**Progression of Parkinson's disease patients' subtypes based on cortical thinning: 4-year follow-up**

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**Abstract**

**Background.** Three cortical atrophy patterns were previously identified in non-demented Parkinson's disease patients using a data-driven approach based on cortical thickness data: i) parieto-temporal pattern of atrophy with worse cognitive performance (pattern 1), ii) occipital and frontal cortical atrophy with younger disease onset (pattern 2), and iii) non-detectable cortical atrophy (pattern 3). We aimed to investigate the evolution of these three patterns over time. **Methods.** Magnetic resonance imaging and neuropsychological assessment were obtained at baseline and follow-up (3.8±0.4 year apart) in a group of 45 Parkinson's disease patients and 22 healthy controls. FreeSurfer was used for cortical thickness analysis and global atrophy measures. **Results.** Temporo-parietal cortical thinning occurred in pattern 2, 3 and controls groups, and patients showed decline in processing speed (as measured by the Stroop Word-Color test, the Symbol Digits Modalities test and the Trail Making Test Part B) and in semantic fluency (animals). Pattern 3 patients showed more progressive cortical thinning in the left prefrontal cortex than controls and more right occipital thinning than pattern 2 patients over time. Pattern 1 patients had greater compromise in activities of the daily living and suffered higher attrition rate. **Conclusion.** The Parkinson's disease phenotypes identified using cluster analysis of cortical thickness data showed different progression over time. The presence of prefrontal thinning and younger disease onset at baseline was associated to less cortical degeneration, while non-atrophic patients progressed showing a temporo-parietal cortical thinning.

## 1. Introduction

Impaired cognitive functions in Parkinson's disease (PD) are present even in untreated patients and around 20% fulfill criteria for mild cognitive impairment (MCI) [1]. The cumulative prevalence of dementia during eight years' evolution is near 80% [2]. A meta-analysis performed in 2007 including 25 heterogeneous longitudinal studies reported that significant cognitive decline was obtained for global cognitive ability, visuoconstructive skills and memory functions [3]. Posteriorly, well-controlled prospective works coincided that the greatest decline was seen in psychomotor speed followed by memory functions, but disagreed regarding the progression of attention deficits [4–6]. It has been suggested that the neuropsychological functions sensitive to cognitive decline and progression to dementia are those supported by regions of the posterior cortex [7,8].

Longitudinal magnetic resonance imaging (MRI) studies have contributed to establish the brain substrates for cognitive decline in PD. Voxel-wise and vertex-wise analyses demonstrated that demented and non-demented PD patients had gray matter (GM) reductions over relatively short periods of time [9–11] and these reductions were more remarkable in patients with visual hallucinations [12]. In addition to hallucinations, the presence of MCI is also a predictor of higher rates of cortical thinning [13]. The differences between studies in cortical and subcortical regions that suffer atrophy during the course of the disease could be due to the heterogeneity of the disease. A clinical subtype named diffuse/malignant presenting non-motor features such as MCI, orthostatic hypotension and rapid eye movement sleep behavior disorder, showed a more rapid progression of cognitive decline [14]. Thus, different phenotypes could lead to different patterns of cortical degeneration.

In a previous study using cluster analysis of cortical thickness data in PD patients, we identified three PD subtypes: (i) parieto-temporal pattern of atrophy associated with significant cognitive impairment, (ii) occipital and frontal cortical atrophy with younger

PD onset, and (iii) patients without manifest cortical atrophy [15]. In the current study, we aimed to investigate longitudinally the evolution of these three different cortical atrophy patterns over a 4-year period.

## 2. Methods

### *2.1 Participants*

Forty-five PD patients from the Parkinson's Disease and Movement Disorders Unit, Hospital Clinic (Barcelona, Spain) and 22 HC from the Aging Institute in Barcelona were assessed twice at 3.8±0.4 years apart (range: 3.1-5.3).

At time 1, 88 PD patients and 31 HC were recruited between October 2010 and March 2012 and classified into three subtypes as previously described [15]. In the present study, only subjects who underwent comprehensive neuropsychological and MRI evaluation at both times were included. Briefly, 7 out of the 30 patients in pattern 1, 16/29 in pattern 2, 22/29 in pattern 3 and 22/31 in the controls group returned to follow-up at time 2 (see the flowchart in Supplementary Figure 1 for dropout reasons).

Inclusion criteria for patients at both time 1 and 2 were: (i) fulfilling the UK PD Society Brain Bank diagnostic criteria for PD; (ii) no surgical treatment with deep-brain stimulation. Exclusion criteria for PD patients and HC were: (i) dementia according to the Movement Disorders Society (MDS) criteria (only applicable for time 1) and clinic assessment performed by clinical neurologist (MJM, FV, YC), (ii) Hoehn and Yahr (H&Y) scale score > 3 (only applicable for time 1), (iii) young-onset PD, (iv) age below 50 years, (v) presence of severe psychiatric or neurological comorbidity, (vi) low global intellectual quotient estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, (scalar score ≤ 7), (vii) Mini Mental State Examination (MMSE) score below 25 (only applicable for time 1), (viii) claustrophobia, (ix) pathological MRI findings other than mild white matter hyperintensities in the FLAIR sequence, and (x) MRI artifacts.

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-DOPA, cathecol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists and amantadine. In order to standardize doses, the L-DOPA equivalent daily dose (LEDD) [16] was calculated.

Written informed consent was obtained from all study participants after full explanation of the procedures. The study was approved by the institutional Ethics Committee from the University of Barcelona (IRB00003099).

*2.2 Neuropsychological and clinical assessment*

In line with MDS PD-MCI task force recommendations [17], we assessed five cognitive domains: visuospatial and visuoperceptual functions, executive functions, verbal memory, attention and working memory and language (see Uribe et al., [15] for detailed protocol). As in the baseline study [15], adjusted z-scores were calculated and the presence of MCI was established if the z-score for a given test was at least 1.5 lower than the expected score in at least two tests. Furthermore, the presence of dementia was determined if MMSE score was below 26, or if there was cognitive impairment in more than one domain and impaired instrumental activities of daily living (IADL).

Neuropsychiatric symptoms were evaluated with the Beck Depression Inventory-II, Starkstein's Apathy Scale and Cumming's Neuropsychiatric Inventory. Functioning in IADL were assessed with the Lawton and Brody scale and the Schwab and England scale. Additionally, the Gottfries-Brane-Steen scale (GBS) was administered to caregivers/family members of PD patients that could not return at time 2 (non-completers) via telephone interview. This scale was administered with the aim to obtain qualitative information from patients lost to follow-up, specially concerning pattern 1 patients.

*2.3 Preprocessing and analysis of longitudinal imaging data*

MRI data were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany) at both times. The scanning protocol included high-resolution 3-dimensional T1-weighted images

acquired in the sagittal plane (TR=2300ms, TE=2.98ms, TI=900ms, 240 slices, FOV=256mm; 1mm isotropic voxel) and an axial FLAIR sequence (TR=9000ms, TE=96ms). Cross sectional preprocessing of both times was estimated using the automated FreeSurfer stream (version 5.1; available at: http://surfer.nmr.harvard.edu). Detailed description of FreeSurfer procedures is reported in the baseline study [15] and information about the longitudinal cortical thickness preprocessing and the computed symmetrized percent of change (SPC) of cortical thickness are described elsewhere, https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalTwoStageModel [18]. Cortical thickness and SPC maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of 15 mm.

### *2.4 Statistical analysis*

#### *2.4.1. Demographic variables*

Group differences in demographic variables (Table 1) were analyzed with Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction for quantitative measures. Chi squared test were used where appropriate for categorical measures. These analyses were conducted using IBM SPSS Statistics 22.0 (2013; Armonk, NY: IBM Corp).

