Cognition in Older Adult MS Patients Compared to Healthy Controls and aMCI Patients

By



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## Abstract

Very little research has been conducted with older adult samples of individuals with multiple sclerosis (MS). In particular, it is not clear whether the cognitive profile of older adult MS patients follows the same patterns observed in younger MS patients. At the level of an individual patient, possible etiologies for changes in cognition include worsening MS, normal consequences of aging, the development of a comorbid condition, or an interaction of these possibilities. This study compared the performance of MS ($n$ = 64), amnestic mild cognitive impairment (aMCI; $n$ = 58), and healthy control ($n$ = 70) samples over the age of 60 on a neuropsychological testing battery. Older adult MS patients consistently performed better than aMCI patients and worse than controls. However, secondary progressive MS patients did not significantly differ from aMCI patients on any cognitive measure. Criteria for cognitive impairment were met by 20% of the MS sample. MS patients were most frequently impaired on tasks of processing speed and memory. Significant predictors of cognitive impairment were physical disability and disease duration. Overall, the cognitive profile of older adult MS patients is largely consistent with that of younger MS patients. However, differences in impairment between secondary progressive and primary progressive patients were not as distinct as previously reported in the literature. Additionally, disease duration was more strongly associated with cognitive impairment than previously thought.

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# COGNITION IN OLDER ADULT MS PATIENTS COMPARED TO HEALTHY CONTROLS AND aMCI PATIENTS

Multiple sclerosis (MS) is an immune-mediated disease of the nervous system. It is a progressive condition characterized by worsening motor, sensory, and cognitive disability over time. Relatively recent advancements in the treatment of MS have resulted in an improved prognosis and life expectancy for patients (Finlayson, 2009). As a result, a new cohort of MS patients – that of older adults – has emerged. From a clinical and research perspective, it is important to consider the medical, psychosocial, and cognitive factors that may be unique to this subsample relative to the broader MS population. However, at this time, there is very little characterization of MS patients over the age of 60 within the research literature (Gray & Arnett, 2014).

One aspect of functioning that may be different between older adult and younger MS patients is that of cognitive performance. Forty-three to 70 percent of MS patients experience cognitive impairment at some point in their disease (Chiaravalloti & DeLuca, 2008). These symptoms typically appear early in the disease course and persist or worsen over time (Amato, Zipoli, & Portaccio, 2006). Currently, it is unclear whether the cognitive patterns observed in younger patients – such as affected domains, rates of impairment, or predictors of cognition – hold true in older adult patients.

The purpose of the present study was to characterize the cognitive profile of a sample of older adult MS patients using a neuropsychological test battery. Performance on the battery was compared to healthy controls, as well as a clinical population of patients with amnestic mild cognitive impairment (aMCI). The aMCI group was selected for two reasons. First, this sample represents a patient group similar to MS in that individuals may experience documented

cognitive impairment in select domains, while their activities of daily living remain largely intact. Second, this sample is also of interest in the context of aging. It is possible that an older adult MS patient may present with concerns about cognition similar to those expressed by an individual diagnosed with aMCI; therefore, being able to differentiate between these groups may be important in a clinical context. Finally, in addition to between-group differences, patterns of cognitive performance and impairment were also explored within the MS sample and across MS subtypes.

**Aging and Multiple Sclerosis**

In general, the topic of aging and MS is currently understudied within the field, and no clear picture exists of the lives of older adults with MS. It is estimated that approximately 9% of MS patients are older than 65 years, which is equal to 225,000-350,000 individuals worldwide (Awad & Stüve, 2010). Within the available literature, some discrepancies exist regarding life expectancy in MS. Many studies suggest MS can shorten the life span by 5 to 10 years; however, other work indicates individuals with MS can live as long as their peers (Finlayson, 2009). Over the last 40 years, mean survival time has improved, which is consistent both with trends in the general population as well as within populations of disabled individuals (Finlayson, 2009). In addition to these general trends, a relatively recent change that has specifically affected those with MS is the introduction of disease-modifying treatments (DMT). These treatments help to reduce disease pathology and, to some degree, slow disease progression (Freedman, 2005). The first DMT was approved by the Food and Drug Administration for use in the United States in 1993. Thus, the relative newness of this sub-population may account for the limited research thus far undertaken with aging MS patients.

What is known about MS and older adulthood has been summarized in a number of recent reviews. Stern (2005) and Awad and Stüve (2010) discussed the epidemiology of MS in old age as well as the clinical, pathological, and neuroimaging presentations of older adult MS patients. Other research has focused on psychosocial factors, including discussions of activity limitations, the subjective experience of aging with MS, and the family and professional care needs of individuals with MS (Finlayson, 2009). The most recent review by Gray and Arnett (2014) sought to supplement areas not previously discussed. They reported on cognitive, emotional, and neuropathological variables associated with old age and MS. Overall, there is a burgeoning interest regarding the aging process within MS, as indicated by the recency of these reviews.

## Multiple Sclerosis and Cognition

The novelty of this interest is reflected by the limited number of studies within the literature reporting on cognition in older adult MS patients. In fact, only three articles were identified that included patient samples with a mean age over 60 years old. Before considering these specific studies, it is helpful to understand the broader state of research in the field of cognition and MS. Additionally, because of the limited amount of research with older adults, the findings of longitudinal studies on cognition can also supplement our understanding of this growing MS sub-population.

**Cognitive Findings.** Consistent with other MS symptoms, cognitive deficits are significantly heterogeneous across individual patients. For this reason, a variety of approaches have been developed to assess cognition in MS patients. Cognitive screening tools – either traditional neurological tests (e.g., Mini Mental Status Exam, MMSE) or single instruments demonstrated to be sensitive to MS (e.g., Symbol Digit Modalities Test, SDMT) – have generally

been viewed as insufficient in identifying patients with cognitive impairment (Aupperle, Beatty, Shelton, & Gontkovsky, 2002; Beatty, Goodkin, Hertsgaard, & Monson, 1990; DeLuca, Yates, Beale, & Morrow, 2014). Therefore, three MS-specific cognitive batteries have been developed over time. Rao's Brief Repeatable Neuropsychological Battery (BRN-B) (Bever, Grattan, Panitch, & Johnson, 1995) assesses auditory and visual processing speed (i.e., Paced Auditory Serial Addition Task, PASAT; SDMT), verbal and visuospatial memory (i.e., Selective Reminding Task, 10/36 Spatial Recall Task), and verbal fluency (i.e., Controlled Oral Word Association Test). In 2002, a panel of researchers developed the Minimal Assessment of Cognitive Function in MS (MACFIMS), which added two additional cognitive domains for assessment: visuospatial perception (i.e., Judgement of Line Orientation) and executive function (i.e., Sorting subtest of the Delis-Kaplan Executive Function System; Benedict et al., 2002). The MACFIMS battery retained the use of the PASAT and SDMT, and modified the memory tasks to include the California Verbal Learning Test, 2nd Edition (CVLT2) and the Brief Visuospatial Memory Test-Revised (BVMT-R). The MACFIMS can take up to two hours to administer, so a recent effort has been made to develop a quicker, 15-minute battery. The Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS) battery consists only of the SDMT and immediate recall on verbal and visual memory tasks (i.e., CVLT2, BVMT; Langdon, et al., 2012).

Across assessment instruments and batteries, a general pattern of cognitive performance has emerged over the past few decades. The two most commonly affected abilities are those of processing speed and memory (see reviews: Chiaravalloti & DeLuca, 2008; DeLuca et al., 2014). Some studies report deficits in executive function, primarily as measured on tasks of verbal fluency; however, these impairments are observed at a lower frequency than those of processing

speed or memory (Chiaravalloti & DeLuca, 2008). Similarly, some studies report poor visuospatial perception and processing; however, more detailed analysis suggests these apparent higher order deficits might be better explained by slowed performance on speed-dependent tasks (Zakzanis, 2000). Simple attention, word naming, and general intelligence are broadly intact. With respect to memory, specific deficits have been reported in both recall and retrieval processes (Chiaravalloti & DeLuca, 2008; Guimarães & Sá, 2012). However, further investigation into poor recall on list learning tasks has suggested that MS cognitive deficits may be better described as deficits in acquisition rather than memory-related problems in storage or retrieval (DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Demaree, Gaudino, DeLuca, & Ricker, 2000). When MS patients and healthy controls are trained to a specific criterion, MS patients require more repetitions to acquire new information; however, once encoded, MS patients have comparable free recall and recognition as healthy controls (DeLuca et al.; Demaree et al.; Diamond, DeLuca, Johnson, & Kelley, 1997). It has been suggested that this deficit in acquisition may be a result of MS patients' slowed processing speed (Faglioni, Bertolani, Botti, & Merelli, 2000). Therefore, the two cognitive deficits most commonly observed in MS patients are that of slowed processing speed and poor acquisition of new information.

