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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

using bilateral mean thickness bh.thickness=((lh.-thickness*lh.surfarea) + (rh.thickness*rh.surfarea))/(lh.surfarea + rh.surfarea).

Ward's clustering linkage method [6,17] was used to combine pairs of clusters at each step while minimizing the sum of square errors from the cluster mean. Each of the 77 patients was placed in their own cluster and then progressively clustered with others. Cluster analysis results are shown as a dendrogram (Fig. 1) and a heatmap representing individual values for each cortical region (Supplementary Figure 1 and Supplementary Table 1 for the order of regions as represented in the figure).

2.5. Statistical analysis

Intergroup cortical thickness comparisons were performed using a vertex-by-vertex general linear model with FreeSurfer. The model included cortical thickness as a dependent factor and group as an independent factor. All results were corrected for multiple comparisons using pre-cached cluster-wise Monte Carlo simulation with 10,000 iterations. Reported cortical regions reached a two-tailed corrected significance level of $p < 0.05$.

Demographic, neuropsychological, and clinical statistical analyses were conducted using IBM SPSS Statistics 24.0 (2011; Armonk, NY: IBM Corp). We tested for group differences in demographic and clinical variables as well as in neuropsychological performance between HC and PD patient subtypes using Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for non-normally distributed quantitative measures as indicated by the Kolmogorov-Smirnov test; for normally distributed measures, an analysis of variance (ANOVA) followed by Bonferroni post hoc test was used. Pearson's chi squared tests were used for categorical measures.

For comparisons between the collapsed PD sample and HC we used Mann-Whitney's test or Student *t*-test as appropriate.

2.6. Cluster evaluation

To determine the optimal number of clusters, we computed the Calinski-Harabasz index with MATLAB. The Calinski-Harabasz criterion is best suited for cluster analysis with squared Euclidean distances.

The higher the ratio is, the better the cluster solution. An optimal ratio is determined by a large between-cluster variance and a small within-cluster variance.

(https://es.mathworks.com/help/stats/clustering.evaluation.calinskiharabaszevaluation-class.html).

3. Results

3.1. Characteristics of the PD sample

Demographic and clinical (Supplementary Table 2), neuropsychological (Fig. 2a), and cortical thickness (Supplementary Figure 2, Supplementary Table 3) differences between all PD patients and HC are shown in Supplementary Results 1.

3.2. PD cortical thickness subtypes based on cluster analysis

We identified 2 patterns of cortical thinning compared with HC (Fig. 3, Supplementary Table 3). Patients in pattern 1 (n = 33, 42.9%) showed reduced cortical thickness in bilateral orbitofrontal, anterior cingulate, and lateral and medial anterior temporal regions, as well as a small cluster of cortical thickening in the right cuneus,

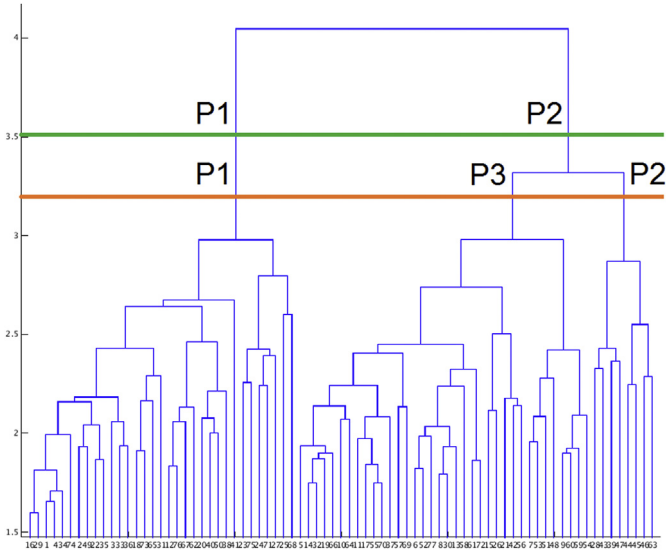

Fig. 1. Dendrogram of PD patients clustered according to mean cortical thickness information.
Abbreviations: P1 = Pattern 1; P2 = Pattern 2; P3 = Pattern 3.

