White matter microstructure deteriorates across cognitive stages in Parkinson disease

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.

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-MCI = Parkinson disease-mild cognitive impairment; 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


Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

© 2013 American Academy of Neurology 1841
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.\cite{3,4} 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.\cite{8,9,10} DTI has identified abnormalities in PD-D,\cite{11,12,13} and some evidence suggests that it may also reveal degeneration in patients without dementia who have lesser cognitive impairment.\cite{14,15} We therefore used DTI to investigate 1) whether the imaging profile of formally diagnosed PD-MCI 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\cite{16} 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). Neuro-radiologic 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 and some evidence suggests that it may also reveal degeneration in patients without dementia who have lesser cognitive impairment.\cite{17,18} We therefore used DTI to investigate 1) whether the imaging profile of formally diagnosed PD-MCI 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\cite{16} 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). Neuro-radiologic 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 and one significant other when appropriate. The study was consented. All subjects gave written consent, with additional consents.

**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/mm²) and 4 acquisitions without diffusion weighting, (b = 0 s/mm²): 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 mm³, unweighted. 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 pre-processing.** Image pre-processing and statistical analyses were performed using tract-based spatial statistics (TBSS\textsuperscript{8}) 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 was 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 aligned FA image was then projected onto this common skeleton, a procedure that minimizes misalignment more prevalent in standard registration procedures.\cite{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,\cite{20} which allows automatic detection of T2 hypointensities 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 learning and memory; and visuospatial/visuoperceptual function). These criteria are consistent with MDS diagnostic criteria for PD-MCI\textsuperscript{4} and provide clear group separation.\textsuperscript{5} 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 naïve 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).\textsuperscript{18}
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 (χ² = 23.7, p < 0.0001) and MD (χ² = 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; F4,136 = 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>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, clinical, and global imaging details of each group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>70.1 (9.0)</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>22:10</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.6 (3.1)</td>
</tr>
<tr>
<td>MMSE b</td>
<td>28.9 (1.1)</td>
</tr>
<tr>
<td>MoCA b</td>
<td>26.9 (2.0)</td>
</tr>
<tr>
<td>Reisberg Activities of Daily Living</td>
<td>—</td>
</tr>
<tr>
<td>Reisberg Global Deterioration Scale b</td>
<td>—</td>
</tr>
<tr>
<td>Global cognitive z score b,c</td>
<td>0.60 (0.38)</td>
</tr>
<tr>
<td>Domain z scores</td>
<td></td>
</tr>
<tr>
<td>Executive function b</td>
<td>0.72 (0.54)</td>
</tr>
<tr>
<td>Attention b</td>
<td>0.32 (0.45)</td>
</tr>
<tr>
<td>Learning and memory b</td>
<td>0.86 (0.78)</td>
</tr>
<tr>
<td>Visuospatial/perceptual b</td>
<td>0.52 (0.52)</td>
</tr>
<tr>
<td>GDS b</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>NPI b</td>
<td>—</td>
</tr>
<tr>
<td>UPDRS-III b</td>
<td>—</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>—</td>
</tr>
<tr>
<td>Hoehn and Yahr b</td>
<td>—</td>
</tr>
<tr>
<td>LED, mg/dl</td>
<td>—</td>
</tr>
<tr>
<td>FA b</td>
<td>0.49 (0.45–0.52)</td>
</tr>
<tr>
<td>MD, ×10⁻⁶ mm²/s</td>
<td>0.79 (0.75–0.84)</td>
</tr>
<tr>
<td>WMH, mL</td>
<td>1.2 (0.55–3)</td>
</tr>
</tbody>
</table>

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.

aValues 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).

bSignificant analysis of variance/Kruskal-Wallis across groups, p < 0.001.

cAggregated across 4 cognitive domains.
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.

The identification of neuroimaging markers sensitive to PD-related cognitive impairments has become...
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.
a prominent goal for the field. Structural MRI studies have demonstrated cortical gray matter atrophy in PD-MCI relative to controls and even relative to PD-N in one instance, but have generally failed to differentiate PD-MCI from both PD-N and PD-D. 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. One study 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. 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.

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 and olfactory regions.

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. 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 cog-
nition. A consistent application of MDs MCI criteria
may bring greater rigor and consistency to future studies.

