Diffusion tensor imaging in parkinsonian syndromes

A systematic review and meta-analysis

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ABSTRACT

Objectives: We performed a systematic review to assess alterations in measures of diffusion tensor imaging (DTI) in parkinsonian syndromes, exploring the potential role of DTI in diagnosis and as a candidate biomarker.

Methods: We searched EMBASE and Medline databases for DTI studies comparing parkinsonian syndromes or related dementias with controls or another defined parkinsonian syndrome. Key details for each study regarding participants, imaging methods, and results were extracted. Estimates were pooled, where appropriate, by random-effects meta-analysis.

Results: Of 333 results, we identified 43 studies suitable for inclusion (958 patients, 764 controls). DTI measures detected alterations in all parkinsonian syndromes, with distribution varying differentially with disease type. Nine studies were included in a meta-analysis of the substantia nigra in Parkinson disease. A notable effect size was found for lowered fractional anisotropy in the substantia nigra for patients with Parkinson disease vs controls (−0.639, 95% confidence interval −0.860 to −0.417, $p < 0.0001$).

Conclusion: DTI may be a promising biomarker in parkinsonian syndromes and have a future role in differential diagnosis. Larger cohort studies are required to investigate some encouraging preliminary findings. Given the complexity of the parkinsonian syndromes, it is likely that any potential DTI biomarker would be used in combination with other relevant biomarkers. *Neurology*® 2013;80:857–864

GLOSSARY

ADC = apparent diffusion coefficient; **CC** = corpus callosum; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **LBD** = Lewy body dementia; **MD** = mean diffusivity; **MSA** = multiple system atrophy; **MSA-P** = multiple system atrophy–parkinsonism; **PD** = Parkinson disease; **PDD** = Parkinson disease dementia; **PSP** = progressive supranuclear palsy; **ROI** = region of interest; **SN** = substantia nigra; **TBSS** = tract-based spatial statistics; **VBA** = voxel-based analysis.

Differences in natural history and therapy options make early and accurate diagnosis of parkinsonian syndromes important.[1] Emission tomography (SPECT or PET) has a role but it can be expensive, with limited availability, and requires radioactive tracers.[2] There is particular interest in the potential of advanced structural MRI techniques to differentiate among parkinsonian syndromes and to offer candidate biomarkers, facilitating early or premanifest diagnosis and monitoring of disease progression.

Diffusion tensor imaging (DTI) is an MRI technique assessing the orientation and integrity of white matter tracts in vivo by measuring the diffusion of water molecules in neural fibers[3] and it also shows promise for studying gray matter areas. It estimates both the degree of directionality using anisotropy (frequently fractional anisotropy [FA]) and the overall movement of molecules (mean diffusivity [MD]; trace; apparent diffusion coefficient [ADC]). These measurements can either be extracted locally in predefined regions using region of interest (ROI) analysis or tractography or, alternatively, globally using voxel-based analysis (VBA) or tract-based spatial statistics (TBSS). Disruptions to microstructural tissue integrity, such as those found in the neurodegeneration of parkinsonian syndromes can be associated with alterations in anisotropy and diffusivity measures.[3] We therefore performed a systematic review of the literature to assess

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the distribution and nature of these alterations, exploring the potential role of DTI in diagnosis of parkinsonian syndromes and as a candidate biomarker.

METHODS **Literature search and data extraction.** We searched MEDLINE (1946 to February 2012) and EMBASE (1980 to February 2012) databases using terms including "diffusion tensor," "Parkinson*," "progressive supranuclear palsy," "multiple system atrophy," "corticobasal," "lewy bod*," "Richardson*," "Shy Drager," "striatonigral degeneration," "olivopontocerebellar atrophy," "PD," "LBD," "PSP," "CBD," and "MSA" combined with Boolean operators as appropriate. There were no language restrictions, and translation was obtained as necessary. All titles and abstracts from the retrieved articles were screened and the full text of those that may be eligible was obtained. Reference lists of identified studies were searched for additional studies. Two independent assessors (C.J.C., K.P.E.) performed the search, reviewing all articles and extracting data. We included studies if they were published as full text articles and used DTI to compare participants with parkinsonian syndromes (Parkinson disease [PD], progressive supranuclear palsy [PSP], multiple system atrophy [MSA], corticobasal syndrome, PD dementia [PDD], or Lewy body dementia [LBD]) with a healthy control group or with a comparison group with a different parkinsonian syndrome. Only studies with more than 5 patients and with a minimum of 6 diffusion-encoding directions were included to be comprehensive while ensuring sufficient reliability. For the parkinsonian syndromes and dementias, a probable diagnosis by standard diagnostic criteria was considered sufficient for inclusion. Patients with MSA with motor features dominated by either parkinsonism (MSA-P) or cerebellar ataxia were included. We excluded studies that did not use formal diagnostic criteria or have participants with established diagnosis, studies including patients undergoing deep brain stimulation, studies analyzing mixed patient groups jointly, for example, including both idiopathic and vascular parkinsonism, as well as duplicate publications. If 2 or more studies contained the same or overlap sample of patients, only the largest relevant study was included.

