ORIGINAL ARTICLE

Progression of subcortical atrophy in mild Parkinson's disease and its impact on cognition

H. Foo[a], E. Mak[b], T. T. Yong[a], M. C. Wen[a], R. J. Chander[a], W. L. Au[a,c], Y. Y. Sitoh[c,d], L. C. S. Tan[a,c] and N. Kandiah[a,c]

[a]*Department of Neurology, National Neuroscience Institute, Singapore;* [b]*Department of Psychiatry, University of Cambridge, Cambridge, UK;* [c]*Duke-NUS, Graduate Medical School; and* [d]*Department of Neuroradiology, National Neuroscience Institute, Singapore*

Keywords:
cognitive impairment, Parkinson's disease, subcortical atrophy

Received 15 July 2016
Accepted 25 October 2016

European Journal of Neurology 2016, **0:** 1–8

doi:10.1111/ene.13205

Background and purpose: Mild cognitive impairment (MCI) is associated with pronounced grey matter atrophy in various brain regions. However, the association between atrophy patterns and progression from no cognitive impairment (NCI) to Parkinson's disease (PD)-MCI is not clearly known. We investigated the pattern and progression of atrophy in subcortical structures and its impact on cognition in patients with mild PD.

Methods: Sixty-five patients with mild PD with baseline and longitudinal clinical and neuropsychological assessments, and structural magnetic resonance imaging scans were studied. Movement Disorder Society Task Force criteria were used to classify patients with PD into PD-NCI (n = 54) and PD-MCI (n = 11). Based on progression over time, those who remained without cognitive impairment were classified as PD-stable (n = 42) and those who converted to MCI over 18 months were classified as PD-converters (n = 12). FreeSurfer was used to measure cortical thickness and subcortical volumes at baseline and follow-up.

Results: Parkinson's disease-MCI showed baseline thalamus atrophy and progressive atrophy in the thalamus, caudate, presubiculum, cornu ammonis 1 and 2–3, and significant memory and executive dysfunction compared with PD-NCI. PD-converters had greater accumbens atrophy at baseline and progressive atrophy in the thalamus, caudate and accumbens with dysfunctions in memory and executive domains.

Conclusions: Progression of cognitive impairment in non-demented PD is associated with a specific pattern of subcortical atrophy. Findings from this study will allow future studies to investigate in the role of subcortical structures as a biomarker for PD dementia.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor and non-motor symptoms [1–3]. Non-motor symptoms, such as cognitive impairment, appear early in the course of disease and affect around 25% of newly diagnosed patients [4]. Mild cognitive impairment (MCI) is a high-risk transitory state for dementia; it has been reported that up to 80% of patients with PD with MCI will develop dementia [5,6]. Therefore, biomarkers, which allow early identification of patients with PD at high risk of developing PD dementia, are of prognostic importance.

Studies investigating cerebral structural changes associated with PD have extended beyond the striatum to include other subcortical structures that were reported to further perturb the basal ganglia–thalamocortical loops important to the pathophysiology of PD [7,8]. However, the pattern of subcortical degeneration related to PD remains unclear. Previous imaging studies reported grey matter reductions and shape alterations in subcortical regions, such as the caudate

Correspondence: N. Kandiah, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433 (tel.: + 65 63577171; fax: +65 63577137; e-mail: nagaendran_kandiah@nni.com.sg).

EUROPEAN JOURNAL OF NEUROLOGY

nucleus, thalamus, putamen and hippocampus [9,10], whereas others reported subcortical preservation in non-demented PD [11,12]. The variable findings could possibly be due to the cognitively heterogeneous groups of patients, particularly where patients with PD-MCI were not distinguished from patients with PD with normal cognition, or the lack of sensitivity to detect subtle changes in subcortical structures in cross-sectional measurements due to between-subject variance. To systematically study the pattern of subcortical grey matter atrophy in mild PD and its impact on cognition, we employed the Movement Disorder Society Task Force criteria to classify the cognitive status of patients with PD. In addition, we used serial imaging to track the progression of subcortical atrophy, which provided insights into the vulnerability of certain subcortical structures as well as their trajectory of atrophy and how cognitive status could exacerbate this atrophy.

We investigated the progression of subcortical atrophy using serial magnetic resonance imaging (MRI) over 18 months in two groups of patients: PD-no cognitive impairment (NCI) and PD-MCI. We also extended the study to investigate the difference between patients with PD-NCI who converted to PD-MCI (PD-converters) and those who did not convert (PD-stable) over 18 months. Correlations between subcortical structures and longitudinal cognitive decline were performed. Furthermore, we examined the predictive utility of baseline subcortical volumes in the progression from PD-NCI to PD-MCI. We hypothesized that PD-MCI and PD-converters would be characterized by significant subcortical atrophy at baseline and over time as compared with PD-NCI and PD-stable.

