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ORIGINAL RESEARCH

Parkinson's disease with mild cognitive impairment: severe cortical thinning antedates dementia

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Abstract Mild cognitive impairment (MCI) in Parkinson's disease (PD) is a risk factor for dementia and thus, it is of interest to elucidate if specific patterns of atrophy in PD-MCI patients are associated with a higher risk of developing dementia. We aim to define pattern(s) of regional atrophy in PD-MCI patients who developed dementia during 31 months of follow-up using cortical thickness analysis Twenty-three PD-MCI patients and 18 controls underwent brain MRI and completed a neuropsychological examination at baseline, PD-MCI patients were followed after a 31 month follow-up in order to assess their progression to dementia. At follow up, 8 PD-MCI patients had converted to dementia (PD-MCI converters) whereas 15 remained as PD-MCI (PD-MCI non-converters). All patients were at least 60 years old and suffered PD $\geq$ 10 years. There were no baseline differences between the two groups of patients in clinical and neuropsychological variables. The cortex of PD-MCI converters was thinner than that of PD-MCI non-converters, bilaterally in the frontal, insula and the left middle temporal areas, also displaying a more widespread pattern of cortical thinning relative to the controls. This study shows that aged and long-term PD patients with MCI who convert to dementia in the short-mid term suffer a thinning of the cortex in several areas (frontal cortex, and middle temporal lobe and insula), even when their cognitive impairment was similar to that of PD-MCI non-converters. Thus, MRI analysis of cortical thickness may represent a useful measure to identify PD-MCI patients at a higher risk of developing dementia.

Keywords Mild cognitive impairment · Dementia · Cortical thickness · Parkinson's disease

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Introduction

Dementia is one of the most frequent and disabling manifestations in patients with Parkinson's disease (PD), with a long-term prevalence of up to 80% (Hely et al. 2008; Aarsland et al. 2005). Mild cognitive impairment (MCI) involves cognitive decline that is not normal with respect to age and yet it is associated with essentially normal functional activity. MCI is a condition that occurs in around 30% of patients with PD (Aarsland et al. 2010; Litvan et al. 2011) and as shown in longitudinal studies (Janvin et al. 2006; Pedersen et al. 2013; Broeders et al. 2013; Gasca-Salas et al. 2014), it is a risk factor for dementia. Nevertheless, not all patients with PD-MCI develop dementia and the risk factors for ongoing cognitive decline in this population are not clear. Better understanding these factors may have important implications for patient care and for the development of clinical trials with new therapeutic agents. Therefore, prospective studies to predict the deterioration of PD-MCI patients and the development of dementia will help define the prognosis of MCI in PD.

Cross-sectional studies have shown PD-MCI patients to exhibit greater brain atrophy than PD patients with normal cognitive capacities (PD-CN) and PDD than PD-MCI patients (Song et al., 2011, Segura et al. 2014, Pereira et al. 2014b). Thus, MRI studies to evaluate the pattern of cerebral atrophy in PD-MCI patients who subsequently develop dementia could provide useful information. Indeed, PD patients who evolved dementia were seen to have a thinner frontal cortex (Compta et al. 2013), although no distinction was made between MCI and normal cognition at the time of analysis. However, frontostriatal, insular cortex and caudate nucleus atrophy (Lee et al. 2014), and hippocampal volume loss (Kandiah et al. 2014), have been associated with the progression to dementia in patients with early PD and MCI using Voxel-Based Morphometry (VBM). Nonetheless, this technique may not be sensitive enough to detect cortical atrophy (Pereira et al. 2014a). Elucidating specific patterns of atrophy by analyzing the thickness of the cortex in PD-MCI patients that will develop dementia should allow patients to be identified that are at highest risk of suffering dementia. The aim of this study was to define the baseline pattern of regional atrophy in terms of cortical thickness in PD patients with MCI who developed dementia during a 31 month follow-up.

