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Abnormal MoCA and Normal Range MMSE scores in Parkinson disease without dementia: Cognitive and Neurochemical Correlates

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Abstract

Background—The Montreal Cognitive Assessment (MoCA) is increasingly being used as a cognitive screening test in Parkinson disease (PD). The MoCA's popularity likely reflects its ability to detect executive dysfunction, a relative deficiency of the Mini-Mental State Examination (MMSE).

Objective—To compare neurochemical and neuropsychological functions in non-demented PD patients with mild cognitive impairment (PD-MCI) and without, as defined by MoCA (PD-MCI=MoCA<26).

Methods—Non-demented PD subjects underwent combined MoCA and MMSE, detailed cognitive testing and [^{11}C]methyl-4-piperidinyl propionate acetylcholinesterase and [^{11}C]dihydrotetrabenazine monoaminergic PET imaging.

Results—Eighteen subjects met MoCA PD-MCI criteria but had MMSE scores in the normal range, compared to 29 subjects with normal MoCA and MMSE scores. The MoCA-defined PD-MCI group had reduced performance in global cognition (t=2.91, P=0.0056), most significantly in executive function (t=3.18, P=0.002), as well as significant reduction in dorsal caudate nucleus dopaminergic innervation (t=2.72, P=0.009) compared to the PD without MCI group. Both MoCA and MMSE had poor diagnostic accuracy for PD-MCI (65.3%) when using the Level 2 Movement Disorder Society Task Force definition.

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Conclusion—PD subjects with normal range MMSE but abnormal MoCA scores had evidence of caudate nucleus dopaminergic denervation and mild cognitive changes, predominantly in executive function. The MoCA may be able to preferentially detect executive dysfunction compared to the MMSE, but the MoCA has limited diagnostic accuracy for PD-MCI, and should not be used alone to make this diagnosis.

Key words/Search Terms

Assessment of cognitive disorders/dementia; MCI (mild cognitive impairment); PD (Parkinson disease); PET (positron emission tomography)

I. Introduction

Mild cognitive impairment in Parkinson disease (PD-MCI) may be present at the time of diagnosis [1] and predicts progression to dementia [2], with over 80% of PD patients eventually developing dementia [3]. Early detection of PD-MCI thus has implications for prognosis and treatment.

Multiple measures exist to screen for PD-MCI, including the Montreal Cognitive Assessment (MoCA) [4] and the Mini-Mental State Examination (MMSE) [5]. The MoCA has been gaining popularity as a global screening test for cognitive dysfunction in PD because of its ability to detect the early cognitive changes (i.e. executive dysfunction) associated with PD [6, 7]. The MMSE is widely used and has been shown to be responsive to progression of cognitive impairment in PD [8], but it does not specifically measure executive dysfunction [6]. Recently, a MDS task force proposed criteria for the diagnosis of PD-MCI using either an abbreviated assessment (Level 1 criteria) or a comprehensive neuropsychological evaluation (Level 2 criteria) [9]. The MoCA was considered an acceptable measure for the Level 1 criteria, but not the MMSE.

The neurochemical substrates of cognition in PD are still being worked out. The executive dysfunction seen in early PD has been attributed to striatal dopaminergic degeneration, particularly in the caudate nucleus [10, 11]. However, the cholinergic system also plays a significant role in PD cognitive impairment, especially when dementia develops [12, 13]. The use of the MoCA to define PD-MCI has not been well investigated using combined neurochemical and detailed neuropsychological testing. In this study, we set out to examine the neurochemical and cognitive correlates of PD-MCI, as defined by the MoCA.

2. Methods

2.1 Subjects and clinical test battery

This was a retrospective analysis of subjects who were originally recruited for 2 separate positron emission tomography (PET) imaging studies (ClinicalTrials.gov Identifier NCT01106976 & NCT01565473). In one of these studies (NCT01106976), subjects were recruited primarily from a VA clinic. For inclusion in our analysis, subjects had to have completed (+) – [^{11}C] dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) and [^{11}C] methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) PET imaging, MoCA, MMSE, the Movement Disorder Society-revised Unified PD Rating

Scale (MDS-UPDRS), Hoehn-Yahr scale, and a detailed neuropsychological examination (see test battery below). Subjects with MMSE scores < 24 were not eligible.

All subjects met UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [14]. The diagnosis of PD was supported in all subjects by the presence of nigrostriatal dopaminergic denervation as demonstrated by [^{11}C]DTBZ VMAT2 PET. The MDS-UPDRS, as well as imaging with the (+)-[^{11}C]DTBZ VMAT2 ligand, were conducted after withholding dopaminergic medications overnight followed by [^{11}C]PMP AChE ligand PET and brain magnetic resonance imaging (MRI).