Materials and methods

Subjects

Eighty-five patients with mild PD, as defined by Hoehn and Yahr staging of <3 without pre-existing dementia, were recruited from a tertiary neurology centre between August 2011 and March 2012, and followed up for 18 months [13]. Of the 85 subjects, 19 subjects did not return for follow-up neuroimaging and one subject died during the follow-up period. A final cohort of 65 subjects was investigated. The Singhealth institutional ethics review board approved the study and informed consent was obtained from all patients.

Assessments

All patients underwent clinical, neuropsychological and MRI assessments at baseline and follow-up. Clinical assessments including Unified Parkinson's Disease Rating Scale and Hoehn and Yahr scoring were performed by neurologists. A psychologist evaluated cognitive function using the following tests: Mini-Mental State Examination [14] and Montreal Cognitive Assessment [15] to evaluate global cognition; word-list delayed and recognition recall to assess episodic memory; 10-point clock drawing and frontal assessment battery to test executive function; digit span forward and digit span backward to evaluate attention; number of errors made on Maze test and constructional praxis to assess visuospatial ability; and animal fluency and comprehension of test instructions to examine language ability [16]. Performance on the individual tasks was transformed into *z*-scores. A composite summary index for each cognitive domain was then derived from the corresponding averages of the tests.

Mild cognitive impairment classification

To qualify as PD-MCI for Movement Disorder Society level 2 [17], we evaluated performance on five cognitive domains, i.e. memory, executive function, visuospatial abilities, language and attention/working memory, wherein performance of 1.5 SD below the norm was considered abnormal [17]. Impairment on at least two cognitive tests as represented by either impairment on two tests in one domain or impairment on one test in two different domains was required. Patients who did not fulfill the criteria were classified as PD-NCI. Within PD-NCI, we tracked patients who remained cognitively stable (PD-stable; $n = 42$) and those who converted to PD-MCI (PD-converters; $n = 12$) over 18 months. We also investigated the differences in subcortical structures between baseline and follow-up MRI in the PD-stable group.

Image acquisition and analysis

All subjects underwent MRI on a 3-Tesla scanner system (GE Healthcare, Singapore). A high-resolution T1-weighted magnetization prepared rapid gradient echo imaging (axial; 176 slices; matrix size, 256 × 256; voxel size, 1.0 × 1.0 × 1.0 mm^3; echo time, 3.2 ms; repetition time, 7 ms; inversion time, 850 ms; flip angle, 8°; field of view, 256 × 256 mm^2) was acquired at baseline and 18 months.

Cortical reconstruction and volumetric segmentation were performed using FreeSurfer 5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Technical details have been previously described [18]. Briefly, the pre-processing procedure includes removal of no-brain tissue, automated Talairach

transformation, intensity normalization, segmentation of subcortical white matter and deep grey matter volumetric structures, tessellation of the grey/white matter boundary, automated topology correction and surface deformation to detect grey/white and grey/cerebrospinal fluid boundaries [19]. For the longitudinal processing, an unbiased within-subject template space and image were created using robust, inverse consistent registration [19]. All segmentations were visually inspected for accuracy and manual corrections were performed in the event of tissue misclassification/white matter errors while blinded to group diagnostic information.

Regional volumes of the thalamus, caudate nucleus, putamen, pallidum, hippocampus, amygdala and nucleus accumbens were automatically measured for each hemisphere at each time point. An automated segmentation tool built in FreeSurfer based on a probabilistic statistical atlas was used to investigate volumetric differences of the hippocampal subfields [20]. The hippocampal subfields segmented were the fimbria, presubiculum, subiculum, cornu ammonis (CA)1, CA2–3, CA4–dentate gyrus fields and hippocampal fissure. Percentage changes in the volumes between two time points in subcortical longitudinal changes were calculated using the following formula: [(volume follow-up – volume baseline)/volume baseline] × 100%. Age, gender, education, disease duration and total intracranial volume were controlled for. Mean cortical thickness volume and total grey matter volume were also computed.

Statistical analyses

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, IL, USA). Skewness–kurtosis and visual inspection of the histogram were used to examine normality for continuous variables. Differences between categorical variables were examined using chi-square tests. Parametric data were assessed using independent-samples *t*-test, whereas non-parametric data were assessed using Mann–Whitney *U* test. ANCOVA was employed followed by *post-hoc* comparisons using Bonferroni corrections. Partial correlations were also used to determine the associations between subcortical structures and cognition and clinical variables. In addition, logistic regression was used to investigate the predictive utility of baseline subcortical volumes in the development of PD-MCI from PD-NCI. All analyses were controlled for age, gender, education and intracranial volume. Results with a two-tailed $P < 0.05$ were considered significant.

