Structural MRI correlates of the MMSE and pentagon copying test in Parkinson's disease

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Running title: Structural correlates of MMSE and pentagon test in PD

Key words: Parkinson disease, screening test, pentagon copying test, global atrophy, cortical thickness.

Disclosure:

This work was funded by the Spanish Ministry of Science and Innovation [PSI2010-16174 grant to C.J., H.C.B. and B.S.], and by Generalitat de Catalunya [2009 SGR0836 to E.T., 2009SGR0941 to C.J.] and an FI-DGR grant [2011FI_B 00045] to H.C.B., and CIBERNED.

The authors report no conflicts of interest.

Word count

Abstract: 250

Manuscript text: 2669

ABSTRACT

Background: Cognitive impairment in Parkinson's disease (PD) is common and recent studies have focused on addressing the most suitable screening tool for its assessment. MMSE is commonly used in clinical practice and longitudinal studies found a relationship between the MMSE pentagon copying item and progression to dementia, but its neuroanatomical correlates have been poorly investigated. The aim of this study is to investigate the MRI structural correlates of the global MMSE and the pentagon item scores in PD patients in the absence of dementia.

Methods: We selected a sample of 92 PD patients and 36 controls. MMSE was used as a global measure of cognitive status, and the pentagon copying test as a measure of visuospatial performance. FreeSurfer software was used to assess intergroup differences in cortical thickness (CTh) and global atrophy measures, as well as their relationship with cognitive performance.

Results: Compared to controls, patients showed significant differences in measures of global atrophy, which correlated with performance on MMSE and the pentagon item. Regional differences in CTh were seen between PD patients and controls bilaterally in the temporo-parietal-occipital region. Patients with impaired performance compared with those of normal performance also showed CTh reductions in these regions.

Conclusion: Our results suggest MMSE and the pentagon item reflect brain changes which at a regional level involve mainly posterior regions. Correlates of the pentagon item were seen in the same regions where PD patients exhibited significant thinning, and involved more areas and bigger cluster sizes than the correlates of MMSE global scores.

Introduction

Cognitive impairment is a frequent [1] and important non-motor symptom in Parkinson's disease (PD) [2, 3], with a significant impact on quality of life [4]. Over time, approximately 80% of patients become demented [5]. The Mini-Mental State Examination (MMSE) is the cognitive screening tool most frequently used to assess global cognitive status in degenerative illnesses [6]. Rate of change of MMSE scores in PD ranged from 1.4 to 6.8 points per year [1]. However, the MMSE is not considered as a suitable screening tool to assess cognitive dysfunctions in PD, because it does not fully address executive functions [6], which is one of the domains usually impaired in this disease [2]. Therefore, other screening tests have been proposed as alternatives, such as the Montreal Cognitive Assessment (MoCA) [7].

Although the MMSE is not commonly used as a single screening tool in PD, scores below the cut-off point of 26 are used as a criterion in the identification of dementia in PD [8]. Despite the broad criticism associated with the MMSE, the pentagon item raised interest in clinical settings because of a population-based longitudinal study where it was found to be predictive of dementia in PD [1, 9, 10], suggesting that the dementing process is heralded by posterior cortical based cognitive deficits [1, 9, 10].

Magnetic resonance imaging (MRI) volumetric research has also shown that PD patients' MMSE scores significantly correlate with measures of global atrophy such as ventricular volume [11]. The correlates with regional gray matter reductions were observed in temporo-parietal regions in voxel-based morphometry studies [12] and also involved frontal regions using cortical thickness (CTh) analyses [13]. A recent study using an ROI-based analysis in non-demented PD patients has shown that the pentagon copying test significantly correlates with volumetric decreases in cortical regions, such as right supplementary motor area, left rostral middle frontal cortex, pars triangularis and left cuneus [14]. However, to our knowledge, there are no previous

studies specifically assessing the correlations between pentagon copying test and whole-brain CTh.

Therefore, the aims of this study were 1) to investigate the MRI structural correlates of the MMSE global scores and the pentagon item and 2) to identify whether impairment in the pentagon item reflects brain atrophy in non-demented PD patients.