Our neuropsychological test battery has been previously reported [13], and covers the cognitive domains of memory, executive, attention and visuospatial function. Briefly, verbal memory was assessed with the California Verbal Learning Test (including immediate, short and delayed verbal scores). Executive/reasoning functions were assessed with the Delis-Kaplan Executive Function System Sorting and Verbal Fluency tests, WAIS III Picture Arrangement test and Stroop Color Word Interference test together with a switching version of the Stroop 3 test in which subjects name the color of the ink, unless the word is surrounded by a box, in which case, they read the word itself (Stroop 4) [13]. Performance of this task is more demanding on cognitive flexibility. Stroop Color Word Interference Test scores were calculated as the time difference for completion of the interference measures minus the non-interference tasks. Attention/psychomotor speed was assessed using absolute times on the Stroop 1 and 2 subtests. The attention and executive tasks were either corrected or not subject to effects of motor slowing. Benton Judgment of Line Orientation measured visuospatial function. Composite z-scores were calculated for these different cognitive domains (memory, executive, attention and visuospatial functions) based on normative data. A global composite z-score was calculated as the average of the four domain z-scores.

For the primary analysis, PD-MCI was defined as a MoCA score of <26 as suggested by Dalrymple-Alford [7]. For a post hoc analysis, PD-MCI was defined using the MDS Task Force Level 2 criteria using a 1.5 SD cutoff score below the normal mean for each of the 4 cognitive domains [9]. Patients with evidence of dementia as defined by a global composite z-score of < −2 and significant impairments of instrumental activities of daily living (as defined by more than 25% impairment on the Lawton and Brody scale [15]) were excluded from the study.

The study was approved by the Institutional Review Boards of the University of Michigan and Veterans Affairs Ann Arbor Health System for studies involving human subjects. Written informed consent was obtained from all subjects.

2.2 Imaging techniques

Magnetic resonance imaging was performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands) utilizing an 8-channel head coil and the "ISOVOX" exam card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; field of view=240×200×160mm; acquired matrix = 240×200. 160 slices were reconstructed to 1 mm

isotropic resolution. This sequence maximizes contrast among gray matter, white matter, and cerebrospinal fluid and provides high-resolution delineation of cortical and subcortical structures.

[^{11}C]PMP and [^{11}C]DTBZ PET Imaging were performed in 3D imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view. Prior to the DTBZ and PMP injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines.

[^{11}C]PMP was prepared in high radiochemical purity (>95%) by N-[^{11}C]methylation of piperidin-4-yl propionate using a previously described method [16]. Dynamic PET scanning was performed for 70 minutes as previously reported [13]. No-carrier-added (+)-[^{11}C]DTBZ (250 to 1000 Ci/mmol at the time of injection) was prepared as reported previously [17]. Dynamic PET scanning was performed for 60 minutes as previously reported [13].

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest on MRI images to include the thalamus, caudate nucleus, and putamen of each hemisphere. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal on the magnetic resonance imaging scan.

AChE [^{11}C]PMP hydrolysis rates (k_3) were estimated using the striatal volume of interest (defined by manual tracing on the MRI scan of the putamen and caudate nucleus) as the tissue reference for the integral of the precursor delivery [18]. AChE PET imaging assesses cholinergic terminal integrity with cortical uptake reflecting largely basal forebrain and thalamic uptake principally reflecting pedunculopontine nucleus integrity.

[^{11}C]DTBZ distribution volume ratio (DVR) was estimated using the Logan plot graphical analysis method with the striatal time activity curves as the input function and the total neocortex as reference tissue, a reference region overall low in VMAT2 binding sites, with the assumption that the non-displaceable distribution is uniform across the brain at equilibrium [19].

2.3 Statistical analyses

Standard pooled-variance t or Satterthwaite's method of approximate t tests (t_{approx}) were used for group comparisons (SAS version 9.2, SAS institute, Cary, North Carolina). Analysis of covariance for cognitive variables used rank transformation because of non-normal distribution of z-scores between cholinergic subgroups. Chi square testing was performed to compare proportions between groups. Yates' continuity corrected χ^2 was used

when at least one cell of the 2×2 table had an expected count smaller than 5. Holm-Bonferroni correction for multiple testing was performed for each main analysis.