Results

Subject characteristics

Subject characteristics are summarized in Table 1. PD-MCI had significantly lower baseline scores in global cognition and changes in memory and executive function compared with PD-NCI. PD-converters also showed significantly lower baseline scores in memory and attention and changes in memory compared with PD-stable.

Comparison of subcortical atrophy

At baseline, PD-MCI had significant atrophy in the left thalamus (Fig. 1; Table 2). Over 18 months, patients with PD-MCI showed significant atrophy in the right thalamus and right caudate nucleus, and demonstrated hippocampal atrophy at trend level compared with PD-NCI. Further analyses showed significant atrophy in the left presubiculum, CA1 and CA2–3 in PD-MCI compared with PD-NCI over 18 months (Fig. 2; Table 2).

Within PD-NCI, we investigated the subcortical atrophy patterns between PD-stable and PD-converters. Over 18 months, PD-converters showed significant atrophy in the left thalamus, caudate nucleus and right accumbens (Fig. 1; Table 3). In addition, among PD-stable patients, the follow-up MRI showed significantly reduced volumes in the right pallidum compared with their baseline scans ($t = 2.243$, d.f. = 41, $P = 0.030$).

Baseline volumes of the right thalamus ($P = 0.028$) and right accumbens ($P = 0.019$) showed predictive utility in determining the conversion from PD-NCI to PD-MCI over 18 months.

Association between subcortical atrophy and cognitive and motor functions

Over 18 months, regression analyses revealed that memory performance was significantly correlated with the left thalamus ($R^2 = 0.085$, $\beta = 0.298$, $P = 0.033$) and right nucleus accumbens ($R^2 = 0.071$, $\beta = 0.313$, $P = 0.037$). Unified Parkinson's Disease Rating Scale was also significantly associated with the right nucleus accumbens ($R^2 = 0.020$, $\beta = 0.302$, $P = 0.050$).

Discussion

The key findings are: (i) PD-MCI showed atrophy in the thalamus at baseline and progressive atrophy in the right thalamus, right caudate nucleus and

