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Age- and disease-related cerebral white matter changes in patients with Parkinson's disease

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ABSTRACT

As age and Parkinson's disease (PD) both play a role in the degeneration of brain white matter, we aimed to investigate a possible interaction effect of age and disease presence on white matter integrity in patients with PD. We studied white matter hyperintensity volume, global fractional anisotropy, mean diffusivity and mean magnetization transfer ratio of normal appearing white matter in 163 patients with PD and 218 age- and gender-matched healthy control subjects. We investigated the relationship between age and these parameters in both groups, and interaction between age and disease presence. Patients with PD had a higher load of white matter hyperintensities with a preferential periventricular and anterior distribution as compared with healthy control subjects. Visuospatial functioning was related to total and postural instability and gait difficulty was related to periventricular white matter hyperintensity volume in patients with PD. The age-related decline of white matter integrity was similar for both groups. Global microstructural integrity of the normal appearing white matter did not differ between patients and healthy control subjects, suggesting that PD-specific changes do not exceed normal age-associated change in white matter without lesions.

1. Introduction

The clinical spectrum of motor and nonmotor symptoms in Parkinson's disease (PD) is linked to a progressive formation of α-synuclein aggregates, predominantly located in presynaptic terminals (Jellinger, 2012; Kramer and Schulz-Schaeffer, 2007). The primary determinant of neurodegeneration in patients with PD may be α-synuclein aggregate–related synaptic and axonal dysfunction (Jellinger, 2012; O'Malley, 2010; Tagliaferro et al., 2015). White matter changes represent degeneration of axons and myelin damage, and white matter degeneration is increasingly recognized in patients with PD (Chiang et al., 2017; Chondrogiorgi et al., 2016; Sterling et al., 2017).

Magnetic resonance imaging (MRI) studies have found white matter changes in patients with PD (Atkinson-Clement et al., 2017; Bohnen and Albin, 2011), but such changes may occur as a consequence of aging (Galluzzi et al., 2008; Lockhart and DeCarli, 2014). With advancing age, the prevalence of white matter hyperintensities (WMHs) increases (Galluzzi et al., 2008; Grueter and Schulz, 2012), and white matter microstructural integrity surrounding these lesions (the so called normal appearing white matter; NAWM), declines (Lockhart and DeCarli, 2014; Vernooij et al., 2008). These findings thus raise the question to what extent white matter changes in patients with PD are related to aging.

We hypothesized that the white matter integrity decline is significantly greater in patients with PD than seen in healthy aging subjects and that there may be an age-by-PD interaction effect on white matter integrity. To this end, we compared macrostructural integrity of global white matter and the microstructural integrity of the surrounding NAWM between patients with PD and control subjects. The relationship between age and white matter integrity was estimated in both groups, and the interaction between age and disease presence was examined to investigate if age-related white matter changes are different in PD compared with healthy aging.

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We further explored associations of clinical variables, other than age, with white matter integrity.

2. Methods

2.1. Participants

We included 163 patients with PD in this cross-sectional MRI study, which is a project of the PROfiling PARKinson's disease (PROPARK) research group. Patients were recruited between 2013 and 2016 from the outpatient clinic for Movement Disorders of the Department of Neurology of the LUMC (Leiden University Medical Center; Leiden, the Netherlands) and nearby university and regional hospitals. All patients with PD fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic Parkinson's disease (Gibb and Lees, 1988). Exclusion criteria were previous or other disorders of the central nervous system, peripheral nerve disorders influencing motor and/or autonomic functioning, and psychiatric comorbidity not related to PD. Patients were matched at group level for age and gender with 218 healthy control subjects from the Leiden Longevity Study (LLS), a study set up to identify genetic and phenotypic determinants of longevity in healthy long-living families (Altmann-Schneider et al., 2013). Written consent was obtained from all participants. The Medical Ethics Committee of the LUMC approved the PROPARK study and LLS.

