Brain Imaging and Behavior (2019) 13:232–240
https://doi.org/10.1007/s11682-018-9863-7

ORIGINAL RESEARCH

Multifocal alterations of white matter accompany the transition from normal cognition to dementia in Parkinson's disease patients

Maria Chondrogiorgi[1] · Loukas G. Astrakas[2] · Anastasia K. Zikou[3] · Luca Weis[4] · Vassilios G. Xydis[3] · Angelo Antonini[4] · Maria I. Argyropoulou[3] · Spiridon Konitsiotis[1]

Published online: 9 April 2018

Abstract

The purpose of the present study was to investigate the pattern of white matter (WM) changes associated with Parkinson's disease (PD)-related cognitive impairment by using fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) measures. Diffusion Tensor Imaging (DTI) was performed in 21 PD-patients with dementia (PDD) and in an age-matched control group including 40 PD-patients without dementia (PD-CTRL). The Parkinson's disease-Cognitive Rating Scale (PD-CRS) was used for patients' neuropsychological assessment. Local microstructural WM differences associated with the presence of cognitive impairment were tested using tract-based spatial statistics analysis. Multiple regression models investigated the association of DTI indices with total PD-CRS score, PD-CRS raw items and other clinical measures across the whole study sample. Significant FA decreases were found in PDD compared to PD-CTRL patients mainly in the body of corpus callosum, corona radiata and cingulum. Lower PD-CRS score was significantly associated with decreased FA, MD and AD values in multiple WM tracts primarily located in prefrontal and limbic areas as well as across the corpus callosum. Lower performance in specific PD-CRS raw items was also associated with FA decreases in major WM tracts. The results suggest that multifocal microstructural changes of WM accompany the transition from normal to demented cognitive state in PD-patients. The corpus callosum, the corona radiata and the cingulum are among the regions mostly affected during this course. A progressive axonal degeneration is proposed as a key underlying mechanism.

Keywords Parkinson's disease dementia · MRI · Diffusion tensor imaging · Tract-based spatial statistics · Axial diffusivity

Introduction

Among the multiple non-motor symptoms emerging during the course of Parkinson's disease (PD), dementia constitutes a milestone in the progression of patients' disability. Attention, constructional and executive functions are considered as the cognitive domains first and foremost impaired in PD patients, leading to a predominantly "subcortical" or "dysexecutive" type of dementia (Emre et al. 2007). Brain imaging studies hold great promise in detecting changes that can be used as biomarkers for timely assessment of cognitive deterioration and therapeutic intervention.

Diffusion Tensor Imaging (DTI) is a cutting edge technique for the in vivo evaluation of white mater (WM) microstructure. Fractional Anisotropy (FA) is the widest used DTI index measuring the anisotropy of water diffusion. Even though FA is highly sensitive to microstructural alterations, its specificity is limited. The specificity of FA can be enhanced by the use of mean diffusivity (MD), which assesses the magnitude of diffusion. Complementarily, the measurement of axial diffusivity (AD) that describes the principal eigenvector (λ_1) of the diffusion tensor, and radial diffusivity (RD) that describes the diffusion orthogonal to the longitudinal axis of WM fibers ($\lambda_2 + \lambda_3/2$) can provide useful information on the directionality of diffusion and consequently on the neuropathological

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-018-9863-7) contains supplementary material, which is available to authorized users.

✉ Maria Chondrogiorgi
mchond@cc.uoi.gr

[1] Department of Neurology, Medical School, University of Ioannina, Stavrou Niarchou Av., University Campus, 45110 Ioannina, Greece

[2] Department of Medical Physics, Medical School, University of Ioannina, Stavrou Niarchou Av., University Campus, 45110 Ioannina, Greece

[3] Department of Radiology, Medical School, University of Ioannina, Stavrou Niarchou Av., University Campus, 45110 Ioannina, Greece

[4] Parkinson Disease and Movement Disorders Unit, IRCCS San Camillo Hospital Foundation, via Alberoni, 70, 30126 Venice-Lido, Italy

foundation of WM changes. AD changes have been associated to alterations in the axonal diameters or density, while RD changes have been observed in presence of de- or dysmyelination (Wozniak and Lim 2006).

Impairments in many major tracts have been reported in the relatively low number of currently available DTI studies in PD-patients with various degrees of cognitive decline (Matsui et al. 2007; Lee et al. 2010; Hattori et al. 2012; Kamagata et al. 2012; Kamagata et al. 2013; Deng et al. 2013; Perea et al. 2013; Melzer et al. 2013; Agosta et al. 2014; Chen et al. 2015). Prefrontal WM was the region most consistently affected in the above studies. FA and/or MD correlations with deficits in executive functions and to a lesser extend in other cognitive domains have been also described in patients without evident dementia (Rae et al. 2012; Koshimori et al. 2015; Zheng et al. 2014; Carlesimo et al. 2012; Theilmann et al. 2013). Changes in directional diffusivities have been only recently reported in a longitudinal study which compared microstructural WM changes in de-novo, non-demented PD patients to normal aging (Zhang et al. 2016). In that study, increased AD and RD values were strongly correlated with progressive cognitive decline as assessed with MoCA test in PD-patients.

Diverse image-analysis protocols were used in the above-mentioned studies.

