Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up.

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ABSTRACT

Background. Growing evidence highlights the relevance of posterior cortically-based cognitive deficits in Parkinson's disease (PD) as possible biomarkers of the evolution to dementia. Cross-sectional correlational studies have established a relationship between the degree of atrophy in posterior brain regions and visuospatial and visuoperceptual (VS/VP) impairment. The aim of this study is to address the progressive cortical thinning correlates of VS/VP performance in PD.

Methods. Forty-four PD patients and 20 matched healthy subjects were included in this study and followed for 4 years. Tests used to assess VS/VP functions included were: Benton's Judgement of Line Orientation (JLOT), Facial Recognition (FRT), and Visual Form Discrimination (VFDT) Tests; Symbol Digit Modalities Test (SDMT); and the Pentagon Copying Test (PCT). Structural magnetic resonance imaging data and FreeSurfer were used to evaluate cortical thinning evolution.

Results. PD patients with normal cognition (PD-NC) and PD patients with mild cognitive impairment (PD-MCI) differed significantly in the progression of cortical thinning in posterior regions. In PD-MCI patients, the change in VS/VP functions assessed by PCT, JLOT, FRT, and SMDT correlated with the symmetrized percent change of cortical thinning of occipital, parietal, and temporal regions. In PD-NC patients, we also observed a correlation between changes in FRT and thinning in parieto-occipital regions.

Conclusion. In this study, we establish the neuroanatomical substrate of progressive changes in VS/VP performance in PD patients with and without MCI. In agreement with cross-sectional data, VS/VP changes over time are related to cortical thinning in posterior regions.

INTRODUCTION

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder that manifests with a wide range of nonmotor symptoms. Recent initiatives have aimed to depict the features and evolution of cognitive decline in PD [1-4].

Impairment in specific cognitive domains has been associated with a differential risk of cognitive decline. While executive functions are widely recognized to be impaired in PD even at early disease stages [1,5,6], interest in the role of posterior cortically-based functions as biomarkers of the cognitive evolution to dementia (PDD) has increased [1,7,8].

Several cross-sectional structural MRI correlational studies have established a relationship between the degeneration of posterior brain regions and cognitive impairment [9-12]. Specifically, previous studies by our group showed that visuospatial and visuoperceptual (VS/VP) tests are suitable to reflect cortical thinning in lateral temporo-parietal regions in PD patients [13,14].

Longitudinal studies have assessed structural gray matter differences over time in PD [15,16], and the progression of cognitive impairment has been related to degeneration of several cortical regions, including bilateral frontal and temporoparietal areas [16-18]. Progressive atrophy in widespread brain regions, such as the bilateral temporal and right occipital medial lobes, left superior frontal gyrus, and inferior parietal cortex, has been related to worsening in measures of global cognition [17,18]. Also, volumetric studies have associated the decline in executive functions with mainly bilateral frontal areas [19,20]. However, to the best of our knowledge, the relationship between the impairment of specific VS/VP functions and cortical thinning over time has yet to be studied. The aims of this study are (1) to address differential progressive gray matter loss between PD patients and healthy controls (HC), as well as (2) to investigate the changes over time in VS/VP functions in PD patients grouped according to cognitive status and their relationship with progressive cortical degeneration.

METHODS

Participants

The cohort of this study was recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain), and HC were recruited from Institut de l'Envelliment (Barcelona, Spain). All participants are part of an ongoing longitudinal study, composed of 121 PD patients and 48 healthy subjects in the initial screening phase. Both groups were matched for age, sex, and years of education.

Inclusion criteria for participants consisted of fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank [21]. Exclusion criteria consisted of: presence of dementia according to the Movement Disorder Society criteria [22], Hoehn and Yahr scale (H&Y) score >3, juvenile-onset PD, presence of psychiatric and/or neurologic comorbidity, low global IQ score estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (scalar score ≤7 points), Mini-Mental State Examination (MMSE) score ≤25, claustrophobia, imaging findings on MRI not compatible with PD other than mild white matter hyperintensities in the FLAIR sequence, and MRI artifacts. The final sample at the baseline assessment consisted of 92 PD patients and 36 controls. A follow-up assessment was pursued after approximately four years (see Table 1), with a sample of of 20 HC and 44 PD patients. Only subjects with baseline and follow-up assessments were included in this study (see Supplementary Figure 1).

Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III). All PD patients were taking antiparkinsonian drugs, consisting of different combinations of L-DOPA, cathecol-O-methyltransferase inhibitors, monoamine oxidase inhibitors, dopamine agonists, and amantadine. In order to standardize doses, the L-DOPA equivalent daily dose (LEDD) [23] was calculated. All assessments were done while patients were under the effect of their usual medication ("on" state).

In line with the PD-MCI Movement Disorder Society Task Force (MDSTF) recommendations [24], we assessed five cognitive domains as previously described [12]. We divided the subjects into three groups: HC, PD patients without MCI (PD-NC), and PD patients with MCI (PD-MCI) at baseline. Expected z scores adjusted for age, sex, and education for each test and each subject were calculated based on a multiple regression analysis performed in the HC group [3]. As in previous studies [12,25], the presence of MCI was established if the z score for a given test was at least 1.5 lower than the expected score in at least two tests in one domain, or in at least one test per domain in at least two domains.

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

Visuospatial and visuoperceptual assessment

All participants underwent a comprehensive neuropsychological assessment with VS/VP tests usually employed to evaluate the cognitive status of PD patients. The battery of tests chosen in this study is the same as that used in a previous cross-sectional study that addressed the neuroanatomical correlates of VS/VP deficits in PD [14]. The tests included were the pentagon copying test (PCT) from the MMSE, scored according to the Modified Mini-Mental State criteria (3MS); Benton's Judgment of Line Orientation test (JLOT), Visual Form Discrimination test (VFDT), and Facial Recognition test (FRT); and Symbol Digits Modalities test (SDMT).

MRI acquisition

Magnetic resonance images (MRI) were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany) at baseline and follow-up. The scanning protocol included high-resolution 3-dimensional T1-weighted images

acquired in the sagittal plane (TR=2300 ms, TE=2.98ms, TI=900ms, 240 slices, FOV=256mm; matrix size=256x256; 1mm isotropic voxel and an axial FLAIR sequence (TR=9000ms, TE=96ms).

Longitudinal cortical thickness

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain structural measures as previously described [13]. After processing each subject cross-sectionally, in order to perform the longitudinal analyses of the data, within-subject templates [26] and corresponding longitudinal files were created for each time point for each subject. Briefly, a template volume for each subject using information from all of their time points and an average image were created using robust, inverse, consistent registration [27]. All time points were constructed through unbiased mean images and later aligned. After registration and creation of the templates, images from all time points are mapped to the template location and averaged, and processed with the default cross-sectional stream. The symmetrized percent change was used for longitudinal analyses of cortical thickness: [(Thickness at time point 1 – Thickness at time point 2)/Interval between assessments)]/[0.5*(Thickness at time point 1 + Thickness at time point 2)].

Comparisons between groups and regressions were assessed using vertex-by-vertex general linear models. Multiple contrasts were carried out to assess differences between all study subgroups (HC vs. all PD patients; HC vs. PD-NC; HC vs. PD-MCI; and PD-NC vs. PD-MCI). Regression models included symmetrized percent change as an independent factor and cognitive scores as dependent factors. In order to avoid clusters appearing significant purely by chance (i.e., false positives), Monte Carlo null-Z simulation with 10,000 iterations was applied to cortical thickness maps to provide clusterwise correction for multiple comparisons. Results were thresholded at a corrected *p* value of 0.05.

Global atrophy measures

Gray matter and lateral ventricular volumes were obtained automatically via whole brain segmentation procedures performed with FreeSurfer (version 5.1; available at http://surfer.nmr.harvard.edu). Intracranial volume (ICV) was entered as a covariate of no interest in comparisons of global atrophy measures. Mean thickness for both hemispheres was calculated as follows: [(left hemisphere thickness * left hemisphere surface area) + (right hemisphere thickness * right hemisphere surface area)]/(left hemisphere surface area + right hemisphere surface area).