From each study, we recorded the following data when available: number of patients and controls, mean age, number of males and females in groups, diagnosis, disease duration, and the use of medications. We recorded the main analysis approach used, all brain structures and abnormalities measured, acquisition characteristics, and field strength of the MRI scanner. The method for labeling neuroanatomy differed among studies, thus for the review, we grouped results according to cerebral lobe (frontal, temporal, parietal, and occipital), structure (substantia nigra [SN], putamen, etc.), or tract (corpus callosum [CC], inferior longitudinal fasciculus, etc.). Cerebral lobes, structures, or tracts that contained a minimum of 1 region with a significantly different ($p < 0.05$) mean anisotropy or MD in group comparison were recorded for each study to provide a neuroanatomical overview of significant differences. TBSS and VBA results reported were taken as significant on corrected p values unless specifically highlighted. The meta-analysis of the SN in PD included studies reporting FA values in or adjacent to the SN as means and SDs and those presenting p values. A conservative estimate of $p = 0.049$ was assumed if p was reported to be $p < 0.05$.

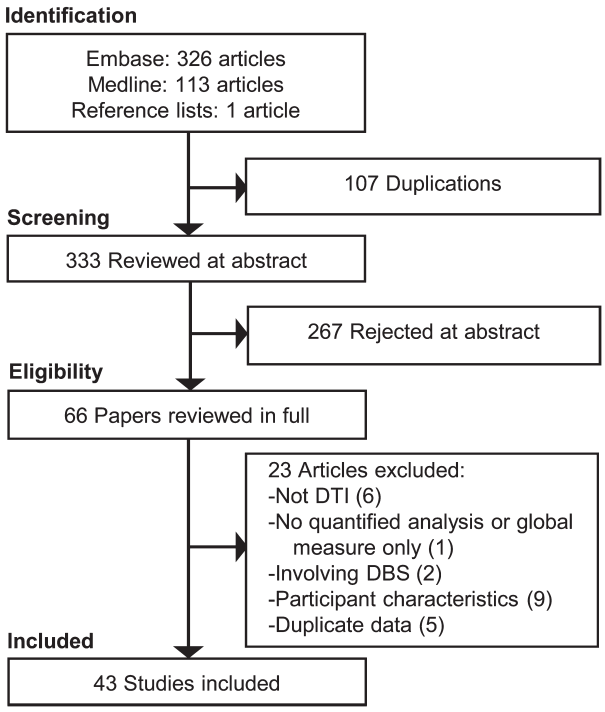
Statistical analysis. Data analysis was performed using Comprehensive Meta-Analysis (version 2.2.048, ©2006; Biostat Inc., Englewood, NJ). Effect size was measured using Hedges' g to correct for bias from small sample size.[4] A random-effects model was selected to calculate the pooled mean effect size. Heterogeneity was assessed using Cochran Q and I^2.[5] Publication bias was examined by visual inspection of funnel plot asymmetry and applying Egger regression intercept test.

RESULTS We identified 333 studies on initial searching. Of these, 43 studies[6–48] were eligible for inclusion with a total of 1,722 participants: 958 with parkinsonian syndromes and 764 controls. A flow diagram of study inclusion is displayed in figure 1. The key details of eligible studies are provided in table 1 (also see tables e-1, e-2, and e-3 on the *Neurology*® Web site at www.neurology.org). An overview of statistically significant FA alterations detected by 3 or more studies is given in figure 2. The ROIs varied across studies.