Some studies adopted a region of interest (ROI) approach (Deng et al. 2013; Matsui et al. 2007; Zhang et al. 2016). ROI-based analysis is time-consuming, subjective, limited (rest of brain unchecked) and mismatched (Astrakas and Argyropoulou 2010). On the other hand, voxel-wise analysis assesses the whole brain and provides statistical inferences at voxel level with good control of statistical error (Astrakas and Argyropoulou 2010). Tract-based spatial statistics (TBSS) is a particular voxel-wise method of statistical analysis of DTI derived data. This method has been widely used because of its robust non-parametric assessment of local differences in WM integrity between groups (Smith et al. 2006).

To our knowledge no previous study has explored alterations in DTI indices according to patients' performance in a scale specifically designed for PD. Commonly used cognitive scales have shown low sensitivity in the diagnosis of PD dementia due to its distinct pattern (Kulisevsky and Pagonabarraga 2009). Parkinson's Disease-Cognitive Rating Scale (PD-CRS) is targeted to cover the full spectrum of cognitive defects associated with PD, including items sensitive to both fronto-subcortical and posterior cortical dysfunction (Pagonabarraga et al. 2008). Additionaly, changes in directional diffusivities have never been examined in PD-patients with dementia. The present study aimed to use TBSS to compare differences in FA, MD, AD and RD between demented and non-demented PD-patients examined with PD-CRS. Progressive changes in WM architecture were investigated through multiple regression analyses of DTI indices with PD-CRS total score and sub-scores.

Material and methods

Subjects

Two age-matched groups consisted of 21 PD-patients with dementia (PDD) and 40 non-demented PD-patients (PD-CTRL) were examined. The neuropsychological and MRI testing were performed within 3 months between each other. Patients were recruited from the movement disorder outpatient clinic of the University Hospital of Ioannina and were diagnosed by a movement disorders neurologist according to UK Brain Bank criteria for idiopathic PD (Hughes et al. 1992). Each patient was interviewed regarding educational level, date of disease onset, duration of treatment with levodopa and current medication. Daily dose of dopaminergic drugs was converted to Levodopa Equivalent Dose (LED) (Tomlinson et al. 2010). The severity of disease was assessed with the modified Hoehn&Yahr (H&Y) scale and the motor subtype (postural instability and gait difficulty-predominant disease (PIGD)/ tremor-dominant/ indeterminate) according to the method suggested by Jankovic et al. (Jankovic et al. 1990). Depressive symptoms were assessed with the Hamilton Depression Rating Scale (HAM-D). No participant included in the study had a HAM-D score over 18 indicating severe depression. Individuals with clinical signs of atypical parkinsonism or Lewy body dementia, noncompensated systematic diseases, serious psychiatric conditions, laboratory abnormalities that could account for dementia and those with limited ability to complete the neuropsychological or MRI evaluation were excluded. Before inclusion in the analysis patient's MRI data were reviewed in order to further exclude cases presenting focal brain lesions, diffuse white matter hyperintensities observed in T2-weighted MRI or T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) or motion artefacts.

Ethics

The study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent was obtained from all participants, with additional consent from a significant other when appropriate.

Neuropsychological testing and cognitive classification

All patients underwent global cognitive assessment with PD-CRS scale. PD-CRS is composed by a total of nine items, seven of which assessing frontal-subcortical functions

(immediate and delayed verbal memory, sustained attention, working memory, clock drawing, alternating and action verbal fluency) and two assessing posterior cortical functions (naming and copy of a clock). Prior to application PD-CRS was adapted in the Greek language (Chondrogiorgi et al. 2015).

The neuropsychological assessment took place in a quiet room. All patients were examined during the "on medication" state. The previously recommended cut-off score of ≤64 points in PD-CRS (Pagonabarraga et al. 2008) was used to separate PDD from non-demented patients. Additionally, for descriptive reasons, all participants underwent examination with Mini-Mental State Examination (MMSE). Cognitive decline in PDD patients should have a considerable effect on day-to-day functioning as assessed with caregiver interview and the Pill questionnaire (Dubois et al. 2007).

MRI acquisition

MRI was performed by use of a 1.5 T scanner (Intera; Philips Healthcare, Best, The Netherlands) using a 8-channel head coil. A single-shot EPI sequence was used for DTI acquisition. Parameters for DTI acquisition were as follows: FOV = 230 × 230 mm, 112 × 128 matrix, section thickness of 3 mm, TE = 131 ms, TR = 9825 ms, number of slices = 42, slice gap = 0 mm, SENSE factor 2.2. We used 16 noncollinear gradient directions, with maximum $b = 700$ s/mm^2 and scanning time 4 min, 34 s. The imaging protocol also included 1) a FLAIR sequence (TR = 6300 ms, TE = 120 ms, FOV = 250 mm, matrix = 256 × 256, slice thickness of 6 mm, interslice gap = 0.6, scanning time = 2 min, 50 s); 2) a T1-weighted, high-resolution (1 × 1 × 1 mm), 3D spoiled gradient-echo sequence (TR = 25 ms, TE = 4.6 ms, acquisition matrix = 256 × 228, FOV = 220 mm, scanning time = 5 min, 43 s).

Image analysis

DTI analysis was performed with the FMRIB Software Library (FSL) (Smith et al. 2004). The preprocessing steps involved motion and eddy current correction and brain extraction. Then FA, MD, AD and RD maps were created by fitting a tensor model to the raw diffusion data and aligned into a common space using the nonlinear registration tool FNIRT to the FSL's MNI FMRIB58FA template. After creating the mean sample template and applying a pre-statistical threshold of 0.2, a voxel-wise statistical analysis of the FA, MD, AD and RD data was carried out using tract-based spatial statistics (TBSS) (Smith et al. 2006), part of FSL. TBSS projects all subjects' FA normalized data onto a mean FA tract skeleton, including only regions with maximum FA intensity along the perpendicular direction (breadth) of a white matter tract before applying voxelwise cross-subject statistics, in order to consider for analysis only WM structures that are almost conserved across population.

