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Cortical atrophy patterns in early Parkinson's disease patients using hierarchical cluster analysis

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ABSTRACT

Introduction: Cortical brain atrophy detectable with MRI in non-demented advanced Parkinson's disease (PD) is well characterized, but its presence in early disease stages is still under debate. We aimed to investigate cortical atrophy patterns in a large sample of early untreated PD patients using a hypothesis-free data-driven approach.

Methods: Seventy-seven *de novo* PD patients and 50 controls from the Parkinson's Progression Marker Initiative database with T1-weighted images in a 3-tesla Siemens scanner were included in this study. Mean cortical thickness was extracted from 360 cortical areas defined by the Human Connectome Project Multi-Modal Parcellation version 1.0, and a hierarchical cluster analysis was performed using Ward's linkage method. A general linear model with cortical thickness data was then used to compare clustering groups using FreeSurfer software.

Results: We identified two patterns of cortical atrophy. Compared with controls, patients grouped in pattern 1 (n = 33) were characterized by cortical thinning in bilateral orbitofrontal, anterior cingulate, and lateral and medial anterior temporal gyri. Patients in pattern 2 (n = 44) showed cortical thinning in bilateral occipital gyrus, cuneus, superior parietal gyrus, and left postcentral gyrus, and they showed neuropsychological impairment in memory and other cognitive domains.

Conclusions: Even in the early stages of PD, there is evidence of cortical brain atrophy. Neuroimaging clustering analysis is able to detect two subgroups of cortical thinning, one with mainly anterior atrophy, and the other with posterior predominance and worse cognitive performance.

1. Introduction

Impaired cognition in Parkinson's disease (PD) is often present in untreated patients, over 20% of whom fulfill criteria for mild cognitive impairment (MCI) affecting a wide range of cognitive domains such as executive function, memory, attention, or visuo-spatial function [1]. Advances in magnetic resonance imaging (MRI) acquisition and analysis allowed the identification of cortical implication in early untreated patients. Cortical thinning is present in *de novo* PD patients with MCI involving frontal, temporal [2,3], and parietal [3] regions. However, in newly diagnosed PD patients without MCI, studies failed to find differences between patients and controls [2] or found thinning in small temporal [3] or parietal [4] cortical regions.

The heterogeneity of PD clinical phenotypes has led to increased interest in patient subtyping [5] in an attempt to understand the underlying mechanisms and improve prognostic accuracy. In line

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with these efforts, we have previously identified three subtypes based on hierarchical cluster analysis of cortical thickness. One subtype showed temporal and parietal involvement; another displayed orbitofrontal and occipital atrophy and younger disease onset; and a third group of patients showed no detectable cortical atrophy [6].

The Parkinson's Progression Markers Initiative (PPMI) is a comprehensive observational, international, multicenter study designed to identify PD progression biomarkers such as cerebral imaging in a cohort of recently-diagnosed PD patients [7]. Recent studies have identified Parkinson's subtypes in this cohort based on motor and non-motor data [8,9]. However, there is no evidence regarding subtypes based on objective structural imaging data in early PD.

Using data from the PPMI database, we aimed to examine cortical atrophy patterns in a large sample of newly diagnosed, drug naïve PD patients using a hypothesis-free data-driven approach. In light of previous results, we hypothesized that we would identify different brain cortical atrophy patterns associated with different clinical and neuropsychological characteristics.