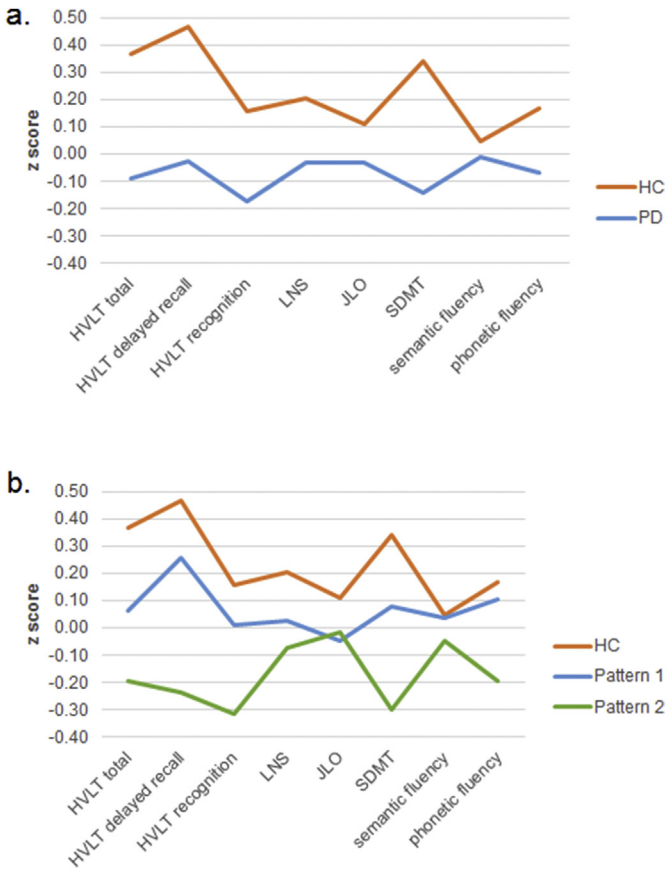

Fig. 2. Neuropsychological performance. (a) Healthy controls in orange and PD collapsed sample in blue. (b) Healthy controls in orange; Pattern 1 patients in blue and Pattern 2 patients in green.
Data are presented as z-scores. Lower z-scores indicate worse performance.
Abbreviations: HC = healthy controls; HVLT total = Hopkins Verbal Learning Test total; HVLT delayed recall = Hopkins Verbal Learning Test recall after 30 min; HVLT recognition = Hopkins Verbal Learning Test recognition after 30 min; JLO = Judgment of Line Orientation Test; LNS = Letter-Number Sequencing; PD = Parkinson's disease; SDMT = Symbol Digits Modalities Test. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

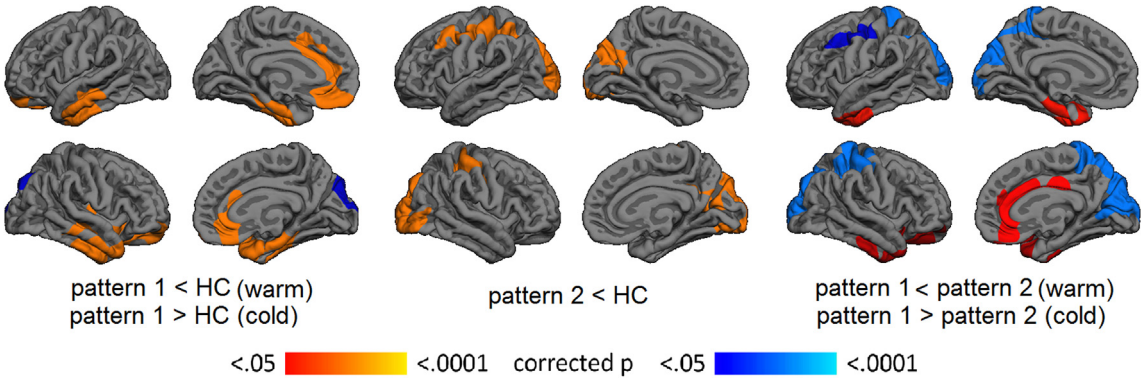

Fig. 3. Cortical thickness differences between groups at 2-cluster level.
Color maps indicate significant differences (corrected $p < 0.05$) between controls and PD subgroups.
Abbreviations: HC = healthy controls. Results were corrected by Monte Carlo simulation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

compared with HC. Pattern 2 patients (n = 44; 57.1%) had cortical thinning in left postcentral gyrus and bilateral posterior superior parietal, cuneus, and occipital gyri.