Table 1 Baseline and longitudinal subject characteristics

	PD-NCI (n = 54)	PD-MCI (n = 11)	P	PD-stable (n = 42)	PD-converters (n = 12)	P
Age (years)	63.39 ± 6.86	69.45 ± 10.19	0.696	63.19 ± 7.21	64.08 ± 5.65	0.696
Gender (male) (%)	41 (75.9%)	6 (54.55%)	0.149	32 (76.19%)	9 (75.0%)	0.653
Education (years)	10.93 ± 3.40	9.73 ± 2.97	0.653	10.83 ± 3.41	11.25 ± 3.49	0.712
Disease duration (years)	4.74 ± 3.02	4.09 ± 3.39	0.431	4.57 ± 3.01	5.36 ± 3.10	0.431
Scan interval (years)	1.31 ± 0.14	1.39 ± 0.22	0.625	1.31 ± 0.14	1.29 ± 0.14	0.625
LEDD (mg)	621.20 ± 447.38	633.88 ± 452.27	0.803	621.20 ± 447.37	633.88 ± 452.27	0.803
Hoehn and Yahr score						
Baseline	2.08 ± 0.41	2.00 ± 0.59	0.762	2.04 ± 0.45	2.17 ± 0.54	0.426
Follow-up	1.87 ± 0.41	1.77 ± 0.52	0.548	1.84 ± 0.46	1.88 ± 0.43	0.849
Change	−0.06 ± 0.29	−0.03 ± 0.43	0.964	−0.05 ± 0.35	−0.11 ± 0.18	0.606
UPDRS III score						
Baseline	18.95 ± 8.96	15.27 ± 5.26	0.667	18.68 ± 8.93	19.92 ± 9.41	0.677
Follow-up	20.00 ± 9.07	17.18 ± 5.53	0.140	19.02 ± 8.35	23.42 ± 10.94	0.140
Change	0.26 ± 0.85	0.17 ± 0.37	0.289	0.26 ± 0.92	0.28 ± 0.55	0.289
Cortical thickness (mm)						
LH	2.19 ± 0.10	2.19 ± 0.11	0.878	2.19 ± 0.11	2.22 ± 0.08	0.286
RH	2.18 ± 0.10	2.18 ± 0.11	0.856	2.18 ± 0.10	2.21 ± 0.09	0.336
Total GM volume (mm^2)						
Baseline	518.85 ± 3.00	509.46 ± 48.11	0.474	517.75 ± 41.27	515.11 ± 30.33	0.835
Change	−0.73 ± 1.73	−0.39 ± 1.55	0.529	−0.60 ± 1.83	−1.04 ± 0.85	0.577
Global cognition (z-score)						
Baseline	0.10 ± 0.90	−0.62 ± 1.11	*0.022*	0.23 ± 0.57	−0.34 ± 1.54	0.052
Follow-up	0.15 ± 0.91	−0.80 ± 1.02	*<0.001*	0.28 ± 0.53	−0.32 ± 1.63	0.154
Change	0.04 ± 0.33	−0.18 ± 0.49	0.067	0.05 ± 0.34	0.02 ± 0.31	0.777
Episodic memory (z-score)						
Baseline	0.14 ± 0.88	−0.06 ± 0.47	0.121	0.03 ± 0.95	0.56 ± 0.37	0.055
Follow-up	0.07 ± 0.71	−0.93 ± 0.96	*0.001*	0.13 ± 0.69	−0.14 ± 0.77	0.178
Change	−0.002 ± 1.09	−0.87 ± 0.78	*0.008*	0.20 ± 0.69	−0.70 ± 0.69	*0.013*
Executive function (z-score)						
Baseline	0.15 ± 0.67	−0.37 ± 1.02	0.130	0.10 ± 0.73	0.31 ± 0.41	0.522
Follow-up	0.12 ± 0.68	−1.59 ± 1.49	*0.001*	0.23 ± 0.54	−0.25 ± 0.97	0.157
Change	−0.03 ± 0.95	−1.28 ± 1.64	*0.036*	0.12 ± 0.89	−0.56 ± 1.02	0.055
Attention (z-score)						
Baseline	−0.04 ± 0.64	0.28 ± 0.63	0.140	0.05 ± 0.65	−0.40 ± 0.45	*0.034*
Follow-up	−0.03 ± 0.54	0.15 ± 0.65	0.404	0.04 ± 0.54	−0.25 ± 0.51	0.106
Change	0.01 ± 0.64	−0.11 ± 0.46	0.793	−0.02 ± 0.66	0.12 ± 0.58	0.105
Visuospatial (z-score)						
Baseline	0.09 ± 0.58	−0.48 ± 1.40	0.210	0.04 ± 0.62	0.31 ± 0.31	0.139
Follow-up	−0.07 ± 0.86	−0.06 ± 0.39	0.961	−0.13 ± 0.93	0.13 ± 0.57	0.152
Change	−0.16 ± 1.04	−0.06 ± 0.39	0.130	−0.16 ± 1.13	−0.16 ± 0.70	0.934
Language (z-score)						
Baseline	0.09 ± 0.77	−0.29 ± 0.89	0.074	0.12 ± 0.83	−0.03 ± 0.48	0.182
Follow-up	−0.004 ± 0.82	−0.05 ± 0.74	0.853	−0.03 ± 0.88	0.09 ± 0.57	0.659
Change	−0.09 ± 1.14	0.24 ± 1.02	0.374	−0.15 ± 1.27	0.11 ± 0.43	0.269

GM, grey matter; LEDD, levodopa equivalent dose; LH, left hemisphere; MCI, mild cognitive impairment; NCI, no cognitive impairment; PD, Parkinson's disease; RH, right hemisphere; ±, standard deviation; values in italics denote significance at $P < 0.05$.

subregional hippocampus, such as the left presubiculum, CA1 and CA2–3, and showed a decline in memory and executive domains; (ii) PD-converters showed progressive left thalamus, caudate nucleus and right nucleus accumbens atrophy with accompanying decline in the memory and executive functions compared with PD-stable over 18 months; and (iii) baseline volumes of the right thalamus and right nucleus accumbens were predictive of the conversion from PD-NCI to PD-MCI over 18 months.

At present, the pathophysiological mechanisms underlying neurodegeneration and its impact on clinical–cognition outcomes, as well as the identification of structural biomarkers of cognitive impairment in patients with PD without dementia remain poorly understood. Previous cross-sectional studies reported varying degrees and significance of atrophy patterns in the subcortical structures [3,7,9–12]. Longitudinal studies, which investigated subcortical atrophy in patients with PD, were also limited by the

