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Neuroimaging Signatures and Cognitive Correlates of the Montreal Cognitive Assessment Screen in a Nonclinical Elderly Sample

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Abstract

The Montreal Cognitive Assessment (MoCA) screen was developed as a brief instrument to identify mild cognitive impairment and dementia among older individuals. To date, limited information is available regarding the neuroimaging signatures associated with performance on the scale, or the relationship between the MoCA and more comprehensive cognitive screening measures. The present study examined performances on the MoCA among 111 non-clinical older adults (ages 51–85) enrolled in a prospective study of cognitive aging. Participants were administered the MoCA, Mini-Mental State Exam (MMSE), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). A subset of participants ($N = 69$) underwent structural 3 T magnetic resonance imaging (MRI) to define the volumes of total frontal gray matter, total hippocampus, T2-weighted subcortical hyperintensities (SH), and total brain volume. The results revealed significant correlations between the total score on the MoCA and total score on the RBANS and MMSE, though the strength of the correlations was more robust between the MoCA and the RBANS. Modest correlations between individual subscales of the MoCA and neuroimaging variables were evident, but no patterns of shared variance emerged between the MoCA total score and neuroimaging indices. In contrast, total brain volume correlated significantly with total score on the RBANS. These results suggest that additional studies are needed to define the significance of MoCA scores relative to brain integrity among an older population.

Keywords: Mild cognitive impairment; Neuroimaging (structural)

Introduction

The Montreal Cognitive Assessment (MoCA) was introduced in 2005 as a brief (10 min) screening instrument to assist physicians with the detection of mild cognitive impairment (MCI; Nasreddine et al., 2005). In the seminal publication, Nasreddine and colleagues (2005) reported a sensitivity level for MCI and mild Alzheimer's disease (AD) of 90% and 100%, respectively. In contrast, performance on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) identified only 18% of patients with MCI and 78% of individuals with mild AD. Other studies have cross-validated the utility of the MoCA to identify MCI and early AD with similar results (Luis, Keegan, & Mullan, 2009; Smith, Gildeh, & Holmes, 2007), suggesting the screen has potential clinical utility to assist with the identification of mild impairment and degenerative dementia.

In addition to AD, studies have demonstrated the utility of the MoCA in medical populations such as Parkinson's disease (Hoops et al., 2009), vascular disease (Popović, Serić, & Demarin, 2007), substance abuse disorders (Copersino et al., 2009), and brain metastases (Olson, Chhanabhai, & McKenzie, 2008). Further, the measure has been translated into multiple languages to facilitate global clinical applications (Wong et al., 2009). In the past several years, the MoCA has gained traction

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as a primary clinical screen, with particular relevance for primary care physicians and other healthcare groups that do not specialize in cognitive assessment. The MoCA has also been recommended as a primary cognitive screen for research protocols. However, limited information is known about the relationships between performance on the MoCA and more comprehensive neuropsychological screens and/or neuroimaging indices. To our knowledge, no study has examined the relationships between performance on the MoCA and quantitative indices of brain volume.

In the present study, we examined the relationships between performances on the MoCA and performances on two common clinical measures of overall cognitive status among older adults enrolled in a prospective study of cognitive aging. We also examined relationships between performances on the MoCA and regional brain volumes determined by magnetic resonance imaging (MRI). We hypothesized that the total score on the MoCA would correlate with performances on the other two common cognitive indices as well as quantitative neuroimaging indices. As an exploratory analysis, we also hypothesized that individuals with performances on the MoCA below the recommended cutoff of 26 (Nasreddine et al., 2005) would perform significantly worse on the other global measures of cognitive function and the neuroimaging indices compared with the individuals with performances on the MoCA above the clinical cutoff.

