Cortical Thinning Across Parkinson's Disease Stages and Clinical Correlates

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Abstract

Background: Imaging studies have revealed cortical thinning and subcortical atrophy occurring in Parkinson's disease (PD); however, the topographical distribution and clinical associations related to advancing stages of PD remains unclear.

Objective: We aimed to investigate the topographical distribution of cortical and subcortical morphometric changes, and their clinical associations, related to increasing disease severity.

Methods: In this cross-sectional imaging study, T1-weighted structural magnetic resonance imaging data for 80 non-demented PD patients and 30 age-matched healthy controls were analysed using FreeSurfer software suite to derive morphometric changes using whole-brain vertex-wise analysis, and surface-based (cortical) and volume-based (subcortical) parcellation maps. PD patients were divided into three groups of mild (n=27), moderate (n=27), and severe (n=26) PD based disease duration and Hoehn and Yahr and Unified Parkinson's Disease Rating Scale Part-III motor severity scores.

Results: Whole-brain vertex-wise analysis revealed cortical thinning in the orbitofrontal cortex in early PD (P=0.011), and in the superior frontal (P=0.002), caudal middle frontal gyrus (P=0.001) and inferior parietal cortex (P=0.006) in moderate PD. Severe PD patients showed additional cortical thinning in temporal and occipital cortices (P<0.005). Subcortical volume loss was detected in the thalamus (P=0.012) and hippocampus (P=0.032) in moderate PD, which extended to the caudate (P=0.012), putamen (P=0.042) and amygdala (P=0.008) in severe PD. Increasing disease duration and motor severity scores, correlated with cortical thinning in frontal, temporal, parietal and occipital cortices, and subcortical volumetric loss in the thalamus, caudate, putamen, amygdala and hippocampus. Lower global cognitive status, measured with MMSE, correlated with cortical thinning in temporal, parietal, frontal and

cingulate cortices, and with volumetric loss in the hippocampus (r=0.31; *P*=0.009); suggesting subclinical pathogenic changes occur prior to the onset of cognitive impairment.

Conclusion: In conclusion, in more severe disease stages PD patients exhibit progressive cortical thinning and subcortical volume loss which could have relevance to the development of cognitive impairment.

Keywords: Parkinson's disease; Cortical thinning; Magnetic Resonance Imaging; Cognition.

Abbreviations: H&Y= Hoehn and Yahr; MRI = magnetic resonance imaging; MMSE = Mini Mental State Examination; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterised by the motor symptoms of tremor, rigidity and bradykinesia. Development of cognitive impairment is a very common feature of PD and often occurs early in the disease [1]. Pathological studies have revealed widespread involvement of cortical and subcortical areas in PD pathology [2]. Structural T1 weighted magnetic resonance imaging (MRI) provides a tool to accurately measure structural changes related to white and grey matter subcortical volumetric and cortical thickness alterations in PD. Previous studies have revealed insights into regional cortical thinning and subcortical atrophy occurring at different stages of PD [3-9]. Furthermore, regional changes have been associated with disease duration [5], motor symptoms [9] and cognitive impairments [3, 4, 6, 8, 10]. However, the topographical distribution of morphometric changes and their clinical associations related to increasing disease severity remains unclear.

Here, we used MR imaging to investigate structural abnormalities within cortical and subcortical regions driven by disease duration and severity of motor symptoms in non-demented PD patients. PD patients were grouped according to disease stage, taking into consideration disease duration and motor symptom severity. We expected to observe limited changes in mild PD with increasing number of brain regions affected in moderate and severe PD stages, driven by increasing disease burden.

2. Methods

2.1 Participants and clinical characteristics

This cross-sectional study analysed structural MR imaging data from 80 non-demented PD patients and 30 healthy controls matched for age and gender with no history of neurological or psychiatric disorders served as the control group (Table 1). PD patients were recruited from specialist Movement Disorder clinics at Imperial College Healthcare NHS Trust; National Hospital of Neurology and Neurosurgery, Queen Square; and Charing Cross Hospital, London. 120 patients with a clinical diagnosis of idiopathic PD, according to the UK Brain Bank Criteria, were screened from this study. Exclusion criteria were (1) the presence of dementia of cognitive impairment diagnosed by a neurologist according to the Movement Disorder Society diagnostic criteria for mild cognitive impairment in PD [11, 12]; (2) presence of other neurological or psychiatric disorders, such as depression defined by a Beck's Depression Inventory score higher than 12 [13]; and (3) the presence of visual hallucinations assessed by the Neuropsychiatric Inventory Questionnaire [14]. PD patients and healthy controls were matched for age and gender.

