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Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally

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Previous studies have shown greater atrophy in grey and white matter of various brain regions in patients with Parkinson's disease with mild cognitive impairment than in those without. These anatomical differences likely account for the distinct clinical profiles observed between those groups, but do not account for the evolution of regional brain degradation observed as the disease evolves. Although we have shown recently that cortical thinning correlates significantly more with disease duration in Parkinson's patients with mild cognitive impairment than in those without, to the best of our knowledge no study to date has explored this longitudinally. The present study investigated the longitudinal changes of the cortical and subcortical grey matter in patients with Parkinson's disease with and without mild cognitive impairment. Additionally, these two groups were compared with healthy controls. We found a higher rate of cortical thinning in the temporal, occipital, parietal and supplementary motor area, in patients with Parkinson's disease with mild cognitive impairment compared with both cognitively stable patients and healthy controls. On the other hand cognitively stable patients had only one lateral occipital and one fusiform cluster with increased rate of thinning compared with healthy individuals. Correlating the rate of change of cortical thickness with the results of Montreal Cognitive Assessment scores revealed significant thinning associated with cognitive decline in the group of all patients, in similar regions including temporal and medial occipital lobe. Finally, a significant decrease in the volume of the amygdala and nucleus accumbens was observed specifically in patients with Parkinson's disease with mild cognitive impairment. These results indicate that the early presence of mild cognitive impairment in patients with Parkinson's disease is associated with a faster rate of grey matter thinning in various cortical regions as well as a significant diminishment of limbic subcortical structures. This specific pattern of brain degradation associated with the early presence of mild cognitive impairment might serve as a marker of development toward dementia.

Keywords: Parkinson's disease; mild cognitive impairment; longitudinal; corticometry; magnetic resonance imaging
Abbreviation: MCI = mild cognitive impairment

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Introduction

Parkinson's disease is the second most frequent chronic neurodegenerative disorder, affecting up to 2% of individuals aged 65 years and older (Rijk *et al.*, 1997) and nearly 10% of people older than 80 years (von Campenhausen *et al.*, 2005). Cognitive deficits in non-demented patients with Parkinson's disease are frequent (Levin and Katzen, 2005; Caballol *et al.*, 2007) and can be found in the early stages of the disease. The scope and intensity of these changes can worsen with disease progression (Muslimović *et al.*, 2005; Williams-Grey *et al.*, 2007). In the early phase of Parkinson's disease, up to 40% of patients have mild cognitive impairment (MCI) (Aarsland and Kurz, 2010). Although cognitive deficits have been traditionally associated with fronto-striatal dysfunction (Ekman *et al.*, 2012), recent MRI studies have shown that other cortical regions may be associated with the presence of MCI in the disease (Song *et al.*, 2011; Melzer *et al.*, 2012; Hanganu *et al.*, 2013). Furthermore, it has been reported that patients with Parkinson's disease with MCI have a higher risk of developing dementia compared with patients who do not have MCI (Emre *et al.*, 2007; Williams-Grey *et al.*, 2007; Kehagia *et al.*, 2010).

Recent studies have shown regional structural grey matter (Hanganu *et al.*, 2013) and white matter (Agosta *et al.*, 2013) abnormalities in patients with Parkinson's disease who have MCI, supporting the presence of specific patterns of change that might contribute to early identification of MCI in patients with Parkinson's disease before the onset of dementia. The measurement of cortical thickness has been proposed (Parent and Carpenter, 1995) as a useful correlate of cortical grey matter morphology, as it has the advantage of providing a direct quantitative index (Lerch and Evans, 2005). It has been shown that neurons within the cerebral cortex are organized into ontogenetic columns that run perpendicular to the brain surface (Mountcastle, 1997) and the cortical thickness measurement is linked to the number of cells within a column reflecting the grey matter volume, density and arrangement of neurons and neuropil in a biologically and topologically meaningful way (Rakic, 1988; Parent and Carpenter, 1995). Cortical thinning has been associated with ageing (Salat *et al.*, 2004) or certain pathologies like temporal lobe epilepsy (Bernhardt *et al.*, 2009), Alzheimer's disease (Du *et al.*, 2007) or Parkinson's disease (Lyoo *et al.*, 2010; Jubault *et al.*, 2011). Still, cortical atrophy does not necessarily imply neuronal loss but rather loss of neuronal and dendritic architecture (Freeman *et al.*, 2008).

In a previous cross-sectional study, we determined abnormalities in specific cortical regions that are associated with MCI in patients with Parkinson's disease (Hanganu *et al.*, 2013). Yet a longitudinal study was needed to confirm our hypothesis of cortical degradation occurring significantly faster in patients with MCI than in those without MCI. This would then constitute the first step towards establishing anatomical markers for predicting cognitive decline (Carlson *et al.*, 2008).

