of impairments in financial capacity can pose

enormous challenges to family members and health care professionals who work with older adults. The older adult who is experiencing difficulties with managing his/her financial affairs but is not fully aware of this might fail to request appropriate assistance or accept such assistance when offered. This exposes the individual to heightened risk of overt (e.g., telephone scams) and covert (e.g., undue influence by third parties) financial exploitation, unintentional self-impoverishment, and in some cases conservatorship proceedings and loss of financial/personal autonomy (Marson, 2001; Nerenberg, 1996). Similarly, the older adult who is beginning to encounter difficulties with driving and is either not aware of them or is unwilling to acknowledge them and modify driving accordingly poses a safety risk to both self and the community. In addition, repeated traffic infractions could precipitate loss of driving privileges (Ball et al., 1998; Carr, Duchek, Meuser, & Morris, 2006; Cotrell & Wild, 1999; Marson, 2002; Rimmo & Hakamies-Blomqvist, 2002).

Patients' unawareness of difficulties also impacts the psychological functioning of family members. Although family members typically assume the caregiving role voluntarily out of genuine love and concern, caregiving for persons with cognitive or medical problems taxes one's mental and psychological resources (Garand, Dew, Eazor, DeKosky, & Reynolds, 2005; Garand et al., 2007; Halm & Bakas, 2007; Roth, Mittelman, Clay, Madan, & Haley, 2005; Zhang, Mitchell, Bambauer, Jones, & Prigerson, 2008). Various studies have shown that the burden experienced by caregivers of patients with dementia is aggravated in the context of unawareness of deficits by the patient (DeBettignies, Mahurin, & Pirozzolo, 1990; Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997). This relationship persists even after adjusting for

potential confounds such as dementia severity, level of functional impairment, amount of additional assistance received by caregiver, and amount of time caregiver spends with patient. (Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997). In turn, a caregiver's psychological distress negatively impacts the care recipient's quality of life and often precipitates institutionalization of the patient (Harwood, Sultzer, & Wheatley, 2000; McClendon, Smyth, & Neundorfer, 2004, 2006). Because this vicious cycle is partly maintained by the appraisals and attributions caregivers make (McClendon, Smyth, & Neundorfer, 2004; Wadley & Haley, 2001), interventions that help family members realize that misestimation of abilities is a characteristic feature of dementia, even in its earliest stages, has the potential to empower them to cope adaptively with the caregiving role and also protect the patient from undue embarrassment and self-blame.

Although diagnostic criteria for MCI have been expanded to accommodate informant report and clinician determination of cognitive and functional difficulties, the patient's report of cognitive and functional abilities is still accorded substantial weight in the diagnostic process (Petersen, 2004). The finding that some patients' self-report of functioning is at variance with actual abilities, at least on the financial management domain, questions the heavy reliance on report-based assessment and underscores the value of objective functional testing in accelerating identification of older adults who have begun to experience more functional decline than is accounted for by age, and therefore likely to meet criteria for MCI. Timely identification is considered a critical clinical goal because certain pharmacologic interventions for AD may be maximally effective when administered in the earliest stages of the disease (Petersen & Morris, 2005).

Related to the foregoing, the reported association between unawareness of difficulties and progression to AD among persons with MCI (Tabert et al., 2002) suggests that the subset of MCI patients who demonstrated overestimation of financial abilities (28.6% of the MCI group) may be at greater risk of progression to AD over time. This empirical question can be addressed more definitively with longitudinal data. In addition, this subset of patients may also benefit from focused clinical care aimed at slowing the disease process.

Neuropsychological predictors of awareness of functional difficulties in MCI

Neurocognitive studies have the potential to improve our understanding of the relationship between cognitive dysfunction and functional loss in MCI by illuminating specific cognitive processes essential to discrete functional abilities (Okonkwo et al., 2008). With regard to awareness of difficulties, such studies could highlight the specific cognitive impairments that threaten accurate perception of functional status among persons with MCI. These findings can, in turn, facilitate the development of targeted interventions that bolster awareness of difficulties in this population (Clare, 2004a; Levine et al., 2000; Requena et al., 2004; Rozzini et al., 2007).

In univariate analyses, we found that composite measures of attention, language, abstraction, and executive function were significant correlates of accuracy of self-report of financial abilities among persons with MCI. Each standard deviation increase in scores on these composites resulted in between two- and four-fold increases in the odds of accurately estimating one's financial abilities relative to one's objective test performance. The global cognition and memory composites demonstrated trends towards significance

but fell short of the .05 criterion. A multivariable analysis provided support for only the impact of attention on accuracy of self-report of financial abilities.

Only one prior study has examined the neuropsychological correlates of awareness of functional difficulties in MCI. Farias, Mungas, and Jagust (2005) computed differences scores by subtracting patients' self-report of functioning from informant reports of patients' functioning. Pearson correlation analyses between these scores and cognitive measures of object naming, verbal attention span, verbal comprehension, spatial localization, verbal memory, and nonverbal memory failed to yield any significant findings. However, they noted that there was a trend toward significance for verbal memory.

