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Imaging changes associated with cognitive abnormalities in Parkinson's disease

Yuko Koshimori,
Division of Brain, Imaging and Behaviour–Systems Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Barbara Segura,
Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada, Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona, Casanova 146, 08035 Barcelona, Spain

Leigh Christopher,
Division of Brain, Imaging and Behaviour–Systems, Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Nancy Lobaugh,
Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Sarah Duff-Canning,
Morton and Gloria Shulman Movement Disorder Unit and E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Department of Neuropsychology, Toronto Western Hospital, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

Romina Mizrahi,
Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Clement Hamani,
Division of Neurosurgery, Toronto Western Hospital, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

Anthony E. Lang,

Correspondence to: Antonio P. Strafella.

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Morton and Gloria Shulman Movement Disorder Unit and E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada

Kelly Aminian,
Division of Brain, Imaging and Behaviour–Systems, Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Sylvain Houle, and
Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada

Antonio P. Strafella
Division of Brain, Imaging and Behaviour–Systems, Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Research Imaging Centre, Centre for Addiction and Mental Health (CAMH), University of Toronto, 250 College St, Toronto, ON M5T 1R8, Canada, Morton and Gloria Shulman Movement Disorder Unit and E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, 399 Bathurst St, Toronto, ON M5T 2S8, Canada, Toronto Western Hospital and Institute, CAMH-Research Imaging Centre, University of Toronto, Toronto, ON, Canada

Abstract

The current study investigates both gray and white matter changes in non-demented Parkinson's disease (PD) patients with varying degrees of mild cognitive deficits and elucidates the relationships between the structural changes and clinical sequelae of PD. Twenty-six PD patients and 15 healthy controls (HCs) were enrolled in the study. Participants underwent T1-weighted and diffusion tensor imaging (DTI) scans. Their cognition was assessed using a neuropsychological battery. Compared with HCs, PD patients showed significant cortical thinning in sensorimotor (left pre- and postcentral gyri) and cognitive (left dorsolateral superior frontal gyrus [DLSFG]) regions. The DLSFG cortical thinning correlated with executive and global cognitive impairment in PD patients. PD patients showed white matter abnormalities as well, primarily in bilateral frontal and temporal regions, which also correlated with executive and global cognitive impairment. These results seem to suggest that both gray and white matter changes in the frontal regions may constitute an early pathological substrate of cognitive impairment of PD providing a sensitive biomarker for brain changes in PD.

Keywords

Parkinson's disease; Cognition; Executive dysfunction; Cortical thickness; White matter; Diffusion tensor imaging

Introduction

Parkinson's disease (PD) is a multisystem neurodegenerative disease, affecting not only dopaminergic nerve cells of the substantia nigra but also other brain regions and neurotransmitters (Braak et al. 2006). PD presents with the cardinal motor symptoms such as tremor, rigidity, bradykinesia, and loss of postural stability along with a set of non-motor symptoms (Bonnet et al. 2012) such as cognitive impairment, depression, sleep disturbances, and autonomic dysfunction (Barnum and Tansey 2012; Chaudhuri et al. 2011; Ferrer et al. 2011). For this reason, PD research has expanded its investigation beyond the nigrostriatal region to the whole brain in order to characterize the different symptoms. In particular, neuroimaging investigation of cognitive impairment is a topic of a growing interest (Christopher and Strafella 2013). It is prevalent and present regardless of the disease stage (Litvan et al. 2011). It ranges from mild deficits demonstrable by means of comprehensive neuropsychological testing, to dementia (Jellinger 2012), and mild cognitive impairment (MCI) increases risk of developing dementia (Janvin et al. 2006). The neural substrate of motor and cognitive symptoms has been investigated using non-invasive brain imaging such as structural MRI, which can offer the opportunity of identifying early biomarkers. In fact, different MRI techniques are providing mounting evidence of both gray and white matter changes in PD (Cochrane and Ebmeier 2013; Pan et al. 2012).