#### *2.4.2 Repeated measures analyses of clinical and neuropsychological variables*

Group by time interaction effects in clinical disease-related variables and neuropsychological performance between pattern 2 and 3 patients and HC were assessed through a repeated-measures general linear model and permutation testing with 10,000 iterations. To control type-I errors, a Bonferroni correction was applied. The repeated measures general linear model was performed with Matlab R2017a (The MathWorks, Inc., Natick, Massachusetts).

#### *2.4.3 Cortical thickness analyses*

Comparisons between groups were assessed using a vertex-by-vertex general linear model.

Intergroup comparisons at baseline were performed between patients in pattern 2, pattern 3 and healthy controls. Vertex-wise cortical thickness information was included as dependent variable and age and years of education were regressed out as variables of no interest (see Table 1).

Longitudinally, two statistical models were performed: one sample t-test was performed to test time effect in groups (if the SPC was different from zero); and to test time by group interaction effects, SPC was included as a dependent factor and group as an independent factor. In the second model, age (controls *vs* pattern 2) and years of education (controls *vs* pattern 2; pattern 2 *vs* pattern 3) were considered as nuisance covariates (see Table 1). Both longitudinal designs were performed as a whole-brain vertex-wise approach.

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 $p < 0.05$.

*2.4.4 Repeated measures analyses of global atrophy measures*

Global atrophy measures including total GM volume, subcortical and cortical GM volume, mean lateral ventricular volume and estimated intracranial volume were obtained automatically via whole brain segmentation with the FreeSurfer suite. Global average thickness for both hemispheres was calculated as:

((lh.thickness*lh.surface area)+(rh.thickness*rh.surface area))/(lh.surface area+rh.surface area).

Matlab R2017a (The MathWorks, Inc., Natick, Massachusetts) was used to perform group by time interaction effects assessed by permutation test statistics with 10,000 iterations using a general linear model of repeated measures. Bonferroni was then used to control for multiple comparison. The estimated intracranial volume was considered as a nuisance covariate in the volumetric analyses.

*2.4.5 Additional analyses*

Due to the high attrition rate, and to further understand the characteristics of the present longitudinal sample in comparison with the initial one, we compared patients within each subgroup that returned to follow-up (completers) with those that were lost to follow-up (non-completers). Group differences in demographic and clinical variables between completers and non- completers were analyzed with Mann-Whitney's U test for quantitative measures and Chi squared test for categorical measures at time 1. In addition, GBS scores at time 2 of the PD non-completers were assessed with Kruskal-Wallis test followed by Mann-Whitney's pairwise comparisons and Bonferroni correction. In GBS analyses, we did not have available healthy controls non-completers information and group comparisons were performed between PD patients' subgroups. These analyses were conducted using IBM SPSS Statistics 22.0 (2013; Armonk, NY: IBM Corp).

## 3. Results

There were no significant differences in the assessment interval between groups (H=6.516; *P*=.089).

### *3.1 Demographical characteristics*

Pattern 2 patients were younger than both HC and pattern 1, younger at disease onset than pattern 1, and had more years of education than patients in pattern 1 and 3 and HC (Table 1).

Regarding functioning in IADLS, patients in pattern 1 had significantly more impairment than HC and pattern 3 patients as measured by the Lawton and Brody scale at time 2. There were also significant differences between HC and pattern 1, pattern 2 and pattern 3 as measured by the Schwab and England scale (Table 1).

### *3.2 Repeated measures of clinical and neuropsychological variables*

*Clinical variables.* Pattern 2 patients and controls had significant time effects in the MMSE scores as measure of global cognition although they were not clinically significant. Regarding L-DOPA intake, a significant interaction was found between the decreased doses of pattern 2 patients compared with an increment in the doses of pattern 3 patients.

Regarding psychiatric symptoms over time, patients in pattern 2 had more severe global neuropsychiatric symptoms than HC (Table 2).

Due to the high attrition rate in Pattern 1 patients, this group (n = 7) was not included in the statistical general linear models to investigate cortical thinning progression, clinical evolution and neuropsychological decline.

*Neuropsychological variables.* Both pattern 2 and 3 patients as well as the controls group had worsened their performance over time in the Trail Making Test (TMT) Part A minus B. Specific effect times were found in pattern 2 and 3 patients' groups. Pattern 2 and pattern 3 patients also had decreased performance in semantic fluency, Stroop Word-Color test, Symbol Digits Modalities test (SDMT) and in the TMT Part B over time. Additionally, pattern 2 patients also showed decline in the Stroop Color test. Pattern 3 patients performed worse over time also in the TMT Part A. Patients in pattern 2 declined significantly more than HC in Stroop Color test and SDMT. Pattern 3 patients differed from HC in TMTA, TMTB and SDMT (Figure 1A). In Supplementary Table 1 means and SD of the neuropsychological performance can be found for all groups.

At time 2, 2 (28.6%) patients in pattern 1 converted to dementia and 3 (28.6%) patients had MCI. From the 3 MCI patients, two were converters and the other already had MCI at time 1. In pattern 2 subtype, there were 7 MCI (43.8%), 4 of whom were converters, whereas in pattern 3 there were 11 MCI (50.0%), 6 of whom were converters. In the HC group, 1 (4.5%) control also converted to MCI (Table 1 and Supplementary Table 2).

### *3.3 Cortical thickness changes*

At time 1, there were no significant regional cortical thickness differences between pattern 2, pattern 3 and healthy controls subjects.

Regarding changes over time, patients in pattern 2 had reductions in left parahippocampal gyrus, left precuneus and right inferior parietal and temporal gyri, fusiform and lateral occipital gyri. Significant cortical thinning in pattern 3 patients was found bilaterally in lateral and medial regions of the temporal and parietal lobes, lateral occipital and

extending to frontal regions such as the precentral and postcentral gyri and the left pars opercularis. HC group also showed a significant effect of time, specifically cortical thinning was found in posterior regions, such as right parahippocampal, bilateral fusiform, posterior cingulate, lateral occipital, lingual gyri and both inferior and superior parietal areas extending to the right precentral gyrus. A small cluster of cortical thickening was found in the right prefrontal cortex (Figure 1B).

Pattern 3 had more cortical thinning in the left pars opercularis and precentral gyri compared with HC over time (see Figure 2). There were no significant intergroup differences in cortical thickness decline between HC and pattern 2.

Differential changes in cortical thinning were also found between pattern 2 and 3 (Figure 2). Pattern 3 patients had more significant decrements in the right lateral occipital, lingual and pericalcarine gyri compared with pattern 2 patients.

Montreal Neurological Institute coordinates, cluster sizes and significance from longitudinal analyses are summarized in Supplementary Table 3.

### *3.4 Global atrophy changes*

Both pattern 2 and pattern 3 patients as well as the controls group suffered significant volume decrements in the total GM volumes. Specifically, pattern 2 patients had significant time effects in subcortical GM volumes whereas pattern 3 patients and healthy controls had significant decrements in the cortical GM volumes over time. From the group x time contrasts, total GM and cortical GM volumes were significantly more decreased in pattern 3 patients than in pattern 2 patients. In addition, pattern 3 patients had more increased lateral ventricle volume over time than pattern 2 patients (Supplementary Table 4).

### *3.5 Additional results*

As supplementary material, we provide the demographic and clinical features between PD patients' completers and non-completers within each pattern and within the controls group (Supplementary Table 5).

In pattern 1 patients, the proportion of females (chi=4.658; P=.031) and the H&Y stages scores (chi=10.784; P=.029) were higher in non-completers than in completers. In the pattern 2 subtype, non-completers had less years of education (U=40.500; P=.004), had lower global cognition scores (U=58.500; P=.045) and were more depressed (U=108.000; P=.026) than completers. Non-completers in the pattern 3 subtype had higher LEDD (U=122.000; P=.021), see Supplementary Table 5.