Methods

Participants

The cohort of this study consisted of 121 PD patients consecutively recruited from an outpatient movement disorders clinic (Parkinson's disease and Movement Disorders Unit, Service of Neurology, Hospital Clínic, Barcelona, Spain) from September 2010 to March 2012. Forty-one healthy subjects were recruited from the *Institut de l'Envelliment* (Barcelona, Spain) and were matched for age, sex and years of education to their patients peers. This study was approved by the ethics committee of the University of Barcelona; all subjects agreed to participate voluntarily and written informed consent was obtained after full explanation of the procedures.

Inclusion criteria for participants consisted of fulfilling the diagnostic criteria for PD established by the UK PD Society Brain Bank [15]. Exclusion criteria consisted of: [1] presence of dementia according to the Movement Disorders Society criteria [8], [2] Hoehn and Yahr (H&Y) scale score >3, [3] juvenile-onset PD, [4] presence of psychiatric and/or neurologic comorbidity, [5] low global IQ score estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (Scalar score ≤7 points) , [6] MMSE score ≤25, [7] claustrophobia, [8] imaging findings on MRI not compatible with PD and [9] MRI artifacts. Levodopa equivalent daily dose (LEDD) was calculated as suggested by Tomlinson *et al*. [16].

Ninety-two PD patients and 36 healthy volunteers were finally selected. Twelve patients and eight controls were excluded as they fulfilled criteria for dementia or other neurological disease, six PD patients for psychiatric comorbidity, one PD patient who scored higher than 3 on the H&Y scale, one PD patient who presented with juvenile-onset PD, three PD patients and one control who had low global IQ scores, two PD patients for claustrophobia, two PD patients and two controls were excluded because of missing tests used in this study and two controls and two PD patients due to MRI artefacts (demographic and clinical data of patients and healthy controls included in study sample are summarized in Table 1). Excluded patients did not differ from final PD participants in terms of demographics and clinical variables.

Cognitive status assessment

The screening test MMSE was used as a global measure of cognitive status. We used two additional grading measurements of the pentagon item: the scoring system of the Modified Mini-Mental State (3MS), a modified MMSE grading system that provides a quantitative, wide-range scoring measurement system; and the simple scoring system (SSS) used by Williams-Gray et al., because of its demonstrated value in predicting conversion to dementia in PD patients [1, 9, 10].

According to the original scoring criteria [17], the pentagon item is considered correct if 5 angles are present in each pentagon and 2 are intersecting. Possible scores are 0 and 1. In the 3MS version, scores range from 0 to 10. Up to 4 points are given for each pentagon and up 2 points for the intersecting quadrilateral. Four points are given to each pentagon when it has 5 approximately equal sides, whereas 3 points account for 5 sides but unequal (>2:1). Lower scores are given when another enclosed figure is drawn (2 points), or 2 or more lines (1 point); less than 2 lines account for 0 points. The simple scoring system used by Williams-Gray et al. [1, 9, 10] grades 2 points to those

pentagons that meet the original criteria, whereas 1 point is given for those that meet the “relaxed criteria”, in which there must be two figures that seem to be intersecting, at least one of them having 5 angles. Zero points are given to less accurate copies, *i.e*., to those figures in which no pentagon exhibits 5 angles and/or there is no intersection present (see Figure 1AS for drawing and grading scores examples). For correlation analyses purposes we scored the test as 1, 2 and 3.

MRI Acquisition

Magnetic resonance images were acquired with a 3T scanner (MAGNETOM Trio, Siemens, Germany). The scanning protocol included high-resolution 3-dimensional T1-weighted images acquired in the sagittal plane (TR=2300 ms, TE=2.98 ms, TI 900 ms, 240 slices, FOV=256 mm; matrix size=256x256; 1 mm isotropic voxel) and an axial FLAIR sequence (TR=9000 ms, TE=96 ms).

