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Regional Alterations of Brain Microstructure in Parkinson's Disease Using Diffusion Tensor Imaging

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Abstract

This study tested the hypothesis that diffusion tensor imaging (DTI) can detect alteration in microscopic integrity of white matter (WM) and basal ganglia (BG) regions known to be involved in Parkinson's disease (PD) pathology. It was also hypothesized that there is an association between the DTI abnormality and PD severity and subtype. DTI at 4 Tesla was obtained in 12 PD and 20 control subjects. The DTI measures of fractional anisotropy (FA) and mean diffusivity (MD) were evaluated using both region of interest (ROI) and voxel-based methods. Movement deficits in PD subjects were assessed using Motor Subscale (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Subtype determination of movement deficits was derived based upon results of subjects' UPDRS ratings. Reduced FA ($p < 0.05$, corrected) was found in PD subjects in a number of regions, including the precentral gyrus, substantia nigra, putamen, posterior striatum, frontal WM, and in regions related to the supplementary motor areas. Reduced FA in the substantia nigra correlated ($p < 0.05$, corrected) with increased UPDRS motor scores. Significant spatial correlations between FA alterations in putamen and other PD-affected regions were also found in the context of PD subtypes index analysis. Our data suggest that microstructural alterations detected with DTI might serve as a potential biomarker for PD.

Keywords

diffusion tensor imaging; magnetic resonance imaging; Parkinson's disease; Subtypes

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the presence of bradykinesia, rigidity, resting tremor, and postural instability.¹ The neuropathologic hallmarks of PD include the loss of dopaminergic neurons in the substantia nigra (SN)² and

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ventral tegmental area (VTA),³ along with the presence of intraneuronal cytoplasmic inclusions known as Lewy bodies.⁴ The majority of neuroimaging studies of PD have focused on the basal ganglia,⁵⁻⁶ while few imaging studies have evaluated the integrity of the associated circuitry. Besides the dopaminergic system, there is evidence showing that serotonergic, noradrenergic, and cholinergic projections are compromised in PD.⁷ These observations suggest that PD involves a widespread neurodegenerative process that extends beyond the basal ganglia (BG) and movement control system.⁸

Diffusion tensor imaging (DTI) is increasingly being used to measure integrity of tissue microstructure and alterations of neuronal fiber tracts.⁹⁻¹⁰ Several DTI studies in PD patients and animal models have reported decreased fractional anisotropy (FA) and increased mean diffusivity (MD) of the substantia nigra (SN), implying degradation of the microstructure,¹¹⁻¹⁴ although negative results have also been reported.¹⁵⁻¹⁶ DTI abnormalities in PD have also been found in other regions, including the frontal lobe,¹⁷ olfactory bulb,¹⁸ inferior temporal gyrus,¹⁴ and superior cerebellar peduncle.¹⁹ More recently, a DTI study²⁰ reported an improved differentiation between a small group of PD patients and control subjects based on diffusion differences in the SN.

Most of the DTI studies in PD have relied upon a region of interest (ROI) methodology for the measurements, with the risk of missing unexpected alterations in other parts of the brain. On the other hand, the few DTI studies in PD using regionally unbiased approaches based on voxelwise analysis have had a limited focus on evaluating primarily the olfactory bulb region rather than the whole brain.^{14,18} Moreover, no prior DTI study has explored whether the distribution of microstructural degradation varies with PD severity or major clinical subtypes of PD, such as tremor-dominant versus akinetic-rigid subtypes.²¹ Addressing these issues is expected to improve the understanding of how PD pathology alters the neuronal pathways, providing the basis for the development of effective clinical MRI biomarkers for PD.

The overall goal of the present DTI study was to evaluate the regional pattern of microstructural degradation in PD using a regionally unbiased approach, supplemented by a region of interest approach for verification. Specifically, we tested the hypothesis that PD is associated with a distinct pattern of microstructural degradation, primarily reflected by FA reduction, involving various subcortical regions (such as the substantia nigra, other components of the basal ganglia, and thalamus) and the white matter regions underlying cortical areas involved in movement control (including the motor, premotor, and supplementary motor cortices). Moreover, we aimed to determine the extent to which these regional microstructural alterations correlate with overall PD severity and differ across subtypes of PD.