Parkinson disease. Of a total of 21 studies (table 1), 9 studies measured FA in the SN. All except 1 found a reduction in FA in comparison with healthy controls and the reduction was statistically significant in 7. Effect sizes for the reduction in FA pooled for the 9 ROI studies (figure 3), with a total of 193 patients with PD and 195 controls, showed a large mean effect size (−0.639, 95% confidence interval −0.860 to −0.417, $p < 0.0001$). Studies were not significantly heterogeneous although low-level heterogeneity was detected ($Q[8] = 8.84$, $p = 0.356$, $I^2 = 9.53\%$). Egger regression intercept for publication bias was not significant ($t = 0.765$; 2-tailed $p = 0.469$). Seven of 9 studies included patients taking antiparkinsonian medications, medication details were unavailable for one,[6] and the final study[13] included only medication-naive patients. The study on early, medication-naive patients[13] found on post hoc analysis that the caudal region of the SN had sensitivity and specificity of 100% for differentiating patients with PD from controls. This study, along with another,[24] did not find an association between disease severity and FA in SN. Two other studies[10,26] did find reduced FA in SN correlated with disease severity. Studies focusing on the SN and integrating T2*[20,24] or volumetric analysis[15] with DTI reported that this improved their ability to discriminate patients with PD from healthy controls. There is evidence suggesting that neurodegenerative changes occur outside the SN. When combined with olfactory testing, one study[22] found reduced FA of the anterior olfactory structures in patients with PD vs controls, and another study[18] found that patients with PD and anosmia have reduced FA in white matter near the gyrus rectus compared with controls (or patients with PD) with no olfactory dysfunction. Five studies found reductions in the frontal white matter, 4 significant.[9,11,21,26] Measures of diffusivity were less frequently reported, and often no significant overall differences were detected.

PSP, MSA, and corticobasal syndrome. ***Progressive supranuclear palsy.*** Frontal white matter FA was investigated in 2 ROI

Figure 1 Summary of study selection



DBS = deep brain stimulation; DTI = diffusion tensor imaging.

studies[6,28]; both detected reductions in patients vs controls (table e-1). One VBA study[30] also detected significant frontal FA reductions but another TBSS study[29] did not. One study looked specifically at the CC, using a partitioning method to divide the CC into 5 areas (CC1–CC5).[12] FA in CC1 and CC2 (CC1—prefrontal area, CC2—premotor and supplementary motor area) was significantly lower in patients with PSP than in controls. ADC in CC1 was significantly higher in PSP than controls. Three other studies[27,30,32] also detected reductions in FA in at least 1 region of the CC and 1 study[29] detected an increase. One of 10 studies in PSP detected elevated FA in at least 1 region.[29]

Multiple system atrophy. All studies investigating the cerebellar region, pons, or cerebellar peduncles in participants with MSA found reduced FA in at least 1 region compared with controls (table e-1). Four of these focused on ROIs in the middle cerebellar peduncles, detecting reduced FA.[7,33,35,37] Three studies found an increase in MCP diffusivity measures[7,23,38]; one other VBA study[36] detected no significant diffusivity differences. One study examined the putamen in MSA finding FA reduced and ADC increased[8]; another found elevated FA.[34] Not all studies analyzed MSA-P or MSA–cerebellar ataxia independently but for those that did, reduced FA was similarly detected in the pons and cerebellum for MSA-P vs controls.

Corticobasal syndrome. Three studies[17,28,40] compared participants with corticobasal syndrome and controls (table e-1). A VBA study[40] showed primarily cortical reduction of FA. Two studies[17,40] detected a significant FA reduction in regions of the CC, one a coexistent increase in MD.