Cortical Thickness Analysis

FreeSurfer software (version 5.1; available at http://surfer.nmr.harvard.edu) was used to obtain CTh and whole brain measurements of brain atrophy. The cortical surface 3D model of CTh is created using intensity and continuity information, as described in detail by authors [18]. Independent steps are performed in the initial preprocessing of images for each subject: removal of non-brain tissue, automated Talairach transformation, intensity normalization [19], tessellation of the gray matter / white matter boundary, automated topology correction [20] and accurate surface deformation to optimally place the gray matter / white matter and gray matter / cerebrospinal fluid (CSF) boundaries [18]. The resulting representation of CTh is calculated as the distance between white and gray matter surfaces at each vertex of the reconstructed

cortical mantle [19]. In our study, results for each subject were carefully visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum (FWHM) of 15 mm.

Comparisons between groups and CTh correlations were assessed using vertex-by-vertex general linear model, including CTh as a dependent factor and cognitive scores as independent factors. In the PD patient group, the vertex-by-vertex general linear model was used to assess the relationship between cognitive scores and CTh. Positive and negative associations between each test were assessed using Qdec. In order to avoid clusters appearing significant purely by chance (i.e., false positives), Monte Carlo Null-Z Simulation with 10000 iterations was applied to CTh maps to provide clusterwise correction for multiple comparisons and results were thresholded at a corrected *p* value of 0.05 [21].

Global atrophy measures

Mean thickness for both hemispheres was calculated ((left hemisphere thickness * left hemisphere surface area) + (right hemisphere thickness * right hemisphere surface area)) / (left hemisphere surface area + right hemisphere surface area)). Total gray matter and lateral ventricular volumes were obtained automatically via whole brain segmentation procedures performed with *FreeSurfer* software [22].

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.). Student *t* tests were used to assess group differences between

patients and healthy subjects in clinical and neuropsychological continuous variables (*i.e.*, MMSE and 3MS scoring system) and Chi square test was applied to assess group differences in categorical variables (*i.e.*, sex and group).

Group differences were assessed with Student *t* test statistics for mean thickness, and with ANCOVA including intracranial volume (ICV) as a covariate in the model for volumetric atrophy measures. We addressed the reliability of the scoring systems used with Cronbach's α.

Correlations between mean thickness and continuous variables were assessed with Pearson's *r* statistics and with and Spearman's ρ for categorical variables. Correlations between cognitive scores and volumetric variables were analyzed using partial Pearson's *r*, accounting for ICV.

Results

Imaging analyses revealed that PD patients compared to controls had significant increases in lateral ventricle volume as well as reduction in mean CTh, but did not differ in global cortical gray matter volume (see Table 2).

Regional CTh maps showed that PD patients had thickness reductions involving lateral and medial temporo-parieto-occipital cortices bilaterally (see Figure 1A and Supplementary Table 1 for details of the location and size of significant clusters).

MMSE scores in PD patients (29.05 ± 1.1) were significantly lower than those of the control group (29.67 ± 0.5) (t=4.429, *P*<.001). Pentagon-copying scores according to 3MS system also differed significantly (t=2.136, *P*=.035) between patients (9.3 ± 1.1) and healthy subjects (9.6 ± 0.5). The scoring systems we used obtained a reliability of 0.762.

Global atrophy measures in PD patients

MMSE correlated with mean CTh and lateral ventricular volume in PD patients. Mean cortical thickness and cortical gray matter volume showed significant correlations with 3MS scores. Correlations between global atrophy measures and the simple scoring system were significant for mean cortical thickness but not for lateral ventricular volume (see Table 3).

Cortical thickness in PD patients

Patients with abnormal scores on the pentagon item according to the original criteria (n=15), compared with those of normal scores (n=77), had significant thickness reductions in the left superior temporal gyrus and precuneus bilaterally, as well as in the right precentral and postcentral gyri, superior parietal region and posterior cingulate cortex (see Figure 1B and Supplementary Table 2). PD patients' MMSE scores significantly correlated with CTh in left occipital and posterior cingulate regions (see Figure 2A and Supplementary Table 3).

Pentagon item scores according to 3MS showed significant correlations with CTh involving bilateral posterior areas, such as parietal and temporal bilateral cortex, but spreading also to anterior regions, including paracentral and medial frontal areas (see Figure 2B and Supplementary Table 3).