Whole-brain gray matter changes have been investigated using voxel-based morphometry (VBM) as well as surface-based analyses including cortical thickness and surface analyses combined with subcortical volumetric analysis. PD patients with dementia (PDD) typically show bilateral diffuse gray matter changes (Beyer et al. 2007; Compta et al. 2012; Melzer et al. 2012; Song et al. 2011; Zarei et al. 2013). On the other hand, non-demented PD patients show regional gray matter changes in areas such as frontal (Biundo et al. 2011; Burton et al. 2004; Ibarretxe-Bilbao et al. 2010; Jubault et al. 2011), temporal and/or limbic regions (Feldmann et al. 2008; Ibarretxe-Bilbao et al. 2009; Pellicano et al. 2012; Tinaz et al. 2011; Wattendorf et al. 2009), or posterior regions including the parieto-occipital cortex (Pereira et al. 2012). Furthermore, non-demented PD patients show faster progression of gray matter changes including atrophy and cortical thinning than healthy controls (HCs) in diffuse areas including frontal, temporal and parietal regions (Hu et al. 2001; Ibarretxe-Bilbao et al. 2012), restricted regions to cortical motor areas and cerebellum (Ibarretxe-Bilbao et al. 2010), or limbic, paralimbic, and temporo-occipital regions (Ramirez-Ruiz et al. 2007). Among PD patients, variability in cortical thickness and/or subcortical volume is also associated with cognitive measures (Biundo et al. 2011; Camicioli et al. 2009; Ibarretxe-Bilbao et al. 2009; Melzer et al. 2012; Pellicano et al. 2012; Zarei et al. 2013), facial emotion recognition (Baggio et al. 2012), duration of disease (Hanganu et al. 2013; Jubault et al. 2011; Lyoo et al. 2011), motor severity (Lyoo et al. 2011; Melzer et al. 2012; Zarei et al. 2013) and stage (Zarei et al. 2013) as well as dopamine (DA) non-responsive symptoms (Brenneis et al. 2003; Camicioli et al. 2009).

White matter changes have been investigated using diffusion tensor imaging (DTI). The two most common indices derived from DTI are fractional anisotropy or FA and mean diffusivity or MD (Cochrane and Ebmeier 2013). FA estimates the degree of anisotropic directionality of water diffusion while MD estimates the magnitude/size of water diffusion. FA and MD in

the whole-brain white matter can be assessed using voxel-based analysis (VBA) or tract-based statistical analysis (TBSS). Contrary to gray matter findings, in which regional changes are more common in non-demented PD, white matter changes are reported in more diffuse brain areas even in non-demented PD (Hattori et al. 2012; Kim et al. 2013; Melzer et al. 2013; Theilmann et al. 2013; Zheng et al. 2014), and the frontal region was one of the most consistently reported regions for white matter changes (Agosta et al. 2013b; Deng et al. 2013; Gattellaro et al. 2009; Rae et al. 2012; Zhan et al. 2012; Zhang et al. 2011). Moreover, variability in FA and/ or MD was primarily associated with cognitive measures (Agosta et al. 2013b; Gallagher et al. 2013; Rae et al. 2012; Theilmann et al. 2013; Zheng et al. 2014.)

Despite the evidence of structural abnormalities and variability associated with clinical and cognitive manifestations in non-demented PD, whether structural abnormalities account for specific clinical sequelae in PD patients is still unclear. This is largely due to the lack of imaging studies investigating both structural group differences, and relationships between these differences and various clinical and cognitive measures. For example, brain regions displaying significant group differences in structure have not been specifically investigated for correlation analyses (Camicioli et al. 2009; Hanganu et al. 2013; Jubault et al. 2011; Tinaz et al. 2011). Even though brain regions demonstrating significant group differences have been shown to correlate with cognition, PD patients did not show impairment on cognitive tasks (Theilmann et al. 2013). Furthermore, only correlations were demonstrated in PD without comparing structural data of PD with those of HCs (Lyoo et al. 2011; Zheng et al. 2014). To date, only a handful of studies have addressed which structural abnormalities account for different PD symptoms by investigating whole-brain gray and white matter changes (Agosta et al. 2013a, 2013b; Hattori et al. 2012). Using both VBM and TBSS analyses, these studies have consistently concluded that white matter and not gray matter changes underlie cognitive impairment in PD (Agosta et al. 2013a, b). This discrepancy may be due to the fact that VBM may not be highly sensitive for detecting subtle cortical atrophy in early stages of PD (Agosta et al. 2013b; Jubault et al. 2011). In fact, cortical thickness analysis appeared more prone to detect cortical gray matter changes in PD than VBM when both analysis methods were compared (Pereira et al. 2012). Thus based on these preliminary observations, the current study aimed at (1) investigating both gray and white matter changes using cortical thickness analysis and TBSS, and thereby also demonstrating which MRI technique can be a promising biomarker for PD and (2) further elucidating the relationships between observed structural abnormalities and clinical and cognitive manifestations in non-demented PD patients.

Materials and methods

Participants

Twenty-six patients meeting UK Brain Bank criteria for the diagnosis of idiopathic PD (Defer et al. 1999; Langston et al. 1992) and 15 HCs participated in the study. PD patients were recruited from the Movement Disorders Clinic of the Toronto Western Hospital. The HCs were recruited from friends and spouses of the patients or through advertisements posted at the hospital and the affiliated university. Exclusion criteria included (1) history of a head injury, psychiatric, neurological or major medical diseases, (2) dementia assessed by a

modified disability assessment for dementia (DAD) with an additional question regarding whether any reported impairment was related to cognitive difficulties or the physical impairments of PD, (3) contraindications for MRI scanning, and (4) for HCs evidence of cognitive impairment as assessed by a neuropsychological test battery. All participants underwent a cognitive assessment by means of an extended neuropsychological test battery and the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005; Tison et al. 1995) as well as the Beck depression inventory (Beck et al. 1961) that assesses levels of depression. PD patients were additionally evaluated for motor severity of the disease using the motor subset of the Unified Parkinson Disease Rating Scale (UPDRS-III). All participants underwent structural MRI scans and 35 participants had additional DTI scans. Among the 35 participants, five subjects (four PD patients and one HC) were excluded due to motion artifacts resulting in 16 PD patients and 14 HCs included in the DTI analysis. PD patients underwent all the study procedures in an “on-medication” state. All participants gave informed consent following full explanation of the study procedures. This study was approved by the Institutional Ethics Committee of the Centre for Addiction and Mental Health and the University Health Network.