PATIENTS & METHODS

Study Population

Twelve patients with mild to moderate idiopathic PD (all men, mean age = 67.4±8 yrs, Mini Mental State Examination [MMSE]²² = 28.9±1.4) were diagnosed following previous descriptions²⁵ and excluded for major cognitive impairment defined as MMSE < 26. These

patients, along with 20 healthy controls (all men, mean age = 67.2±8 yrs, MMSE = 29.7±0.5), provided informed written consent in this study that was approved by the Institutional Review Board (IRB) of the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center. Subjects were excluded if they were outside the age range of 50 – 75 years or had a diagnosis of any other neurological disorder, history of central nervous system infection, seizures, significant cognitive impairment, or a history of alcohol and/or drug abuse. The upper age limit was chosen to reduce the incidence of concomitant Alzheimer's disease and vascular disease, and male subjects were selected to reflect the gender risk factor in PD and to null the gender effects in data analysis.

Evaluation of PD motor signs was assessed by rating subjects on the motor score (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS).²³ The majority (11 out of 12) of these subjects were evaluated in the off-medication state (i.e., subjects having refrained from taking their PD medications for at least 12 hours) in an attempt to obtain ratings that most closely reflected their underlying motoric severity. The average UPDRS motor score of the PD subjects was 26.3±12.2, with scores ranging from 14 to 53. The subtyping of PD subjects was performed in a manner that followed the paradigm described in prior publications.²⁴⁻²⁵ Subscores and subtype indices were derived by the following formulas: 1) Tremor Subscore (TSC) was defined as the average rating per question in UPDRS Part III Items 6 and 7; 2) Akinetic-Rigid Subscore (ARC) was defined as the average rating per question in UPDRS Part III Items 8-13 and 17; and 3) we defined a subtype index $SI = \frac{TSC}{TSC+ARC}$ to express dominance of tremor and akinetic-rigid symptoms on a scale from zero to one. See supplementary material S-Table 1 for detailed information.

Image Acquisition and Processing

All subjects were scanned on a 4T MRI system (Medspec Bruker/Siemens). DTI acquisitions were based on echo-planar imaging (EPI) using parallel imaging (GRAPPA)²⁶ with two fold acceleration with parameters of TR/TE = 6s/77ms, matrix size = 128×128×40 yielding 2×2×3 mm nominal resolution, and 6 diffusion encoding directions with b=1000 s/mm². Four times of DTI acquisitions were repeated to boost the signal-to-noise ratio (SNR) in the averaged images. T1-weighted images (MPRAG) were acquired for spatial normalization purposes, and fluid attenuated inversion recovery (FLAIR) images were also obtained for detecting white matter lesions. Raw MRI images were manually evaluated to ensure no significant motion artifacts or white matter hyperintensities were present.

The DTI derived measures of FA and MD were calculated offline for each imaging voxel using the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl/). DTI processing tools of tract-based spatial statistics (TBSS)²⁷ were implemented in the following steps: (i) A representative subject in the control group (65 years of age) was selected as the co-registration “target” to which the 3D FA maps of all subjects were aligned by using a 12 degrees of freedom affine transformation, followed by a nonlinear registration procedure in TBSS; (ii) The aligned FA maps were interpolated to 1×1×1 mm resolution and spatially normalized with respect to a T1-weighted template in Talairach space;²⁸ and (iii) For each subject, the MD map was spatially normalized through the transformation pipeline that was estimated in the FA map normalization in steps (i) and (ii).

Data Analysis

Voxel-based DTI analysis was applied within a mask obtained at threshold of mean FA > 0.2 for all subjects in the normalized space. Group comparisons between PD and control subjects were performed using non-parametric permutation t-tests in FSL.²⁹ A linear regression program in Analysis of Functional NeuroImages (AFNI)³⁰ was applied to remove the age-related effects in DTI data on a voxelwise basis. Correction for multiple comparisons was performed on a cluster level by generating a null distribution of the cluster size of significant voxels using Monte Carlo simulations³¹.