Statistical analyses

Statistical analyses of neuropsychological, demographic, clinical, and MRI volumetric data variables were carried out using the statistical package SPSS-20 (2011; Armonk, NY: IBM Corp.). For the baseline analysis of demographic variables, Student *t* tests, ANOVA, Pearson's χ^2 statistics, and Mann-Whitney's U were used as appropriate.

A longitudinal variable was created for each test used to pair neuropsychological data with the structural longitudinal measure of symmetrized percent change, and was used in all statistical and structural analyses of the study.

For longitudinal clinical, neuropsychological, and structural variables, repeated measures general linear model was used to assess group differences over time in quantitative variables; and post-hoc tests were performed using Bonferroni correction for multiple comparisons. To address group and time effects in qualitative variables, Kruskal-Wallis H, Friedman's F, or Pearson's χ^2 statistics were used as appropriate.

RESULTS

Sociodemographic and clinical data

Demographic and clinical data of the participants at baseline are summarized in Table 1. No significant differences were found between study groups in age, sex, education, clinical variables associated with PD, or the interval between assessments. The characteristics of the subjects who remained as study participants and those who dropped out are summarized in Supplementary Table 1.

The longitudinal evolution of clinical variables in all PD patients is summarized in Supplementary Table 2. Medication and motor measures showed no significant progression in this follow-up period, and did not differ between PD-NC subjects and patients with impaired cognition. MMSE showed significant group differences at baseline as well as group and time effects in the longitudinal analysis.

The progression of the detailed neuropsychological evaluation can be found in Table 2 and Supplementary Table 3. Aside from VS/VP measures, significant group-by-time interactions were seen in tests of attention and working memory. At follow-up, 17 patients remained as PD-NC (60.71%), 9 remained as PD-MCI (56.25%), 5 PD-MCI patients reverted to PD-NC (31.25%), 11 PD-NC patients progressed to PD-MCI (39.29%) and 2 PD-MCI patients fulfilled criteria for PDD (3.1%).

Visuospatial and visuoperceptual performance

All VS/VP tests showed significant group differences (see Table 2). Significant time and group-by-time interaction effects were observed for the SDMT. Post-hoc analyses evidenced that differences were found between HC and PD-MCI in all contrasts.

PCT differed between groups at baseline and follow-up when scored according to the original MMSE criteria (χ^2=12.800, p=0.002; χ^2=8.957, p=0.011 respectively) as well as according to Williams-Gray *et al*. criteria [1,7,8] (χ^2=9.295, p=0.010; χ^2=8.987, p=0.011 respectively); however, no significant time effects were observed for any groups.

MRI evolution

Imaging analyses revealed that, compared with PD-NC patients, PD-MCI patients exhibited significantly greater progressive cortical thinning in left lateral occipital and inferior parietal regions, and in right medial temporal regions (see Figure 1 and Supplementary Table 4). Cortical thinning differences between HC and PD-NC, and between HC and all PD patients, were not significant.

Group comparison of global MRI atrophy parameters evidenced that mean thickness differed between groups and had a time effect (F(Group)=7.711; p=0.001; F(Time)=9.891, p=0.003; Post-hoc *P*: PD-MCI vs HC=0.001; PD-MCI vs PD-NC=0.016), whereas the increase in the volume of the lateral ventricular system achieved statistical significance for time and the interaction between group and time (F(Time): 88.596; p<0.0001; F(GroupxTime)=4.745; p=0.012) (see Supplementary Figure 2).

Cortical thickness correlates of visuospatial and visuoperceptual changes

Whole-brain imaging analyses showed significant correlations between changes in VS/VP measures and cortical thinning over time. In the PD-NC group, FRT also correlated with cortical thinning in the left lateral occipital area.

In PD-MCI patients, changes in PCT scores over time showed a significant cluster in the left entorhinal region that involved the middle and inferior temporal gyri, the medial temporal pole, and the parahippocampal, fusiform, lingual, and lateral occipital cortices. JLOT was significantly related to cortical atrophy in clusters located in the left insula, inferior and superior temporal areas, and the right fusiform gyrus, which extended to the left temporal pole, entorhinal, fusiform, and lingual cortices. FRT scores correlated significantly with cortical thinning in the left lingual gyrus. SDMT showed significant correlations with reductions in the left superior temporal, parahippocampal and lingual, as well as the right parahippocampal cortices (see Figure 2 and Supplementary Table 5).

We performed complementary analyses to study the cross-sectional correlates of the tests used in this study and we observed a pattern of posterior atrophy more pronounced in PD-MCI patients (see Supplementary

Figure 3a and 3b and Supplementary Table 6). We analyzed the association between cortical thinning over time and the significant longitudinal differences found in neuropsychological measures relative to other cognitive domains. In PD-NC patients, the Stroop colors test correlated significantly with left superior parietal and frontal regions. In PD-MCI patients, a non-specific widespread pattern of anterior and posterior regions correlated bilaterally with TMT-A and Stroop colors tests (see Supplementary Figure 4 and Supplementary Table 7).

DISCUSSION

In the present study, we aimed to investigate the longitudinal differences in cortical thinning between PD patients and healthy subjects, as well as the relationship between the progressive loss of VS/VP functions and the cortical degeneration underlying these changes in PD patients, grouped according to their cognitive status using the Movement Disorder Society Task Force criteria.

Our results evidence that all the neuropsychological tests with a posterior cortically-based component used in this work are sensitive to detect VS/VP impairment in MCI patients. However, among the five VS/VP tests used, only the SDMT showed a significant time effect as well as a significant group-by-time interaction, indicating that it may be useful for the evaluation of progressive cognitive impairment in PD. Previous research in PD cognitive deterioration has also described the progressive decline of visuospatial and visuoconstructive functions [1,4,7,8,28,29]. In longitudinal studies, an important issue is the distinction between cognitive and motor deficits, as there are several VS/VP tests, such as the clock drawing, the pentagon test drawing or the block design, that have a strong motor component. By contrast, in the SDMT, the motor component is very low, mainly involving eye tracking. It thus seems to be a suitable test for PD follow-up studies. In agreement with our findings, a 3-year multi-center follow-up of a large sample of PD patients, using short versions of the JLOT and the SDMT, found statistically significant effects for both tests, but the differences were stronger for the SDMT [29].

In our previous cross-sectional studies, we demonstrated a relationship between visuospatial and visuoperceptual performance and cortical thickness in bilateral temporo-parietal-occipital areas, and widespread posterior-anterior white matter microstructure alterations [13,14]. Interestingly, in the present study, we have established a relationship between the progressive worsening in VS/VP performance and bilateral degeneration of posterior cortical regions. In PD-MCI patients, PCT, JLOT, FRT, and SDMT evidenced significant correlates with temporal, occipital, and parietal cortices. In PD-NC we also observed a relationship between decreases in FRT scores and the rate of thinning in the occipito-parietal cortex. We highlight the emergence of specific neuroanatomical correlates in PD-MCI patients, in absence of a significant time effect in neuropsychological performance for most VS/VP tests. This finding reflects that, although performance in these tests did not change significantly over time at the group level, there was a variable progressive loss of visuospatial and visuoperceptual functions in some PD patients that was explained by the variability in thinning of specific posterior cortical brain regions. This notion is supported by the finding that PD-MCI patients exhibited extensive progressive reductions in posterior parieto-temporal cortical regions in comparison with their cognitively unimpaired PD patient peers, which is in agreement with recent findings using the same technique in large study samples [17,18].

