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Neural Correlates of Daily Function: A Pilot Study of the White Matter Retrogenesis Hypothesis and Three Separate Performance-Based Functional Assessments

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Abstract

Objective: Increasing evidence points to mild alterations in everyday functioning early in the course of Alzheimer’s disease and related dementias (ADRD), despite prior research suggesting functional declines occur primarily in later stages. However, daily function assessment is typically accomplished with subjective self- or informant-report, which can be prone to error due to various factors. Performance-based functional assessments (PBFAs) allow for objective evaluation of daily function abilities, but little is known on their sensitivity to the earliest ADRD-related brain alterations. We aimed to determine the neural correlates of three different PBFAs in a pilot study.

Method: A total of 40 older participants (age=70.9±6.5 years; education=17.0±2.6 years; 51.5% female; 10.0% non-White; 67.5% cognitively normal) completed standardized PBFAs related to medication management (MM), finances (FIN), and communication abilities (COM). Participants underwent diffusion tensor imaging (DTI) scans, from which mean fractional anisotropy (FA) composite scores of late- (LMF) and early-myelinated (EMF) fibers were calculated. Linear regression analyses controlling for age and global cognition were used to assess the relationship of PBFAs with FA.

Results: Better performance on MM was associated with higher mean FA on LMF composite (t₃₈=2.231, p=0.032), while FIN and COM were not (p>0.05). PBFAs were not associated with EMF (p>0.05).

Conclusions: Our preliminary findings demonstrate better performance on a PBFA of medication management is associated with higher FA in late-myelinated white matter tracts. Despite a small sample size, these results are consistent with growing evidence that performance-based functional assessments may be a useful tool in identifying early changes related to ADRD.
Keywords
aging; Alzheimer’s disease; mild cognitive impairment; cognition; activities of daily living

Introduction
Pathological changes associated with Alzheimer’s disease and other neurodegenerative
dementias have been well documented to begin years prior to clinical manifestation (Jack
et al., 2018), raising important questions as to how to best detect the earliest cognitive and
functional changes in aging adults. Moreover, as noted by the National Plan to Address
Alzheimer’s Disease (NAPA, 2018), there is a clear need to identify these early stages of
Alzheimer’s disease and related dementias (ADRD) using cost-effective methods that can be
implemented across diverse communities. Objective assessment of cognitively demanding
activities of daily living, which could be more adaptable and broadly disseminated than
traditional paper-and-pencil neuropsychological testing, may offer such a method for earlier
detection of cognitive decline in ADRD.

Recent studies of everyday function associated with healthy aging and neurodegenerative
disease have challenged the notion that people with mild cognitive impairment (MCI)
maintain a level of intact daily function (Seligman & Giovannetti, 2015). While loss of
functional independence is the primary diagnostic distinction between MCI and dementia,
there is increasing evidence that impairments in instrumental activities of daily living
(IADLs), such as managing medications and finances, occur early in the continuum of
cognitive impairment. In one study using a functional self-report questionnaire, difficulties
with household and financial management were particularly predictive of progression from
normal cognition to MCI and were useful in discriminating between the two groups
(Marshall et al., 2015). These early functional impairments may have previously gone
undetected due to inherent limitations of self- and informant-report functional measures,
such as lack of insight, mood, or caregiver distress (Shulman et al., 2006). Utilization of
objective performance-based functional assessments (PBFAs) may provide additional insight
into early functional changes that may be otherwise missed. For example, by employing a
PBFA, Giovannetti and colleagues found evidence for clear functional deficits in individuals
with MCI compared to cognitively normal individuals (Giovannetti et al., 2008). Individuals
with MCI and subtle IADL deficits may also be more likely to progress to a dementia
syndrome than those without IADL deficits (Teng et al., 2010). These findings make
intuitive sense, as MCI has been conceptualized as an intermediary severity between healthy
aging and a dementia diagnosis (Petersen et al., 1999; Reisberg et al., 2008), suggesting that
functional changes likely occur on a measurable continuum.