Neuropsychological assessment

Cognitive function in the domains of executive function, attention/working memory, language, visuospatial function, and memory was assessed using the following neuropsychological tests (Litvan et al. 2012). For executive function: Visual Verbal Test total number of shifts (Wicklund et al. 2004), Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference (Stroop task); time to complete condition 3: inhibition, and D-KEFS Verbal Fluency, total score for category fluency (Delis et al. 2001). For attention and working memory: Wechsler Memory Scale-III (WMS-III) Digit Span and Letter-Number Sequencing total score (Wechsler 1997), Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference (Stroop task); time to complete condition 1: color naming (attention). For language: the category fluency from the Verbal Fluency subtest (Delis et al. 2001). For visuospatial function: Judgment of Line Orientation (JLO) total score (Benton et al. 1994). For memory: California Verbal Learning Test-II (CVLT-II) long delay free recall score (Delis et al. 2001). Global composite z scores were calculated for each domain of cognition. When the cognitive domain had only one test, the individual test score was used. For executive function, the average of the z scores from the visual verbal test, inhibition segment of the Stroop task, and verbal fluency was used, while for attention/working memory, the average of the z scores from the digit span, letter-number sequencing, and color-naming segment of the Stroop was used.

MRI acquisition

Whole-brain T1-weighted and diffusion-weighted images were acquired using a 3.0 T GE Signa HD × MRI system (General Electric, Milwaukee, WI) equipped with an eight-channel phased array head coil. For gray matter analysis, a high-resolution three-dimensional (3D) anatomical scan was acquired with a T1-weighted 3D IR-FSPGR sequence (TR/TE/TI, 7.8/min full/450 ms; matrix, 256 × 256; voxel size, 1 × 1 × 1 mm; filed of view, 256 × 256 mm; flip angle, 15°; 180 axial slices). For white matter analysis, a DWI scan was acquired with spin-echo single-shot echo planar imaging with diffusion encoding in 60 noncolinear

directions (TR/TE, 17,000/min ms; field of view, 230 × 230 mm; matrix, 128 × 128, voxel size, 1.8 × 1.8 × 2.4 mm; *b* value, 1,000 s/mm^2; 64 slices). Parallel imaging was employed using the Array Spatial Sensitivity Encoding Technique (ASSET) with an acceleration factor of two. DWI images were acquired in the axial plane. In addition, ten non-diffusion-weighted scans were acquired at the beginning of each scan. The DWI scans were repeated three times to increase signal-to-noise ratio. Two PD patients and two HCs underwent only two DWI scans due to inability to lie down in the scanner for an extended period of time.

MRI processing

Cortical thickness processing—Cortical thickness (CTh) analysis was performed using the FreeSurfer image analysis suite (version 5.1; available at http://surfer.nmr.mgh.harvard.edu). The processing of T1 high-resolution images for the cortical surface reconstruction involved several steps (Dale et al. 1999): automated Talairach transformation, intensity normalization (Sled et al. 1998), skull stripping, white matter segmentation, tessellation of the gray/white matter boundary, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location (Dale and Sereno 1993; Dale et al. 1999; Fischl and Dale 2000). All surface models were visually inspected for accuracy. Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale 2000).

Subcortical volume processing—Segmentation of brain volume was obtained based on the automatic procedure included in FreeSurfer (version 5.1; available at: http://surfer.nmr.harvard.edu; Fischl et al. 2002). The labels were created using an automated subcortical labeling algorithm based on a probabilistic atlas obtained from a manually labeled training set. The image was rigid body registered to the probabilistic brain atlas, followed by non-linear morphing to the atlas. Then, an automated segmentation procedure assigned a label to each voxel in a dataset based on signal intensity information and the spatial relationship of the subcortical labels in the training sets. Volumetric measures from 18 structures in each hemisphere as well as intracranial volume (ICV) were automatically obtained. Among these structures, we selected the thalamus, putamen, caudate nucleus, pallidum, nucleus accumbens, hippocampus, amygdala and brainstem for our regions of interests (ROIs).