Studies that investigated the neuropsychological underpinnings of awareness of deficits in AD have suggested the involvement of diverse cognitive domains including object naming (Sevush & Leve, 1993), attention (Mangone et al., 1991), visuospatial abilities (Mangone et al., 1991; Ott et al., 1996), verbal memory (Migliorelli et al., 1995; Reed, Jagust, & Coulter, 1993; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996), nonverbal memory (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991; Mangone et al., 1991), executive function (Dalla Barba, Parlato, Iavarones, & Boller, 1995; Harwood et al., 2005; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Van Wielingen, Tuokko, Cramer, Mateer, & Hultsch, 2004), and global cognitive impairment (Harwood, Sultzer, & Wheatley, 2000; Kashiwa et al., 2005; Seltzer, Vasterling, Hale, & Khurana, 1995; Smith, Henderson, McCleary, Murdock, & Buckwalter, 2000). Interestingly, just as many studies have failed to find the suggested associations, indicating that the

relationship between awareness of deficits and neuropsychological functioning in dementia may not be straightforward (for a systematic review, see Clare, 2004a).

In the present study, we expected that the composite measure of executive function would explain the greatest portion of the variance in awareness of functional difficulties in MCI relative to other cognitive domains. The emergence of attention as the predominant neurocognitive correlate of accuracy of self-report was unanticipated. However, prior dementia studies have shown that attention is an important cognitive factor with regards to awareness of deficits in Parkinson's disease (Seltzer, Vasterling, Mathias, & Brennan, 2001) and AD (Mangone et al., 1991). In addition, a prior study that investigated the neuropsychological correlates of financial abilities among persons with MCI found that a composite measure of attention was strongly associated with financial capacity across multiple financial domains (Okonkwo, Wadley, Griffith, Ball, & Marson, 2006). Therefore, it is possible that attentional capacities are particularly relevant to financial abilities, as assessed using the FCI, and the accurate estimation thereof.

Nonetheless, it bears noting that the measures that constitute the attention composite arguably encompass and assess skills that are executive in nature, such as temporal integration and manipulation of information, response inhibition, mental flexibility, self-monitoring, tracking, and set shifting (D'Esposito & Postle, 1999; Farah, 2003; Lezak, Howieson, & Loring, 2004; Sheline et al., 2006; Steffens et al., 2004). Furthermore, the dorsolateral prefrontal cortex which is known to be the neuroanatomical substrate for executive functions of sequential planning, goal-formulation, organization, and self-monitoring equally mediates complex attention (Fuster, 1997; Luria, 1973; Sterling, 2004). Indeed, the *central executive* component of Baddeley's working memory

system is also interchangeably referred to as the *attentional controller* and the *supervisory attention system* (Baddeley & Hitch, 1994; Norman & Shallice, 1986).Therefore, in a more general and removed sense, one might contend that executive function is the most important cognitive domain for understanding diminution in awareness of deficits in dementia.

It is also noteworthy that in both univariate and multivariable analyses, neuropsychological measures were substantially and consistently better at classifying patients who accurately estimated their financial abilities than they were at classifying those who overestimated their abilities. In addition, the attention composite, which was the only significant multivariable correlate of accuracy of self-report of financial abilities among MCI patients, only accounted for twenty-five percent of the variance in accuracy of self-report. These observations suggest that diminution in awareness of functional difficulties in MCI may be more heavily undergirded by patient characteristics that are not fully represented in the neuropsychological armamentarium. A similar notion was proposed by Clare (2004a) who stated that, "neuropsychological factors are unlikely to provide a complete explanation for variations in awareness in AD, and that other factors should be considered (p. 118)." Future studies should, therefore, consider the impact of factors such as age, gender, educational attainment, race, cerebrovascular burden, medical comorbidity, and duration of illness on awareness of functional difficulties in MCI.

Relationship between awareness of functional difficulties and depression in MCI

There is ample evidence in the literature, suggesting that AD patients who are more aware of their deficits experience increased depressed mood possibly as a reaction

to the perceived decline in functional and cognitive abilities (Agnew & Morris, 1998; Clare, Wilson, Carter, Roth, & Hodges, 2004; Harwood, Sultzer, & Wheatley, 2000; Seltzer, Vasterling, & Buswell, 1995; Sevush & Leve, 1993). Accordingly, we expected to find that MCI patients who exhibit intact awareness of functional difficulties would report elevated depressive symptoms relative to those with diminished awareness of functional difficulties. However, this expectation was not realized. We found that MCI patients who accurately estimated their financial abilities relative to objective performance reported no more depressive symptoms compared to those who overestimated their own financial abilities.

Although this finding was contrary to what was expected, it is not without precedent. The association between depression and awareness of deficits in dementia is complex and equivocal. Whereas the studies noted above suggested that elevated depressed mood is present among AD patients with relatively preserved awareness of deficits, other studies have found either marginal (Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991) or no evidence (DeBettignies, Mahurin, & Pirozzolo, 1990; Derouesne et al., 1999; Ott et al., 1996; Reed, Jagust, & Coulter, 1993; Verhey, Rozendaal, Ponds, & Jolles, 1993) for such an association. Some researchers have argued that dysthymia in dementia is conceivably tied to awareness of deficits whereas major depression is an independent endogenous mood disorder (Migliorelli et al., 1995; Starkstein et al., 1997; Zubenko, Moossy, & Kopp 1990). It is likely that some of the discrepancies across studies may the due to methodological differences in the assessment of depression and awareness of deficits, as well as to sample considerations (such as varying sample sizes and levels of dementia severity) (Aalten, van Valen, Clare, Kenny, & Verhey, 2005;

Clare, 2004a). There is also some indication that unawareness of deficits may extend to mood states, especially given the symptom-overlap between cognitive dysfunction and depression, such that persons with cognitive impairment may not accurately report depressive symptoms (Agnew & Morris, 1998; Bruce et al., 2008; Vasterling, Seltzer, Foss, & Vanderbrook, 1995).