2.2. Clinical assessments

Standardized assessments were performed in all patients, including an evaluation of demographic and clinical characteristics. Patients were tested while on dopaminergic medication, except for 24 "de novo" patients, defined as dopaminergic drug-naïve patients with a disease duration shorter than 5 years, and 2 other drug-naïve patients with a disease duration longer than 5 years. Motor symptoms were quantified with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scale (part III) (Goetz et al., 2008). Missing values were imputed with the average score of the remaining questions, allowing a maximum of 7 missing values (Goetz et al., 2015). We calculated motor domain scores as well: bradykinesia (items 3.4, 3.5, 3.6, 3.7, 3.14); rigidity (item 3.3); tremor (items 3.16, 3.17, 3.18); and postural instability and gait difficulty (items 3.9, 3.10, 3.11, 3.12, 3.13). We used the SEverity of Nondopaminergic Symptoms in Parkinson's Disease (SENS-PD) scale, representing a coherent complex of symptoms that largely do not improve with dopaminergic medication, that is already present in the early disease stages, and increases in severity when the disease advances (Van der Heeden, Marinus, Martinez-Martin, 2016). It comprises 3 items with 4 response options (0–3) from each of the following 6 domains: postural instability and gait difficulty, psychotic symptoms, excessive daytime sleepiness, autonomic dysfunction, cognitive impairment, and depressive symptoms (total range: 0–54) (Van der Heeden, Marinus, Martinez-Martin, 2016). Higher scores on both scales reflect more severe impairment. Cognitive performance was assessed with the SCales for Outcomes in PArkinson's disease-COGnition (SCOPA-COG; cognitive functioning; range 0–43), which is a valid and reliable instrument examining the following domains: memory, attention, executive functioning, and visuospatial functioning (Marinus et al., 2003); lower scores reflect more severe impairment. A levodopa dose equivalent (LDE) was calculated according to the formula developed by Tomlinson et al. (Tomlinson et al., 2010). Patients were further asked if they had vascular risk factors: smoking, myocardial infarction, diabetes mellitus, hypertension, use of statins, transient ischemic attack, and stroke, although previous stroke was an exclusion criterion for the study.

2.3. MRI acquisition and analysis

Imaging was performed on a 3 Tesla MRI scanner (Philips Achieva, Best, the Netherlands). Three-dimensional T1-weighted anatomical images were acquired with the following parameters: repetition time (TR)/echo time (TE) = 9.8/4.6 ms, flip angle = 8°, field of view (FOV) = 220 × 174 × 156 mm, voxel size = 1.15 × 1.15 × 1.20 mm. Fluid attenuated inversion recovery (FLAIR) images were acquired with TR/TE = 9249/56 ms, flip angle = 90°, FOV = 220 × 220 × 128 mm, voxel size = 1.96 × 1.96 × 2.00 mm. Diffusion tensor images were acquired along 32 noncollinear directions with a b-value of 1000 s/mm^2 and one b = 0 image with TR/TE = 9249/56 ms, flip angle = 90°, 32 axial slices, voxel size = 1.96 × 2.00 × 2.00 mm, FOV = 220 × 220 × 128. Magnetization transfer imaging parameters were TR/TE = 100/11 ms, flip angle = 9°, voxel size = 1.00 × 1.00 × 7.20 mm, FOV = 224 × 180 × 144 mm. Before analysis, all MRI scans were visually checked to ensure that no major artifacts or abnormalities were present in the data. MR images were analyzed with software provided by FSL (version 5.0.8, Oxford, United Kingdom) (Smith et al., 2004).

