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Longitudinal brain volumetric changes and their predictive effects on cognition among cognitively asymptomatic patients with Parkinson's disease

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ABSTRACT

Introduction: Existing literature on brain volumetric alterations in patients with Parkinson's disease (PD) have mainly focused on gray matter (GM) and are largely cross-sectional. Little is known about white matter (WM) volumetric features and their impact on cognitive symptoms in PD. Therefore, the present study aims to examine both GM and WM volumes of cognitively asymptomatic PD patients with a longitudinal design.

Methods: A total of 42 cognitively asymptomatic patients with early stage PD were recruited and followed up for 1.5 years. At follow-up, 12 patients progressed to mild cognitive impairment (MCI) and were classified as "converters" while the remaining 30 patients remained cognitively asymptomatic and were classified as "non-converters". All patients underwent clinical and neuropsychological assessments as well as MRI scans at baseline and at follow-up.

Results: At baseline, non-converters and converters had comparable cognitive scores. At follow-up, converters showed more deficits in frontal-related cognitive function than non-converters. Volumetric analyses revealed that converters had more longitudinal reduction in WM, but not GM, volume compared to non-converters. The decreased volumes among converters were mainly localized in the frontal areas. Moreover, baseline global WM volume significantly predicted conversion to PD-MCI, while baseline GM and WM volumes of the frontal and parietal regions were associated with frontal cognitive changes across time.

Conclusion: PD patients who develop MCI demonstrate longitudinal reduction in WM volume, especially in the frontal areas. While both regional GM and WM volumes associate with frontal cognitive decline, baseline global WM volume may be a neuroimaging marker of conversion to PD-MCI.

1. Introduction

Parkinson disease (PD) is a common neurodegenerative disease. The diagnosis mainly rests on the identification of motor symptomatology, including bradykinesia, resting tremor, rigidity, and postural instability accounted for, by the loss of dopaminergic neurons [1–3]. Despite the traditional emphasis on motor symptomatology, growing evidence has indicated non-motor features, such as depression, anxiety, and cognitive impairment to have a major impact on quality of life and hospitalization [4]. Cognitive dysfunction in PD may present as mild cognitive impairment (PD-MCI) or dementia (PDD). PD-MCI is frequent and often associated with frontostriatal dysfunction [5,6].

PD-MCI can be seen as a transitional state between normal cognition and dementia [7]. Thus, early identification of MCI among PD patients is of clinical importance in order to retard progression to PDD. Neuroimaging studies have indicated alterations in widespread cortical regions among PD-MCIs, compared to healthy controls [8,9], though some have reported negative findings [6,10]. Compared with cognitively asymptomatic PD patients, our previous work [11] and the work of others have revealed reduced gray

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matter (GM) volume in PD-MCI [3,12], especially in the frontal and subcortical regions, supporting the frontostriatal dysfunctional theory for cognitive impairment in PD.

Compared with GM changes, thus far, little is known about the characteristics of white matter (WM) in PD-MCI. A recent study demonstrated that PD-MCI patients who progressed to dementia already showed greater white matter hyperintensities at baseline, compared to PD-MCI patients who did not progress to dementia [13]. A previous study comparing patients with PD and healthy controls, demonstrated that despite absence of differences in age, cognitive scores, and global GM volume, PD patients had lower global WM [14]. Similarly, a recent cross-sectional study showed that compared to healthy controls and PD patients without cognitive symptoms, PD-MCI patients showed more distributed WM abnormalities in anterior and posterior parts of the brain (e.g., the corona radiata and the uncinated fasciculus) [15]. Given these findings, PD may be considered a disconnection syndrome, implying axonal dysfunction of white matter [16], which however, has not been adequately investigated [17].

Previous neuroimaging studies mainly were cross-sectional without follow-up scans, therefore determining if volumetric reduction is a stable hallmark or only a manifestation of late stage of disease, could not be elucidated. Furthermore, it remains unclear if volumetric difference occurs even before the onset of MCI in PD, and if so, whether volumetric information can be a useful predictor of PD-MCI. In the present study, we adopted a longitudinal design to investigate GM and WM changes in patients with early PD not having any cognitive impairment. We hypothesized that 1) compared to cognitively stable PD patients, patients who convert to PD-MCI at follow-up would consistently show lower GM and WM volumes, 2) baseline global GM and WM volumes would predict the conversion to MCI among cognitively asymptomatic PD patients, and 3) baseline GM and WM volumes in the regions where volumetric differences between converters and non-converter were observed, would be associated with changes in specific cognitive domains.

2. Methods

2.1. Subjects

We recruited 56 mild PD patients from a tertiary neurology center. All patients were diagnosed by senior movement disorder neurologists according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria [18]. They were in early stages of the disease and received motor assessment with the motor subscale of the Unified PD Rating Scale (UPDRS-III) [19]. Clinical and neuropsychological assessments and MRI protocol were administered in the medication ON state at baseline and at 1.5-year follow up. At the time of recruitment, all patients did not have cognitive symptoms, nor significant medical or psychiatric illness. At follow-up, 14 patients withdrew from the study and were therefore removed from analysis. For the 42 patients who completed the entire study, 12 of them met the PD-MCI criteria (see below) at follow-up and hence were classified as "converters", while the remaining 30 remained cognitively asymptomatic and were classified as "non-converters". Converters and non-converters were demographically well matched, except that converters had less education than non-converters (Table 1). The study was approved by the Centralized Institutional Review Board. Informed consent was obtained from all patients.