Motor symptom severity was assessed with the Unified Parkinson's Disease Rating Scale part-III (UPDRS-III) and Hoehn and Yahr (H&Y) and performed OFF medication after overnight

withdrawal of dopaminergic medications. Global cognitive status was assessed by Mini Mental State Examination (MMSE), patients with MMSE scores >26, indicating absence of cognitive impairments, were included.

The study was approved by the institutional review boards and the research ethics committee. Written informed consent was obtained from all study participants in accordance with the Declaration of Helsinki.

2.2 Modelling disease stage

Classification of disease stage in PD is typically characterised by Hoehn and Yarh staging (H&Y), or disease duration or UPDRS-III scores. However, due to the complexity of PD, a combination of these clinical measures could serve as an efficient method for stratification of PD patients to assess disease severity. Therefore, to reduce rater-dependent bias and variability which can be introduced when staging based on a single clinical measure we stratified PD patients into three groups using H&Y scores, disease duration and UPDRS-III scores: (1) mild PD (n=27) reflecting H&Y stage 1-2, average UPDRS-III of 20.6±7.7, average disease duration 3.4±1.5 years; (2) moderate PD (n=27) reflecting H&Y stage 2-3, average UPDRS-III of 32.1±8.4, average disease duration 7.0±2.0 years; (3) severe PD (n=26) reflecting H&Y stage 3-4, average UPDRS-III of 49.1±10.8, average disease duration 13.3±4.7 years (Table 1). To account for possible confounding factors, and to control for the effects of age and cognitive impairments on cortical thinning, PD patients were matched for age and not demented.

2.3 Image acquisition and processing

Participants were scanned on 3-T Siemens MRI scanner acquiring T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE; time repetition: 2300 ms; time echo: 2.98 ms; flip angle of 9°; time inversion = 900 ms; matrix: 240 x 256; voxel size: 1 x 1 x 1mm).

FreeSurfer image analysis suite (version 5.3.0; http://surfer.nmr.mgh.harvard.edu) was used to derive measures of cortical thickness and deep grey matter nuclei volume. The automated procedures for cortical reconstruction and volumetric segmentation have been previously described and are outlined in detail in the supplemental materials. In brief, this process consists of whole brain T1-weighted images corrected for intensity homogeneity, skull strip and segmentation into grey matter and white matter with intensity gradient and connectivity among voxel. Cortical thickness was measured as the distance from the grey/white matter boundary to the corresponding pial surface. Reconstructed data sets were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Cortical parcellation maps were created using spatial intensity gradients across tissue classes and are capable of detecting submillimetre differences between groups. Subcortical structure volumes were derived by automated procedures, which automatically assign a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labelled training set [15]. Subcortical grey matter nuclei volumes included in the analysis were: caudate, putamen, globus pallidum, hippocampus, nucleus accumbens and amygdala. All individual nuclei volumes were normalised for intracranial volume (ICV) automatically generated by FreeSufer [16]. Averaged hemispheric cortical thickness and grey matter values were processed to minimise the number of comparisons.

2.4 Statistical analysis

Statistical analysis was performed with Statistical Package for Social Science version 22.0 (SPSS, Inc, Chicago, IL, USA) and graph illustration with GraphPad Prism (version 6.0c). For all variables, homogeneity and Gaussianity were tested with Bartlett and Kolmogorov-Smirnov tests. Multivariate analysis of variance (MANOVA) was used to assess group differences in clinical (age, disease duration, UPDRS-III OFF, H&Y-OFF and MMSE scores) and imaging (cortical thickness and subcortical grey matter nuclei volume from parcellation maps) variables. If the overall multivariate test was significant, *P*-values for each variable were

calculated using independent parametric (t-test) and non-parametric (Mann-Whitney U) tests, followed by Benjiamini-Hochberg multiple comparisons test to control the false discovery rate [17]. The α level was set for all comparisons at $P<0.05$; and the false discovery rate cut-off was set at 0.05.