While objective assessment for subtle IADL deficits using PBFAs may offer a novel method
of earlier detection of cognitive decline, avoiding potential biases of self- and informant-
report, there is limited evidence for the connections between functional measures and
underlying neurodegenerative pathophysiology (Jekel et al., 2015). Furthermore, previous
studies are limited by the use of self- or informant-report functional measures in their
comparisons to neuroimaging biomarkers of ADRD (Vemuri et al., 2009). While objective
measures of cognitive functional abilities may be a superior tool for assessing the earliest functional changes in MCI and dementia, little is known regarding the relationship between PBFAs and neuroimaging biomarkers associated with pathological aging and neurodegenerative disease. Better characterization of these relationships would support the wider use of PBFAs and allow for integration of earlier functional impairments into the accepted continuum of cognitive decline in ADRD.

Although dementias are often considered diseases of grey matter, alterations in white matter integrity are a common finding and very early marker of ADRD. In a recent study of AD mutation carriers, evidence of white matter disease was noted up to 22 years prior to manifestation of symptoms, suggesting that white matter alterations not only play a critical role in the pathogenesis of ADRD but moreover may presage clinical presentation (Lee et al., 2018; Nasrabad et al., 2018). According to the white matter retrogenesis hypothesis, late-myelinated fiber tracts are the earliest and most affected in ADRD via pathways related to increased susceptibility to amyloid deposition (Bartzokis, 2004; Bartzokis et al., 2007; Brickman et al., 2012). Indeed, diffusion tensor imaging studies in individuals with ADRD have shown lower fractional anisotropy in late-myelinated fibers (LMF) compared to early-myelinated fibers (EMF) (Stricker et al., 2009). Summary measures of these fibers have been developed and validated in aging and an association between LMF and cognitive decline has been reported (Brickman et al., 2012). In the current study, we examined the relationship between PBFAs and these measures of white matter integrity, differentiating EMF and LMF, in an aging and MCI population. We hypothesized that worse PBFA scores would be associated with lower integrity (as measured by fractional anisotropy [FA]) of LMF but not EMF. Given noted limitations of questionnaire-based assessment of daily function, we also hypothesized that there would be no significant association between these measures and EMF or LMF. As a secondary aim of the current study, we examined the possible mediating role of cognitive function on the relationship between PBFAs and white matter integrity. Given the strong relationship between PBFAs and traditionally-defined cognitive domains, we expected that the relationship between LMF and PBFA would be mediated by performance on traditional cognitive tests. Lastly, as an exploratory aim, we examined differences in this relationship between those with normal cognition and those with MCI.

Methods

Participants

A total of 40 individuals (age=70.9±6.5 years; education=17.0±2.6 years; 51.5% female; 10.0% non-White; 67.5% cognitively normal) were recruited from a larger cohort study on aging and ADRD through the University of Colorado Alzheimer’s and Cognition Center. This larger longitudinal study, the Bio-AD Study, entails comprehensive cognitive testing, health history assessment, neurological and physical examination, informant interview, and brain magnetic resonance imaging (MRI) scans of all participants. In order to characterize the very earliest functional changes within the spectrum of cognitive decline, only clinically healthy older adults and adults with MCI were approached to participate in the current study. Inclusion as a “clinically healthy” participant was determined by a Clinical Dementia Rating (CDR) (Morris, 1997) score of 0, no informant report of significant cognitive decline during
the previous year, and consensus conference adjudication as a normal control. Inclusion as a participant with mild cognitive impairment was based on 2011 NIA-AA core clinical criteria (Sperling et al., 2011). Participants were excluded if they had a major psychiatric disorder, current neurological condition known to affect cognition (e.g., Parkinson’s disease; large vessel infarct; multiple sclerosis), current evidence or history in the past 2 years of a focal brain lesion, current substance abuse, significant systemic medical illness or active neoplastic disease (e.g., current cancer), significant sensory or motor deficits that would interfere with cognitive testing, or traumatic brain injury with loss of consciousness greater than 5 minutes. All participants were reviewed at a case conference with a board-certified neuropsychologist [BB], neurologist, and clinical research coordinator. A subset of cognitive measures from the research protocol was reviewed in a consensus conference and used in the adjudication of diagnosis as a clinically normal older adult or adult with MCI; however, to reduce circularity in our methodological approach, cognitive measures that were reviewed in the consensus conference for adjudication of diagnosis were separate from those used as primary outcomes in our research study.