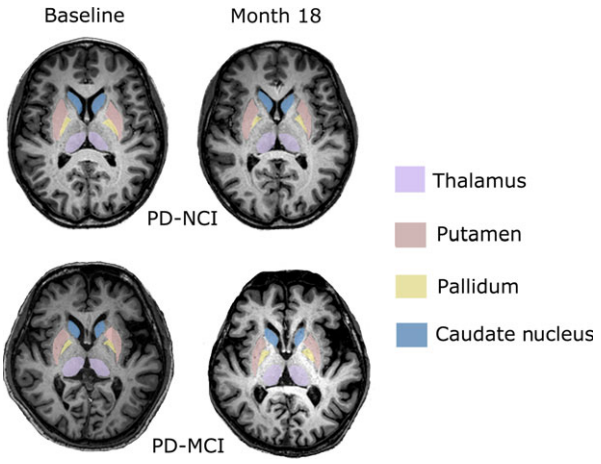

Figure 1 Comparisons of subcortical atrophy. MCI, mild cognitive impairment; NCI, no cognitive impairment; PD, Parkinson's disease. [Colour figure can be viewed at wileyonlinelibrary.com]

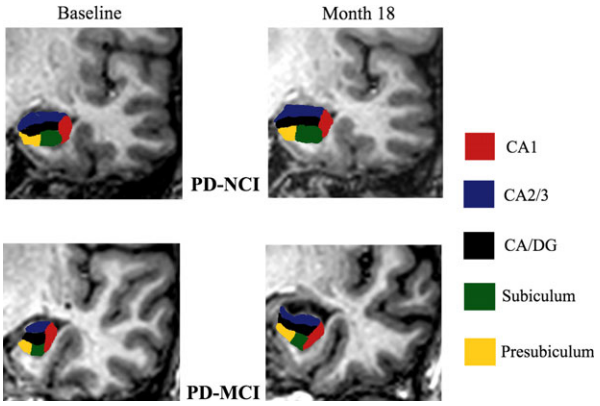

Figure 2 Comparisons of hippocampal subfield atrophy. CA, cornu ammonis; DG, dentate gyrus; MCI, mild cognitive impairment; NCI, no cognitive impairment; PD, Parkinson's disease. [Colour figure can be viewed at wileyonlinelibrary.com]

heterogeneity of cognitive status of their PD cohort [4,21] and the relatively small sample size [1].

Findings of subcortical volumetric reductions suggest that there might be a specific pattern of subcortical atrophy accompanied by cognitive decline that can be identified at the early stages of mild PD. In this study, PD-MCI and PD-converters showed similar patterns of progression of atrophy in the thalamus and caudate nucleus. As there is evidence showing that the thalamus actively modulates the function of basal ganglia and cortical neurons, atrophy in the thalamus could disrupt the basal ganglia–thalamocortical circuit and result in dysfunction in motor behaviour [21,22]. In addition to motor dysfunction, thalamic atrophy might also have an impact on the cognition of patients with PD. The thalamus is functionally connected to the hippocampus as part of the hippocampal–anterior thalamic interconnections that

Table 2 Subcortical volumetric and hippocampal subfield comparison between Parkinson's disease-no cognitive impairment (PD-NCI) and Parkinson's disease-mild cognitive impairment (PD-MCI)

	PD-NCI (n = 54)		PD-MCI (n = 11)		P, partial η^2	
Subcortical segmentation	Baseline	% change	Baseline	% change	Baseline	% change
LH						
Thalamus	6.6 ± 0.8	−1.3 ± 7.8	5.8 ± 0.7	−2.0 ± 1.6	*0.041*, 0.070	0.749, 0.002
Caudate	3.4 ± 0.5	0.5 ± 4.0	3.2 ± 0.6	−1.5 ± 3.4	0.318, 0.017	0.060, 0.060
Putamen	5.5 ± 0.8	1.0 ± 6.2	5.0 ± 0.6	0.8 ± 7.7	0.094, 0.048	0.932, <0.001
Pallidum	1.6 ± 0.3	−3.4 ± 12.0	1.5 ± 0.3	−2.5 ± 6.9	0.575, 0.005	0.822, 0.001
Hippocampus	3.7 ± 0.4	−1.0 ± 3.9	3.6 ± 0.5	−3.3 ± 2.1	0.678, 0.003	0.115, 0.042
Amygdala	1.5 ± 0.2	−0.2 ± 5.3	1.4 ± 0.2	0.61 ± 6.6	0.390, 0.013	0.565, 0.006
Accumbens	0.6 ± 0.2	−0.3 ± 15.8	0.5 ± 0.1	−3.7 ± 11.2	0.209, 0.027	0.468, 0.009
RH						
Thalamus	6.0 ± 0.6	−0.2 ± 4.8	5.9 ± 0.7	−4.1 ± 4.9	0.950, <0.001	*0.037*, 0.073
Caudate	3.6 ± 0.5	−0.03 ± 4.7	3.4 ± 0.5	−3.9 ± 5.7	0.291, 0.019	*0.027*, 0.081
Putamen	5.5 ± 0.6	−0.6 ± 5.4	5.1 ± 0.8	−3.1 ± 6.6	0.182, 0.030	0.221, 0.026
Pallidum	1.6 ± 0.2	−3.4 ± 11.9	1.6 ± 0.2	−5.4 ± 7.3	0.544, 0.006	0.977, <0.001
Hippocampus	3.9 ± 0.4	−0.9 ± 4.0	3.8 ± 0.5	−3.5 ± 2.0	0.818, 0.001	*0.050*, 0.065
Amygdala	1.8 ± 0.3	−1.0 ± 10.4	1.8 ± 0.2	−0.8 ± 11.6	0.305, 0.018	0.826, 0.001
Accumbens	0.6 ± 0.1	−2.2 ± 10.6	0.6 ± 0.1	−5.6 ± 8.0	0.887, <0.001	0.226, 0.025
Hippocampal subfields						
Left presubiculum	0.44 ± 0.05	−0.45 ± 5.40	0.43 ± 0.09	−4.61 ± 2.53	0.326, 0.017	*0.035*, 0.074
Left CA1	0.31 ± 0.04	−0.23 ± 5.89	0.31 ± 0.04	−4.76 ± 3.67	0.920, <0.001	*0.028*, 0.080
Left CA2–3	0.92 ± 0.13	−0.06 ± 4.60	0.93 ± 0.14	−3.42 ± 3.58	0.912, <0.001	*0.049*, 0.065
Right CA1	0.33 ± 0.05	2.69 ± 5.46	0.33 ± 0.04	−2.70 ± 3.29	0.859, 0.001	*0.005*, 0.126
Right CA2–3	1.00 ± 0.13	0.88 ± 4.64	1.03 ± 0.11	−2.13 ± 2.52	0.094, 0.047	*0.026*, 0.082