A significant body of research has also investigated various factors and predictors that may be associated with cognitive dysfunction. Impairment can be seen regardless of disease duration, and only moderate associations have been found with physical disability (Chiaravalloti & DeLuca, 2008). Disease subtype, however, is relevant. More severe cognitive deficits have been reported in progressive subtypes relative to relapsing remitting (RRMS) patients. A meta-analysis also reported different patterns in impairment across subtypes, with progressive patients

experiencing more frontal-executive deficits, and relapsing remitting patients being characterized more by deficits on tests of memory function (Zakzanis, 2000). Among the progressive subtypes, some studies report a higher frequency of cognitive impairment in secondary progressive (SPMS) relative to primary progressive (PPMS) patients; however, others studies find no difference (DeLuca et al., 2014). Depression has also been demonstrated to be significantly associated with cognitive functioning in MS patients (Chiaravalloti & DeLuca, 2008). The lifetime prevalence of depression in MS nears 50%, which is approximately three times the rate of the general population (Feinstein, 2011) Therefore, it is recommended that depression is assessed in studies of cognition. Finally, a growing interest in the field is identification of pathological correlates of cognitive impairment. Cortical, deep grey matter, and white matter structures are all affected by MS pathology. Lesion load, whole brain atrophy, and volume changes in specific structures have all been linked to cognitive impairment (DeLuca et al., 2014). However, at this time, the link between MS pathology and cognition remains poorly understood.

**Cognitive Profile of Older Adult MS Patients.** While there is generally accepted knowledge regarding patterns of cognitive performance in MS as well as significant factors that affect cognition, it is not yet clear whether these patterns persist as patients age. Only three identified studies have begun to address this question. The first of these studies focused specifically on processing speed across the lifespan in MS patients (Bodling, Denney, & Lynch, 2009). The authors analyzed data from five previously published studies investigating information processing speed, as assessed by a computerized Stroop task. The researchers divided their patient and healthy control samples into five age cohorts and conducted an ANOVA to identify whether there were main effects for group (patients; controls) or age. Significant main effects were found for both group and age, such that MS patients were slower

than healthy controls, and older individuals were slower than younger. The researchers also hypothesized a significant interaction, such that group differences in processing speed would become greater as MS patients aged. They cited theoretical discussions in the literature regarding observed similarities in the cognitive profiles of MS patients and healthy aging adults as well as the hypothesis that MS might involve an acceleration of the normal aging process with respect to cognitive variables. However, within their sample (MS: $n$ = 245; Controls: $n$ = 188), no significant interaction was found. Possible explanations included the use of only a single measure of processing speed, a highly educated sample with a potentially greater cognitive reserve than representative of the population, and a small sample within the oldest cohort aged 59 and older (MS: $n$ = 18; Controls: $n$ = 16). The authors suggested that further research is needed to better understand the relationship among MS disease trajectories and the aging process, and they particularly encouraged future investigators to not rule out the possibility of an interaction between these processes.

The second study identified used a cross-sectional, population-based design. Individuals living in Oslo, Norway, and diagnosed between the years of 1940 and 1980 were recruited from a comprehensive patient registry (Smestad, Sandvik, Landrø, & Celius, 2010). Participants completed a testing battery assessing psychomotor speed, attention, learning/memory, and executive function. Ages ranged from 45 to 81 ($M$ = 61), with an average disease duration of 34.5 years. In at least two of four cognitive domains, individuals needed to score 1.5 standard deviations (SD) below a normative mean on at least one subtest in order to be labeled as cognitively impaired. Of the sample completing neuropsychological testing ($n$ = 84), 48% met criteria for cognitive impairment, with the typical pattern involving moderate impairment of

information processing speed, attention, and memory. The investigators concluded that after 30 years of MS, about half of patients will experience reduced cognitive functioning.

A third study focused on the possibility of comorbid memory conditions in older adult MS patients (Müller et al., 2013). The researchers sought to identify which neuropsychological tasks would best differentiate a sample of SPMS patients ($n$ = 40; $M$ = 60.78 years) from aMCI ($n$ = 40; $M$ = 61.05 years) and healthy control samples ($n$ = 40; $M$ = 60.13 years). The results indicated that across all instruments, healthy controls performed significantly better than both patient groups. More interestingly, no significant differences were observed between SPMS and aMCI patients on any task, except recognition of a word list after a delayed recall. On this task, aMCI patients were significantly worse than SPMS patients, whose performance was equal to that of healthy controls. The ability of SPMS patients to perform better on recognition tasks compared to free recall is consistent with the broader MS literature describing impairments in acquisition but not memory storage. Also consistent with the larger literature was the authors' conclusions–based on correlations between memory performance and other test variables–that poor recall may be due to impairment in executive function and poor processing speed (Müller et al., 2013).

**Longitudinal Findings.** In light of the limited research on cognition in older adult MS patients, an alternative source of information is longitudinal trends in cognitive changes over the course of MS. Most longitudinal studies of cognition in MS have relatively brief (i.e., two to three year) follow-up periods. Only six published studies have investigated cognitive changes in MS patients for a period of time longer than five years, with follow-up periods ranging from seven (Haase et al., 2004) to 18 years (Strober, Rao, Lee, Fischer, & Rudick, 2014). All longitudinal studies observed cognitive deterioration in MS patients, though there was substantial

variation across studies in the degree of deterioration observed. Reported rates of the percentage of a sample shifting from an intact cognitive profile to an impaired profile ranged from 5% (Schwid, Goodman, Weinstein, McDermoot, & Johnson, 2007) to 30% (Amato, Ponziani, Siracusa, & Scorbi, 2001) over a 10-year period. Other studies reported an 18% shift over 18 years (Strober et al., 2014) and a 16% change over eight years (Bergendal, Fredrikson, & Almkvist, 2007). One challenge in making comparisons across these studies is that impairment was operationally defined differently within each study. Impairment was sometimes relative to a control group; while at other times, it was relative to a normative sample. The degree of required deviation from the comparative sample also varied across studies (i.e., 0.5 SDs to 2.0 SDs). However, while there are some inconsistencies and limitations to the existing literature, a consistent finding across all studies is that cognitive abilities decline over time.

The specific cognitive abilities that change over time is also somewhat variable across studies. Cognitive domains with reported declines include processing speed/attention (Schwid et al., 2007; Strober et al., 2014), visuospatial processing (Haase et al., 2004; Strober et al.), motor function (Bergendal et al., 2007), and executive function (Strober et al). Of the longer longitudinal studies, four out of five studies observed deterioration over time and significant impairment in either verbal memory (Amato, Ponziani et al., 2001; Piras et al., 2003; Strober et al.) or visual memory (Amato, Ponziani et al.; Bergendal et al.; Piras et al.). Consistent with cross sectional studies, intelligence and linguistic abilities appear to be largely preserved over time (Haase et al., Bergendal et al., Piras et al., Strober et al.). Additionally, the observed declines in memory and processing speed are consistent with the few studies conducted with older adult MS patients (Bodling et al., 2009; Müller et al., 2013; Smestad et al., 2010).

One goal of many of the longitudinal studies involved identifying predictors of cognitive decline. Specifically, in light of the fact that many MS patients display cognitive impairment throughout their disease course, investigators have examined whether current cognitive status is related to later cognitive status. No research consensus exists, however. Some studies reported that patients classified as impaired worsen more rapidly than a sample classified as cognitively intact (Amato, Portaccio et al., 2010; Bergendal et al., 2007; Kujala, Portin, & Ruutianinen, 1997). Other studies report the opposite – patients within an intact group demonstrate greater relative decline, while the impaired sample remains stable (Schwid et al. 2007; Strober et al., 2014). Still others report no relationship between baseline and follow-up cognitive status, although these studies tend to have follow-up periods of less than five years (Denney, Lynch, & Parmenter, 2008; Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006).

A challenge when interpreting this literature is that the first or baseline assessment occurs at a different average disease duration, age, and level of physical disability for each patient sample. Thus, each study is capturing only a small snapshot of change occurring over the lifespan and, therefore, describing a different portion of a broader picture. The lack of consensus on the significance of current cognitive status for later cognitive status indicates that this cannot be used as a reliable predictor to infer the cognitive profile of older adult patients.

**Multimorbidity in Older Adult MS Patients.** Another important consideration when discussing cognition in older adult MS patients is the possibility of a comorbid condition contributing to symptoms. There is increasing recognition that the presence of multiple, co-existing pathologies is a frequent occurrence in aging brains (Jellinger & Attems, 2014). Of particular concern within the cognitive domain is the development of a comorbid degenerative dementia in addition to MS. In general, the most common form of dementia is Alzheimer's

disease (AD; Alzheimer's Association, 2013). Estimates from two national studies of older adults suggest that one in nine individuals aged 65 years or older and one in three individuals over the age of 85 are diagnosed with AD (Alzheimer's Association, 2013). Combined with the prevalence estimates of older adult MS patients, these statistics suggest anywhere from 25,000 to 39,000 MS patients worldwide may have comorbid AD. This estimate does not take into account other possible etiologies of cognitive decline, such as alternative forms of dementia or vascular complications, which may also interact with MS.

