White matter microstructure deteriorates across cognitive stages in Parkinson disease

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ABSTRACT

Objectives: To characterize different stages of Parkinson disease (PD)-related cognitive decline using diffusion tensor imaging (DTI) and investigate potential relationships between cognition and microstructural integrity of primary white matter tracts.

Methods: Movement Disorder Society criteria were used to classify 109 patients with PD as having normal cognition (PD-N, n = 63), mild cognitive impairment (PD-MCI, n = 28), or dementia (PD-D, n = 18), and were compared with 32 matched controls. DTI indices were assessed across groups using tract-based spatial statistics, and multiple regression was used to assess association with cognitive and clinical measures.

Results: Relative to controls, PD-N showed some increased mean diffusivity (MD) in corpus callosum, but no significantly decreased fractional anisotropy (FA). Decreased FA and increased MD were identified in PD-MCI and PD-D relative to controls. Only small areas of difference were observed in PD-MCI and PD-D compared with PD-N, while DTI metrics did not differ significantly between PD-MCI and PD-D. Executive function, attention, memory, and a composite measure of global cognition were associated with MD, primarily in anterior white matter tracts; only attention was associated with FA. These differences were independent of white matter hyperintensity load, which was also associated with cognition in PD.

Conclusions: PD is associated with spatially restricted loss of microstructural white matter integrity in patients with relatively normal cognition, and these alterations increase with cognitive dysfunction. Functional impairment in executive function, attention, and learning and memory appears associated with microstructural changes, suggesting that tract-based spatial statistics provides an early marker for clinically relevant cognitive impairment in PD. *Neurology*® 2013;80:1841–1849

GLOSSARY

DTI = diffusion tensor imaging; **FA** = fractional anisotropy; **LED** = levodopa equivalent dose; **MCI** = mild cognitive impairment; **MD** = mean diffusivity; **MDS** = Movement Disorder Society; **PD** = Parkinson disease; **PD-D** = Parkinson disease-dementia; **PD-N** = Parkinson disease–normal cognition; **TBSS** = tract-based spatial statistics; **TE** = echo time; **TR** = repetition time; **UPDRS** = Unified Parkinson's Disease Rating Scale; **WMH** = white matter hyperintensity.

Parkinson disease (PD) is a multisystem neurodegeneration characterized by changes that progress beyond its well-known brainstem neuropathology.[1] Superimposed on the classic motor symptoms, cognitive impairments and dementia are also common features in PD.[2] Patients with PD exhibiting mild cognitive impairment (PD-MCI) are at increased risk for developing dementia and are thus targets for disease-modifying intervention before irreversible changes, an awareness that has stimulated efforts to formalize suitable PD-MCI criteria.[3,4] Nevertheless, controversy remains about whether a PD-MCI classification identifies a group of patients whose neurodegeneration corresponds to the kind of harmful changes evident in patients meeting criteria for PD with dementia (PD-D).[5,6] The identification of suitable brain-imaging biomarkers that enhance disease characterization and track progression or treatment effectiveness is therefore of paramount importance.[4]

Supplemental data at www.neurology.org

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Conventional structural MRI has generated mixed evidence as to whether gray matter atrophy suitably distinguishes PD-MCI from either PD with normal cognition (PD-N) or PD-D.[7,8] Diffusion tensor imaging (DTI) provides a quantitative measure of microstructural integrity and organization, and is thus more suited to subtle damage not evident with conventional MRI.[9–11] DTI has identified abnormalities in PD-D,[12,13] and some evidence suggests that it may also reveal degeneration in patients without dementia who have lesser cognitive impairment.[10,12] We therefore used DTI to investigate 1) whether the imaging profile of formally diagnosed PD-MCI[4] is more similar to the "malignancy" evident in patients with PD-D and can be distinguished from those with PD-N and controls, and 2) whether impairments in specific cognitive domains produce unique patterns of microstructural damage.

METHODS

Subjects. A convenience sample of 118 participants meeting the United Kingdom Parkinson's Disease Society's criteria for idiopathic PD[14] was recruited from the Movement Disorders Clinic at the New Zealand Brain Research Institute (Christchurch, New Zealand) from May 2007 to September 2010. Individuals representative of the full spectrum of cognitive status in PD were invited to participate. Exclusion criteria included atypical parkinsonian disorder; prior learning disability; history of other neurologic conditions including moderate–severe head injury, stroke, vascular dementia; and major psychiatric or medical illness in the previous 6 months. The control group comprised 38 healthy volunteers matched to the mean characteristics of the PD sample (age, sex, and years of education). Neuroradiologic screening (R.J.K.) excluded participants showing moderate–severe white matter disease (1 control, 4 PD), marked cerebral atrophy (1 PD), or cerebellar infarcts (1 control). A further 4 PD subjects and 1 control were excluded because of excessive motion or extreme susceptibility artifacts. Three controls met our criteria for MCI and were excluded. Analyses were conducted on the remaining 109 PD and 32 control subjects.

Standard protocol approvals, registrations, and patient consents. All subjects gave written consent, with additional consent from a significant other when appropriate. The study was approved by the Regional Ethics Committee of the New Zealand Ministry of Health.