Methods

Subjects

The individuals included in this study were recruited from the Movement Disorders Unit of the University Clinic of Navarra, and they were patients with PD (according to the UK Brain Bank criteria: Hughes et al. 1992) over 60 years of age, with disease duration of at least 10 years. MCI was diagnosed according to the level II guidelines of the Movement disorders Criteria Task Force, when: 1) cognitive decline was reported by either the patient or informant, or observed by the neurologist; 2) the patient scored 1.5 standard deviations or more below the mean for age- and education-matched healthy controls in at least two tests of the ten that explore five cognitive domains (two tests per domain); 3) no evidence of abnormal activity in daily living. Dementia was diagnosed according to the MDS criteria (Emre et al. 2007), and it was typified by the patient having cognitive impairment in more than one cognitive domain that represented a decline from premorbid levels and by deficits that were severe enough to significantly impair functional independence. Activities of daily living/functional independence were assessed with the Interview for Deterioration in Daily Living Activities in Dementia (IDDD: Teunisse and Derix 1997).

Patients with other neurological or psychiatric disorders, including severe depression (a score higher than 20 in the Yesavage Geriatric Depression Rating Scale), abnormal findings in the cerebral MRI (i.e. tumour, hydrocephalus or severe vascular lesions), or other medical causes of cognitive impairment were excluded. In addition, 18 healthy controls were recruited from members of the Association of Blood Donors of Navarre (Spain) after excluding any history of major illness, psychiatric or neurological disease, memory complaints, neuropsychological assessment below normal scores, or MRI abnormalities.

Patients and controls underwent a neuropsychological evaluation and a brain MRI at baseline. Patients were clinically and neuropsychologically re-evaluated after a minimum of 24 months of follow-up (MRIs were not acquired at this point in time).

At this time, the patients were classified as PD-MCI converters if they had developed dementia (PDD), or PD-MCI non-converters if they remained with a diagnosis of MCI. Neuropsychological evaluation was undertaken with the Mini Mental State Examination (MMSE) and with a comprehensive neuropsychological battery evaluating five cognitive domains (attention, memory, language, and executive and visuospatial functions), as recommended by the MDS task force (Litvan et al., 2012) and as we used previously (Garcia-Garcia et al. 2012; Gasca-Salas et al. 2014; Gonzalez-Redondo et al. 2014). We also analyzed the composite score of each cognitive domain, which was calculated by averaging the Z-scores of the individual tests evaluating each domain. The Z-score of the tests was obtained as follows: (test score – mean score of control sample) / (standard deviation of control sample).

The Hoehn and Yahr scale and the motor section of the UPDRS (UPDRS-III) were used to assess parkinsonism. Dopaminergic treatment, as well as demographic and clinical variables were recorded.

The local Medical Ethics Committee approved the study and all the participants provided their written informed consent prior to enrolment.

MRI acquisition

Structural MR images were acquired using a Magnetom SP 1.5 T apparatus (Siemens Erlangen, Germany), acquiring three-dimensional (3D) T1-weighted images with 144 coronal slices. The imaging parameters employed were: repetition time (TR) = 1900 ms, echo time (TE) = 3.93 ms, flip angle = 15°, inversion time (TI) = 1100 ms, Matrix size = 192 × 144 × 256, voxel size = 0.977 × 1.5 × 0.977 mm^3.

MRI processing

Cortical thickness was analyzed using Freesurfer version 5.1 software (https://surfer.nmr.mgh.harvard.edu), as described elsewhere (Du et al. 2007; Gutierrez-Galve et al. 2009). Image processing included the following steps: motion correction of volumetric T1-weighted images (Reuter et al. 2010); skull strip where non-brain tissue was removed using a hybrid watershed/surface deformation procedure (Segonne et al. 2004); automated Talairach transformation; segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al. 2002); intensity normalization (Sled et al. 1998); tessellation of the gray matter/white matter boundary; automated topology correction; and surface deformation to optimally place the gray/white and gray/cerebrospinal fluid borders, located where the greatest shift in intensity defines the transition to the other tissue (Dale et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000).