Regarding GBS information, only PD non-completers were contacted for telephonic interview. PD non-completers in pattern 1 had more severe intellectual impairment, more impairment in IADL, more symptoms associated to dementia and more GBS global scores than non-completers in both pattern 2 (GBS-I: P=.004; GBS-ADL: P=.007; GBS-S: P=.017; GBS total score: P=.005) and pattern 3 (GBS-I: P=.007; GBS-ADL: P=.004; GBS-S: P=.016; GBS total score: P=.004). Pattern 1 non-completers also had more emotional impairment than pattern 3 non-completers (P=.021). See Supplementary Table 6.

## 4. Discussion

Remarkably, the results from MRI structural analyses showed that cortical thickness has a high sensitivity to time effects. In a period of four years, both patients and controls had cortical thinning mainly in parieto-temporal regions, as well as global gray matter atrophy. However, PD patients differed in clinical, cognitive and structural degeneration over time according to their initial regional cortical thinning pattern.

Patients from pattern 1 characterized by an extensive parieto-temporal atrophy [15] showed a higher attrition rate and for that reason they were not included in the quantitative MRI analyses. This group showed higher severity of motor symptoms measured by the H&Y scale at baseline, more IADL, and more cognitive impairment assessed by telephone interview at follow-up. Previous longitudinal studies also reported that patients who were lost to follow-up were older, had higher age at disease onset, more axial impairment, scored higher on H&Y and showed higher percentage of PD dementia

[5]. Considering the initial sample, we estimated that 15% of PD patients converted to dementia during the follow-up period. This percentage was similar to other population-based studies [5,8,19,20].

The time effect in pattern 2 patients, initially identified as frontal and occipital atrophy pattern [15], showed localized cortical thinning over time mainly in temporal, parietal and occipital lobes. These patients were initially younger, with higher education and younger age at onset, probably as indicators of better prognosis. Patients from pattern 2 who dropped out of the study had less years of education, more global cognitive impairment and had more depressive symptoms. Thus, patients from pattern 2 who completed the follow-up assessment probably represent a PD group with better progression of these disease aspects. Indeed, the lack of cortical thickness differences between pattern 2 patients that returned to follow-up in comparison with healthy controls and pattern 3 patients at time 1 supports the idea that completers had better disease progression than non-completers.

On the other hand, pattern 3 and healthy controls that initially were identified as the less atrophic groups, showed an extensive cortical thinning effect in bilateral parietal and temporal regions. This time effect in pattern 3 was similar to cortical atrophy previously detected in pattern 1 at baseline [15] and it is similar to the cortical degeneration observed in the controls group. Additionally, a small cluster of cortical thickening was found in the right prefrontal cortex within the controls group. This finding could be due to methodological issues.

Inter-group comparisons of symmetrized percent of cortical thickness change showed that pattern 3 patients had statistically significant greater cortical atrophy compared with healthy controls and pattern 2. Although this group was initially non-atrophic, after a four-year period, they presented significant cortical thinning. These patients differed from normal aging in the left frontal lobe and showed higher symmetrized percent of change in the right occipital lobe than pattern 2 PD patients that already showed atrophy in this

region. Occipital thinning compared to controls has been observed in cross sectional [21] and longitudinal studies in demented PD patients [9], in PD-MCI [22] and in PD with visual hallucinations [23,24]. However, these studies also reported more widespread atrophy including other lobes.

Global atrophy measures also revealed higher volume decrements in pattern 3 patients than in pattern 2, as well as increased ventricular enlargement. Previous literature has reported an association between global atrophy measures [25,26] with cognitive impairment. However, the proportion of MCI was not significantly different between pattern 2 and 3.

Regarding the neuropsychological assessment, our results identified that semantic fluency, TMT, SDMT and Stroop tests were sensitive to time effect. Decline in TMT, SDMT and Stroop tests as measured of processing speed agrees with previous findings in longitudinal studies showing processing speed impairment in PD over time assessed by Digit Symbol Test and TMTA [4,5]. Contrarily to the expected results accounted by aging effects, we did not find statistical memory decline. This could be due to a test-retest effect. In favor of this interpretation we can see that, although non-significant, the healthy control group showed a slight increase in their performance. Other longitudinal studies reported memory loss but the follow up was longer [3,5]. After four years, patients from patterns 2 and 3 showed reduced semantic fluency performance. At baseline, semantic fluency test differentiated the parieto-temporal pattern from other PD subtypes [15]. In light of our new findings, such worsened performance could be related to the progressive posterior parietal and temporal thinning observed in PD.

At last but not least, we would like to highlight as important limitation the high attrition rate, especially concerning pattern 1 patients. For this reason, we stated in the methods section that this group was assessed qualitatively and not entered into the intergroup statistical analyses.

In summary, patients from pattern 1 were mainly lost to follow-up due to functional impairment in IALD. Patients from pattern 2 showed modest progressive temporal and parietal cortical thinning and probably better evolution. Finally, pattern 3 patients were non-atrophic at baseline but progressed showing temporo-parietal cortical thinning. In conclusion, cortical thinning in PD subtypes follows different progression over time.

**Disclosures.**

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**Declaration of interest.** None.

**Authors' contribution.**

CJ and BS contributed to the research project conception and in the design of the study. CU, AA and AC contributed to the acquisition of the data. CU, AA, AIGD and AC contributed to the analysis of the data and CU, BS, HCB, AA, AIGD, AC, MJM, FV, YC, NB and CJ contributed to the interpretation of the data. CU, BS contributed to the draft of the article.

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**Figure Legends.**

**Figure 1 Neuropsychological and cortical thinning effect times.** A) Neuropsychological performance of pattern 2 and 3 PD patients and controls at both times. Time 1 in blue and time 2 in orange. Data are presented as adjusted *z-scores*. *z-scores* were calculated based on the control group's means and standard deviations at time 1. 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. Lower *z-scores* indicate worse performance. Abbreviations: BNT = Boston Naming Test; JLO = Judgment of Line Orientation Test; RAVLT = Rey's Auditory Verbal Learning Test; SDMT = Symbol Digits Modalities Test; TMT = Trail Making Test; VFD = Visual Form Discrimination Test. B) symmetrized percent of change of cortical thickness. Color maps indicate significant time effect in each group. Results were corrected by Monte Carlo simulation.

**Figure 2 Symmetrized percent of change of cortical thickness from the group per time interaction** Results were corrected by Monte Carlo simulation.

**Table 1 Demographic and clinical characteristics of the sample at both times**

| | Parkinson's Disease subtypes | | | Healthy controls (n=22) | Test stats/ *P*-values |
|---|---|---|---|---|---|
| | Pattern 1 (n=7) | Pattern 2 (n=16) | Pattern 3 (n=22) | | |
| **Age, y, median (IQ range)** | | | | | |
| **Time 1** | *76.0 (18.0)* | *57.5 (13.0)* | 63.0 (10.0) | *66.0 (13.0)* | *13.740/.003* |
| **Time 2** | *80.0 (18.0)* | *61.0 (13.0)* | 67.5 (11.0) | *70.0 (13.0)* | *14.017/.003* |
| **Education, y, median (IQ range)** | *8.0 (6.0)* | *17.5 (8.0)* | *10.5 (6.0)* | *10.0 (8.0)* | *16.492/.001* |
| **Sex, male, n (%)** | 6 (86.7) | 13 (81.3) | 12 (54.5) | 11 (50.0) | 6.081/.108 |
| **Disease duration, y, median (IQ range)** | | | | | |
| **Time 1** | 4.0 (7.0) | 6.0 (8.3) | 6.0 (9.0) | NA | 1.564/.457 |
| **Time 2** | 7.0 (7.0) | 9.0 (7.0) | 9.0 (7.0) | NA | 0.278/.870 |
| **Age of onset, y, median (IQ range)** | *67.0 (19.0)* | *47.5 (14.6)* | 54.5 (12.7) | NA | *10.583/.005* |
| **Hoehn &Yahr stage, n 1/1.5/2/2.5/3/4** | | | | | |
| **Time 1** | 2/0/5/0/0/0 | 5/1/7/2/1/0 | 11/0/8/1/2/0 | NA | 6.466/.595 |
| **Time 2** | 0/0/2/0/4/1 | 2/0/6/0/8/0 | 4/0/11/0/7/0 | NA | 8.629/.196 |
| **Instrumental Activities of Daily Living Scales, median (IQ range)** | | | | | |
| **Lawton and Brody Scale** | *3.5 (2.0)* | 7.0 (3.0) | *8.0 (2.0)* | *8.0 (2.0)* | *17.096/.001* |
| **Schwab and England Scale, %** | *70.0 (20.0)* | *85.0 (30.0)* | *90.0 (20.0)* | *100.0 (0.0)* | *33.105/<.001* |
| **noMCI[1]** | 2 (28.6) | 9 (56.2) | 11 (50.0) | 21 (95.5) | 80.136/<.001 11.734/.019[2] |
| **MCI[1]** | 3 (42.8) | 7 (43.8) | 11 (50.0) | 1 (4.5) | |
| **Dementia[1]** | 2 (28.6) | 0 | 0 | 0 | |