For this purpose we performed an automated processing and analysis of MRI data of two time points in two groups of patients with Parkinson's disease: those with MCI, and those without MCI, to study longitudinally the rate of change of cortical thickness and volumes of subcortical segmentations. We predicted that anatomical degradation in the supplementary motor area, as well as the occipital and temporal lobes would evolve faster with the presence of MCI in patients with Parkinson's disease. Additionally we performed the correlation of cortical thickness with Montreal Cognitive Assessment scores (Nasreddine *et al.*, 2005) to assess which regions correlate with longitudinal cognitive decline.

Materials and methods

Subjects

Thirty-four non-demented patients with Parkinson's disease at the early stages of the illness (Hoehn and Yahr I and II stage) and 18 healthy controls were included in this study. Patients were diagnosed by movement disorders neurologists and met the UK Brain Bank criteria for idiopathic Parkinson's disease (Hughes *et al.*, 1992). Clinical characteristics, including medication, are presented in Table 1. All patients were responsive to dopamine medication, and we excluded patients with other comorbidities. Participants were studied twice at 19.8 ± 2.7 months apart. In each session (Time 1 and Time 2) they received a comprehensive neuropsychological assessment and an MRI investigation (occurring at 2 ± 4.1 weeks apart). Based on the neuropsychological scores at Time 1, patients were divided in two groups: those with MCI and those without MCI. MCI is defined as a cognitive deficit commonly quantified as a performance level 1 to 2 standard deviations below the population mean in one or more cognitive domains (Litvan *et al.*, 2012). Inclusion criteria for MCI, both for Parkinson's disease and healthy controls, were: (i) objective evidence of cognitive decline: performance > 1.5 standard deviations below standardized mean on two or more subtests within a cognitive domain; (ii) subjective complaint of cognitive decline by the patient or accompanying person [the neuropsychologist assessed the presence of various symptoms including those used by other studies (Singh-Manoux *et al.*, 2014): forgetfulness in daily activities, difficulty recalling memories, difficulty retaining new information, difficulty in mental calculation, language difficulties, orientation difficulties]; (iii) absence of significant decline in daily living activities (based on clinical observations of the referring neurologists and neuropsychologist); (iv) absence of dementia as diagnosed by the evaluating neuropsychologist [based on the Movement Disorder Society Task Force guidelines (Level I testing) for the diagnosis of dementia in Parkinson's disease (Dubois *et al.*, 2007)]; and (v) evidence of cognitive abnormalities that cannot be attributed to age. These criteria are consistent with the newly proposed guidelines (Level II, comprehensive assessment) for the diagnosis of MCI in patients with Parkinson's disease by the Movement Disorder Society Task Force (Litvan *et al.*, 2012). Cognitively stable patients who converted to MCI at the neuropsychological assessment at Time 2 were excluded from the analysis ($n = 2$, for a total of 32 analysed). Healthy controls also underwent a neuropsychological assessment and those with MCI were excluded. No significant differences were observed between the three groups with respect to sex, age and education. Similarly, no significant differences existed between the two patients groups with respect to time since diagnosis or disease advancement as measured by the motor part of the Unified Parkinson's Disease Rating Scale at Time 1 (Table 1). All participants provided informed consent, and the protocol was approved by the Research Ethics Committee of the Regroupement Neuroimagerie Québec.

Table 1 Demographic data for all groups

Characteristic	Mean ± SD			P^a		
	PD-MCI ($n = 17$)	PD-non-MCI ($n = 15$)	HCs ($n = 18$)	PD-MCI versus PD-non-MCI	PD-MCI versus HCs	PD-non-MCI versus HCs
Sex: males/females	11/6	8/7	7/11	0.52	0.13	0.42
Age, years	64.01 ± 5.36	60.98 ± 3.83	61.85 ± 4.53	0.079	0.2	0.56
Education, years	13.47 ± 3.37	14.36 ± 2.37	14.67 ± 3.53	0.4	0.3	0.7
Time since diagnosis, years	5.35 ± 2.96	5.09 ± 4.90	–	0.85	–	–
UPDRS ON at Time 1	23.69 ± 8,46	21.9 ± 7.37	–	0.55	–	–
UPDRS OFF at Time 1	30.5 ± 10.2	26.4 ± 8.04	–	0.22	–	–
MoCA ON at Time 1	26.25 ± 2.02	27.27 ± 1.91	27.88 ± 1.31	0.1	0.01*	0.3
Duration T2-T1, m	18.62 ± 1.36	19.06 ± 1.28	21.64 ± 3.51	0.35	0.002*	0.011*
L-DOPA daily, mg	488.2 ± 343.0	353.3 ± 290.6	–	0.24	–	–
Medication, *n* patients						
DDCI	15	11				
DOPA agonist	9	7				
MAO-B inhibitor	9	7				
COMT inhibitor	6	6				

*This value indicates a significant difference between groups.
[a]Significance of differences between groups is presented, computed with Student's *t*-test.
PD-MCI = patients with Parkinson's disease with mild cognitive impairment; PD-non-MCI = patients with Parkinson's disease without mild cognitive impairment; HCs = healthy controls; SD = standard deviation; MoCA = Montreal Cognitive Assessment, Duration T2-T1 = period of time between Time 1 and Time 2; m = months; UPDRS = Unified Parkinson's Disease Rating Scale; ON = On medication; OFF = Off medication; DDCI = DOPA decarboxylase inhibitor; MAO-B = monoamine oxidase isoform B; COMT = catechol-*O*-methyl transferase.