Methods

Participants

A total of 111 older individuals enrolled in a longitudinal study of cognitive aging were included in the current study. Of these 111 individuals, 69 individuals completed the neuroimaging. Fewer individuals completed the neuroimaging as these individuals did not meet inclusion criteria for MRI safety (almost exclusively exposure to metal) or they were unable to be scheduled within 2 months of imaging and neuropsychological acquisition. The average time between imaging and neuropsychological acquisition was 23 days. Eligible individuals included both male and female English-speaking individuals over the age of 50. All individuals were recruited from the local community via print and radio advertisement with a focus on healthy aging. Individuals were excluded from the study if they reported a history of neurological disease including a current diagnosis of dementia, stroke, Parkinson's disease, or other neurological condition. Individuals with other conditions that would likely affect cognition (e.g., thyroid disease, etc.) were also excluded. In addition, individuals with diabetes requiring treatment, head injury with loss of conscious (LOC) >30 min, alcohol or drug abuse, or a major psychiatric condition (e.g., Attention Deficit Hyperactivity Disorder, Schizophrenia, Bipolar Disorder, Axis I Anxiety or Mood Disorder, etc.) were excluded. Of note, two individuals reported a history of LOC (both <30 min) and neither of these individuals reported post-traumatic amnesia or diagnosis of mild traumatic brain injury.

The sample was subdivided according to the total score on the MoCA. Individuals with scores <26 ($N = 51$) were identified as meeting guidelines for MCI (Nasreddine et al., 2005), whereas those with scores ≥ 26 ($N = 47$) were identified as cognitively healthy. Demographic information for the two samples is provided in Supplementary material online, Table S1. As evident from the table, the sample with subclinical scores on the MoCA was slightly older (65 years of age vs. 62 years of age) and slightly less educated (14 years of education vs. 15 years of education). A t-test revealed that the differences in mean age were not statistically significant, though there was a strong trend; $t(96) = -1.7$, $p = .08$. In contrast, the mean years of education did differ significantly between the groups, $t(96) = 2.4$, $p = .01$, though the difference between the means was <1 year of education and therefore the discrepancy in education was not considered clinically meaningful.

Procedures

All participants provided signed informed consent before participation in the parent study. All individuals were administered a neuropsychological battery by a trained research assistant, and they underwent a neuroimaging protocol during a separate visit. On average, individuals completed the MRI within 23 days of the neuropsychological assessment. All individuals were financially compensated for their participation. The study was approved by the local institutional IRB committees.

Neuropsychological Tests

The MoCA was administered according to the standard instructions. The instrument consists of 13 tasks organized into eight cognitive domains including Visuospatial/Executive Function, Naming, Memory, Attention, Language, Abstraction, Delayed Recall, and Orientation. A total score is generated by summing scores across the eight domains. For the purpose of the present study, we calculated the total score as well as individual domain scores. The cognitive tasks associated with each domain are described at http://www.mocatest.org/.

Mini-Mental State Exam

The MMSE was administered according to the standard protocol (Folstein et al., 1975). For the working memory task (serial sevens/"world" backwards), participants were administered only the serial sevens task. Total points served as the dependent variable.

Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998)

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; version A) was administered according to the standard instructions. The RBANS is a widely used neuropsychological battery with excellent psychometric properties. The test includes 12 subtests that tap the following cognitive domains: Attention, Visuospatial Function, Verbal Learning (list-learning and prose passage), Verbal Recall, and Psychomotor Speed. Subtest scores were converted to standard scores using the normative tables in the manual, and a total standard score was determined (normal mean = 100, $SD = 15$).

Neuriomaging Acquisition

All MRI scanning was performed using an FDA-approved head-only Magnetom Allegra 3 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) optimized for brain imaging. This scanner has high-performance gradients (maximum strength 40 mT m^{-1} in a 100 μs rise time; maximum slew rate 400 T m^{-1} s^{-1}) to minimize scan times. For consistency, the same MRI scanner, pulse sequences, acquisition protocols, and MRI operator were used for the duration of the study. Daily quality-assurance (Q/A) tests were performed in-house to further assure the consistency of scanner performance.