TBSS processing—Individual FA and MD images were generated to conduct TBSS analysis using FSL tools from the FMRIB software library (FSL version 4.1.5, http://www.fmrib.ox.ac.uk/; Smith et al. 2004; Woolrich et al. 2009). First, each volume upsampled to create isotropic voxel size (2.4 × 2.4 × 2.4 mm) was affine registered to the nineth b0 volume using FLIRT to correct motion and eddy current distortion (Jenkinson and Smith 2001; Jenkinson et al. 2002). Then, an averaged DWI image was generated from the three sets of DWI images. Non-brain tissue of the averaged DWI image was removed using brain extraction tool (BET) (Smith 2002), and FA and MD images were derived using DTIfit from FMRIB's Diffusion Toolbox. The FA maps of all participants were warped to the FMRIB58_FA template using FNIRT (Andersson et al. 2007a,b). A mean FA map of all

subjects was created and thinned to generate a mean FA skeleton, which represents the centers of white matter tracts common to all subjects included in the present study. The mean skeleton was thresholded and binarized at FA value of 0.2 to minimize partial voluming. The individual FA and MD maps were projected onto the mean skeleton resulting in a skeletonised FA and MD maps.

Statistical analysis

The cortical thickness analysis was performed using Freesurfer's QDEC application that fits a general linear model (GLM) at each surface vertex. CTh maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum (FSHM) of 15 mm. Z Monte Carlo simulations with 10,000 iterations were applied to CTh maps to provide clusterwise correction for multiple comparisons, and the results were thresholded at a corrected P value of 0.05 ($Z = 1.3$). Mean thickness was calculated for each significant cluster.

Voxelwise statistics were performed on the skeletonised FA and MD maps using the Threshold-Free Cluster Enhancement (TFCE, Smith and Nichols 2009). A $P < 0.05$ voxelwise correction for multiple comparisons was considered significant. The JHU DTI-based white matter atlases including the Johns Hopkins University WM tractography atlas and the ICBM-DTI WM labels (Hua et al. 2008; Mori et al. 2005; Wakana et al. 2007) were used to identify white matter tracts that showed significant group differences and correlations in FA and MD values.

Age, years of education, MoCA, BDI and neuropsychological tests were compared between groups using independent samples t tests. Gender and handedness were compared using Pearson's Chi square tests. Subcortical volume in a priori ROIs (thalamus, putamen, caudate nucleus, pallidum, nucleus accumbens, hippocampus, amygdala, and brainstem) in each hemisphere was compared between groups using independent t test or Analysis of Variance (ANOVA) after testing the effects of intracranial volume (ICV) on the subcortical volume in each ROI.

From the clusters displaying significant group differences, mean individual values were extracted to investigate the relationships between structural changes (cortical thickness, subcortical volume, and DTI) and (1) cognitive data (MoCA and neuropsychological test scores) and (2) clinical data (UPDRS-III scores and duration of disease). Prior to the correlation analyses, bivariate correlation was performed among all relevant covariates including demographic (age, gender, years of education, and handedness), clinical (symptom-dominant side, UPDRS-III scores, disease duration, LEDD, and BDI), cognitive (MoCA, visual verbal test, JLO, and global and executive composite z) and MRI findings from the group analysis using Pearson's correlation tests to determine the effects of nuisance variables, which would be then controlled for in the correlations, if necessary. All statistical analyses were two-sided and statistical significance was set at $P < 0.05$ corrected for multiple comparisons. All of the statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS 13.0).

Results

Demographic, clinical, and cognitive characteristics

Table 1 shows the demographic and clinical characteristics as well as neuropsychological data of all of the patients with Parkinson's disease (PD) and healthy controls (HC). There was no difference between the two groups regarding age, gender, education, BDI, and handedness (P >0.05). However, they were significant differences on MoCA (P = 0.006), global composite z (P = 0.007) and executive composite z (P = 0.001), visual verbal test (P <0.001), and judgement of line orientation (P = 0.027).

Cortical thickness

We found that the PD patients showed significant reduction in cortical thickness in the left superior frontal gyrus (SFG) (cluster size: 1,585 mm^2; P = 0.03) and the left precentral gyrus extending back into the postcentral gyrus (PCG) (cluster size: 2,555.42 mm^2; P = 0.01) compared with the HCs (Fig. 1). The PD patients did not show significant increase in cortical thickness in any brain region compared with the HCs.

We further investigated whether the cortical thickness in these two significant clusters was correlated with clinical sequelae. To this end, first, we ran bivariate correlations among different covariates including the cortical thickness values in the SFG and PCG clusters and demographic, clinical and cognitive measures to determine the effects of nuisance variables. In particular, age showed significant negative correlation both with SFG cortical thickness (r = −0.497, P = 0.01) and cognitive scores including MoCA (r = −0.423, P = 0.031), visual verbal test (r = −0.499, P = 0.009), and executive composite z scores (r = −0.541, P = 0.004). Thus controlling for the effect of age, we found significant positive correlations between the SFG thickness and global composite z (r = 0.597, P = 0.002), and executive composite z (r = 0.430, P = 0.032) scores (Fig. 2). In HCs, we found a significant positive correlation between the SFG thickness and visual verbal test scores (r = 0.607, P = 0.016).

