ARTICLE

Mild behavioral impairment is linked to worse cognition and brain atrophy in Parkinson disease

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Neurology® 2019;93:e766-e777. doi:10.1212/WNL.0000000000007968

Abstract

Objective

To evaluate the associations of mild behavioral impairment (MBI) with cognitive deficits and patterns of gray matter changes in Parkinson disease (PD).

Methods

Sixty patients with PD without dementia and 29 healthy controls underwent a cognitive neuropsychological evaluation and structural MRI scan. MBI was evaluated with the MBI Checklist (MBI-C), a rating scale designed to elicit emergent neuropsychiatric symptoms in accordance with MBI criteria. We divided the patients with PD into 2 groups: 1 group with high MBI-C scores (PD-MBI) and the other with low MBI-C scores (PD-noMBI).

Results

Among 60 patients with PD, 20 were categorized as having PD-MBI (33.33%). In healthy controls, no participants met the MBI cut-point threshold. The PD-MBI group had significantly lower Montreal Cognitive Assessment and *z* scores in all 5 domains and the global score compared to healthy controls and those with PD-noMBI. In addition, all cognitive domains except language and global cognition negatively correlated with the MBI-C total score in all patients with PD. For cortical structures, the PD-MBI group revealed middle temporal cortex thinning and decreased volume compared with the PD-noMBI group, and decreased volume in this area negatively correlated with the MBI-C total score.

Conclusions

The impaired cognitive function over all domains and atrophy in the temporal area in the PD-MBI group are in line with posterior cortical circuit deficits in PD, which have been associated with a faster rate of progression to dementia. These initial results suggest that MBI might be an early and important marker for incident cognitive decline and dementia in patients with PD.

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Glossary

MBI = mild behavioral impairment; **MBI-C** = MBI Checklist; **MCI** = mild cognitive impairment; **MoCA** = Montreal Cognitive Assessment; **NPS** = neuropsychiatric symptoms; **PD** = Parkinson disease; **UPDRS-III** = motor section of the Unified Parkinson's Disease Rating Scale.

It is now clear that cognitive deficits can exist in the early stages of Parkinson disease (PD)[1] and that the presence of these deficits impedes daily activities.[2] A growing body of evidence suggests that emergent neuropsychiatric symptoms (NPS) in older adults are early markers of cognitive decline and progression along the neurodegenerative spectrum, in both clinical and community settings.[3–5] NPS are among the most common nonmotor symptoms in PD[6] that affect the patients even in early, untreated stages[7] and are more common in those with mild cognitive impairment (MCI)[8] or dementia.[9]

Mild behavioral impairment (MBI) is a neurobehavioral syndrome characterized by later-life emergence of sustained NPS, as an at-risk state for incident cognitive decline and dementia.[10] MBI represents the neurobehavioral axis of predementia risk states as a complement to the neurocognitive risk axis represented by MCI. In a 5-year longitudinal study, older adults with MBI had a higher conversion rate to dementia than a comparator group consisting of individuals with psychiatric conditions recurring in late life.[11] Furthermore, the presence of MBI has been shown to significantly increase the rate of progression to dementia in those with normal cognition or MCI compared to those without MBI.[12] To characterize MBI, the MBI Checklist (MBI-C), a rating scale designed to elicit emergent NPS in a community-dwelling, functionally independent older population in accordance with the MBI criteria, was developed as a simple and efficient MBI case ascertainment tool.[13]

Thus, early detection of the NPS that constitute MBI may aid in earlier detection of dementia at the preclinical or prodromal phase, in advance of cognitive impairment. However, no study to date has evaluated the relationship between MBI and cognitive deficits and its neuroanatomic correlates in PD. In the present study, we investigated for the first time the associations of MBI with cognitive function and brain structure changes in patients with PD.

Methods

Participants

Sixty patients with PD without dementia at Hoehn & Yahr stage II to III[14] and 29 age- and sex-matched healthy controls were included in this study. Patients were diagnosed by movement disorders neurologists and met the UK Brain Bank criteria for idiopathic PD.[15] All patients with PD were receiving dopaminergic medication and were responsive to it. No patient was asked to change her/his medication for this study. The severity of motor symptoms was rated with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Exclusion criteria were alcohol dependency, presence or history of severe psychiatric disorders having lasted >6 months, neurologic disorders other than PD, cerebrovascular disorders, and general anesthesia in the past 6 months.

MBI checklist

The MBI-C is a validated and freely available instrument in the public domain (available at MBItest.org) developed specifically as a case ascertainment instrument for MBI.[13] The MBI-C was designed to elicit emergent NPS in accordance with the MBI criteria, especially with respect to the 6-month reference range and explicit criteria for the later-life emergence of symptoms.[13] Validation studies of the MBI-C have determined cutoff points in subjective cognitive decline[16] and in MCI[17] and have demonstrated internal consistency, test-retest reliability,[18] and discriminative validity from the Neuropsychiatric Inventory Questionnaire.[18,19]

Completed by the informant, the MBI-C is a 2-page questionnaire consisting of 34 items organized according to the 5 MBI domains: (1) impaired drive/motivation (apathy): 6 questions including assessments of cognitive, behavioral, and emotional apathy; (2) affective/emotional dysregulation (mood and anxiety symptoms): 6 items including low mood, anhedonia, hopelessness, and guilt and 1 question each for worry and panic; (3) impulse dyscontrol (agitation and abnormal reward salience): 12 questions assessing agitation, aggression, impulsivity, recklessness, and abnormal reward and reinforcement; (4) social inappropriateness (impaired social cognition): 5 questions describing sensitivity, empathy, and tact; and (5) abnormal thoughts/perception (psychotic symptoms): 5 questions assessing suspiciousness, grandiosity, and auditory and visual hallucinations. For each item, a "yes" or "no" question is followed by a severity rating scale of 1 (mild), 2 (moderate), or 3 (severe). Symptoms should be persistent for at least 6 months and represent a meaningful change from baseline. Using the cut point of 7.5,[16,17,20] we divided the patients with PD into 2 groups: a group with high MBI-C scores referred to as the PD-MBI group and another with low MBI-C scores referred to as the PD-noMBI group.