IQ range, interquartile range; MCI, mild cognitive impairment; NA, not applicable.
*P*-values are from Kruskal-Wallis test followed by Mann-Whitney pairwise test and Bonferroni correction for continuous variables and chi-squared test for categorical variables.
[1] Proportions of noMCI, MCI and dementia at time 2.
[2] Chi squared test between all groups was 80.136; *P*<.001. Chi squared test between PD groups was 11.734; *P*=.019.
*Age showed significant differences between pattern 2 and HC (P=.013 at time 1; P=.015 at time 2) and pattern 1 (P=.009 at time 1; P=.007 at time 2). Years of education showed significant differences between pattern 2 and HC (P=.016), pattern 1 (P =.003) and pattern 3 (P =.011). Age of onset showed significant differences between pattern 1 and pattern 2 (P =.005). At time 2, Lawton and Brody Scale showed significant differences between pattern 1 and HC (P=.001) and*

*pattern 3 (P=.003); Schwab and England Scale showed significant differences between pattern 1 and HC (P<.001), and pattern 2 (P<.001), and pattern 3 (P=.003).*

**Table 2 Clinical measures of the sample at both times**

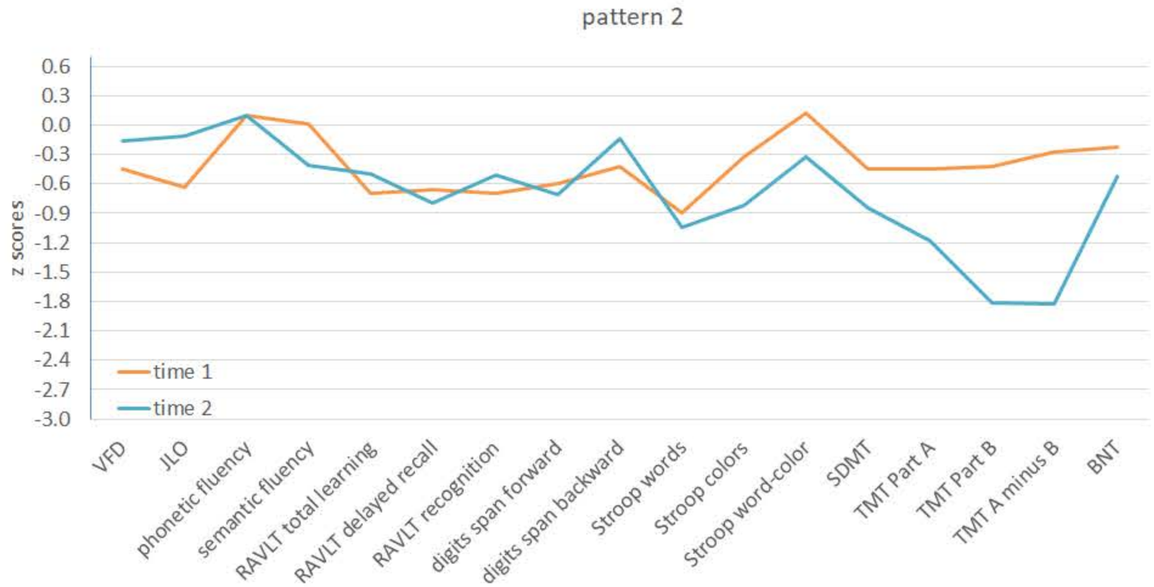
| | Parkinson's Disease subtypes | | | Healthy controls (n=22) |
|---|---|---|---|---|
| | Pattern 1 (n=7) | Pattern 2 (n=16) | Pattern 3 (n=22) | |
| **Mini Mental State Examination, mean (SD)** | | | | |
| **Time 1** | 28.3 (2.0) | 29.6 (0.6) | 29.3 (0.9) | 29.8 (0.4) |
| **Time 2** | 25.7 (4.5) | 29.1 (1.0) | 29.1 (1.0) | 29.3 (0.8) |
| **UPDRS part III, mean (SD)** | | | | |
| **Time 1** | 13.7 (7.0) | 13.8 (11.3) | 12.5 (9.5) | NA |
| **Time 2** | 23.9 (15.4) | 19.1 (9.5) | 14.5 (7.8) | NA |
| **LEDD, mg, mean (SD)** | | | | |
| **Time 1** | 552.9 (386.0) | 849.4 (557.9) | 603.3 (445.5) | NA |
| **Time 2** | 924.3 (484.5) | 672.8 (326.6) | 694.6 (462.1) | NA |
| **Beck Depression Inventory II, mean (SD)** | | | | |
| **Time 1** | 13.9 (5.2) | 6.4 (6.1) | 8.9 (4.7) | 6.6 (5.5) |
| **Time 2** | 19.7 (9.4) | 6.6 (5.3) | 8.3 (4.8) | 5.1 (4.6) |
| **Starkstein's Apathy Scale, mean (SD)** | | | | |
| **Time 1** | 19.1 (7.5) | 11.1 (7.3) | 10.7 (5.7) | 8.6 (5.8) |
| **Time 2** | 23.0 (7.0) | 10.6 (8.2) | 11.3 (5.9) | 9.1 (5.5) |
| **Cummings' Neuropsychiatric Inventory, mean (SD)** | | | | |
| **Time 1** | 9.1 (13.7) | 5.8 (10.5) | 5.4 (6.4) | 1.8 (3.5) |
| **Time 2** | 20.6 (16.4) | 9.8 (9.8) | 6.2 (6.0) | 2.2 (2.5) |