Neuropsychological assessment

Before the scanning session, the Montreal Cognitive Assessment scale (Nasreddine *et al.*, 2005) was administered. At both time points, all participants (healthy controls and patients) underwent a comprehensive neuropsychological evaluation. During this evaluation, all patients were OFF medication (at both time points), and did not receive any drugs related to Parkinson's disease for at least 12 h before the sessions. This was done to diminish medications' potential effect on cognitive tests. The neuropsychological assessment targeted five main cognitive domains, as suggested previously by the Movement Disorders Society Task-Force (Litvan *et al.*, 2012): (i) attention and working memory; (ii) executive function; (iii) language; (iv) memory; and (v) visuospatial functions. To assess the attention and working memory domain, the following tests were used: Trail Making Test Part A (Reitan and Wolfson, 1985), Digit Span Test (Wechsler, 1997) as well as the reading and colour naming parts of the Stroop Colour-Word Test (Golden and Freshwater, 1998). The evaluation of the executive function domain was based on: the Tower of London Test (Culbertson and Zillmer, 2005), the Brixton Test (Burgess and Shallice, 1997), Orthographic Verbal Fluency subtest of the Montreal Evaluation of Communication protocol (Joanette *et al.*, 2004), Trail Making Test Part B (Reitan and Wolfson, 1985) and the interference part of the Stroop Colour-Word Test (Golden and Freshwater, 1998). The assessment of the language domain included: the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), Boston Naming Test (Kaplan *et al.*, 1983) and the Semantic Verbal Fluency subtest of the Montreal Evaluation of Communication protocol (Joanette *et al.*, 2004). The domain of the memory was tested by the Rey Auditory Verbal Learning Test (Schmidt, 1996) and the Logical Memory subtest of the Wechsler Memory Scale third edition (immediate and delayed recalls) (Wechsler, 1997). Finally, the evaluation of visuospatial function included the Hooper Visual Organization Test (Hooper, 1958) and the Clock-drawing subtest of the Montreal Cognitive Assessment (Nasreddine *et al.*, 2005), which was evaluated based on the scores of Shulman *et al.* (1993).

Image acquisition and analyses

Participants were scanned using the Siemens Tim Trio 3.0 T scanner at the Unité de Neuroimagie Fonctionnelle of the Centre de recherche de l'Institut Universitaire de Gériatrie de Montréal. A high-resolution 3D T_1-weighted imaging of MP-RAGE sequence was acquired for each patient (repetition time, 2300 ms; echo time, 2.91 ms; inversion time, 900 ms; flip angle, 9°; 160 slices; field of view, 256 × 240 mm; matrix, 256 × 240; voxel size, 1 × 1 × 1 mm; 12-channel coil).

Cortical reconstruction and volumetric segmentation was performed with FreeSurfer 5.3 image analysis suite. Briefly, this includes motion correction and averaging of multiple volumetric T_1-weighted images, removal of non-brain tissue using a hybrid surface deformation procedure (Ségonne *et al.*, 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (Fischl *et al.*, 2004), intensity normalization (Sled *et al.*, 1998), tessellation of the grey/white matter boundary, automated topology correction (Ségonne *et al.*, 2007), and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale *et al.*, 1999; Fischl and Dale, 2000). To extract reliable volume and thickness estimates, images where automatically processed with the longitudinal stream (Reuter *et al.*, 2012). Specifically an unbiased within-subject template space and image was created using robust, inverse consistent registration (Reuter *et al.*, 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter *et al.*, 2012).

Misclassification of tissue types was corrected by minimal manual adjustment. Cortical thickness was calculated as the closest distance from the grey/white matter boundary to the grey/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas *et al.*, 2002) and manual measurements (Kuperberg *et al.*, 2003; Salat *et al.*, 2004). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han *et al.*, 2006; Reuter *et al.*, 2012).

Statistical analyses for cortical thickness were performed using the longitudinal two stage model (Reuter *et al.*, 2012) and we computed the rate of change of cortical thickness (mm/year) between the Parkinson's disease groups and the healthy controls using the formula:

(Thickness at Time 1 − Thickness at Time 2)/(Time 2 − Time 1).

Additionally the correlation between rate of change of cortical thickness and the difference of Montreal Cognitive Assessment scores between Times 1 and 2 was determined. Cortical thickness was smoothed with a 10-mm full-width half-height Gaussian kernel to reduce local variations in the measurements (Du *et al.*, 2007). We had a significant difference in the duration between the two time points between the two patients groups and the control group (~2 months, Table 1), which was used as a nuisance factor. A vertex-by-vertex analysis was carried out using a univariate general linear model. Multiple comparisons were taken into account for the vertex data using a false discovery rate correction at a $P < 0.05$ level of significance (Genovese *et al.*, 2002). The statistical results are presented at a *P*-value of 0.05, corrected and 0.001, uncorrected (Lyoo *et al.*, 2006, 2010; Tae *et al.*, 2008) as this threshold has been considered equivalent to a *P*-value of 0.05 corrected for multiple comparisons when an *a priori* hypothesis is present (Fischl *et al.*, 1999; Lyoo *et al.*, 2006). In the case of our study the *a priori* hypothesis was selected on the basis of the results observed in our cross-sectional analysis comparing Parkinson's disease patients with MCI and those without MCI (Hanganu *et al.*, 2013), which included the supplementary motor area, temporal lobe and the medial occipital lobe.