3. Results

3.1 Subject characteristics

Forty-nine PD subjects (42M/7F) were included in this analysis. Mean age of the cohort was 66.0 ± 7.6 (range 50 – 84) years with mean duration of disease 5.8 ± 3.6 (range 1–15) years. Twenty-two PD subjects were taking both a dopamine agonist and carbidopa-levodopa, 20 were using carbidopa-levodopa alone, 3 were taking dopamine agonists alone, and 4 were not receiving dopaminergic drugs. No subjects were on anti-cholinergic drugs or cholinesterase inhibitors. Most subjects had moderate severity of disease: 2 patients stage 1, 2 in stage 1.5, 10 in stage 2, 25 in stage 2.5, 9 in stage 3, and 1 in stage 5 of the modified Hoehn and Yahr classification [20]. Mean MMSE score was 29.1±1.2 (range 25–30); mean MoCA score was 25.8±2.2 (range 21–30).

3.2 Comparison of MoCA and MMSE scores

e-Figure 1 shows a plot of the distribution of the paired MMSE and MoCA scores. The distribution of the MMSE scores shows a striking ceiling effect with 27 out of 49 (55%) of PD subjects having a maximum score of 30. In contrast, only 2 out of 49 (4.1%) PD subjects have a maximum score of 30 on the MoCA. Based on the recommended cut-off score of <27 for detecting cognitive impairment in highly educated individuals [21], only 2 patients would have abnormal range MMSE scores and would have been classified as having PD-MCI based on the MMSE. There were 20 subjects (40.8%) who met the MoCA-defined PD-MCI criteria [7]; 18 of them had normal range MMSE scores.

3.3 Clinical correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores

No significant differences in demographic and clinical characteristics (age, education, gender, duration of motor disease, and MDS-UPDRS scores) were seen between the MoCA-defined PD-MCI and PD without MCI groups (Table 1).

3.4 Cognitive correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores

Results of detailed neuropsychological testing showed that the executive cognitive domain z-score was most significantly abnormal in the PD-MCI compared to the PD without MCI group (table 2). Although decrements in the verbal learning and attention domains tended to be lower in the PD-MCI group, these variables were not significant after correction for the effects of multiple testing.

3.5 Dopaminergic and cholinergic PET correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores

Caudate nucleus dopaminergic denervation was significantly greater in the PD-MCI compared to the PD without MCI group (table 3). Although forebrain and thalamic cholinergic and putaminal dopaminergic denervation tended to be more severe in the PD-

MCI group, these variables were not significant after correction for the effects of multiple testing.

3.6 Post hoc analysis of MoCA and MMSE based PD-MCI classification and comprehensive neuropsychological PD-MCI definition

There were 17 subjects who had evidence of PD-MCI based on MDS Task Force Level 2 criteria using a cut-off of 1.5 SD below the normal mean. Amnestic PD-MCI was present in 10, executive PD-MCI in 11 and visuospatial domain PD-MCI in 4 subjects with variable overlap. There were no subjects with attentional domain PD-MCI. There were 11 subjects with single domain PD-MCI (4 amnestic, 5 executive and 2 visuospatial). Four subjects had dual domain amnestic and executive MCI. Two subjects had three domain PD-MCI (amnestic, executive and visuospatial). Measures of accuracy for MoCA and MMSE-defined PD-MCI classification versus MDS Task Force Level II definition of PD-MCI are presented in Table 4. Relative to the MDS Task Force Level II definition of PD-MCI, both the MoCA and MMSE had an overall diagnostic accuracy of 65.3%.

4. Discussion

In this study, subjects with PD-MCI based on a MoCA cutoff of <26, but normal MMSE scores, had significantly worse performance in executive function on neuropsychological testing than subjects without PD-MCI. Additionally, MoCA-defined PD-MCI subjects had significantly greater dopaminergic denervation in the caudate nucleus than PD without MCI subjects. Relative to the MDS Task Force Level II definition of PD-MCI, the MoCA and MMSE were similarly poor in diagnostic accuracy.

These results confirm previous reports that the MoCA is more sensitive than the MMSE for detecting cognitive changes in early PD [6, 8, 22]. However, our results also show that this effect may be largely attributed to the MoCA's sensitivity in detecting executive function impairment. Executive cognitive impairments encompass a diverse range of different functions, including judgment, insight, problem solving and cognitive set shifting, among others [23]. We found the following executive functions most affected in the subjects with MoCA-defined PD-MCI: card sorting, which measures concept-formation skills, modality-specific problem-solving skills (verbal/nonverbal), and the ability to explain sorting concepts abstractly; letter verbal fluency; and picture arrangements measuring logical/sequential reasoning and social insight.