Neuropsychological assessment

All participants underwent a comprehensive neuropsychological assessment that targeted 5 cognitive domains; attention, executive function, language, memory, and visuospatial function.[21] The neuropsychological battery included the following: (1) attention: the Digit Span forward of Wechsler Adult Intelligence Scale-IV, symbol span of Wechsler Memory Scale-IV, and Trail Making Test A; (2)

executive function: Trail Making Test B, the Stroop Color and Word test, the Hayling Sentence Completion Test, the Brixton Spatial Anticipation Test, Digit Span backward and sequencing of Wechsler Adult Intelligence Scale-IV, the Clock Drawing Test command, and Letter Fluency (F-A-S); (3) language: the Boston Naming Test and Semantic Fluency (animals and actions); (4) memory: the Hopkins Verbal Learning Test, Rey-Osterrieth Complex Figure Test–Delayed Recall, and logical memory of Wechsler Memory Scale-IV; and (5) visuospatial function: the Hooper Visual Organization Test and Rey-Osterrieth Complex Figure Test-copy. The performance on the neuropsychological tests was transformed into a *z* score based on the age-, sex-, and education-adjusted normative performance data and then averaged to derive a composite score within each domain. Global cognitive function was assessed by a mean global score from all the tests in the battery and the Montreal Cognitive Assessment (MoCA). All the neuropsychological evaluations were administered before and within 2 weeks of the imaging sessions.

MCI criteria

We determined MCI status in patients with PD according to the level II criteria of Movement Disorder Society Task Force,[21] requiring the following: (1) objective evidence of cognitive decline: performance 1.5 SDs below the standardized mean on at least 2 tests within a domain or across different cognitive domains; (2) subjective complaint of cognitive decline by the patient or accompanying person; (3) absence of significant decline in daily living activities (based on clinical observations of the referring neurologist and neuropsychologist); and (4) no dementia as diagnosed by the evaluating neuropsychologist on the basis of the Movement Disorder Society Task Force guidelines.[22] Patients with PD with MCI were further classified into 4 subtypes depending on the number and type of cognitive impairments: amnestic multiple domain, nonamnestic multiple domain, amnestic single domain, and nonamnestic single domain. A domain was considered affected if at least 1 test in the domain was scored as impaired.[21] Healthy controls were also assessed for MCI using the same criteria, and only participants without MCI were included in this study.

MRI acquisition and preprocessing

Two high-resolution T1-weighted images of 3D inversion recovery fast spoiled prepared gradient recalled sequence sequence were acquired for each patient with the GE DISCOVERY MR750 3.0T MRI at the Seaman Family Imaging Centre at the University of Calgary (repetition time/echo time 7.176/2.252 milliseconds, flip angle, acquisition matrix 256 × 256; voxel size 1 × 1 × 1 mm^3; 172 slices). The FreeSurfer imaging analysis suite (version 6.0.0, surfer.nmr.mgh.harvard.edu/) was used to estimate cortical thickness, volume, and surface area. The details of these procedures have been extensively described in prior publications.[23] Briefly, 2 volume images underwent motion correction and averaging to enhance the gray-to-white contrast to noise, skull stripping, transform to Talairach space, segmentation of subcortical white and gray matter structures, intensity normalization, tessellation of the gray/white matter boundaries, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white (white matter surface) and gray/CSF (pial surface) borders that most accurately define the transition to the other tissue class. Segmented volumes were visually inspected, and the appropriate manual corrections were performed. The local cortical thickness was measured on the basis of the difference between the position of equivalent vertices in the pial and white matter surfaces. Each face of the white surface and its matching face in the pial surface are used to define an oblique truncated pyramid; then cortical volume is computed as the volume of a truncated tetrahedron. The surface area of a vertex was defined as the average area of the triangles of which the vertex was a member. The data were smoothed on the surface with a 10-mm full-width half-maximum gaussian kernel. We also segmented and calculated the volume of subcortical structures, including the bilateral caudate nucleus, putamen, pallidum, nucleus accumbens, hippocampus, amygdala, and thalamus.