Cortical maps were smoothed using a circularly symmetric Gaussian Kernel across the surface with a full width at half maximum (FWHM) of 10mm and results were visualised by overlapping significant cortical areas onto a semi-inflated cortical surface. For each hemisphere, the general linear model computed vertex-by-vertex analysis of cortical thickness; the three PD groups (mild, moderate and severe) were each compared with the healthy control group using FreeSurfer's command line "mri_glmfit". Multiple comparisons were corrected with Monte Carlo Simulations using a *P*-value set at $P<0.05$ for mild and moderate PD groups, and $P<0.001$ for the severe PD group. A more conservative thresholding was applied to the severe PD group (set at $P<0.001$) in order to avoid detection of widespread cortical thinning as false positives.

The association between cortical morphometric measures (from whole-brain maps) and clinical variables (disease duration, UPDRS-II, H&Y and MMSE scores) was examined using linear regression FreeSurfer's QDEC (Query, Design, Estimate, Contrast) analysis with Monte Carlo Stimulations using threshold $P<0.05$. Correlations between cortical thickness and subcortical volume measures (derived from cortical and subcortical parcellation maps) and clinical variables (disease duration, UPDRS-II, H&Y and MMSE scores) were also interrogated using Pearson's (parametric variable) or Spearman's (non-parametric variable) rank correlation, and *P*-values corrected using Benjiamini-Hochberg correction for multiple-comparisons was used to control the false discovery rate using a cut-off set at 0.05 [17]. All data are presented as mean ±SD.

3. Results

The mild PD group had shorter disease duration, and fewer symptoms compared to the other two groups (Table 1). There was no significant difference in age between the four groups (P>0.10).

3.1 Structural changes between groups

Multivariate analysis across the four groups revealed significant differences in cortical thickness in the frontal (P=0.022), parietal (P=0.032), temporal (P=0.002), occipital (P<0.001) and cingulate (P=0.002) cortices, and significant changes in subcortical nuclei volumes (P=0.004) (Supplementary Table S1).

3.1.1 Mild PD

Group comparisons, of cortical parcellation maps, showed significant decreases in cortical thickness in the lateral orbitofrontal cortex in mild PD compared to healthy controls (Fig. 1A; Supplementary Table S1). Moreover, whole-brain vertex-wise comparison of cortical thickness also showed significant cortical thinning in the right lateral orbitofrontal in mild PD compared to healthy controls (P=0.011; Fig. 1D; Table 2). There were no differences in subcortical nuclei volumes in mild PD patients compared to the group of healthy controls.

3.1.2 Moderate PD

Moderate PD patients showed significantly reduced cortical thickness in lateral orbitofrontal, superior frontal gyrus, caudal middle frontal, inferior parietal gyrus and posterior cingulate (Fig.1A; Supplementary Table S1). Whole-brain vertex-wise comparisons demonstrated significant cortical thinning in the right inferior parietal (P=0.006), right superior frontal (P=0.002) and left caudal middle frontal (P=0.001) in moderate PD compared to healthy controls (Fig. 1D; Table 2). Significant loss of subcortical nuclei volumes was observed in the thalamus (P=0.012) and hippocampus (P=0.032) in moderate PD (Fig. 1C).

3.1.3 Severe PD

Regions affected in mild and moderate PD, including the lateral orbitofrontal, caudal middle frontal, superior frontal gyrus, inferior parietal gyrus and posterior cingulate, showed trends of progressive cortical thinning into severe disease stages (Fig. 1A; Supplementary Table S1). Specifically, the superior frontal gyrus, caudal middle frontal and inferior parietal gyrus showed significant decreases in cortical thickness in severe PD compared to healthy controls (Fig. 1A). Whole-brain vertex-wise analysis showed significant cortical thinning in the superior parietal (P<0.001), inferior parietal (P<0.001), precuneus (P=0.012), postcentral (P=0.001), paracentral (P=0.001), precentral (P=0.003), superior frontal (P=0.001), inferior temporal (P=0.010), lateral occipital (P=0.015), pericalcarine (P=0.002), lingual (P<0.001), isthmus (P=0.011) and posterior cingulate (P=0.001) (Fig. 1D; Table 2).