WM group differences were assessed with a GLM analysis including educational level as covariate. Multiple regression models investigated the association between FA/MD/AD/RD and total PD-CRS score across all participants, including age and educational level as covariates. Further regression analyses were performed examining the relationship between FA and the scores of the nine PD-CRS raw items including the same covariates. Since previous studies have shown differences in neuronal integrity according to motor phenotype in PD-patients (Nagae et al. 2016; Lenfeldt et al. 2016), all analyses except for those concerning PD-CRS raw items were rerun with the inclusion of motor subtype (PIGD/ tremor-dominant/ indeterminate) as an additional covariate. Regression analyses assessing the relationship of FA and MD with the duration and the stage of the disease and the total LED were also conducted. Results were thresholded at $p < 0.05$ with correction for multiple comparisons (family-wise error) adopting the Threshold-Free Cluster Enhancement (TFCE) randomize (5000 permutation) method (Smith et al. 2006) included in FSL.

Tracts were localized according to the "John Hopkins University ICBM-DTI-81 White Matter Labels" and "John Hopkins University White Matter Tractography" atlases provided in FSL.

Statistical analysis

All analyses of clinical data were performed with SPSS Statistics 24 (IBM, Armonk, NY, USA). The normality of distribution was evaluated with Kolmogorov-Smirnov test. The t-test was used for normally distributed continuous data, while the Mann-Whitney U-test was performed for ordinal and non-normally distributed continuous data. The chi-square test was applied for comparison of dichotomous data. Significance was set at 2-tailed p value = 0.05 level for all analyses.

Results

Patient characteristics

The basic demographic, clinical and neuropsychological data are summarized in Table 1.

The two patient groups did not differ in terms of sex, disease duration, H&Y stage, daily levodopa dose and total LED. Compared to PD-CTRL, PDD patients scored significantly lower in all PD-CRS items.

Group comparisons

Decreased FA values, without changes in MD, AD and RD, were shown in the PDD group in the body of corpus callosum,

Table 1 Patient demographical, clinical and neuropsychological characteristics

	PD-CTRL ($n = 40$)	PDD ($n = 21$)	p-value
Age (mean, SD)	68.4 (6)	70.9 (5.7)	0.12
Sex, m	31	16	0.91
Education, *y* (mean, SD)	9.4 (4.4)	5.8 (1.5)	0.01
Hoehn & Yahr stage (mean)	2.2	2.5	0.13
Stage 1 (n)	1	0	
Stage 1.5 (n)	9	1	
Stage 2 (n)	10	8	
Stage 2.5 (n)	15	6	
Stage 3 (n)	4	5	
Stage 4 (n)	1	1	
Stage 5 (n)	0	0	
Disease duration, *y (mean, SD)*	5.7 (4.8)	7.9 (6.8)	0.13
PIGD subtype (n)	21	10	0.72
Levodopa dose, *mg/day* (mean, SD)	533.1 (541.6)	631.7 (329.8)	0.38
Total LED, *mg/day* (mean, SD)	802.6 (620.1)	808.2 (342)	0.96
MMSE score (mean, SD)	27.5 (2)	23.5 (3.7)	0.93×10^{-4}
HAM-D score (mean, SD)	4.3 (4.9)	4.5 (4.8)	0.88
Total PD-CRS score (mean, SD)	84.5 (15.1)	45.5 (12.4)	0.18×10^{-9}

Abbreviations: PIGD, postural instability/gait difficulty; LED, Levodopa equivalent dose; HAM-D, Hamilton Depression Scale; PD-CRS, Parkinson's Disease-Cognitive Rating Scale

bilaterally in superior corona radiata and cingulum (cingulate gyrus) and on the left side in anterior corona radiata, inferior fronto-occipital fasciculus (IFF), uncinate fasciculus, anterior thalamic radiation (ATR) and forceps minor (Fig. 1, Table 2).

After the inclusion of motor subtype as covariate, FA decreases in the PDD group were observed in larger clusters of the previously described tracts, but also in the right anterior corona radiata (Online Resource 1).

Regression analyses

Lower total PD-CRS score was associated with FA decreases in the genu, body and splenium of corpus callosum and bilaterally in the following tracts: anterior, superior and posterior corona radiata, forceps minor, forceps major, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), cingulum (cingulate gyrus), cingulum (hippocampus), IFF and uncinate fasciculus. Lower total PD-CRS score was also associated with MD and AD decreases in multiple tracts, while no association was found with RD (Fig. 2, Online Resource 2).

FA decreases involving almost all of the major WM tracts throughout the brain, were associated with lower performance in immediate verbal memory and confrontation naming tasks, while a somehow more spatially restricted, but still widespread, pattern of decreased FA was shown to associate with low working memory scores (Fig. 3, Online Resource 2).

The inclusion of motor subtype as covariate slightly affected significance without changing the overall regional pattern of diffusion indices alterations concerning the association between total PD-CRS score and FA/MD/AD (Online Resource 3).

No significant relationship was identified between FA/MD and any other PD-CRS sub-score or with disease duration, disease stage and total LED.