Diagnostic criteria and assessment. The Unified Parkinson's Disease Rating Scale (UPDRS; part III)[15] was used to assess motor impairment. Comprehensive neuropsychological testing (detailed previously[3,7,16]) classified the patients with PD as cognitively normal (PD-N; n = 63), with mild cognitive impairment (PD-MCI; n = 28), or with dementia (PD-D; n = 18). Dementia diagnosis was based on Movement Disorder Society (MDS) Task Force criteria.[17] MCI cases had unimpaired functional activities of daily living, as verified by interview with a significant other, but scored ≥1.5 SDs below normative data on at least 2 measures within at least 1 of 4 MDS cognitive domains (executive function; attention, working memory, and processing speed; learning and memory; and visuospatial/visuoperceptual function). These criteria are consistent with MDS diagnostic criteria for PD-MCI[4] and provide clear group separation.[3] Within each cognitive domain, standardized scores from the constituent neuropsychological tests were averaged to provide individual cognitive domain scores; global cognition for each participant was expressed as an aggregate *z* score obtained by averaging these 4 domain scores. At the time of assessment, 50 subjects with PD were drug naive for antiparkinsonian medication. Motor, cognitive, and MRI assessments in the remaining 59 PD participants were performed on medication, with no change to their usual drug regimen. Daily dopaminergic medications were standardized into a levodopa equivalent dose (LED).[18]

MRI acquisition. Imaging was conducted on a 3-tesla General Electric HDxt scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. A 2-dimensional diffusion-weighted, spin-echo, echo planar imaging sequence was used to measure microstructural integrity, with diffusion weighting in 28 uniformly distributed directions ($b = 1{,}000$ s/mm^2) and 4 acquisitions without diffusion weighting ($b = 0$ s/mm^2): echo time (TE)/repetition time (TR) = 86.4/13,000 milliseconds, flip angle = 90°, acquisition matrix = 128 × 128 × 48, reconstruction matrix = 256 × 256 × 48, field of view = 240 mm, slice thickness = 3 mm, and reconstructed voxel size = 1.07 × 1.07 × 3 mm^3, ungated. A T1-weighted (spoiled gradient recalled echo; TE/TR = 2.8/6.6 milliseconds, inversion time = 400 milliseconds, flip angle = 15°, acquisition matrix = 256 × 256 × 170, field of view = 250 mm, slice thickness = 1 mm) and a T2-weighted, fluid-attenuated inversion recovery sequence (TE/TR = 105/9,000 milliseconds, inversion time = 2,250 milliseconds, slice thickness 3 mm, gap = 1.5 mm) were also conducted.

MRI preprocessing. Image preprocessing and statistical analyses were performed using tract-based spatial statistics (TBSS)[19] in FSL 4.1.6 (www.fmrib.ox.ac.uk/fsl). Diffusion-weighted images were motion- and eddy current distortion–corrected. The diffusion tensor was then calculated at each voxel using DTIFIT, producing fractional anisotropy (FA) and mean diffusivity (MD) images, and then brain-extracted using BET. All FA images were aligned to a common space (FMRIB58 FA template) using the nonlinear registration tool FNIRT. The mean FA image was thinned (FA >0.25) to create a mean FA skeleton that represented the centers of all tracts common to the group. Each subject's aligned FA image was then projected onto this common skeleton, a procedure that minimizes misalignment more prevalent in standard registration procedures.[19] The nonlinear warps and skeleton projection were then applied to MD images to create a separate skeleton representing the MD values. White matter disease was quantified using the Lesion Segmentation Toolbox,[20] which allows automatic detection of T2 hyperintensities based on the T2 fluid-attenuated inversion recovery and T1-weighted images. This analysis derived a total white matter hyperintensity (WMH) volume for each subject.

Statistical analyses. Clinical and cognitive measures were compared across controls and PD groups in MATLAB (analysis of variance or Kruskal-Wallis, pending distributions). After analysis of FA and MD averaged across the entire skeleton, voxel-wise statistics on the skeletonized images used a permutation-based inference tool for nonparametric statistical thresholding (FSL's "randomize"). Group differences were assessed (control/PD-N/PD-MCI/PD-D) with age, sex, years of education, and scanner software version (2 updates occurred over the acquisition period) as covariates. Separate FA and MD models excluding controls assessed the 3 PD groups (PD-N/PD-MCI/PD-D) with the same

covariates plus UPDRS, disease duration, and LED. Multiple regression models investigated the association between FA/MD and aggregate cognitive *z* score, as well as the 4 individual cognitive domain scores, across all PD patients including all covariates. For each contrast, the null distribution was generated over 5,000 permutations and the α level set at $p < 0.05$, corrected for multiple comparisons using threshold-free cluster enhancement.[21] All analyses were rerun with the inclusion of WMH volume as an additional covariate, as WMH may contribute to cognitive dysfunction in PD and affect DTI metrics.[22]

RESULTS Table 1 summarizes demographic and clinical details. When averaged across the entire skeleton, both median FA ($\chi^2 = 23.7$, $p < 0.0001$) and MD ($\chi^2 = 27.8$, $p < 0.0001$) showed differences across groups, with decreased FA and increased MD in PD-MCI and PD-D relative to controls and PD-N, but the cognitively impaired groups did not show a difference (Kruskal-Wallis with post hoc Bonferroni comparisons). After covarying for age, there remained a significant effect of WMH volume, with PD-MCI and PD-D exhibiting larger WMH load (log-transformed data; $F_{4,136} = 23.6$, $p < 0.0001$).