2.2. Neuropsychological assessment

As suggested by the Movement Disorder Society (MDS) Task Force [20], we assessed the five cognitive domains in addition to global cognition. Global cognition was measured with the Montreal Cognitive Assessment (MOCA) [21]. Attention and working memory were assessed using the Digit Span Test [22] and Color Trail Making-1 Test [23]; executive function was assessed with the Frontal Assessment Battery (FAB) [24] and Sunderland Clock Drawing Test [25]; memory was assessed with the Word-List Test (immediate recall and delayed recall) and Word Recognition Test; language was assessed with the Object Naming Test and the Receptive Speech Test, and visuospatial ability was assessed with the Figure Copy test and Maze test [26]. Performance on each individual test was standardized using z-score transformation based on locally validated norms.

Table 1
Demographic, clinical, and neuropsychological characteristics of non-converters and converters at baseline.

	Non-converters (n = 30)	Converters (n = 12)	p value
Demographics			
Age (years)	62.50 (8.19)	65.32 (6.34)	0.29
Sex (male, %)	80.0	75.0	0.72
Education (years)	12.17 (3.46)	9.25 (1.86)	0.001[a]
Clinical data			
Hoehn & Yahr	1.81 (0.49)	1.88 (0.43)	0.69
Duration of PD (years)	5.38 (3.40)	4.09 (3.15)	0.27
UPDRS–Motor	15.05 (7.49)	19.75 (11.62)	0.13
Levodopa equivalent dose (mg)	673.24 (491.74)	622.83 (418.40)	0.76
Vascular risk factors (%)			
Diabetes mellitus	6.7	16.7	0.32
Hypertension	26.7	33.3	0.67
Hyperlipidemia	53.3	33.3	0.24
Smoking	36.7	33.3	0.84
Global cognition			
MOCA	27.40 (2.57)	27.50 (1.93)	0.90
Cognitive domains			
Attention/working memory			
Digit Span Test- Forward	2.14 (1.60)	2.76 (1.69)	0.29
Digit Span Test-Backward	1.69 (1.64)	2.65 (2.38)	0.15
Color Trail Making-1 Test	0.22 (1.05)	1.22 (1.74)	0.085[b]
Executive function			
Sunderland Clock Test	0.70 (0.82)	0.56 (0.81)	0.67
FAB	0.49 (0.64)	0.50 (0.46)	0.94
Memory			
Word List Delayed Recall Test	0.39 (1.08)	0.86 (1.13)	0.22
Word Recognition Test	0.40 (1.30)	0.05 (0.86)	0.39
Language			
Object Naming Test	0.59 (1.09)	0.23 (0.84)	0.32
Receptive Speech Test	0.62 (1.66)	0.58 (1.26)	0.94
Visuospatial ability			
Constructional Praxis Test	−2.40 (1.35)	−2.11 (1.62)	0.55
Maze Test (Error score)	−0.19 (0.003)	−0.19 (0.00)	0.36

Note: UPDRS-Motor = the Unified PD Rating Scale-Motor subscale; MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment; FAB = Frontal Assessment Battery. [a]: $p < 0.05$, [b]: $0.05 < p < 0.10$.

To fulfill the MDS Task Force Level II criteria for PD-MCI [20], impairment defined as 1.5 standard deviations below the appropriate norm, should be present on at least two tests, either within any single aforementioned cognitive domain or across these five cognitive domains. Moreover, subjective report of gradual cognitive decline by the patient or reliable informant was required for all PD-MCI patients. However, cognitive decline did not significantly interfere with their functional independence, and hence criteria for PD-dementia were not met.

2.3. Image acquisition and processing

Brain images were acquired using a Philips 3-T Achieva scanner (Philips Medical Systems, The Netherlands). High-resolution three-dimensional T1-weighted images were acquired with a magnetization prepared rapid gradient echo (MPRAGE) sequence (axial acquisition, 180 contiguous slices, voxel size = 1.0 × 1.0 × 1.0 mm^3, TR/TE = 7/3.2 ms, TI = 850 ms, flip angle = 8°, field of view = 256 mm).

The following data preprocessing algorithm was conducted with the VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is incorporated in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2012a (Mathworks). The default longitudinal pre-processing approach in the VBM8 toolbox was used with the following standardized steps: (1) registering the follow-up image to the baseline image for each subject; (2) calculating the mean image from the realigned images for each subject and used it as a reference image for subsequent spatial realignment; (3) correcting the realigned images for signal inhomogeneities with regard to the reference mean image; (4) performing tissue segmentation in the bias-corrected mean reference image and the bias-corrected realigned images; (5) estimating DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) spatial normalization parameters with the tissue segments (GM and WM) of the bias-corrected mean reference image; (6) applying the normalization parameters to the tissue segments of the bias-corrected realigned images; (7) the resulting normalized tissue segments for each time point of each subject were smoothed with an 8 mm full-width-half-maximum Gaussian kernel.

2.4. Statistical analysis

To compare group differences in demographic, clinical, and neuropsychological characteristics, χ^2, two-sample t-tests and non-parametric Mann–Whitney U tests