The scanning protocol was designed to limit the participants' total time in the MRI scanner to 45–60 min (MRI session time). Surgical tape was placed firmly across the forehead and RF coil to reduce movement and to provide tactile feedback. First, a scout scan was acquired (15 s) consisting of three orthogonal planes to confirm head positioning. Structural MRI scans of the whole brain were then collected using: (1) a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence (Mugler & Brookeman, 1990); (2) a double-echo proton-density (PD)/T2-weighted turbo spin echo (TSE) sequence; and (3) a T2-weighted fluid-attenuated inversion-recovery (FLAIR) TSE sequence (Hajnal et al., 1992). Standard shimming was used. In general, the acquisition parameters were designed for whole-brain coverage with practical scan times for the subject population. For all acquisitions, the field of view (FOV) and slice coverage were determined based on an initial pilot study of a few participants, such that there was no cutoff of brain structures, and no wrap-around (aliasing) of soft tissues (e.g., nose, ears) onto any part of the brain. The total scan time for the scout and three structural MRI scans was only 18 min 53 s.

The T1-weighted MP-RAGE data were acquired in the sagittal plane with TR = 2,100 ms, TE = 3.93 ms, TI = 1,000 ms (non-selective inversion), flip angle = 7°, in-plane FOV = 269 × 269 mm, and matrix size = 256 × 256, phase-encoding in the anterior–posterior and left–right directions, slab thickness = 184.8 mm, 176 slices acquired in 3D mode, $N_{av} = 1$ (number of signals averaged), voxel size = 1.05 × 1.05 × 1.05 mm^3, acquisition bandwidth = 130 Hz $pixel^{-1}$, and scan time = 8:58 (min:s). The PD/T2-weighted TSE images were acquired in the transverse plane with TR = 8,040 ms, $TE_1 =$ 18 ms, $TE_2 =$ 105 ms, FOV = 256 × 180 mm, matrix size = 256 × 180, turbo factor = 5 (echo-train length), phase encoding in the left–right direction, slice thickness = 3.0 mm, 43 slices acquired in interleaved 2D multislice mode, no slice gaps, $N_{av} = 1$, voxel size = 1.0 × 1.0 × 3.0 mm^3, bandwidth = 191 Hz $pixel^{-1}$, and scan time = 4:58. The images were reconstructed with an in-plane interpolation of a factor of 2 in each dimension. The T2-weighted FLAIR images were acquired in the transverse plane with TR = 10,000 ms, TE = 98 ms, TI = 2,150 ms (slice-selective inversion), FOV = 256 × 180 mm, matrix size = 256 × 164 (frequency × phase encoding), turbo factor = 13, phase encoding in the left–right direction, slice thickness = 3.0 mm, 39 slices acquired in interleaved 2D multislice mode, no slice gaps, $N_{av} = 1$, voxel size = 1.0 × 1.1 × 3.0 mm^3, bandwidth = 130 Hz $pixel^{-1}$, and scan time = 4:42. The slices were acquired with RF fat saturation and concatenation of two TR intervals. The images were reconstructed with a 2-fold interpolation as above. The FLAIR was acquired for assessment of T2-weighted white matter hyperintensities (particularly adjacent to ventricles). The number of slices was reduced slightly compared with the PD/T2-weighted TSE (keeping the same mean z-position of the slice group). This change enabled the slices to be acquired with only two concatenations, shortening the scan time while spanning the white matter structures.

Neuroimaging Post-processing

FreeSurfer's built-in mri_convert function was used to convert scans to a format compatible with FreeSurfer (.mgz). Resulting 8-bit images were processed using FreeSurfer v4.2.0 (Martinos Center, Harvard University, Boston, MA, USA) on a local computing cluster running the Red Hat Enterprise Linux (ES 4). The workflow consists of several steps, which

have been previously described in detail elsewhere (Fischl et al., 2002). Briefly, major intensity inhomogeneities were corrected and the image was then mapped to Talairach space through an affine registration. The skull and meningeal surfaces were removed from the scan, leaving only the brain and overlying pial surface. Overall, white matter intensity was standardized and a tentative segmentation was created for subcortical gray/white matter structures. The image was transformed to Talairach space through a high-dimensional, non-linear alignment. Then, volume labels were applied to subcortical structures based on the prior probabilities of voxel identity assigned by the default FreeSurfer atlas and the probability of voxel identity based on the tissue class assignment of surrounding voxels. FreeSurfer and its documentation can be freely downloaded at http://surfer.nmr.mgh.harvard.edu.