Regional differences in the TBSS skeleton. Relative to controls, no significant FA decreases were identified in PD-N (figure e-1A on the *Neurology*® Web site at www.neurology.org), whereas both PD-MCI (Figure e-1B) and PD-D (Figure e-1C) exhibited extensive FA decreases in widespread cerebral white matter. All 3 PD groups exhibited increased MD relative to controls, the extent of which increased with cognitive impairment. PD-N showed localized MD increases (Figure e-2A), whereas PD-MCI and PD-D groups showed more widespread evidence of

Table 1 Demographic, clinical, and global imaging details of each group[a]

	Controls	PD-N	PD-MCI	PD-D
No.	32	63	28	18
Age,[b] y	70.1 (9.0)	64.0 (9.2)	71.0 (7.3)	73.7 (6.5)
Sex, M:F	22:10	43:20	18:10	16:2
Education, y	13.6 (3.1)	13.4 (3.0)	12.5 (3.0)	12.4 (2.5)
MMSE[b]	28.9 (1.1)	29.0 (1.1)	27.4 (1.5)	24.1 (3.0)
MoCA[b]	26.9 (2.0)	26.7 (2.3)	23.0 (2.3)	16.4 (3.7)
Reisberg Activities of Daily Living	—	0.23 (0–1.81)	0.63 (0–1.60)	1.95 (1.23–3.25)
Reisberg Global Deterioration Scale[b]	—	1 (1–2)	2 (1–3)	4 (3–6)
Global cognitive *z* score[b,c]	0.60 (0.38)	0.33 (0.40)	−0.70 (0.36)	−1.71 (0.54)
Domain *z* scores				
Executive function[b]	0.72 (0.54)	0.50 (0.64)	−0.85 (0.76)	−2.03 (0.53)
Attention[b]	0.32 (0.45)	0.04 (0.45)	−0.96 (0.50)	−1.94 (0.56)
Learning and memory[b]	0.86 (0.78)	0.36 (0.80)	−0.77 (0.58)	−1.68 (0.67)
Visuospatial/perceptual[b]	0.52 (0.52)	0.44 (0.45)	−0.22 (0.63)	−1.20 (0.82)
GDS[b]	0 (0–1)	0 (0–13)	0 (0–11)	2 (0–8)
NPI[b]	—	0 (0–31)	3 (0–23)	8 (0–28)
UPDRS-III[b]	—	25.3 (13.7)	30.6 (12.3)	52.9 (16.3)
Disease duration,[b] y	—	3.7 (3.2)	5.8 (5.1)	12.3 (8.6)
Hoehn and Yahr[b]	—	2 (1–3)	2 (1.5–4)	4 (2–4)
LED,[b] mg/d	—	208 (306)	308 (373)	727 (399)
FA[b]	0.49 (0.45–0.52)	0.49 (0.45–0.54)	0.47 (0.42–0.52)	0.46 (0.43–0.50)
MD,[b] $\times 10^{-3}$ mm^2/s	0.79 (0.75–0.84)	0.79 (0.72–0.84)	0.81 (0.75–0.90)	0.83 (0.77–0.90)
WMH,[b] mL	1.2 (0–55.3)	1.0 (0–78.54)	6.4 (0.1–58.4)	10.5 (2.9–74.5)

Abbreviations: FA = fractional anisotropy averaged along entire white matter skeleton; GDS = Geriatric Depression Scale; LED = levodopa equivalent dose; MD = mean diffusivity averaged along entire white matter skeleton; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PD-D = Parkinson disease with dementia; PD-MCI = Parkinson disease with mild cognitive impairment; PD-N = Parkinson disease with normal cognition; UPDRS-III = Unified Parkinson's Disease Rating Scale part III; WMH = white matter hyperintensity.
[a] Values are mean (SD), except median (range) for FA, GDS, Hoehn and Yahr stage, MD, NPI, and WMH. Global Deterioration Scale and NPI scores were available for a subset of patients (PD-N, n = 31; PD-MCI, n = 23; PD-D, n = 18).
[b] Significant analysis of variance/Kruskal-Wallis across groups, $p < 0.001$.
[c] Aggregated across 4 cognitive domains.[3]

increased MD in white matter tracts (figure e-2, B and C). With the inclusion of WMH volume as a covariate, results remained stable, but the PD-N group exhibited fewer regions of increased MD compared with controls (FA: figure 1, A–C; MD: figure 2, A–C). Specific white matter regions exhibiting significant group differences are listed in table e-1.