Analysis of covariance controlled for age, gender, education, disease duration and intracranial volume (only for volumetric comparison). CA, cornu ammonis; LH, left hemisphere; RH, right hemisphere; ±, standard deviation; values in italics denote significance at $P < 0.05$.

Table 3 Subcortical volumetric comparisons between Parkinson's disease (PD)-stable and PD-converters

	PD-stable (n = 42)		PD-converters (n = 12)		P, partial η^2	
Subcortical segmentation	Baseline	% change	Baseline	% change	Baseline	% change
LH						
Thalamus	6.6 ± 0.8	0.1 ± 7.8	6.5 ± 0.7	−6.1 ± 5.4	0.821, 0.001	*0.016*, 0.117
Caudate	3.4 ± 0.4	1.2 ± 4.0	3.4 ± 0.3	−2.1 ± 3.0	0.291, 0.024	*0.007*, 0.145
Putamen	5.5 ± 0.7	1.8 ± 6.6	5.6 ± 0.7	−1.9 ± 2.4	0.845, 0.001	0.092, 0.059
Pallidum	1.6 ± 0.3	−2.3 ± 12.7	1.6 ± 0.3	−7.0 ± 8.7	0.728, 0.003	0.219, 0.032
Hippocampus	3.8 ± 0.5	−0.7 ± 4.2	3.7 ± 0.3	−2.2 ± 1.6	0.621, 0.005	0.343, 0.019
Amygdala	1.5 ± 0.2	−0.6 ± 10.4	1.6 ± 0.2	−2.6 ± 5.5	0.356, 0.018	0.637, 0.005
Accumbens	0.6 ± 0.1	1.6 ± 16.4	0.6 ± 0.1	−6.9 ± 11.7	0.607, 0.006	0.149, 0.044
RH						
Thalamus	6.1 ± 0.6	0.3 ± 5.4	5.8 ± 0.8	−1.9 ± 2.3	0.197, 0.035	0.232, 0.030
Caudate	3.6 ± 0.6	0.7 ± 4.9	3.6 ± 0.4	−2.4 ± 2.4	0.595, 0.006	0.059, 0.074
Putamen	5.5 ± 0.6	0.02 ± 6.0	5.5 ± 0.5	−2.7 ± 1.8	0.859, 0.001	0.168, 0.040
Pallidum	1.6 ± 0.2	−3.1 ± 12.4	1.6 ± 0.2	−4.4 ± 10.1	0.833, 0.001	0.567, 0.007
Hippocampus	3.9 ± 0.4	−0.4 ± 4.2	3.9 ± 0.3	−2.9 ± 2.5	0.939, <0.001	0.109, 0.054
Amygdala	1.9 ± 0.3	−0.1 ± 11.2	1.8 ± 0.2	−3.8 ± 7.8	0.685, 0.004	0.473, 0.011
Accumbens	0.6 ± 0.1	−0.3 ± 10.9	0.7 ± 0.1	−9.0 ± 6.1	0.078, 0.064	*0.025*, 0.102