After automated segmentation and labeling, each image was visually inspected and manually corrected for any gross errors using tkmedit segmentation brush tools in FreeSurfer. Total brain and hippocampal volumes were derived from the statistic output files (aseg.stats), whereas frontal lobe gray and white matter volumes were derived by adding up the frontal gyral gray matter volumes (rh.aparc.a2009.stats and lh.aparc.a2009.stats) from each hemisphere. Gyri included in the frontal volume were caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, paracentral, pars opercularis, pars orbitalis, pars triangularus, precentral, rostral frontal, rostral middle frontal, superior frontal, and frontal pole. These brain regions were selected as previous studies have demonstrated that age-related reductions in brain volume in these regions and increased SH in these regions is associated with poorer performance on neuropsychological testing among healthy older adults (Mungas et al., 2005; Paul et al., 2005; Raz, Rodrigue, Head, Kennedy, & Acker, 2004; Raz et al., 2005). Volumes for all brain indices were corrected for total brain volume.

Statistical Analysis

Pearson's correlation coefficients were computed to examine the degree of shared variance between total score on the MoCA and performance on the MMSE and RBANS, as well as brain volumes defined by MRI. Pearson's correlation coefficients were also calculated to determine associations between individual cognitive domain scores on the MoCA and the neuroimaging indices. Finally, independent *t*-tests were computed to determine whether individuals with scores <26 on the MoCA differed from individuals with scores >25 on the MoCA in terms of performance on the cognitive and imaging variables.

Results

Correlations Between the MoCA, MMSE, and RBANS

Supplementary material online, Table S2 provides the descriptive statistics for both groups regarding their performances on the cognitive measures and the neuroimaging indices. As evident from the mean scores both groups performed within the normal range on both the MMSE and the RBANS. Initial correlation analyses revealed that performance on the MoCA correlated significantly with performance on both the MMSE and the RBANS, with higher scores on the MoCA associated with higher scores on both the MMSE and the RBANS. Of interest is that the correlation between the MoCA and the RBANS ($r = .56$, $p < .000$) is stronger than the correlation between the MoCA and the MMSE ($r = .49$, $p < .000$), accounting for 31% of shared variance compared with 24% of shared variance.

Correlations Between the MoCA and Neuroimaging Indices

The total MoCA score did not significantly correlate with any of the neuroimaging measures though a strong trend was noted between total MoCA score and total SH, with greater SH burden associated with lower total score on the MoCA ($r = -.26$, $p = .07$). Total score on the MMSE did not significantly correlate with any of the neuroimaging indices. In contrast, total score on the RBANS correlated modestly with whole brain volume (WBV; $r = .27$, $p = .02$).

Individual domain scores on the MoCA correlated with several neuroimaging indices (Supplementary material online, Table S3). Specifically, better performance on the Visuospatial/Executive, Attention, and Learning domains correlated significantly with larger WBV. Better performance on Naming correlated significantly with total hippocampal volume and frontal lobe volume. SH volume did not correlate significantly with any of the individual cognitive domains.

Neuropsychological and Neuroimaging Contrasts Based on MoCA Classification

Individuals with total MoCA scores >25 (healthy) performed significantly better on the MMSE, $t(96) = 3.3$; $p < .00$, and RBANS, $t(96) = 3.6$, $p < .00$, indicating that the recommended clinical cutoff of 26 on the MoCA identifies significant

differences in cognitive performance captured on other cognitive screens. In contrast, individuals with scores <26 on the MoCA did not exhibit lower brain volumes, or increased SH, compared with individuals with scores >25.