For the analysis of subcortical longitudinal changes, the subcortical structures were segmented in order to obtain their volumes. The volumes were then corrected by performing a regression over the estimated total intracranial volume. Previous studies have shown that estimated total intracranial volume provides a robust method for head size correction that is equivalent to manual intracranial volume correction (Buckner *et al.*, 2004) and the regression-based correctional method may provide advantages over the proportion-based method (Sanfilipo *et al.*, 2004). After this, the differences between the two time points of corrected subcortical volumes were computed, and additional corrections were performed using the averages of the two time points for each subject as a regression. This was done to reduce the variability linked to the differences in the initial volumes for each participant. The percentage of change was computed with respect to the first time point for each subject. Significant differences between groups were computed using the Student's *t*-test analysis and were set to $P \leqslant 0.05$. We also correlated the evolution of subcortical volumes between Time 1 and Time 2 and the evolution of Montreal Cognitive Assessment scores between Times 1 and 2. This was performed by using the Pearson product-moment correlation coefficient (Pearson, 1896) with a significance level of $P \leqslant 0.05$.

Results

The most significant longitudinal changes in the Parkinson's disease with MCI versus Parkinson's disease without MCI groups were revealed by an increased rate of thinning of the cortical grey matter in the temporal and the supplementary motor area in the first group. Furthermore, longitudinal changes in the medial occipital lobe were observed in Parkinson's disease with MCI versus healthy controls but not in the comparison between the two patients groups. Finally, a positive correlation between rate of change of cortical thickness and Montreal Cognitive Assessment scores was observed when considering all of the patients with Parkinson's disease (All-PD group), which was driven by the Parkinson's disease with MCI group. Subcortically, a significant decrease in volume of the amygdala and nucleus accumbens was observed in the group with Parkinson's disease with MCI versus both Parkinson's disease without MCI and healthy controls.

The analysis of rate of change in patients with Parkinson's disease with MCI showed a significantly increased rate of thinning in this group compared with both patients with Parkinson's disease without MCI and healthy controls (Fig. 1). Firstly, patients with MCI showed a significant decrease of the whole brain cortical thickness ($P < 10^{-6}$) when compared with the other groups (Table 2). More specifically, when comparing the two patients groups, increased thinning was detected in the right temporal lobe (middle temporal gyrus, transverse temporal gyrus, temporal pole), the right insula, right inferior frontal gyrus and the right supplementary motor area. When comparing patients with MCI with healthy controls, increased thinning was again detected in the right temporal lobe and right supplementary motor area. Additional significant clusters included the bilateral precuneus, bilateral cuneus, bilateral lingual, as well as right inferior parietal, right lateral occipital and left orbitofrontal region. On the other hand the comparison between patients with Parkinson's disease without MCI and healthy controls, revealed an increased rate of thinning only in the left lateral occipital and left fusiform regions.

The analysis of correlation between rate of change of cortical thickness and Montreal Cognitive Assessment scores revealed clusters of positive correlation when analysing the whole Parkinson's disease group indicating that a decrease of Montreal Cognitive Assessment score correlates with an increased rate of cortical thinning (Fig. 2). Further these correlations were shown to be driven by the group with Parkinson's disease with MCI. Significant clusters were revealed in the temporal lobe bilaterally, the right occipital medial lobe and the left postcentral gyrus. Clusters of negative correlation were revealed in the anterior cingulate region in the All Parkinson's disease group and in the transverse temporal gyrus in Parkinson's disease with MCI.

Longitudinal changes of subcortical structures showed decreased volumes in both Parkinson's disease groups of the thalamus, caudate nucleus, putamen and hippocampus. Yet, only the amygdala and nucleus accumbens showed a significant decrease of grey matter over time in the Parkinson's disease with MCI versus the Parkinson's disease without MCI group (Table 2). Furthermore, a significant correlation between change of cognition over time and change of amygdala volume was identified in the All Parkinson's