To better understand the initial null finding, we re-analyzed the depression data after splitting the MCI group into four subgroups: those who accurately reported that they had no difficulties with financial management, those who accurately reported that they had some difficulties with financial management, those who overestimated their financial abilities, and those who underestimated their financial abilities. We found that the patients who underestimated their financial abilities reported significantly greater depressive symptoms compared to those who accurately reported that they had no difficulties with financial management or those who overestimated their abilities. This finding is consistent with findings from an earlier study of accuracy of self-report of financial abilities in MCI (Okonkwo et al., in press). In that study, the authors found that MCI patients who underestimated their global financial abilities reported significantly more depressive symptoms compared to those who were accurate or those who overestimated their abilities.

Prior studies have noted that non-demented depressed persons often report more functional and cognitive difficulties than is objectively verifiable (Fischer et al., 2008; Migliorelli et al., 1995; Mullen, Howard, David, & Levy, 1996; O'Connor, Pollitt, Roth, Brook, & Reiss, 1990; Smith, Henderson, McCleary, Murdock, & Buckwalter, 2000; Vance, Ross, & Downs, 2008). In the context of MCI, this exaggeration of difficulties

might be due to hypersensitivity to both perceived and actual decline from prior functional status (Gallassi, Bisulli, Oppi, Poda, & Di Felice, 2008; Smith, Henderson, McCleary, Murdock, & Buckwalter, 2000). However, a misdiagnosis of AD may occur for patients with MCI who, due to their depression, exaggerate impairments in functional status. Therefore, it will be important for clinicians to routinely assess and treat depression in MCI (Furio, Brusco, & Cardinali, 2007; Lyketsos et al., 2000; Teri & Gallagher-Thompson, 1991). Such treatment may also ameliorate the adverse effects that untreated depression could have on cognitive (Greenwald et al., 1989; Sheline et al., 2006; Steffens et al., 2004) and functional (Fitz & Teri, 1994) abilities, overall quality of life (Alexopoulos et al., 2002; Burns, Lewis, Jacoby, & Levy, 1991; Steffens et al., 2006), and caregiver adjustment (Garand, Dew, Eazor, DeKosky, & Reynolds, 2005; Garand et al., 2007; Rabins, Mace, & Lucas, 1982; Zanetti et al., 1998). In recognition of these deleterious effects of depression, the MCI community is paying increasing attention to the impact of depression on various cognitive, health- and psychosocial-related indices in MCI (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Ellison, Harper, Berlow, & Zeranski, 2008; Garand et al., 2007; Steffens et al., 2006).

Summary

The primary conclusion from this study is that there is heterogeneity in awareness of functional difficulties among persons with MCI. Specifically, MCI patients are not as accurate in their estimations of financial abilities as they are in their estimations of driving skills, medication management, telephone use, and grocery shopping. The estimation errors made by MCI patients on the financial management domain predominantly involved overestimation of abilities. Such errors raise concerns that some

persons with MCI may be at risk for unintentional self-impoverishment and various forms of financial exploitation. For this group of MCI patients, increased vigilance of their financial transactions and affairs by family members appears warranted. In addition, geriatric healthcare professionals are well-positioned to educate family members about the possibility for misestimation of functional abilities among persons with MCI, as a consequence of the disease process. This knowledge might help modify the attributions family members make regarding patients' behaviors and empower them to cope adaptively with the caregiving role (Rabins, Mace, & Lucas, 1982; Wadley & Haley, 2001; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). The subset of patients who overestimated their abilities may also be at increased risk for progression to AD (Tabert et al., 2002), a question that can be addressed more conclusively upon completion of this longitudinal study (MILES).

The findings from this study also suggest that disruption in cognitive abilities of attention and, more generally, executive function may partially explain reduced awareness of functional difficulties in MCI. It is plausible to surmise that neuropathological alterations in AD result in attentional and executive dysfunction that, in turn, impacts the accurate perception of one's functional abilities because of diminished capacities for temporal integration and manipulation of information, self-monitoring, and response inhibition. In view of this, impairments in attention and executive function could be considered clinical markers of reduced awareness of functional difficulties in MCI. Interventions that bolster attention and executive function may, therefore, be of value in enhancing accuracy of self-report of functioning in MCI (Acevedo & Loewenstein, 2007; Levine et al., 2000; Requena et al., 2004).