Two recent publications report evidence of comorbid MS and AD. A case series out of the Mayo Clinic described three cases of MS patients with comorbid AD, one identified postmortem and two identified premortem (Flanagan, Knopman, & Keegan, 2014). The first case involved a 56-year-old woman presenting with progressive dementia over seven years and an atypical MS course. Her autopsy confirmed MS pathology and also revealed severe AD pathology (Braak stage VI of VI). The other two cases involved diagnosis–and treatment–of MS and AD premortem. Diagnoses were arrived at via measurement of cerebrospinal fluid levels of tau and amyloid-$\beta_{1\text{-}42}$ concentrations, as well as evidence of bilateral hypometabolism on FDG-PET scans. One patient was treated with donepezil and memantine and self-reported mild improvement; the second individual was prescribed donepezil but continued to decline. Neither of these cases included autopsy confirmed diagnoses. Each, however, provides some measure of evidence for comorbid MS and AD.

More robust evidence of comorbidity comes from an archival autopsy study of 45 MS cases (Dal Bianco et al., 2008). Of the sample, 22 were 65 years or younger (age range: 28-64) and 23 were over the age of 65 (age range: 66-85). Pathology was staged according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria and Braak stages.

Of the 45 MS cases, 16 individuals (all over the age of 64) demonstrated Alzheimer's pathology and eight of those met CERAD criteria for probable AD. The incidence of AD pathology in MS patients was compared to a previously published non-selected autopsy population of 1,258 patients in a Swiss geriatric hospital viewed as representative of "normal aging" (i.e., Giannakopoulous, Hof, Mottier, Michel, & Bouras, 1994). The rate of AD pathology in MS patients appeared consistent with normal aging before the age of 64 and moderately (but not significantly) greater in patients over the age of 64. The authors concluded that "in aged MS patients, a cognitive decline may not only be related to MS-specific lesions but also to concomitant age-related development of AD pathology" (Dal Bianco et al., p. 180).

Evidence of documented comorbidity highlights the need to include other conditions in clinical differentials when MS patients report worsening cognition. Additionally, this supports the benefit within MS research of including other clinical samples in cognitive studies. Being able to directly compare clinical groups can inform our understanding of relative deficits. It can also, hopefully, facilitate clinical decision making when determining whether a patient's reported complaints warrant further evaluation or not.

**Discussion.** A number of challenges exist when trying to understand the cognitive profile of older adult MS patients. There is a scarcity of studies directly addressing this topic, and more indirect routes of estimating cognitive abilities within this population have limitations, including wide variation in the clinical characteristics of patient samples, the definitions of impairment, and the cognitive domains selected for evaluation. Practical obstacles to the direct assessment of cognitive abilities in older adult MS patients may also exist. Greater age is often related to longer disease durations, which in turn, is related to greater levels of physical disability (Beatty et al., 1990). Physical impairment may interfere with the ability to complete neuropsychological

batteries, particularly speeded tasks. For example, in Smestad and colleagues' (2010) population-based study of older MS patients, 32% of eligible patients declined to participate in cognitive testing. Attrition analyses indicated that these individuals were significantly older than those assessed (mean age 64.4 years vs. 60.6 years) and had a higher mean Expanded Disability Status Scale (EDSS) score (6.8 vs. 5.0). The absence of information from the most disabled individuals likely skews the collected data.

Theoretical challenges also exist when trying to understand the underlying cause or causes of observed deficits in older adults. Possible attributions include worsening MS pathology, the effects of normal aging, the development of a comorbid cognitive disorder associated with aging, or an interaction of these possibilities. Various hypotheses exist as to how MS disease processes might interact with normal aging processes. For example, slowed processing speed is a widely recognized consequence of MS. However, reduced speed of processing is also associated with aging (Salthouse, 1992). Thus far, it is unclear how these parallel processes might intersect in older adult patients (Bodling et al., 2009; Kail, 1997). Similarly, at a neuropathological level, MRI lesion load has been associated with cognition in MS patients (Amato et al., 2006; Chiaravalloti & DeLuca, 2008). Specifically, MRI images in MS patients are characterized by subcortical hyperintense lesions in T2-weighted images. However, MRIs in older adults also show subcortical white matter hyperintensities that increase at a rate of 5% to 9% per year (Stern, 2005). Therefore, when studying older adults with MS, it remains unclear whether observed patterns in cognition or neuropathology should be viewed as characteristics of the disease, as normal aging, or as an interaction of the two.

## Current Study

The present study adds to the existing literature by investigating cognitive performance across three MS subtypes using a sample that has an older mean age than what is currently described in the literature. The performance of MS patients on a neuropsychological testing battery is compared to that of healthy controls and an aMCI patient sample. The study addresses four main aims and related hypotheses.

**Aim 1.** We sought to characterize the cognitive profile of a sample of older adult MS patients using a neuropsychological testing battery that assesses attention, processing speed, executive function, memory, language, and visuospatial domains. Relative to other cognitive domains, it was hypothesized that MS patients would demonstrate the greatest impairment on tests of processing speed, followed by tests of memory. Additionally, we sought to explore differences across subtypes. We hypothesized that among the three subtypes, secondary progressive patients would demonstrate the highest degree of cognitive impairment. Finally, demographic and clinical characteristics that may be significant predictors of cognitive impairment were also explored.

**Aim 2.** We sought to compare the cognitive performance of MS patients to a sample of healthy older adults. It was anticipated that MS patients would have significantly slower processing speed than controls, as demonstrated on the Digit-Symbol, Trails A, and Stroop tasks. It was also expected that MS patients would demonstrate impaired performance on a list learning task (i.e., Free & Cued Selective Reminding Test, FCSRT) and identify fewer items on the free recall trials than healthy controls.

**Aim 3.** We sought to compare the cognitive performance of MS patients to a sample of aMCI patients. Amnestic MCI typically involves impaired memory function, while other

cognitive abilities remain broadly intact (Petersen et al., 2001). The specific pattern of memory performance typically involves deficits in free recall and delayed recall (Chen et al., 2000; Tabert et al., 2006). Additionally, mild deficits have been observed in verbal fluency, object naming, psychomotor speed, visuospatial processing, and attention (Tabert et al., 2006). It was hypothesized that MS patients would differ from aMCI patients on memory tasks. Specifically, on the FCSRT, MS patients would show a greater benefit from repetition and cued prompts, such that total free recall and overall accuracy will be better than aMCI patients. Additionally, we hypothesized that MS patients would perform significantly better than aMCI patients on language tasks.

**Aim 4.** Finally, we sought to identify the cognitive variables that best illustrated differences between the MS and aMCI patient samples. It was anticipated that performance on the FCSRT would best characterize this difference.

## Method

### Participants

Patients between the ages of 60 and 80 who met the revised McDonald criteria for MS (Polman, et al., 2005) were recruited from the University of Kansas Medical Center in Kansas City, KS. All patients were under the care of the same neurologist (S. G. L.) and had a diagnosis of relapsing remitting, secondary progressive, or primary progressive MS of at least one year duration. Patients were excluded from participation on the basis of any of the following: relapse within the past three months; neurological disorder other than MS; history of drug or alcohol abuse; severe visual impairment or no color vision; impairment in the use of their dominant hand; severe cognitive or psychiatric impairment of sufficient magnitude to interfere with the

ability to comprehend testing instructions or provide informed consent; or less than a high school education.

The remaining sample was extracted from archival data collected through the University of Kansas Alzheimer's Disease Center (ADC). Individuals were self-referred to the ADC to participate in longitudinal research on cognition and aging. Individuals participated in neuropsychological testing and a Clinical Dementia Rating interview (CDR: Morris, 1993) annually. Based on the results, participants were classified into disease groups via consensus among a neurologist, neuropsychologist, and nurse clinician. A patient sample classified as aMCI with a CDR of 0.5 on their first visit to the ADC was used in this study. A sample of healthy controls meeting the relevant inclusion/exclusion for the study were also selected from ADC research participants. These individuals had a CDR of 0 and no evidence of impairment on testing.

## Measures

**Uniform Data Set, Version 2 (UDS) neuropsychological test battery.** The UDS neuropsychological test battery is a standardized collection of tests used at all ADCs across the country. Ten instruments assess attention, processing speed, executive function, memory, and language abilities (Weintraub et al., 2009). Measures and outcome scores are reported in Table 1.

**Supplemental neuropsychological battery.** An additional four tests were administered, consistent with the practice of the local ADC (see Table 1). These tests assess visuospatial reasoning (Block Design; Wechsler, 1987), attention/working memory (Letter Number Sequencing; Psychological Corporation, 1997), list learning/recall (Free and Cued Selective Reminding Test; FCSRT; Buschke, 1984; Grober & Buschke, 1987), and processing

speed/executive function (Stroop Test, Kaplan administration, with 45 sec time limit; Comalli, Wapner, & Werner, 1962; Mitrushina et al., 2005).