The simple scoring system showed significant correlations with bilateral parietotemporal regions, including the left precuneus and right supramarginal, superior parietal, fusiform and posterior cingulate regions (see Figure 2C and Supplementary Table 3). There were no significant correlations between structural measures and pentagon scores in control subjects. Scores in the latter group exhibited a ceiling effect.

Discussion

In our study, non-demented PD patients showed mean CTh decreases and ventricular enlargement. In addition, we observed cortical thinning in bilateral posterior parieto-temporal regions. Both MMSE and pentagon item scores correlated with measures of global atrophy and with regional CTh but with different extent and patterns.

MMSE scores correlated with measures of global cerebral atrophy, namely, mean cortical thickness and ventricular enlargement. Our results about correlations with ventricular enlargement are in agreement with previous studies that tested such relationship with samples that included cognitively impaired patients [11]. As expected, the pattern of regional correlations that we have observed was less extended than that previously reported in samples which included demented patients [13]. We only obtained significant correlations in regions limited to the left hemisphere. The left hemisphere predominance could be due to the fact that MMSE scores include several verbal items [23]. MMSE decreases in PD are probably indicating evolution to dementia. In this sense, Compta *et al*. [24] reported that Braak tau stages along with the parietal, cingulate, entorhinal and total cortical amyloid-B scores negatively correlated with MMSE scores ante-mortem, whereas such correlation was not found for the Lewy body score or Braak Parkinson's disease stage. Thus, there is some neuropathological evidence suggesting that MMSE decreases in PD are related to Alzheimer's-type pathology.

The scores of the pentagon copying test are also reflecting the degree of diffuse cerebral atrophy, but have a further pattern of CTh correlations involving bilateral posterior temporo-parietal regions. These results are in agreement with previous studies performed with non-demented PD patients that focused on the correlates of visuospatial and visuoperceptual functions using more complex tests, such as Benton's Visual Form Discrimination and Facial Recognition Test [25]. In demented PD, it has

been reported that visuospatial functions assessed by clock copying correlated with left precuneus and lingual gyrus thickness [26]. The only previous study that reported the anatomical correlates of the pentagon item test using ROI-based analyses also found correlations in medial bilateral posterior areas but also in the left anterior regions [14]; differences in both studies may be due to the MRI analyses and the procedures used to quantify the performance of the pentagon test.

We investigated the possible differential patterns of correlations in relation to the cognitive measurements. Interestingly, the pentagon's pattern of correlations observed was very similar to CTh reductions obtained in the comparison between PD patients and controls. Previous research assessing the relevance of cognitive deficits heralded by posterior cortical changes has evidenced that these deficits act as predictors of a dementing process in PD [1, 9, 10], in which dementia has been said to be largely due to an age-dependent and tau-dependent posterior cortically based process, rather than a dopaminergic dysfunction in frontostriatal networks [10]. In sum, our results indicate that the MMSE can reflect the global atrophy present in medium to long duration PD, but has poor power to detect these changes in bilateral temporo-parietal regions. In contrast, the specific regional posterior correlates of the pentagon copying test correspond to the differences in CTh between patients and controls. Our study has some limitations. There is currently no generally accepted standard for in vivo cortical thickness measurements, because in vivo reference values of cortical thickness or systematic comparison of post mortem data with an in vivo estimation are not available [27]. However, studies regarding which method best monitors cerebral involution in PD have exhibited that surface-based methods, especially CTh, are sensitive to PD-related neural degeneration [28].

Another limitation of our study is the lack of previous information about the reliability of the scoring systems used. However, Ala *et al*., [29], applying the original scoring system of the pentagon's item, reported high inter-raters reliability (Cronbach's α: 0.98).

Finally, our results cannot be generalized to all the pre-dementia stages of PD, because our sample of patients had a relatively long duration of disease, thus they are not representative of early stages.

In summary, our study suggests that both MMSE and the pentagon item reflect global brain degeneration that at a regional level is mainly located in the posterior regions, but the pentagon copying test correlated with more areas and with bigger cluster sizes**.** Our data supports the utility of the pentagon's item as a tool in patient care to monitor evolution of cognitive status.