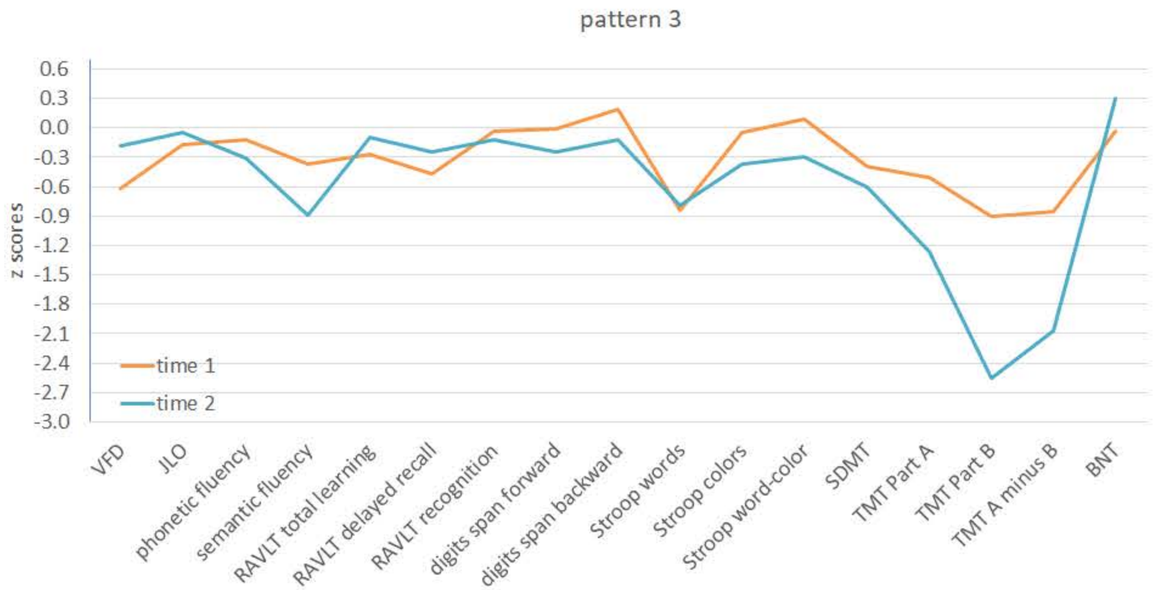
LEDD, L-dopa equivalent daily dose; SD, Standard deviation; UPDRS part III, Unified Parkinson's Disease Rating Scale motor section.

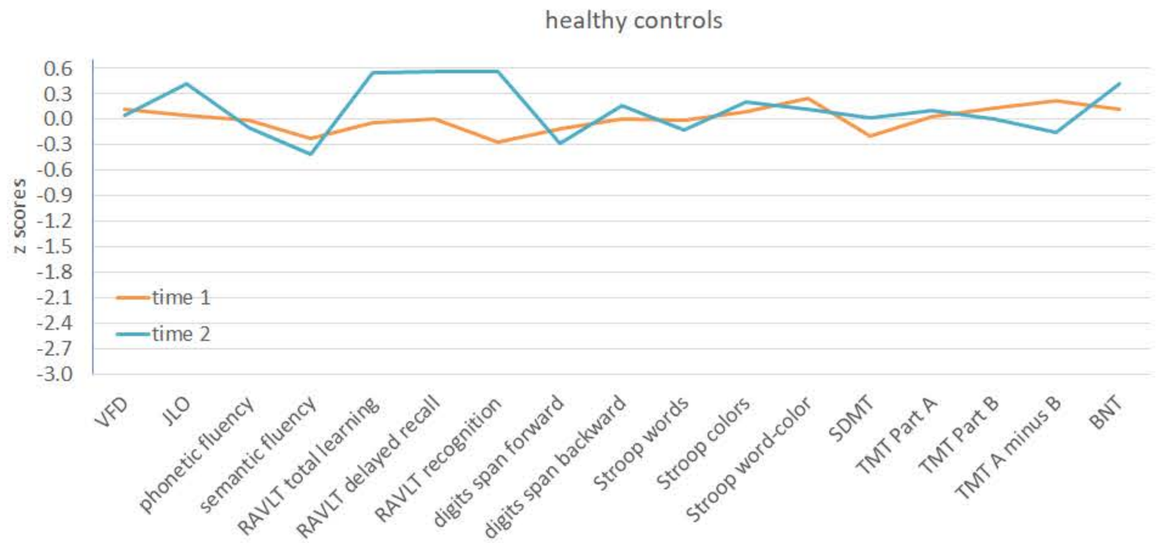
Pattern 1 patients were not included into the permutation testing general linear model. All reported significant effects were corrected by Bonferroni.

There were significant time effects in MMSE in pattern 2 (t=1.804; =.054) and in controls (t=1.923; P=.035). There was a significant interaction time x group in LEDD medication between pattern 2 and pattern 3 (t=1.825; P=.047). Cummings' Neuropsychiatric Inventory showed significant differences between HC and pattern 2 (t=1.665: P=.036).