Subcortical volume

We found no significant group differences in any ROIs and therefore, no correlation analysis was pursued.

White matter

We found that PD patients showed white matter changes with significantly higher MD values compared to HCs. The significant cluster with increased MD was detected in widespread regions including the frontal, temporal, parietal and occipital regions (Fig. 3). These changes were located primarily in a larger area of bilateral frontal and temporal regions and smaller areas of the left parietal and occipital regions. More specifically, white matter tracts with MD changes included forceps minor, cingulum, anterior thalamic radiation, superior corona radiata, external capsule, body of corpus callosum, uncinate fasciculus, inferior fronto-occipital fasciculus, superior and inferior longitudinal fasciculi, and forceps major. PD patients did not show any significantly lower MD values in any white matter tracts compared with HCs.

We extracted mean MD values from the significant cluster resulting from the group analysis for each subject and investigated correlations between the MD values and (1) cognitive measures that showed significant group differences (i.e., visual verbal test, $P<0.01$; global composite z, $P<0.03$; and executive composite z, $P<0.01$) in both PD patients and HCs as well as clinical measures (duration of disease and UPDRS-III scores) in PD patients. We first ran bivariate correlations among all relevant covariates. In PD patients we found a significant negative correlation between age and executive z scores ($r=-0.622$, $P=0.01$) and a positive correlation between age and the mean MD values in the significant cluster ($r=0.525$, $P=0.037$). In this group of patients, we also observed a significant correlation between gender and cognitive measures (scores of global composite z ($r=0.667$, $P=0.005$) and executive composite z ($r=0.583$, $P=0.018$). Thus, controlling for the effects of age and gender, we found significant negative correlations between the MD values and scores of global composite z ($r=-0.39$, $P<0.05$) and executive composite z ($r=-0.44$, $P=0.018$) in PD patients, suggesting that white matter damage (mainly in frontal and temporal regions) was associated with cognitive impairment. In HCs, we found no correlations among any of the considered variables.

Discussion

The present study corroborated structural changes in PD patients and demonstrated specific relationships between gray and white matter damages and cognitive deficits in PD, suggesting that these abnormalities may represent a sensitive biomarker for detecting brain changes associated with cognitive changes.

Our results provided evidence of gray matter changes at the cortical level in PD. PD patients showed significant cortical thinning in the left superior frontal, caudal middle frontal, precentral and postcentral gyri compared to HCs. Gray matter changes in these regions have previously been reported in non-demented PD patients (Kostic et al. 2010; Melzer et al. 2012; Pereira et al. 2012; Zarei et al. 2013). In addition, the superior frontal, caudal middle frontal gyrus and precentral sulcus were among the areas showing significantly greater progression of cortical thinning in PD patients compared to HCs (Ibarretxe-Bilbao et al. 2012).

We further investigated whether these cortical abnormalities would explain the clinical sequelae including motor and cognitive manifestations in PD and found that cortical thinning in the dorsolateral SFG was associated with global and executive cognitive measures. The dorsolateral SFG including BA8 and BA9 that showed significant thinning, is involved in a variety of cognitive functions including working memory (Levy and Goldman-Rakic 2000; Owen et al. 1998), attention (Corbetta et al. 2008), episodic memory (Desgranges et al. 1998) and spatial cognition (Courtney et al. 1998; du Boisgueheneuc et al. 2006). In particular, the left SFG is involved in higher levels of cognitive processing (du Boisgueheneuc et al. 2006) or executive functions. This may well explain the significant correlation between the SFG thinning and global composite and executive z scores. We also found a significant positive correlation between the left SFG thickness and visual verbal test scores in HCs but not in PD patients. This is most likely due to a lack of variability in the scores of the PD patients.

We did not find any correlation between the reduced cortical thickness in the sensorimotor area and UPDRS-III scores or duration of disease. These observations seem to be consistent with previous studies where cortical thinning was found in motor areas including the left medial SMA and right dorsal pre-SMA without any correlation with UPDRS-III scores or disease duration in those regions (Jubault et al. 2011). On the other hand, correlations between cortical gray matter measures in the sensorimotor area and motor symptoms (Lyoo et al. 2011; Rosenberg-Katz et al. 2013) as well as between cortical thickness in several cortical areas and duration of disease (Lyoo et al. 2011; Rosenberg-Katz et al. 2013) have been reported in other studies. However, it is unknown whether PD patients had cortical abnormalities in those areas compared to HCs, as those studies did not include control data. The lack of a significant correlation between cortical abnormality in the sensorimotor area and UPDRS-III scores in our patients may well be due to the fact that UPDRS evaluations were performed during an on-medication state (instead of during an off-medication state), and this could have very likely diminished the possibility of detecting a significant relationship with the cortical thinning in those regions.