2. Methods

2.1. Participants

Data used in this study were obtained from the PPMI database [7]. For up-to-date information on the study, visit www.ppmi-info.org. T1-weighted images acquired on 3-tesla Siemens MRI scanners and clinical and neuropsychological data obtained from 119 PD patients and 77 HC assessed between 2010 and 2015 were included. All imaging and non-imaging data corresponded to the same time points and were acquired prior to any L-DOPA intake. Inclusion criteria were: (i) recent diagnosis of PD with asymmetric resting tremor or asymmetric bradykinesia, or two of: bradykinesia, resting tremor, and rigidity; (ii) absence of treatment for PD; (iii) neuroimaging evidence of significant dopamine transporter deficit consistent with the clinical diagnosis of PD and ruling out PD *look-alike* conditions such as drug-induced and vascular parkinsonism or essential tremor; (iv) available T1-weighted images in a 3T Siemens scanner (for both PD patients and HC) and (v) age > 50 years old (for both PD patients and HC). Exclusion criteria for all participants were: (i) diagnosis of dementia; (ii) significant neurologic or psychiatric dysfunction; (iii) first-degree family member with PD, and (iv) presence of MRI motion artifacts, field distortions, intensity inhomogeneities, or detectable brain injuries. A total of 77 *de novo* PD patients and 50 HC were selected. The following participants were excluded from the study: 4 patients and 1 HC due to other neurological disease, 18 PD patients and 20 HC due to MRI motion artifacts at visual inspection performed by an expert radiologist (HCB), and 18 PD patients and 5 HC due to cortical thickness preprocessing problems (see MRI images section). Finally, we performed an initial cluster analysis for the PD group and another for the control group to detect possible abnormal outliers on MRI data. From these, we discarded 2 PD patients and 1 HC that constituted independent clusters by themselves.

Each participating PPMI site received approval from an ethical standards committee on human experimentation before study initiation and obtained written informed consent for research from all individuals participating in the study.

2.2. Clinical and neuropsychological assessments

Motor symptoms were assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III and motor subtypes were established based on the ratio from the means of several items of the MDS-UPDRS Part III. Activities of daily living (ADL) were evaluated with the Schwab and England Scale for PD patients and MDS-UPDRS Part II for all participants. Global cognition was assessed with the MoCA, and depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15) with a cutoff score of 5 or more indicating clinically significant symptoms as described in www.ppmi-info.org [7].

All subjects underwent comprehensive neuropsychological assessment following Movement Disorder Society task force recommendations [10] (except for the absence of tests evaluating the language domain). Memory was assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R); visuospatial function was evaluated with the Benton Judgment of Line Orientation short form (15-item version); attention and working memory through the Symbol Digit Modalities Test and Letter-Number Sequencing; and executive function with phonemic (letter 'f') and semantic (animal) verbal fluency [11].

Initially, z scores for each test and for each subject were calculated based on the control group's means and standard deviations. Expected z scores adjusted for age, sex, and education for each test and each subject were calculated based on a multiple regression analysis performed in the HC group [1]. The presence of MCI was defined using PD-MCI diagnostic criteria level I [10]: (i) MoCA scores as measure of global cognition below 26 [12] and/or (ii) the z score of a given test was at least 1.5 lower than the expected score on any 2 test scores. Impairment in each cognitive domain was also established if at least 1 test in the domain was impaired.

University of Pennsylvania Smell Identification Test (UPSIT) scores were available in a subsample of 55 PD patients and 28 HC due to missing values. The cutoff indicating anosmia was 18 or less [13].

2.3. MRI images

All three-dimensional T1-weighted MRI scans were acquired in the sagittal plane on 3T Siemens scanners (Erlangen, Germany) at different centers using an MPRAGE sequence. The acquisition parameters were as follows: repetition time = 2300/1900 ms; echo time = 2.98/2.96/2.27/2.48/2.52 ms; inversion time = 900 ms; flip angle: 9°; matrix = 240 × 256/256 × 256; voxel = 1 × 1 × 1 mm^3. Cortical thickness was estimated using the automated FreeSurfer stream (version 5.1, http://surfer.nmr.harvard.edu). Detailed information about the processing FreeSurfer stream is described in Segura et al. [14]. After Freesurfer preprocessing, results for each subject were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Possible errors were fixed by manual intervention following standard procedures (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData#Fixingerrors). In addition, we extracted the mean thickness for each of the 360 cortical areas defined in the Human Connectome Project Multi-Modal Parcellation version 1.0 (HCP-MMP1.0) [15,16].

2.4. Cluster analysis

MATLAB (release 2014b, The MathWorks, Inc., Natick, Massachusetts) was used to perform an agglomerative hierarchical cluster analysis using cortical thickness data from the 77 untreated PD patients. To reduce dimensionality and improve the model's performance calculating similarity/distance measures, mean cortical thickness values for the 360 areas from the HCP-MMP1.0 were used as features in the cluster analysis instead of whole-brain vertex information. To control for variations in global atrophy between patients [6], vertices were normalized

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