We also found evidence that the presence of depressive symptoms in MCI is an important co-morbidity that warrants special attention because of its potential to bias accuracy of self-report of functional status. This bias is of concern because in clinical decision making regarding MCI, diagnostic consideration is likely to shift from MCI to AD when substantial restriction in functional activities is reported (Gauthier et al., 2006; Petersen, Stevens et al., 2001). As such, misdiagnosis of AD may occur for patients with MCI who exaggerate impairments in functional status as a result of depression. Therefore, it is important for clinicians to carefully screen for and treat depression when evaluating patients with MCI.

Limitations

The conclusions from this study are subject to certain caveats. Although self-objective discrepancies were significantly higher among MCI patients relative to healthy older adults on the financial management domain, the discordance between self-rating and objective test outcome was generally similar for both study groups across all functional domains assessed (ranging from 11% to 69% for controls and from 36% to 56% for MCI patients). This indicates that misestimation of abilities may not be entirely specific to MCI but may represent a more general phenomenon that worsens in the context of putative dementia. Alternatively, this poor self-objective correspondence may also be indicative of the weak association that has been severally documented between self-report measures and performance-based tests (Cress et al., 1995; Kempen, Steverink, Ormel, & Deeg, 1996; Zanetti, Bianchetti, & Trabucchi, 1995; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). An often-cited reason for the modest association between self-report and objective performance is the potential mismatch between the skills

assessed with the performance measures and the questions asked on questionnaire instruments (Clare, 2004a; Kempen, Steverink, Ormel, & Deeg, 1996; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999). In the present study, the report-based measures were developed to closely parallel the functional skills assessed on the objective tests, thereby strengthening isomorphism between them (Clare, 2004a). Nonetheless, the finding that concordance between self-report and objective outcome was highest between the FCI and the CFCF — instruments founded on a conceptual model of financial capacity — raises the possibility that the MILES Self-Report Questionnaire items may not have sufficiently paralleled the skills assessed on the OTDL, TIADL, and on-road driving evaluation. In addition, the study was likely underpowered to detect smaller but clinically-meaningful differences in awareness of functional difficulties across MCI and controls groups. Finally, the neurocognitive models developed in this study did not optimally classify MCI patients who misestimated their financial abilities, suggesting that misestimation of functional status in MCI may be dependent on patient characteristics not entirely captured by neuropsychological measures (Clare, 2004a).

Despite the foregoing, compared to prior studies of awareness of functional difficulties in MCI, the present study is unique in a number of ways: (i) it used a sample of older adults recruited from both community and clinical sources, and subsequently characterized carefully using neurological, neuropsychological, and neuroradiological data, (ii) it assessed awareness of difficulties across multiple functional domains and provided evidence for heterogeneity in this clinical phenomenon, (iii) it compared participants' self-report to their objective test performance thereby obviating the methodological difficulties inherent in the use of informant report as the yardstick against

which to appraise accuracy of patient report in dementia (Clare, 2004a; DeBettignies, Mahurin, & Pirozzolo, 1990; Loewenstein et al., 2001; Okonkwo et al., in press; Wadley, Harrell, & Marson, 2003), (iv) it investigated neurocognitive correlates of awareness of difficulties using a comprehensive neuropsychological test battery, and (v) it examined the impact of depression on the accuracy of self-report in MCI.

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Table 1. Demographic and clinical characteristics of study participants

Variable	Controls, n = 68	MCI, n = 57	p
Age	67.92 (7.42)	70.13 (8.15)	.113
Gender, n (%)			
Female	42 (61.76)	27 (47.37)	.107
Male	26 (38.24)	30 (52.63)	
Race, n (%)			
African American	13 (19.12)	10 (17.54)	.821
Caucasian	55 (80.88)	47 (82.46)	
Education	15.15 (2.46)	15.38 (3.01)	.643
DRS-2 Total Score	139.45 (3.88)	132.98 (7.88)	.001
GDS	4.00 (5.16)	4.53 (4.39)	.545

Except for gender and race, values are mean (SD).

MCI = mild cognitive impairment; DRS-2 = Dementia Rating Scale, 2nd edition; GDS = Geriatric Depression Scale.

Table 2. Group performance on neuropsychological measures†

Measure	Range	Controls, n = 68	MCI, n = 57
Attention			
DRS-2 Attention	0-37	35.82 (1.82)	35.55 (1.23)
Digit Span Total	0-24	15.89 (3.84)	14.07 (3.32)
Spatial Span Total	0-32	14.22 (2.95)	12.80 (2.51)
CPT Omissions		3.04 (8.19)	9.00 (11.17)
CPT Commissions		7.70 (4.96)	10.53 (6.53)
CPT Hit Reaction Time		445.92 (71.61)	462.62 (77.50)
Language			
Boston Naming	0-30	27.74 (1.82)	25.14 (4.70)
Semantic Fluency		20.22 (3.12)	15.89 (3.48)
Memory			
DRS-2 Memory	0-25	24.17 (0.86)	21.89 (3.14)
Logical Memory I	0-50	29.20 (4.84)	20.25 (7.38)
Logical Memory II	0-50	25.75 (5.43)	14.32 (8.80)
Visual Reproduction I	0-104	77.29 (13.35)	64.27 (17.19)
Visual Reproduction II	0-104	49.83 (19.31)	34.61 (22.28)
CVLT-2 Total Recall	0-80	46.88 (7.97)	32.05 (8.83)
10/36 Immediate Recall	0-30	20.82 (4.55)	14.88 (4.89)
10/36 Delayed Recall	0-10	7.20 (2.03)	4.84 (2.42)
Visuospatial			