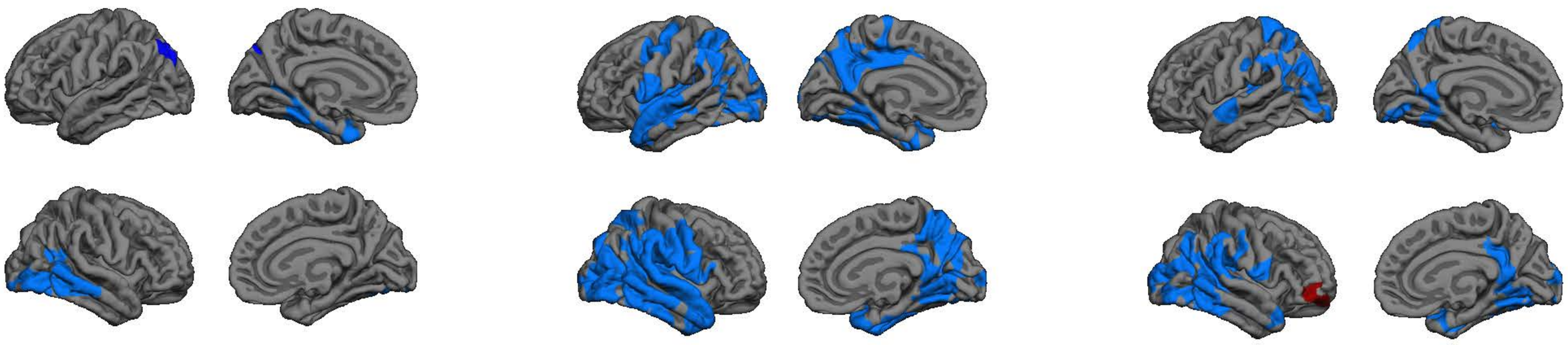
**A.**



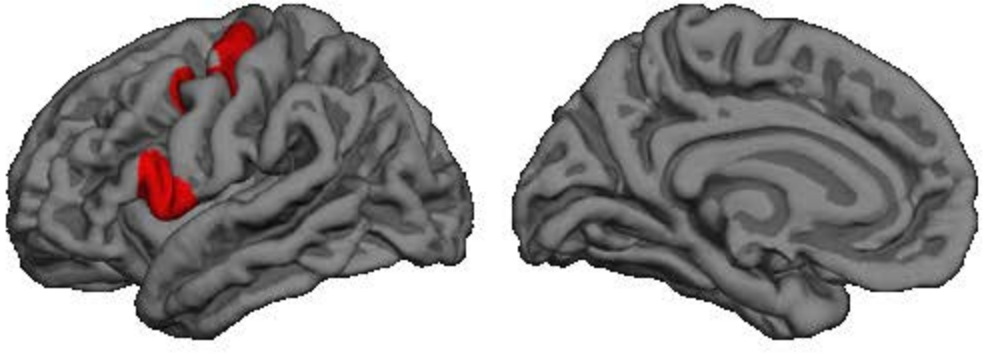

**B.**



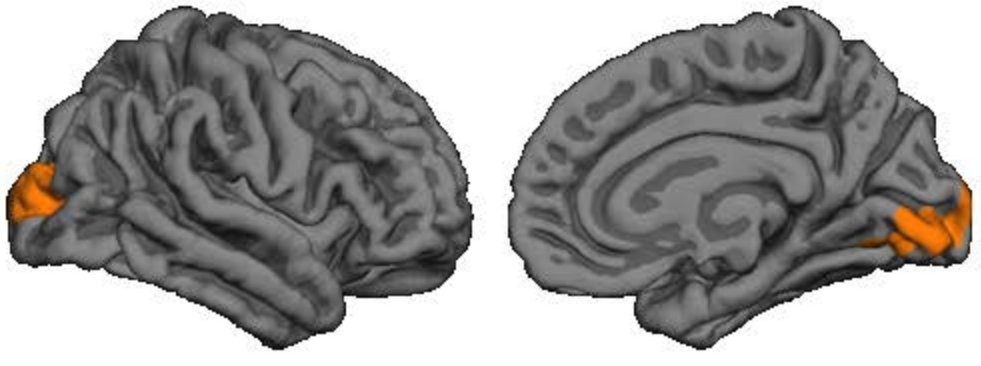
pattern 2 patients

pattern 3 patients

healthy controls



pattern 3 < healthy controls



pattern 3 < pattern 2

**corrected P <.05** **<.0001**

*Supplementary material*

# Progression of Parkinson's disease patients' subtypes based on cortical thinning: 4-year follow-up

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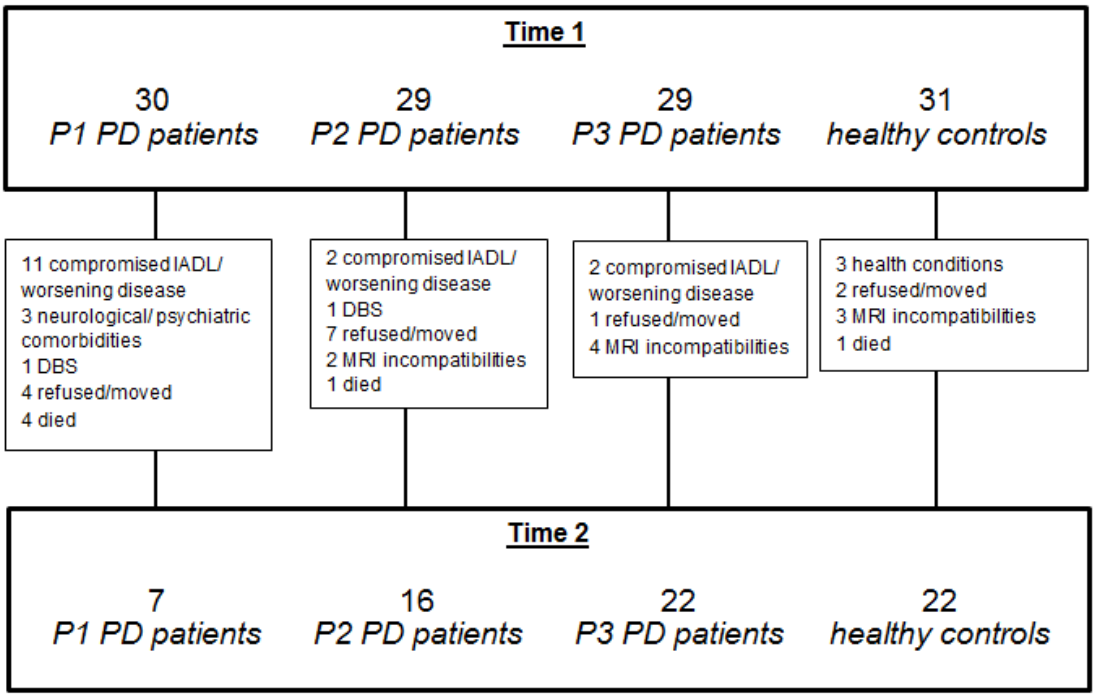
**Supplementary Figure 1 Flowchart of participants who participated at both times and those lost to time 2**




Abbreviations: DBS = deep brain stimulation; IADL = instrumental activities of daily living; MRI = magnetic resonance imaging; P1 = Pattern 1; P2 = Pattern 2; P3 = Pattern 3; PD = Parkinson's disease.

**Supplementary Table 1 Neuropsychological performance at time 1 and 2 of PD subtypes and healthy controls**

| | Parkinson's disease subtypes | | | healthy controls (n=22) |
|---|---|---|---|---|
| | Pattern 1 (n=7) | Pattern 2 (n=16) | Pattern 3 (n=22) | |
| **Visual Form Discrimination, mean (SD)** | | | | |
| **Time 1** | -0.9 (1.2) | -0.5 (0.7) | -0.6 (1.3) | 0.1 (0.8) |
| **Time 2** | -1.2 (1.6) | -0.2 (1.0) | -0.2 (0.9) | 0.1 (0.9) |
| **Judgement of Line Orientation, mean (SD)** | | | | |
| **Time 1** | -0.6 (1.0) | -0.6 (1.3) | -0.2 (1.0) | 0.1 (0.7) |
| **Time 2** | -0.8 (1.5) | -0.1 (0.7) | -0.0 (0.9) | 0.4 (0.6) |
| **Phonetic fluency, mean (SD)** | | | | |
| **Time 1** | -0.1 (0.9) | 0.1 (1.1) | -0.1 (1.2) | -0.0 (1.0) |
| **Time 2** | -1.1 (1.0) | 0.1 (1.1) | -0.3 (0.8) | -0.1 (1.0) |
| **Semantic fluency, mean (SD)** | | | | |
| **Time 1** | -1.0 (0.7) | 0.0 (1.1) | -0.4 (1.1) | -0.2 (0.6) |
| **Time 2** | -1.9 (1.3) | -0.4 (0.7) | -0.9 (1.5) | -0.4 (0.7) |
| **RAVLT total, mean (SD)** | | | | |
| **Time 1** | -0.5 (1.2) | -0.7 (1.4) | -0.3 (1.3) | -0.0 (0.8) |
| **Time 2** | -0.9 (2.2) | -0.5 (1.4) | -0.1 (1.2) | 0.6 (0.9) |
| **RAVLT recall, mean (SD)** | | | | |
| **Time 1** | -0.6 (1.0) | -0.7 (1.4) | -0.5 (1.1) | 0.0 (0.9) |
| **Time 2** | -1.1 (0.8) | -0.8 (1.5) | -0.2 (1.6) | 0.6 (1.0) |
| **RAVLT recognition, mean (SD)** | | | | |
| **Time 1** | 0.5 (1.7) | -0.7 (1.9) | -0.0 (1.3) | -0.3 (0.9) |
| **Time 2** | 0.3 (1.1) | -0.5 (1.4) | -0.1 (1.3) | 0.6 (0.5) |
| **Digits forward, mean (SD)** | | | | |
| **Time 1** | -0.2 (0.6) | -0.6 (0.9) | -0.0 (1.0) | -0.1 (0.8) |
| **Time 2** | -0.3 (0.6) | -0.7 (1.0) | -0.3 (0.9) | -0.3 (0.9) |
| **Digits backward, mean (SD)** | | | | |
| **Time 1** | 0.1 (0.7) | -0.4 (0.7) | 0.2 (1.0) | 0.0 (0.9) |
| **Time 2** | -0.1 (0.6) | -0.1 (1.1) | -0.1 (0.8) | 0.2 (0.7) |