Sample demographics of individuals who completed the pilot study are provided below in Table 1. All participants signed informed consent approved by the University of Colorado Institutional Review Board. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado (Harris et al., 2009).

**Procedures**

Participants completed cognitive testing with the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), the Spanish English Neuropsychological Assessment Scales [SENAS (Mungas et al., 2005)], a battery of self-reported [Lawton & Brody Instrumental Activities of Daily Living Scale, or IADLS (Lawton & Brody, 1969)], informant-reported [Functional Activities Questionnaire, or FAQ (Pfeffer et al., 1982)], and performance-based [UCSD Performance-based Skills Assessment, or UPSA (Patterson, Goldman, McKibbin, Hughes, & Jeste, 2001); Medication Management Ability Assessment, or MMAA (Patterson et al., 2002)] measures of daily function, and neuroimaging with diffusion tensor imaging (DTI).

**Cognition.**—The SENAS battery was based on item response theory (IRT), and psychometrically matched measures were created across different scales, thus assuring reliability across the full ability continuum (Mungas, Reed, Crane, Haan, & Gonzalez, 2004; Mungas, Reed, Haan, & Gonzalez, 2005; Mungas, Reed, Marshall, & Gonzalez, 2000; Mungas, Reed, Tomaszewski Farias, & DeCarli, 2005; Mungas, Widaman, Reed, & Tomaszewski Farias, 2011). For data reduction purposes, we examined the Executive and Semantic abilities composites as well as the Verbal Memory composites. SENAS composite scores are unadjusted standard scores based on a diverse, older adult sample (≥60 years of age) and are not corrected for age or other demographics (Mungas et al., 2005). These composites were chosen due to extant research that suggests PBFAs are largely associated with aspects of these cognitive abilities (Goldberg et al., 2010).
Function.—The UPSA is a standardized battery comprised of cognitively demanding real-world daily activities, completed by the respondent through role-playing and scored by a trained examiner. Five domains are measured – (1) Finances; (2) Communication; (3) Planning/Organization; (4) Travel; and (5) Household Chores. The tasks employ a standardized set of props (i.e., U.S. currency, utility bill, telephone, bus map and schedule, and pantry stocked with nonperishable goods). Examples of tasks assessed include making change and calling the doctor’s office to reschedule an appointment. Index scores for each domain range from 0–20. The UPSA has been previously validated in MCI and ADRD (Goldberg et al., 2010). Additional validation studies have supported use of a brief version of the UPSA, comprised of the Finances and Communication sub-sections (Mausbach et al., 2007) and can be administered in 10–15 minutes; index scores for Finances and Communication were used in the current study.

The MMAA, similar to the UPSA, is a cognitively demanding, standardized PBFA that uses roleplaying to assess the respondent’s ability to develop and carry out a hypothetical medication regimen. Respondents are given standardized props in the form of four pill bottles with specific instructions on dosing and when the medications should be taken (e.g., before bed, with/without food). The respondent is then asked to describe and carry out a plan to take the medications by walking the examiner through a given day. Administration time is about 10 minutes and scores for the MMAA range from 0–33 possible points. Evidence suggests the MMAA is sensitive to functional changes in MCI (Sumida et al., 2018).