**Geriatric Depression Scale – Short Form (GDS).** The GDS is a 15-item instrument that asks individuals yes or no questions regarding how they have felt over the past week. It is a screening instrument for depression designed for use with older adult populations (Sheikh & Yesavage, 1986). Both the long and short forms have demonstrated adequate sensitivity and specificity. All study participants completed the GDS.

**Expanded Disability Status Scale (EDSS).** The degree of MS patients' neurological impairment was assessed by their neurologist (S. G. L.) using the EDSS scale. The scale describes physical disability and ranges from 0 (no neurological abnormality) to 10 (death from MS; Kurtzke, 1983).

**Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) – Short Form.** The IQCODE is a 16-item instrument that asks a patient's friend or family member about changes in the individual's cognition over the past 10 years (Jorm, 1994). The short form is strongly correlated with the long form, which has demonstrated adequate reliability, sensitivity, and specificity. The short form tends to be mildly but significantly correlated with the subject's level of depression ($r$ = 0.13; Jorm). The IQCODE was only collected from MS patients. The purpose was to identify a subset of patients that would most closely replicate the clinical scenario of a patient reporting cognitive concerns to their neurologist. In our effort to characterize the cognitive profile of MS patients, we were interested in whether a subset of patients with subjective complaints would differ from the collective sample and whether subjective complaints would significantly predict objective performance.

**Procedure**

MS patients were introduced to the study during the course of their regular appointment at the MS Clinic. All patients meeting inclusion and exclusion criteria were approached about participating in the study. If interest was expressed, a research assistant met with the patient to obtain written consent and schedule an appointment for a later testing session. Each session began with the administration of the UDS testing battery followed by the supplemental neuropsychological tests and GDS. The testing session lasted approximately 60 minutes. The IQCODE was completed either at the time of recruitment or, if the patient attended their clinic appointment alone, completed at a later date and mailed to the researchers. All participants signed informed consents.

**Statistical Analyses**

Data analysis was conducted using IBM SPSS Version 23. Descriptive statistics are used to summarize demographic and study measures where appropriate. Neuropsychological test results are reported both as raw scores and scaled scores. The UDS battery was converted to *z*-scores and then scaled scores using an online normative calculator based on a large descriptive study of nationwide UDS results (Shirk et al., 2011). Four additional normative samples were used to convert the raw scores in the supplemental neuropsychological battery to scaled scores (Ivnik et al., 1992; Ivnik et al., 1996; Ivnik et al., 1997; Psychological Corporation, 1987). All primary analyses were completed on raw scores; scaled scores were used to identify impairment. Group differences on neuropsychological test measures were assessed using one-way ANOVAs. All pairwise comparisons were Bonferroni-corrected. Only relevant comparisons (i.e., MS vs. healthy controls; MS vs. aMCI) are reported; differences between controls and aMCI patients are not discussed. Additionally, when significant differences in processing speed were found among

groups, speed on a simpler task (i.e., Trails A, Stroop Color Naming) was used to create covariate-adjusted scores for more complex tasks (i.e., Trails B, Stroop Interference). Finally, logistic regression was used to identify variables that best differentiated between MS and aMCI patients.

One-way ANOVAs were also used to explore subtype differences in demographic and neuropsychological test performance. Scaled scores were used to identify areas of impairment, and a repeated measures ANOVA compared rates of impairment across cognitive domains. Predictors of cognitive impairment were identified using multiple linear regression. Lastly, the significance of subjective cognitive concerns was also explored.

## Results

### Participants

Sixty-four individuals with MS participated in the study, including 23 RRMS, 22 SPMS, and 19 PPMS patients. Additionally, data from 70 healthy controls and 58 individuals diagnosed with aMCI were extracted from a larger database based on inclusion/exclusion criteria for this study. The clinical and demographic characteristics of the participants are summarized in Table 2. On average, individuals with MS had been diagnosed for 21.19 years ($SD$ = 11.51). Significant variability was observed, however, with a range from two to 47 years since diagnosis. The median EDSS of the sample was 5.0 (range 1.0-8.0), which represents a moderate level of disability. Within the sample, 83% of MS patients were retired, and of those, half (50%) indicated retirement was due to disability.

Across samples, there were a number of significant differences in demographic characteristics. The MS and aMCI patient groups had a significantly different distribution of men and women ($\chi^2$ (1) = 17.14, $p < .001$, $\Phi = .375$) with women making up 77% of the MS sample

and only 40% of the aMCI group. There were no significant differences in sex distribution between the MS sample and healthy controls (81% female; $\chi^2$ (1) = 0.48, $p$ = .489, $\Phi$ = .06). There was also a significant group difference in age ($F$(2, 189) = 26.43, $p$ < .001, $\eta^2$ = .22), such that individuals in the aMCI group were older than MS patients ($p$ < .001, $d$ = 1.15). Groups also differed significantly in their self-report of depressive symptoms on the GDS ($F$(2, 189) = 13.00, $p$ < .001, $\eta^2$ = .12). MS patients endorsed a greater number of statements than both healthy controls ($p$ < .001, $d$ = 0.93) and aMCI patients ($p$ = .05, $d$ = 0.07), indicating they experienced more mood symptoms than either of these other groups. All subsequent analyses were conducted with and without age and sex as covariates. If the covariates altered the findings, adjusted results are also reported.

**Between Group Analyses**

Comparisons of MS, aMCI, and healthy individuals' performance on cognitive tests are reported in Table 3. MS patients differed significantly from healthy controls across tests of processing speed (Trails A, Digit-Symbol, Stroop Color Naming, and Stroop Word Reading), memory (Logical Memory Immediate, LM-I; Logical Memory Delayed, LM-II; FCSRT-Trial 1 Free Recall, FCSRT-1F; and Total Free Recall, FCSRT-TF), verbal fluency (category fluency for animals and vegetables, CFA, CFV), and attention (Digit Span Forward, DSF) as well as on a cognitive screener (MMSE). The most robust differences, as indicated by effect sizes, were found on the Digit-Symbol test ($d$ = 0.97) followed by performance on memory tasks (FCSRT-TF: $d$ = 0.92; LM-I and LM-II: $d$ = 0.77); MS patients were significantly slower and recalled less information than healthy controls.

When comparing the two patient groups to one another, MS patients differed significantly from aMCI patients on a cognitive screener (MMSE) and tests of memory (LM-I;

LM-II; FCSRT-1F; FCSRT-TF; FCSRT-Trial 1 Free and Cued Recall, FCSRT-1FC; FCSRT-Accuracy, FCSRT-Acc.), language (Boston Naming Test, BNT; CFA; CFV), and executive function (Trails B). On all of these tasks, MS patients performed significantly better than aMCI patients. When corrected for age, the same general patterns are present, though group differences on verbal fluency tasks (CFA: $p = .109$, CFV: $p = .187$) and story memory (LM-I: $p = .769$, LM-II: $p = .275$) were no longer significantly different. Similarly, when corrected for sex, the group differences on the story memory tasks were no longer significant (LM-I: $p = .207$, LM-II: $p = .187$).

Based on the ANOVA findings, a logistic regression was conducted to further investigate the ability of cognitive variables to differentiate between MS and aMCI patients. Age, years of education, memory (FCSRT-1FC), and naming (BNT) were all significant predictors in the final model ($\chi^2 (4) = 56.55$, $p < .001$, Nagelkerke's $R^2 = .50$). MS patients were significantly younger, correctly named more pictures, and recalled fewer items from a list than aMCI patients. Overall, 52 of 64 MS (81%) and 44 of 58 aMCI patients (76%) were correctly classified. The addition of executive function (i.e., Trails B), processing speed (i.e., Digit-Symbol, Stroop Color Naming), or other memory (i.e., Logical Memory) or language (i.e., verbal fluency) measures did not significantly improve classification.