| | | | | |
|---|---|---|---|---|
| **Stroop Word test, mean (SD)** | | | | |
| **Time 1** | -1.0 (1.6) | -0.9 (1.5) | -0.8 (1.5) | -0.0 (0.9) |
| **Time 2** | -1.8 (1.7) | -1.1 (0.9) | -0.8 (0.9) | -0.1 (0.7) |
| **Stroop Color test, mean (SD)** | | | | |
| **Time 1** | -0.6 (0.8) | -0.3 (0.9) | -0.0 (0.8) | 0.1 (1.0) |
| **Time 2** | -1.1 (1.2) | -0.8 (0.9) | -0.4 (0.8) | 0.2 (0.7) |
| **Stroop Word-Color test, mean (SD)** | | | | |
| **Time 1** | -0.3 (0.7) | 0.1 (0.9) | 0.1 (0.7) | 0.2 (0.8) |
| **Time 2** | -0.6 (1.1) | -0.3 (0.8) | -0.3 (0.7) | 0.1 (0.8) |
| **Symbol Digits Modalities test, mean (SD)** | | | | |
| **Time 1** | -1.0 (1.3) | -0.4 (1.1) | -0.4 (0.9) | -0.2 (0.6) |
| **Time 2** | -1.4 (1.2) | -0.8 (1.1) | -0.6 (0.9) | 0.0 (0.7) |
| **Trail Making Test Part A, mean (SD)** | | | | |
| **Time 1** | -2.0 (4.8) | -0.4 (1.1) | -0.5 (1.8) | -0.0 (0.9) |
| **Time 2** | -5.7 (8.0) | -1.2 (2.2) | -1.3 (2.0) | 0.1 (0.7) |
| **Trail Making Test Part B, mean (SD)** | | | | |
| **Time 1** | NA | -0.4 (0.7) | -0.9 (2.4) | 0.1 (0.7) |
| **Time 2** | NA | -1.8 (3.4) | -2.6 (4.9) | 0.0 (1.1) |
| **Trail Making Test A minus B, mean (SD)** | | | | |
| **Time 1** | NA | -0.3 (0.6) | -0.9 (2.3) | 0.2 (0.6) |
| **Time 2** | NA | -1.8 (3.1) | -2.1 (4.1) | -0.2 (0.9) |
| **Boston Naming Test, mean (SD)** | | | | |
| **Time 1** | -0.1 (0.7) | -0.2 (0.8) | 0.0 (0.9) | 0.1 (0.8) |
| **Time 2** | 0.1 (1.0) | -0.5 (0.8) | 0.3 (0.7) | 0.4 (0.6) |

NA, not applicable; RAVLT, Rey's Auditory Verbal Learning Test; SD, standard deviation. Data are z-scores adjusted by age, education and sex.

Permutation tests were calculated with 10,000 iterations. Pattern 1 patients were not included in the permutation testing due to small sample size.

There was a significant time effect in pattern 2 concerning semantic fluency (t=2.041; P=.010), Stroop Color (t=2.284; P=.049), Stroop Word-Color (t=2.985; P=.009), Symbol Digits Modalities (t=2.231; P=.048), Trail Making Test Part B (t=2.188; P=.029) and Part A minus B (t=2.545; P=0.001). There was a trend between pattern 2 and controls in Stroop Color (t=2.182; P=.058) and there was significant group effect in Symbol Digits Modalities (t=2.639; P=.018).

There was a significant time effect in pattern 3 concerning semantic fluency (t=2.592; P=.029), Stroop Word-Color (t=2.970; P=.001), Symbol Digits Modalities (t=1.728; P=.006), Trail Making Test Part A (t=3.390; P=.004), Part B (t=2.775; P=.005) and A minus

B (t=2.192; P=.059). There were significant differences between pattern 3 and HC in Symbol Digits Modalities (t=2.218; P=.008), Trail Making Test Part A (t=2.615; P=.032) and Part B (t=1.826; P=.030).
There was a significant time effect in controls in Trail Making Test A minus B (t=0.709; P=.0.054).

**Supplementary Table 2 Proportion of mild cognitive impairment or PD dementia converters within groups**

| | Parkinson's disease subtypes | | | healthy controls (n=22) |
|---|---|---|---|---|
| | Pattern 1 (n=7) | Pattern 2 (n=16) | Pattern 3 (n=22) | |
| **converters, n (%)** | 4 (57.1) | 4 (25.0) | 6 (27.3) | 1 (4.5) |
| **no-converters, n (%)** | 3 (42.9) | 12 (75.0) | 16 (72.7) | 21 (95.5) |

Chi squared test between all groups was 9.262; *P*=.026. Chi squared test between PD groups was 2.643; *P*=.267.

**Supplementary Table 3 Cortical thickness information of longitudinal analysis**

| Cortical area | Cluster size ($mm^2$) | Stats | *P*-value | MNI coordinates (x,y,z)[1] |
|---|---|---|---|---|
| *Time effects* | | | | |
| **healthy controls** | | | | |
| Left superior temporal | 2,106.4 | -4.561 | <.001 | -45 -11 -15 |
| Left lingual | 2,147.1 | -4.207 | <.001 | -19 -49 -2 |
| Left inferior parietal | 5,899.5 | -3.948 | <.001 | -42 -72 32 |
| Left superior parietal | 2,472.0 | -3.198 | <.001 | -29 -45 55 |
| Right supramarginal | 18,882.9 | -5.265 | <.001 | 59 -42 24 |
| Right pars orbitalis | 973.5 | 2.513 | 0.040 | 41 43 -6 |
| **Pattern 2** | | | | |
| Left inferior parietal | 1,481.1 | -3.537 | .003 | -33 -78 38 |
| Left fusiform | 2,512.0 | -3.478 | <.001 | -37 -40 -23 |
| Right middle temporal | 4,387.0 | -3.801 | <.001 | 57 -44 -10 |
| **Pattern 3** | | | | |
| Left precuneus | 13,671.2 | -5.683 | <.001 | -10 -53 24 |
| Left superior temporal | 7,047.5 | -4.885 | <.001 | -51 6 -21 |
| Left lingual | 2,832.7 | -4.345 | <.001 | -29 -56 -7 |
| Left caudal middle frontal | 2,128.7 | -2.830 | <.001 | -39 5 46 |
| Right lingual | 33,004.4 | -5.612 | <.001 | 20 -51 -4 |
| *Group per time effects* | | | | |
| **healthy controls vs Pattern 3** | | | | |
| Left pars opercularis | 1,343.8 | 2.548 | .006 | -49 12 2 |
| Left precentral | 1,232.1 | 2.395 | .012 | -34 -15 43 |
| **Pattern 3 vs Pattern 2** | | | | |
| Right lateral occipital | 2,492.9 | 4.440 | <.001 | 28 -94 8 |

[1]MNI305 space.

Results were obtained using Monte Carlo simulation with 10.000 iterations applied to cortical thickness maps to provide clusterwise correction for multiple comparisons (1.3). Significant clusters were reported at $p<0.05$.

**Supplementary Table 4 Global atrophy measures**

| | Parkinson's disease subtypes | | | healthy controls (n=22) |
|---|---|---|---|---|
| | Pattern 1 (n=6) * | Pattern 2 (n=16) | Pattern 3 (n=22) | |
| **Mean thickness, mm, mean (SD)** | | | | |
| **Time 1** | 2.4 (0.1) | 2.4 (0.1) | 2.5 (0.1) | 2.5 (0.7) |
| **Time 2** | 2.4 (0.2) | 2.4 (0.1) | 2.4 (0.2) | 2.5 (0.1) |
| **Lateral ventricles, $mm^3$, mean (SD)** | | | | |
| **Time 1** | 13,794.3 (7,381.0) | 10,731.0 (4,664.2) | 11,273.2 (6,970.8) | 9,359.2 (4,167.1) |
| **Time2** | 17,815.2 (9,865.6) | 12,397.3 (5,857.7) | 13,029.1 (7,903.5) | 11,009.1 (4,837.8) |
| **Total gray matter, $mm^3$, mean (SD)** | | | | |
| **Time 1** | 412,884.6 (26,132.0) | 457,530.6 (42,379.1) | 435,619.7 (49,877.4) | 442,086.2 (31,781.1) |
| **Time 2** | 408,021.3 (35,260.5) | 453,746.1 (46,130.0) | 421,838.7 (49,118.0) | 434,227.8 (33,086.1) |
| **Cortical gray matter, $mm^3$, mean (SD)** | | | | |
| **Time 1** | 591,136.9 (42,135.8) | 642,346.8 (52,725.5) | 605,341.1 (67,393.5) | 612,253.5 (44,795.3) |
| **Time 2** | 581,585.6 (55,598.3) | 636,953.8 (57,142.7) | 587,168.3 (59,403.5) | 599,098.0 (45,617.0) |
| **Subcortical gray matter, $mm^3$, mean (SD)** | | | | |
| **Time 1** | 178,252.3 (17,724.7) | 184,816.3 (17,956.6) | 169,721.5 (22,292.9) | 170,167.4 (19,916.5) |
| **Time 2** | 173,564.3 (21,207.5) | 183,207.7 (13,614.8) | 165,329.6 (15,479.9) | 164,870.2 (17,891.0) |

* one PD patient was excluded due to motion artifacts.
SD, standard deviation.
Permutation tests were calculated with 10,000 iterations.
Pattern 1 patients were not included in the permutation testing due to small sample size. There were significant time effects in total gray matter (pattern 2: t=3.226; P=.018; pattern 3: t=6.412; P<.001; controls: t=3.228; P=.005), in cortical gray matter (pattern 3: t=4.969; P<.001; controls: t=2.476; P=.032) and in subcortical gray matter (pattern 2: t=2.674; P=.053). There was an interaction group x time between pattern 2 and pattern 3 patients in lateral ventricles (t=-2.827; P=.008), total gray matter (t=3.124; P=.003) and cortical gray matter (t=3.027; P=.004) volumes.