There were also cortical thickness differences between PD patterns (Fig. 3). Patients in pattern 1 showed cortical thinning in right orbitofrontal, right anterior cingulate, and bilateral anterior temporal regions when compared with pattern 2 patients. Pattern 2 patients had cortical thinning in bilateral cuneus, precuneus, and posterior superior parietal regions compared with pattern 1.

The two-cluster solution was selected because it had the highest variance ratio (3.36) of the Calinski-Harabasz values. Three and four-cluster solutions offered small cluster partitions and had variance ratios of 2.85 and 2.55, respectively (Supplementary Figure 3).

3.3. Clinical features of PD subtypes

PD patient subgroups showed no significant differences in demographical variables when compared with HC. Patients in pattern 2 scored significantly lower in the MoCA ($U = 17.997$; $P = 0.046$) and scored higher in GDS-15 scale than HC ($U = 20.340$; $P = 0.015$), and had more severe motor symptoms ($U = 938.5$; $P = 0.029$) than pattern 1 patients as measured by the MDS-UPDRS Part III. Both pattern 1 and 2 patients had more disability in ADL (P1: $U = 63.486$; $P < 0.0001$; P2: $U = 58.921$; $P < 0.0001$) than HC as measured by the MDS-UPDRS Part II. They also scored lower in the UPSIT test (P1: $U = 31.326$; $P < 0.0001$; P2: $U = 33.250$; $P < 0.0001$) and had a greater proportion of anosmic cases (P1: $\chi^2 = 7.638$; $P = 0.006$; P2: $\chi^2 = 7.693$; $P = 0.006$) than the HC group (Table 1).

Both PD patterns had more impairment in global cognition scores as measured with the MoCA < 26 (P1: $\chi^2 = 7.539$; $P = 0.006$; P2: $\chi^2 = 10.438$; $P = 0.001$) than HC (Table 1). Regarding neuropsychological results (Fig. 2b), pattern 2 patients performed significantly worse in HVLT-R total learning ($F = 2.971$; $P = 0.055$; post hoc test: $P = 0.050$), HVLT-R delayed recall ($F = 4.352$; $P = 0.015$; post hoc test: $P = 0.013$), and the Symbol Digits Modalities Test ($F = 6.056$; $P = 0.003$; post hoc test: $P = 0.002$) than HC.

4. Discussion

To the best of our knowledge, this is the first study to distinguish cortical atrophy patterns in early drug-naïve PD patients based on objective brain imaging data. Two patterns were identified: one with orbitofrontal, anterior cingulate and temporal atrophy, and another involving occipital and parietal atrophy.

Orbitofrontal involvement seen in Pattern 1 has not been previously described in *de novo* patients. There are previous studies that reported cortical thinning in *de novo* patients in other regions probably due to the different methodology used. These studies classified patients *a priori* according to their cognitive status [3,18]. In these studies, patients with MCI had widespread atrophy involving anterior and posterior regions. Pereira et al. [3] also found cortical thinning in patients with normal cognition but restricted to the right temporal cortex.

Despite showing cortical thinning in orbital regions, pattern 1 patients had no detectable neuropsychological impairments. This could be explained by the lack of tests sensitive to orbitofrontal functions in the PPMI battery, such as facial emotion recognition tasks, which we previously found to be correlated with gray matter reduction in these structures in PD patients [6,19].

In addition, we identified a region of cortical thickening in right cuneus in Pattern 1 patients compared to controls. No previous studies reported gray matter increases in early unmedicated PD patients; this phenomenon was only identified in certain studies raising a debate about a possible plastic effect of long term L-LDOPA administration [20], and therefore would not correspond to the clinical status of our patient sample. Increased cortical thickness in temporo-parietal regions and in precuneus and posterior cingulate was described in asymptomatic mutation carriers of presenilin 1 gene mutation compared with controls. This finding has been interpreted as initial neuroinflammation [21].

Pattern 2 was characterized by atrophy in occipital and parietal regions. Similar parietal thinning has also been described in PD-MCI *de novo* patients [3]. Our sample was not classified *a priori* according to cognitive status, but 32% of cases had MCI. Moreover, pattern 2 patients had a neuropsychological profile of semantic memory impairment that agrees with the thinning of posterior cortical regions as previously reported [14]. The finding of cortical thinning in the primary occipital cortex at the time of diagnosis is noteworthy. It could underlie the color deficits described in manifest PD and even in prodromal stages [22].