Marras et al. [24] recently investigated the accuracy of the MoCA in detecting PD-MCI using the Level II MDS Task Force criteria as a gold standard, and found that it did not provide adequate sensitivity or specificity for detecting PD-MCI. Our results are consistent with these findings and suggest that the MDS task force Level 1 criteria, which state that the MoCA is adequate for classifying PD-MCI, should be reconsidered. Given the current available evidence, neither the MoCA nor MMSE is sufficient to make a diagnosis of PD-MCI. Only a comprehensive neuropsychological examination should be used to make this diagnosis.

It is being increasingly recognized that PD-MCI is heterogeneous [2, 24], and many PD patients without dementia may show deficits not only in executive function, but other domains, including memory, visuospatial function, psychomotor speed, and attention [24, 25]. Cognitive impairment in PD probably reflects several processes, including degeneration of several neurotransmitter systems as well as cortical pathology associated with Lewy body and β-amyloid plaque depositions [26, 27]. Dopaminergic degeneration has been reported to be a main contributor to the frontal lobe and executive function deficits seen in early PD [10, 11]. Our dopaminergic PET imaging findings show more significant denervation in the caudate nucleus compared to the putamen in our MoCA-defined PD-MCI group. This is consistent with the prevailing theory that the putamen is primarily involved in motor function, while the caudate is thought to contribute more to executive (cognitive) function [28]. Our findings are also in agreement with previous studies using FDOPA PET who reported associations between cognitive dysfunction and decreased dopaminergic uptake in the caudate nucleus [10, 11].

In addition to the well-known reductions in dopaminergic pathways, there is also evidence for alterations in cholinergic pathways in PD. Our group has recently demonstrated that cognitive performance in executive function, verbal learning and attention in PD patients without dementia independently correlates with both striatal dopaminergic and cortical cholinergic denervation [13]. *In vivo* imaging studies have also demonstrated that PD dementia is associated with more severe and widespread cholinergic denervation than PD without dementia [12, 29]. These findings may explain the less robust cholinergic reductions in the non-demented population of PD subjects in this study and are in keeping with a proposed framework for cognitive decline in PD where fronto-subcortical executive cognitive deficits may relate to dopaminergic anterior cerebral denervation whereas dementia may be associated with more widespread posterior cortical changes associated with Lewy body deposition, amyloid plaques and cholinergic denervation [30, 31].

It should be noted that our study sample was cross-sectional, consisting of subjects with predominant mild PD-MCI. Our study cohort was also predominantly male, as subjects were recruited primarily from a VA clinic. Thus, our study population may not be representative of a prospectively recruited PD-MCI cohort. Further larger scale prospective studies are needed to explore these limitations and to determine if gender-specific cognitive effects may be present in PD. Additionally, our neuropsychological test battery was limited, including limited memory and visuospatial tests. The results of this study were obtained in non-demented PD subjects and no inferences can be drawn about the utility of the MMSE versus the MoCA for their respective use in PD dementia.

5. Conclusions

MoCA-defined PD-MCI, in the presence of normal range MMSE scores, is associated with dopaminergic denervation of the caudate nucleus and mild cognitive changes, particularly in executive function. This may reflect the MoCA's preferential sensitivity to detect executive dysfunction. However, the MoCA had limited diagnostic accuracy for PD-MCI using formal neuropsychological testing as a gold standard, and alone, is insufficient to make a diagnosis of PD-MCI. Further research is needed to compare performance of the MoCA and MMSE

over time in PD subjects and to see how this may relate to dopaminergic and cholinergic denervation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We studied Parkinson disease subjects with abnormal MoCA, but normal MMSE scores.
- MoCA-defined PD-MCI subjects had worse performance on executive function than subjects without PD-MCI.
- MoCA-defined PD-MCI subjects also had greater dopaminergic caudate denervation than PD without MCI subjects.
- Using the MDS Task Force Level II definition of PD-MCI, both MoCA and MMSE were poor in diagnostic accuracy.

Table 1

Demographic and clinical correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores. Mean values with standard deviation or percentages are given.