We did not find any changes in subcortical volume between groups. Previous studies using the same method also failed to find significant group differences (Tinaz et al. 2011; Zarei et al. 2013). These consistent observations suggest that current imaging analysis may lack sensitivity for detecting subtle gray matter changes.

Our TBSS analysis revealed that PD patients showed white matter damage in multiple white matter tracts in widespread areas, more extensively in the bilateral frontal and temporal regions compared to HCs. White matter changes in these regions were consistently reported in previous TBSS findings (Agosta et al. 2013a, b; Deng et al. 2013; Hattori et al. 2012; Matsui et al. 2007; Melzer et al. 2013; Rae et al. 2012). We detected group differences with an increase in MD (but not in FA) in our patients. MD appears to be more sensitive in detecting subtle white matter changes than FA as suggested in other studies in early PD (Melzer et al. 2013), early Alzheimer patients (Acosta-Cabronero et al. 2010) and individuals with concussion (Cubon et al. 2011).

We further found that the frontotemporal white matter damage significantly correlated with the global and executive cognitive measures. Our findings combined with previous studies (Agosta et al. 2013b; Gallagher et al. 2013; Hattori et al. 2012; Melzer et al. 2013) suggest that frontal white matter damage is a core pathological substrate of mild cognitive deficits in PD. White matter damage did not correlate UPDRS-III scores. This is very likely because UPDRS evaluation was representative of the on-medication state for the same explanation provided above.

Our gray and white matter data consistently showed structural changes in the frontal region in PD. The frontal cortex includes part of the frontostriatal loops (Alexander et al. 1986), which have important implications for motor and non-motor symptoms of PD. Prefrontostriatal dysfunction is thought to underlie the basis for the most prominent executive impairment in PD (Nagano-Saito et al. 2013; Owen 2004; Pagonabarraga and Kulisevsky 2012; Zgaljardic et al. 2006). Abnormality in the SFG in particular can be an early indicator for further decline of cognitive function. For example, PD patients who

converted to dementia showed cortical thinning in the frontal regions including the SFG, PCG, and anterior cingulate at a baseline assessment and showed wider areas of cortical thinning in temporal, parietal and occipital regions at a follow-up assessment (Compta et al. 2013). The white matter underlying the prefrontal cortex contains projections from striatum via thalamus, to the striatum via thalamus, and directly to striatum. Although the TBSS does not allow for specific identification of the frontostriatal pathway, it reveals that the white matter comprising the frontostriato-thalamic loop was affected in our PD patients. For example, the anterior thalamic radiation includes white matter tracts from thalamus to prefrontal cortex and vice versa. The lateral anterior ventral and medial dorsal nuclei of thalamus, in particular, receive input from the basal ganglia. White matter damage found in our study extended beyond the frontal region and thus, it is still to be determined whether white matter changes in the prefrontal region alone can contribute to cognitive impairment. However, prefrontal white matter alone appears to be able to contribute to executive cognitive functions in PD (Gallagher et al. 2013).

Our PD patients also showed extensive white matter changes in bilateral temporal regions. A few studies consistently showed that PD with MCI may be associated with gray matter atrophy in limited regions of frontal and temporal regions (Hanganu et al. 2013; Melzer et al. 2012; Song et al. 2011) while one of them additionally showed parietal volume loss (Melzer et al. 2012) and others, occipital volume loss (Hanganu et al. 2013; Song et al. 2011). A longitudinal study also demonstrated higher rates of cortical thinning in the frontal and temporal regions, extending to parietal cortex (Ibarretxe-Bilbao et al. 2012). Although our PD patients did not show gray matter abnormalities in the temporal region, the white matter changes may have preceded gray matter changes. The topography of white matter changes in our study is similar to the previous gray matter findings mentioned above with extensive frontal and temporal abnormalities as core changes and unilateral focal parietal and occipital changes. Abnormality in the temporal region may be associated with developing dementia in PD patients. For example, compared to the PD with normal cognition, PD-MCI and PDD had significantly smaller hippocampal volumes, and PDD additionally showed the medial temporal lobe atrophy (Weintraub et al. 2011). Furthermore, PDD showed significant atrophy in the entorhinal cortex compared with PD with normal cognition (Goldman et al. 2012).

Our findings in gray and white matter changes in PD are in line with previous studies showing widespread white matter abnormalities but limited (Agosta et al. 2013a) or absent (Agosta et al. 2013b; Hattori et al. 2012) cortical gray matter changes. However, differently from those studies using VBM, the significant gray matter abnormalities reported here seem to suggest that cortical thickness analysis may be a better approach. Thus, the combination of DTI and cortical thickness analyses appear to be sensitive approaches for detecting subtle white and gray matter changes associated with PD.