The neurobiological basis for cognitive dysfunction in PD is unclear, and several factors have been implicated, including loss of dopaminergic, noradrenergic, serotonergic, and cholinergic projections to limbic and cortical areas, as well as AD-type pathology [30]. Enhanced α-synuclein pathology, together with lysosomal deficits, have been linked to poor cognitive evolution in PD patients [31]. Functional cross-sectional studies with dopamine tracers and metabolic parameters have established the relevance of posterior regions in cognitive decline in PD [32,33], as well as the relationship between visuospatial impairment, posterior cortical regions, predominant α-synucleinopathy, and worse cognitive evolution [34,35].

The strengths of our study are that we applied validated criteria and tests to determine cognitive diagnoses [24], established a considerable follow-up interval, used a sensitive technique to identify regional gray matter changes associated with PD [36], and used the same MRI scanner, avoiding the variability of multi-center data. Our study is limited by the size of the sample due to the considerable attrition, which could in turn affect the

results observed. However, cross-sectional as well as large-scale longitudinal studies of other groups are in line with our current findings [11,17,18]. In our study, mean group ages could appear as relatively low considering the epidemiological data of PD patents. This might be due to the exclusion of demented PD patients, who tend to be older. In fact, the mean age of our sample is similar to those in the abovementioned studies that also focused on non-demented PD patients using larger cohorts [17,18].

In conclusion, the present study establishes the neuroanatomical substrate of the progressive deterioration of visuospatial and visuoperceptual performance in PD patients with and without mild cognitive impairment. This study reinforces previous findings on the differential progression of atrophy in patients with MCI, thus supporting the validity of this construct. These findings give evidence to the notion that the progression of posterior-cortically based cognitive tests is indicative of progressive cortical thinning in posterior brain regions.

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FIGURES

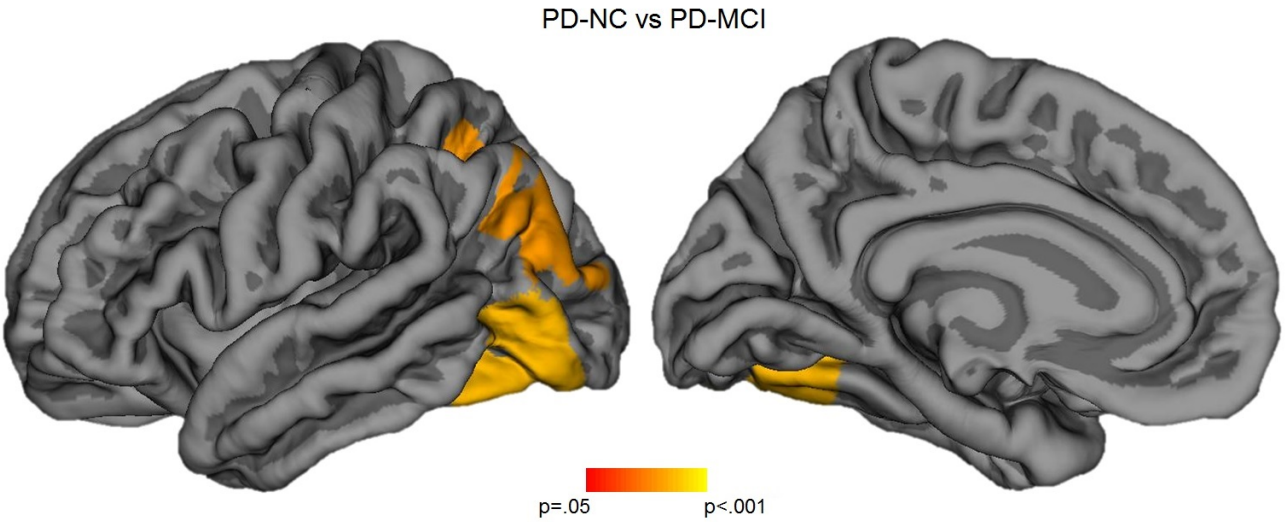


Figure 1. Vertex-wise symmetrized percent change in cortical thickness differences between study groups. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.

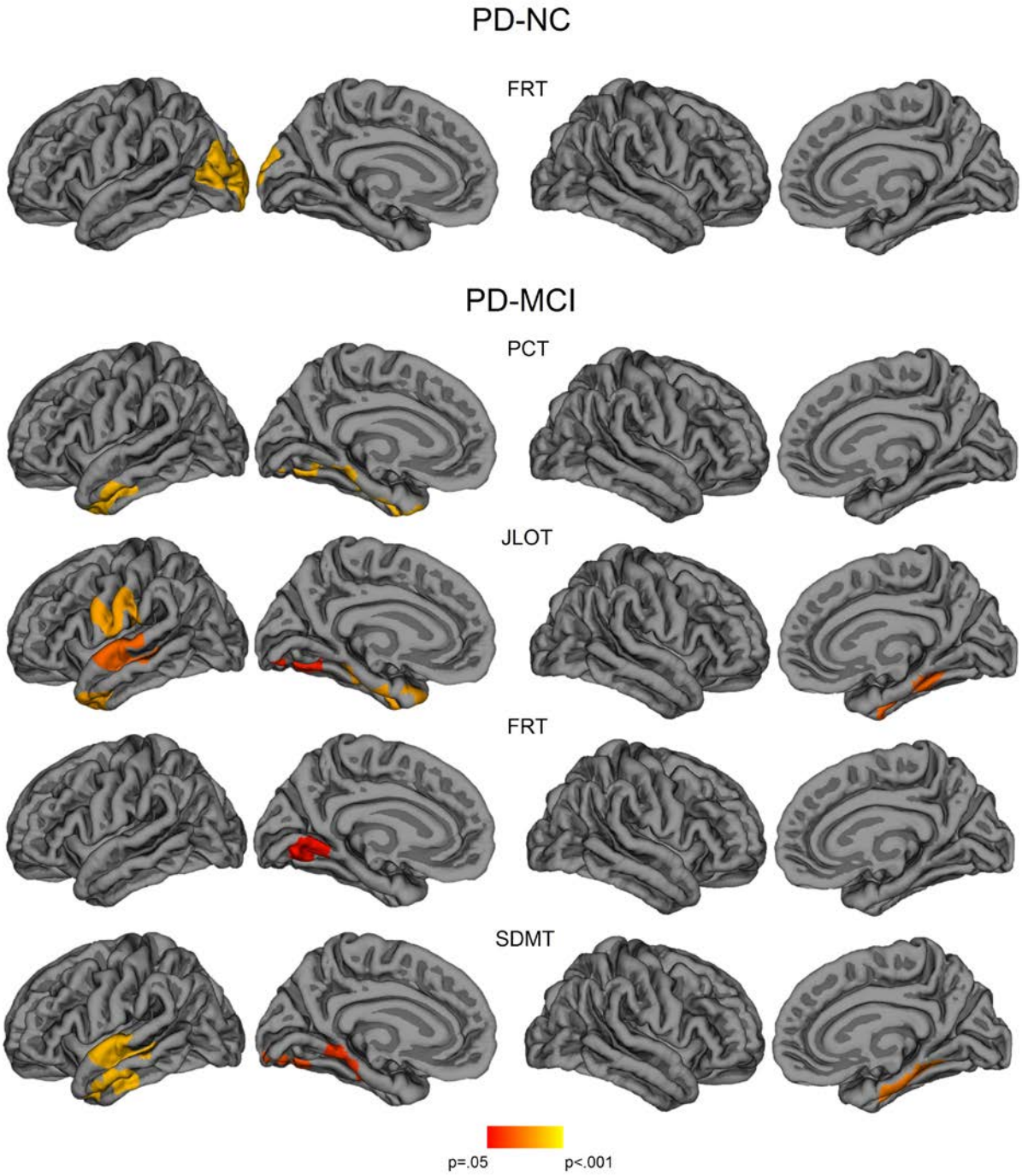


Figure 2. Vertex-wise symmetrized percent change in cortical thickness correlations with VS/VP measures in PD patients. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test.

TABLES

Table 1. Demographic and clinical data of the participants at baseline.