Once the cortical models were complete, deformable procedures could be performed for further data processing and analysis, including: surface inflation (Fischl et al. 1999a); registration to a spherical atlas, which utilized individual cortical folding patterns to match cortical geometry across subjects (Fischl et al. 1999b); parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al. 2006; Fischl et al. 2004); and the creation of a variety of surface based data, including maps of curvature and sulcal depth. This method used both intensity and continuity information from the entire 3D MR volume for segmentation and deformation procedures in order to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale 2000). The maps were created using spatial intensity gradients across tissues and therefore, they were not simply reliant on absolute signal intensity. The maps produced were not restricted to the voxel resolution of the original data and thus, they were capable of detecting submillimeter differences between groups. Finally, the resulting images were smoothed with a full width at half maximum (FWHM) of 20 mm (Rahayel et al. 2015; Weston et al. 2016).

Statistical analysis

Baseline demographic features between controls and patients were compared with an analysis of variance or a Kruskall-

Table 1 General features of control subjects, PD-MCI non-converters and PD-MCI converters

	Controls (*n* = 18)	PD-MCI non-converters (*n* = 15)	PD-MCI converters (*n* = 8)
Age, (years)	67.6 (65–69)	70.1 (67–74)	69.6 (66–73.2)
Male, n (%)	11 (61%)	9 (60%)	6 (75%)
Disease duration, (years)	-	13.3 (11.5–15)	12.2 (11–13.2)
UPDRS III ON	-	17.8 (7.7–25)	14.6 (9–24)
LEDD, mg/day	-	1198.1 (1010–1500)	961.2 (625–1417)
H&Y	-	1.5:0%	1.5:25.0%
	-	2:13.3%	2:37.5%
	-	2.5:6.7%	2.5:0%
	-	3:73.3%	3:25.0%
	-	4:6.7%	4:12.5%
Educational level	< 8 years: 72.2%	<8 years: 86.7%	<8 years: 62.5%
	≥ 8 years: 27.8%	≥8 years: 13.3%	≥8 years: 37.5%

Continuous variables are represented by the mean and the interquartile range

There were no significant differences between groups

PD-MCI PD patients with mild cognitive impairment; *H&Y* Hoehn and Yahr scale; *LEDD* L-dopa equivalents daily dose; *MMSE* Mini Mental state examination

Wallis test for continuous variables, followed by post-hoc comparisons, and with a Chi-Squared test for categorical variables. The neuropsychological test scores and Z-scores were compared between PD-MCI converters and PD-MCI non-converters using a general linear model (GLM), with age and educational level as covariates. The baseline regional differences between groups (control, PD-MCI non-converters and PD-MCI converters) were assessed using a GLM with age and gender as covariates. Significance was set at p-value <0.001 uncorrected first and afterwards results were corrected for multiple comparisons analysis, $p < 0.05$ (i.e. a false discovery rate (FDR)).

Results

This study was carried out on 23 patients with PD-MCI and 18 healthy controls. After a 31 month follow-up (interquartile range: 25–36), 8 PD-MCI patients had converted to PDD (PD-MCI converters), whereas 15 remained as PD-MCI (PD-MCI non-converters). There were no differences at baseline between the two groups of patients in terms of the clinical, neuropsychological and demographic variables (Tables 1 and 2) and no patient reverted to PD-CN at follow-up.