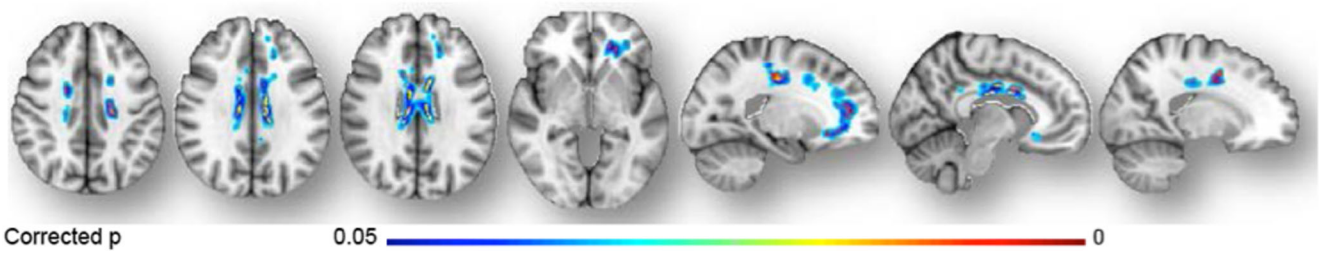

Fig. 1 FA comparison between PD-CTRL and PDD patient groups, covarying for educational status. Colored clusters correspond to regions in which decreased FA values ($p < 0.05$ TFCE corrected) were found in PDD compared to PD-CTRL patients

Table 2 Location and size of brain regions in which significantly decreased FA values were observed in PDD versus PD-CTRL patients

	Anatomical regions	Cluster index	Volume ($mm^{3)}$	Tailarach Coordinates (x,y,z) (mm)	Clusterwise TFCE corrected *p*-value
FA PDD < FA PD-CTRL	Corpus callosum (body), SCR[b], Cingulum (cingulate gyrus)[b], ACR[l], IFF[l], Uncinate fasciculus[l], ATR[l], Forceps minor[l]	1	5	−12, 43, 32	0.05
		2	5	−8,-43, 32	0.05
		3	7	−17, 28, 33	0.05
		4	11	−13, 46, 27	0.05
		5	13	5, 17, 27	0.05
		6	21	−18, 12, 31	0.05
		7	21	14, 14, 26	0.05
		8	29	−19, −28, 50	0.05
		9	60	−16, 9, 32	0.05
		10	128	1, 15, 19	0.05
		11	1061	−21, 38, −1	0.036
		12	1433	−19, −21, 38	0.026

MNI coordinates and *p*-values correspond to voxels of maximal statistical significance for each region ([b] = bilaterally, [l] = left)

Abbreviations: FA, fractional anisotropy; SCR, Superior corona radiata; ACR, Anterior corona radiata; IFF, Inferior fronto-occipital fasciculus; ATR, Anterior thalamic radiation

Discussion

The present study investigated WM abnormalities through the use of multiple diffusion indices in PD-patients with cognitive impairment. The latter was assessed with a scale explicitly designed to detect cognitive deficits related to PD. A significant pattern of subcortical WM alteration in areas including corpus callosum, the corona radiata, and the cingulum was found to be associated with cognitive impairment as assessed with PD-CRS. In addition, lower performance on particular tasks assessing specific cortical and subcortical functions was associated with FA decreases in major WM tracts.

The total PD-CRS score associated positively with FA in WM tracts primarily located in prefrontal and limbic areas as well as across the corpus callosum. Previous studies using the same image analysis protocol (TBSS) have reported significant correlations between FA values and MMSE score in corpus callosum, IFF, SLF, ILF, uncinate fasciculus and cingulum (Hattori et al. 2012; Kamagata et al. 2013). A novel finding of the present study is a linear association of AD with the PD-CRS score, involving most of the major WM tracts, without concurrent RD alterations. This finding might suggest that an extensive and progressive axonal degeneration, without evident demyelination (Song et al. 2003; Sun et al. 2005), underlies cognitive impairment in PD-patients. A decrease of MD implying the presence of restricted diffusion was also observed in patients with poorer cognitive performance. Although rather unexpected for neurodegenerative processes, decreases in MD, either with or without concomitant AD fall, have been previously demonstrated in presymptomatic cases of familial Alzheimer's disease (Ryan et al. 2013; Fortea et al. 2010) with greater MD decreases being associated with higher amyloid burden (Racine et al. 2014). Axonal beading and fragmentation, along with amyloid depositions and compensatory cellular swelling and glial activation, have been all proposed as possible mechanisms introducing barriers that can restrict diffusion in both the intracellular and extracellular space (Ryan et al. 2013; Racine et al. 2014; Budde and Frank 2010). Similar mechanisms could also explain our findings since the presence of Alzheimer's disease-related protein aggregates is also well recognized in PDD (Braak et al. 2005). Moreover, considering previous evidence that supports a parallel progression of neuropathological PD stage with cognitive decline (Braak et al. 2006), we could hypothesize that an increased accumulation of axonal α-synouclein inclusions, mainly in the form of Lewy neurites, could further impede free water molecular motion in certain WM regions of demented individuals. In terms of localization, MD changes highly mirrored those of AD but with a relative sparing of frontal regions, a finding potentially and partially explained by the caudo-rostral spreading of Lewy pathology as proposed by Braak (Braak et al. 2003).