Comparing parkinsonian syndromes. Few studies contrasted parkinsonian syndromes directly with each other (table e-2). One study comparing MSA with PD detected FA reductions in the cerebellum in MSA,[8] and increases in diffusivity have been detected in the pons[7,8] and cerebellum.[8] This study[8] also found FA reductions in the pons and putamen in MSA vs PD. Using FA and ADC measures in the pons, a similar sensitivity (70%) and a higher specificity (100%) to differentiate MSA-P from PD was found than with measures of putamen or cerebellum. One study[7] found significantly reduced FA in the middle cerebellar peduncles in MSA compared with PSP or PD. The same study found that, in PSP, FA was significantly reduced and diffusivity was significantly increased in the decussation of superior cerebellar peduncles compared with PD. A study partitioning the CC[12] proposed that reduced FA and elevated ADC in CC1 (prefrontal region) may differentiate PSP from PD with receiver operating characteristic analysis showing reliability of FA (85.7% sensitivity, 65.5% specificity, and 69.4% accuracy) and ADC (100% sensitivity, 75.9% specificity, and 80.6% accuracy).

Dementias: LBD and PDD. Comparisons of PDD with controls found primarily cortical reductions of FA in PDD (table e-3). LBD vs controls comparison had somewhat mixed findings, ranging from local alterations in the inferior longitudinal fasciculus or parietal lobe to widespread reductions in FA. One study, comparing PDD with PD,[9] found significantly reduced FA bilaterally in the posterior cingulum in patients with PDD. PDD and LBD were compared in 1 identified study.[44] Using VBA, statistically significant differences, although reported with uncorrected p values with a cluster size of >50 mm^3, were in the temporooccipital and posterior cingular areas.

DISCUSSION

Overall, studies consistently detected an alteration in anisotropy of at least 1 region in patients with parkinsonian syndromes and related dementias. There were differences in the ROIs studied and the acquisition and analysis characteristics of the studies.

A DTI biomarker for PD? All except one DTI study of PD targeting the SN reported FA reductions, consistent with the recognized neuropathologic hallmark in PD of selective loss of A9 dopaminergic neurons in the SN pars compacta. By the point of onset of clinical symptoms in PD, approximately half of the dopaminergic cells in the SN are thought to have been lost.[49] DTI may offer an opportunity to detect this cell loss in vivo, both to aid initial diagnosis and also to act as a noninvasive biomarker predicting future disease onset and monitoring disease progression. DTI measures, in

Table 1 Diffusion tensor imaging of Parkinson disease vs controls: Subject details, methods, and results

Study (reference)	Group	No. of subjects	Mean age ± SD, y	Field strength, tesla	Direction no.	Analysis method	Regions studied	Differences in fractional anisotropy (statistically significant)	Diffusion changes (statistically significant)
6	PD	12	71.3 ± 7.7	1.5	6	ROI	PMC, BG	↓SN	NA
	C	8	70.1 ± 8.4						
7	PD	12	65.1 ± 7.3	1.5	64	ROI	MCP, DSCP, pons	NS	NS
	C	12	63.4 ± 6.3						
8	PD	21	62 ± 11	3	6	ROI + tract	P, cerebellum, pons	NS	NS
	C	20	62 ± 11						
9	PD	26	70 ± 8.6	1.5	6	ROI	Frontal, temporal, occipital, parietal, cingulate bundles	↓Frontal (L), ↓temporal, ↓occipital	NA
	C	10	70.7 ± 17.4						
10	PD	73	63.6 ± 9.8	1.5	12	ROI	Ca, GP, P, SN, T	↓SN	NS
	C	78	61.9 ± 9.3						
11	PD	12	62.1 ± 12.7	3	12	VBA	VBA	↓Frontal, ↓SLF (R), ↓CC (L)	NS
	C	13	58 ± 7.3						
12	PD	29	67 ± 9	1.5	6	ROI	CC	NS	NS
	C	19	73 ± 5						
13	PD	14	57.2 ± 9.6	3	27	ROI	SN, cerebral peduncle	↓SN	RD: ↑SN, LD: ↓SN, average: nil
	C	14	58						
14	PD	10	63.8 ± 15.7	1.5	12	ROI	CST, SLF, CI, CC genu and splenium	↓CC genu, ↓SLF	MD: ↑SLF, ↑CI, ↑CC genu
	C	10	58.1 ± 8.0						
15	PD	10	63.7 ± 6.7	3	60	ROI	SN	NS	NA
	C	10	64.4 ± 9.9						
16	PD	15	64.6 ± 6.3	1.5	6	ROI	DN, cerebellum, MCP, RN, SCP, T	NS	NS
	C	15	62.4 ± 5.4						
17	PD	14	57.9 ± 7.7	1.5	12	ROI	CC	NS	NS
	C	14	58.6 ± 10.6						
18[a]	PD1	6	50.7 ± 11.3	3	30	TBSS + ROI	POC, gyrus rectus, UF	↓Gyrus rectus (PD2, 3 vs C)	NA
	PD2	9	58.0 ± 5.8					↓POC (PD3 vs C)	
	PD3	9	57.9 ± 7.9						
	C	23	57.3 ± 8.9						
19	PD	29	70.8 ± 4.6	1.5	6	Tract	CC, CI	NS	NS
	C	15	70.7 ± 4.0						
20	PD	30	61.9 ± 11.1	3	30	ROI	T, P, SN, C, pallidum, RN	↓ SN, ↓T	MD: ↑T
	C	22	57.4 ± 9.7						
21	PD	25	58.4 ± 9.8	3	12	VBA	VBA	↓Cerebellum, ↓gyrus rectus (R)	MD: ↑OFC, ↑ITG ↓parietal, ↓PG (L)
	C	25	58.4 ± 9.3						
22	PD	14	56 ± 4.8	1.5	31	ROI	SN, AOS	↓SN, ↓AOS	RD: ↑SN
	C	14	55.2 ± 6.2						
23	PD	20	68.9 ± 11.8	1.5	13	VBM	VBM	NS	NS
	C	20	52.4 ± 19.5						