Table 2 Neuropsychological test scores of the PD-MCI non-converters and PD-MCI converters

	PD-MCI non-converters (n = 15)	PD-MCI converters (n = 8)	p value PD-MCI converters vs non-converters
MMSE	26.1 (24–28)	26.7 (25.2–28)	0.51
Attention z-score	−1.49 (0.8)	−1.48 (1.43)	0.78
*Digits	10.1 (8–12.2)	9.7 (7.2–14)	0.31
*TMTA	99.7 (63–110)	98.7 (57.7–147.2)	0.12
SW	32.9 (28–35)	31.5 (20.7–45.5)	0.31
SC	30.1 (27–33)	30.8 (24.7–37.7)	0.71
Executive function z-score	−1.47 (0.74)	−1.64 (0.76)	0.47
*TMTB	246 (187–301)	254 (228.5–301)	0.86
*Phonemic fluency	9.1 (5–12)	8.25 (3.2–13)	0.16
RPM	21 (18–24)	21 (13.5–28.7)	0.19
SWC	39.5 (32–41)	36.8 (32.7–41)	0.94
Memory z score	−1.33 (0.81)	−1.36 (0.74)	0.83
*Cerad Word delayed recall	1.6 (1–3)	1.8 (0.2–3)	0.76
Cerad Word recognition	7.2 (7–9)	8 (6.2–9.7)	0.79
*FCSRT total score	48 (47–48)	45.9 (45–48)	0.17
Figure Recall	3.7 (0–7)	2.3 (0.2–4)	0.55
Language z score	−1.53 (0.85)	−1.71 (1.56)	0.92
*Boston	43 (36–48)	40.8 (37.7–46)	0.27
*Semantic fluency	11.5 (9–15)	12.3 (9.5–15)	0.48
Visuospatial z score	−0.73 (1.08)	−1.04 (1.41)	0.64
*[a] Copy of Figure	9.3 (8–10)	9.2 (10–10)	0.27
*[b] Copy of intersecting pentagons	2:53.3% (8) 1:13.3% (2) 0:33.3% (5)	2:50% (4) 1:25% (2) 0:25% (2)	0.46

[*] Tests used for the diagnosis of PD-MCI following MDS level II guidelines

Data of ordinal variables are expressed as the mean (interquartile range)

PD-MCI PD patients with mild cognitive impairment; *MMSE* Mini-mental state examination; *TMT-A* Trail making test a; *SW* Stroop words; *SC* Stroop colors; *SWC* Stroop words-colors; *RPM* Raven progressive matrices; *TMT-B* Trail making test B; *FCSRT* Free and cue selective reminding test; Boston Boston naming test

[a] Copy and delayed recall of the most complex figure from the two simple figures of Massachusetts General Hospital (Sala et al., 2008)

[b] Copy of intersecting pentagon is represented by the frequency of presentation of each score given its small range. Scoring was performed using a 0–2 rating scale in which: 2 points indicated that all 10 angles were present and the 2 pentagons were intersecting; 1 point indicated that the two intersecting figures were present and one of them had 5 angles; and 0 indicating a poorer performance than the first two cases (Ala et al., 2001)

Cortical thickness

PD-MCI converters and PD-MCI non-converters versus control subjects

PD-MCI converters had a thinner cortex than healthy controls in several brain regions, bilaterally in the frontal cortex (mainly superior and medial frontal and precentral cortex), the insula and in the parietal cortex (bilateral superior parietal cortex, supramarginal, precuneus and left inferior parietal). Small regions with a thinner cortex were also observed in the occipital cortex and fusiform gyrus (Fig. 1a, Table 3).

The areas with a thinner cortex in PD-MCI non-converters than in healthy subjects was more restricted, and such a reduction was evident in the bilateral frontal (predominantly in the precentral cortex) and parietal cortex (mostly in the bilateral supramarginal gyrus, left superior parietal and precuneus and right inferior parietal), and to a lesser extent in the temporal and occipital cortices (Fig. 1b, Table 4).

With the exception of occipital areas, most areas of the frontal, parietal and temporal lobes survived to the multiple comparisons analysis (FDR, $p < 0.05$) (Supplementary Fig. A and B).