Analysis of covariance controlled for age, gender, education, disease duration and intracranial volume (only for volumetric comparison). LH, left hemisphere; RH, right hemisphere; ±, standard deviation; values in italics denote significance at $P < 0.05$.

are highly involved in episodic memory. Therefore, anterior thalamic atrophy could affect the hippocampus via the loss of inputs and so impair memory [23]. Moreover, atrophy in the caudate nucleus could reflect a nigrostriatal dopaminergic deafferentation and is consistent with the role of dopaminergic disruption in cognitive impairment in PD [24]. The loss of dopaminergic input to the caudate nucleus projecting to the dorsolateral prefrontal cortex could contribute to cognitive decline, particularly in frontal executive functions, in cognitively impaired patients with PD [25]. Previous studies have also supported the relationship between caudate dopamine transporter binding and cognition [26,27]. Taken together, progressive cognitive decline in PD could be associated with a multitude of neural networks and neurotransmitter systems associated with the thalamus–caudate nucleus atrophy seen in our PD-MCI and PD-converters.

Parkinson's disease-MCI demonstrated progressive hippocampal subfield atrophy in the left presubiculum together with CA1 and CA2–3 volumes in PD-MCI compared with PD-NCI despite insignificant whole hippocampal atrophy. Although hippocampal atrophy has been closely related to cognitive dysfunction in PD, the findings have been inconclusive. Although some cross-sectional studies have found significant hippocampal reductions in non-demented patients with PD [28,29], others did not report such a change [30,31]. A longitudinal study, however, has found progression of hippocampal atrophy [24]. The results suggest that, even in the absence of total hippocampal atrophy, given the high risk of developing dementia in PD and the finding that subregional hippocampal atrophy may herald the onset of dementia, subregional hippocampal atrophy could be an early indicator of dementia in PD [9].

Our findings also showed that PD-stable patients have progressive reduction in right pallidum volume at the end of 18 months. Previous studies have shown that atrophy in the pallidum could disrupt the thalamus and thalamocortical pathway, which could result in disruption to the motor pathways [11]. Hence, atrophy in the pallidum could explain the progressive motor changes in PD-stable patients with no resulting cognitive impairment.

Interestingly, among PD-converters, baseline volumes of the thalamus and nucleus accumbens were predictive of the conversion from PD-NCI to PD-MCI, and progression of nucleus accumbens atrophy was associated with concomitant memory and motor dysfunction. Thalamic and accumbens atrophy could result in a loss of dopamine innervations from the dorsal striatum to the ventral striatum as the disease progresses [1]. In addition, given evidence demonstrating that cholinergic interneurons are found in the nucleus accumbens and the theory that deficiency of acetylcholine in the brain is a major cause of cognitive symptoms [32], it could be postulated that atrophy in the nucleus accumbens in PD could result in the inadequate acetylcholinesterase for neurotransmission and, in turn, lead to the development of dementia in PD. Taken together, dopamine degeneration, coupled with the cholinergic denervation and baseline volumes of the thalamus and nucleus accumbens, could promote memory and motor dysfunction, and might serve

as early indicators and potential biomarkers for the conversion from PD-NCI to PD-MCI.

The limitations of our study include the lack of control subjects, which prevented comparisons between the changes found in patients with PD and physiological ageing. As such, these findings need to be confirmed in larger prospective studies with an additional group of well-matched healthy controls. In addition, the imbalance of sample size in the different groups suggests the need to interpret the results with caution. Future studies should aim to have similar number of subjects in each group so that comparisons can be made with greater confidence.

In conclusion, the present results show that patients with PD-MCI have a faster rate and extent of subcortical atrophy in the thalamus, caudate nucleus and subregional hippocampus together with declines in the clinical–cognitive characteristics that were reported in previous cross-sectional studies. More importantly, this study also showed that baseline volumes of the thalamus and nucleus accumbens are important structural biomarkers that could predict the conversion from PD-NCI to PD-MCI over 18 months. Therefore, early identification of subcortical atrophy could be a biomarker for cognitive decline in non-demented patients with mild PD.

Acknowledgements

This study was supported by the Ministry of Health, National Medical Research Council, Singapore (grant number NMRC/NIG/1043/2011).