Although the MRI techniques used in the present study are validated methods to assess structural changes, the biological underpinnings of these changes are not fully understood. Subtle cortical thinning may reflect changes in size of cell bodies, dendritic arborisation, and/or presynaptic terminals (Morrison and Hof 1997; Pellicano et al. 2012). Changes in DTI indices can result from a number of processes including neuronal loss and gliosis, as

well as disturbances in axonal membranes, myelin sheath, microtubules, and neurofilaments (Shenton et al. 2012). PD has been associated with cytoskeletal damage of various neuronal cells including dopaminergic, glutamatergic, cholinergic, tryptaminergic, GABAergic, noradrenergic and adrenergic neurons (Braak et al. 1994, 1995, 1998; Foley and Riederer 1999; Jellinger 1991). The cytoskeletal damage leads to Lewy pathologies including Lewy bodies and Lewy neuritis mostly located in presynaptic terminals and in axons of affected nerve cells, respectively (Braak et al. 2004). The major components of Lewy pathologies include aggregations of misfolded alpha synuclein (Braak et al. 2004) and abnormally phosphorylated neurofilaments (Braak and Braak 2000). Thus, MRI changes may reflect the Lewy pathologies and/or neuronal degeneration secondary to the Lewy pathologies.

The current study has a few potential limitations. First, PD patients included in the present study had been taking parkinsonian medications for quite some time. The effects of chronic dopaminergic medication on brain structures remain to be determined. Second, our PD patients underwent all study procedures in an on-medication state. It is well known that dopaminergic medications in general can influence cognition (Kehagia et al. 2010). For example, while they can ameliorate certain cognitive deficits (e.g. executive functions), dopaminergic medications can also worsen other cognitive abilities (Kehagia et al. 2010; MacDonald et al. 2013; Ryterska et al. 2013). Our decision not to study them in an off-medication state was justified by the risk of worsening their motor symptoms increasing the risk of motion artifacts during MRI acquisitions.

Conclusions

The present study further demonstrates that both gray and white matters are affected in PD and these anatomical changes may represent the neural substrate underlying mild cognitive deficits in non-demented PD patients. The structural changes in the frontal region in particular may be an early pathological substrate of cognitive impairment of PD, and may represent a sensitive biomarker for brain changes in PD.

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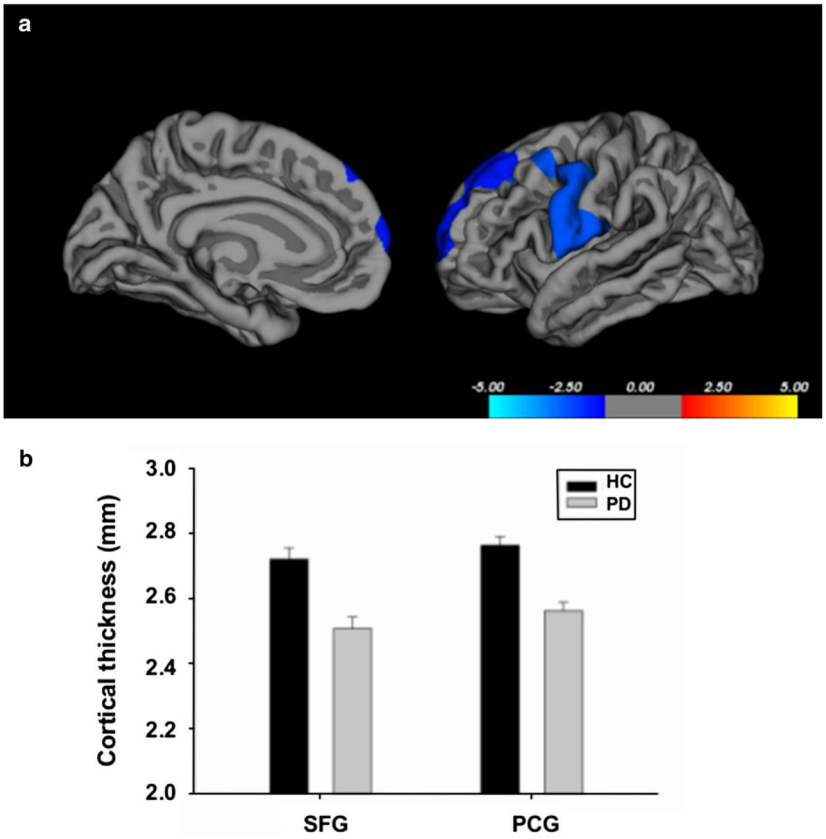

Fig. 1.

a Cortical areas showing significant cortical thinning in patients with Parkinson's disease compared to healthy controls. *Color bar* indicates the significance levels in the clusters in Z values. **b** *Bar graphs* on extracted cortical thickness values (mm) from the significant clusters in the left superior frontal gyrus (SFG) and left precentral gyrus (PCG) between healthy controls (HC) and PD patients (PD). *Error bars* represent sem