	HC (n=20)	PD-NC (n=28)	PD-MCI (n=16)	F, χ^2, t, U
Interval (years)	3.90 ± 0.32	3.89 ± 0.41	3.94 ± 0.59	0.065[a]
Age	65.50 ± 8.00	59.50 ± 9.58	64.63 ± 9.67	3.010[a]
Sex (male/female)	10/10	20/8	10/6	2.286[b]
Education	11.10 ± 4.13	12.96 ± 4.87	11.25 ± 5.94	1.045[a]
MMSE	29.75 ± 0.44	29.54 ± 0.69	28.69 ± 1.54	6.481[a]*
Evolution (years)		6.50 ± 3.87	8.03 ± 6.73	-0.814[c]
Age at onset		53.00 ± 10.21	56.91 ± 12.22	-1.136[c]
LEDD		700.79 ± 470.61	675.63 ± 535.21	0.162[c]
UPDRS-III		13.93 ± 9.19	11.75 ± 11.01	185.000[d]
H&Y		1: 11 1,5: 1 2: 12 2,5: 2 3:2	1: 6 2: 8 2.5: 1 3: 1	219.000[d]

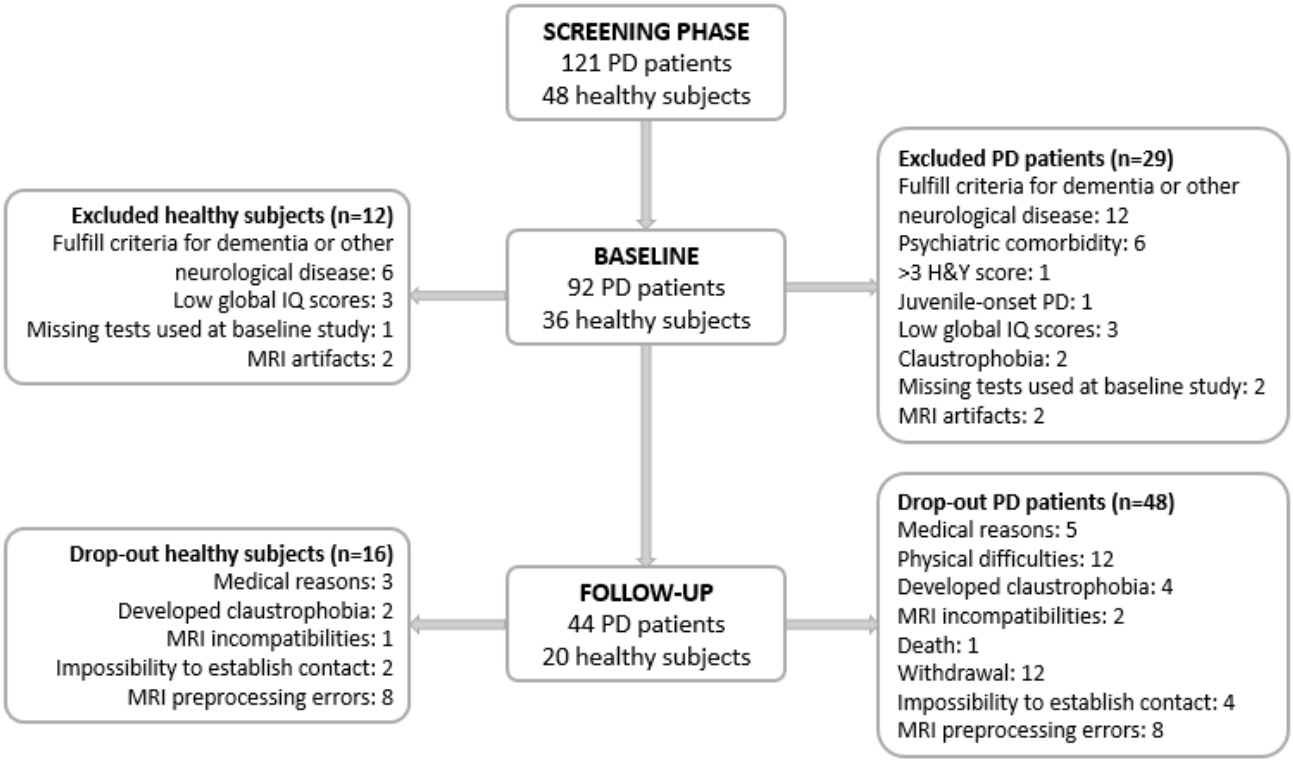
HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; MMSE: Mini-Mental State Examination; LEDD: Levodopa Equivalent Daily Dose; UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn and Yahr scale. Values are presented as mean ± standard deviation. [a]: F ANOVA statistics; [b]: Pearson's χ^2 statistics; [c]: Student t test statistics; [d]: Mann-Whitney U statistics. *significant at p<0.01.

Table 2. Group comparison of VS/VP performance between healthy subjects, PD patients without MCI, and PD patients with MCI.

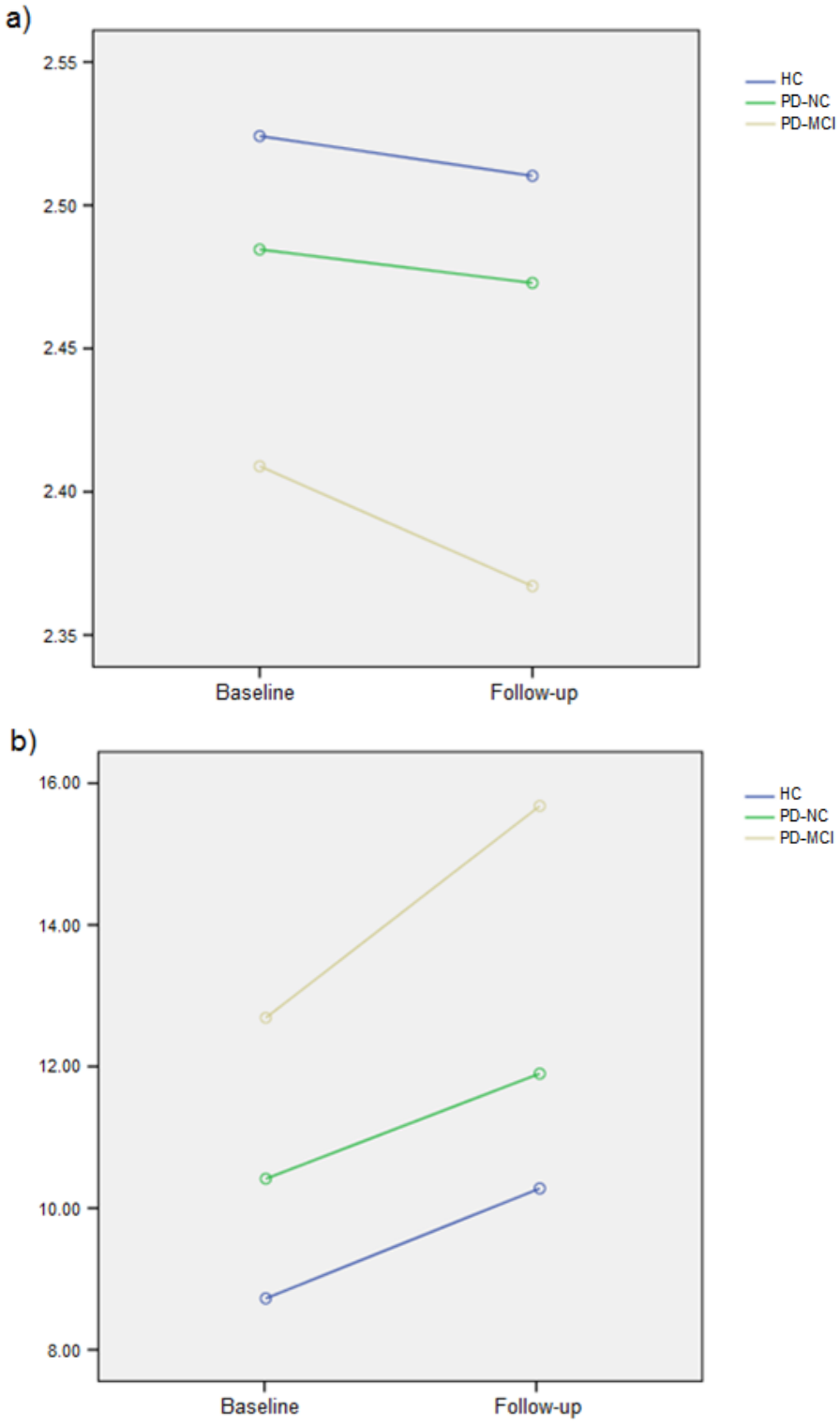
	HC		PD-NC		PD-MCI		F (Group)	F (Time)	F (Group by time)	Post-hoc *P*
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up				
PCT	9.70 ± 0.48	9.65 ± 0.59	9.79 ± 0.57	9.64 ± 0.68	9.19 ± 1.11	8.56 ± 2.73	4.428 (p=0.016)	2.749 (p=0.102)	1.022 (p=0.366)	HC / PD-MCI: 0.047
JLOT	23.80 ± 2.91	25.00 ± 3.45	24.07 ± 3.81	25.21 ± 3.24	21.06 ± 5.74	19.56 ± 8.27	6.311 (p=0.003)	0.292 (p=0.591)	2.597 (p=0.083)	HC / PD-MCI: 0.013
VFDT	30.00 ± 2.25	29.40 ± 2.26	29.54 ± 2.25	29.64 ± 2.53	26.88 ± 3.52	27.81 ± 4.20	6.028 (p=0.004)	0.130 (p=0.720)	1.024 (p=0.365)	HC / PD-MCI: 0.008
FRT	22.70 ± 1.92	22.85 ± 1.87	22.14 ± 2.48	21.79 ± 2.73	20.44 ± 3.39	20.07 ± 3.26	4.992 (p=0.010)	0.447 (p=0.506)	0.346 (p=0.709)	HC / PD-MCI: 0.008
SDMT	44.67 ± 8.40	46.90 ± 7.51	48.54 ± 10.61	43.75 ± 12.68	36.38 ± 18.91	31.31 ± 19.87	5.109 (p=0.009)	7.552 (p=0.008)	6.574 (p=0.003)	HC / PD-MCI: 0.029

HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment. PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test; VFDT: Visual Form Discrimination Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test. Values are presented as mean ± standard deviation.

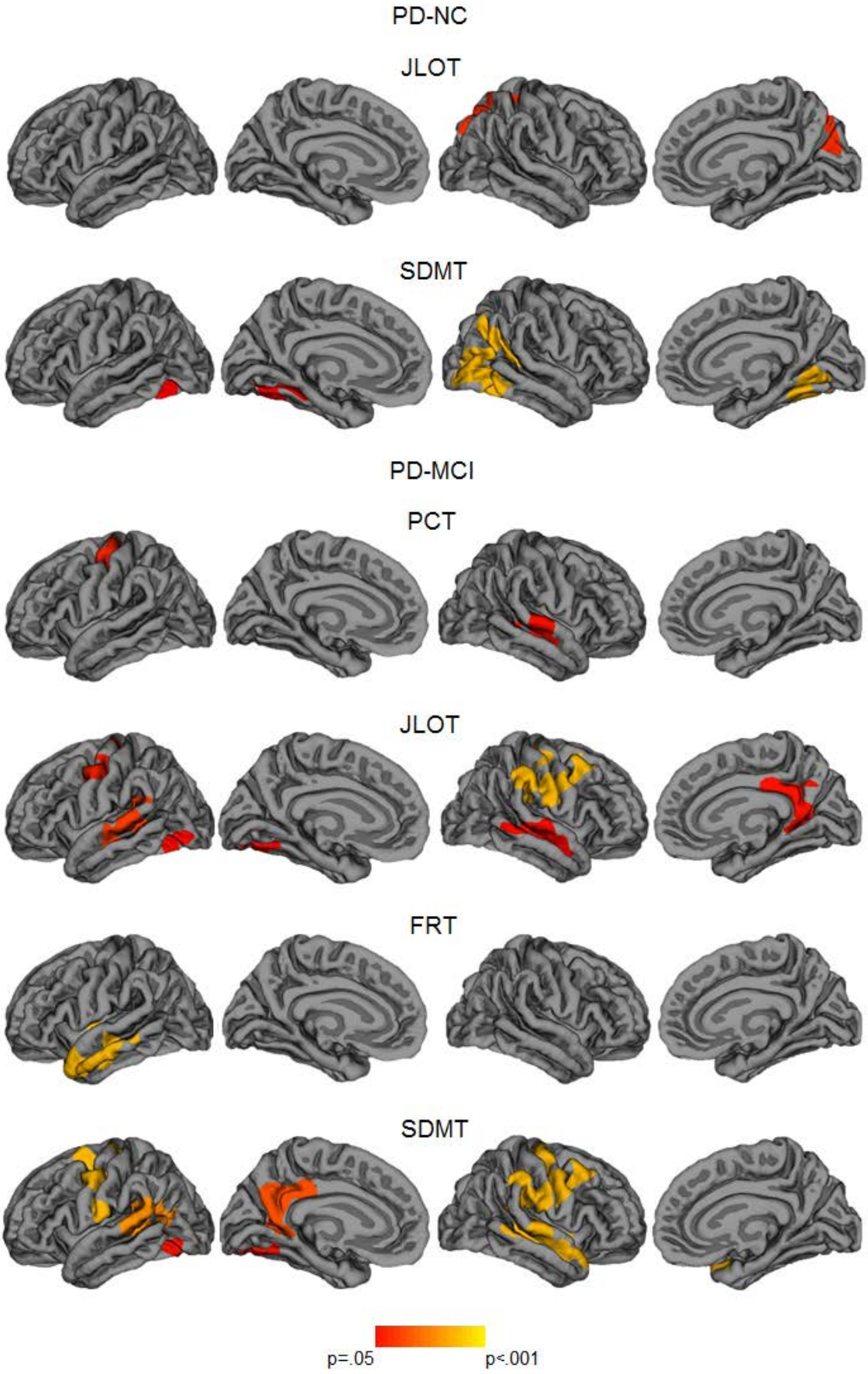
SUPPLEMENTARY FIGURES



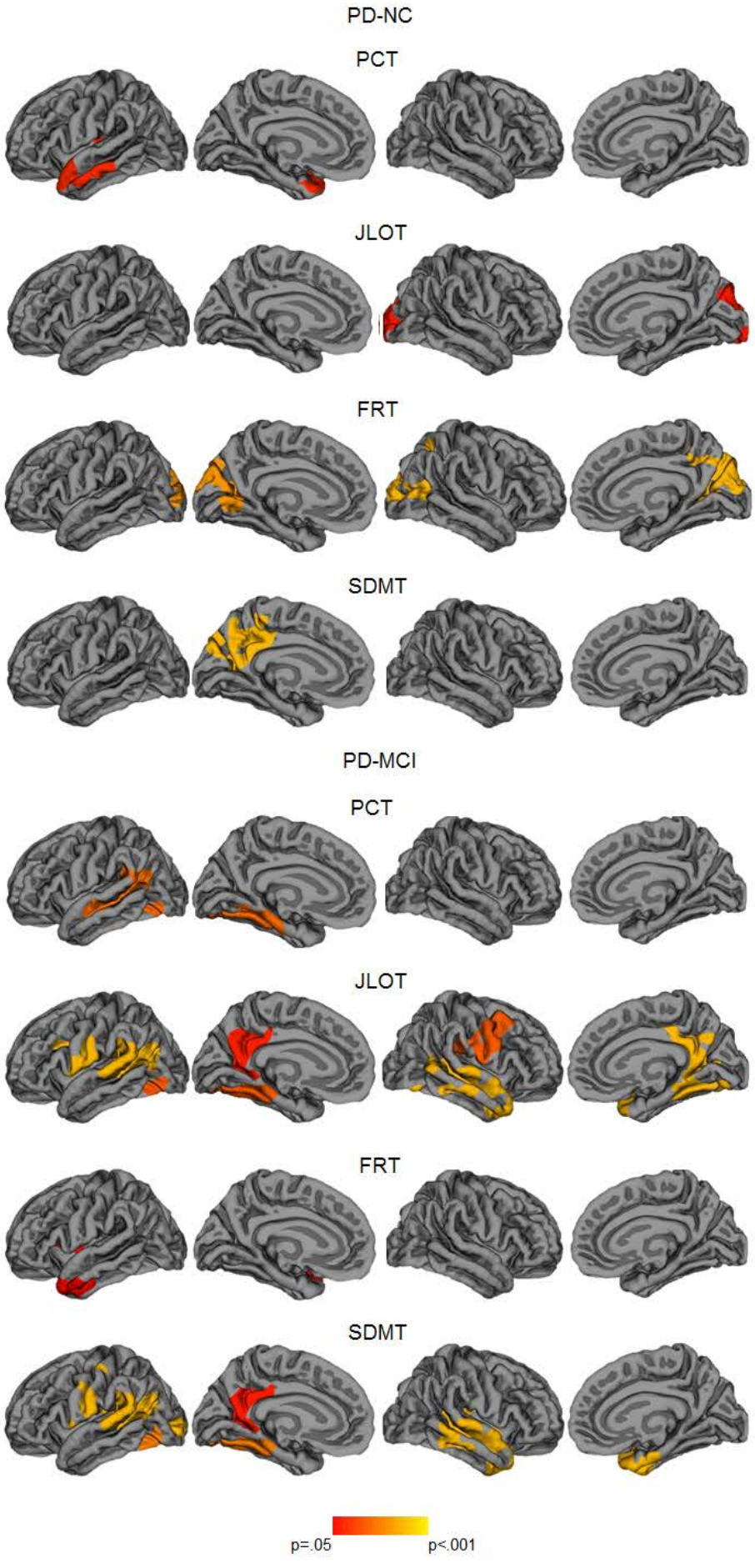
Supplementary Figure 1. Flowchart summarizing sample evolution from screening phase to follow-up. PD: Parkinson's disease; HC: Healthy controls; H&Y: Hoehn and Yahr.



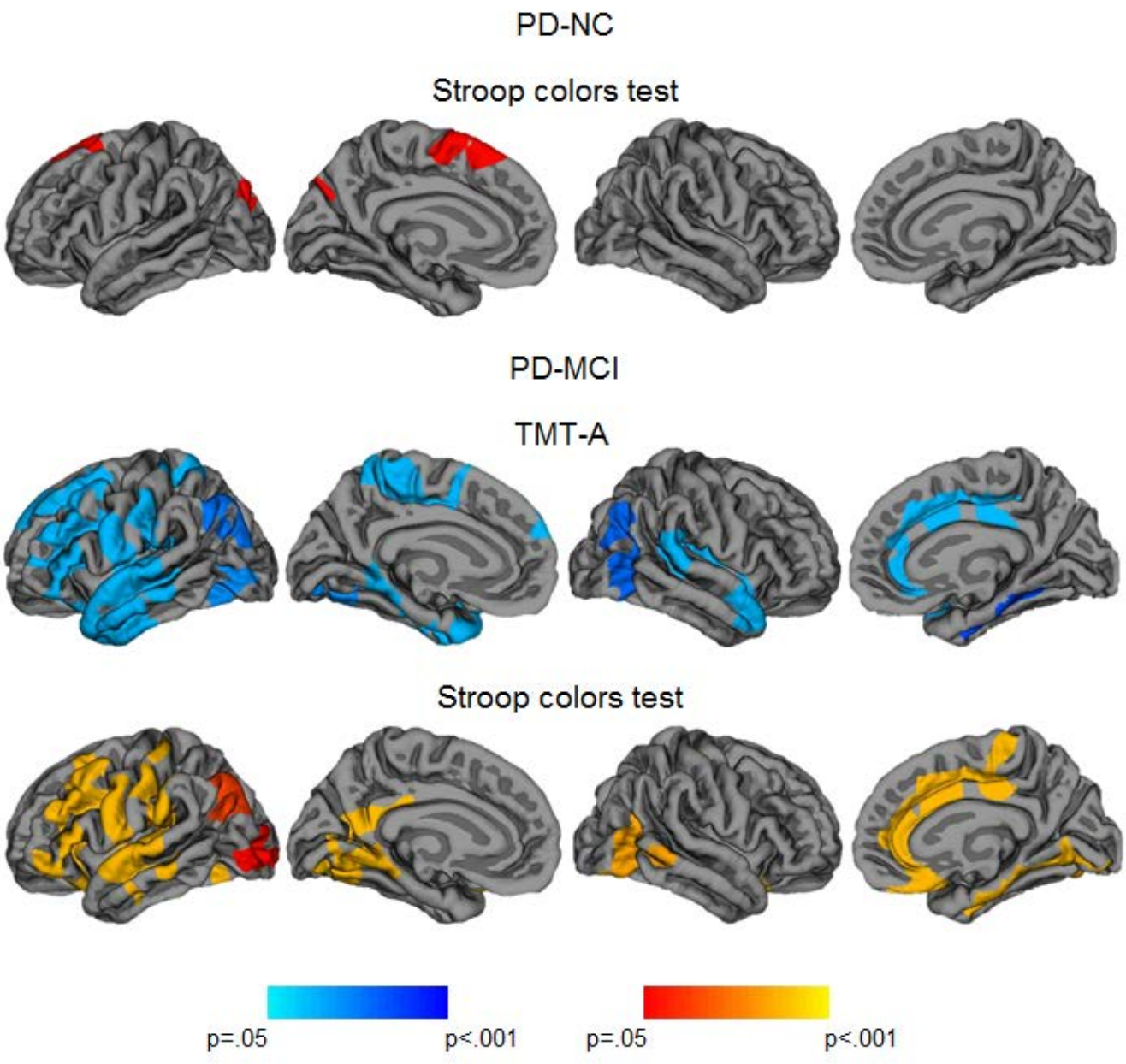
Supplementary Figure 2. a) Mean Thickness (mm^2) and b) LVS (cm^3) estimated marginal means at baseline and follow-up in study groups. HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.


PD-NC
JLOT
SDMT
PD-MCI
PCT
JLOT
FRT
SDMT
p=.05
p<.001

Supplementary Figure 3a. Vertex-wise cortical thickness one-tail correlations with VS/VP measures in PD patients at baseline. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; JLOT: Judgment of Line Orientation Test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; FRT: Facial Recognition Test.


PD-NC
PCT
JLOT
FRT
SDMT
PD-MCI
PCT
JLOT
FRT
SDMT
p=.05
p<.001

Supplementary Figure 3b. Vertex-wise cortical thickness one-tail correlations with VS/VP measures in PD patients at follow-up. The scale bar shows *P* values. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation Test; FRT: Facial Recognition Test; SDMT: Symbol Digit Modalities Test.



Supplementary Figure 4. Vertex-wise symmetrized percent change in cortical thickness one-tail correlations with neuropsychological measures in PD patients. The scale bar shows *P* values; warmth scale represents positive correlations; cold scale represents negative correlations. PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT-A: Trail Making Test part A.