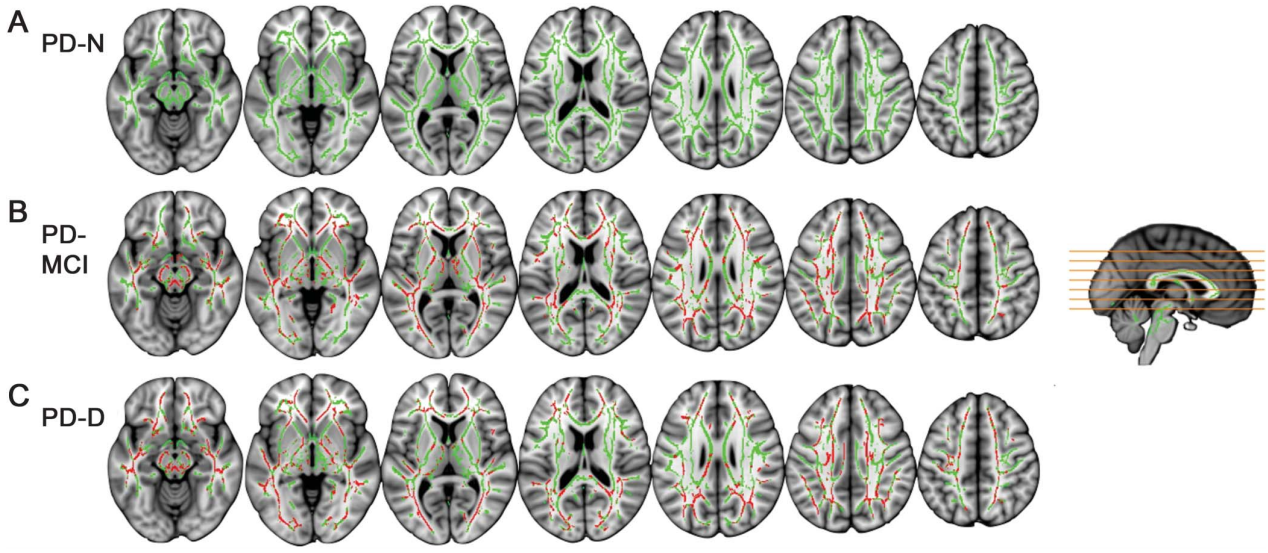
When the analysis was limited to PD groups only, without WMH as a covariate, PD-MCI (figure e-3A) and PD-D (figure e-3B) groups exhibited reduced FA relative to PD-N in similar but more spatially restricted regions than when compared with controls. Similarly, we identified significantly increased MD in widespread white matter tracts in both PD-MCI (figure e-3C) and PD-D (figure e-3D) relative to PD-N. Unlike their clear differences in terms of cognition, there were no significant FA or MD differences between PD-MCI and PD-D. When WMH volume was included as a covariate, a more spatially restricted pattern of decreased FA was observed in PD-MCI (figure 3A) and PD-D (figure 3B) relative to PD-N at a slightly more lenient threshold-free cluster enhancement–corrected $p < 0.06$, along with increased MD in PD-MCI (figure 3C, corrected $p < 0.06$) and PD-D (figure 3D, corrected $p < 0.05$; table e-1).

Association with cognitive scores. Results from multiple regression models including WMH volume are reported (table e-2) because there was minimal difference when omitting WMH volume (figure e-4). Significant association was identified between increased MD and decreased global cognitive *z* score (figure 4A), executive function domain score (figure 4B), and learning and memory domain score (figure 4D) in anterior white matter tracts. The attention, working memory, and processing speed score was significantly associated with MD (figure 4C) in anterior and posterior white matter and with FA in right anterior and posterior regions (data not shown). No significant association was identified between FA and any other cognitive score, nor were DTI metrics significantly associated with visuospatial/visuoperceptual scores, UPDRS scores, disease duration, or LED.

DISCUSSION Abnormal DTI metrics along multiple white matter tracts were evident in patients with PD-MCI compared with healthy controls, but only in limited white matter tracts relative to PD-N. Localized MD changes in corpus callosum were also found in PD-N relative to controls. DTI metrics in white matter tracts correlated with aggregate cognitive measures across multiple domains. Thus, whereas small but detectable microstructural white matter differences occur in patients with PD, irrespective of cognitive status, they become substantial once formal MCI is established and may worsen only slightly with progression to dementia. This evidence is consistent with the view that PD-MCI reflects significant pathology.[4]

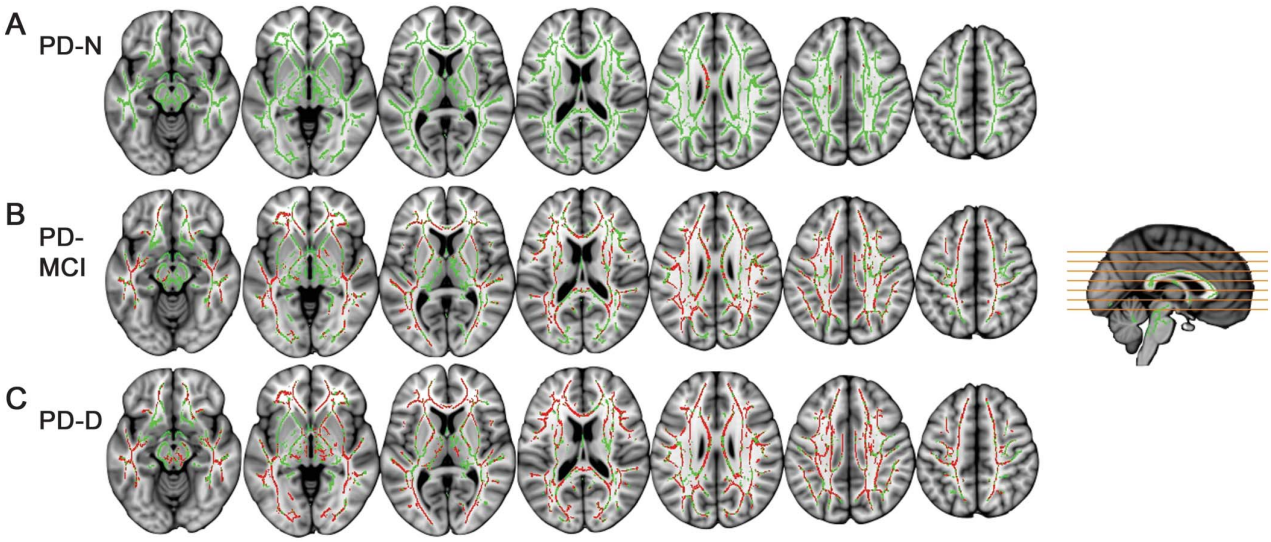
The identification of neuroimaging markers sensitive to PD-related cognitive impairments has become

Figure 1 Reduced fractional anisotropy in Parkinson disease relative to healthy controls