Regions which showed significant cortical thinning only in severe PD included the precentral gyrus, paracentral, fusiform cortex, transverse temporal, superior, middle and inferior temporal gyrus, superior parietal, precuneus, postcentral, lingual gyrus, pericalcarine cortex, cuneus cortex, lateral occipital cortex and isthmus (Fig. 1B, Supplementary Table S1). There were also significant decreases in cortical thickness in severe compared to moderate PD in the inferior temporal G, lingual G, cuneus, pericalcarine and lateral occipital (Fig. 1B; Supplementary Table S1).

In subcortical nuclei the thalamus, putamen, amygdala and hippocampus followed linear decreases from mild to severe stages, with significant volume loss in the thalamus (P=0.008), putamen (P=0.042), hippocampus (P=0.028) and amygdala (P=0.008) in advanced PD (Fig. 1C; Supplementary Table S1). There was significant volume loss in the caudate observed only in severe PD (P=0.012), with mild and moderate stages showing no changes (Fig. 1C). Group comparisons showed no changes in volumes in the pallidum and accumbens.

3.2 Clinical and cognitive correlates of cortical thinning

Cortical thinning correlated with longer disease duration in the superior, middle and inferior temporal gyrus, the middle and superior frontal cortex, the orbitofrontal gyrus, the paracentral gyrus, the precentral, paracentral and postcentral gyrus, the precuneus cortex, the lingual cortex, lateral occipital cortex, fusiform gyrus, the supramarginal gyrus, the superior and inferior parietal gyrus and the insula cortex (Fig. 2).

Measures of motor symptom severity, assessed with UPDRS-III and H&Y, were associated with cortical thinning in the superior and inferior temporal gyrus, the precentral, paracentral and postcentral gyrus, the supramarginal gyrus, the middle and superior frontal cortex, the medial orbitofrontal gyrus, the cuneus cortex, the lingual cortex, the pericalcarine cortex, lateral occipital cortex, fusiform gyrus, the superior and inferior parietal gyrus and the precuneus cortex (Fig. 2).

Lower MMSE scores correlated with cortical thinning in the superior frontal cortex, supramarginal gyrus, inferior parietal cortex, superior temporal cortex and posterior cingulate gyrus (Fig. 2).

The exact anatomical location, cluster size, P value and coordinates from whole-brain vertex-wise associations between clinical variables (disease duration, UPDRS-III, H&Y and MMSE scores) can be found in the Supplemental Data Table S2. Moreover, correlations between cortical parcellations maps and clinical variables can be found in Supplemental Data Figure S1-S3.

3.3 Clinical and cognitive correlates of subcortical volumetric loss

Subcortical volume loss correlated with longer disease duration in the thalamus (r= -0.42; P<0.001), caudate (ρ= -0.25; P = 0.042), putamen (r= -0.325; P = 0.005), hippocampus (r= -0.290; P = 0.009) and amygdala (ρ= -0.42; P<0.001) (Fig. 3A). Subcortical volume loss correlated with motor symptom severity (Fig. 3B & C) in the thalamus (UPDRS-III: r= - 0.39,

P = 0.003; H&Y: r= -0.39, *P*<0.001), caudate (UPDRS-III: ρ= - 0.30, *P* = 0.015; H&Y: ρ= -0.33, *P* = 0.013), putamen (UPDRS-III: r= - 0.23, *P* = 0.042), hippocampus (UPDRS-III: r= -0.27, P = 0.017; H&Y: r = -0.26, *P* = 0.019) and amygdala (UPDRS-III: ρ= - 0.30, *P* = 0.010; H&Y: ρ= -0.33, *P* = 0.004). Lower MMSE scores correlated with volumetric loss in the hippocampus (r= 0.31; *P* = 0.009) (Fig. 3D).