DRS-2 Construction	0-6	5.78 (0.54)	5.77 (0.47)
CLOX 2	0-15	13.77 (1.07)	13.21 (1.12)
Abstraction			
DRS-2 Conceptualization	0-39	37.18 (2.14)	35.09 (3.09)
Cognitive Competency	0-20	17.96 (1.66)	16.43 (1.92)
Executive Function			
DRS-2 I/P	0-37	36.37 (1.53)	34.63 (3.82)
Trails A	0-300	33.66 (8.83)	43.61 (19.20)
Trails B	0-300	76.26 (26.11)	130.72 (74.37)
Trails C	0-360	80.20 (33.58)	143.07 (87.82)
CPT Perseverations		0.28 (0.58)	1.10 (1.55)
CLOX 1	0-15	12.31 (2.14)	11.16 (2.68)
Digit Symbol	0-133	62.22 (12.48)	44.81 (13.23)

Values are mean (SD).

† With the exception of CPT Omissions, CPT Commissions, CPT Hit Reaction Time, Trails A, Trails B, Trails C, and CPT Perseverations, higher scores indicate better cognitive functioning on the above neuropsychological measures.

MCI = mild cognitive impairment; DRS-2 = Dementia Rating Scale, 2nd edition; CPT = Conners' Continuous Performance Test; CVLT-2 = California Verbal Learning Test, 2nd edition; CLOX = Executive Clock Drawing Task.

Table 3. Tests of group proportions on difficulty experienced on objective measures of functional ability

Functional domain	No difficulty	Some difficulty	p
Driving			
Control	49.2	50.8	.032
MCI	29.2	70.8	
Financial Management			
Control	93.8	6.2	.001
MCI	60.7	39.3	
Medication Management			
Control	20.6	79.4	.338
MCI	14.0	86.0	
Grocery Shopping			
Control	76.5	23.5	.155
MCI	64.9	35.1	
Telephone Use			
Control	32.4	67.6	.008
MCI	12.3	87.7	

Values are row percentages

MCI = mild cognitive impairment.

Table 4. Tests of group proportions on the Discrepancy Index across functional domains†

Functional domain	-1	0	1	p
Driving				
Control	13.8	56.9	29.2	.143
MCI	6.3	47.9	45.8	
Financial Management				
Control	6.3	89.1	4.7	.001
MCI	7.1	64.3	28.6	
Medication Management				
Control	4.4	30.9	64.7	.309
MCI	5.3	43.9	50.9	
Grocery Shopping				
Control	14.7	61.8	23.5	.378
MCI	24.6	52.6	22.8	
Telephone Use				
Control	7.4	48.5	44.1	.289
MCI	1.8	56.1	42.1	

Values are row percentages

†Discrepancy Index scores were computed as [(self-rating minus objective test outcome) (-1)]. "-1" = self-rating worse than objective test outcome; "0" = self-rating same as objective test outcome; "1" = self-rating better than objective test outcome

MCI = mild cognitive impairment.

Table 5. Neuropsychological correlates of accuracy of self-report on the financial management domain among persons with MCI†

A: Univariate analyses

Neuropsychological composite	β	SE	OR (95% C.I.)	p	Classification accuracy‡	Nagelkerke R^2
Global cognition	0.58	.32	1.79 (0.96, 3.53)	.069	94.4, 6.7, 68.6	.10
Attention	1.18	0.44	3.25 (1.37, 7.73)	.008	94.4, 31.3, 75.0	.23
Language	1.43	0.58	4.17 (1.35, 12.87)	.013	91.7, 25.0, 71.2	.21
Memory	0.85	0.46	2.35 (0.95, 5.78)	.064	94.4, 13..3, 70.6	.10
Visuospatial	0.28	0.40	1.32 (0.61, 2.88)	.480	100.0, 0.0, 70.6	.01
Abstraction	0.87	0.40	2.39 (1.09, 5.24)	.029	97.2, 20.0, 74.5	.16
Executive Function	0.86	0.43	2.35 (1.01, 5.49)	.048	94.4, 18.8, 71.2	.11

B: Multivariable analysis

Neuropsychological composite	β	SE	OR (95% C.I.)	p	Classification accuracy‡	Nagelkerke R^2
Attention	1.25	0.46	3.48 (1.42, 8.50)	.006	91.7, 26.7, 72.5	.25

†For these analyses, the event being modeled is the probability of being in the "accurate" subgroup.

‡Classification accuracy values are given as percent of the “accurate” subgroup correctly classified, percent of the “overestimated” subgroup correctly classified, and percent of the overall sample correctly classified.

MCI = mild cognitive impairment.

Table 6. Comparison between "accurate" and "overestimated" subgroups on the Geriatric Depression Scale

Accurate, n = 36	Overestimated, n = 16	p
4.22 (3.69)	4.00 (4.03)	.846

Values are mean (SD).

APPENDIX

A1. MILES SELF-REPORT QUESTIONNAIRE

The following questions will be asking about some activities most older adults do in their daily life. Some questions ask about your driving, some ask about your use of health care and ability to manage your medications, others ask about your ability to do grocery shopping, and others ask about your ability to use the telephone. Please feel free to ask me to clarify any question that may not be clear to you.