There are previous studies that have independently addressed the value of the pentagon item [1, 9, 10] and cortical thinning [30] as markers for cognitive decline or dementia. However, to our knowledge there are no previous studies analyzing in the same sample the predictive power of cortical thickness and pentagon's item to predict future dementia in individual patients. Future longitudinal studies are needed to address these questions.

ACKNOWLEDGMENT

Without the support of the patients, their families and control subjects this work would not have been possible.

AUTHOR ROLES:

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript: A. Writing of the first draft, B. Review and Critique

Garcia-Diaz: 1C, 2A, 2B, 3A; Segura: 1B, 1C, 2A, 2B, 3B; Baggio: 1B, 1C, 2B, 2C, 3B; Marti: 1B, 1C, 2C, 3B; Valldeoriola: 1B, 1C, 2C, 3B; Compta: 1B, 1C, 2C, 3B; Vendrell: 1B, 1C ,2C, 3B; Bargallo: 1B, 1C, 2C, 3B; Tolosa: 1B, 1C, 2C, 3B ; Junque: 1A, 1B, 1C, 2A, 2B, 2C, 3B;

FINANCIAL DISCLOSURES OF ALL AUTHORS (for the preceding 12 months)

AI Garcia-Diaz, B.Segura, HC Baggio, MJ Marti, Y Compta, P Vendrell and C. Junque report no financial disclosures. F Valldeoriola is member of the Advisory board of Boehringer, Ingelheim, Solvay. E. Tolosa has grants from Michael J. Fox Foundation for Parkinson Disease (MJFF).

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Figure legends:

Figure 1. CTh differences between A) patients and healthy controls (Healthy controls > PD patients) and B) patients with correct or incorrect pentagon according to the original grading criteria used in the MMSE. Monte-Carlo Null Z Simulations at corrected $p<0.05$. Color bar indicates the level of statistical significance

Figure 2. CTh areas showing significant correlations in PD patients with A) MMSE, B) Pentagon item scored according to 3MS system and C) Pentagon item scored according to the simple scoring system. Monte-Carlo Null Z Simulations at $p<0.05$. Color bar indicates the level of statistical significance

Figure S1. Drawing and grading scores examples of patients' pentagon copying test.

Table 1. Demographic and clinical data of the participants

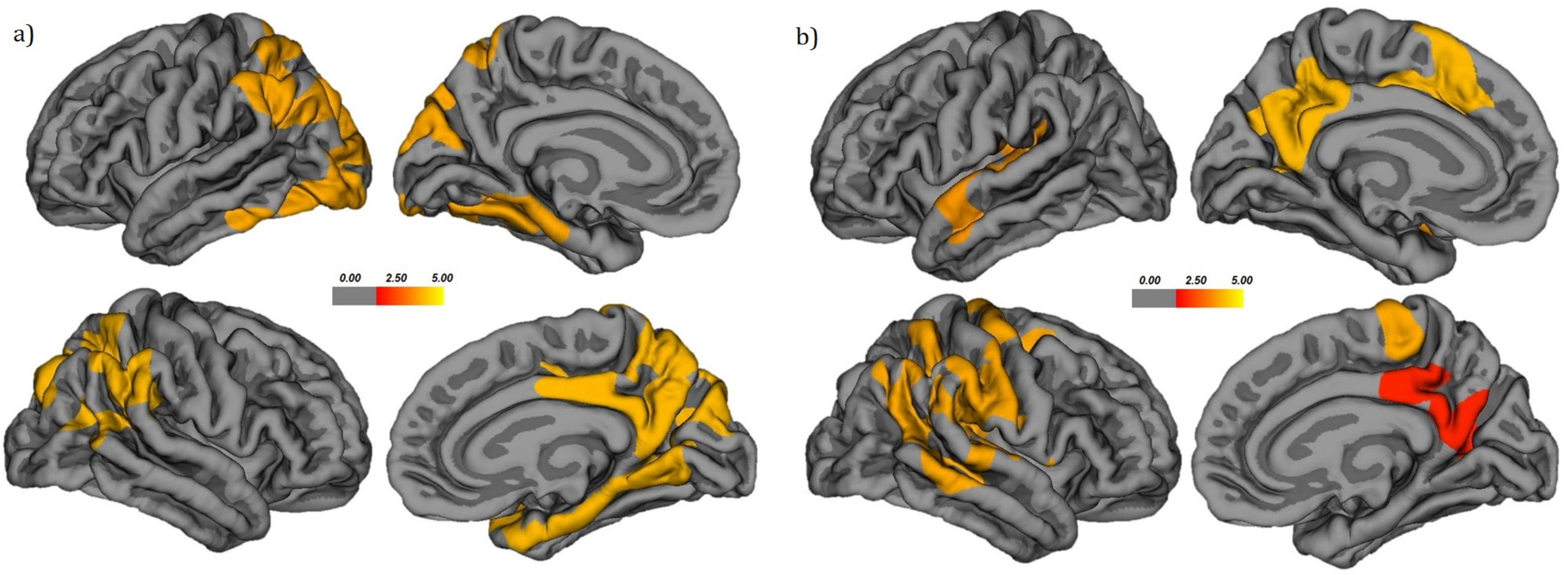
	Patients (n=92)	Controls (n=36)	t^a, χ^b	*p* value
Age	64 ± 11.1	63.4 ± 10.5	.287[a]	.775
Sex (male/female)	37/55	19/17	.521[b]	.300
Education, years	10.6 ± 5.4	11.4 ± 4.3	.750[a]	.454
Age at onset	56 ± 12.2			
Evolution, years	8.4 ± 5.9			
H&Y	1: 21 1.5: 5 2: 47 2.5: 9 3: 10			
UPDRS-III	16.4 ± 9.3			
LEDD	803.7 ± 494.2			