A set of regions of interest (ROI) were bilaterally identified for each individual subject on the native FA map (see supplementary material S-Fig.1), including white matter regions in superior precentral gyrus (PRG) at the level of primary motor cortex (PMC), postcentral gyrus (POG) at the level of somatosensory cortex (SSC), supplementary motor areas (SMA), inferior precentral gyrus (PRG) at the level of insular cortex (INS), posterior limb of internal capsule (IC), external capsule (EC), and sub-cortical regions in substantial nigra (SN), anterior putamen (PUT), and anterior thalamus (THA). Regional FA and MD were measured by averaging within each ROI.

We tested for correlations between the PD subtype index (SI) and regional variations in FA. Further, to determine if correlations between PD subtypes and regional variations in FA are also spatially related, we compared two regression models (M1 and M2) of pair-wise regional FA correlations with the subtype index SI, according to:

$$\begin{aligned} \text{M1: } SI &= a_0 + a_1 FA^{(i)} + a_2 FA^{(j)} + a_3 FA^{(i)} FA^{(j)} + \varepsilon \\ \text{M2: } SI &= a_0 + a_1 FA^{(i)} + a_2 FA^{(j)} + \varepsilon \end{aligned} \quad (1)$$

Here, $FA^{(i)}$ and $FA^{(j)}$ represent the FA measurements at regions i and j . a_1, a_2 are the coefficients of independent contributions from each region that explain variability in SI; and coefficient a_3 represents the contribution from the interaction term, which depicts the spatial correlations of FA measurements between the two regions. ε is the error term in the general linear model. A Wald chi-squared³² was used to compare the regression coefficients and determine whether the spatial correlations between a pair of regions contributed significantly to the model.

RESULTS

Voxel-Based Analysis

The regional pattern of significant FA reductions ($p < 0.05$ for 1 mm^3 voxel, corrected) in PD patients compared to control subjects from a voxelwise analysis is illustrated in Figure 1. Significant regions, shown in blue, are superimposed on the mean FA map averaged across all subjects. Reduced FA is found in PD primarily in the superior and inferior precentral gyrus, superior postcentral gyrus, posterior striatum, frontal white matter, and along projection fibers to the supplementary motor areas, including internal and external capsule, as well as in the proximity of the putamen, thalamus, and substantia nigra. No significantly higher FA was shown in PD compared to the control.

Regions of significant negative correlations ($p < 0.05$ for 1 mm^3 voxel, corrected) (in blue) between reduced FA and increasing PD severity, as measured using total UPDRS motor scores, were found at the level of the substantia nigra, as shown in Figure 2. Four equally-spaced axial slices of FA maps with 5 mm distance are depicted for display. No other regions showed significant correlations between FA and UPDRS.

ROI-Based Analysis

ROI-based testing was also performed to verify that the voxelwise findings were not artifacts of image misregistrations. In Table 1, FA reductions in PD compared with controls remained significant in most regions from the voxelwise analysis. Specifically, significant regions derived from both voxel-wise and ROI analysis included the superior precentral gyrus (sup. PRG), postcentral gyrus (POG), white matter areas close to supplementary motor areas (SMA), substantia nigra (SN), inferior PRG, external and internal capsule (EC and IC), right thalamus (THA), and left putamen (PUT). In these ROIs, differences in FA values were all significant at the level $p < 0.05$ with adjustment for family-wise error correction rate (FWER).³³ In contrast, no significant differences in regional MD were found between PD patients and control subjects after FWER correction, although PD patients had on average globally higher MD values than control subjects.

Scatter plots of cross-subject correlations between total UPDRS scores and DTI measurements in PD patients are shown in Figure 3 for the regions with significant correlations ($p < 0.05$). Mean FA or MD values of left and right regions were averaged for the analysis. In SN, reduced FA correlated with increased total UPDRS (Figure 3a). In postcentral gyrus, increased FA correlated with increased UPDRS (Figure 3b). In putamen, no significant correlation between FA and UPDRS was found (Figure 3c), whereas decreased MD of the putamen was associated with increased UPDRS (Figure 3d). No other ROIs exhibited significant correlations with UPDRS scores.