Statistical analysis

The differences in demographical and clinical data between healthy controls, patients with PD-MBI, and those with PD-noMBI were analyzed with 1-way analysis of variance with the Tukey post hoc test, Mann-Whitney *U* test, and χ^2 test as appropriate. The differences between the 3 groups with respect to MBI-C total and domain scores were examined with the Kruskal-Wallis test followed by the Mann-Whitney *U* test with Bonferroni correction for multiple comparisons. One-way analyses of variance with the Tukey post hoc tests were performed to compare the 3 groups on the global and individual cognitive domain scores and MoCA. Correlations between the MBI-C total score and cognitive function in patients with PD were tested using Spearman ρ. Although we used age-, sex-, and education-adjusted *z* scores for neuropsychological performance data, some clinical characteristics could have association with cognitive performance of patients. We found a significant group difference between PD-MBI and PD-noMBI in UPDRS-III score (table 1), and the UPDRS-III score negatively correlated with neuropsychological measures except MoCA and visuospatial function in PD (attention: $\rho = -0.272$, $p = 0.036$; executive function: $\rho = -0.348$, $p = 0.006$; language: $\rho = -0.258$, $p = 0.046$; memory: $\rho = -0.307$, $p = 0.017$; global: $\rho = -0.350$, $p = 0.006$). Therefore, the group differences in cognitive function and correlations with the MBI-C total score were also evaluated with the general linear model and Spearman partial correlation ρ, respectively, while controlling for UPDRS-III score. We also conducted a χ^2 test to evaluate the difference in proportions of MCI between the PD-MBI and PD-noMBI groups. To further characterize the effect of MBI on each cognitive domain scores, we compared PD-MBI and PD-noMBI within patients with PD who have MCI (PD-MCI) using the independent *t* test and general linear model with UPDRS-III score as a covariate of no interest. The analyses were carried out with SPSS 25.0.

Table 1 Demographic and clinical characteristics of participants

Characteristics	HC (n = 29)	PD-noMBI (n = 40)	PD-MBI (n = 20)	*p* Value		
				HC vs PD-noMBI	HC vs PD-MBI	PD-noMBI vs PD-MBI
Age, mean ± SD (range), y[a]	68.7 ± 5.9 (60.1–80.9)	70.2 ± 6.2 (60.7–80.1)	71.3 ± 6.5 (57.9–81.3)	0.600	0.334	0.793
Female, n (%)[b]	15 (52)	13 (33)	5 (25)	0.108	0.075	0.550
Education, mean ± SD (range), y[a]	16.7 ± 2.6 (12–21)	15.4 ± 2.6 (9–21)	14.4 ± 3.2 (9–20)	0.134	0.011	0.330
Disease mean ± SD (range), y[c]	NA	5.3 ± 3.4 (0.8–12.5)	6.4 ± 4.0 (1.2–15.5)	NA	NA	0.384
LED, mean ± SD (range), mg/d[c]	NA	730.9 ± 342.5 (225–1862)	910.7 ± 430.6 (300–1,600)	NA	NA	0.131
UPDRS-III score, mean ± SD (range)[c]	NA	16.7 ± 9.1 (5–41)	22.0 ± 8.4 (8–40)	NA	NA	0.022
MBI-C score, mean ± SD (range)[d]						
Total	0.0 ± 1.4 (0–7)	1.6 ± 2.0 (0–7)	15.1 ± 9.3 (8–44)	<0.001	<0.001	<0.001
Drive/motivation	0.1 ± 0.4 (0–2)	0.6 ± 0.9 (0–3)	3.4 ± 2.9 (0–11)	0.004	<0.001	<0.001
Mood/anxiety	0.1 ± 0.4 (0–2)	0.5 ± 1.0 (0–4)	4.5 ± 2.3 (1–9)	0.079	<0.001	<0.001
Impulse dyscontrol	0.2 ± 0.8 (0–4)	0.4 ± 0.8 (0–4)	5.0 ± 5.4 (0–21)	0.072	<0.001	<0.001
Social inappropriateness	0.0 ± 0.0	0.1 ± 0.3 (0–1)	1.5 ± 2.3 (1–10)	0.134	<0.001	<0.001
Abnormal perception/ thought	0.0 ± 0.0	0.2 ± 0.7 (0–4)	0.7 ± 1.0 (0–3)	0.082	<0.001	0.006
MCI, n (%)		17 (42.5)	15 (70.0)	NA	NA	0.017
Amnestic multiple		7 (41)	9 (60)			
Nonamnestic multiple		5 (29)	5 (33)			
Amnestic single		1 (6)	0 (0)			
Nonamnestic single		4 (24)	1 (7)			

Abbreviations: HC = healthy controls; LED = levodopa equivalent dose; MBI = mild behavioral impairment; MBI-C = MBI Checklist; NA = not applicable; PD = Parkinson disease; UPDRS-III = motor section of the Unified Parkinson's Disease Rating Scale.
[a] One-way analysis of variance with the Tukey post hoc test.
[b] Chi-square test.
[c] Mann-Whitney *U* test.
[d] Kruskal-Wallis test followed by Mann-Whitney *U* test using Bonferroni correction; $p < 0.016$ was considered significant ($p = 0.05/3$).

Vertex-by-vertex analyses of thickness, volume, and surface area were carried out with the general linear model. Age and education were included as covariates for all comparisons. For comparisons between PD-MBI and PD-noMBI, UPDRS-III score was included as an additional covariate. Correlation analyses between cortical maps and MBI-C total score were performed in the PD group with adjustment for age, education, and UPDRS-III score. Estimated intracranial volume was included as an additional covariate for all volume and surface area analyses. In all imaging analyses, cluster-wise correction using Monte Carlo simulation was applied (cluster-wise probability 0.01, $\alpha = 0.05$). Volumes of subcortical structures were analyzed in the same manner as the vertex-by-vertex analyses with the general linear model and Spearman partial correlation ρ, and results were considered statistically significant when surviving $p < 0.05$, corrected for multiple comparisons using false discovery rate.

To further confirm our findings and to remove a possible ambiguity linked to the cut point of the MBI-C, we replicated the group comparison and correlation analyses on cognition and anatomic MRI after excluding participants who obtained total scores close to the cut point, that is, 7 or 8. Those analyses were performed only for patients with PD and while controlling for UPDRS-III score.

Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent according to the Declaration of Helsinki, and the study was approved by

the Conjoint Health Research Ethics Board at the University of Calgary.

Data availability

The data that support the findings of this study are available on request from the corresponding author (oury.monchi@ucalgary.ca).

Results

MBI classification and characteristics of the sample

The demographic and clinical characteristics of the sample are shown in table 1. Among 60 participants with PD, 20 were categorized as having PD-MBI (33.33%). In healthy controls, no participants met the MBI cut-point threshold; 90% of them (26 of 29) scored 0. The PD-MBI group showed higher MBI domain scores than the PD-noMBI group in all domains. The PD-MBI group had higher UPDRS-III scores than the PD-noMBI group and fewer education years than healthy controls.

Four patients of the PD-MBI group scored 8, and 1 participant of PD-noMBI group scored 7. When we compared the group differences after excluding them, the main statistical results remained the same as for the full sample size. We briefly report those results but focus on the full group of 20 with PD-MBI and 40 with PD-noMBI; all tables and figures in this article show results based on those groups.

Cognitive impairment in PD-MBI

The results of neuropsychological testing are presented table 2. We found significant group differences in global and domain-specific cognitive function. The PD-MBI group had significantly lower MoCA and z scores in all 5 domains and the global score compared to healthy controls and those with PD-noMBI (MoCA $F_{2,86}$ = 15.45, attention $F_{2,86}$ = 11.38, executive $F_{2,86}$ = 14.10, language $F_{2,86}$ = 7.55, memory $F_{2,86}$ = 13.71, visuospatial $F_{2,86}$ = 10.68, global $F_{2,86}$ = 23.52, all

Table 2 Results of neuropsychological evaluation

	Score,[a] mean ± SD			*p* Value,[b] partial η^2				Spearman ρ, *p* value
Domain	HC	PD-noMBI	PD-MBI	HC vs PD-noMBI	HC vs PD-MBI	PD-noMBI vs PD-MBI		Correlation with MBI-C total score in all PD
Attention	0.20 ± 0.52	−0.11 ± 0.53	−0.54 ± 0.57	0.052, 0.080	<0.001, 0.321		0.011, 0.128	−0.313, 0.015
						UPDRS-III score controlled[c]	0.023, 0.088	−0.260, 0.047
Executive	0.27 ± 0.38	0.05 ± 0.52	−0.51 ± 0.64	0.187, 0.053	<0.001, 0.379		<0.001, 0.183	−0.366, 0.004
						UPDRS-III score controlled[c]	0.005, 0.129	−0.304, 0.019
Language	0.42 ± 0.73	0.13 ± 0.61	−0.34 ± 0.69	0.185, 0.046	0.001, 0.221		0.034, 0.109	−0.288, 0.026
						UPDRS-III score controlled[c]	0.034, 0.076	−0.236, 0.071
Memory	0.28 ± 0.40	0.21 ± 0.71	−0.66 ± 0.90	0.899, 0.004	<0.001, 0.343		<0.001, 0.223	−0.409, 0.001
						UPDRS-III score controlled[c]	0.001, 0.170	−0.358, 0.005
Visuospatial	0.26 ± 0.42	−0.00 ± 0.79	−0.71 ± 0.96	0.307, 0.039	<0.001, 0.335		0.002, 0.138	−0.370, 0.003
						UPDRS-III score controlled[c]	0.011, 0.107	−0.354, 0.006
Global	0.30 ± 0.34	0.05 ± 0.42	−0.55 ± 0.55	0.061, 0.088	<0.001, 0.484		<0.001, 0.278	−0.440, <0.001
						UPDRS-III score controlled[c]	<0.001, 0.223	−0.385, 0.003
MoCA	27.4 ± 2.1	27.1 ± 2.4	23.3 ± 4.3	0.888, 0.005	<0.001, 0.305		<0.001, 0.259	−0.431, 0.001
						UPDRS-III score controlled[c]	<0.001, 0.227	−0.396, 0.002

Abbreviations: HC = healthy controls; MBI = mild behavioral impairment; MBI-C = MBI Checklist; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; UPDRS-III = motor section of the Unified Parkinson's Disease Rating Scale.
[a] z Scores except MoCA.
[b] One-way analysis of variance with the Tukey post hoc test.
[c] General linear model when controlling for UPDRS-III score.

$p \leq 0.001$; p values for each post hoc comparison in table 2). Comparisons between healthy controls and the PD-noMBI group revealed no significant differences in global and any domain-specific cognitive function. The group differences between PD-MBI and PD-noMBI were still significant after controlling for UPDRS-III (MoCA $F_{1,57} = 16.76$, $p < 0.001$; attention $F_{1,57} = 5.50$, $p = 0.023$; executive $F_{1,57} = 8.43$, $p = 0.005$; language $F_{1,57} = 4.71$, $p = 0.034$; memory $F_{1,57} = 11.65$, $p = 0.001$; visuospatial $F_{1,57} = 6.86$, $p = 0.011$; global $F_{1,57} = 16.32$, $p < 0.001$). In patients with PD, MoCA and z scores in all 5 domains and the global score showed significant negative correlations with the MBI-C total score. When we evaluated the correlation between the MBI-C total score and cognitive functions after controlling for UPDRS-III, we found significant negative correlations with all cognitive scores except language (ρ and p values for each correlation are reported in table 2).