2.3.1. White matter hyperintensities

WMH volume was quantified in an automated manner, defined as hyperintense regions on FLAIR. The T1-weighted images were brain-extracted (Smith, 2002) and FLAIR and T1-weighted images were nonlinearly registered to MNI standard space (Andersson et al., 2007). White matter was extracted from the FLAIR image using an MNI152 white matter mask. A threshold of 2.5 standard deviations above the mean of FLAIR intensities for white matter was set to identify which white matter voxels were hyperintense. We additionally calculated WMH volumes for periventricular and deep white matter (Fazekas et al., 1987). We created a periventricular white matter mask by subtracting an MNI ventricle mask from an MNI ventricle mask that was dilated using a 4 × 4 × 4 kernel. An anterior deep white matter mask was created using the anterior part of the previously used MNI white matter mask (most frontal part of the corpus callosum, MNI coordinate Y = 33), of which the periventricular white matter mask was subtracted. A posterior deep white matter mask was created similarly (most posterior part of the corpus callosum, MNI coordinate Y = −44).

2.3.2. Diffusion tensor imaging

The preprocessing of the DTI data consisted of brain extraction (Smith, 2002), motion, and eddy current correction (Andersson and Sotiropoulos, 2016). The corrected DTI data were subsequently used to create individual fractional anisotropy (FA) and mean diffusivity (MD) images using a weighted least squares fitting procedure. All subjects' FA and MD data were aligned into a common space using nonlinear registration (Andersson et al., 2007). The resulting images were used for quantification of global mean FA and MD values of each subjects' NAWM (i.e., white matter without lesions). T1-weighted images were brain-extracted (Smith, 2002) and segmented to create individual white matter masks (Zhang et al., 2001), which were linearly registered to MNI space (Jenkinson et al., 2002). Then, WMHs of each subject were dilated using a 3 × 3 × 1 kernel and subtracted from the individual white matter mask to create a NAWM mask. Finally, individual mean FA and MD values were calculated using the normal appearing white matter mask.

Voxelwise statistical analyses of the FA and MD data were carried out with tract-based spatial statistics (TBSS), using default settings (Smith et al., 2006). TBSS projects all subjects' aligned FA (or MD) data onto a mean white matter tract skeleton. The resulting four-dimensional data were used for further statistical analysis.

2.3.3. Magnetization transfer imaging

The MT images and the previously derived individual NAWM (WMHs subtracted from white matter) were linearly registered to T1 space (Jenkinson et al., 2002). Global magnetization transfer ratio (MTR) values were calculated per voxel as (M0 − Ms)/M0 (Ms: saturated image; M0: unsaturated image). MTR histograms were generated using the normal appearing white matter mask to calculate the mean MTR from each histogram, which is the mean of the MTR value of all voxels in the histogram.

2.4. Statistical analysis

Differences between patients and control subjects in WMH volumes, global mean FA, MD and mean MTR values of NAWM (white matter integrity measurements), and age were analyzed with independent-sample T-tests, dichotomous variables were analyzed using a χ^2 test or Fisher exact test. We used linear regression analyses for estimating the relationships between age and measurements of white matter integrity in patients and control subjects. Total WMH volumes were transformed using the logarithm function to meet normality assumptions. We examined the interaction between age and disease presence on white matter integrity (dependent variable) in a general linear model, with disease presence and age also included as independent variables; gender was included in the model as an independent variable as well. Within the PD group, we used a linear regression analysis to estimate the relationships between clinical variables (independent variable; disease duration, MDS-UPDRS motor, SENS-PD and SCOPA-COG score, total LDE, presence of vascular risk factors, and hypertension) and WMH volumes (dependent variable; total, deep anterior and periventricular WMH volume). With regard to the sum scores of the MDS-UPDRS motor, SENS-PD and SCOPA-COG scale, we first examined associations between sum scores and WMH volume. We subsequently examined associations between the domain scores and WMH volume if there was a statistically significant association (defined as $p < 0.05$) with one of the MDS-UPDRS motor, SENS-PD, or SCOPA-COG scale sum scores. We added age to the statistical model if a relationship was statistically significant after Bonferroni correction was applied. Statistics were performed in SPSS (IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp.).

Voxelwise statistical analysis of the FA and MD data was carried out using a general linear model approach as implemented in FSL, with gender used as covariate in the model as we did in the other statistical analyses. The spatial relationship between age and FA, and age and MD data was studied in the PD as well as in the control group. Permutation-based nonparametric testing was used (Winkler et al., 2014), with 5000 permutations, correcting for multiple comparisons across space. The statistical threshold was set at $p < 0.05$, familywise error corrected, using the threshold-free cluster enhancement technique (Smith and Nichols, 2009).