Subtype Analysis

Table 2 depicts the results of the linear regression models for pair-wise regional FA measures in predicting the PD subtype index (SI) as outlined in Equation 1. P values here reflect the significance of spatial correlations between the FA measures in the two regions. Only the pairs with the spatial correlation at significance level $p < 0.05$ are listed.

Significant spatial correlations ($p < 0.01$) between several regions with abnormal FA findings are shown in the regression models to predict PD subtype index. The most frequent links between the pairs of regions involved the putamen, primarily on the left side. These links indicate the strong spatial correlations between the putamen and other PD affected regions, including primary motor cortex, supplementary motor areas, and substantia nigra.

DISCUSSION

We have three major findings: First, PD is associated with a distinct pattern of microstructural degradation at the level of the substantia nigra, thalamus, and motor, premotor, and supplementary motor cortical areas, consistent with the known neuroanatomy of the movement control circuit.¹ In addition, the pattern of microstructural degradation in

PD also includes somatosensory areas in postcentral gyrus, which may reflect the critical role of sensory feedback in motor planning and execution.³⁴ Second, the degree of microstructural degradation significantly correlated with the degree of PD severity, especially for FA measurements in the SN. Third, some regional FA variations in PD were spatially correlated and the most frequent spatial correlations involved the putamen, consistent with the central role of the putamen in movement control. Taken together, the findings suggest that PD is associated with widespread microstructural degradation, and DTI may have value as an imaging marker for PD.

The first finding of a distinct pattern of microstructural degradation in PD is consistent with other DTI studies showing that PD is associated with decreased FA and/or increased MD in the SN and PUT.^{12,20-21,36} In addition to previous findings, our study indicates that white matter close to cortical regions involved in motor control, such as the supplementary motor area, are also affected. Taken together, the present findings support our primary hypothesis that PD is associated with widespread degradation of neuronal pathways known to be involved in the movement control circuit. Compared to previous DTI studies, we assessed the pattern of regional alterations in PD using a spatially unbiased voxelwise analysis supplemented by post-hoc region-of-interest analyses to exclude possible errors from image transformations.

We found PD-related microstructural degradation in postcentral gyrus at the level of the somatosensory cortex, which has not been reported in previous DTI studies. We interpret this finding as an indication of PD-related sensory response abnormalities. Somatosensory dysfunction in PD patients, such as pain, restless legs, akathisia, paresthesia, and dysesthesia, is well-established.^{1,37} Functional MRI³⁸ and PET³⁹ studies have revealed abnormal cortical and subcortical activations upon sensory stimulation. We therefore hypothesize that microstructural degradations in the somatosensory area are associated with PD-related sensory response abnormalities. Although the possibility of spurious DTI findings in somatosensory areas was minimized by applying a correction for family-wise errors or non-parametric permutation tests for group comparison, the findings in the somatosensory areas need to be replicated by additional studies in combination with functional neuroimaging and more specific sensory tests.

Our results also indicate that regional variations in DTI measures correlate with PD severity, supporting the view that microstructural degradation seen in DTI reflects PD pathology. Specifically, decreased FA values at the level of SN as well as increased MD values of PUT were strongly associated with increasing disease severity. These findings are partially supported by recent DTI studies, which found marked alterations in MD in the SN in PD patients,²⁰ presumably reflecting the loss of dopaminergic neurons in PD.^{1,40} The correlations between nigral dopaminergic neuronal degeneration and PD severity as characterized by total UPDRS scores have been observed in PET⁴¹⁻⁴² and SPECT⁴³⁻⁴⁴ studies. Our DTI results provide evidence that PD pathology extends beyond the neuron loss in SN and can involve microstructural degeneration of neuronal pathways. An unexpected finding was that, in contrast to the findings above where microstructural integrity of SN and PUT degraded with disease severity, FA values of the postcentral gyrus at the level of somatosensory cortex *increased* with increasing PD severity. This finding may reflect a

compensatory mechanism of the brain in response to motor control deficits,⁴⁵ as implied by functional MRI studies in PD.⁴⁶