**Supplementary Table 5 Demographical and clinical characteristics of completers and non-completers**

| | Parkinson's disease subtypes | | | healthy controls |
|---|---|---|---|---|
| | Pattern1 | Pattern2 | Pattern3 | |
| ***n* non-completers** | 23/30 | 13/29 | 7/29 | 9/31 |
| **Age, y, median (IQ range)** | | | | |
| **completers** | 76.0 (18.0) | 57.5 (13.0) | 63.0 (10.0) | 66.0 (13.0) |
| **non-completers** | 73.0 (13.0) | 64.0 (19.0) | 66.0 (11.0) | 65.0 (18.0) |
| **Education, y, median (IQ range)** | | | | |
| **completers** | 8.0 (6.0) | 17.5 (8.0) | 10.5 (6.0) | 10.0 (8.0) |
| **non-completers** | 7.0 (5.0) | 9.0 (8.0) | 10.0 (5.0) | 9.0 (8.0) |
| **Sex, male, n (%)** | | | | |
| **completers** | 6 (86.7) | 13 (81.3) | 12 (54.5) | 11 (50.0) |
| **non-completers** | 9 (39.1) | 7 (53.8) | 4 (57.1) | 5 (55.6) |
| **Mini Mental State Examination, median (IQ range)** | | | | |
| **completers** | 29.0 (4.0) | 30.0 (1.0) | 30.0 (1.0) | 30.0 (0.0) |
| **non-completers** | 29.0 (2.0) | 29.0 (1.0) | 30.0 (1.0) | 29.0 (1.0) |
| **Disease duration, y, median (IQ range)** | | | | |
| **completers** | 4.0 (7.0) | 6.0 (8.3) | 6.0 (8.5) | NA |
| **non-completers** | 9.0 (12.0) | 8.0 (9.0) | 5.0 (11.0) | NA |
| **Age of onset, y, median (IQ range)** | | | | |
| **completers** | 67.0 (19.0) | 47.5 (14.6) | 54.5 (12.8) | NA |
| **non-completers** | 63.0 (22.0) | 55.0 (12.5) | 61.0 (21.0) | NA |
| **UPDRS part III, median (IQ range)** | | | | |
| **completers** | 13.0 (12.0) | 12.0 (20.0) | 11.5 (14) | NA |
| **non-completers** | 17.0 (13.0) | 12.0 (16.0) | 15.0 (3.0) | NA |
| **Hoehn&Yahr stage, n 1/1.5/2/2.5/3** | | | | |
| **completers** | 2/0/5/0/0 | 5/1/7/2/1 | 11/0/8/1/2 | NA |
| **non-completers** | 0/3/11/4/5 | 4/1/6/1/1 | 0/0/6/1/1 | NA |
| **LEDD, mg, median (IQ range)** | | | | |
| **completers** | 400.0 (450.0) | 800.0 (1150.0) | 485.0 (639.0) | NA |

| | | | | |
|---|---|---|---|---|
| **non-completers** | 780.0 (580.0) | 1,000.0 (1,035.0) | 1,033.0 (1,007.0) | NA |
| **Beck Depression Inventory II, median (IQ range)** | | | | |
| **completers** | 14.0 (6.0) | 5.0 (7.0) | 8.0 (5.0) | 6.0 (9.0) |
| **non-completers** | 15.5 (9.0) | 11.5 (11.0) | 7.0 (12.0) | 2.0 (8.0) |
| **Starkstein's Apathy Scale, median (IQ range)** | | | | |
| **completers** | 17.0 (12.0) | 8.0(11.0) | 10.0 (10.0) | 10.0 (11.0) |
| **non-completers** | 14.0 (14.0) | 13.5 (13.0) | 11.0 (9.0) | 9.0 (4.0) |
| **Cummings' Neuropsychiatric Inventory, median (IQ range)** | | | | |
| **completers** | 2.0 (26.0) | 2.5 (6.0) | 4.0 (9.0) | 0.0 (3.0) |
| **non-completers** | 3.5 (9.0) | 1.0 (5.0) | 7.0 (9.0) | 0.0 (0.0) |
| **MCI at time 1, n (%)** | | | | |
| **completers** | 3 (42.9) | 6 (37.5) | 7 (31.8) | NA |
| **non-completers** | 17 (73.9) | 8 (61.5) | 4 (57.1) | NA |

IQ range, Interquartil range; LEDD, L dopa equivalent daily dose; MCI, mild cognitive impairment;NA, not applicable; UPDRS part III, Unified Parkinson's Disease Rating Scale motor section.

Mann-Whitney pairwise test for continuous variables and chi-squared test for categorical variables were calculated.

There were significant differences between completers and non-completers of pattern 1 in sex (chi=4.658; P=.031) and Hoehn & Yahr stage (chi=10.784; P=.029). There were significant differences between completers and non-completers of pattern 2 in education (U=40.500; P=.004), Mini Mental State Examination (U=58.500; P=.045) and Beck Depression Inventory-II (U=108.000; P=.026). There were significant differences between completers and non-completers of pattern 3 in LEDD (U=122.000; P=.021).

**Supplementary Table 6 Gottfries-Brane-Steen scale results**

| | Pattern1 (n=12) | Pattern2 (n=4) | Pattern3 (n=6) | Test stats / *P*-value |
|---|---|---|---|---|
| **GBS-I, median (IQ range)** | 14.5 (25.5) | 3.5 (5.5) | 5.5 (2.8) | 15.240/<.001 |
| **GBS-E, median (IQ range)** | 5.5 (10.0) | 1.0 (2.3) | 1.0 (0.8) | 9.861/.007 |
| **GBS-ADL, median (IQ range)** | 16.5 (14.3) | 1.0 (2.8) | 2.0 (1.8) | 15.082/.001 |
| **GBS-S, median (IQ range)** | 9.0 (10.3) | 1.5 (5.3) | 4.0 (3.5) | 11.939/.003 |
| **GBS total score, median (IQ range)** | 43.5 (50.3) | 6.0 (12.3) | 12.0 (6.5) | 15.791/<.001 |

GBS-I, intellectual impairment; GBS-E, emotional impairment; GBS-ADL, impairment of Activity Daily Living performance; GBS-S, symptoms common in dementia.

Two familiars refused to complete the interview and 14 were impossible to contact for telephonic interview. From these 14, two patients were still working.

*P*-values are from Kruskal-Wallis test followed by Mann-Whitney pairwise test and Bonferroni correction.

There were significant differences between pattern 1 and pattern 2 in GBS-I (P=.004), GBS-ADL (P=.007), GBS-S (P=.017) and GBS total score (P=.005). There were significant differences between pattern 1 and pattern 3 in GBS-I (P=.007), GBS-E (P=.021), GBS-ADL (P=.004), GBS-S (P=.016) and GBS total score (P=.004).