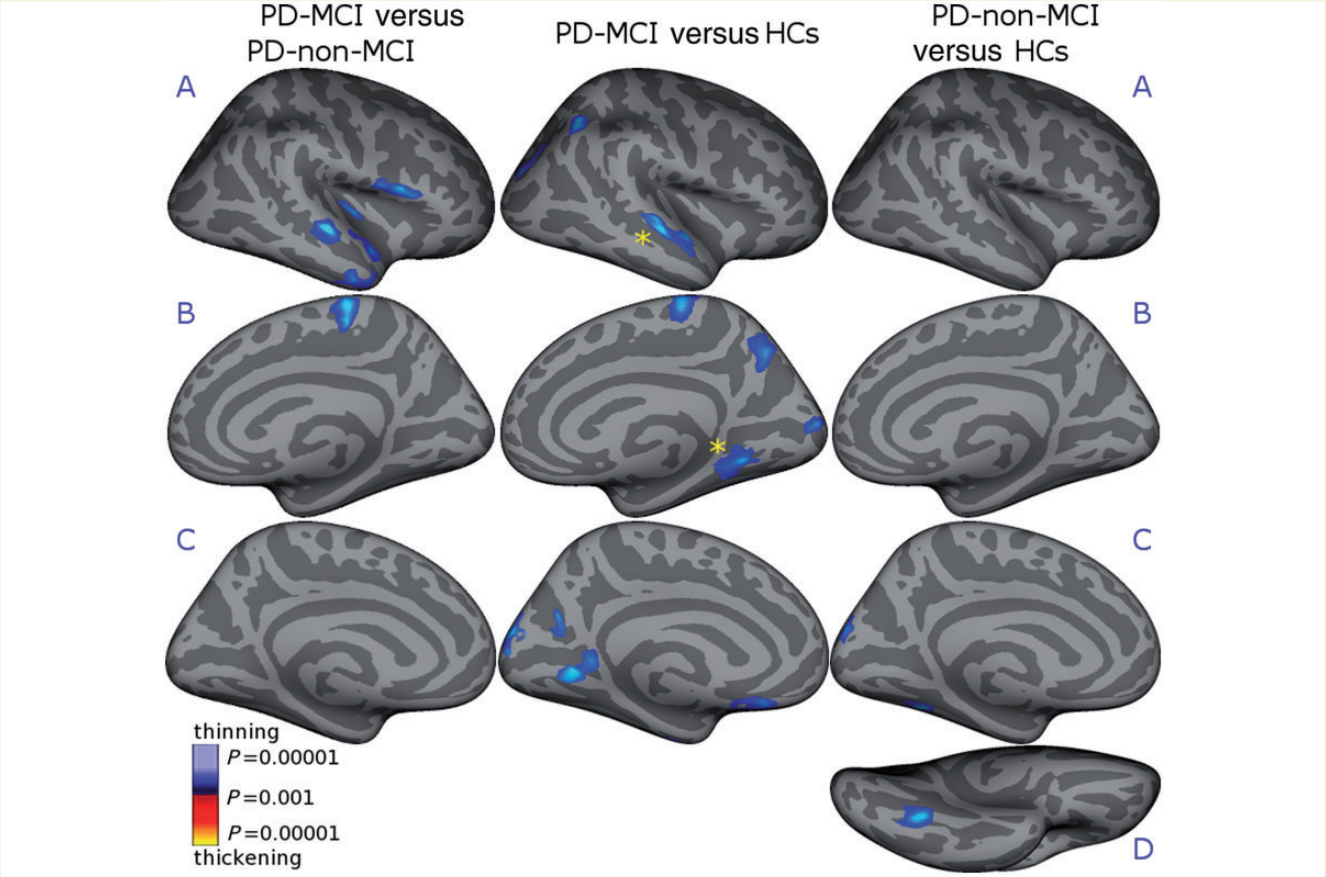

Figure 1 Rate of change of cortical thickness in patients with Parkinson's disease. Clusters significant after correction using the false discovery rate at $*P < 0.05$ and clusters with a significance of $P < 0.001$ uncorrected are displayed. Images are presented at $P < 0.05$ threshold to better illustrate the anatomic extent of the areas and the relative specificity of the findings. Bar shows the *P*-values. PD-MCI = patients with Parkinson's disease with mild cognitive impairment; PD-non-MCI = patients with Parkinson's disease without mild cognitive impairment; HCs = healthy controls; **A** = right hemisphere, lateral view; **B** = right hemisphere, medial view; **C** = left hemisphere medial view; **D** = left hemisphere inferior-temporal view.

Table 2 Longitudinal differences between the groups

	Mean / Percentage of change[a]			*P*[b]		
	PD-MCI	PD-non-MCI	HCs	PD-MCI versus PD-non-MCI	PD-MCI versus HCs	PD-non-MCI versus HCs
CoTh[c]	−0.039 / −1.34%	−0.02 / −0.67%	−0.013 / −0.34%	$<10^{-6}$*	$<10^{-9}$*	0.1
THA[c]	−207.47 / −1.51%	−245.18 / −1.80%	−523.09 / −3.71%	0.6	0.08	0.1
CAU	−134.71 / −1.92%	−151.56 / −2.05	−72.34 / −0.99%	0.8	0.3	0.052
PUT	−166.21 / −1.64%	−145.17 / −1.41	−50.96 / −0.40%	0.8	0.2	0.3
PAL	−43.67 / +1.40%	96.29 / +3.51	44.51 / +1.57%	0.2	0.9	0.2
HIP	−155.84 / −2.07%	−153.94 / −1.96	−245.29 / −3.08%	0.9	0.3	0.3
AMY	−191.57 / −6.05%	18.70 / +0.58	12.23 / +0.80%	0.001*	0.001*	0.9
NACC	−65.36 / −5.98%	−16.30 / −0.91	20.39 / +2.19%	0.1	0.005*	0.1