In addition to between-group comparisons using the full MS sample, comparisons among MS subtypes and other groups were also conducted. Relapsing remitting patients did not differ from healthy controls except in endorsing more items on the GDS ($p < .001$, $d = 1.30$). In contrast, the two groups of progressive patients showed a similar pattern of differences relative to controls, with poorer performance on story memory (LM-I: SPMS, $p = .003$, $d = 0.94$, PPMS, $p = .005$, $d = 1.03$; LM-II: SPMS, $p = .006$, $d = 0.89$, PPMS, $p = .016$, $d = 0.91$), free recall

(FCSRT-TF: SPMS, $p = .002$, $d = 1.17$, PPMS, $p = .045$, $d = 1.04$), processing speed tasks (Digit-Symbol: SPMS, $p = .001$, $d = 1.08$, PPMS, $p < .001$, $d = 1.69$; Stroop Color Naming: SPMS, $p = .019$, $d = 0.83$, PPMS, $p = .028$, $d = 0.86$; Stroop Word Reading: SPMS, $p = .048$, $d = 0.69$; Trails A: PPMS, $p < .001$, $d = 1.21$), and a verbal fluency task (CFV: SPMS, $p = .002$, $d = 0.95$, PPMS, $p = .001$, $d = 1.02$). Additionally, primary progressive patients reported significantly more depressive symptoms on the GDS than healthy controls ($p = .002$, $d = 1.17$). With respect to differences with the aMCI sample, the relapsing remitting patients differed across more measures than the progressive patients. Relapsing remitting patients were significantly younger than aMCI patients ($p < .001$, $d = 1.45$), so differences were considered with and without age as a covariate. Before correcting for age, significant differences were found on story memory (LM-I: $p = .016$, $d = 0.75$, LM-II: $p = .048$, $d = 0.68$), free recall (FCSRT-TF: $p = .001$, $d = 0.82$), verbal fluency (CFV: $p = .002$, $d = 0.94$), and the MMSE ($p = .047$, $d = 0.61$). After age correction, the only variable remaining significant was total free recall. Primary progressive patients differed significantly from aMCI patients on the same measure (FCSRT-TF: $p = .027$, $d = 0.64$) as well as a measure of executive function (Trails B: $p = .018$, $d = 0.11$). On all measures, MS patients outperformed aMCI patients. However, secondary progressive patients did not significantly differ from aMCI patients on any measure except age ($p < .001$, $d = 1.56$).

**Analyses Among MS Subtypes**

In addition to group differences among MS patients, aMCI patients, and healthy controls, patterns of cognitive performance and impairment across the different subtypes of MS were explored. Demographic characteristics of the different subtypes are summarized in Table 4. There was a significant group difference across subtypes in age ($F(2, 61) = 10.15$, $p < .001$, $\eta^2 = .25$), such that PPMS patients were significantly older than both RRMS ($p = .001$, $d = 1.09$) and

SPMS patients ($p < .001$, $d = 1.23$). The groups also differed significantly in EDSS score ($F(2, 61) = 10.32$, $p < .001$, $\eta^2 = .25$), with RRMS patients demonstrating less disability than SPMS ($p = .006$, $d = 0.93$) and PPMS patients ($p < .001$, $d = 1.39$). All subsequent analyses were conducted with and without age and EDSS as a covariate. When adjusted for age, no significant group differences among MS subtypes were identified for any cognitive variable. Prior to being corrected for age, the only test for which there was a significant difference was that of Digit-Symbol ($F(2, 61) = 3.69$, $p = .031$, $\eta^2 = .11$), with PPMS patients demonstrating poorer performance than RRMS patients ($p = .026$, $d = 0.41$).

In addition to analyzing raw scores, MS performance was also converted to age-corrected scaled scores, as described in the Method section. Scaled score means and standard deviations are reported by subtype and overall MS group in Table 5. Scaled scores were used to identify cognitive impairment at an individual level as well as to explore patterns in performance across different cognitive domains. First, test scores were coded as within normal limits or as impaired. Impairment was defined as a scaled score of 4 or lower, representing two standard deviations below the normative mean. Next, the number of tests with impaired performance was summed both within and across cognitive domains in order to classify an individual's cognitive status as intact or impaired. Cognitive impairment, at an individual level, was defined as impaired performance on at least one test across two or more cognitive domains. Of the 64 MS patients in the study, 13 (20%) met these criteria. Across subtypes, four RRMS (17%), five SPMS (23%), and four PPMS (21%) patients met criteria for cognitive impairment.

A repeated measures mixed ANOVA was conducted to explore differences in impairment across subtype and cognitive domain. The Greenhouse-Geisser correction was applied. There was no significant difference in impairment across cognitive domains among MS subtypes

($F(2,61) = 0.36$, $p = .701$, $\eta^2 = .01$). However, frequency of impaired test performance did differ significantly across cognitive domains ($F(2.85,173.97) = 9.74$, $p < .001$, $\eta^2 = .03$). Pairwise comparisons revealed that performance on tests of processing speed was significantly worse than performance on tests of attention ($p = .019$, $d = 0.49$), executive function ($p < .001$, $d = 0.53$), language ($p = .001$, $d = 0.64$), and visuospatial processing ($p < .001$, $d = 0.73$). Performance on memory tasks was also significantly worse than performance on tests of language ($p = .034$, $d = 0.48$) and visuospatial processing ($p = .019$, $d = 0.58$). See Figure 1 for a representation of the frequency of impairment across cognitive domain.

A hierarchical regression analysis was conducted to investigate potential predictors of cognitive impairment. Specifically, the ability of three models to predict the sum of cognitive tests within an impaired range was evaluated. Model 1 consisted of demographic variables: age and years of education. Model 2 added clinical variables: length of diagnosis and EDSS score. Model 3 added cognitive and mood screeners and questionnaires: GDS, IQCODE, and MMSE scores. A bootstrapped Model 3 predicted the largest amount of variance ($r^2 = .39$; see Table 6). Individual variables contributing significantly to the model included length of diagnosis ($p = .038$) and EDSS score ($p = .039$).

Informant report of perceived cognitive decline as measured on the IQCODE was further investigated as a potential predictor of cognitive impairment. Of the 51 patients with completed forms, 13 (26%) met criteria for cognitive impairment based on the cut score described in Jorm (1994). However, subjective report of cognitive change was not significantly related to other relevant variables, such as age, education, disease duration, EDSS, or MMSE, based on Spearman correlations. Additionally, a chi-square analysis comparing classification rates (i.e., impaired or not impaired) across the two definitional approaches (i.e., informant report or

cognitive performance) found significant differences ($\chi^2$ (1) = 7.80, $p$ = .005, Φ = .391), indicating that informant report of cognitive concerns was not consistent with the results of cognitive testing. Only 46% of individuals labeled as impaired based on the IQCODE were also identified as impaired based on cognitive performance. Sixty percent of MS patients classified as impaired based on test performance were labeled as impaired based on informant report. This inconsistency indicates that subjective report of cognitive decline is not meaningfully connected to cognitive impairment as identified on objective tests.

## Discussion

### Memory Performance Relative to Healthy Controls

Comparisons of cognitive performance among MS, aMCI, and healthy samples were largely consistent with our hypotheses and findings previously reported in the literature. MS patients performed more poorly than healthy controls most consistently and robustly across measures of processing speed and memory. The pattern of memory performance is also consistent with findings in the broader MS population. Patients demonstrated poor free recall of a story (i.e., Logical Memory) as well as a series of items presented in a visually- and orally-mediated controlled learning procedure (i.e., Free and Cued Selective Reminding Test). Cued recall improved patients' performance such that overall accuracy was comparable with that of healthy controls. Additionally, MS patients retained information over time without a greater rate of forgetting than healthy individuals, as demonstrated by the retention rate from immediate to delayed recall of a story.

There are two competing explanations for the dissociation between free recall and recognition performance typically observed in MS patients. Historically, this this pattern of performance has been characterized as a retrieval deficit (e.g., Rao, Leo, St. Aubin-Faubert,

1989). Others, however, have suggested that poor recall can be attributed to an acquisition deficit instead (e.g., DeLuca, Barbieri-Berger, & Johnson, 1994). When MS patients and healthy controls are both trained to a criterion (i.e., 100% immediate recall on two consecutive trials), MS patients require more trials to reach criterion; subsequently, though, delayed free recall becomes equivalent between groups (DeLuca et al., 1994, DeLuca et al., 1998). Thus, when initial learning is controlled, an apparent deficit in memory is attenuated. Clinically-oriented studies, such as the present one, are not suited to adequately test these hypotheses, which require modification of standardized administration procedures. Thus, either the retrieval or the acquisition hypothesis may account for the pattern of performance observed in this study.

Further, other factors may also have contributed to MS patient's performance on memory tasks. For example, slowed processing speed might explain lower free recall scores on the FCSRT. The free recall portion of each trial was limited to 90 seconds or ended after a 15-second interval with no response. If MS patients were significantly slower to respond, this may have depressed their free recall scores relative to healthy controls. A second consideration involves performance on cued recall tasks. Both MS patients and healthy controls, at a group level, approached perfect performance (i.e., 99% accuracy) on cued recall tasks, indicating the presence of ceiling effects. It may be that differences exist between MS and healthy controls that were not observed because the task was too simple. Overall, while the MS patients' pattern of performance on memory tasks is consistent with that described in the literature, multiple factors must be considered when interpreting the implications of their performance.

**Cognitive Similarities and Differences with an aMCI Sample**

Perspectives on cognitive performance can also be informed by comparing different patient samples to one another. In this study, comparisons were made between MS and aMCI

patients. This comparison represents a possible differential that clinicians might realistically encounter. Therefore, it is helpful to consider variables that distinguish these two groups. Importantly, there was no measure on which MS patients performed significantly worse than individuals with aMCI. Performance was similar on measures of processing speed and attention. Consistent with hypotheses, aMCI patients differed the most from MS patients on tasks assessing memory and language. Specifically, while MS patients demonstrated significantly poorer free recall than healthy controls, aMCI patients' recall was even worse. Further, in contrast to the MS sample, the performance of aMCI patients does not improve when cues are provided, suggesting that information is not available for retrieval and is, therefore, not being adequately encoded or stored. These results are largely consistent with the one other study comparing MS and aMCI samples (Müller et al., 2013). However, we found more group differences than reported by Müller and colleagues. In their study, groups only differed on a recognition task. One possible explanation for this difference is that only SPMS patients were included in the Müller et al. study. When we analyzed our data at the subtype level, SPMS patients did not significantly differ from aMCI patients on any measure. These findings suggest that, while the cognitive profile of aMCI patients is more severe than that of MS patients, there are also a number of commonalities, at a group level, between these samples.