Among the nine raw items of PD-CRS, performance in one "cortical-type" (confrontation naming) and two "subcortical-type" (immediate verbal memory and working memory) items demonstrated a positive association

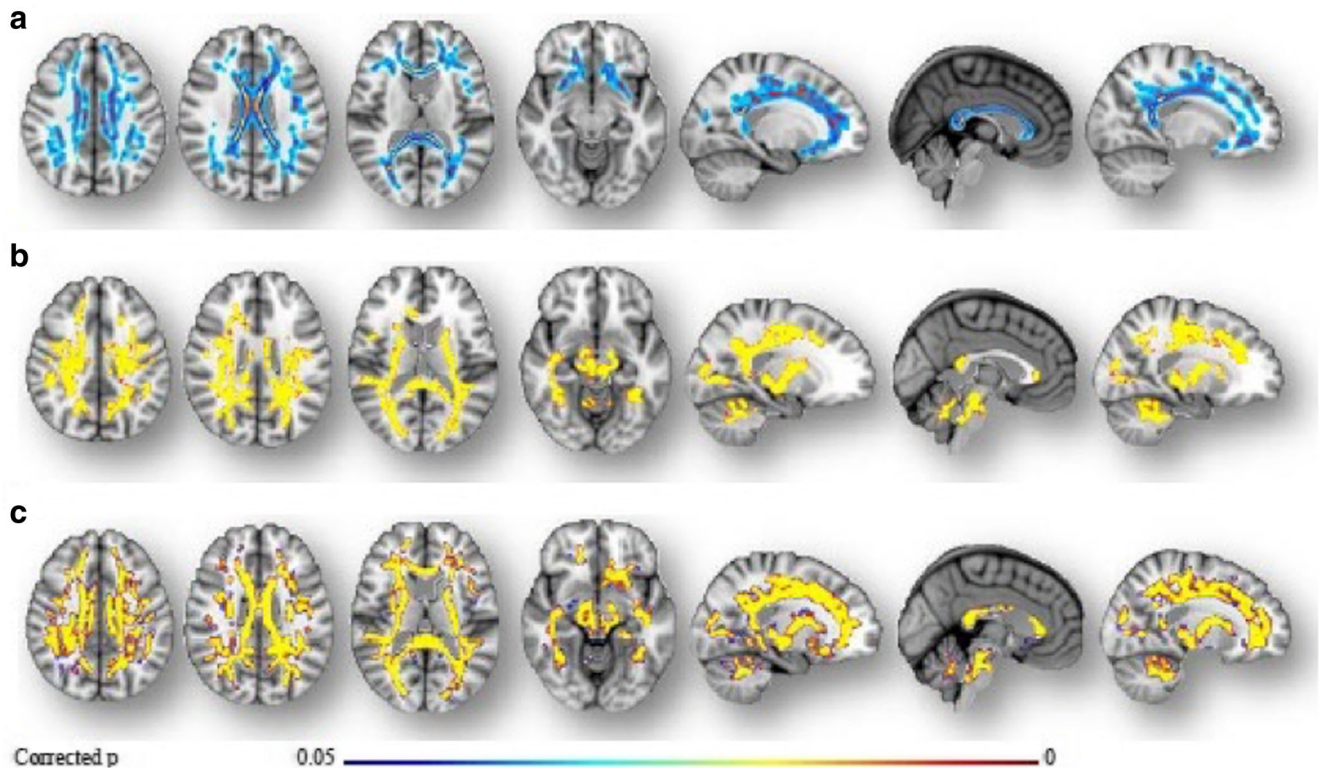

Fig. 2 Regression analysis between total PD-CRS score and **a** FA, **b** MD and **c** AD values, covarying for age and educational level, across all study participants. Colored clusters correspond to regions in which significant ($p = 0.05$, TFCE corrected) positive associations were found between total PD-CRS score and **a** FA, **b** MD and **c** AD values

with FA. All associations were of high statistical significance and involved multiple WM tracts. The "dual-syndrome hypothesis" suggests that executive impairment, mainly mediated from fronto-striatal dopaminergic dysfunction, appears first in PD and is later superimposed by additional deficits with a strong cholinergic basis, that define the onset of PDD (Kehagia et al. 2013). Without contradicting the above theory, our findings indicate that decline in certain, presumably dopamine-independent cognitive domains, such as visual recognition and recall, may be also associated with considerable WM microstructural disorganization even in PD-patients with relatively preserved general cognitive status.

Regarding the two-group analysis, in line with our findings, previous studies have also provided evidence for FA decreases in corpus callosum (Deng et al. 2013; Hattori et al. 2012; Kamagata et al. 2013), superior corona radiata (Melzer et al. 2013), cingulum (Hughes et al. 1992; Perea et al. 2013), IFF (Kamagata et al. 2013; Perea et al. 2013), ATR (Perea et al. 2013), uncinate fasciculus (Hattori et al. 2012; Perea et al. 2013) and forceps minor (Perea et al. 2013) in demented versus non-demented PD-patients. Changes in SLF (Hattori et al. 2012; Perea et al. 2013), ILF (Hattori et al. 2012; Perea et al. 2013) and CST (Melzer et al. 2013) have been also reported, while our study is the first to show low FA values also in the anterior corona radiata.