*This value indicates a significant difference between groups.
[a]Mean scores for each group and the percentage of change between the two time points, measured according with Time 1.
[b]Significance of differences between groups, computed with Student's *t*-test.
[c]Cortical thickness is presented in mm, subcortical volumes are presented in mm^3.
PD-MCI = patients with Parkinson's disease with mild cognitive impairment; PD-non-MCI = patients with Parkinson's disease without mild cognitive impairment; HCs = healthy controls; CoTh = cortical thickness; THA = thalamus; CAU = nucleus caudate; PUT = putamen; PAL = nucleus pallidus; HIP = hippocampus; AMY = amygdala; NACC = nucleus accumbens.

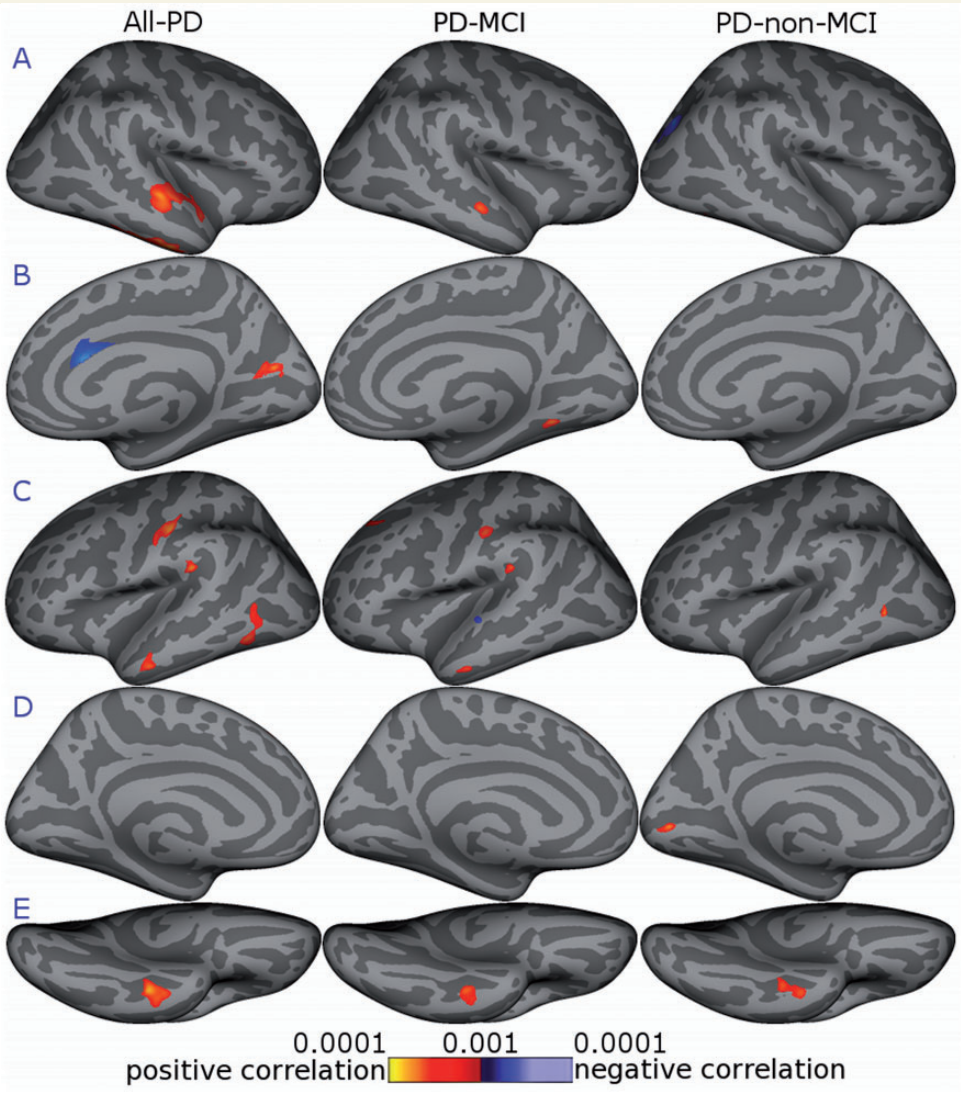

Figure 2 Correlation between rate of change of cortical thickness and the Montreal Cognitive Assessment scores. Clusters with a significance of $P < 0.001$ uncorrected, are displayed at $P < 0.05$ threshold to better illustrate the anatomical extent of the areas and the relative specificity of the findings. Bar shows the *P*-values. PD-MCI = patients with Parkinson's disease with mild cognitive impairment; PD-non-MCI = patients with Parkinson's disease without mild cognitive impairment; All-PD = group of patients with Parkinson's disease with and without mild cognitive impairment; **A** = right hemisphere, lateral view; **B** = right hemisphere, medial view; **C** = left hemisphere lateral view; **D** = left hemisphere medial view; **E** = left hemisphere inferior-temporal view.

disease group, and this was driven by the near-significant result observed in the Parkinson's disease with MCI group ($P = 0.059$). Additionally both the Parkinson's disease with MCI and All Parkinson's disease groups revealed a correlation between cognition and the volume of the thalamus (Table 3).