4. Discussion

In this cross-sectional study, we demonstrate that as disease severity increases PD patients exhibit cortical thinning and subcortical volumetric loss, which could have relevance to future development of cognitive decline. In mild PD, cortical thinning starts from the orbitofrontal cortex, extending to other frontal regions, parietal and cingulate cortices in moderate disease stages. Subcortical volume loss in the thalamus and hippocampus is detectable from moderate disease stages. In severe PD, there is additional cortical thinning and subcortical volume loss in temporal and occipital cortices and in the caudate, putamen and amygdala. Morphometric changes are associated with longer disease duration and increasing motor symptom severity. These findings indicate that cortical thinning and subcortical volume loss, from mild stages, are associated with clinical performance in cognitively normal PD patients. Furthermore, associations between cortical thinning and lower MMSE scores, in cognitively normal PD patients, indicates subclinical changes which could contribute towards future development of cognitive decline.

Our results are compatible with other cross-sectional studies, showing localised cortical thinning in mild and moderate PD with increasingly widespread cortical involvement in severe stages [5, 9, 18-22]. In cognitively normal patients, cortical thinning has been reported in the orbitofrontal cortex in mild PD [3, 18, 23, 24]; caudal middle frontal [6], superior frontal, inferior parietal and posterior cingulate in moderate PD [20, 21]; and frontal, temporal, parietal

and cingulate cortices in advanced PD [9]. Posterior aspects of the cingulate cortex, inferior parietal, precuneus and portions of frontal cortex areas have a central role in integrating information across functionally segregated brain regions and appear particularly vulnerable to atrophy in neurodegenerative disorders [25]. Moreover, topographic distribution of cortical thinning is also consistent with localised changes in glucose metabolism seen at the early disease stages, which gradually extends to involve several regions as the disease progresses [26, 27]. Decreases in cerebral perfusion alongside cortical thinning supports the role of cortical neuropathology in PD [19]. Thus, structural changes observed here could be associated with the combined effects of impaired metabolism and perfusion. Further studies are required to fully understand the relationship between cortical thickness and pathophysiological processes.

Early involvement of frontal regions in cognitively normal PD patients is in line with previous findings [18-20]. Thinning in frontal regions has been suggested to cause progressive degeneration of the reciprocal cortico-cortical connections between frontal and temporal cortices [28]. A recent longitudinal study has also shown fronto-striatal deficits are already prominent in cognitively normal PD [6]. Furthermore, functional MRI (fMRI) studies have shown cognitive decline is associated with altered frontal and corticostriatal functional connectivity [29]. Therefore, suggesting that early frontal structural changes, in cognitively normal patients, could contribute to patterns of progressive cortical thinning and future development of cognitive impairment.

Structural connectivity analysis has revealed alterations of cerebral networks in cognitively normal, untreated and newly diagnosed Parkinson patients [7]. Alterations in structural networks include changes in the communication between distinct brain areas and the breakdown of highly connected regions [30]. This localised cortical thinning in frontal and parietal regions in mild and moderate disease stages, which coincides with structural network changes in orbitofrontal, superior frontal, inferior parietal, middle frontal regions in cognitively normal mild PD patients [7]. Cortical thinning in frontal and parietal regions has also been

suggested as an early marker of cognitive impairment in PD [31]. We found that worse MMSE scores correlated with increased cortical thinning in the frontal, temporal, parietal and cingulate cortices, and with hippocampal volume loss. Previous studies also show correlations between regional cortical thinning in frontal, temporal, parietal and posterior cingulate and decreased MMSE scores [9, 22]. Longitudinal studies revealed that progressive cortical thinning in temporal, occipital, parietal and frontal cortices and further loss of hippocampal volume are associated with cognitive deterioration [6, 32]. Findings of cortical changes in PD patients who do not meet criteria for mild cognitive impairment suggests cortical changes are already present at the time of diagnosis [10]. Our findings support growing evidence that early progressive cortical and subcortical changes precede, and may contribute to, cognitive dysfunction.