The proportion with MCI was higher in PD-MBI group than in PD-noMBI group ($\chi^2 = 5.658$, $p = 0.017$). Fifteen patients with PD of 20 with PD-MBI (75.0%) and 17 patients with PD of 40 PD-noMBI (42.5%) were classified as having MCI. Within the PD-MCI group, the overall distribution of MCI subtypes was similar between the PD-MBI and PD-noMBI groups. Amnestic, multiple-domain impairment was the most common subtype of MCI in both groups (table 1). However, we found significant differences in global and domain-specific cognitive function in PD-MBI compared to PD-noMBI. The PD-MBI group showed lower MoCA and z scores in global cognition, attention, executive function, and memory with and without controlling for UDPRS-III. The visuospatial function was significantly different only without controlling for UPDRS-III (table 3).

When we excluded participants with total score 7 or 8 in PD, we found significant group differences in MoCA and z scores of global cognition and all 5 domains except language after controlling for UPDRS-III (MoCA $F_{1,52} = 15.32$, $p < 0.001$; attention $F_{1,52} = 6.689$, $p = 0.011$; executive $F_{1,52} = 9.90$, $p = 0.003$; language $F_{1,52} = 3.04$, $p = 0.087$; memory $F_{1,52} = 13.52$, $p = 0.001$; visuospatial $F_{1,52} = 8.01$, $p = 0.006$; global $F_{1,52} = 17.08$, $p < 0.001$). The correlations with MBI-C scores also showed significant negative correlations in all cognitive scores except language with controlling for UPDRS-III (MoCA $\rho = -0.41$, $p = 0.002$; attention $\rho = -0.27$, $p = 0.046$; executive $\rho = -0.32$, $p = 0.018$; language $\rho = -0.25$, $p = 0.073$; memory $\rho = -0.32$, $p = 0.020$; visuospatial $\rho = -0.34$, $p = 0.012$; global $\rho = -0.37$, $p = 0.006$).

Brain thickness, volume, and surface area

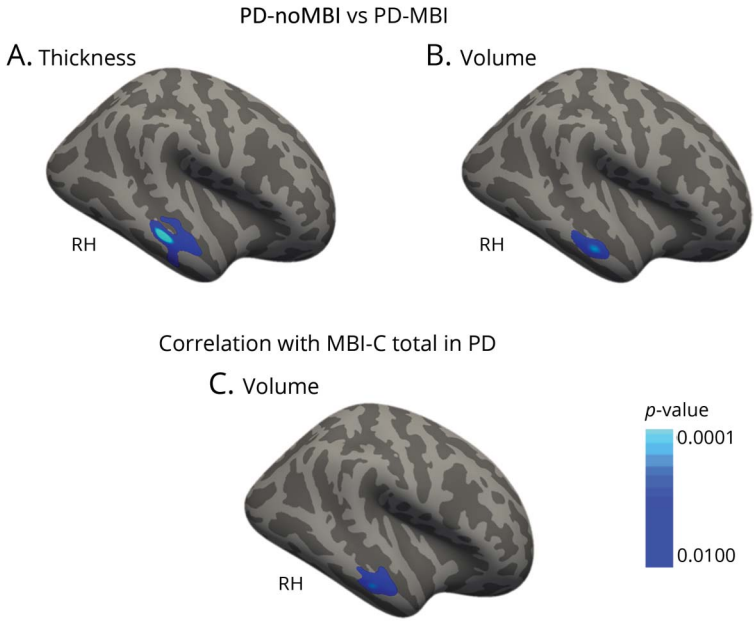
Patients with PD-MBI showed cortical thinning and reduced cortical volume and surface area compared to both those with PD-noMBI and healthy controls. The right middle temporal cortex showed thinning and decreased volume in the PD-MBI group compared with the PD-noMBI group (figure 1, A and B

Table 3 Results of neuropsychological evaluation in patients with PD with MCI

	Score,[a] Mean ± SD		p Value,[b] partial η^2	
Domain	**PD-noMBI**	**PD-MBI**	**PD-noMBI vs PD-MBI**	
Attention	−0.25 ± 0.44	−0.73 ± 0.48		0.006, 0.224
			UPDRS-III score controlled[c]	0.015, 0.186
Executive	−0.25 ± 0.52	−0.78 ± 0.47		0.006, 0.228
			UPDRS-III score controlled[c]	0.014, 0.191
Language	−0.13 ± 0.63	−0.47 ± 0.67		0.156, 0.066
			UPDRS-III score controlled[c]	0.254, 0.045
Memory	−0.13 ± 0.74	−0.95 ± 0.80		0.006, 0.229
			UPDRS-III score controlled[c]	0.014, 0.192
Visuospatial	−0.25 ± 1.06	−0.97 ± 0.94		0.050, 0.122
			UPDRS-III score controlled[c]	0.077, 0.104
Global	−0.20 ± 0.41	−0.78 ± 0.42		0.001, 0.334
			UPDRS-III score controlled[c]	0.001, 0.305
MoCA	26.7 ± 2.7	21.8 ± 3.7		<0.001, 0.382
			UPDRS-III score controlled[2c]	<0.001, 0.369

Abbreviations: MBI = Mild Behavioral Impairment; MBI-C = MBI Checklist; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; UPDRS-III = motor section of the Unified Parkinson's Disease Rating Scale.
[a] z Scores except MoCA.
[b] Independent t test.
[c] General linear model when controlling for UPDRS-III score.