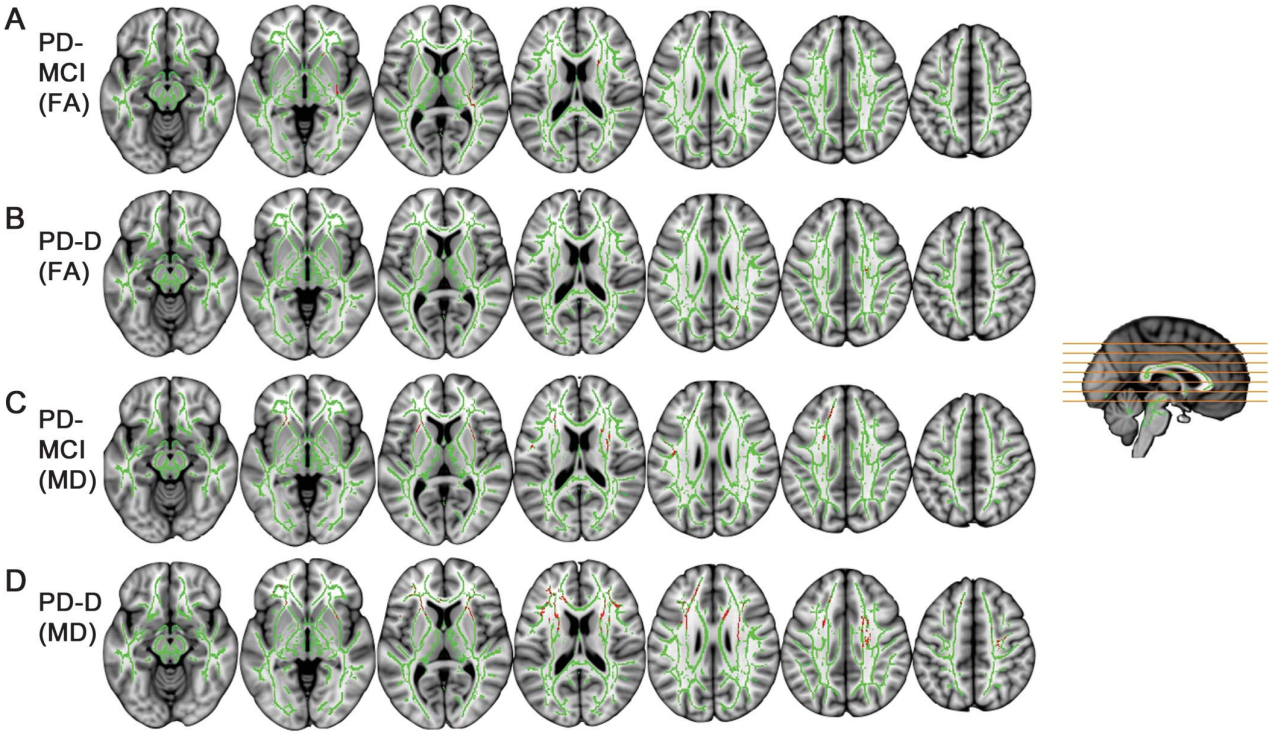
The study-specific FA skeleton, representing the centers of principal white matter tracts, is displayed in green, overlaid on the MNI152 T1-weighted template. (A) PD-N showed no significant difference by comparison with controls. Red indicates significant FA reduction in (B) PD-MCI and (C) PD-D relative to controls ($p < 0.05$ corrected for multiple comparisons using threshold-free cluster enhancement). The horizontal lines on the sagittal view indicate the axial slices displayed. Specific white matter regions exhibiting significant group differences are listed in table e-1. FA = fractional anisotropy; PD-D = Parkinson disease–dementia; PD-MCI = Parkinson disease–mild cognitive impairment; PD-N = Parkinson disease–normal cognition.

Figure 2 **Increased mean diffusivity in Parkinson disease relative to healthy controls**