In line, with previous studies we did not find subcortical volume loss in mild PD patients [9]. In moderate disease stages, we report volume loss in the thalamus and hippocampus. Previous studies have reported volume loss in hippocampus [33] and putamen [22] in moderate disease stages. DTI studies have shown that cognitively normal PD patients have increased mean diffusivity in the hippocampus [34] and thalamus [35], and decreased fractional anisotropy in thalamus [35]. Furthermore, lower hippocampal fraction anisotropy correlated with measures of global cognitive decline [34]. Thus, suggesting that hippocampal volume could act as a biomarker of cognitive decline and progression to dementia in PD [9, 36]. In non-demented PD patients with mild to moderate disease stages, studies have reported volume loss in the caudate, putamen [3, 37, 38] and amygdala [4, 39]. In the present study, significant volume loss in the putamen, caudate and amygdala was only detected in severe PD patients. These findings are supported by longitudinal studies, which report significant volume loss in the caudate and putamen as PD advances [6, 38]. Moreover, we found that subcortical atrophy in the caudate, putamen, amygdala and thalamus was associated with disease duration, UPDRS-III and H&Y scores. At the subcortical level, negative correlations between caudate volume and UPDRS-III, and between putamen volume and H&Y stages have previously been reported

[9]. Together these findings indicate that, while subtle changes may occur, subcortical atrophy is not detectable in mild PD, suggesting that striatal volume loss occurs several years after the onset of motor symptoms and is a secondary event to the presence of PD pathology.

A limitation to this study is the limited information on subject's cognitive status. The MMSE is the most commonly used scale to assess mild cognitive impairment in clinical practice and has about 70% sensitivity for identifying dementia in PD [40]. However, cognitive deficits are common especially in advanced stages, thus, it's possible some advanced PD patients, in our severe PD cohort, had subtle cognitive impairments that the MMSE failed to identify. A more detailed battery of cognitive assessments in this cohort, to assess individual cognitive domains affected in PD including visual episodic memory, visual recognition memory, executive functions, visuospatial working memory, and working memory, would enhance our understanding of the cognitive status of these patients. Validated computerised cognitive assessments, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB®) and Cogstate, could be used to detect subtle changes in cognitive status within specific cognitive domains which are associated with cortical thinning. This would also further enhance our understanding of which specific cognitive domains are most affected by cortical thinning and subcortical volumetric loss. A second potential limitation is that we did not find an association between age and disease duration or disease severity. This might indicate that our cohort is not representative of the general idiopathic PD population where we might expect to see an association between age and disease duration and severity. Furthermore, it is worth noting that additional factors could drive cortical atrophy and subcortical volumetric loss; thus, warranting future large, longitudinal studies to elucidate these findings further.

In conclusion, our findings support evidence for the progressive loss of cortical thickness and subcortical volumes with greater disease severity in PD patients, which could have implications for future development of cognitive impairments. Progressive cortical thinning and subcortical volumetric loss is associated with disease duration and motor symptom severity. By grouping

patients in disease stages, based on disease duration and clinical measures of motor symptom severity, topographic patterns of cortical thinning can be established which could act as markers of disease severity and cognitive dysfunction.

Figure legends

Figure 1. Cortical and subcortical regions affected in mild, moderate and severe Parkinson disease stages. Group comparisons of cortical and subcortical regions affected in (**A**) mild, (**B**) moderate and (**C**) severe Parkinson disease stages. *P <0.05; **P<0.01; ***P<0.001; no asterisk indicates significance that did not survive correction for multiple comparisons. (**D**) Vertex-wise comparison between healthy controls and mild PD (right), moderate PD (middle) and severe PD (left). The colour bar shows the logarithmic scale of P values ($-\log_{10}$). PD=Parkinson's disease; Lh=left hemisphere; Rh=right hemisphere.

Figure 2. Vertex-wise correlation between cortical thickness and disease duration, motor severity scores, as assessed with UPDRS-III and H&Y, and MMSE cognitive measure scores in patients with Parkinson's disease. The colour bar shows the logarithmic scale of P values ($-\log_{10}$). Lh = left hemisphere; Rh = right hemisphere. The exact anatomical location, cluster size, P value and coordinates of the results can be found in the Supplemental Data Table S2.

Figure 3. Associations between subcortical volumetric loss and disease duration (**A**), motor severity scores, as assessed with UPDRS-III (**B**) and H&Y (**C**) , and MMSE (**D**) cognitive measure scores in patients with Parkinson's disease.