PD-MCI converters versus PD-MCI non-converters

In PD-MCI converters the cortex was thinner bilaterally in the frontal cortex (mostly in the pars opercularis and orbitofrontal cortex), insula and in the left middle temporal cortex than in PD-MCI non-converters. In no area was the cortex of PD-MCI non-converters thinner than in PD-MCI converters (Fig. 1c, Table 5).

No significant differences were found between the two groups of patients when correcting for multiple comparisons analysis (FDR, $p < 0.05$).

Discussion

In this study we found that, patients with PD-MCI who developed dementia (PD-MCI converters) had a thinner cortex at baseline than patients whose MCI remained stable after a 31 month follow-up in the orbitofrontal cortex, the inferior areas of the frontal lobe, the insula and the temporal cortex. In addition, we showed that PD-MCI converters had more extensive cortical thinning in the frontal lobe than healthy controls, as well as in the parietal, temporal and occipital lobes relative to PD-MCI non-converters. These findings are critically important, because not all patients with PD-MCI will develop dementia and identifying a specific pattern of brain atrophy in such patients may be useful in predicting cognitive deterioration.

Although previous cross-sectional studies have shown a varied reduction in grey matter (GM) volume (Song et al., 2011) and cortical thickness (Pagonabarraga et al. 2013; Segura et al. 2014; Pereira et al. 2014a) in PD-MCI patients compared to controls, only two studies have separately analyzed and compared PD-MCI patients who evolved to dementia with stable MCI patients (Lee et al. 2014; Kandiah et al. 2014). In these studies the PD-MCI converters had a lower GM density than PD-MCI non-converters in the frontal lobe, insula and caudate nucleus when assessed using a VBM approach (Lee et al. 2014), as well as a smaller hippocampal volume assessed by a ROI approach (Kandiah et al. 2014). We found more extensive GM loss in PD-MCI converters when compared with controls and PD-MCI non-converters than that reported previously (uncorrected results, $p < 0.001$) (Lee et al. 2014), probably due to the higher sensitivity of the technique we used. However, the difference with previous studies may be related with the higher risk for dementia in our more advanced patients and also that we used MCI criteria specific for PD according with the MDS task force. Moreover, baseline cognitive features of PD patients in Lee et al. study are not comparable with our patient population as while we did not detect significant differences in the cognitive outcome

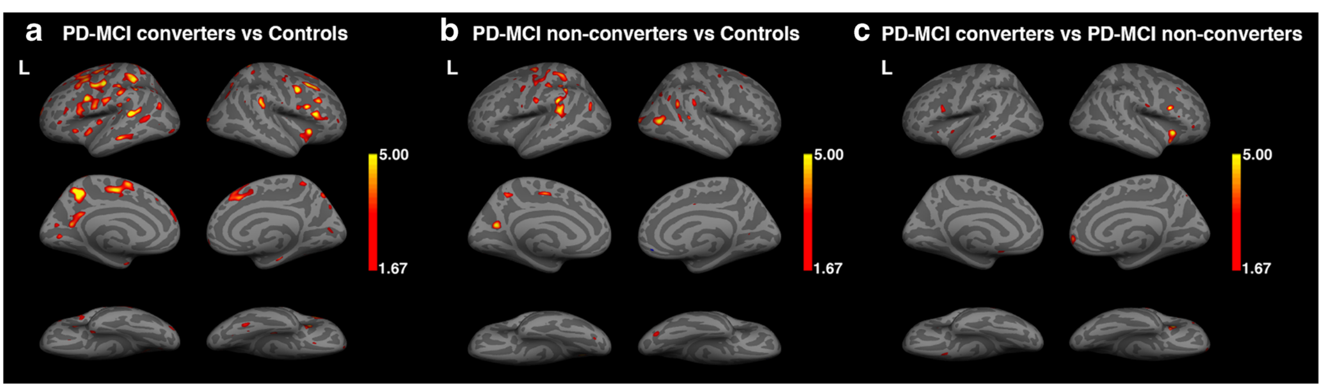

Fig. 1 Reduced regional cortical thickness in PD-MCI converters compared to healthy controls. (**a**) PD-MCI converters < controls ($p < 0.001$ uncorrected: age and sex as covariates). (**b**)PD-MCI non-converters < controls ($p < 0.001$ uncorrected: age and sex as covariates). (**c**) PD-MCI converters < PD-MCI non-converters ($p < 0.001$ uncorrected: age and sex as covariates)