Figure 1 Cortical regions showing atrophy in PD-MBI compared to PD-noMBI and correlation with MBI-C total score



The PD-MBI group with Parkinson disease (PD) with mild behavioral impairment (MBI) showed (A) thinning and (B) decreased volume in the right middle temporal cortex compared to the PD-noMBI group. (C) The decreased volume in the right middle temporal cortex correlated significantly with MBI Checklist (MBI-C) total score. RH = right hemisphere.

and table 4), and decreased volume in this area negatively correlated with the MBI-C total score (figure 1C and table 4). Compared with healthy controls, we found thinning in the left parahippocampal cortex, decreased volume and surface area in the right precuneus, and decreased volume in the right lingual cortex and lateral frontal pole in patients with PD-MBI (figure 2 and table 5). These cortical changes were not found in the PD-noMBI group. The PD-noMBI group showed decreased volume and area in the right superior parietal cortex and decreased area in the left inferior parietal cortex compared to healthy controls. Both PD-MBI and PD-noMBI groups revealed reduced volume of the left inferior parietal cortex compared to healthy controls. In subcortical structures, there were no differences between the 3 groups and correlations with MBI-C total scores in patients with PD.

When we analyzed the group differences between PD-MBI and PD-noMBI and the correlation with the MBI-C total score after excluding participants with total score 7 or 8 in PD, we found the same cluster with the results from all the participants, namely the right middle temporal cortex. This area showed significant thinning in those with PD-MBI than compared with those with noMBI and a negative volume correlation with MBI-C total scores. The volume difference between groups was also found in the right middle temporal cortex, but the cluster was smaller than before, not surviving a significance of $p < 0.05$ after multiple-comparisons correction (data not shown).

Discussion

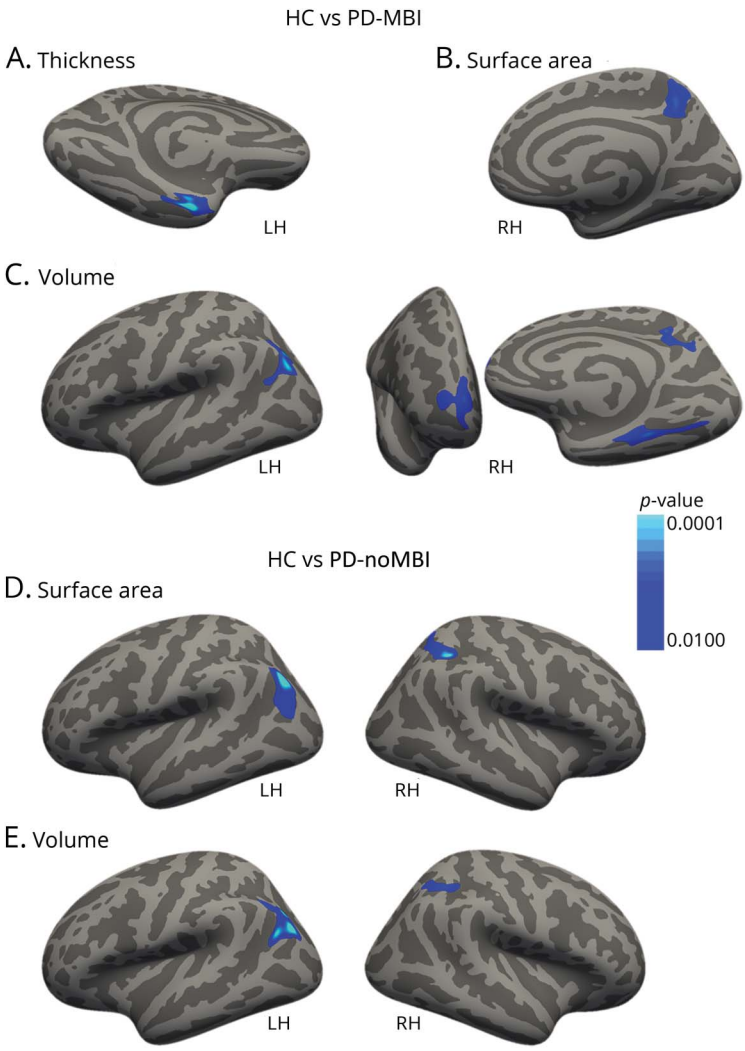
The present study is the first to investigate the associations of MBI with cognitive deficits and brain atrophy in PD. Regarding neuropsychological performance, patients with PD-MBI had greater impairment in global cognition and all 5

Table 4 Brain regions showing atrophy and correlation with MBI-C total score in PD

Region	Peak MNI coordinates: x, y, z:	Size, mm^2	Cluster-wise *p* value
Thickness, PD-noMBI vs PD-MBI			
Right middle temporal cortex	64, −24, −13	779.87	0.0006
Volume, PD-noMBI vs PD-MBI			
Right middle temporal cortex	63, −14, −17	408.60	0.0433
Volume, correlation with MBI-C total			
Right middle temporal cortex	63, −17, −20	526.91	0.0085

Abbreviations: MBI = mild behavioral impairment; MBI-C = MBI Checklist; MNI = Montreal Neurological Institute; PD = Parkinson disease.