The most consistent finding across our analyses was the decrease of FA in the corpus callosum, corona radiata and cingulum in patients with major cognitive involvement. The absence of overt callosal atrophy in PD-patients irrespectively of their cognitive condition has been proposed as an aspect differentiating PD from other neurodegenerative diseases (Wiltshire et al. 2005). However, FA decreases in various parts of corpus callosum, has been repeatedly shown in studies comparing PDD to non-demented PD-patients (Deng et al. 2013; Hattori et al. 2012; Kamagata et al. 2013). The observed fiber damage could either reflect or induce a topographically associated cortical pathology. On the other hand, corona radiata is a dense WM arc carrying almost all of the neural connections from and to the cerebral cortex. Although its involvement in PDD has received relatively little attention, diffusion abnormalities in the anterior, the superior or the posterior corona radiata have been previously correlated with attentional, executive and visuospatial skills (Zheng et al. 2014; Theilmann et al. 2013). Microstructural changes in this region, along with similar changes in other projection fibers as found in this study, probably underlie a disconnection syndrome in subcortical thalamic-basal-prefrontal circuits. To end with, the present study confirms and extends previous knowledge of the

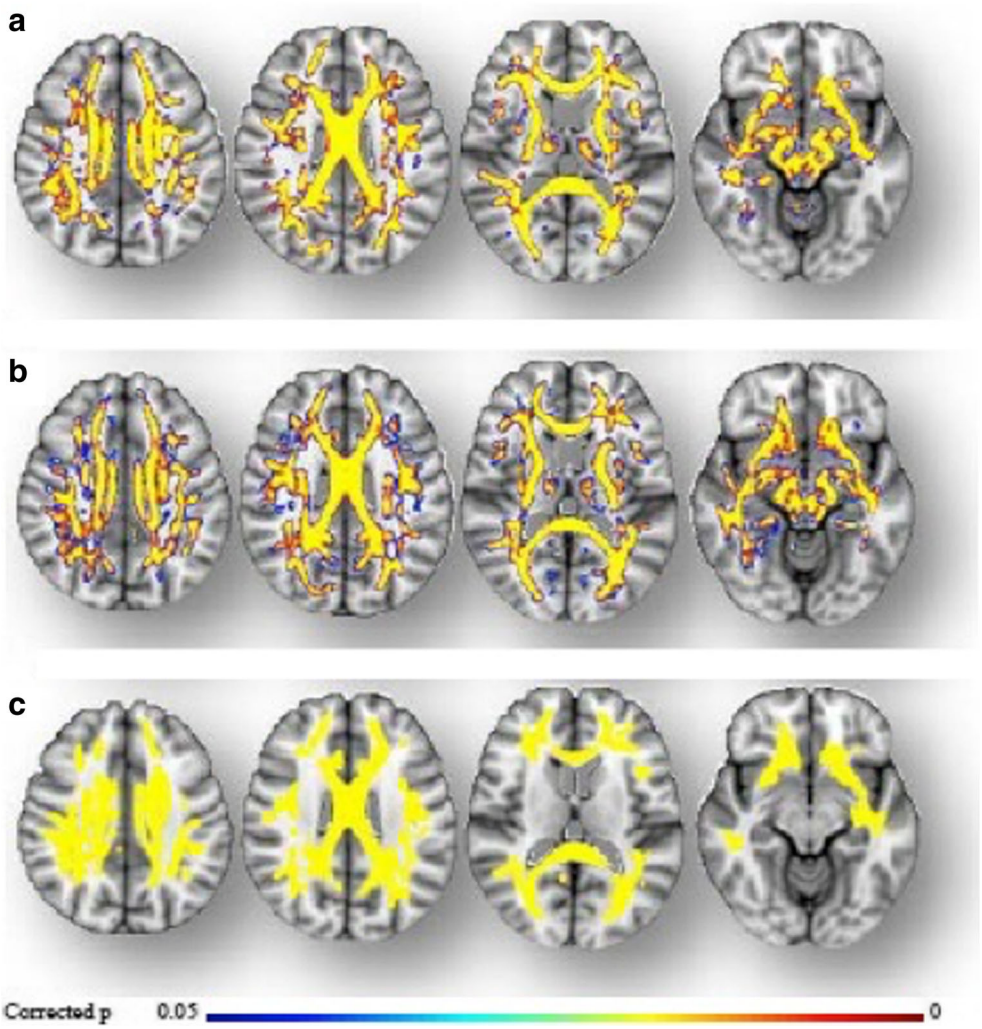

Fig. 3 Regression analysis between PD-CRS raw items score and FA, covarying for age and educational level, across all study participants. Colored clusters correspond to regions in which significant ($p < 0.05$, TFCE corrected) positive associations were found between **a** immediate free recall, **b** confrontation naming, and **c** working memory score and FA values

significant role of cingulum in cognition, also in PD (Deng et al. 2013; Perea et al. 2013; Kamagata et al. 2012). The cingulum connects the hippocampus to the posterior cingulate gyrus and prefrontal cortex and changes across its course have been mostly associated with deficits in episodic memory and visuospatial processing (Kamagata et al. 2012; Wu et al. 2010).

Some limitations of the present study need to be addressed. First of all, the purely cross-sectional design of the study does not allow firm conclusions on the progressive nature of changes to be drawn. Secondly, comparison of results with that of previous studies should be made in the light of limitations arising from different cognitive scales and imaging protocols used. Additional study limitations include the absence of control group consisted of healthy participants and the use of 1.5 T MRI scanner with 8-channel RF head coil and only 16 diffusion directions. Furthermore, despite the validity of PD-CRS in the discrimination of cognitive categories has been previously proved (Pagonabarraga et al. 2008), potential cases of misclassification cannot be excluded. The stage and duration of the disease, as well as the total LED, differed insignificantly across the groups and did not correlate significantly with FA in any WM region, and therefore the risk of these parameters to substantially interfere with our results is small.