	PD without MCI (n=29)	PD-MCI (n=18)	Statistical significance
Age (yr)	66.6±7.9	65.4±7.8	t=0.50, P=0.62
Duration of motor disease (yr)	5.8±3.4	6.1±4.0	t=0.32 P=0.75
Education (yr)	15.5±2.7	14.7±2.5	t=1.02, P=0.31
Gender (males)	22 (75.9%)	18 (100%)	Yates' χ^2=3.38, P=0.066
MMSE score	29.5±0.7	28.9±1.2	t_{approx}=1.85; P=0.076
MDS-UPDRS Part I: Non-motor experiences of daily living	7.24±4.45	6.67±6.30	t=0.37, P=0.72
MDS-UPDRS Part 2: Motor experiences of daily living	8.21±6.43	9.11±6.68	t=0.46, P=0.65
MDS-UPDRS Part 3: Motor Examination	29.93±11.68	33.31±11.51	t=0.97, P=0.34

Note: t_{approx}= Satterthwaite's method of approximate t tests)

Table 2

Cognitive correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores.

	PD without MCI (n=29)	PD-MCI (n=18)	Statistical significance
Global composite z-score	**−0.02±0.67**	**−0.62±0.70**	**t=2.91, P=0.0056***
Verbal learning z-score	**−0.09±1.07**	**−0.92±1.14**	**t=2.53, P=0.015**
CVLT Immediate learning	*9.7±1.9*	*8.0 ±2.3*	*t=2.58, P=0.013*
CVLT short-term memory	*10.7±3.5*	*8.3 ±3.1*	*t=2.32, P=0.025*
CVLT long-term memory	*11.1±3.2*	*8.9 ±3.5*	*t=2.17, P=0.035*
Executive functions z-score	**−0.02±0.79**	**−0.81±0.86**	**t=3.18, P=0.0027***
DKEFS card sorting test 1	*19.1±4.1*	*15.8±5.9*	*t=2.22, P=0.032*
DKEFS card sorting test 2	*20.7±5.0*	*16.1±6.1*	*t=2.80, P=0.008*
DKEFS verbal fluency letter test (F-A-S)	*46.9±13.7*	*36.4 ±11.4*	*t=2.71, P=0.0096*
Picture Arrangement test	*14.7±5.2*	*11.4±5.4*	*t=2.06, P=0.045*
Stroop Color Word Interference test 3 vs. 1–2	*64.2 ±21.9s*	*85.9±s44.5*	t_{approx}*=1.88, P=0.074*
Stroop Color Word Interference test 4 vs. 1–2	*77.5 ±30.8s*	*99.6±51.8s*	t_{approx}*=1.60, P=0.122*
Visuospatial function z-score	**0.32±0.76**	**−0.18±1.06**	**t=1.93, P=0.060**
Benton Judgment of Line Orientation	*26.0±3.3*	*23.8±4.6*	*t=1.93, P=0.060*
Attention z-score	**−0.28±0.80**	**−0.84±1.10**	**t=1.98, P=0.054**
Stroop test 1	*52.2±9.7s*	*59.0±14.8s*	*t=1.75, P=0.091*
Stroop test 2	*68.6 ±11.2s*	*76.7±15.9s*	*t=2.03, P=0.048*

Mean values with standard deviation are given. Raw test scores on the domain-specific cognitive sub-tests in italics. Stroop test scores are presented in seconds (s). Abbreviations: CVLT=California Verbal Learning Test; DKEFS=Delis-Kaplan Executive Function System; t_{approx}*=Satterthwaite's t-test approximation.*

*Significant variable after Holm-Bonferroni correction applied for the domain-specific Z-scores.

Table 3

Neurochemical PET correlates of MoCA-based PD-MCI classification in PD subjects with normal range MMSE scores. Mean values with standard deviation are given. [^{11}C]DTBZ VMAT2 binding values are presented as distribution volume ratio and [^{11}C]PMP as k_3 AChE hydrolysis rate (min^{-1}).

	PD without MCI (n=29)	PD-MCI (n=18)	Statistical significance
Neocortical acetylcholinesterase k_3	0.0245±0.0030	0.0231±0.0019	t_{approx}=1.95; P=0.057
Thalamic acetylcholinesterase k_3	0.0566±0.0057	0.0534±0.0040	t=2.04; P=0.047
Putaminal VMAT2 distribution volume ratio	1.90±0.30	1.74±0.29	t=1.89, P=0.065
Caudate Nucleus VMAT2 distribution volume ratio	2.27±0.39	1.95±0.38	t=2.72, P=0.0093*

Note: t_{approx}= Satterthwaite's method of approximate t tests)

*Significant variable after Holm-Bonferroni correction.

Table 4

Measures of accuracy for MoCA and MMSE-defined PD-MCI vs. comprehensive MDS Task Force Level 2 definition of PD-MCI

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MoCa-defined MCI	58.8%	68.8%	50.0%	75.9%
MMSE-defined MCI	5.9%	96.9%	50.0%	70.0%