Pattern 2 patients showed impaired performance in HVLT-R total learning, delayed recall, Symbol Digits Modalities Test, and MoCA. Impairment in total learning and delayed recall have been found to be good markers of future cognitive deterioration in PD [23], and the Symbol Digits Modalities Test is a suitable marker of cortical thinning in lateral temporo-parietal regions [24]. Posterior cortical-based neuropsychological deficits have been related to higher risk of evolution to dementia [25]. Pattern 2 patients seem to show a worse cognitive phenotype, with greater proportion of MCI

Table 1
Demographic and clinical characteristics of PD subtypes.

	PD patients		HC (n = 50)	Test stats	P value
	Pattern 1 (n = 33)	Pattern 2 (n = 44)			
Sex, male, n (%)	20 (60.6)	28 (63.6)	30 (60.0)	0.143[a]	0.931
Age, y, mean (SD)	61.7 (7.9)	64.2 (8.2)	62.3 (7.5)	1.084[b]	0.341
Education, y, median, (IQ)	16.0 (4.0)	16.0 (6.0)	16.0 (4.3)	0.677[c]	0.713
MoCA, median (IQ)	28.5 (3.0)	27.0 (3.0)	28.0 (2.0)	6.257[c]	0.044[e]
Disease duration, y, median (IQ)	1.0 (2.0)	1.0 (1.8)	NA	705.5[d]	0.822
Age of onset, y, mean (SD)	60.7 (8.1)	63.3 (8.2)	NA	852.5[d]	0.192
MDS-UPDRS part III, median (IQ)	19.0 (9.5)	24.0 (10.8)	NA	938.5[d]	0.029
Hoehn & Yahr stage, n, 1/2/3	12/21/0	16/27/1	NA	0.766[a]	0.682
Motor subtype, n, tremor/PIGD/undetermined	25/3/5	31/10/3	NA	3.410[a]	0.182
GDS-15, median (IQ)	1.5 (3.0)	2.0 (4.0)	0.0 (1.0)	9.458[c]	0.009[e]
Depression, n (%)	6 (18.8)	3 (7.0)	5 (10.0)	2.678[a]	0.262
Apathy item MDS-UPDRS Part I, n (%)	11 (33.3)	6 (13.6)	2 (4.0)	13.538[a]	0.001
Subjective cognitive decline item MDS-UPDRS Part I, n (%)	11 (33.3)	12 (27.3)	7 (14.0)	4.616[a]	0.099
UPSIT, median (IQ)	22.0 (9.0)	20.0 (12.0)	35.5 (4.0)	33.779[c]	<0.0001[f]
Anosmia, n (%)	9 (39.1)	12 (37.5)	2 (7.1)	8.94[a]	0.011
Schwab and England scale, median (IQ)	90.0 (8.0)	95.0 (10.0)	NA	866.0[d]	0.125
MDS-UPDRS Part II, median (IQ)	7.0 (5.5)	5.0 (5.8)	0.0 (0.0)	86.838[c]	<0.0001[f]
Total MCI, n (%)	7 (21.9)	14 (31.8)	3 (6.0)	10.340[a]	0.006
Global cognition impaired, n (%)	6 (18.8)	10 (22.7)	0 (0.0)	12.322[a]	0.002
Visuospatial functions, n (%)	4 (12.9)	4 (9.5)	4 (8.0)	0.526[a]	0.769
Executive functions, n (%)	3 (9.4)	3 (6.8)	2 (4.1)	0.925[a]	0.630
Memory, n (%)	5 (16.1)	16 (38.1)	7 (14.0)	8.575[a]	0.014
Attention and WM, n (%)	2 (6.5)	6 (14.3)	1 (2.0)	5.126[a]	0.077

Abbreviations: GDS-15 = Geriatric Depression Scale shortened version; HC = Healthy Controls; IQ = interquartile range; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; NA = not applicable; PD = Parkinson's disease; PIGD = Postural Instability Gait Difficulty; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test; WM = Working Memory.
Global cognition impairment was established from the cut-off < 26 in MoCA test. Visuospatial, executive, memory and attention WM impairment was establish from the number of subjects with at least one test impaired in each domain.
Data are presented as mean (SD) or median (IQ) for continuous variables as appropriate or frequencies for categorical.
[a] The Chi-squared test was used.
[b] Analysis of variance test was used.
[c] Kruskal-Wallis test was used.
[d] Mann-Whitney *U* test was used.
[e] Significant differences were found between HC and pattern 2 using pairwise Mann-Whitney test. P-values are given in the text.
[f] Significant differences were found between HC and both patterns using pairwise Mann-Whitney test. P-values are given in the text.

and higher proportion of memory impairment than controls. This pattern is similar to that identified in our previous study using hierarchical cluster analysis in more advanced and medicated PD patients [6].