3. Results

3.1. Demographic characteristics

There were no statistically significant differences in age and gender between the patient and the control group (Table 1). Patients with PD had higher WMH volumes ($p < 0.001$) compared with control subjects. The periventricular ($p < 0.001$) and deep anterior ($p < 0.001$) WMH volumes were larger in patients with PD than in control subjects. We did not find statistically significant differences in deep posterior WMH volumes, and also white matter microstructure parameters (i.e., FA, MD, MTR) did not significantly differ between groups.

Table 1
Main characteristics of participants

Characteristic (score range)	Patients with PD	Controls	*p*-value
N	163	218	
Men/women	59/104 (63.8)	137/81 (62.8)	0.915
Age, years	64.8 (7.2)	65.0 (6.2)	0.462
Disease duration, years	9.1 (4.9)	n/a	n/a
MDS-UPDRS motor score (0–132)	34.3 (15.6)	n/a	n/a
SENS-PD (0–54)	13.2 (6.1)	n/a	n/a
SCOPA-COG (0–43)	27.5 (11–41)	n/a	n/a
Total LDE, mg/d	1017.1 (558.7)	n/a	n/a
Vascular risk factors			
Hypertension	32 (20.0)	39 (25.0)	0.345
Use of statins	19 (11.7)	15 (7.8)	0.211
Diabetes mellitus	6 (3.9)	10 (5.0)	0.616
Myocardial infarction	4 (2.6)	5 (3.2)	0.748
Transient ischemic attack	2 (1.3)	2 (1.3)	1.000
Smoking	10 (6.1)	29 (13.4)	0.006[b]
White matter hyperintensity volume, ml	8.8 (7.2)	4.8 (5.1)	<0.001[b]
Periventricular white matter	3.6 (2.3)	2.2 (1.7)	<0.001[b]
Anterior deep white matter	0.2 (0.2)	0.03 (0.1)	<0.001[b]
Posterior deep white matter	1.6 (1.7)	1.7 (1.7)	0.378
Mean FA normal appearing white matter	0.30 (0.02)	0.29 (0.02)	0.090
Mean MD[a] normal appearing white matter	0.92 (0.06)	0.92 (0.05)	0.850
Mean MTR normal appearing white matter	0.33 (0.02)	0.33 (0.01)	0.858

Values are means (standard deviation) for continuous variables, except for SCOPA-COG score (range), and numbers for gender (% men) and vascular comorbidity (% yes).
Key: FA, fractional anisotropy; LDE, Levodopa dosage equivalent; MD, mean diffusivity; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MTR, magnetization transfer ratio; n/a, not applicable; SCOPA-COG, SCales for Outcomes in PArkinson's disease-COGnition; SENS-PD, SEverity of Non-dopaminergic Symptoms in Parkinson's Disease.
[a] Absolute mean MD white matter values multiplied by 1000.
[b] $p < 0.05$.

3.2. Age and white matter hyperintensity volume

In the PD group and the control group, total WMH volume increased with age (PD group: $\beta = 0.329$, $p < 0.001$; control group: $\beta = 0.341$, $p < 0.001$; see Fig. 1A). There was no statistically significant interaction of age and disease presence in their effects on WMH volume. Periventricular (PD group: $\beta = 0.364$, $p < 0.001$; control group: $\beta = 0.364$, $p < 0.001$) and deep posterior (PD group: $\beta = 0.242$, $p < 0.002$; control group: $\beta = 0.312$, $p < 0.001$) WMH volumes also increased with age, but anterior WMH volume did not.