Figure 2 Cortical regions showing atrophy in PD-noMBI and PD-MBI compared to HCs



The PD-MBI group with Parkinson disease (PD) with mild behavioral impairment (MBI) showed cortical atrophy in various regions of (A) thickness, (B) volume, and (C) surface area. The PD-MBI group had thinning in the left parahippocampal cortex and decreased volume and surface area in the right precuneus and decreased volume in the right lingual cortex and lateral frontal pole compared to healthy controls (HC). The PD-noMBI group revealed (D) decreased volume and (E) surface area in the left inferior and right superior parietal lobules compared to HCs. LH = left hemisphere; RH = right hemisphere.

cognitive domains than patients with PD-noMBI and healthy controls, and these cognitive impairments correlated with a high MBI-C total score in patients with PD. Moreover, the proportion with MCI was significantly higher in the PD-MBI group than the PD-noMBI group. For neuroimaging analyses, we found thinning and decreased volume in the right middle temporal cortex in patients with PD-MBI compared to those with PD-noMBI, and the decreased volume negatively correlated with MBI-C total score. These results are in line with the notion that MBI is a possible risk marker for incident cognitive decline and dementia.[10]

Most prior studies of the link between NPS and cognitive function in PD have focused on individual NPS and assessed only global cognitive ability or limited cognitive domains, particularly executive function. Executive dysfunction in patients with PD with NPS has been consistently reported in prior studies[24] and is associated with most individual NPS, including depression,[25] apathy,[26] visual hallucinations,[27] anxiety,[28] and impulse control disorders.[29] In addition, total Neuropsychiatric Inventory scores correlated with executive dysfunction in patients with PD without dementia.[30] Impairment of executive functions mirroring frontostriatal dysfunction in PD is common in early disease.[31] On the basis of this evidence, previous studies have emphasized the association between NPS and executive function in PD.[24] However, the PD-MBI group in the present study revealed impairment in all 5 cognitive domains and global cognition, which could not be captured by previous studies of specific NPS in PD. The multiple-domain impairment in the PD-MBI group could be explained by the characteristics of MBI-C. The MBI-C total score is a sum of 5 MBI domain scores—impaired drive/motivation, affective/emotional dysregulation, impulse dyscontrol, social inappropriateness, and abnormal thoughts/perception—that incorporate a range of NPS.[13] In the present study, patients in the PD-MBI group scored ≥1 in at least 3 domains of the MBI-C, which implies that multiple NPS are co-occurring in our patients with PD-MBI. These results

Table 5 Brain regions showing atrophy in PD-MBI and PD-noMBI compared to healthy controls

Region	Peak MNI coordinates: x, y, z	Size, mm^2	Cluster-wise *p* value
Volume, HC vs PD-noMBI			
Left inferior parietal lobule	−40, −75, 28	1,174.29	0.0002
Right superior parietal lobule	28, −57, 46	508.05	0.0118
Surface area, HC vs PD-noMBI			
Left inferior parietal lobule	−37, −75, 38	1,015.44	0.0046
Right superior parietal	34, −47, 37	812.91	0.0118
Thickness, HC vs PD-MBI			
Left parahippocampal cortex	−34, −8, −34	633.51	0.0044
Volume, HC vs PD-MBI			
Left inferior parietal lobule	−32, −76, 34	943.72	0.0002
Right superior frontal cortex	12, 64, 4	652.64	0.0016
Right lingual cortex	36, −45, −13	643.69	0.0020
Right precuneus	13, −45, 45	412.06	0.0402
Surface area, HC vs PD-MBI			
Right precuneus	10, −51, 46	717.98	0.0296

Abbreviations: HC = healthy controls; MBI = mild behavioral impairment; MNI = Montreal Neurological Institute; PD = Parkinson disease.

suggest that multiple NPS are associated with overall cognitive impairment in multiple domains, not only executive function, and that the MBI-C is a useful instrument to evaluate the elevated global NPS in PD.

Moreover, the findings of memory and visuospatial function impairment and the higher proportion of MCI in PD-MBI suggest that MBI could be more closely linked to cognitive impairment and conversion to dementia than each individual NPS in PD. The posterior and temporal region–based cognitive deficits such as memory, visuospatial, and language function might be more predictive of dementia than frontal executive dysfunction in patients with PD according to the dual syndrome hypothesis.[32] In MCI without PD, NPS are associated with higher risk for incident dementia compared to no NPS,[5] and patients with MCI with MBI have more severe cognitive impairment and higher dementia conversion rates than those without MBI.[12] In agreement with these previous and our findings, we also found greater impairment in global cognition, memory, and executive function in patients with PD with both MBI and MCI than in patients with PD with only MCI. Overall, these results support the role of MBI as a noncognitive marker of dementia in PD. Furthermore, it is interesting to note that higher MBI-C scores were associated with higher UPRDS-III scores even though the 2 PD groups had similar disease duration. Severe motor symptoms and global cognitive deficits in the PD-MBI group might indicate that MBI in patients with PD is associated with faster global disease progression. Longitudinal studies are needed to clarify the association between disease progression and MBI in PD.