Another finding in the context of PD subtypes is our observation of significant spatial correlations between FA alterations in putamen and other PD-affected regions. Specifically, FA alterations in putamen correlate with the FA alterations in the vicinities of the primary motor cortex, supplementary motor area, insular cortex, thalamus, and substantia nigra in the regression models to explain the variations of motor subtype index across the subjects. This finding implies that microstructural integrity degradation in the putamen, evidenced by reduced FA, might play a central role for tremor dominance by accentuating deficits that occur in other basal ganglia regions. The correlations of FA reductions between putamen and other regions also agree with postmortem studies that reveal in the tremor-dominant subtype more severe cell loss in the medial SN,³⁵ compared to generally less cell loss in the putamen in the akinetic-rigid subtype.⁴⁷

Several limitations of our study ought to be mentioned: 1) The relatively small number of PD patients limits generalization of the findings. Therefore, more studies involving a large number of patients are warranted to replicate the findings. 2) The lower resolution and the geometric distortion of EPI compared to the anatomical T1 images may have affected the localization of small anatomical structures, such as substantia nigra. We used both voxel- and ROI-based analysis as a remedy to this problem, although difficulties in accurately localizing DTI alterations in small structures remain. As more powerful MRI systems become available, DTI studies at higher spatial resolution will be important.

CONCLUSION

Our findings suggest that PD is associated with a characteristic regional pattern of microstructural degradation in the vicinity of the substantia nigra, putamen, and thalamus, as well as in motor, premotor, and supplementary motor cortices. Moreover, the regional microstructural alterations detected by DTI are associated with PD severity, and the pattern varies across the main motor PD subtypes. Taken together the results suggest that DTI is a promising tool to assess PD-related neurodegeneration and potentially could serve as marker for PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Regions of reduced FA ($p < 0.05$, corrected) in PD patients compared to control subjects, superimposed on the mean FA map from all subjects. No significant FA increase ($p < 0.05$, corrected) in PD compared to controls.

Fig. 2. Significant voxelwise correlations ($p < 0.05$, corrected) between decreased FA and increased total UPDRS scores were detected in the white matter at the level of the substantia nigra.

Fig.3.

Inter-subject correlations ($p < 0.05$) in PD between total UPDRS and FA measures in (a) substantia nigra, (b) postcentral gyrus at the level of somatosensory cortex, and (c) putamen. In (d) is shown the correlation between UPDRS and MD in the putamen. Note, FA and MD values represent the bilateral average for each region.

Table 1

ROI - based DTI comparisons between controls (CN) and PD patients (PD).