Fewer participants completed the neuroimaging acquisition and therefore it is possible that the lack of group differences on the imaging indices reflects lower power compared with the behavioral indices. To examine this possibility, we also contrasted performances on the MMSE and the RBANS for only those individuals who completed the neuroimaging acquisition. These results revealed the same outcomes with significantly poorer performance on the RBANS and the MMSE among those individuals with lower MoCA scores ($ps < .05$).

Discussion

Results from our study provide several novel and important insights regarding the MoCA. First, the total score on the MoCA correlates significantly with total score on other well-known cognitive screens in a sample of older adults. Of note, the degree of shared variance was greater between the MoCA and the more comprehensive assessment provided by the RBANS compared with the more brief MMSE. Second, although the total MoCA score did not correlate significantly with the neuroimaging indices examined in this study, several MoCA subscales shared significant variance with neuroimaging indices that typically reflect brain changes associated with common aging (WBV, frontal gray matter, hippocampal volume). Finally, individuals who scored below the recommended cutoff on the MoCA performed significantly worse on the other cognitive screens compared with the individuals that performed above the cutoff, but there were no group differences on the neuroimaging measures.

The observation that the total score on the MoCA correlates significantly with performance on the MMSE and the RBANS is encouraging as it provides further convergent validity of the MoCA as a screening tool. Further, the stronger correlation between the total score on the MoCA and the more comprehensive RBANS suggests that the MoCA is capturing more behavioral data than what is obtained via the MMSE. This is particularly important as the MMSE has been criticized as lacking sensitivity to forms of cognitive dysfunction that involve executive impairment (O'Sullivan, Morris, & Markus, 2005; Pachet, Astner, & Brown, 2010), and the MMSE may not adequately identify neuropsychological abnormalities associated with etiologies that preferentially involve frontal or frontal-subcortical circuits (e.g., Hoops et al., 2009; Popović, Serić, & Demarin, 2007; Swirsky-Sacchetti et al., 1992). The inclusion of tasks in the MoCA that tap executive function represents strength of the scale.

It is important to note, however, that the correlation between the total score on the MoCA and the total score on the RBANS was modest, with nearly 70% of the variance unaccounted for between the two scales. Given the depth of the RBANS relative to the MoCA, one interpretation of this finding is that the MoCA may lack ideal sensitivity to cognitive disorders compared with the RBANS. Alternatively, it is possible that the MoCA is capturing information not typically acquired by the RBANS. The RBANS has very good breadth of coverage though executive function is not a core feature of this battery. Nevertheless, performance on the RBANS correlated with WBV whereas performance on the MoCA did not, suggesting that overall the RBANS is more tightly associated with indices of brain integrity.

In contrast to our hypothesis, the total score on the MoCA did not correlate significantly with any of the neuriomaging variables though a modest trend was noted between total MoCA score and SH burden. The lack of significant relationships between these variables was surprising as the neuroimaging variables selected for analysis in this study are well-known biomarkers of cognitive aging (Mungas et al., 2005; Raz et al., 2004, 2005; for review, *see* Raz & Rodrigue, 2006). The trend association between SH volume and total score on the MoCA is consistent with previous studies that have examined the impact of vascular burden on cognitive status among the elderly (Paul et al., 2005), though the relationship in this study was modest, likely due to the relatively healthy nature of the cohort.

Individual domain scores on the MoCA did correlate significantly with several neuroimaging indices and the direction of these relationships were consistently in the predicted direction (i.e., better performances associated with higher volumes of brain regions). One surprising lack of association was between Delayed Memory and total hippocampal volume. Hippocampal volume did correlate inversely with performance on several MoCA subscales but this was not the case for the Delayed Memory trial. The absence of a significant correlation between these two variables may reflect the limited range in performance on the Delayed Memory trial. The Memory test includes only five words, presented twice to the individual. Further, the delay between presentation and delayed recall is only several minutes, and therefore, this task may not sufficiently engage hippocampal mechanisms to drive a correlation between these two variables in a relatively healthy sample. It may also be the case that inclusion of a recognition trial on the MoCA would more accurately reflect hippocampal integrity.