SUPPLEMENTARY TABLES

Supplementary Table 1. Sociodemographic and clinical data of PD subjects that participated in the study and those who dropped out after baseline assessment

	Study PD participants (n=44)	Dropped out (n=48)	T, χ^2, U
Age	61.68 ± 9.93	66.08 ± 11.79	-1.927 (p=0.057)[a]
Sex (male/female)	30/14	25/23	2.474 (p=0.116)[b]
Education	12.07 ± 5.58	9.27 ± 4.84	2.575 (p=0.012)[a]
LEDD	716.33 ± 495.85	889.09 ± 482.90	-1.646 (p=0.103)[a]
UPDRS-III	14.41 ± 9.40	20.44 ± 11.52	386.000 (p=0.019)[c]
H&Y	1.60 ± 0.65	2.00 ± 0.65	421.000 (p=0.016)[c]
Age at onset	54.71 ± 10.88	57.28 ± 13.30	-0.995 (p=0.322)[a]
Evolution	7.33 ± 5.34	9.35 ± 6.28	-1.658 (p=0.101)[a]
MMSE	29.16 ± 1.24	28.96 ± 0.99	0.863 (p=0.390)[a]
MCI	13	11	0.778 (p=0.438)[b]
Hallucinations	7	12	1.158 (p=0.282)[b]
BDI	8.33 ± 5.39	13.43 ± 5.87	-4.051 (p<0.001)[a]
AES	11.68 ± 7.06	14.66 ± 7.85	-1.805 (p=0.075)[a]
JLOT	22.75 ± 4.77	20.57 ± 4.85	2.156 (p=0.034)[a]
VFDT	28.66 ± 2.92	27.02 ± 3.83	2.293 (p=0.024)[a]
FRT	21.32 ± 3.06	21.00 ± 2.44	0.551 (p=0.583)[a]
PCT 3MS	9.52 ± 0.88	9.09 ± 1.30	1.871 (p=0.065)[a]
PCT Original (incorrect)	5	10	1.622 (p=0.203)[b]
Attention and working memory	0.18 ± 0.61	0.47 ± 0.78	-1.790 (p=0.078)[a]
Executive functions	-0.24 ± 1.10	-0.71 ± 0.99	2.107 (p=0.038)[a]
Memory	-0.46 ± 1.36	-1.16 ± 1.44	2.347 (p=0.021)[a]
Language	0.05 ± 0.90	-0.51 ± 1.21	2.474 (p=0.015)[a]
Visuospatial and visuoperceptual	-0.37 ± 0.94	-0.88 ± 1.06	2.368 (p=0.020)[a]

PD: Parkinson's disease patients; LEDD: Levodopa Equivalent Daily Dose; UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn & Yahr; MMSE: Mini-Mental State Examination; MCI: Mild Cognitive Impairment; BDI: Beck Depression Inventory: AES: Apathy Evaluation Scale; JLOT: Judgment of Line Orientation test; VFDT: Visual Form Discrimination test; FRT: Facial Recognition Test; PCT: Pentagon Copying Test; 3MS: Modified Mini-Mental State. Values are presented as mean ± standard deviation. [a]: Student t test statistics; [b]: Pearson's χ^2 statistics; [c]: Mann-Whitney U statistics.

Supplementary Table 2. Progression of clinical variables in PD participants

	Baseline			Follow-up			F (Group)	F (Time)	F (Group by time)
	HC	PD-NC	PD-MCI	HC	PD-NC	PD-MCI			
MMSE	29.75 ± 0.44	29.54 ± 0.69	28.69 ± 1.54	29.30 ± 0.87	29.14 ± 0.97	27.56 ± 3.41	6.421*	11.116*	1.289
LEDD		700.79 ± 470.61	675.63 ± 535.21		720.48 ±	693.28 ± 481.07	0.044	0.068	0.989
UPDRS-III		13.93 ± 9.19	11.75 ± 11.01		17.79 ± 9.03	17.40 ± 12.70	31.036[d] 14.605[d]	366.333[d] 106.205[d]	
H&Y		1: 11 1,5: 1 2: 12 2,5: 2 3:2	1: 6 2: 8 2.5: 1 3: 1		1: 3 2: 14 3: 11	1: 3 2: 5 3: 7 4: 1	0.718[d] 3.111[d]	8.527[d] 9.257[d]	

HC: Healthy controls; PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; GxT: Group by time interaction; MMSE: Mini-Mental State Examination; LEDD: Levodopa Equivalent Daily Dose, UPDRS-III: Unified Parkinson's disease Rating Scale; H&Y: Hoehn & Yahr. *Significant at p<0.01.

Supplementary Table 3. Group comparison of neuropsychological performance between healthy subjects, PD patients without MCI, and PD patients with MCI

	HC		PD-NC		PD-MCI		F (Group)	F (Time)	F (Group by time)
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up			
TMT A	38.42 ± 13.95	36.63 ± 11.75	33.19 ± 10.10	44.42 ± 19.84	42.60 ± 19.69	49.60 ± 17.95	6.900 (p=0.002)	9.965 (p=0.002)	3.871[a] (p=0.026)
TMT B	88.58 ± 27.94	94.00 ± 50.51	80.65 ± 18.80	104.73 ± 53.02	90.60 ± 48.13	190.20 ± 220.31	6.025 (p=0.004)	14.137 (p<0.001)	4.248[a,b] (p=0.019)
DS Forward	5.58 ± 1.47	5.26 ± 1.45	6.12 ± 1.21	5.54 ± 1.42	5.80 ± 1.48	5.60 ± 1.27	0.931 (p=0.400)	3.181 (p=0.079)	0.878 (p=0.421)
DS Backwards	4.16 ± 1.30	4.32 ± 1.20	4.65 ± 0.94	4.69 ± 1.29	4.30 ± 1.16	4.10 ± 1.10	4.126 (p=0.021)	0.627 (p=0.432)	1.563[b] (p=0.218)
Stroop words	100.95 ± 13.71	95.47 ± 12.07	102.50 ± 15.57	92.85 ± 15.01	77.00 ± 19.98	78.50 ± 18.25	13.544 (p<0.001)	10.624 (p=0.002)	1.393[a,b] (p=0.256)
Stroop colors	62.05 ± 16.99	62.89 ± 11.03	66.50 ± 11.93	61.46 ± 10.59	54.80 ± 12.29	48.70 ± 13.80	7.589 (p=0.001)	7.353 (p=0.009)	3.263[a,b] (p=0.045)
Stroop W-C	37.47 ± 11.44	36.11 ± 10.17	41.73 ± 11.05	38.04 ± 9.28	35.20 ± 12.23	28.60 ± 12.94	4.361 (p=0.017)	25.019 (p<0.001)	2.845[b] (p=0.066)
Phonemic fluency	15.47 ± 4.44	15.53 ± 4.94	18.35 ± 5.31	15.73 ± 4.62	13.70 ± 6.24	15.40 ± 6.93	4.534 (p=0.015)	1.070 (p=0.305)	1.916[b] (p=0.156)
Semantic fluency	19.74 ± 2.92	18.79 ± 3.63	20.62 ± 5.10	17.73 ± 6.10	18.20 ± 5.47	16.80 ± 3.74	3.129 (p=0.051)	16.454 (p<0.001)	1.521 (p=0.227)
BNT	13.63 ± 1.01	13.84 ± 0.96	13.69 ± 1.05	13.77 ± 1.14	13.70 ± 1.06	13.70 ± 1.06	0.520 (p=0.597)	0.835 (p=0.364)	0.643 (p=0.529)
RAVLT Total	43.26 ± 5.15	47.47 ± 6.96	46.73 ± 7.94	47.46 ± 8.59	37.10 ± 6.26	41.30 ± 8.10	13.837 (p<0.001)	4.526 (p=0.037)	1.989[a] (p=0.146)
RAVLT Recall	8.74 ± 1.79	10.05 ± 2.61	9.27 ± 2.49	9.69 ± 2.94	6.40 ± 1.96	6.80 ± 3.01	14.182 (p<0.001)	0.395 (p=0.0532)	2.619[a] (p=0.081)

HC: Healthy controls, PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT: Trail Making Test; DS: Digit Span; Stroop W-C: Stroop Words-Colors test; BNT: Boston Naming Test; RAVLT: Rey Auditory Verbal Learning Test. Values are presented as mean ± standard deviation. [a]: Significant post-hoc contrasts between HC and PD-MCI at p<0.01. [b]: Significant post-hoc contrasts between PD-NC and PD-MCI at p<0.05.