Conclusion: A widespread network of WM diffusion abnormalities is associated with the degree of PD-related cognitive impairment. The corpus callosum, the corona radiata and the cingulum are among the regions mostly affected during this course. DTI indices provide valuable information in the comprehension and extent of the underlying pathology. Longitudinal research is warranted to elucidate the chronological sequence of changes and confirm the presence of cognitive and imaging patterns predicting progression to dementia.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflicts of interest Nothing to report

References

Agosta, F., Canu, E., Stefanova, E., Sarro, L., Tomić, A., Špica, V., Comi, G., Kostić, V. S., & Filippi, M. (2014). Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. *Human Brain Mapping, 35*(5), 1921–1929.

Astrakas, L. G., & Argyropoulou, M. I. (2010). Shifting from region of interest (ROI) to voxel-based analysis in human brain mapping. *Pediatric Radiology, 40*(12), 1857–1867.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*, 197–211.

Braak, H., Rüb, U., Jansen Steur, E. N., Del Tredici, K., & de Vos, R. A. (2005). Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology, 64*, 1404–1410.

Braak, H., Rüb, U., & Del Tredici, K. (2006). Cognitive decline correlates with neuropathological stage in Parkinson's disease. *Journal of the Neurological Sciences, 248*, 255–258.

Budde, M. D., & Frank, J. A. (2010). Neurite beading is sufficient to decrease the apparent diffusion coefficient after ischemic stroke. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 14472–14477.

Carlesimo, G. A., Piras FM Assogna, F., Pontieri, F. E., Caltagirone, C., & Spalletta, G. (2012). Hippocampal abnormalities and memory deficits in Parkinson disease: A multimodal imaging study. *Neurology, 78*(24), 1939–1945.

Chen, B., Fan, G. G., Liu, H., Wang, S. (2015) Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status. *European Journal of Radiology, 84*(7), 1318–1324.

Chondrogiorgi, M., Aretouli, E., Lafi, C., Karamitsou, V., Gkantzios, E., Georgiou, D., et al. (2015). Adaptation in Greek language and psychometric analysis of PD-CRS. *Nevrologia (Greek Journal), 24*, 89–90.

Deng, B., Zhang, Y., Wang, L., Peng, K., Han, L., Nie, K., Yang, H., Zhang, L., & Wang, J. (2013). Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. *American Journal of Alzheimer's Disease and other dementias, 28*, 154–164.

Dubois, B., Burn, D., Goetz, C., Aarsland, D., Brown, R. G., Broe, G. A., Dickson, D., Duyckaerts, C., Cummings, J., Gauthier, S., Korczyn, A., Lees, A., Levy, R., Litvan, I., Mizuno, Y., McKeith, I. G., Olanow, C. W., Poewe, W., Sampaio, C., Tolosa, E., & Emre, M. (2007). Diagnostic procedures for Parkinson's disease dementia: Recommendations from the movement disorder society task force. *Movement Disorders: Official Journal of the Movement Disorder Society, 22*(16), 2314–2324.

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., Broe, G. A., Cummings, J., Dickson, D. W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., Quinn, N., Sampaio, C., Tolosa, E., & Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society, 22*(12), 1689–1707.

Fortea, J., Sala-Llonch, R., Bartrés-Faz, D., Bosch, B., Llado, A., Bargallo, N., et al. (2010). Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers. *Journal of Alzheimer's Disease: JAD, 22*, 909–922.

Hattori, T., Orimo, S., Aoki, S., Ito, K., Abe, O., Amano, A., Sato, R., Sakai, K., & Mizusawa, H. (2012). Cognitive status correlates with white matter alteration in Parkinson's disease. *Human Brain Mapping, 33*, 727–739.

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology Neurosurgery and Psychiatry, 55*, 181–184.

Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L., Huber, S., Koller, W., Olanow, C., Shoulson, I., Stern, M., Tanner, C., Weiner, W., & Parkinson Study Group. (1990). Variable expression of Parkinson's disease: A base-line analysis of the DATATOP cohort, the Parkinson study group. *Neurology, 40*, 1529–1534.

Kamagata, K., Motoi, Y., Abe, O., Shimoji, K., Hori, M., Nakanishi, A., Sano, T., Kuwatsuru, R., Aoki, S., & Hattori, N. (2012). White matter alteration of the cingulum in Parkinson disease with and without dementia: Evaluation by diffusion tensor tract-specific analysis. *AJNR American Journal of Neuroradiology, 33*, 890–895.

Kamagata, K., Motoi, Y., Tomiyama, H., Abe, O., Ito, K., Shimoji, K., Suzuki, M., Hori, M., Nakanishi, A., Sano, T., Kuwatsuru, R., Sasai, K., Aoki, S., & Hattori, N. (2013). Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: Tract-based spatial statistics and tract-specific analysis. *European Radiology, 23*, 1946–1955.

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2013). Cognitive impairment in Parkinson's disease: The dual syndrome hypothesis. *Neuro-Degenerative Diseases, 11*, 79–92.

Koshimori, Y., Segura, B., Christopher, L., Lobaugh, N., Duff-Canning, S., Mizrahi, R., Hamani, C., Lang, A. E., Aminian, K., Houle, S., & Strafella, A. P. (2015). Imaging changes associated with cognitive abnormalities in Parkinson's disease. *Brain Structure & Function, 220*(4), 2249–2261.

Kulisevsky, J., & Pagonabarraga, J. (2009). Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. *Movement Disorders: Official Journal of the Movement Disorder Society, 24*(8), 1103–1110.