Table 3 Reduced regional cortical thickness in PD-MCI converters compared to healthy controls

PD-MCI converters < Controls		Talairach coordinates						
Left side	Anatomical location	Cluster size (mm2)	x	y	z	Number of vertices	VtxMax	p
	Rostral middle frontal, superior frontal	252.17	−19.1	57.5	8.3	330	54,504	0.00004
	Rostral middle frontal	152.61	−22.2	41.4	23.1	211	152,177	0.0003
	Superior frontal	212.23	−7.0	53.9	24.0	400	106,163	0.00016
	Pars triangularis	143.57	−48.0	33.6	−1.7	202	33,381	0.00036
	Precentral, superior frontal, caudal middle frontal	3413.15	−36.7	−12.5	36.4	7010	105,700	0.000002
	Precentral, pars opercularis, postcentral	1459.52	−42.8	1.8	26.0	3266	66,538	0.000002
	Paracentral,precentral	785.40	−7.4	−12.7	46.4	1798	151,487	0.0000057
	Postcentral	482.04	−18.3	−38.8	67.0	1080	47,266	0.000008
	Lateral orbitofrontal	56.59	−19.0	23.3	−17.2	99	64,824	0.0009
	Insula	339.49	−33.7	−8.4	−5.2	784	38,229	0.000055
	Insula	181.28	−34.8	−16.0	2.6	366	68,244	0.000085
	Superior temporal, supramarginal, inferior parietal	589.48	−6.9	−48.3	46.5	1261	147,602	0.0000003
	Middle temporal	370.30	−60.8	−28.0	−9.1	658	972	0.000014
	Middle temporal, inferior parietal	345.76	−50.8	−57.3	10.7	594	156,986	0.0002
	Entorhinal	95.33	−27.6	−3.5	−23.8	219	62,479	0.0001
	Supramarginal	739.44	−50.2	−44.1	43.7	1802	38,287	0.00002
	Supramarginal	308.19	−53.6	−28.4	19.3	706	68,414	0.00047
	Superior parietal, postcentral	612.73	−35.2	−41.3	47.7	1363	67,036	0.000005
	Inferior parietal	360.90	−28.2	−62.5	39.5	697	112,081	0.0005
	Precuneus	589.48	−6.9	−48.3	46.5	1261	147,602	0.0000003
	Precuneus, isthmus cingulate	520.67	−11.2	−55.4	16.3	1123	112,997	0.00002
	Lateral occipital	170.28	−34.8	−87.8	−3.2	245	119,145	0.0001
	Pericalcarine, lingual	132.47	−8.6	−72.6	7.1	224	162,507	0.0001
	Pericalcarine, cuneus	132.73	−9.0	−65.5	11.9	172	126,423	0.00025
Right side	Frontal pole	96.92	7.0	60.6	−10.9	141	33,381	0.0006
	Rostral middle frontal	221.60	43.8	24.1	25.5	375	152,333	0.00001
	Superior frontal	720.85	8.1	20.6	39.8	1449	54,945	0.00003
	Superior frontal	257.34	21.2	20.3	49.8	446	116,706	0.00006
	Caudal middle frontal, rostral middle frontal	529.50	39.8	18.2	44.6	809	152,461	0.000005
	Lateral orbitofrontal	21.26	14.5	18.9	−21.1	66	153,660	0.0005
	Pars opercularis, parstriangularis	556.67	52.7	24.1	14.7	958	145,653	0.000004
	Pars opercularis, precentral	292.67	41.4	12.1	18.8	617	129,670	0.000004
	Precentral, frontal medio caudal	596.50	45.4	1.2	35.8	1154	67,419	0.0000009
	Postcentral	35.92	62.7	−11.6	21.1	96	3.110	0.0008
	Insula	387.60	32.5	19.4	−1.5	932	60,674	0.000002
	Parahippocampus	48.56	23.0	−20.3	−18.6	160	10,961	0.00009
	Supramarginal	323.57	58.1	−35.7	27.1	733	9728	0.00001
	Superior parietal	135.32	18.2	−43-0	60.0	254	123,707	0.00002
	Superior parietal, precuneus	537.07	8.2	−68.9	45.8	920	42,622	0.00008
	Superior parietal, inferior parietal	395.30	25.8	−57.0	42.8	766	55,572	0.00009
	Superior paritetal	142.05	16.8	−57.6	57.0	293	86,907	0.0001
	Precuneus	102.83	12.0	−43.2	58.0	297	67,088	0.0001
	Pericalcarine	139.96	13.4	−73.3	16.7	207	86,472	0.0006
	Fusiform	181.0	40.0	−52.3	−13.6	325	90,804	0.0002
	Lateral occipital	295.91	24.4	−92.7	9.4	391	87,899	0.00005