Driving

D1. How difficult is it for you to stay within your lane while driving?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

D2. How difficult is it for you to drive safely around a sharp curve to the right?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

D3. How difficult is it for you to drive safely around a sharp curve to the left?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

D4. How difficult is it for you to merge onto a less busy road (e.g. a street) from a busier road (e.g. a highway or interstate)?

- Not difficult…….1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

D5. How difficult is it for you to drive into and back out of designated parking slots?

- Not difficult…….1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

Medication/Health care management

M1. How difficult is it for you to find and read the directions on medicine containers?

- Not difficult…….1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

M2. How difficult is it for you to determine how many days a refill of your medication will last?

- Not difficult…….1

- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

M3. How difficult is it for you to identify the side effects of your medications?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

M4. How difficult is it for you to figure out the right dosage of your medications and how often to take them?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

M5. How difficult is it for you to properly fill out medical history forms when you go to see the doctor?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

Grocery shopping

G1. How difficult is it for you to find the items you are looking for on the shelves when you go grocery shopping?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

G2. How difficult is it for you to find and read the ingredients on cans of food?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

Telephone use

T1. How difficult is it for you to find the phone number of people in the white pages of the phone book?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

T2. How difficult is it for you to locate the phone number of specific services in the yellow pages of the phone book?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

T3. How difficult is it for you to use rate charts or tables to find the rates for long distance calls made at various times of the day or certain days of the week?

- Not difficult……1
- A little difficult……2
- Moderately difficult…… 3
- Very difficult……..….....4

A2. SPECIFIC ITEMS USED TO EVALUATE FUNCTIONAL DOMAINS IN THIS DISSERTATION

Functional domain	Measures used	Composite formed by computing:	Original scale	Definition of objective difficulty
Driving	On-road driving evaluation	Mean of CDRS-assigned ratings on driving skills that relate to parking, lane control, turning, and exiting highways and interstates	Ratings were done on a 1 (CDRS took control of car and ended road test) to 5 (skill performed in an optimal manner) scale	Ratings recoded as 0 (optimal execution of skill) or 1 (less than optimal execution of skill)
Financial Management	Financial Capacity Instrument	Mean of domain scores on the Financial Conceptual Management, Cash Transactions, Bank Statement Management, and Bill Payment domains.	Possible range was from 0 to 35.25	Scores recoded as 0 (can do without difficulty) or 1 (experiences some difficulty)†
Medication Management‡	(i) Medication management domain from the TIADL	Mean of scores on items that required participants to find and read the directions on medicine containers	Possible scores were 1 (completed correctly within the time limit with no errors), 2 (completed within the time limit with minor errors), or 3 (not completed in the time limit or completed with	Scores recoded as 0 (task was completed correctly within the time limit with no errors) or 1 (task was completed with some error or was not completed within the time limit)

			major errors)	
	(ii) Medication use domain from the OTDL	Mean of scores on items that required participants to (i) indicate the number of days a refill of a medication presented to them will last, (ii) indicate which medications, from a set of medications presented to them, could cause drowsiness, (iii) indicate the correct dosage for a medication presented to them, (iv) fill out a patient record form with specific details	Possible scores were 0 (task completed correctly) or 1 (task completed incorrectly)	Scoring preserved as 0 (task completed correctly) or 1 (task completed incorrectly)
Grocery Shopping	Grocery shopping domain from the TIADL	Scores on an item that required participants to find target food items in a shelf full of distractor food items	Possible scores were 1 (completed correctly within the time limit with no errors), 2 (completed within the time limit with minor errors), or 3 (not completed in the time limit or completed with major errors)	Scores recoded as 0 (task was completed correctly within the time limit with no errors) or 1 (task was completed with some error or was not completed within the time limit)

Telephone Use§	Telephone use domain from the TIADL	Scores on an item that required participants to find and read aloud the phone number of a specified individual in the white pages of a phone book	Possible scores were 1 (completed correctly within the time limit with no errors), 2 (completed within the time limit with minor errors), or 3 (not completed in the time limit or completed with major errors)	Scores recoded as 0 (task was completed correctly within the time limit with no errors) or 1 (task was completed with some error or was not completed within the time limit)
	Telephone use domain from the OTDL	Mean of scores on items that required participants to (i) find the phone number of specified services on a page extracted from the yellow pages of a phone book, and (ii) identify the applicable rate for a long distance call made at a certain time of the day	Possible scores were 0 (task completed correctly) or 1 (task completed incorrectly)	Scoring preserved as 0 (task completed correctly) or 1 (task completed incorrectly)

CDRS = Certified Driving Rehabilitation Specialist

SD = standard deviation

TIADL = Timed Instrumental Activities of Daily Living

OTDL = Observed Tasks of Daily Living

† A *can do without difficulty* (0) outcome was defined as a score better than 1.5 SD below the control group mean (33.13) on the FCI composite variable whereas an *experiences some difficulty* (1) outcome was defined as a score falling at or worse than 1.5 SD below the control group mean on the FCI composite variable.