**Impairment within the MS Sample**

In addition to differences relative to healthy controls or aMCI patients, patterns of cognitive performance and impairment were also explored within the MS sample. The reported rate of 20% in this study is lower than what is typically reported in the literature. The most consistently cited range of cognitive impairment is 40% to 70% (Chiaravalloti & DeLuca, 2008). The only other study with older adult patients to report a rate of impairment was also much

higher (48%) than the present study (Smestad et al., 2010). One consideration for these differences is that the definition of impairment in the present study was relatively stringent. We required performance two standard deviations below a normative mean on at least one test in two different cognitive domains. Smestad and colleagues had slightly more liberal criteria with impairment defined at 1.5 standard deviations below a mean. A recent review reported on the effect of variable definitions of cognitive impairment across MS studies and demonstrated that definitions can dramatically alter reported rates of impairment (Fischer et al., 2014). Because our definition was based on standardized scaled scores as reported in available normative samples, it was not possible to consider fractional standard deviations below the mean; the scaled scores could only be translated into whole integers. Another possible explanation for the lower rate of impairment is that, rather than being a function of definitional factors, it reflects a characteristic of this sample. In particular, there is a high level of educational attainment within the MS sample ($M$ = 15.34, $SD$ = 2.33). Years of education is thought to correspond to cognitive reserve. Multiple studies within MS have demonstrated that cognitive reserve can protect from or reduce the consequences of cognitive decline and impairment (DeLuca et al., 2014; Feinstein, Lapshin, O'Connor, & Lanctôt, 2013).

While the overall rate of impairment was lower than anticipated, the pattern of cognitive domains affected is very consistent with the broader literature. The domain demonstrating the highest rate of impairment was processing speed, with 36% of MS patients demonstrating impaired performance on at least one measure of processing speed. The second domain in which patients demonstrated significant impairment was memory (25%). The percentages of the sample demonstrating impairment on the remaining tasks were all low and did not differ significantly from one another (attention, 16%; executive function, 11%; language, 11%; visuospatial

processing, 6%). This pattern of deficits is consistent with multiple reviews of cognition in MS (i.e., Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Guimarães & Sá, 2012).

Patterns across subtypes observed in the present study are also generally consistent with the literature. Direct comparisons of subtypes with one another did not find any significant differences in test performance or rates of impairment; however, comparisons with external groups illustrate some important differences among subtypes. There appear to be separate patterns of performance for patients with a relapsing remitting versus progressive disease courses. RRMS patients showed very few differences relative to healthy controls, while progressive patients differed significantly. In contrast, relative to an aMCI sample, individuals with a progressive disease course showed minimal differences, while RRMS patients differed across a greater number of measures. The lack of differentiation between RRMS patients and healthy controls is somewhat surprising. Most studies report evidence of relative impairment across all subtypes and severity levels of disease course, particularly on tasks of processing speed (Denney, Sworowski, & Lynch, 2005; De Sonneville, et al., 2002; Zakzanis, 2000). It may be that this patient group–individuals whose disease course has remained stable and relatively mild for decades–represents some of the healthiest individuals with MS. So much so, that older adult RRMS patients may appear as cognitively intact as their healthy same-age peers.

Differentiating between the cognitive profiles of the two progressive subtypes is somewhat challenging. Again, these groups do not significantly different from one another on any direct comparison across raw or normed scores or rate of impairment (SPMS, 23%, PPMS, 22%). Similarly, their performance relative to healthy controls and comparable with one another. There are some relative differences when compared to the aMCI sample. PPMS patients differ significantly from aMCI patients on two measures, one of memory and one of executive

function, while SPMS patients do not differ significantly on any measure. The literature on differences in cognitive impairment between SPMS and PPMS patients is inconclusive. The SPMS disease course is generally thought to be associated with greater cognitive impairment (Chiaravalloti & DeLuca, 2008). Reported rates of impairment are typically between 50% and 70% (Cáceres, Vanotti, Rao, & RECONEM Workgroup, 2011; Comi et al. 1995; Foong et al., 2000; Smestad et al., 2010). However, it is challenging to compare these findings to rates of impairment in PPMS patients because estimates vary so dramatically (i.e., 7% in Comi et al. versus 100% in Cáceres et al.). The variability is probably attributable to very small sample sizes (e.g., $n < 10$), which quickly distort percentages. Our findings are most consistent with those studies reporting little difference between progressive subtypes (Camp et al., 1991, Smested et al.). However, it should also be noted that a limitation of our results is the relatively small sample sizes within subtypes (SPMS, $n = 22$; PPMS, $n = 19$) and the corresponding reduction in power to detect significant group differences.

In general, knowing a patients' disease course, particularly whether it is relapsing remitting or progressive in nature, will inform predictions of cognitive performance. Other factors found to be significantly associated with cognitive impairment in this study included EDSS scores and disease duration. EDSS has been found to have mild to moderate associations with cognitive impairment, though the relationship between physical and cognitive disability is typically weaker than what might be assumed (Chiaravalloti & DeLuca, 2008; Lynch, Parmenter, & Denney, 2005). The second variable found to be associated with cognitive impairment in this study was that of disease duration, or, more specifically, years since diagnosis. This is not consistent with the broader literature, though our findings do replicate a handful of more recent studies with older patient samples and wider ranges of disease durations. Previously, disease

duration has not, in general, been associated with cognitive impairment. Impairment can be found at all durations, even in patients with clinically isolated syndrome, which is considered by some to be a prodromal stage of MS (DeLuca et al., 2014). Additionally, disease duration does not predict performance on neuropsychological test measures (Beatty et al., 1990). However, a recent large scale study investigating 1,500 patients with a broad range of disease durations (1 to 55 years) reported significant associations between disease duration and cognitive impairment across various cognitive domains (Achiron et al., 2014). Further, in a specific sample of older adults also demonstrating a wide range of disease duration (i.e., 12-53 years), Smestad and colleagues (2010) similarly found a significant relationship between age of onset and cognitive impairment. These studies suggest that perhaps there has been a restricted range of disease duration in prior studies with younger patients, and this has affected the conclusions reached. Evidence from the present study and other recent work with broad ranges of disease duration suggests the relationship between cognitive impairment and disease duration warrants further consideration.

**Conclusions**

This study expands upon the existing literature in multiple ways. It is one of the largest samples of older adult MS patients and it is the oldest sample, on average, to be described in the literature. At a subtype level, it comprises the largest sample of older adult primary progressive patients to be characterized. Additional strengths of the study are the inclusion of multiple disease courses and the wide range of disease durations. Some of the conclusions are limited by small sample sizes within the MS subtypes. Additionally, while the range in disease duration is a strength, it is also important to recognize that this variable was determined via self-reported time since diagnosis, which may differ from the actual time of disease onset. Definitions of cognitive

impairment are variable in the literature. Our definition is one of the more stringent; therefore, estimates of impairment are likely more conservative than in other studies. Further, impairment was defined based on normative scores. Multiple normative samples were needed to calculate scaled scores for all the measures in our battery, which is not ideal. Finally, a significant age difference between MS and aMCI patients is problematic. It would have been preferable to create equivalency on this variable at the recruitment stage rather than correcting for age through statistical means.

Overall, this study adds to our knowledge of cognitive abilities in older adult MS patients. Similar to patterns seen in younger adults, processing speed and memory functions remain the most frequently impaired cognitive abilities. In contrast to younger samples, disease duration emerged as a relevant predictor of cognitive impairment. Comparisons with another clinical sample – aMCI patients – reveal a high degree of overlap between these two patient groups. This demonstrates the challenge clinicians face when trying to understand the etiology of cognitive changes in their older adult MS patients. As MS patients age, there will be a greater need to consider comorbid conditions that may contribute to cognitive complaints. Finally, while much can be learned from cross-sectional studies such as the present one, there is also a substantial need for long-term, controlled longitudinal studies on cognitive change in MS that follow patients into older adulthood. As several of the participants in this study observed at the end of their testing session, “Well, what you really need to do is come test me again in a few years. Now that would be interesting!”