UPDRS-III: Unified Parkinson's Disease Rating Scale-III; H&Y: Hoehn & Yahr; LEDD: Levodopa Equivalent Daily Dose. Values are mean ± Standard Deviation (SD); [a]Student t test statistics; [b]χ^2 statistics

Table 2. Differences between PD patients and healthy subjects in global atrophy measures and correlations between cognitive status and pentagon item and atrophy measures

	Group differences						**Correlations in PD patients**					
	PD Patients		**Controls**		**t[a]/F**	**p**	**MMSE**		**3MS**		**WG-A**	
	Mean	**SD**	**Mean**	**SD**			**r**	**p**	**r**	**p**	**ρ**	**p**
Mean CTh*	2.4	0.1	2.5	0.1	2.610[a]	0.010	0.251	0.016	0.224	0.033	0.958	<0.0001
Cortical GMV**	601.55	64.2	611.62	54.3	2.027	0.157	0.189	0.075	0.279	0.008	0.185	0.082
LVV**	25.2	14.3	20.0	8.4	4.219	0.042	0.222	0.035	0.179	0.063	0.179	0.063

CTh: Cortical Thickness; LVV: Lateral Ventricular Volume; GMV: Gray Matter Volume; SD: Standard Deviation; MMSE: Mini-Mental State Examination; 3MS: Modified Mini-Mental State; WG: simple scoring system used