We found that in the PD group, visuospatial functioning (SCOPA-COG score) was related to total WMH volume ($\beta = -0.214$, $p = 0.006$) and postural instability and gait difficulty (UPDRS motor score) to periventricular WMH volume ($\beta = 0.257$, $p = 0.001$). Both relationships remained significant after including age in the model: visuospatial functioning with total WMH volume: $\beta = -0.175$, $p = 0.020$ (age with total WMH volume: $\beta = 0.307$, $p < 0.001$) and postural instability and gait difficulty with periventricular WMH volume: $\beta = 0.163$, $p = 0.037$ (age with periventricular WMH volume: $\beta = 0.314$, $p < 0.001$). No other significant relationships between clinical variables and WMH volumes emerged.

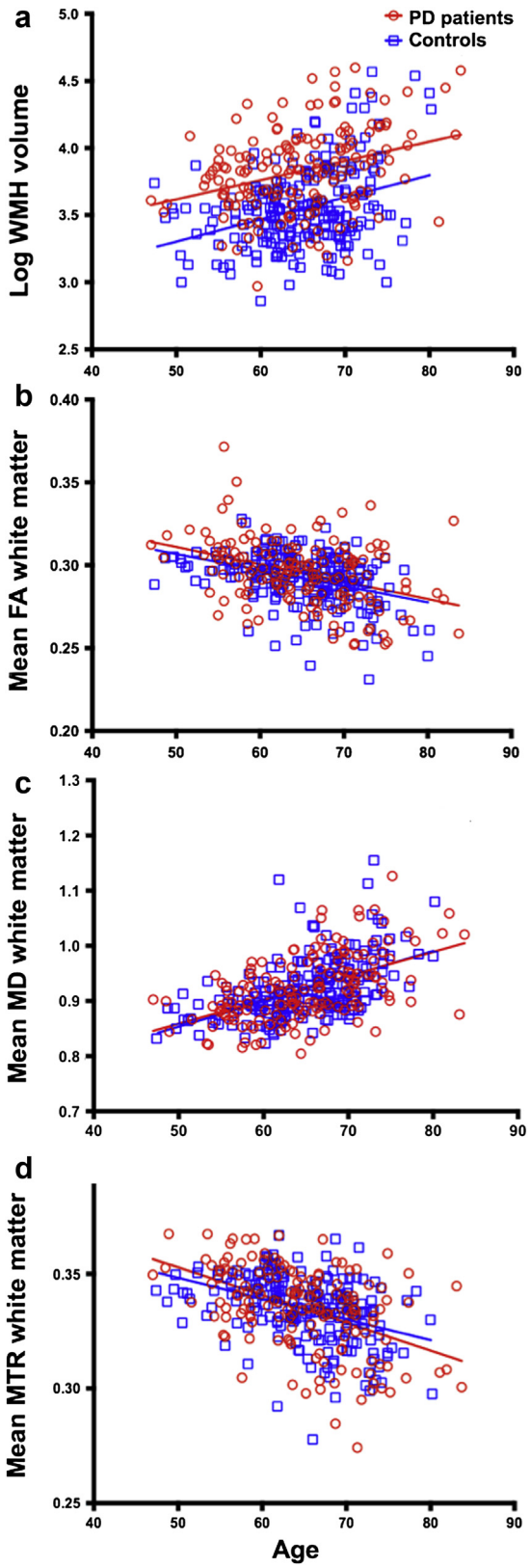

Fig. 1. Scatterplot of the relation between age and log-transformed white matter hyperintensity (WMH) volume (A), normal appearing white matter fractional anisotropy (FA; B), normal appearing white matter mean diffusivity (MD) multiplied by 1000 (C) and normal appearing white matter mean magnetization transfer ratio (MTR; D). Abbreviation: PD, Parkinson's disease.

3.3. Age and global white matter microstructural integrity

Age had a statistically significant association with FA (PD group: $\beta = -0.380$, $p < 0.001$; control group: $\beta = -0.392$, $p < 0.001$; see Fig. 1B), MD (PD group: $\beta = 0.522$, $p < 0.001$; control group: $\beta = 0.528$, $p < 0.001$; see Fig. 1C), and mean MTR (PD group: $\beta = -0.470$, $p < 0.001$; control group: $\beta = -0.393$, $p < 0.001$; see Fig. 1D) in both groups. There was no statistically significant interaction effect of age and disease presence on FA, MD, or mean MTR.