‡ The Medication Management composite was ultimately formed by averaging mean outcomes on the TIADL and OTDL. Therefore, individuals who had a mean outcome of 0 *(task was completed correctly within the time limit with no errors)* on the TIADL and a mean outcome 0 *(task completed correctly)* on the OTDL received an overall outcome of 0 *(experiences no difficulty)* on the Medication Management domain. Other individuals received an overall outcome of 1 *(experiences some difficulty*) on this domain.

§ The Telephone Use composite was ultimately formed by averaging mean outcomes on the TIADL and OTDL. Therefore, individuals who had a mean outcome of 0 *(task was completed correctly within the time limit with no errors)* on the TIADL and a mean outcome 0 *(task completed correctly)* on the OTDL received an overall outcome of 0 (*(experiences no difficulty*) on the Telephone Use domain. Other individuals received an overall outcome of 1 *(experiences some difficulty)* on this domain.

A3. INSTITUTIONAL REVIEW BOARD APPROVAL FORM FOR PARENT STUDY

OMB No. 0990-0263
Approved for use through 11/30/2008

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule. Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[ ] ORIGINAL [X] CONTINUATION [ ] EXEMPTION	[ ] GRANT [ ] CONTRACT [ ] FELLOWSHIP [ ] COOPERATIVE AGREEMENT [ ] OTHER:_____	
4. Title of Application or Activity Everyday Functional Performance in MCI		5. Name of Principal Investigator, Program Director, Fellow, or Other WADLEY, VIRGINIA G

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity.
Assurance Identification No. FWA00005960, the expiration date 10/26/2010 IRB Registration No. IRB00000196

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____*(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[X] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [ ] Full IRB Review on (date of IRB meeting) _____ or [X] Expedited Review on (date) 3-26-08
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments
Protocol subject to Annual continuing review.

Title X040716001
Everyday Functional Performance in MCI

IRB Approval Issued: 3-26-09

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution University of Alabama at Birmingham 701 20th Street South Birmingham, AL 35294
11. Phone No. *(with area code)* (205) 934-3789 12. Fax No. *(with area code)* (205) 934-1301 13. Email: smoore@uab.edu	
14. Name of Official Marilyn Doss, M.A.	15. Title Vice Chair, IRB
16. Signature Marilyn Doss	17. Date 3-26-08

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A4. INSTITUTIONAL REVIEW BOARD AMENDMENT FORM FOR APPENDING DISSERTATION SUB-STUDY TO PARENT STUDY

UAB Project Revision/Amendment Form **irb**

(Rev. 4/7/2004)

PLEASE TYPE: In MS Word, highlight the shaded, underlined box and replace with your text; double-click checkboxes to check/uncheck.)

Link: Project Revision/Amendment Form

Federal regulations require IRB approval before implementing proposed changes.
Please complete this form and attach the changed research documents. Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.)

RECEIVED
SEP 28 2005
OFFICE OF INSTITUTIONAL REVIEW BOARD

Principal Investigator: *Virginia G. Wadley* Date: *9/26/05*
Contact: *Shernine Lee* Phone #: *4-7516* Fax #: *5-2295* E-mail: *sklee@uab.edu*
Campus Address: *HMB 113, zip 2100*
Study/Protocol Title: *Everyday Functional Performance in MCI*
IRB Protocol #: *X040716001*

Current Status of Project: (check only one)

☒ Currently in Progress (# participants entered: *64*)
☐ Study has not yet begun (no participants entered)
☐ Closed to participant enrollment (remains active); # participants on therapy/intervention_____; # participants in long-term follow-up only_____

This submission changes the status of this study in the following manner: (check all that apply)

☐ Protocol Revision
☒ Protocol Amendment
☐ Study Closed to participant entry
☐ Study Terminated
☒ Revised Consent Form
☐ Addendum (new) consent form
☐ Enrollment temporarily suspended by sponsor
☒ Other, (specify) *adding a self-report questionnaire and a doctoral student co-investigator* ✓
Added Co-PI in SIRB 9/20/05. ckk

1. Briefly describe, and explain the reason for, the revision or amendment. Include a copy of supportive documents with changes highlighted. Please highlight changes/revisions/additions to the consent form, protocol, research questionnaire, etc.
A self-report evaluation of everyday skills (attached) will be added to other measurements of these skills in order to more fully tap the construct of everyday function. This questionnaire contains items from validated instruments as well as newly constructed items. Administration will require an additional 10 minutes of participants. However, we have experienced that many participants' study visits take less than the 3 hours provided for in the consent form. Therefore, the addition of this questionnaire, which is consistent with the rest of the study battery, will not necessitate a change in the consent form. The only change to the consent form (attached) is the addition of a doctoral student co-investigator, Ozioma Okonkwo, who will work with a subset of the data for his dissertation.

2. Does this revision/amendment revise or add a genetic or storage of samples component? ☐ Yes ☒ No
If yes, please see the Guidebook to assist you in revising or preparing your submission documents or call the IRB office at 4-3789.