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Table 1

*Neuropsychological outcome measures organized by cognitive domain*

| Cognitive Domain | Test Measure | Abbrev. | Outcome Scores |
|---|---|---|---|
| Screener | Mini-Mental State Examination | MMSE | Total score |
| Attention | Digit Span Forward | DSF | Total correct |
| | Digit Span Backward | DSB | Total correct |
| | Letter Number Sequencing [a] | LNS | Total correct |
| Processing Speed | Digit Symbol | D-S | Total correct |
| | Trail Making Test, Part A | TMA | Completion time |
| | Stroop Test, Color Naming [a] | -- | Total correct |
| | Stroop Test, Word Reading [a] | -- | Total correct |
| Executive function | Trail Making Test, Part B | TMB | Completion time |
| | Stroop Test, Interference [a] | -- | Total correct |
| Memory | Logical Memory, Story A | LM-I<br>LM-II<br>LM-Ret | Immediate recall total correct<br>Delayed recall total correct<br>Percent retained |
| | Free & Cued Selective Reminding Test [a] | FCSRT-1F<br>FCSRT-1FC<br>FCSRT-TF<br>FCSRT-Acc | Trial 1 free recall<br>Trial 1 free & cued recall<br>Total free recall<br>Total accuracy |
| Language | Semantic fluency – animals, vegetables | CFA, CFV | Total correct |
| | Boston Naming Test (30 items) | BNT | Total correct |
| Visuospatial | Block Design [a] | BD | Total points |

[a] Supplemental test that is not part of the Uniform Data Set.

Table 2

*Demographic and clinical data of participants*

| | MS (*n* = 64) | | aMCI (*n* = 58) | | HC (*n* = 70) | | ANOVA (*df* = 189) | | MS vs. aMCI | | MS vs. HC | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | M | SD | M | SD | M | SD | F | *p* | *p* | *d* | *p* | *d* |
| Age | 66.08 | 4.53 | 71.48 | 4.91 | 66.29 | 4.50 | 26.43 | <.001 | **<.001** | 1.15 | .991 | 0.05 |
| Education (years) | 15.34 | 2.33 | 16.14 | 3.02 | 15.61 | 2.45 | 1.46 | .235 | -- | -- | -- | -- |
| GDS (score) | 3.25 | 3.09 | 2.14 | 2.80 | 1.01 | 1.56 | 13.00 | <.001 | **.050** | 0.07 | **<.001** | 0.93 |
| Diagnosis (years) | 21.19 | 11.51 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| EDSS (median, range) | 5.0 | 1.0-8.0 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

*Note*. EDSS, Expanded Disability Status Scale; GDS, Geriatric Depression Scale; HC, healthy controls

Table 3

*Performance on neuropsychological tests with raw scores*

| | MS (*n* = 64) | | aMCI (*n* = 58) | | HC (*n* = 70) | | ANOVA (*df* = 189) | | MS vs. aMCI | | MS vs. HC | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | F | *p* | *p* | *d* | *p* | *d* |
| MMSE | 28.53 | 1.85 | 27.60 | 2.14 | 29.54 | 0.88 | 21.44 | <.001 | **.008** | 0.47 | **.002** | 0.71 |
| LM-I | 11.69 | 4.15 | 9.76 | 4.25 | 14.61 | 3.46 | 24.75 | <.001 | **.023** | 0.46 | **<.001** | 0.77 |
| DSF | 7.86 | 2.00 | 8.10 | 1.78 | 8.71 | 1.90 | 3.62 | .029 | .999 | 0.13 | **.030** | 0.44 |
| DSB | 6.02 | 2.09 | 5.71 | 1.95 | 6.61 | 2.14 | 3.23 | .042 | .999 | 0.15 | .287 | 0.28 |
| CFA | 20.14 | 5.37 | 16.86 | 5.50 | 22.73 | 5.86 | 17.46 | <.001 | **.004** | 0.60 | **.024** | 0.46 |
| CFV | 13.19 | 3.83 | 11.03 | 3.76 | 16.03 | 3.67 | 28.64 | <.001 | **.005** | 0.57 | **<.001** | 0.76 |
| TMA | 40.89 | 23.80 | 37.17 | 17.41 | 28.34 | 9.23 | 8.98 | <.001 | .740 | 0.18 | **<.001** | 0.71 |
| TMB [a] | 104.39 | 62.24 | 113.21 | 57.34 | 74.73 | 25.65 | 6.09[a] | .003 | **.020** | 0.15 | .999 | 0.63 |
| D-S | 39.30 | 13.57 | 40.03 | 11.73 | 50.86 | 10.24 | 19.85 | <.001 | .999 | 0.06 | **<.001** | 0.97 |
| LM-II | 9.84 | 4.48 | 7.60 | 4.55 | 13.01 | 3.79 | 26.12 | <.001 | **.013** | 0.50 | **<.001** | 0.77 |
| LM-Ret. | 81.60 | 22.67 | 74.23 | 30.00 | 89.12 | 17.39 | 6.37 | .002 | .257 | 0.28 | .199 | 0.37 |
| BNT | 28.36 | 1.70 | 26.88 | 3.82 | 28.41 | 1.53 | 7.43 | .001 | **.004** | 0.51 | .999 | 0.03 |
| BD | 32.45 | 11.68 | 28.36 | 8.67 | 35.03 | 11.68 | 6.01 | .003 | .117 | 0.39 | .516 | 0.22 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroop-C | 65.29 | 17.88 | 66.51 | 12.68 | 74.01 | 11.62 | 7.31 | .001 | .999 | 0.08 | **.002** | 0.58 |
| Stroop-W | 86.44 | 17.09 | 87.04 | 15.58 | 95.80 | 13.90 | 7.58 | .001 | .999 | 0.04 | **.002** | 0.60 |
| Stroop-I [b] | 32.35 | 10.50 | 29.84 | 10.00 | 38.41 | 8.37 | 7.76 | .001 | .108 | 0.24 | .195 | 0.64 |
| FCSRT-1F | 7.64 | 2.14 | 6.49 | 2.79 | 8.90 | 1.75 | 18.42 | <.001 | **.016** | 0.47 | **.004** | 0.65 |
| FCSRT-1FC | 15.94 | 0.24 | 14.91 | 3.01 | 16.01 | 0.65 | 7.92 | <.001 | **.003** | 0.49 | .999 | 0.15 |
| FCSRT-TF | 26.72 | 5.58 | 21.60 | 8.52 | 31.29 | 4.31 | 38.10 | <.001 | **<.001** | 0.72 | **<.001** | 0.92 |
| FCSRT-Acc | 99.74 | 0.87 | 94.04 | 17.73 | 99.88 | 1.50 | 7.05 | .001 | **.005** | 0.47 | .999 | 0.11 |
| LNS | 9.27 | 2.81 | 8.47 | 2.42 | 10.29 | 2.44 | 7.99 | <.001 | .274 | 0.30 | .067 | 0.39 |

*Note.* All pairwise comparisons are Bonferroni-corrected.
[a] Covariate-adjusted for performance on TMA
[b] Covariate-adjusted for performance on Stroop-C

Table 4

*Demographic and clinical data of MS subtypes*

| | RR (*n* = 23) | | SP (*n* = 22) | | PP (*n* = 19) | | RR vs. SP | | RR vs. PP | | SP vs. PP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | M | SD | M | SD | M | SD | *p* | *d* | *p* | *d* | *p* | *d* |
| Age | 64.83 | 3.66 | 64.41 | 3.28 | 69.53 | 5.00 | .999 | 0.12 | **.001** | 1.09 | **<.001** | 1.23 |
| Education (years) | 14.91 | 2.84 | 16.09 | 1.80 | 15.00 | 2.08 | -- | -- | -- | -- | -- | -- |
| Diagnosis (years) | 20.96 | 12.13 | 24.64 | 12.45 | 17.47 | 8.59 | -- | -- | -- | -- | -- | -- |
| EDSS (mdn., range) | 3.5 | 1.0-6.0 | 5.75 | 2.0-8.0 | 6.0 | 2.5-8.0 | **.006** | 0.93 | **<.001** | 1.39 | .705 | 0.38 |
| GDS (score) | 3.61 | 2.97 | 2.68 | 2.95 | 3.47 | 3.43 | -- | -- | -- | -- | -- | -- |

*Note*. RR, relapsing remitting; SP, secondary progressive; PP, primary progressive; EDSS, Expanded Disability Status Scale; GDS, Geriatric Depression Scale