It is clear that extensive microstructural damage accompa-
nies the development of dementia in PD. A previ-
sous region of interest–based analysis demon-
strated 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. A traditional
voxel-based approach identified decreased FA in
PD-D relative to controls in bilateral orbitofrontal,
anterior and middle cingulum, right dorsolateral pre-
frontal, left anterior temporal, and parietal white
matter. 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 individ-
uals, but did not address WMHs. 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 spa-
tially localized. This is not surprising because WMHs
are expected to contribute to cognitive dysfunction
in PD. Associations between DTI metrics and indi-
cidual 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 prefron-
tal white matter, genu, and internal and external caps-
ules, which connect prefrontal cortex and striatum.
The current DTI findings therefore provide direct
microstructural evidence for the involvement of fron-
tostriatal white matter pathology in the frontal execu-
tive network in PD. 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, namely,
the frontal eye fields and middle temporal regions,
but also extending to include anterior regions. Learn-
ning 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. Although visuospatial/visuo-spatial 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 cur-
rent 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. Sec-
ond, participants completed scanning and neuropsy-
chological assessment with no disruption to their
antiparkinsonian drug regimen. It is unlikely, how-
ever, that levodopa influenced our results because
previous investigators 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 sim-
ilarity 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), white
matter alterations in PD have been associated
with axonal degeneration and injury of neuronal cell
bodies as a result of cytoskeletal changes. Recent his-
tologic work suggests that major contributors to the
development of PD-MCI include limbic and neocor-
tical Lewy body and Alzheimer disease histopathology,
as well as cerebrovascular pathology. 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. Comor-
bid small-vessel ischemia/WMHs may also affect DTI
results. Indeed, after accounting for age, we identi-
ified 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 identi-
fication 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 fronto-occipital
and superior longitudinal fasciculi. This suggests that
substantial white matter pathology does occur in
PD-MCI relative to PD-N, where some of the

Neurology 80 May 14, 2013 1847
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.

ACKNOWLEDGMENT
The authors thank Eve Welch for assistance in preparation of the figures. The authors also thank one of the reviewers for drawing attention to the importance of WMHs on cognition and DTI metrics in PD.

STUDY FUNDING
This work was supported by the Neurological Foundation of New Zealand, the Canterbury Medical Research Foundation, and the Neurology Trust. T.R.M. is supported by a Health Sciences Career Development Postdoctoral Fellowship from the University of Otago.

DISCLOSURE
T. Melzer reports no disclosures. R. Watts has received research support from the Canterbury Medical Research Foundation and the Neurological Foundation of New Zealand. M. MacAskill has received research support from the Canterbury Medical Research Foundation and Supreme Grand Royal Arch Chapter (Freemasons) of New Zealand. T. Pitcher has received research support from the Neurological Foundation of New Zealand. L. Livingston has received support from the Neurology Trust. R. Keenan is employed by the Christchurch Radiology Group. J. Dalrymple-Alford has received support from the Canterbury Medical Research Foundation, the Health Research Council of New Zealand, the Supreme Grand Royal Arch Chapter (Freemasons) of New Zealand, the Neurological Foundation of New Zealand, and the Government Accident Compensation Corporation of New Zealand. T. Anderson has received research support from the Canterbury Medical Research Foundation, the Health Research Council of New Zealand, and The Neurological Foundation of New Zealand, has received honoraria from Boehringer Ingelheim, and is a board member of the New Zealand Institute of Language, Brain and Behavior. Go to Neurology.org for full disclosures.

Received August 7, 2012. Accepted in final form January 29, 2013.

REFERENCES


This Week’s Neurology® Podcast

The midbrain to pons ratio: A simple and specific MRI sign of progressive supranuclear palsy (See p. 1856)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the May 14, 2013, issue of Neurology®. In the second segment, Dr. John Morgan talks with Dr. Luke Massey about his paper on an MRI sign of progressive supranuclear palsy. Dr. Roy Strowd then reads the e-Pearl of the week about progressive supranuclear palsy and the “hummingbird” sign. In the next part of the podcast, Dr. Matthew Barrett focuses his interview with Dr. Fred Wooten on late treatment of motor symptoms. Disclosures can be found at www.neurology.org.

At www.neurology.org, click on the “Download Latest Issue” link or “Subscribe Now” to subscribe to the RSS Feed.

CME Opportunity: Listen to this week’s Neurology® Podcast and earn 0.5 AMA PRA Category 1 CME Credits™ by answering the multiple-choice questions in the online Podcast quiz.