Tables

Table 1 Clinical characteristic of healthy controls and Parkinson's disease patients

	Healthy controls	Mild Parkinson's disease	Moderate Parkinson's disease	Severe Parkinson's disease
Number of subjects (M/F)	30 (16/14)	27 (15/12)	27 (14/13)	26 (12/14)
Age years (±SD)	60.2 (±9.5)	57.2 (±8.4)	60.7 (±9.1)	60.1 (±10.1)
Disease Duration years (±SD) [range]	-	3.4 (±1.5) [1-7]	7.2 (±2.0) [4-12]	13.3 (±4.7) [6-24]
H&Y OFF [number (n) subjects in each score]	-	1-2 [H&Y 1: n=8; H&Y 2: n=19]	2-3 [H&Y 2: n=16; H&Y 3: n=11]	3-4 [H&Y 3: n=17; H&Y 4: n=9]
UPDRS-III OFF Mean (±SD) [range]	-	20.6 (±7.7) [6-32]	32.1 (±8.4) [19-47]	49.1 (±10.8) [33-71]
MMSE Mean (±SD) [range]	29.8 (±0.3) [28-30]	29.6 (±0.6)[a] [28-30]	29.6 (±0.9)[b] [27-30]	29.6 (±0.8)[c] [27-30]

[a]Data from 25 subjects: quality if data=92.6%; [b]Data from 21 subjects: quality if data=77.8%; [c]Data from 24 subjects: quality if data=92.3%. MMSE = Mini-Mental State Examination; M = Male; F = Female; UPDRS-III = Unified Parkinson's Disease Rating Scale part-III; H&Y = Hoehn and Yahr.

Table 2 Significant cortical thickness differences in Parkinson's disease groups compared to healthy controls from vertex-wise analysis

Anatomical region	**Talairach Coordinates**			**Cluster size (mm^2)**	**No. of Vertices**	***P* value**
	X	**Y**	**Z**			
Mild PD < HC						
Lateral orbitofrontal R	14.8	23.4	-15.1	1585.7	2943	0.011
Moderate PD < HC						
Superior Frontal R	11.0	14.6	62.2	1961.7	4637	0.002
Inferior Parietal R	34.0	-71.1	28.7	1710.3	2851	0.006

Caudal Middle Frontal L	-30.8	9.3	53.6	2138.9	3640	0.001
Severe PD < HC						
Superior Parietal L	-16.5	-86.6	36.1	3188.6	4893	<0.001
Superior Parietal R	12.5	-81.2	36.4	1138.2	1725	<0.001
Inferior Parietal R	44.0	-67.7	7.0	579.6	823	<0.001
Precuneus R	13.3	-62.7	30.0	282.1	535	0.012
Postcentral L	-36.4	-33.6	64.2	426.3	953	0.001
Paracentral L	-14.4	-41.4	71.3	808.9	1973	<0.001
Paracentral R	3.3	-32.8	65.1	414.5	1042	0.001
Precentral L	-36.8	-18.3	64.5	352.7	884	0.003
Superior Frontal L	-11.2	10.6	61.7	425	753	0.001
Inferior Temporal L	-41.7	-61.6	-5.3	284.3	432	0.010
Inferior Temporal R	46.9	-21.2	-26.6	733	1196	<0.001
Posterior Cingulate L	-6.8	-6.4	40.2	488.2	1326	0.001
Isthmus Cingulate L	-4.1	-33.4	30.5	275.9	757	0.011
Lateral Occipital L	-42.6	-79.6	0.1	252.7	392	0.015
Lateral Occipital R	27.5	-83.9	14.0	840.9	1210	<0.001
Pericalcarine R	15.8	-85.1	5.2	384.8	561	0.002
Lingual L	-19.5	-56.6	-6.4	573.0	883	<0.001
Lingual R	12.5	-85.6	-13.4	1591.2	2143	<0.001

Abbreviations: HC = healthy controls; PD = Parkinson's disease; L=left; R=right. Mild and moderate PD corrected threshold $P<0.05$; severe PD corrected threshold $P<0.001$.

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