Pattern 2 patients also had more severe motor symptoms. The results from previous studies seem to show that PD patients with predominant resting tremor at onset have a more benign disease course and slower progression compared with those with a postural instability and gait difficulty (PIGD) dominant subtype. PIGD variant is commonly associated with a faster rate of cognitive decline, higher prevalence of non-motor symptoms, and faster progression [5]. In light of the aforementioned findings, we would expect that pattern 2 patients, with higher rates of MCI, would be related to a predominantly non-tremoric subtype. However, our results showed that, although Pattern 2 showed more severe motor symptoms, the two patient groups did not differ in the proportion of motor subtypes. The instability of motor-feature diagnosis in the first year of the disease might explain the lack of predominance in motor subtyping in this sample of *de novo* PD patients [26]. On the other hand, previous studies showed an association between cognitive dysfunction and clinical phenotypes, such as anosmia. Fullard et al. [27] related the presence of severe olfactory deficits to worse cognitive impairment in untreated PD patients, using PPMI data. Nevertheless, we did not observe differences either in the proportion of anosmia or the UPSIT score between the patient groups. Longitudinal studies could clarify the evolution of these patterns; clearer clinical phenotypes based on motor subtypes or non-motor symptoms would be expected to be identified in more advanced stages of the disease. Future studies could thus clarify the relationship between the identified patterns of atrophy and other PD symptomatology.

In the present study, we did not find a non-atrophic group as found in other studies with newly-diagnosed drug-naïve PD patients [28,29] or even with medicated patients with more advanced disease [6,30–32]. This could be explained by the high sensitivity of our methodological approach to detect subtle differences between patients and HC. We improved the cluster analysis technique using the HCP-MMP1.0 to perform a feature reduction of the imaging data. In the last few years, there has been an increased interest in the potential of machine learning techniques due to their ability to manage large amounts of data, and because they allow hypotheses to be guided by data itself using unsupervised approaches. Nonetheless, clustering algorithms perform better when data sets avoid multicollinearity and the curse of dimensionality. This method seems to be sensitive for detecting subtle cortical atrophy even at early stages of the disease, although further studies are needed to replicate these results. In addition, unsupervised machine learning techniques allowed us to detect PD subtypes from a hypothesis-free data driven approach using objective imaging data rather than clinical data that is examiner-dependent. The use of objective data is especially relevant in multicenter studies, in which there is increased variability of data collection.

One strength of this study is the use of a multicenter cohort of patients from the PPMI data base with a large sample of HC, well-matched with patients regarding age and education. Another strength is that the sample of PD patients is very homogeneous, as it is composed of *de novo* and untreated subjects. Despite this homogeneity on several variables (such as age, time of evolution, and

clinical severity) we were able to detect subtypes of cortical thinning and neuropsychological profile.

The limitations include the short neuropsychological battery that did not allow using level II criteria to diagnose PD-MCI, and the fact that MRI acquisitions were acquired at different research centers (although all scanners were similar and acquisition protocols were standardized). In addition, the PPMI is a research cohort with highly educated participants that might not be representative of the general population. The PPMI sample have scarce cognitive or psychiatric symptoms at baseline, restricting the use of correlational approaches with neuroimaging findings. We would also like to highlight the complexity of PD diagnosis at early stages of the disease. Patients were selected based on 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. However, certain diagnoses can only be established by pathological findings.

To sum up, two different cortical atrophy patterns can be identified at the time of diagnosis in unmedicated PD patients. Our results establish a starting point to investigate the evolution of these patterns as possible useful markers of clinical prognosis. Moreover, the MRI findings indicate the necessity to review the neuropsychological tests included in cohort studies trying to cover the functional assessment of all cortical regions that have been found to be impaired in PD.

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Declaration of interest

None.

Authors' roles

Research project conception and acquisition of data are explained in Marek et al., 2011 as cited in the text. CJ contributed in the design of the study. CU, AA, AIGD and AC contributed to the analysis of the data and CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, ET and CJ contributed to the interpretation of the data. CU, BS contributed to the draft of the article. CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, ET, CJ revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.02.006.

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