Supplementary Table 4. Significant clusters showing cortical thickness differences over time between PD patients without MCI and PD patients with MCI

Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
		X	Y	Z		
PD-NC vs PD-MCI						
Left lateral occipital	2505.31	-41.9	-78.3	-2.8	3.440	0.00010
Left inferior parietal	2013.90	-40.7	-64.8	30.6	2.333	0.00030

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment.

Supplementary Table 5. Significant clusters showing cortical thickness correlations over time with VS/VP measures in PD patients without MCI and PD patients with MCI

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
PD-NC	**FRT**						
	Left lateral occipital	3027.57	-19.9	-94.5	8.0	3.766	0.00010
PD-MCI	**PCT**						
	Left entorhinal	3430.28	-32.1	-16.9	-24.3	4.734	0.00010
	JLOT						
	Left insula	1873.12	-37.5	-19.2	20.0	5.084	0.00020
	Left inferior temporal	1927.49	-37.7	1.7	-31.5	4.705	0.00020
	Left fusiform	1053.63	-29.5	-69.5	-5.6	4.571	0.01660
	Left superior temporal	1475.99	-56.0	-13.6	-5.1	3.490	0.00160
	Right fusiform	1475.55	35.1	-43.2	-9.6	4.136	0.00180
	FRT						
	Left lingual	1054.57	-13.1	-56.8	2.5	3.264	0.02880
	SDMT						
	Left superior temporal	2779.89	-53.5	-13.6	-6.6	4.351	0.00010
	Left parahippocampal	1182.41	-31.7	-24.3	-18.5	3.920	0.00770
	Left lingual	1311.56	-14.0	-85.3	-4.2	3.761	0.00360
	Right parahippocampal	1651.06	31.9	-22.5	-20.4	4.158	0.00070

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; FRT: Facial Recognition Test; PCT: Pentagon Copying Test; JLOT: Judgment of Line Orientation test; SDMT: Symbol Digit Modalities Test.

Supplementary Table 6. Significant clusters showing cross-sectional cortical thickness correlations with VS/VP measures in PD patients without MCI and PD patients with MCI at baseline and follow-up assessments

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
Baseline							
PD-NC	**JLOT**						
	Right superior parietal	2602.51	19.5	-60.4	42.7	2.804	0.01350
	SDMT						
	Left fusiform	2026.16	-38.8	-62.4	-3.5	2.189	0.05090
	Right fusfirom	6744.71	40-4	.50.3	-10.0	3.032	0.00020
PD-MCI	**PCT**						
	Left precentral	1528.65	-23.8	-20.9	51.2	4.799	0.01690
	Right superior temporal	2004.66	65-2	-20.3	4.3	2.668	0.03130
	JLOT						
	Left superior temporal	2324.53	-48.7	-17.4	-9.9	3.793	0.00760
	Left precentral	2039.85	-23.6	-26.2	48.9	4.422	0.01840
	Left fusiform	1764.37	-26.1	-79.1	-3.8	3.439	0.04110
	Right precentral	5038.47	27.6	-25.0	46.2	3.819	0.00020
	Right precuneus	2017.40	11.9	-51.5	14.2	3.876	0.03000
	Right superior temporal	1936.40	46.6	-25.3	-1.2	5.428	0.03780
	FRT						
	Left middle temporal	3327.92	-62.3	-18.1	-13.4	4.158	0.00020
	SDMT						
	Left precentral	3347.49	-22.7	-23.5	48.7	4.047	0.00020
	Left inferior parietal	2978.70	-48.0	-61.4	10.4	3.777	0.00070
	Left isthmus cingulate	2458.70	-9.1	-54.0	11.4	4.488	0.00430
	Left fusiform	1890.21	-27.0	-77.2	-2.3	2.682	0.02840
	Right superior temporal	5620.20	57.0	-17.0	-1.2	3.927	0.00020
	Right precentral	2594.66	25.3	-23.3	46.3	3.742	0.00020

Follow-up							
PD-NC	**PCT**						
	Left superior temporal	2765.13	-42.7	-3.0	-18.3	2.856	0.01320
	JLOT						
	Right lateral occipital	2510.83	18.7	-95.5	-6.3	2.649	0.02230
	FRT						
	Left precuneus	3939.25	-20.8	-60.9	12.3	3.947	0.00050
	Right cuneus	7475.92	8.7	-82.4	24.4	2.948	0.00020
	SDMT						
	Left precuneus	4138.70	-21.3	-60.7	17.5	3.381	0.00020
PD-MCI	**PCT**						
	Left middle temporal	3196.58	-51.3	-26.0	-9.4	5.016	0.00150
	Left parahippocampal	3141.48	-22.4	-38.6	-8.0	3.072	0.00200
	JLOT						
	Left bankssts	6566.60	-48.9	-39.5	5.5	3.308	0.00020
	Left fusiform	2971.92	-31.6	-42.9	-11.9	3.020	0.00310
	Left precuneus	2309.59	-9.1	-56.5	18.0	2.939	0.01960
	Right superior temporal	5655.28	46.2	4.2	-18.6	3.430	0.00020
	Right parahippocampal	5118.58	24.3	-41.3	-5.1	4.188	0.00020
	Right caudal middle frontal	3236.30	39.8	2.7	34.9	4.450	0.00300
	FRT						
	Left middle temporal	1989.50	-48.1	-3.4	-27.5	2.832	0.04150
	SDMT						
	Left inferior parietal	7774.24	-50.1	-61.2	12.5	3.701	0.00020
	Left fusiform	3399.89	-40.3	-54.6	-4.8	3.234	0.00100
	Left precuneus	2266.55	-23.6	-56.2	8.9	3.355	0.02190
	Right superior temporal	6331.24	46.3	1.7	-17.8	4.620	0.00020

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; JLOT: Judgment of Line Orientation test; SDMT: Symbol Digit Modalities Test; PCT: Pentagon Copying Test; FRT: Facial Recognition Test.

Supplementary Table 7. Significant clusters showing cortical thickness correlations over time with neuropsychological measures in PD patients without MCI and PD patients with MCI

	Cluster anatomical annotation	Cluster size (mm^2)	Talairach coordinates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
PD-NC	**Stroop colors test**						
	Left superior frontal	1397.49	-9.0	30.6	48.6	3.390	0.04230
	Left superior parietal	1380.02	-17.7	-76.4	34.6	2.253	0.04450
PD-MCI	**TMT-A**						
	Left parahippocampal	23479.36	-32.0	-25.0	-17.3	-5.626	<0.00001
	Left lateral occipital	2288.44	-39.1	-83.7	2.8	-4.640	0.00070
	Left inferior parietal	2092.69	-31.3	-68.0	40.0	-2.677	0.00050
	Right superior temporal	4174.33	51.2	6.8	-13.3	-4.111	0.00020
	Right superior frontal	3023.02	13.3	15.6	34.1	-4.092	0.00020
	Right lateral occipital	2021.06	41.0	-69.1	4.6	-4.244	0.00200
	Right lingual	1851.08	28.1	-49.3	-2.0	-3.457	0.00480
	Stroop colors test						
	Left supramarginal	14221.99	-57.0	-25.0	18.5	6.435	0.00020
	Left pericalcarine	4167.83	-16.4	-73.9	12.8	3.409	0.00020
	Left inferior parietal	1744.34	-42.3	-67.2	24.2	3.487	0.00660
	Left lateral occipital	1267.06	-33.5	-85.4	-0.6	3.655	0.04410
	Right paracentral	5438.37	16.0	-20.6	36.8	5.442	0.00020
	Right parahippocampal	2506.54	32.8	-22.8	-19.1	4.769	0.00020
	Right lateral occipital	2373.49	39.8	-67.2	3.4	3.294	0.00040

PD-NC: Parkinson's disease patients without mild cognitive impairment; PD-MCI: Parkinson's disease patients with mild cognitive impairment; TMT-A: Trail Making Test part A.