We used TBSS to investigate the spatial voxelwise relationship between age and FA and MD values in the PD as well as in the control group (Fig. 2). This shows that the spatial effect of age on FA and MD is distributed throughout the entire brain across white matter tracts in both patients with PD and control subjects.

4. Discussion

As age and PD both play a role in the degeneration of brain white matter, we investigated the relationship between age and white matter integrity in patients with PD and control subjects.

Although patients with PD had a higher load of white matter lesions, the influence of age on the decline of white matter integrity was similar to healthy control subjects. In both groups, measures of white matter integrity were associated with advancing age, which appeared homogeneously distributed across white matter tracts. No differences were found in the degree of NAWM degeneration.

The patients with PD in this study had a higher WMH load than expected for their age. The excess of WMHs was partly located in periventricular and deep frontal white matter of patients with PD. Besides age, visuospatial functioning and postural instability and gait difficulty were related to WMH volume in patients with PD. Given the similar age-related increase of WMHs in patients with PD and control subjects, our findings may suggest that the pathobiology of PD plays a role in the development of WMHs. Our findings are in line with those of other studies showing more WMHs in patients with PD (Compta et al., 2016; Dunet et al., 2019; Ham et al., 2016; Piccini et al., 1995). Nevertheless, other studies did not show differences between patients with PD and control subjects (Acharya et al., 2006; Beyer et al., 2006; Dalaker et al., 2009; Sartor et al., 2017). Differences in field strength (ranging from 0.5 to 3 Tesla), methodology to asses WMHs, and selection of a specific subset of patients with PD (i.e., with/without dementia or mild cognitive impairment) in these studies likely contributed to the inconsistent findings. Importantly, previous MRI studies investigating WMHs in patients with PD used visual rating scales, such as the Fazekas grading system and the Scheltens visual rating scale, or semiautomated visual approaches that require manual contouring of the lesions. Increased field strength can possibly result in a better delineation of white matter lesions (Zwanenburg et al., 2010) and the accuracy of visual rating systems may depend on the WMH load. Some scales do not discriminate between no abnormalities and few WMHs or moderate and severe quantities of WMHs, or suffer from ceiling effects in patients with a more extensive WMH load (Tiehuis et al., 2008; Wardlaw et al., 2004). The automated threshold method to measure WMH volume used in our study, however, provides objective and quantitative data (Tiehuis et al., 2008).

Previous studies have shown that WMHs independently contribute to postural instability and gait difficulty in patients with PD as well (for review, see (Bohnen and Albin, 2011)). There are indications that WMHs may have a substantial impact especially on axial motor disability (Lee et al., 2009; Moccia et al., 2016). There are also indications that WMHs contribute to cognitive impairment in patients with PD (Dadar et al., 2018; Veselý and Rektor, 2016). A recent study found increased MD in frontal and parietal white matter