The atrophy in right middle temporal cortex associated with MBI in PD supports the effect of MBI on cognitive deficits in PD. Previously, it has been shown that atrophy in the temporal area is associated with cognitive decline in patients with PD in cross-sectional and longitudinal studies. Patients with PD with MCI and those with dementia have greater temporal atrophy than patients with PD with normal cognitive function,[33,34] and the atrophy correlated with memory and visuospatial function[35,36] and CSF β-amyloid level.[37] In longitudinal studies, patients with PD with MCI had a faster rate of cortical thinning in the lateral temporal cortex.[38,39] Moreover, patients with PD who progressed to MCI over 18 months later had temporal cortex thinning at baseline,[39] and those who converted to dementia had greater longitudinal thinning in the temporal cortex than nonconverters.[40] The temporal cortical atrophy, together with the impairment of visuospatial and memory function in the PD-MBI group in the present study, seems in line with the posterior cortical profile of the dual syndrome hypothesis of cognitive decline in PD, which has been associated with faster cognitive decline compared with the dopamine-sensitive frontostriatal profile.[32] The posterior cortical profile is thought to reflect the early stages of a dementing process due to cortical Lewy body deposition or Alzheimer-type changes in posterior cortical areas.[41] Further longitudinal and multimodal studies are required to find out the degree to which MBI in PD is associated

with Lewy body or Alzheimer disease pathology. These studies will help determine the underlying mechanisms of the interaction between MBI and cognitive decline in PD and whether MBI is predictive of a specific dementia phenotype in PD.

The temporal atrophy in PD-MBI might also be associated with NPS. In previous studies, the temporal cortical thinning was associated with the presence of agitation/aggression and correlated with the total Neuropsychiatric Inventory score in PD.[42] In a longitudinal study, depressive symptoms in PD were associated with thickness at baseline and faster thinning in temporal area.[43] In addition, cerebral blood flow in the superior and middle temporal gyri was associated with visual hallucination in PD.[44] However, previous studies identified that NPS in PD are frequently associated with frontal regions. Recent studies have demonstrated that global NPS in patients with PD evaluated with the Neuropsychiatric Inventory[42] and Cambridge Behavioural Inventory–Revised[45] are associated with prefrontal atrophy. In addition, frontal lobe atrophy was commonly observed in patients with PD with depression, visual hallucination, apathy, and impulse control disorders.[24] In the present study, we found prefrontal atrophy in patients with PD-MBI compared to healthy controls. However, compared to patients with PD-noMBI, those with PD-MBI showed no prefrontal differences but rather showed atrophy in the middle temporal cortex. It is possible that both the PD-MBI and PD-noMBI groups have mild frontal atrophy that is more pronounced in PD-MBI. However, frontal atrophy does not seem to be a major factor associated with MBI in PD in our sample. These results might highlight the differences between the NPS previously studied in PD and the MBI-C, which has been designed as an NPS risk construct for incident cognitive decline. This is the case, given the importance of temporal lobe structural and functional changes in cognitive decline in PD mentioned above. The MBI-C was developed explicitly to capture emergent and sustained NPS and behavioral changes in individuals without dementia as a dementia risk marker,[13] while many studies of NPS have used the Neuropsychiatric Inventory, which was developed to capture NPS in a dementia population.[46] Of note, MBI-C validation studies have demonstrated divergent validity between the MBI-C and Neuropsychiatric Inventory Questionnaire,[18,19] such that they do indeed measure different things. Thus, the differences in the ability of these scales to capture NPS in preclinical and prodromal states may account for our temporal lobe findings.

Data from non-PD dementia studies suggest that the temporal regions may be associated with NPS and behavioral changes, and we can speculate as to the relevance to PD. Cortical thinning in the inferior temporal cortex was associated with increased apathy over time in the AD continuum, including participants with normal cognition, MCI, and AD,[47] and greater apathy in both cognitive normal elderly and those with MCI[48] without correlation with prefrontal area. In patients with frontotemporal dementia, psychiatric features such as disinhibition, anxiety, and dysthymia were correlated with atrophy[49] and hypoperfusion[50] in temporal rather than frontal areas. These results suggest that the temporal lobe has a role in NPS that could be independent of prefrontal regions. Further studies are needed to clarify the origin of the correlation between atrophy in the middle temporal cortex and MBI, in particular, studies analyzing the relationship between MBI-C subdomain scores and regional brain volume and thickness.

This study has several limitations worthy of discussion. We could not evaluate the associations of each MBI domain with cognitive and gray matter changes because a larger sample size is required to do so. In addition, this is a cross-sectional study, so we could not directly evaluate the predictive value of MBI on cognitive decline in PD. Further large cohort and longitudinal studies are required to determine the utility of MBI-C total and domain scores in predicting the future development of dementia and the time frame for cognitive decline.

We determined that a recently developed burden of sustained NPS, manifested as a high MBI-C total score, is associated with cognitive deficits and brain structural changes in PD. Impaired memory and visuospatial function in the PD-MBI group are in line with posterior cortical circuit deficits in PD, which have been associated with a faster rate of progression to dementia. Moreover, a high MBI-C score was associated with atrophy in the temporal area, which suggests greater cognitive deficits and decline in PD. These initial results indicate that MBI might be an early and important marker for incident cognitive decline and dementia in those with PD, similar to the prognostic role of MBI in Alzheimer disease.

Acknowledgment

The authors thank Dr. Liu Shi Gan for proofreading the manuscript.

Study funding

This study was funded by an operating grant from the Canadian Institutes of Health Research (MOP-126017), the Tourmaline Oil Chair in Parkinson's Disease, The Canada Research Chair in Nonmotor Symptoms of Parkinson's Disease to O.M., and Natural Sciences and Engineering Research Council CREATE I3T Program and the E. Marie and R. Garey Cameron Postdoctoral Fellowship in Dementia from the Hotchkiss Brain Institute to E.J.Y.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* November 29, 2018. Accepted in final form March 27, 2019.

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Mild behavioral impairment is linked to worse cognition and brain atrophy in Parkinson disease

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Neurology 2019;93;e766-e777 Published Online before print July 18, 2019
DOI 10.1212/WNL.0000000000007968