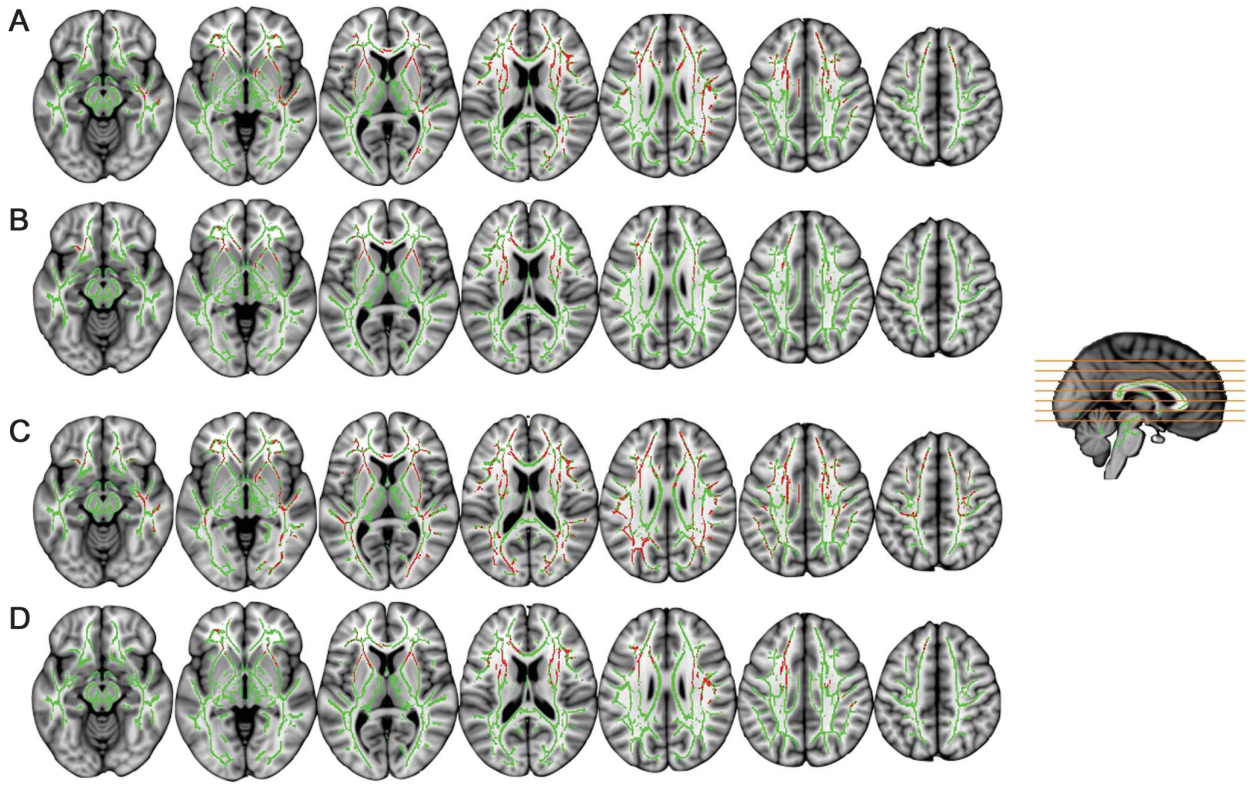
Red clusters of significantly increased MD relative to controls in (A) PD-N, (B) PD-MCI, and (C) PD-D ($p < 0.05$ threshold-free cluster enhancement–corrected). All 3 PD cognitive groups displayed increased MD compared with controls; PD-N exhibited the most spatial restriction whereas PD-MCI and PD-D showed extensive MD increases throughout white matter. Specific white matter regions exhibiting significant group differences are listed in table e-1. MD = mean diffusivity; PD-D = Parkinson disease–dementia; PD-MCI = Parkinson disease–mild cognitive impairment; PD-N = Parkinson disease–normal cognition.

Figure 3 **Abnormal diffusion tensor imaging metrics in cognitively impaired Parkinson disease relative to Parkinson disease with normal cognition**



Red clusters of significantly reduced FA along the skeleton in (A) PD-MCI and (B) PD-D, and increased MD in (C) PD-MCI and (D) PD-D relative to PD-N, after covarying for age, sex, years of education, scanner version, UPDRS-III score, disease duration, LED, and WMH volume (A–C: $p < 0.06$ TFCE-corrected; D: $p < 0.05$ TFCE-corrected). There were no significant differences between PD-MCI and PD-D. Specific white matter regions exhibiting significant group differences are listed in table e-1. FA = fractional anisotropy; LED = levodopa equivalent dose; MD = mean diffusivity; PD-D = Parkinson disease–dementia; PD-MCI = Parkinson disease–mild cognitive impairment; TFCE = threshold-free cluster enhancement; UPDRS-III = Unified Parkinson's Disease Rating Scale part III; WMH = white matter hyperintensity.

Figure 4 Significant associations between mean diffusivity and cognition in Parkinson disease



Red clusters depict significant association between MD and the following cognitive domains in PD: (A) global cognitive *z* score, (B) executive function, (C) attention, working memory, and speed of processing, and (D) learning and memory, covarying for age, sex, years of education, scanner software version, UDPRS-III score, disease duration, LED, and WMH volume. Correlation occurred primarily in anterior white matter regions, with posterior regions also evident in the attention domain. No significant associations were found for the visuospatial/visuoperceptual domain. In terms of FA, only the attention domain score revealed significant associations with white matter tracts. Specific white matter regions are listed in table e-2. FA = fractional anisotropy; LED = levodopa equivalent dose; PD = Parkinson disease; UPDRS-III = Unified Parkinson's Disease Rating Scale part III; WMH = white matter hyperintensity.

a prominent goal for the field.[4,23] Structural MRI studies have demonstrated cortical gray matter atrophy in PD-MCI relative to controls[7,24] and even relative to PD-N in one instance,[8] but have generally failed to differentiate PD-MCI from both PD-N and PD-D.[7,25,26] Our DTI results (covarying for WMH volume) showed widespread microstructural differences between PD-MCI and controls, with smaller differences relative to PD-N, and support the validity of MCI in PD as a distinct condition in which significant brain pathology exists.

Few studies have explored MCI in PD with DTI. Those that did lacked formal criteria to diagnose PD-MCI and did not address the potential confounding influence of WMHs. Informal or different criteria may produce instances of misclassification.[3] One study[12] defined PD-MCI using a Clinical Dementia Rating value of 0.5 and reported widespread FA reduction relative to controls, but did not detect differences between this MCI group and PD-N or PD-D. Others demonstrated significantly reduced FA in left parietal white matter in patients with PD who did not have dementia but had impairments in executive tasks relative to those without these disturbances.[27] In the current study, more spatially extensive reduced FA and increased MD was identified in a carefully classified group of patients with PD-MCI relative to controls. Although the pattern of microstructural damage was similar to that in PD-D, our patients with PD-MCI met the recent MDS criteria and had no dementia as their activities of daily living were unimpaired.[4,17] Although subtle, our findings suggest that patients with MCI exhibit microstructural integrity more akin to that in PD-D than PD-N. Although we did not find reduced FA in PD-N relative to controls in this study, increased MD was identified in corpus callosum, superior corona radiata, and cingulum bundle, but not the consistently identified regions of substantia nigra[28,29] and olfactory regions.[30]

In many previous studies, possible inclusion of patients with PD and subtle cognitive impairments in a single "nondementia" PD group may have substantially affected results and their interpretation by including different proportions of patients with neuropsychological

deficits consistent with PD-MCI diagnosis.[10,28,29] Cognitive heterogeneity provides a possible explanation for the presence of FA abnormalities in nondementia groups in earlier studies and its absence in PD-N in the current study (figure 1A). The only other study to investigate patients with PD separately classed as normal or MCI found no FA/MD difference in those with normal cognition.[12] A consistent application of MDS MCI criteria may bring greater rigor and consistency to future studies.