ROI	FA (mean/std)			MD (*e-6 mm ² /s)		
	CN	PD	P (CN>PD)	CN	PD	P (CN<PD)
r. sup. PRG	0.45 (0.06)	0.35 (0.06)	0.0007*	8.12 (0.90)	8.91 (1.23)	0.2
l. sup. PRG	0.47 (0.04)	0.37 (0.04)	0.000001*	8.00 (0.59)	8.34 (1.03)	0.7
r. POG	0.36 (0.04)	0.30 (0.02)	0.00003*	9.84 (1.23)	10.36 (1.33)	0.7
l. POG	0.40 (0.04)	0.33 (0.03)	0.0002*	8.37 (0.72)	8.82 (0.74)	0.4
r. SMA	0.50 (0.05)	0.43 (0.06)	0.02*	8.09 (0.68)	8.13 (0.78)	0.9
l. SMA	0.48 (0.03)	0.39 (0.08)	0.003*	7.74 (0.68)	8.06 (0.88)	0.7
r. THA	0.35 (0.05)	0.30 (0.04)	0.04*	8.18 (0.55)	8.31 (0.73)	0.9
l. THA	0.34 (0.03)	0.32 (0.04)	0.5	8.12 (1.28)	8.04 (0.86)	0.9
r. inf. PRG	0.42 (0.05)	0.36 (0.07)	0.05*	8.07 (0.79)	8.14 (0.89)	0.9
l. inf. PRG	0.37 (0.04)	0.31 (0.03)	0.001*	8.76 (0.75)	9.04 (0.70)	0.8
r. EC	0.34 (0.05)	0.29 (0.04)	0.007*	9.17 (0.86)	9.40 (1.00)	0.9
l. EC	0.33 (0.05)	0.27 (0.05)	0.02*	9.06 (1.22)	9.30 (1.02)	0.9
r. IC	0.61 (0.03)	0.56 (0.04)	0.003*	7.07 (0.49)	7.44 (0.73)	0.4
l. IC	0.62 (0.04)	0.56 (0.06)	0.02*	6.97 (0.38)	7.06 (0.79)	0.9
r. SN	0.47 (0.06)	0.34 (0.06)	0.00001*	10.36 (1.29)	10.40 (0.52)	0.9
l. SN	0.51 (0.07)	0.38 (0.04)	0.000003*	8.62 (1.34)	9.29 (0.71)	0.4
r. PUT	0.27 (0.03)	0.24 (0.03)	0.09	7.60 (0.76)	7.78 (1.59)	0.9
l. PUT	0.28 (0.02)	0.24 (0.05)	0.007*	7.49 (0.85)	7.62 (0.89)	0.9

• P values include adjustments for multiple comparisons using a family-wise error rate (FWER) correction.³³ The sign “*” marks regional FA reductions at the significant level $p < 0.05$ after FWER correction.

• sup.PRG= superior Precentral Gyrus (at the level of primary motor cortex); inf.PRG= inferior Superior Precentral Gyrus (at the level of insular cortex); POG= Postcentral Gyrus (at the level of somatosensory cortex); SMA= Supplementary Motor Areas; THA= Thalamus; EC= External Capsule; IC=Internal Capsule; SN= Substantia Nigra; PUT= Putamen

Table 2

List of significant spatial correlations ($p < 0.05$) in the regression models of pair-wise regional FA measures in relation to PD subtype index (see Equation 1)

Region (i)	Region (j)	a_1	a_2	a_3	P
r. PMC	r. IC	-7.68E-3	-5.62E-3	1.42E-6	0.02
r. PMC	l. PUT	-3.12E-3	-4.23E-3	1.26E-6	0.001*
r. SMA	l. PUT	-2.72E-3	-4.25E-3	1.05E-6	0.002*
r. PUT	l. PUT	-2.66E-3	-1.85E-3	9.67E-7	0.005*
r. INS	r. EC	-2.77E-3	-3.07E-3	8.52E-7	0.01
r. EC	l. PUT	-2.77E-3	-2.56E-3	1.05E-6	0.01
r. IC	l. PUT	-3.12E-3	-6.96E-3	1.28E-6	0.04
r. IC	l. EC	-4.31E-3	-8.59E-3	1.59E-6	0.05
l. PMC	l. PUT	-4.96E-3	-7.20E-3	2.03E-6	0.004*
l. SMA	l. PUT	-1.88E-3	-2.65E-3	7.63E-7	0.006*
l. PUT	l. THA	-2.96E-3	-2.61E-3	1.02E-6	0.03
l. PUT	l. EC	-1.89E-3	-2.54E-3	8.97E-7	0.0002*
l. PUT	l. IC	-5.11E-3	-2.27E-3	9.50E-7	0.02

• See Equation 1, a_1 , a_2 are the coefficients representing independent contributions of each region to the PD subtype index (SI); and a_3 represents the contributions from the interaction term between a pair of regions. Sign “*” marks the spatial correlations with significance level $p < 0.01$.

• PMC= Primary Motor Cortex (at superior precentral gyrus); SMA= Supplementary Motor Areas; INS= Insular (at inferior precentral gyrus); THA= Thalamus; EC= External Capsule; IC=Internal Capsule; PUT= Putamen