Neuroimaging.—Whole brain MRI scans were obtained on a 3.0 Tesla Siemens (Iselin, NJ) Skyra scanner equipped with a 20-channel head coil. Diffusion imaging data were acquired via a spin-echo, echo planar imaging sequence with 56 slices 2.2 mm thick (TR/TE = 8400/105 ms, matrix = 112×112) in monopolar series (multi-shell; B2500: 64 diffusion directions, B0 [9 averages]). Diffusion tensor imaging (DTI) data were preprocessed and analyzed using FMRIB’s Diffusion Toolbox (FDT) (Smith et al., 2006). Raw data were corrected for head movement and eddy current distortions using FDT. Brain extraction and binary brain mask creation used the b0 mean image through the FMRIB Software Library (FSL) Brain Extraction Tool (BET). Fractional anisotropy (FA) maps were created using FSL DTIFIT. All subjects’ FA data were registered using the nonlinear registration FNIRT to the IXI Aging DTI Template (Zhang, Yushkevich, Rueckert, & Gee) masked by a study-specific average image. The mean FA and mean FA skeleton were created from the study sample. For region of interest (ROI) analyses, we employed the Johns Hopkins University ICBM-DTI-81 white matter labels (Mori et al., 2008) to label and mask areas of the white matter skeleton. Mean FA values for each white matter region was calculated using the FSL utility fslstats. Composite FA scores were calculated consistent with prior studies (Brickman et al., 2012). In order to calculate the early-myelinated fibers (EMF), we obtained the mean FA of the following regions: inferior cerebellar peduncles, superior cerebellar peduncle, anterior limb of the internal capsule, retrolenticular part of the internal capsule, and superior fronto-occipital fasciculus. For late-myelinated fibers (LMF), we used: genu, body, and splenium of the corpus callosum, fornix, and uncinate fasciculus. The composite EMF and LMF scores were calculated as the overall mean fractional anisotropy (FA) values of all the tracts included after averaging left and right hemispheres (where applicable).
Analysis

Data were checked for normality and outliers. Linear regression analysis was used to examine the relationship of ROIs and PBFAs; analyses controlled for age and global cognition [as measured by the Montreal Cognitive Assessment, or MoCA (Nasreddine et al., 2005)] in order to test if PBFAs explained meaningful variance in brain structure above and beyond a proxy of global cognitive function. In order to examine the possible mediating role of cognition on the relationship between ROIs and PBFAs, the PROCESS macro v. 3.3 (Hayes, 2018) for SPSS was used with 5000 bootstraps. Simple mediation models, which rely on causal inference, tested direct and indirect paths between ROIs as predictors, PBFAs as outcomes, and performance on traditionally-defined cognitive domains as mediators. All analyses were done using SPSS v. 25 (IBM Corp., 2017).

Results

Clinical characteristics for the entire sample as well as by clinical subgroup are described in Table 2. Pearson correlations revealed that age, education, and gender were not correlated with any of the three PBFAs (all ps>0.05). Global cognition as measured by the MoCA was significantly correlated with all three PBFAs (Finances: r=0.435, p=0.006; Communication: r=0.538, p<0.001; Medication Management: r=0.494; p=0.001). Age was significantly correlated with both EMF (r=−0.481, p=0.002) and LMF (r=−0.584, p<0.001), but the MoCA was not (both ps>0.05). Separate linear regression analyses with EMF or LMF as dependent variables and age, education, and gender as independent variables revealed age was the sole predictor of both summary scores (EMF: β=−0.00164, 95% CI [−0.00252, −0.00076], p=0.001; LMF: β=−0.00247, 95% CI [−0.00362, −0.00132], p<0.001).

Relationship between Functional Questionnaires and White Matter Tracts

Informant report on the FAQ (Range=0–10 out of 30 possible points, Mean=1.41±2.4) was not associated with LMF or EMF (all ps>0.05). The relationship between self-report appraisal of daily function abilities as measured by the IADLS and ROIs could not be examined due to a ceiling effect of a highly restricted range of responses on this measure (Range = 7–8 out of 8 possible points; 95% of responses were a score of 8).

Relationship between PBFAs and White Matter Tracts

Separate regression models were tested for Finances, Communication, and Medication Management as predictor variables with ROIs as the outcome variables after controlling for covariates (age, MoCA). Finances and Communication were not associated with EMF or LMF (ps>0.05). Better performance on Medication Management was significantly associated with higher mean FA values in LMF, but not EMF (EMF: p>0.05); β=0.002, t36=2.231, p=0.032, 95% CI: 0.0002, 0.0044, partial r²=0.125. To assess whether performance on Finances and Communication sections of the UPSA impacted the relationship between Medication Management and white matter tracts, an exploratory follow-up analysis controlling for Finances and Communication further strengthened this relationship; β=0.003, t34=2.668, p=0.012, 95% CI: 0.001, 0.005, partial r²=0.177. However, adding Finances and Communication did not significantly improve the model with Medication Management and covariates, ΔR²=0.067, ΔF=2.151, p=0.132.
Relationship between PBFAs and White Matter Tracts as Mediated by Cognition