Lee, J. E., Park, H. J., Park, B., Song, S. K., Sohn, Y. H., Lee, J. D., & Lee, P. H. (2010). A comparative analysis of cognitive profiles and white-matter alterations using voxel-based diffusion tensor imaging between patients with Parkinson's disease dementia and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery, and Psychiatry, 81*(3), 320–326.

Lenfeldt, N., Holmlund, H., Larsson, A., Birgander, R., & Forsgren, L. (2016). Frontal white matter injuries predestine gait difficulties in Parkinson's disease. *Acta Neurologica Scandinavica, 134*(3), 210–218.

Matsui, H., Nishinaka, K., Oda, M., Niikawa, H., Kubori, T., & Udaka, F. (2007). Dementia in Parkinson's disease: Diffusion tensor imaging. *Acta Neurologica Scandivanica, 116*(3), 177–181.

Melzer, T. R., Watts, R., MacAskill, M. R., Pitcher, T. L., Livingston, L., Keenan, R. J., et al. (2013). White matter microstructure deteriorates across cognitive stages in Parkinson disease. *Neurology, 80*, 1841–1849.

Nagae, L. M., Honce, J. M., Tanabe, J., Shelton, E., Sillau, S. H., & Berman, B. D. (2016). Microstructural changes within the basal ganglia differ between Parkinson disease subtypes. *Frontiers in Neuroanatomy, 10*, 17.

Pagonabarraga, J., Kulisevsky, J., Llebaria, G., Garcia-Sanchez, C., Pascual-Sedano, B., & Gironell, A. (2008). Parkinson's disease-cognitive rating scale: A new cognitive scale specific for Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society, 23*, 998–1005.

Perea, R. D., Rada, R. C., Wilson, J., Vidoni, E. D., Morris, J. K., Lyons, K. E., et al. (2013). A comparative white matter study with Parkinson's disease, Parkinson's disease with dementia and Alzheimer's disease. *Journal of Alzheimer's disease and Parkinsonism, 3*, 123.

Racine, A. M., Adluru, N., Alexander, A. L., Christian, B. T., Okonkwo, O. C., Oh, J., Cleary, C. A., Birdsill, A., Hillmer, A. T., Murali, D., Barnhart, T. E., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Dowling, N. M., Asthana, S., Sager, M. A., Bendlin, B. B., & Johnson, S. C. (2014). Associations between white matter

microstructure and amyloid burden in preclinical Alzheimer's disease: A multimodal imaging investigation. *NeuroImage Clinical, 4*, 604–614.

Rae, C. L., Correia, M. M., Altena, E., Hughes, L. E., Barker, R. A., & Rowe, J. B. (2012). White matter pathology in Parkinson's disease: The effect of imaging protocol differences and relevance to executive function. *NeuroImage, 62*(3), 1675–1684.

Ryan, N. S., Keihaninejad, S., Shakespeare, T. J., Lehmann, M., Crutch, S. J., Malone, I. B., Thornton, J. S., Mancini, L., Hyare, H., Yousry, T., Ridgway, G. R., Zhang, H., Modat, M., Alexander, D. C., Rossor, M. N., Ourselin, S., & Fox, N. C. (2013). Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease. *Brain, 136*, 1399–1414.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*, S208–S219.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31*, 1487–1505.

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage, 20*, 1714–1722.

Sun, S. W., Song, S. K., Harms, M. P., Lin, S. J., Holtzman, D. M., Merchant, K. M., & Kotyk, J. J. (2005). Detection of age-dependent brain injury in a mouse model of brain amyloidosis associated with Alzheimer's disease using magnetic resonance diffusion tensor imaging. *Experimental Neurology, 191*, 77–85.

Theilmann, R. J., Reed, J. D., Song, D. D., Huang, M. X., Lee, R. R., Litvan, I., & Harrington, D. L. (2013). White-matter changes correlate with cognitive functioning in Parkinson's disease. *Frontiers in Neurology, 4*, 37.

Tomlinson, C. L., Stowe, R., Patel, S., Rick, C., Gray, R., & Clarke, C. E. (2010). Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society, 25*, 2649–2653.

Wiltshire, K., Foster, S., Kaye, J. A., Small, B. J., & Camicioli, R. (2005). Corpus callosum in neurodegenerative diseases: Findings in Parkinson's disease. *Dementia and Geriatric Cognitive Disorders, 20*, 345–351.

Wozniak, J. R., & Lim, K. O. (2006). Advances in white matter imaging: A review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neuroscience and Biobehavioral Reviews, 30*(6), 762–774.

Wu, T. C., Wilde, E. A., Bigler, E. D., Yallampalli, R., McCauley, S. R., Troyanskaya, M., et al. (2010). Evaluating the relationship between memory functioning and cingulum bundles in acute mild traumatic brain injury using diffusion tensor imaging. *Journal of Neurotrauma, 27*, 303–307.

Zhang, Y., Wu, I. W., Tosun, D., Foster, E., Schuff, N., & Parkinson's Progression Markers Initiative. (2016). Progression of regional microstructural degeneration in Parkinson's disease: A multicenter diffusion tensor imaging study. *PLoS One, 11*(10), e0165540.

Zheng, Z., Shemmassian, S., Wijekoon, C., Kim, W., Bookheimer, S. Y., & Pouratian, N. (2014). DTI correlates of distinct cognitive impairments in Parkinson's disease. *Human Brain Mapping, 35*, 1325–1333.