by Williams-Gray et al. (2007-2013), modified from Ala et al. (2001). t: Student *t* test statistics; F: ANCOVA (ICV used as covariate); r: Pearson's r; ρ: Spearman's rho. *mm; **cm^3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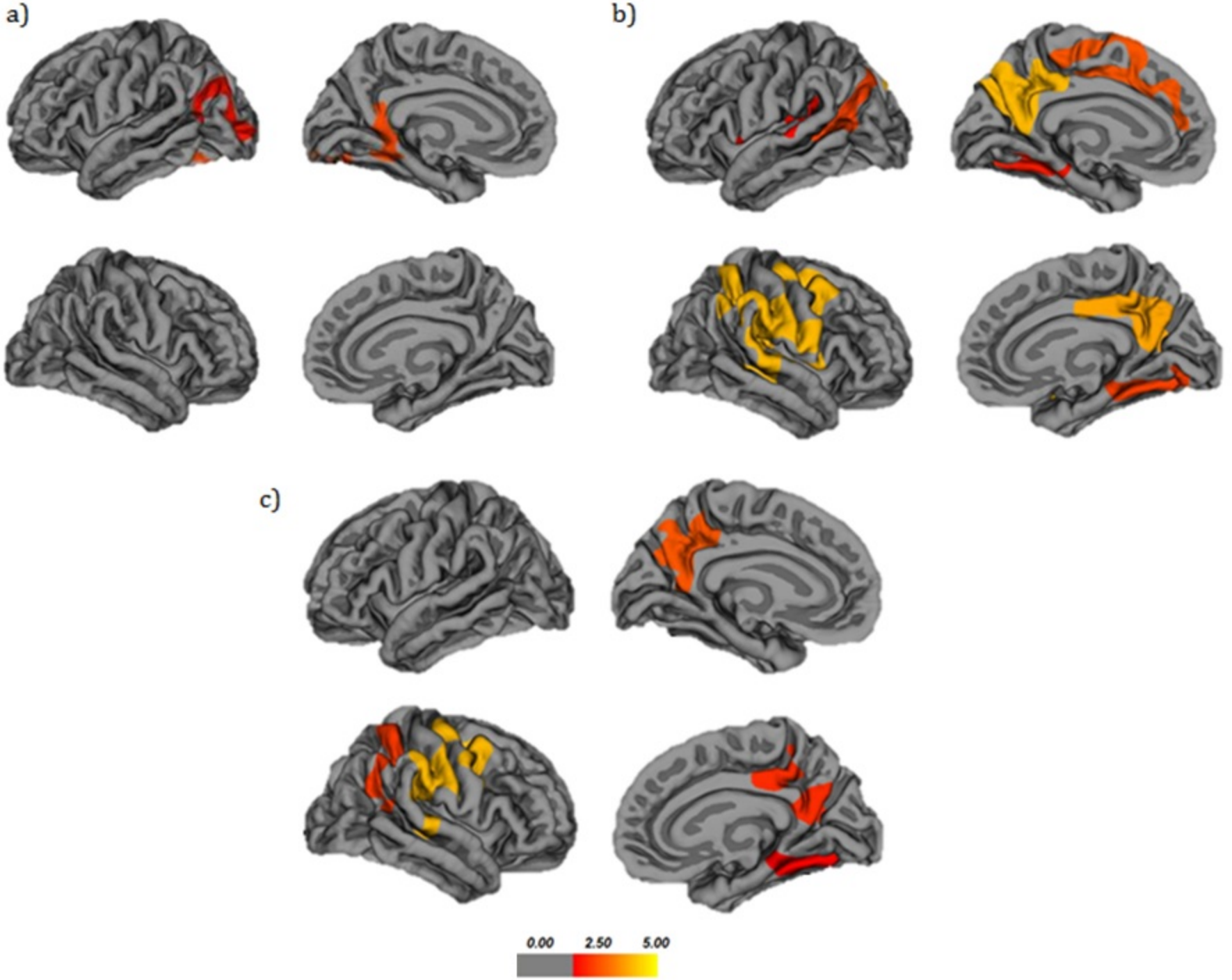
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SUPPLEMENTARY TABLES

Table S1. Significant clusters showing CTh differences between PD patients and healthy subjects

	Anatomical region	Cluster size	Talairach coordenates of the maxima			Z value	Clusterwise probability
			X	Y	Z		
Left	Supramarginal	8006.70	-48.6	-48.8	37.3	-4.682	0.0001
	Fusiform	3503.77	-26.6	-51.0	-10.0	-3.536	0.0001
Right	Superior parietal	112522.39	26.8	-56.9	43.1	-4.420	0.0001

Results were corrected using family wise error correction with Monte Carlo Null-Z Simulation and thresholded at p=.05

Table S2. Significant clusters showing differences between patients with acceptable or incorrect pentagon (Acceptable >Incorrect) according to the original grading criteria