Mediation models tested the SENAS Executive, Semantic, and Verbal Memory composites as mediators of the relationship between LMF and MM. Better performance on MM was associated with better performance on all three composites, but most strongly with the Semantic composite: Executive: $\beta=2.462$, $t_{39}=2.270$, $p=0.029$, 95% CI: 0.267, 4.656, partial $r^2=0.120$; Semantic: $\beta=3.037$, $t_{39}=3.866$, $p<0.001$, 95% CI: 1.447, 4.627, partial $r^2=0.282$; Verbal Memory: $\beta=1.969$, $t_{39}=2.890$, $p=0.006$, 95% CI: 0.590, 3.348, partial $r^2=0.181$.

After controlling for age, these findings held for Semantic ($t_{38}=3.720$, $p=0.001$) and Verbal Memory ($t_{38}=2.626$, $p=0.013$) but not for Executive ($t_{38}=1.904$, $p=0.065$). Mediation models did not find a significant indirect path with any of the three cognitive composite scores (bootstrapped lower- and upper-level confidence intervals included 0, all $p>0.05$). Notably, only Verbal Memory was associated with LMF: $\beta=11.343$, $t_{39}=2.577$, $p=0.014$, 95% CI: 2.432, 20.253, $r^2=0.149$. This effect was attenuated after controlling for age ($t_{38}=1.983$, $p=0.055$). This modest association (verbal memory) and lack of association (other domains) with ROIs explains the statistical lack of mediation effect after controlling for age in our model.

Relationship between PBFAs and White Matter Tracts by Cognitive Classification

For this exploratory goal, the Clinical Dementia Rating (CDR) (Morris, 1997) scale was used to categorize individuals as having normal cognition (CDR=0; n=27) or as showing evidence of early cognitive decline (CDR=0.5 or 1; n=13). Notably, one individual was included in the latter group despite having a global score of CDR=1, suggestive of mild dementia; review of the individual’s sum of boxes score on the CDR, which was 4.5, indicated very mild symptoms and the individual received a consensus conference diagnosis of mild cognitive impairment. The cognitively impaired group differed from the cognitively normal group on LMF ($F_{1,39}=4.846$, $p=0.034$) but not on EMF ($F_{1,39}=0.079$, $p=0.780$). Sub-group analyses with linear regression controlling for age demonstrated a significant relationship of MMAA with LMF in the cognitively impaired group only ($t_{10}=2.324$, $p=0.045$ vs $t_{25}=0.116$, $p=0.909$; Figure 1).

Discussion

Consistent with the white matter retrogenesis hypothesis, we found that performance on a PBFA related to medication management was associated with LMF, but not with EMF. However, performance on PBFAs related to financial management and communication abilities were not associated with either LMF or EMF. Contrary to our hypotheses, results from mediation analysis suggested this relationship between PBFA performance and LMF was not explained by cognitive ability as measured by traditional neuropsychological tests. Moreover, this relationship between daily function and LMF was not observed with self- or informant-report measures of functional ability.

Our results are partially consistent and extend prior literature that supports a possible relationship between PBFAs and white matter integrity (Wijtenburg et al., 2017). Specifically, our findings suggest that worse performance on objective measures of medication management are sensitive to lower integrity of late-myelinated white matter
fibers. Consistent with the age-related effects on both early and late myelinated fibers reported by Brickman et al. (2012), we found evidence that aging is associated with declines in the integrity of both sets of fibers, but to a greater degree in late myelinated fibers compared to early myelinated fibers. Given that late myelinated white matter fibers are more vulnerable to the aging process and are sensitive to early stages of neurodegenerative disease, results indicate that a medication management PBFA may offer a window into pathological aging processes. This has several important implications. Medication use – and particularly use of multiple medications – is generally common in older adults. Poor medication management may lead to poor health outcomes, including further decline in neuroanatomical integrity. Medication management can also be easily and quickly assessed objectively in clinical practice and followed over time, meeting dual needs of improved cognitive assessment and associated clinical care.