Discussion

The major findings of this study are: (i) Parkinson's disease with MCI is associated with a faster rate of cortical thinning in the temporal lobe, supplementary motor area and medial occipital lobe, whereas a different pattern in intensity and space is found in patients with Parkinson's disease without MCI involving primarily the lateral occipital lobe; (ii) decreased Montreal Cognitive Assessment scores correlated with cortical thinning over time in patients with Parkinson's disease; and (iii) amygdala and nucleus accumbens showed a significant loss of volume in patients with Parkinson's disease with MCI. These results are in agreement with previous cross-sectional studies in patients with Parkinson's disease that showed cortical thinning in the temporal lobe, occipital lobe and the supplementary motor area, as well as a specific longitudinal degradation associated with the early presence of MCI in the disease (Jubault *et al.*, 2011; Weintraub *et al.*, 2011; Hanganu *et al.*, 2013).

As predicted, the occipital and temporal lobes revealed significant thinning over time in Parkinson's disease with MCI.

Table 3 Correlation between volumes differences of subcortical segmentations at Times 1 and 2 with the Montreal Cognitive Assessment scores differences at Times 1 and 2

Subcortical segmentations		ALL–PD		PD-MCI		PD-non-MCI	
		MoCA T2–T1		MoCA T2–T1		MoCA T2–T1	
		r[a]	P[b]	r	P	r	P
Right	THA[c]	0.3817	0.031*	0.5537	0.021*	0.2000	0.475
	CAU	0.0265	0.885	0.1086	0.678	−0.0481	0.865
	PUT	−0.1741	0.341	−0.1839	0.480	−0.2077	0.458
	PAL	0.0907	0.621	0.1822	0.484	−0.0539	0.849
	HIP	0.1331	0.468	0.1881	0.470	−0.1168	0.679
	AMY	0.3812	0.031*	0.4669	0.059†	0.1018	0.718
	NACC	−0.1510	0.409	−0.1817	0.485	−0.2037	0.467
Left	THA	0.0729	0.692	0.2417	0.350	−0.1322	0.639
	CAU	0.2025	0.266	0.2478	0.338	−0.0735	0.795
	PUT	−0.0641	0.728	−0.1403	0.591	0.1172	0.677
	PAL	−0.0608	0.741	0.1002	0.702	−0.3972	0.143
	HIP	0.0006	0.997	−0.0846	0.747	0.1675	0.551
	AMY	0.2089	0.251	0.2662	0.302	0.0479	0.865
	NACC	−0.0319	0.862	−0.2121	0.414	0.0710	0.801

*This value indicates a significant correlation.
†This value indicates a near-significant correlation.
[a]Pearson product-moment correlation coefficient.
[b]Significance of correlations.
[c]Subcortical volumes are presented in mm^3.
PD-MCI = patients with Parkinson's disease and mild cognitive impairment; PD-non-MCI = patients with Parkinson's disease without mild cognitive impairment; ALL-PD = group of patients with Parkinson's disease with and without mild cognitive impairment; MoCA T2-T1 = difference of Montreal Cognitive Assessment score at Time 2 and Time 1; THA = thalamus; CAU = nucleus caudate; PUT = putamen; PAL = nucleus pallidus; HIP = hippocampus; AMY = amygdala; NACC = nucleus accumbens.

Previously it has been shown that temporal and occipital grey matter loss are observed in both non-demented and demented patients with Parkinson's disease, but in the latter group the occipital atrophy is the most distinguishing feature (Burton *et al.*, 2004). Additionally other studies reported occipital changes in the form of hypoperfusion in non-demented patients (Abe *et al.*, 2003; Nagamachi *et al.*, 2008) as well as hypoperfusion and hypometabolism of the occipital lobe, parietal lobe and cingulate gyrus in patients with idiopathic Parkinson's disease (Braune *et al.*, 1999). Our results show that the changes in non-demented patients from previous studies may be driven by those with MCI. Additionally, up to 40% of patients with Parkinson's disease are reported to have hallucinations, and they are all almost exclusively visual (Sanchez-Ramos *et al.*, 1996; Pappert *et al.*, 1999; Fénelon *et al.*, 2000; Holroyd *et al.*, 2001). A link between occipital grey matter volume reduction and visual hallucinations in Parkinson's disease has also been reported (Ramírez-Ruiz *et al.*, 2007). Thus, our results suggest that occipital atrophy in Parkinson's disease might be a marker for future development of hallucinations, in patients with MCI only.