Table 4 Reduced regional cortical thickness in PD-MCI non-converters compared to healthy controls

PD-MCI non converters < Controls		Talairach coordinates						
Left side	Anatomical location	Cluster size (mm2)	x	y	z	Number of vertices	VtxMax	p
	Caudal middle frontal	71.55	−31.2	5.6	48.6	115	3983	0.0008
	Precentral, postcentral	1077.90	−28.1	−10.8	57.4	2539	32,297	0.00004
	Postcentral	222.24	−44.1	−23.7	36.7	536	47,096	0.00006
	Paracentral, superior frontal	153.45	−8.7	−12.9	45.7	378	151,490	0.00004
	Supramarginal, superior temporal, bankssts	1207.42	−52.7	−36.7	30.2	2737	141,713	0.000002
	Superior temporal	38.68	−64.8	−26.6	3.8	3.8	101	0.0009
	Superior parietal, postcentral	463.01	−31.7	37.9	50.0	993	26,678	0.00003
	Inferior parietal	137.30	−45.2	−67.7	25.7	242	64,614	0.00008
	Precuneus	250.72	−19.3	−57.0	20.9	504	46,151	0.00001
	Fusiform	49.36	−28.7	−79.4	−5.2	60	35,989	0.0005
Right side	Superior frontal	144.18	20.1	20.0	51.6	265	99,853	0.0001
	Caudal middle frontal	80.60	41.6	17.6	40.6	116	19,885	0.0005
	Precentral	108.63	37.3	−5.2	52.3	238	116,186	0.0004
	Supramarginal	162.59	55.3	−35.9	27.2	354	159,224	0.0001
	Posterior cingulate	25.56	7.4	−1.6	38.0	61	65,782	0.0008
	Inferior parietal,lateral occipital	391.86	45.2	−67.7	10.1	643	158,502	0.000008
	Inferior parietal, bankssts	123.43	47.6	−48.9	12.2	293	39,031	0.0002
	Inferior parietal	193.45	33.7	−68.4	36.2	327	78,581	0.0004
	Precuneus	22.92	27.3	−61.1	9.1	52	86,604	0.0008
	Fusiform, lateral occipital	140.27	34.6	−75.0	−6.2	206	8581	0.0003
	Lateral occipital	336.28	26.4	−91.8	10.3	460	39,256	0.00003

at baseline between the two groups of patients, they reported more severe impairment in the group that evolved to dementia (Lee et al. 2014). Our comparison between PD-MCI converters and non-converters did not survive for multiple comparisons analysis, however, we believe that this is due to the small sample size as in the other comparisons (PD-MCI groups vs healthy controls) corrected results with FDR showed similar regions to the uncorrected ones.