Notably, objective measures related to financial management and communication abilities were not sensitive to the decline in LMF integrity. While these abilities are impacted in early stages of dementia (e.g., Kenney, Margolis, Davis, & Tremont, 2019), the lack of relationship between these abilities with LMF in a healthy aging and MCI participant sample is consistent with other research. Building on previous work with Parkinson’s disease patients that found little correlation between PBFA related to medication management and to financial management (Pirogovsky et al., 2013), researchers found medication management was sensitive to subtle functional declines in a Parkinson’s disease MCI group relative to a Parkinson’s disease normal cognition group while financial management was not (Pirogovsky et al., 2014). Moreover, the PBFA were not associated with measures of cognitive function. Similar to the findings we present here, the authors concluded that instrumental activities of daily living may not be a monolithic domain (Pirogovsky et al., 2013) and may represent a functional domain separate from other cognitive functioning (Pirogovsky et al., 2014).

Our results suggest performance-based measures of daily function may be an early indicator of brain health. Moreover, we did not find support of a mediating role of cognition on the relationship between PBFA and white matter. Taken together with the work reported by Pirogovsky et al. (2013, 2014), it may be possible that PBFA are tapping into a different metric than what is captured by traditional cognitive testing. Indeed, results reported by Royall and colleagues (Royall et al., 2007) suggest that cognition alone accounts for less than 20% of unique variance in functional outcomes. In relation to cognition and white matter, results by Grieve and colleagues (Grieve et al., 2007) suggest traditional cognitive testing may explain as little as 6% of variance in FA values for late-myelinating regions. In a recent systematic review of cognitive and neuropathological correlates of instrumental activities of daily living in older adults, Overdorp and colleagues (Overdorp et al., 2016) concluded that cognition and neuroanatomical changes identified by neuroimaging may contribute independently of each other to daily function, a finding supported by our results. Demanding functional assessments might be more sensitive than classic neuropsychological tests to early change for several reasons, including ecological validity, cultural appropriateness, and maybe a multifactorial nature. In light of the limitations of the current gold standard (traditional neuropsychological assessment), a broader view of cognition, predicated on functional abilities, is needed.
Notably, subjective measures of daily function, both self- and proxy-report, were not associated with white matter integrity. This further highlights the limitations of these types of measures in a healthy and MCI cohort (i.e., lack of range compared to the larger range observed on the PBFAs). These limitations also speak to the strengths of using a PBFA related to medication management in the earliest stages of suspected decline.

We interpret these preliminary findings with caution given the small sample size and no external confirmation of AD pathology. It is possible that in the context of this pilot study that meaningful associations were missed, because we were not powered to detect small effect sizes. Our sample was well educated, limiting our ability to examine the potential role of cognitive reserve proxies (e.g., years of education). In addition, while the participant sample was well characterized and the MCI sample met NIA-AA clinical criteria, biomarkers of AD pathology were not available. Nonetheless, in a small participant sample comprised of cognitively healthy and MCI individuals, associations between medication management and LMF suggest that these alterations are early and map on measurable brain changes. This study was strengthened by the use of psychometrically matched cognitive assessments validated for use in aging populations; the lack of circularity in diagnosis whereby the measures of interest included in analyses were not part of the consensus diagnosis process of the participants; and implementation of traditional self- and informant-report functional measurement that allowed for direct comparison with performance-based measures of daily function. Moreover, these findings are consistent with the growing body of literature suggesting PBFAs are sensitive to the earliest stages of neurodegeneration.

Our conclusions highlight several points: (1) a PBFA of medication management abilities is sensitive to early clinical and neuroanatomical changes known to occur in ADRD, (2) this measure is more sensitive than the self- and informant-report options typically used in ADRD research, and (3) these relationships do not appear to be mediated by performance on traditional cognitive testing. Future work is needed to extend these results in a diverse sample of individuals that can help further examine their utility and sensitivity cross-culturally. Longitudinal studies may also help elucidate the continuum of functional decline. Additionally, these studies can aid in clarifying connections between PBFAs and biomarkers of neurodegenerative disease.

Acknowledgments

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Key Points

- **Question:** Are performance-based functional assessments (PBFAs) sensitive to early white matter changes related to neurodegeneration?

- **Findings:** A PBFA related to medication management abilities was more sensitive to early white matter changes than traditional cognitive tests or self-/informant-report measures of daily function.

- **Importance:** Demanding functional assessments might be more sensitive than classic assessments to early neuropathological changes.