When the sample was subdivided according to individuals with performance above and below a score of 26 (recommended cutoff for impairment), the groups differed significantly on both the MMSE and the RBANS. These findings provide additional confidence regarding the utility of the MoCA as a brief cognitive screen as individuals with scores <26 exhibited significantly

poorer performance on the other common neurocognitive measures. Like other cognitive screens, performance on the MoCA does not define the etiology of cognitive impairment and individuals with performances <26 on the MoCA will require a referral for more comprehensive neuropsychological assessment to define the potential etiology and characterize cognitive strengths and weaknesses. However, some caution is warranted regarding the utility of the cutoff score since both groups performed within normal limits on the MMSE and the RBANS, which is not surprising given that participants were enrolled in a study of "normal" aging. That is, although the group that earned a score below the recommended cutoff on the MoCA performed more poorly than individuals with scores above the cutoff, both groups performed in the average range on the other measures. This raises question as to whether the MoCA may lead to false positives in a clinical setting, particularly since on average individuals identified as impaired on the MoCA earned a total standardized score on the RBANS that was within normal limits.

In contrast to the differences in cognitive status, individuals with performances <26 on the MoCA did not reveal any significant differences in neuroimaging variables compared with those with scores above the clinical cutoff. This finding suggests that either the neuroimaging variables or the MoCA lacked the requisite sensitivity to define cerebral structural differences between these groups. Given that the neuroimaging variables were acquired using high power resolution MRI and we selected regions of interest known to relate to cognitive aging the former explanation is unlikely. Alternatively, the lack of association between these variables may reflect the cutoff criterion on the MoCA or the general health of the cohort. Further work is needed using receiver operating characteristic (ROC) curves and similar analyses to determine the stability of these findings.

A few limitations of the study should be noted. First, the sample included individuals enrolled in a longitudinal study of healthy individuals. Individuals were excluded from the parent study if they were previously diagnosed with cognitive impairment or other major health issues that increase the risk of cognitive impairment (e.g., diabetes, thyroid disease, etc.). The degree of shared variance between the total MoCA score and the individual neuriomaging variables does not reflect the associations that might be expected among a traditional clinical sample. Nevertheless, the individual MoCA scales did correlate significantly with individual neuroimaging variables. This suggests that the absence of a significant correlation between the total score on the MoCA and the neuroimaging variables reflected limited sensitivity of several select MoCA tests (i.e., delayed recall, repetition, and orientation). It is possible that the total score on the MoCA would exhibit greater sensitivity to normal aging indices if these tests were removed from the total score equation.

The present study did not incorporate ROC curves to clearly define the sensitivity and specificity of the MoCA as this was not the intent of the present investigation. Our data suggest that future studies of large cohorts are warranted to conduct these analyses and ensure that the MoCA has optimal psychometric properties for routine clinical use. It should also be noted that our sample size was sufficient to identify significant group differences on the RBANS on the MMSE when these contrasts were completed only for individuals that completed the neuroimaging protocol. Although neuroimaging differences were not observed, it is possible that significant group differences in neuroimaging indices would be obtained using more sensitive methods such as functional MRI, magnetic resonance spectroscopy, or diffusion tensor imaging.

In summary, the present study provides information regarding the utility of the MoCA by demonstrating correlations with the MMSE and the more comprehensive RBANS, as well as relationships between MoCA subscales and neuroimaging variables. However, some caution is also raised about the MoCA cutoff score since the recommended score of 26 did not discriminate groups on neuroimaging variables and performances were within normal limits on the other cognitive measures for individuals performing below the cutoff on the MoCA. Further studies are needed to determine whether more advanced imaging modalities (e.g., diffusion tensor imaging, fMRI, etc.) reveal significant differences in neuroanatomical integrity based on performance on the MoCA.

Supplementary material

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

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Conflict of Interest

None declared.

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