Table 5 Reduced regional cortical thickness in PD-MCI converters compared to PD-MCI non-converters

PD-MCI converters < PD-MCI non-converters		Talairach coordinates						
Left side	Anatomical location	Cluster size (mm^2)	x	y	z	Number of vertices	VtxMax	p
	Lateral orbitofrontal	30.38	−28.1	22.5	−0.8	82	61,120	0.0007
	Medial orbitofrontal	54.43	−6.2	6.9	−10.0	97	58,997	0.0003
	Pars opercularis	156.23	−42.8	10.6	18.4	305	73,334	0.0002
	Insula	63.38	−35.0	−7.5	−3.1	131	5000	0.0005
	Middle temporal	80.49	−6.1	−39.2	−7.0	155	122,714	0.0003
Right side	Medial orbitofrontal, frontal pole, superior frontal	242.89	9.3	54.9	−4.2	322	134,563	0.00006
	Pars triangularis	123.49	46.4	36.4	−3.8	180	145,999	0.0004
	Pars opercularis	125.08	42.3	11.1	18.5	258	103,712	0.0000076
	Caudal middle frontal	85.83	36.2	27.3	40.1	141	103,554	0.0003
	Insula, lateral orbitofrontal	282.43	32.2	19.5	−2.0	720	20,351	0.000003
	Postcentral	68.51	63.9	−9.0	17.6	193	145,639	0.0008
	Superior parietal	50.63	8.8	−69.1	45.8	95	42,623	0.0007

Here, we examined long lasting (more than 10 years of disease duration) and aged PD patients, patients more typically at high risk of dementia, with MCI diagnosed according to the MDS criteria. Our data suggest that advanced and aged PD-MCI patients at higher risk of dementia have more advanced disturbances in the brain, which while still below the threshold for detection by clinical and neuropsychological assessment, may be evident in MRI that can aid the identification of such patients. In this sense, some of the regions with a thinner cortex in PD-MCI converters to dementia (medial occipital, middle temporal, superior frontal and orbitofrontal cortex) are typically hypometabolic in PD-MCI patients and these changes are evident as a loss of GM volume in PDD patients (Gonzalez-Redondo et al. 2014). In addition, a longitudinal study found similar regions of cortical thickness reduction in PD patients with cognitive decline (Mak et al. 2015). Hence, cortical thickness appears to be more sensitive than VBM to detect brain changes earlier and to predict dementia. Indeed, previous cross-sectional studies showed that PDD patients had a lower GM volume (Song et al., 2011) and a thinner cortex (Pagonabarraga et al. 2013) than PD-MCI patients, mainly in the temporal and frontal cortical areas. These changes coincide with the differences we found between PD-MCI converters and non-converters. Thus, PD-MCI converters would appear to have a more similar pattern to PDD than PD-MCI non-converters.

We must acknowledge the limitation of the small number of patients studied here, which makes it necessary to replicate these data in larger studies. However, our study has the strength of having studied the most typical group of patients at high risk of dementia in clinical practice (aged and long term disease). In addition, MDS diagnostic criteria for MCI were used and cortical thickness was measured, which is more sensitive than VBM to detect differences in the GM.

Conclusions

This is the first study to show that aged and long-term PD patients with MCI who develop dementia in the short-medium term have a thinner cortex in several areas than PD-MCI patients that remain stable or controls. The areas affected include the orbitofrontal cortex, middle temporal lobe and insula. Importantly, we found out that this was observed even in the absence of cognitive differences at baseline. More studies in homogeneous groups of patients will be needed to confirm that brain MRI analysis of cortical thickness represents a suitable tool to identify PD-MCI patients at a higher risk of developing dementia.

Compliance with ethical standards

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Author Daniel García-Lorenzo declares that he has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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