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Hanganu A, Beditti C, Degroot C, *et al*. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. *Brain* 2014; **137:** 1120–1129.
2. Kandiah N, Zainal NH, Narasimhalu K, *et al*. Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease. *Parkinsonism Relat Disord* 2014; **20:** 1203–1208.
3. Zhang YC, Zhang JQ, Xu JP, *et al*. Cortical gyrification reductions and subcortical atrophy in Parkinson's disease. *Mov Disord* 2014; **29:** 122–126.
4. Ibarretxe-Bilbao N, Junque C, Segura B, *et al*. Progression of cortical thinning in Parkinson's disease. *Mov Disord* 2012; **27:** 1746–1754.
5. Agosta F, Canu E, Stefanova E, *et al*. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. *Hum Brain Mapp* 2014; **35:** 1921–1929.
6. Duncan GW, Firbank MJ, O'Brien JT, Burn DJ. Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease? *Mov Disord* 2013; **28:** 425–438.
7. Nemmi F, Sabatinic U, Rascol O, Péran P. Parkinson's disease and local atrophy in subcortical nuclei: insight from shape analysis. *Neurobiol Aging* 2015; **36:** 424–433.
8. Xia JG, Miu JL, Ding HB, *et al*. Changes of brain gray matter structure in Parkinson's disease patients with dementia. *Neural Regen Res* 2013; **8:** 1276–1285.
9. Lee HM, Kwon KY, Kim MJ, *et al*. Subcortical grey matter changes in untreated, early stage Parkinson's disease without dementia. *Parkinsonism Relat Disord* 2014; **20:** 622–626.
10. Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical atrophy is associated with cognitive impairment in mild Parkinson's disease: a combined investigation of volumetric changes, cortical thickness, and vertex-based shape analysis. *AJNR Am J Neuroradiol* 2014; **35:** 2257–2264.
11. Menke R, Szewczyk-Krolikowski K, Jbabdi S, *et al*. Comprehensive morphometry of subcortical grey matter structures in early-stage Parkinson's disease. *Hum Brain Mapp* 2014; **35:** 1681–1690.
12. Tinaz S, Courtney MG, Stern CE. Focal cortical and subcortical atrophy in early Parkinson's disease. *Mov Disord* 2011; **26:** 436–441.
13. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999; **56:** 33–39.
14. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinicians. *J Psychiatr Res* 1975; **12:** 189–198.
15. Dalrymple-Alford JC, MacAskill MR, Nakas CT, *et al*. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology* 2010; **75:** 1717–1725.
16. Saumier D, Duong A, Haine D, Garceau D, Sampalis J. Domain-specific cognitive effects of Tramiprosate in patients with mild to moderate Alzheimer's disease: ADAS-Cog subscale results from the alphase study. *J Nutr Health Aging* 2009; **13:** 808–812.
17. Litvan I, Goldman JG, Tröster AI, *et al*. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. *Mov Disord* 2012; **27:** 349–356.
18. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *NeuroImage* 1999; **9:** 195–207.
19. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage* 2012; **61:** 1402–1418.
20. Van Leemput K, Bakkour A, Benner T, *et al*. Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. *Hippocampus* 2009; **19:** 549–557.
21. Tessa C, Lucetti C, Giannelli M, *et al*. Progression of brain atrophy in the early stages of Parkinson's disease: a longitudinal tensor-based morphometry study in de novo patients without cognitive impairment. *Hum Brain Mapp* 2014; **35:** 3932–3944.
22. Halliday GM. Thalamic changes in Parkinson's disease. *Parkinsonism Relat Disord* 2009; **3** (Suppl.3)**:** 152–155.

23. Aggleton JP, O'Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT. Hippocampal–anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *Eur J Neurosci* 2010; **31:** 2292–2307.
24. Mak E, Li S, Williams GB, Firbank MJ, *et al*. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLED-PD study. *Brain* 2015; **138:** 1–13.
25. Jokinen P, Brück A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. *Parkinsonism Relat Disord* 2009; **15:** 88–93.
26. Polito C, Berti V, Ramat S, *et al*. Interaction of caudate dopamine depletion and brain metabolic changes with cognitive dysfunction in early Parkinson's disease. *Neurobiol Aging* 2012; **33:** e29–e39.
27. Ravina B, Marek K, Eberly S, *et al*. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. *Mov Disord* 2012; **27:** 1392–1397.
28. Camicioli R, Moore MM, Kinney A, *et al*. Parkinson's disease is associated with hippocampal atrophy. *Mov Disord* 2003; **18:** 784–790.
29. Beyer M, Brønnick K, Hwang K, *et al*. Memory impairment is associated with hippocampal atrophy in newly diagnosed Parkinson's disease. *Alzheimers Dement* 2011; **7:** S204–S205.
30. Apostolova LG, Beyer M, Green AE, *et al*. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. *Mov Disord* 2010; **25:** 687–695.
31. Carlesimo GA, Piras F, Assogna F, Pontieri FE, Caltagirone C, Spalletta G. Hippocampal abnormalities and memory deficits in Parkinson disease: a multimodal imaging study. *Neurology* 2012; **78:** 1939–1945.
32. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron* 2012; **76:** 116–129.