3. Does the change affect subject participation (e.g. procedures, risks, costs, etc.)? ☐ Yes ☒ No

4. Does the change affect the consent document? ☒ Yes ☐ No
If yes, briefly discuss the changes. *Addition of co-investigator (see response to item 1).*

Revised 7-15-02

Include the revised consent form with the changes highlighted.
Will any participants need to be reconsented as a result of the changes? ☐ Yes ☒ No
If yes, when will participants be reconsented?____

Signature of Principal Investigator Virginia D Wadley Date 9/26/05

FOR IRB USE ONLY

DOLA 5/2005

APPROVED
Marilyn Doss 9-30-05
MARILYN DOSS, M.A.
Vice Chair – IRB

Revised 7-15-02

A5. CURRENT CONSENT FORM FOR PARENT STUDY SHOWING OZIOMA OKONKWO AS A CO-INVESTIGATOR

UAB Consent Form irb

TITLE OF RESEARCH: Everyday Functional Performance in MCI

IRB PROTOCOL NUMBER: X040716001

INVESTIGATORS: Drs. Virginia Wadley, Karlene Ball, and David Vance, and Ozioma Okonkwo, M.A.

SPONSOR: National Institute on Aging

Explanation of Procedures

As a participant in the Alzheimer's Disease Research Center (ADRC), you are being invited to participate in a research study that is examining how people with Mild Cognitive Impairment (MCI) carry out everyday activities such as handling their medications and finances, driving, and shopping for groceries. Individuals with and without MCI are being asked to participate in this study, so we can compare the performance of people with and without this diagnosis over time. About 180 individuals from the ADRC at the University of Alabama at Birmingham will take part in this study.

If you agree to be in this study, you will be asked to participate in one 3-hour study session each year for up to five years. Each study visit will take place at the research offices of the Holley Mears Building, 924 19th Street South. Parking is available at no cost in the lot behind the building. Each annual visit will consist of computer-based evaluations of your visual attention and ability to process information quickly, an evaluation of your everyday skills including tasks such as counting change and reading medication labels, an evaluation of your driving by a Certified Driving Rehabilitation Specialist from the UAB Driving Assessment Clinic, and questionnaires about your mobility, physical activity, and social support. All information obtained in these evaluations is for research purposes only. No information about your individual performance in these evaluations will be made public.

In addition to participating in one study visit each year, if you agree to participate in this study, you also are giving permission for the study investigators to obtain the following information about you: (1) summaries of your annual ADRC neuropsychological test performance, (2) monthly updates from ADRC personnel about any change in your MCI diagnosis and yearly updates from ADRC personnel about any change in your general health, and (3) yearly review of public records from the state of Alabama containing any motor vehicle crashes or violations you might have had during the time period of this study. All of this information is necessary to help us understand whether and how MCI influences skills that are important to everyday living.

UAB – IRB
Consent Form Approval 3-26-08
Expiration Date 3-26-09

Participant's initials _____

Disclosure

Dr. Karlene Ball, the study Co-Principal Investigator, developed the UFOV procedure that will be used in this study and is Executive Vice President, and a stock owner and consultant of Visual Awareness, Inc, the company that licenses the UFOV test. The outcome of this study may result in Dr. Ball receiving financial benefit.

Risks and Discomforts

There are minimal risks associated with participating in this study. No participant in this study will be deprived of any standard of care or experimental interventions for MCI, including medications, nor will they be deprived of any standard-of-care treatments that may become available during the course of the study.

Benefits

You may not personally benefit from your participation in this research; however, your participation may provide valuable information to the medical community about the impact of Mild Cognitive Impairment over time on abilities that are important for carrying out everyday activities. This information can then be used in the future to develop interventions designed to maintain everyday functioning in individuals with MCI.

Alternatives

This is not a treatment study. Therefore, the alternative to participation is to choose not to participate.

Confidentiality

The information gathered during this study will be kept confidential to the extent permitted by law. However, the study investigators and their staff, and representatives of the National Institute on Aging (NIA), the Office of Human Research Protections (OHRP), and UAB's Institutional Review Board (IRB) will be able to inspect your research records and have access to confidential information that identifies you by name. The results of this study may be published for scientific purposes; however, your identity will not be revealed.

Participant's initials _____

Refusal or Withdrawal without Penalty

Your taking part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time.

Significant New Findings

Any significant new findings that develop during the course of the study that may affect your willingness to continue in the research will be provided to you by Dr. Wadley or her staff.

Cost of Participation

There will be no cost to you from participation in the research.

Payment for Participation in Research

You will be paid $50 for each annual study visit that you complete. You will receive this payment by check within about six weeks after each visit. Should you withdraw from the study, you will receive payments only for the visits you completed.

Payment for Research Related Injuries

Neither UAB nor the NIA have provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Virginia Wadley. She will be glad to answer any of your questions. Dr. Wadley's number is 205-975-2294.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact Ms. Sheila Moore. Ms. Moore is the Director of the Office of the Institutional Review Board for Human Use (OIRB). Ms. Moore may be reached at (205) 934-3789 or 1-800-822-8816. If calling the toll -free number, press the option for "all other calls" or for an operator/attendant and ask for extension 4-3789.Regular hours for the Office of the IRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Participant's initials _____

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed informed consent.

_____

Signature of Participant or Legally Authorized Representative — Date

_____

Signature of Investigator — Date

_____

Signature of Witness — Date

_____

Signature of person obtaining consent (if other than the investigator). Date