It is clear that extensive microstructural damage accompanies the development of dementia in PD. A previous region of interest–based analysis demonstrated significant FA reduction in frontal, temporal, and occipital white matter in PD-D compared with controls, and in bilateral posterior cingulum bundles relative to PD without dementia.[31] A traditional voxel-based approach identified decreased FA in PD-D relative to controls in bilateral orbitofrontal, anterior and middle cingulum, right dorsolateral prefrontal, left anterior temporal, and parietal white matter.[13] Most recently, TBSS analysis was used to identify reduced FA in many major white matter tracts in PD-D relative to PD-N and healthy individuals, but did not address WMHs.[12] We also identified extensive FA reduction in PD-D relative to controls and PD-N when WMH volume was not considered. With the inclusion of WMH load, the difference between PD-D and PD-N became much more spatially localized. This is not surprising because WMHs are expected to contribute to cognitive dysfunction in PD.[22]

Associations between DTI metrics and individual cognitive domains suggest that loss of microstructural integrity may contribute to cognitive impairments in PD. We identified significant association between the executive function domain score and MD in prefrontal white matter, genu, and internal and external capsules, which connect prefrontal cortex and striatum. The current DTI findings therefore provide direct microstructural evidence for the involvement of frontostriatal white matter pathology in the frontal executive network in PD.[32,33] We also observed association between MD and attention, working memory, and processing speed in white matter tracts underlying key regions of the dorsal attention network,[33] namely, the frontal eye fields and middle temporal regions, but also extending to include anterior regions. Learning and memory domain scores correlated with MD in the anterior cingulum and lateral frontal white matter, both underlying cortical areas implicated in functional networks associated with memory.[34] Although visuospatial/visuoperceptual function was impaired in our PD-MCI and PD-D groups, we did not detect any significant relationship with DTI metrics, suggesting that non–white matter processes may have a larger influence on visuospatial function.

There are several potential limitations to the current study. First, cardiac gating was not performed during image acquisition. Although gating may improve data quality, it is time consuming and may have a negligible effect in group-level analyses.[35] Second, participants completed scanning and neuropsychological assessment with no disruption to their antiparkinsonian drug regimen. It is unlikely, however, that levodopa influenced our results because previous investigators[36] observed no significant effect of levodopa on DTI metrics. Nevertheless, we included LED as a covariate in all relevant comparisons. Third, we interpreted the absence of significant difference between PD-MCI and PD-D groups as a general similarity between the 2 groups, but it is possible that we were unable to detect subtle differences because of the smaller number in the PD-D group. Fourth, as with all DTI investigations, the direct interpretation of FA and MD in vivo is complex. While DTI metrics have been attributed to numerous processes (e.g., neuronal loss, gliosis, degradation of axonal membranes or myelin sheaths, reduced axonal fiber density, cellular density, and integrity of microtubules and neurofilaments),[9,37] white matter alterations in PD have been associated with axonal degeneration and injury of neuronal cell bodies as a result of cytoskeletal changes.[38] Recent histologic work suggests that major contributors to the development of PD-MCI include limbic and neocortical Lewy body and Alzheimer disease histopathology, as well as cerebrovascular pathology.[39,40] It seems likely that abnormal DTI measures along white matter tracts connecting key regions affected by PD pathology may indicate microstructural degeneration associated with cell loss, α-synuclein, and amyloid pathology. Comorbid small-vessel ischemia/WMHs may also affect DTI results.[22] Indeed, after accounting for age, we identified significantly larger WMH volume in cognitively impaired PD participants than in healthy individuals. Separate DTI analyses with and without WMH load as a covariate did not substantially change the identification of differences between PD cognitive groups and controls or any associations with cognitive scores, but did markedly reduce the spatial distribution of significant differences between cognitively impaired PD (PD-MCI, PD-D) and PD-N. Without WMH, we observed significant and widespread FA and MD difference between PD-N and both PD-MCI and PD-D, suggesting similar amounts of white matter pathology in cognitively impaired PD. When WMH volume was included, DTI differences between PD-N and cognitively impaired PD were spatially restricted to focal areas of internal and external capsule, anterior and superior corona radiata, and left inferior frontooccipital and superior longitudinal fasciculi. This suggests that substantial white matter pathology does occur in PD-MCI relative to PD-N, where some of the

difference is explained by the presence of WMHs, but DTI reveals an additional and independent relationship between microstructural integrity and PD-related cognitive impairment. Future work may benefit from investigating the influence of the spatial distribution of WMHs on DTI metrics and cognition in PD.

Our findings show that even early PD is associated with some alterations in white matter pathways that worsen once significant cognitive impairments develop. Localized differences imply that functional impairment in executive function, attention, and learning and memory are influenced by these microstructural changes. Relevance as a surrogate marker requires further investigation, but our findings suggest that DTI and TBSS provide a promising method to evaluate and potentially track anatomical substrates of cognitive decline in PD.