- **Next Steps:** Additional cross-sectional and longitudinal data in a diverse sample are needed to extend these results.
Figure 1.
Subgroup Comparison of the Late-Myelinating Fibers Composite Score on the Medication Management Score by Clinical Dementia Rating (CDR) Group. The shaded area reflects 95% confidence intervals.
<table>
<thead>
<tr>
<th>Sample Demographics</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.85 (6.49)</td>
<td>55–81</td>
</tr>
<tr>
<td>Education</td>
<td>16.95 (2.56)</td>
<td>12–21</td>
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<tr>
<td>Handedness – Right</td>
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<td>Gender—Female</td>
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Table 2.

Clinical Characteristics of Sample

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<td></td>
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<td>%</td>
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<td>2.5</td>
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</table>

**Cognitive**

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<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td>25.20 (2.93)</td>
<td>20 to 30</td>
<td>26.22 (2.67)</td>
<td>21 to 30</td>
<td>23.08 (2.29)</td>
<td>20 to 28</td>
</tr>
<tr>
<td>Executive</td>
<td>0.36 (0.55)</td>
<td>−0.78 to 1.72</td>
<td>0.54 (0.52)</td>
<td>−0.56 to 1.72</td>
<td>0.00 (0.45)</td>
<td>−0.78 to 1.10</td>
</tr>
<tr>
<td>Semantic</td>
<td>1.45 (0.69)</td>
<td>−0.38 to 2.69</td>
<td>1.68 (0.60)</td>
<td>0.37 to 2.69</td>
<td>0.96 (0.63)</td>
<td>−0.38 to 2.01</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>0.68 (0.85)</td>
<td>−0.97 to 2.64</td>
<td>0.99 (0.69)</td>
<td>−0.78 to 2.64</td>
<td>0.03 (0.81)</td>
<td>−0.97 to 1.28</td>
</tr>
</tbody>
</table>

**Function**

<table>
<thead>
<tr>
<th>Function</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication</td>
<td>14.53 (3.45)</td>
<td>2 to 20</td>
<td>15.67 (2.53)</td>
<td>10 to 20</td>
<td>12.15 (3.98)</td>
<td>2 to 17</td>
</tr>
<tr>
<td>Finances</td>
<td>17.90 (2.05)</td>
<td>13 to 20</td>
<td>18.33 (1.94)</td>
<td>13 to 20</td>
<td>17.00 (2.04)</td>
<td>13 to 20</td>
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<tr>
<td>Medication Management</td>
<td>29.97 (4.00)</td>
<td>19 to 33</td>
<td>31.48 (2.39)</td>
<td>24 to 33</td>
<td>26.58 (4.85)</td>
<td>19 to 33</td>
</tr>
<tr>
<td>IADLS</td>
<td>7.95 (0.22)</td>
<td>7 to 8</td>
<td>8.00 (0.00)</td>
<td>8 to 8</td>
<td>7.85 (0.38)</td>
<td>7 to 8</td>
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<tr>
<td>FAQ</td>
<td>1.41 (2.43)</td>
<td>0 to 10</td>
<td>0.12 (0.44)</td>
<td>0 to 2</td>
<td>4.08 (2.71)</td>
<td>1 to 10</td>
</tr>
</tbody>
</table>

**ROI Mean Composite**

<table>
<thead>
<tr>
<th>ROI Mean Composite</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMF</td>
<td>0.53 (0.02)</td>
<td>0.48 to 0.58</td>
</tr>
<tr>
<td>LMF</td>
<td>0.54 (0.03)</td>
<td>0.49 to 0.59</td>
</tr>
</tbody>
</table>

Note: CDR=Clinical Dementia Rating; MoCA=Montreal Cognitive Assessment; IADLS=Instrumental Activities of Daily Living Scale; FAQ=Functional Activities Questionnaire; ROI=Region of Interest; EMF=Early-Myelinated Fiber composite; LMF=Late-Myelinated Fiber composite

All SENAS scores were presented in unadjusted z-score like units where a score of zero corresponded to the mean of a demographically diverse, non-demented normative sample composed primarily of Hispanics and Whites and differences from the mean were expressed in standard deviation units.