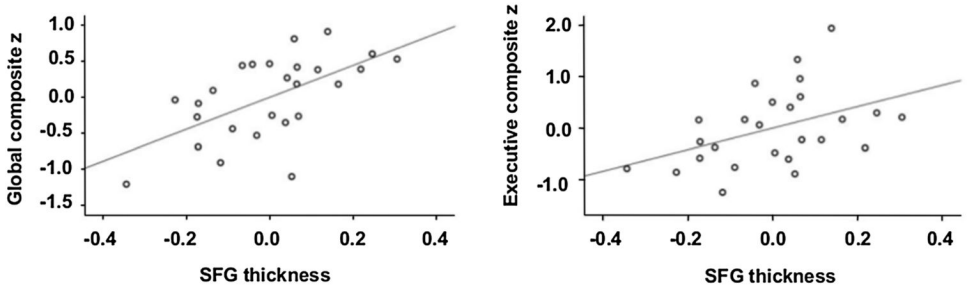

Fig. 2.

Partial correlations with age as a covariate between superior frontal gyrus (SFG) thickness (extracted from the significant cluster) and global composite z (*left*) and executive composite z (*right*) in 26 patients with Parkinson's disease showing the significant positive correlations

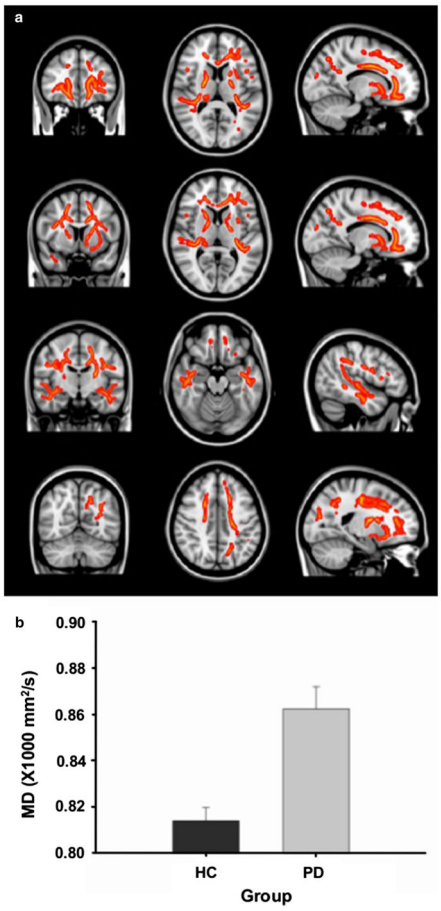

Fig. 3.

a Clusters of significantly increased mean diffusivity (MD) in 16 patients with Parkinson's disease (PD) compared with 15 healthy controls in tract-based spatial statistics. Result images are overlaid on the MNI152 template. **b** *Bar graphs* on mean MD values derived from the significant clusters in tract-based spatial statistics between healthy control and PD groups. *Error bars* represent sem

Table 1

Demographic, clinical, and cognitive characteristics of patients with Parkinson's disease (PD) and healthy controls (HC)

	PD (*n* = 26)	HC (*n* = 15)
Age (years)	70.5 (5.6)	67.13 (5.1)
Sex (male/female)	13/13	4/11
Handedness (right/left)	24/2	14/1
Education (years)	15.6 (2.1)	17.0 (2.5)
MoCA[a]	25.2 (2.8)	27.6 (2.2)**
BDI[b]	6.5 (5.5)	3.8 (3.6)
Disease duration (years)	6.7 (4.2)	–
Symptom-dominant side (right/left)	17/9	
UPDRS-III[c] (on-medication)	25.3 (15.3)	–
Total LEDD[d] (mg/day)	731.3 (459.8)	–
Neuropsychological tests		
Global composite z	−0.22 (0.60)	0.30 (0.50)**
Attention/WM composite z	0.12 (0.63)	0.27 (0.70)
Executive composite z	−0.64 (0.89)	0.25 (0.60)**
Digit span forward	0.31 (0.73)	0.46 (1.02)
California verbal test	0.19 (1.06)	0.23 (0.92)
Letter-number sequencing	0.20 (0.77)	0.15 (0.68)
Visual verbal test	−2.21 (1.93)	−0.380 (0.48)**
Judgement of line orientation	−0.78 (1.57)	0.24 (0.88)*
STROOP		
Color naming	−1.44 (0.86)	0.19 (1.17)
Inhibition	0.13 (0.72)	0.29 (1.00)
Category fluency	0.21 (1.21)	0.86 (0.83)

Data are presented in mean (standard deviation) and neuropsychological data are presented in group based mean Z scores (standard deviation)

WM working memory

[a] Montreal cognitive assessment

[b] Beck depression inventory

[c] Unified Parkinson's Disease Rating Scale III

[d] Levodopa Equivalent Daily Dose: 1-L dopa dose + 1-L dopa-CR × 0.75 + pramipexole (mg) × 67 (Evans et al. 2004)

* $P < 0.03$,

** $P < 0.01$