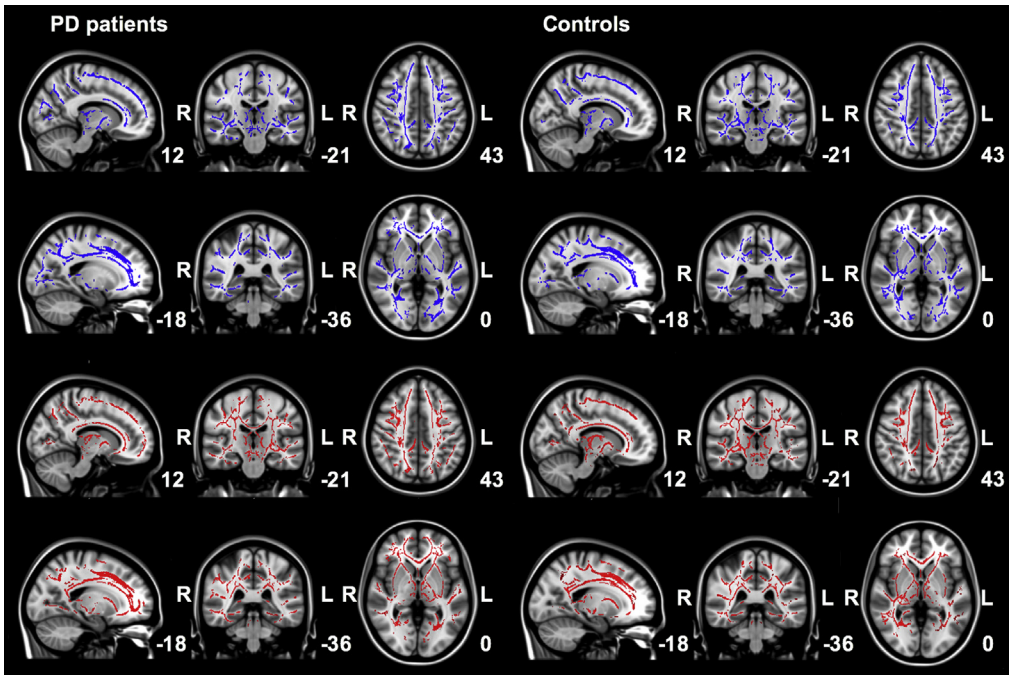

Fig. 2. Areas of age-related decline in white matter fractional anisotropy (FA, blue) and age-related increase in white matter mean diffusivity (MD, red), overlaid on the MNI standard cerebral image with accompanying coordinates. Left: Patients with Parkinson's disease. Right: control subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

tracts in newly diagnosed, cognitively intact, patients with PD as compared with control subjects, which was related to cognitive performance tasks (Duncan et al., 2016). These findings suggest that white matter may already be affected in the very early stages of PD, predicting future cognitive decline (Dadar et al., 2018; Duncan et al., 2016; Veselý and Rektor, 2016). However, some studies reported that the correlations found between cognitive measures and WMHs disappeared after adjusting for strong confounders, such as age (Bohnen and Albin, 2011; Lee and Lee, 2016). Indeed, our findings show that postural instability, gait difficulty, and visuospatial functioning are related to the total and to periventricular WMH volume in patients with PD, but the relationship between visuospatial functioning and WMHs weakened after adjustment for the effect of age in our study too. In addition, the relationship between age and WMHs appeared stronger than the relationship between visuospatial functioning and WMHs. WMHs might exacerbate cognitive or motor dysfunction in patients with PD through aggravation of already impaired neuronal connectivity (Veselý and Rektor, 2016). Especially periventricular WMHs could interfere with cortico-subcortical circuits that are important for gait and balance (Blahak et al., 2009; Bohnen and Albin, 2011). It is debatable whether the associations that we found are specific for PD, as WMHs are associated with motor and cognitive symptoms in otherwise normal elderly individuals as well (Bohnen and Albin, 2011).

WMHs have been linked to vascular disease, including depositions of amyloid-β (Pantoni, 2010). A recent study found more severe WMH burden in patients with PD with dementia compared with nondemented patients with PD and control subjects, which was related to decreased amyloid-β levels in the cerebrospinal fluid in the entire PD sample. Because this finding was independent of age, dementia, APOE-4, and vascular risk factors, the authors suggested a possible relationship between brain amyloid deposition and the occurrence of WMHs in patients with PD (Compta et al., 2016). At this stage, it remains unclear whether the relationship between amyloid-β levels in the cerebrospinal fluid and WMHs in patients with PD also reflects vascular amyloid-β deposition. Periventricular WMHs may further result from chronic hemodynamic insufficiency (hypoperfusion), Wallerian degeneration secondary to neocortical neuron loss in neurodegenerative diseases (Bohnen and Albin, 2011; Kim et al., 2008; Leys et al., 1991), or low-grade inflammation (Bohnen and Albin, 2011; Wersching et al., 2010) to which regional differences in gene expression may contribute, resulting in a spatial distribution of pathogenic pathways (Ritz et al., 2017).