An additional cluster with a faster rate of thinning was revealed in the supplementary motor area, which was also an expected outcome. This region already showed decreased fractional anisotropy (Karagulle Kendi *et al.*, 2008) and a trend of cortical thinning in non-demented patients with Parkinson's disease when compared with healthy individuals (Jubault *et al.*, 2011). Additionally, in Parkinson's disease the connection between supplementary motor area and the cerebellum has been shown to be inhibitory, whereas in healthy controls this connection was excitatory (Husárová *et al.*, 2013). Considering that our previous cross-sectional study showed that changes in supplementary motor area were specific only for the Parkinson's disease with MCI group and not for the Parkinson's disease without MCI group (Hanganu *et al.*, 2013), the present longitudinal results outline the specificity of this region for the Parkinson's disease with MCI group and reveals its decline over time. Additionally, it is interesting to note that studies in pre-Alzheimer's disease MCI patients and in those with Alzheimer's disease did not reveal the involvement of the supplementary motor area (Lerch and Evans, 2005; Lerch *et al.*, 2008; Du *et al.*, 2007; Misra *et al.*, 2009). Given that our present and previous study results showed an increased rate of thinning in this secondary motor region only for Parkinson's disease with MCI, we suggest that the atrophy of the supplementary motor area, medial occipital lobe and the temporal lobe could be considered in the future as markers for cognitive decline in Parkinson's disease.

The present results on longitudinal changes of subcortical segmentations volumes showed a decrease in all analysed structures in the three groups. Previous cross-sectional studies showed significant atrophy of subcortical structures in non-demented patients with Parkinson's disease compared with healthy controls in the caudate nucleus, putamen, thalamus (Lisanby *et al.*, 1993; Burton *et al.*, 2004; Nagano-Saito *et al.*, 2005; Geng *et al.*, 2006), and the hippocampus (Laakso *et al.*, 1996). Another study revealed no significant differences for the caudate nucleus between patients with early stage of the disease, advanced stage and healthy controls (Geng *et al.*, 2006). Our longitudinal results are in agreement with these studies, showing shrinkage over time

in the caudate nucleus, putamen, and thalamus in all three groups, but no significant differences between the groups. Interestingly, a statistically significant decrease in the volume of nucleus accumbens and amygdala was shown in patients with Parkinson's disease with MCI compared with healthy controls and patients with Parkinson's disease without MCI. Furthermore, the volume loss of amygdala over time correlated with cognition in the All Parkinson's disease group and was driven by the Parkinson's disease with MCI group. These results can be explained by the fact that dopamine depletion in Parkinson's disease progresses from the dorsal striatum to the ventral striatum, and in the early stage of the disease the dorsal striatum is severely depleted, whereas the ventral striatum is relatively intact (Farley *et al.*, 1977; Kish *et al.*, 1988). Therefore, the results of this study indicate that dopamine depletion in the ventral striatum of Parkinson's disease with MCI might be significantly greater than in patients with Parkinson's disease without MCI. Furthermore, Carlsen and Heimer (1988) emphasized that amygdala projects richly to the nucleus accumbens, which further led to the conceptualization of the nucleus accumbens as a 'limbic-motor interface' (Mogenson *et al.*, 1980; Everitt *et al.*, 1999). Also, both the amygdala and the nucleus accumbens receive rich afferent dopaminergic innervations from the ventral tegmental area (Alheid and Heimer, 1988; Heimer *et al.*, 1997). Functional associations between the two subcortical structures have also been shown—the amygdala and nucleus accumbens have been associated with depression and anxiety (Tremblay *et al.*, 2005; Epstein *et al.*, 2006). In Parkinson's disease with MCI, recent studies have indicated a larger presence of anxiety and depressive symptoms than in patients with normal cognition (Monastero *et al.*, 2013). Thus the results of longitudinal changes in subcortical structures are potentially expressing this ventral/dorsal striatum imbalance.

Our study has a number of limitations. Firstly, our sample is fairly small and this may explain why the great majority of our peaks in the cortical thickness analysis only reached an uncorrected threshold of $P < 0.001$. Although non-corrected statistics may not carry the same weight as those that are corrected, the fact that our results are in agreement with previous cross-sectional neuroimaging data increases their reliability. Furthermore, this study does not account for the potential impact of dopaminergic medication on cognitive performance and evolution.

In conclusion, the current results show that patients with Parkinson's disease and MCI have a faster rate of cortical thinning in the temporal lobe, medial occipital lobe and supplementary motor area, regions that were previously reported to be thinner in cross-sectional studies. Additionally, increased atrophy over time in the temporal and occipital lobes is associated with cognitive decline, as suggested by the present Montreal Cognitive Assessment correlation. Finally, this study suggests that atrophy of the temporal lobe, occipital lobe, supplementary motor area and limbic subcortical structures should be considered as correlate of cognitive decline in Parkinson's disease, and not necessarily fronto-striatal decline. These regions might be good predictors of dementia in Parkinson's disease. To test this directly, similar longitudinal studies are warranted that follow patients over longer periods until some of them get demented. Furthermore, future longitudinal studies are also needed to reveal the distinct grey matter changes between patients with Parkinson's disease and MCI and those with pre-Alzheimer's disease MCI.

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