Table 5

*Performance on neuropsychological tests with age-corrected scaled scores (M = 10, SD = 3)*

| | MS | | RR | | SP | | PP | |
|---|---|---|---|---|---|---|---|---|
| Score | *M* | *SD* | *M* | *SD* | *M* | *SD* | *M* | *SD* |
| MMSE | 8.81 | 3.47 | 9.04 | 3.01 | 8.18 | 3.84 | 9.26 | 3.62 |
| Logical Memory, Immediate Recall | 8.06 | 3.25 | 8.96 | 3.07 | 7.59 | 3.58 | 7.52 | 2.96 |
| Digit Span – Forward | 8.80 | 3.00 | 8.65 | 2.33 | 8.77 | 3.12 | 9.00 | 3.59 |
| Digit Span – Backward | 8.48 | 2.92 | 8.30 | 3.11 | 8.45 | 3.00 | 8.74 | 2.70 |
| Category Fluency – Animal | 9.56 | 2.91 | 9.70 | 2.60 | 9.86 | 3.44 | 9.05 | 2.68 |
| Category Fluency – Vegetable | 8.52 | 2.71 | 9.52 | 2.74 | 7.86 | 2.38 | 8.05 | 2.82 |
| Trail Making Test, Part A | 8.39 | 3.08 | 8.43 | 3.30 | 8.82 | 2.42 | 7.84 | 3.55 |
| Trail Making Test, Part B | 8.66 | 3.00 | 8.78 | 3.18 | 8.45 | 3.13 | 8.74 | 2.77 |
| Digit-Symbol Test | 7.03 | 3.46 | 8.00 | 3.67 | 6.82 | 3.20 | 6.11 | 3.36 |
| Logical Memory, Delayed Recall | 8.00 | 3.19 | 8.39 | 2.86 | 7.73 | 3.73 | 7.84 | 3.00 |
| Boston Naming Test | 10.64 | 1.71 | 10.48 | 2.21 | 10.36 | 1.50 | 11.16 | 1.12 |
| Block Design[a] | 12.03 | 3.75 | 12.17 | 3.96 | 11.77 | 3.66 | 12.16 | 3.78 |
| Stroop – Color Naming[b] | 9.70 | 3.94 | 10.35 | 4.17 | 8.86 | 3.67 | 9.89 | 3.98 |
| Stroop – Word Reading[b] | 8.75 | 3.03 | 9.00 | 2.70 | 8.36 | 3.47 | 8.89 | 2.97 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stroop – Interference[b] | 9.40 | 3.14 | 9.87 | 2.62 | 8.64 | 3.05 | 9.72 | 3.82 |
| FCSRT – Trial 1 Free Recall[c] | 8.44 | 2.90 | 8.87 | 2.78 | 7.86 | 3.11 | 8.58 | 2.83 |
| FCSRT – Trial 1 Free & Cued Recall[c] | 9.78 | 0.86 | 9.87 | 0.63 | 9.50 | 1.30 | 10.00 | 0.00 |
| FCSRT – Accuracy[c] | 9.83 | 0.55 | 9.83 | 0.58 | 9.68 | 0.72 | 10.00 | 0.00 |
| Letter Number Sequencing[d] | 10.31 | 3.07 | 10.65 | 3.24 | 10.14 | 3.37 | 10.11 | 2.58 |

*Note*. RR, relapsing remitting; SP, secondary progressive; PP, primary progressive. Age-corrected scaled scores are based on Shirk et al. (2011), unless otherwise noted.

[a] Age-corrected scaled scores, Ivnik et al. (1992)

[b] Age-corrected scaled scores, Ivnik et al. (1996)

[c] Age-corrected scaled scores, Ivnik et al. (1997)

[d] Age-corrected scaled scores, Psychological Corporation (1987)

Table 6

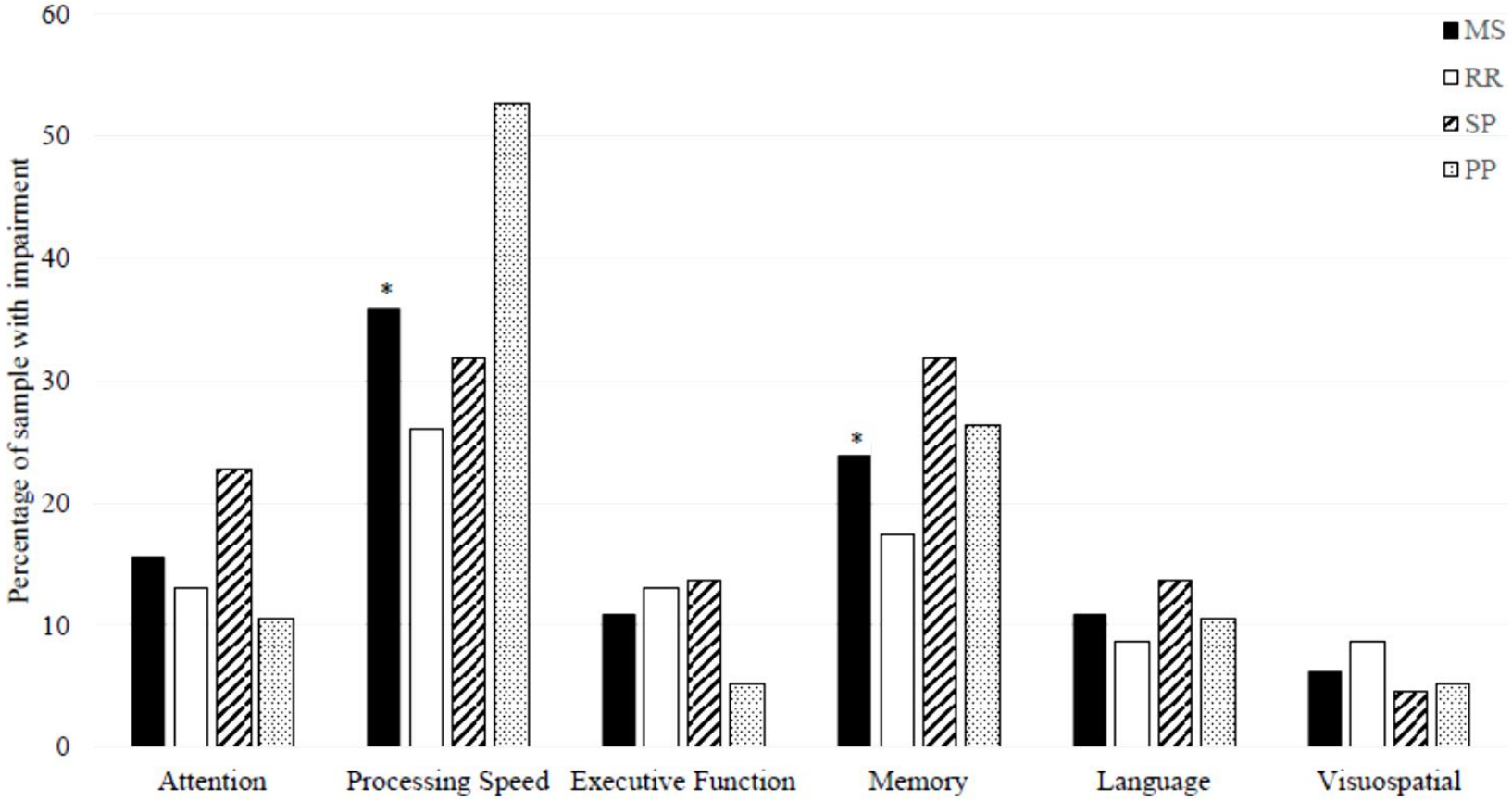
*Linear regression models of predictors of impaired performance on cognitive tests, with 95% bias corrected and accelerated confidence intervals reported. Confidence intervals and standard errors based on 1000 bootstrap samples.*

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | B | CI | *p* | B | CI | *p* | B | CI | *p* |
| Constant | 1.69 | -5.71, 10.74 | .619 | 2.13 | -6.04, 12.80 | .606 | 11.87 | -6.04, 40.88 | .375 |
| Age | 0.01 | -0.08, 0.09 | .862 | -0.05 | -0.17, 0.04 | .358 | -0.03 | -0.13, 0.03 | .575 |
| Education | -0.06 | -0.32, 0.16 | .635 | -0.07 | -0.34, 0.11 | .541 | -0.06 | -0.28, 0.09 | .525 |
| Duration | -- | -- | -- | 0.07 | 0.02, 0.12 | **.024** | 0.06 | 0.02, 0.10 | **.038** |
| EDSS | -- | -- | -- | 0.50 | 0.20, 0.85 | **.012** | 0.45 | 0.11, 0.94 | **.039** |
| GDS | -- | -- | -- | -- | -- | -- | 0.02 | -0.14, 0.16 | .826 |
| IQCODE | -- | -- | -- | -- | -- | -- | -0.01 | -0.45, .34 | .972 |
| MMSE | -- | -- | -- | -- | -- | -- | -0.38 | -1.09, 0.12 | .334 |
| $R^2$ | | .01 | | | .29 | | | .39 | |
| F | | 0.13 | | | 5.47 | | | 4.72 | |
| $\Delta R^2$ | | -- | | | .28 | | | .10 | |
| $\Delta$ F | | - | | | 10.77 | | | 2.95 | |

*Note*. EDSS, Expanded Disability Status Scale; GDS, Geriatric Depression Scale; MMSE, Mini Mental Status Exam

Figure 1

*Percentage of sample with impaired test performance across cognitive domain by MS subtypes*




* Processing speed significantly different from attention ($p = .019$), executive function ($p < .001$), language ($p = .001$), and visuospatial ($p = .034$). Memory significantly different from language ($p = .034$) and visuospatial processing ($p = .019$).