AUTHOR CONTRIBUTIONS

Dr. Melzer: drafting/revising the manuscript, study concept and design, analysis and interpretation of data, acquisition of data, statistical analysis. Dr. Watts: revising the manuscript, study concept and design, interpretation of data, acquisition of data, study supervision. Dr. MacAskill: revising the manuscript, study concept and design, interpretation of data, obtaining funding. Dr. Pitcher and Ms. Livingston: revising the manuscript, acquisition of data, study coordination. Dr. Keenan: interpretation of data, revising the manuscript. Assoc. Prof. Dalrymple-Alford and Prof. Anderson: revising the manuscript, study concept and design, interpretation of data, study supervision, obtaining funding.

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REFERENCES

1. Braak H, Tredici KD, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
2. Aarsland D. Epidemiology of dementia associated with Parkinson's disease. In: Emre M, editor. Cognitive Impairment and Dementia in Parkinson's Disease. New York: Oxford University Press; 2010:5–14.
3. Dalrymple-Alford JC, Livingston L, MacAskill MR, et al. Characterizing mild cognitive impairment in Parkinson's disease. Mov Disord 2011;26:629–636.
4. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349–356.
5. Martinez-Horta S, Kulisevsky J. Is all cognitive impairment in Parkinson's disease "mild cognitive impairment"? J Neural Transm 2011;118:1185–1190.
6. Rektorova I. Mild cognitive impairment exists in Parkinson's disease. J Neural Transm 2011;118:1179–1183.
7. Melzer TR, Watts R, MacAskill MR, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:183–194.
8. Weintraub D, Doshi J, Koka D, et al. Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol 2011;68:1562–1568.
9. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003;4:469–480.
10. Karagulle Kendi AT, Lehericy S, Luciana M, et al. Altered diffusion in the frontal lobe in Parkinson disease. AJNR Am J Neuroradiol 2008;29:501–505.
11. Wiltshire K, Concha L, Gee M, et al. Corpus callosum and cingulum tractography in Parkinson's disease. Can J Neurol Sci 2010;37:595–600.
12. Hattori T, Orimo S, Aoki S, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 2012;33:727–739.
13. Lee JE, Park HJ, Park B, et al. 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. J Neurol Neurosurg Psychiatry 2010;81:320–326.
14. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
15. Fahn S, Elton R. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, Goldstein M, editors. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan Healthcare Information; 1987:153–163.
16. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology 2010;75:1717–1725.
17. Emre M, Aarsland D, Brown RG, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689–1707.
18. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649–2653.
19. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487–1505.
20. Schmidt P, Gaser C, Arsic M, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. Neuroimage 2012;59:3774–3783.
21. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44:83–98.

22. Bohnen NI, Albin RL. White matter lesions in Parkinson disease. Nat Rev Neurol 2011;7:229–236.
23. Aarsland D, Bronnick K, Fladby T. Mild cognitive impairment in Parkinson's disease. Curr Neurol Neurosci Rep 2011;11:371–378.
24. Meyer JS, Huang J, Chowdhury MH. MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias. J Neurol Sci 2007; 257:97–104.
25. Dalaker TO, Zivadinov R, Larsen JP, et al. Gray matter correlations of cognition in incident Parkinson's disease. Mov Disord 2010;25:629–633.
26. Apostolova LG, Beyer M, Green AE, et al. Hippocampal, caudate, and ventricular changes in Parkinson's disease with and without dementia. Mov Disord 2010;25: 687–688.
27. Matsui H, Nishinaka K, Oda M, et al. Wisconsin Card Sorting Test in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 2007;116:108–112.
28. Chan LL, Rumpel H, Yap K, et al. Case control study of diffusion tensor imaging in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:1383–1386.
29. Zhan W, Kang GA, Glass GA, et al. Regional alterations of brain microstructure in Parkinson's disease using diffusion tensor imaging. Mov Disord 2012;27:90–97.
30. Ibarretxe-Bilbao N, Junque C, Marti MJ, et al. Olfactory impairment in Parkinson's disease and white matter abnormalities in central olfactory areas: a voxel-based diffusion tensor imaging study. Mov Disord 2010;25:1888–1894.
31. Matsui H, Nishinaka K, Oda M, et al. Dementia in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 2007;116:177–181.
32. Rae CL, Correia MM, Altena E, et al. White matter pathology in Parkinson's disease: the effect of imaging protocol differences and relevance to executive function. Neuroimage 2012;62:1675–1684.
33. Raichle ME. The restless brain. Brain Connect 2011;1:3–12.
34. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 2006;103:13848–13853.
35. Habib J, Auer DP, Morgan PS. A quantitative analysis of the benefits of cardiac gating in practical diffusion tensor imaging of the brain. Magn Reson Med 2010;63:1098–1103.
36. Degirmenci B, Yaman M, Haktanir A, et al. The effects of levodopa use on diffusion coefficients in various brain regions in Parkinson's disease. Neurosci Lett 2007;416:294–298.
37. Beaulieu C. The basis of anisotropic water diffusion in the nervous system: a technical review. NMR Biomed 2002; 15:435–455.
38. Braak H, Braak E. Pathoanatomy of Parkinson's disease. J Neurol 2000;247:II3–II10.
39. Adler CH, Caviness JN, Sabbagh MN, et al. Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. Acta Neuropathol 2010;120:827–828.
40. Jellinger KA. Neuropathology in Parkinson's disease with mild cognitive impairment. Acta Neuropathol 2010;120: 829–830.

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