Anatomical region	Cluster size (mm^2)	Talairach coordenates of the maxima			Z value	Clusterwise probability
		X	Y	Z		
L Superior temporal	3236.85	-46.4	-31.4	5.5	-4.057	.0001
L Precuneus	4220.40	-13.9	-39.7	33.5	-3.369	.0001
R Postcentral	8607.50	26.8	-25.5	48.0	-3.493	.0001
R Superior parietal	2792.71	30.9	-39.0	40.6	-3.271	.0003
R Posterior cingulate	2165.76	5.7	-29.4	34.9	-3.001	.005
R Precentral	1515.57	47.9	5.6	27.5	-2.363	.0464

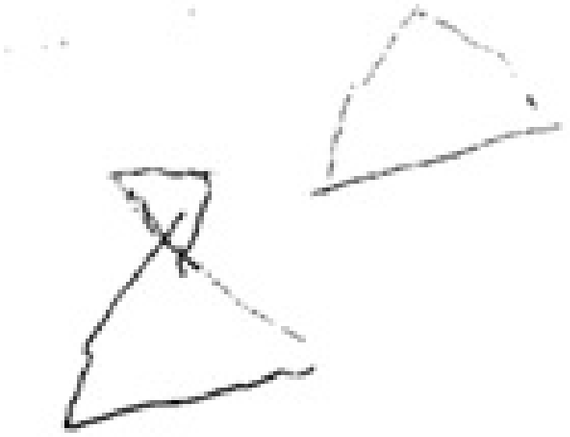
L: Left; R: Right

Table S3. Significant clusters showing correlations between cognitive scores and CTh

	Anatomical region	Cluster size (mm^2)	Talairach coordenates of the maxima			Z value	Cluster-wise probability
			X	Y	Z		
MMSE	*L Lateral occipital*	1646.00	-27.7	-83.0	4.4	2.965	.0237
	L Isthmus cingulate	2194.28	9.6	-49.9	8.5	2.365	.0034
3MS	*L Inferior parietal*	2133.70	-47.7	-61.0	12.7	4.649	.0056

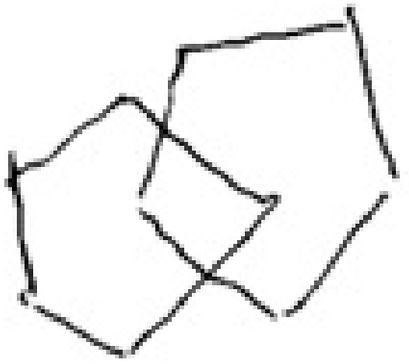
	L Precuneus	3544.58	-9.3	-55.2	28.9	3.839	.0001
	L Superior temporal	1565.52	-48.2	-31.5	6.4	3.824	.0344
	L Fusiform	1700.77	-32.8	-44.6	-10.0	3.626	.0208
	L Paracentral	2292.86	-13.0	-11.9	42.2	2.810	.0208
	R Superior temporal	11309.12	50.0	-33.5	14.9	5.318	.0001
	R Fusiform	2097.70	29.0	-66.0	-3.2	3.538	.006
	R Posterior cingulate	2152.39	5.0	-30.0	38.1	3.473	.0002
Williams-Gray *et al*.	*L Precuneus*	2322.96	-7.8	-43.0	45.0	2.759	.0028
	R Supramarginal	6373.23	56.1	-23.4	35.9	3.750	.0001
	R Superior parietal	2001.60	35.4	-44.2	57.6	3.600	.0076
	R Fusiform	1502.36	29.1	-66.4	-4.1	2.589	.0477
	R Posterior cingulate	1888.19	5.5	-29.9	36.0	2.304	.0116

MMSE: Mini-Mental State Examination; 3MS: Modified Mini-Mental State; L: Left; R: Right



Example 1

Example 2



Example 3

- Example 1:
  - Original grading criteria: Incorrect
  - 3MS: 4 points
  - Simple scoring system by Williams-Gray *et al.*: 0 points
- Example 2:
  - Original grading criteria: Incorrect
  - 3MS: 7 points
  - Simple scoring system by Williams-Gray *et al.*: 1 point
- Example 3:
  - Original grading criteria: Correct
  - 3MS: 10 points
  - Simple scoring system by Williams-Gray *et al.*: 2 points