The microintegrity of the white matter in patients with PD without WMHs was normal in terms of global FA, MD, and MTR, compared with age-matched control subjects. Previous cross-sectional studies have shown that DTI and MTR are particularly relevant for subcortical areas (Atkinson-Clement et al., 2017; Tambasco et al., 2015), and show conflicting results in cortical white matter, which might be explained by the low statistical power because of small sample sizes these studies (Atkinson-Clement et al., 2017; Hall et al., 2016; Tambasco et al., 2015). A recent meta-analysis, however, suggested that the cognitive status of patients with PD is associated with damage in the temporal and cingulate cortices (Atkinson-Clement et al., 2017). A major difference between previously conducted studies and our study is that these studies generally applied region-of-interest approaches (Cochrane and Ebmeier, 2013; Tessitore et al., 2016), whereas we used global FA and MD measures of white matter, to investigate the relationship between age and global white matter integrity in patients with PD. Two previous longitudinal studies used a whole-brain white matter approach as well, and observed similar levels of decline in white matter integrity in patients with PD and control subjects (Melzer et al., 2015; Rossi et al., 2014). Other studies measured FA reductions and increased MD over time in regions of interest (including regions of gray matter), such as the substantia nigra and caudal and cerebellar white matter (Pozorski et al., 2018; Zhang et al., 2016). Collectively, all findings suggest that PD-specific changes do not exceed normal age-associated change in cortical white matter tracts.

The strengths of our study are the large sample patients with PD and control subjects in whom we performed structural MRI as well as DTI and MTI to investigate the relationship between age and

white matter integrity. We further used automated techniques for individual quantification of WMH volume, based on thresholding of hyperintense white matter voxels, which have the advantage of improved quantitative assessment of WMHs compared with visual grading (Bohnen and Albin, 2011). A limitation of our study is the cross-sectional design to assess the age-related decline of white matter, as cross-sectional data rely on between-person comparisons and not model intraindividual change. White matter changes, aging, and cardiovascular risk factors are closely related to each other (Debette and Markus, 2010; Erten-Lyons et al., 2013; Wardlaw et al., 2013). It could be assumed that the control subjects in this study, who were selected from the LLS, may have had a more favorable cardiovascular risk profile as compared with the patients with PD in this study. However, cardiovascular risk factors did not differ between groups, although it should be noted that the assessed cardiovascular risk factors may not have been complete (e.g., the use of statins were compared, but not the presence of hyperlipidemia). Of note is that there were more missing values in the control group than in the patient group, but we consider it unlikely that this may have led to additional bias because there is no reason to assume a relationship between missingness and the risk profile of the patient. WMH volume may be associated with a worse response to dopaminergic medication for postural stability and gait difficulty (Arena et al., 2016). We therefore added total LDE score to the model, but this did not change our results. The effects of dopaminergic medication on white matter microstructure are not really known, except for a study that showed that DTI is not affected by acute antiparkinsonian medication (Chung et al., 2017). In our study, microintegrity of white matter without WMHs did not differ between patients with PD and age-matched control subjects, but subtle differences between groups may become apparent through the use of a region of interest approach (Pozorski et al., 2018; Zhang et al., 2016). In addition, the rate of age-related change may vary across multiple white matter regions, although the spatial effect of age on FA and MD was uniformly distributed across white matter tracts in both groups.

5. Conclusion

Patients with PD had a higher load of WMHs with a preferential periventricular and anterior distribution as compared with healthy control subjects. Visuospatial functioning was related to total and postural instability and gait difficulty were related to periventricular WMH volume in patients with PD. The age-related decline of white matter integrity was similar for both groups. Global mean FA, MD, and MTR of the NAWM were relatively normal in patients with PD, suggesting that PD-specific changes do not exceed normal age-associated change in white matter without lesions.

Disclosure

The authors have no actual or potential conflicts of interest.

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