Continued

Table 1 Continued

Study (reference)	Group	No. of subjects	Mean age ± SD, y	Field strength, tesla	Direction no.	Analysis method	Regions studied	Differences in fractional anisotropy (statistically significant)	Diffusion changes (statistically significant)
24	PD	16	59.2 ± 6.9	3	42	ROI	SN	↓SN	NS
	C	16	57.2 ± 6.8						
25	PD	12	66.3 ± 7.8	3	24	ROI	GP, SN, P, Ca	NS	NS
	C	13	67.6 ± 10.5						
26	PD	12	67.4 ± 8	4	6	ROI and VBA	Frontal, parietal, SN, EC, IC, T, P	↓Frontal, ↓parietal, ↓SN, ↓EC, ↓IC, ↓T (R), ↓P (L)	NS
	C	20	67.2 ± 8						

Abbreviations: AOS = anterior olfactory structures; BG = basal ganglia; C = controls; Ca = caudate; CI = cingulum; CC = corpus callosum; CST = corticospinal tract; DN = dentate nucleus; DSCP = decussation of superior cerebellar peduncles; EC = external capsule; GP = globus pallidus; IC = internal capsule; ITG = inferior temporal gyrus; LD = longitudinal diffusivity; MD = mean diffusivity; MCP = middle cerebellar peduncles; NA = not applicable; NS = not significant; OFC = orbitofrontal cortex; P = putamen; PD = Parkinson disease; PG = precentral gyrus; PMC = premotor cortex; POC = primary olfactory cortex; RD = radial diffusivity; RN = red nucleus; ROI = region of interest; SCP = superior cerebellar peduncles; SN = substantia nigra; SLF = superior longitudinal fasciculus; T = thalamus; TBSS = tract-based spatial statistics; tract = tractography; UF = uncinate fasciculus; VBA = voxel-based analysis; VBM = voxel-based morphometry to diffusion tensor imaging.
[a] PD1 = PD without severe olfactory dysfunction; PD2 = PD with severe microsomia; PD3 = PD with anosmia.

a murine model of PD, were found to correlate with loss of SN dopaminergic neurons.[50] Our meta-analysis detected a large pooled effect size for reduction of FA in the SN. It is not known, however, if these techniques can robustly identify patients with PD, a necessity for translation into a viable biomarker, and conclusions on diagnostic accuracy cannot be drawn from our meta-analysis results. Tantalizingly, post hoc receiver operator characteristic analysis in the caudal SN in one small, early-stage study[13] of nonmedicated patients showed 100% sensitivity and specificity for distinguishing patients with PD from healthy controls. Such work, however, remains experimental and requires replication. Interestingly, although FA was reduced, often no changes in overall diffusivity were detected. This finding could be the result of a relative decrease in axial diffusivity and increase in radial diffusivity, possibly reflecting a mild loss of microstructural integrity without gross tissue loss.

Figure 2 Overview of fractional anisotropy alterations in parkinsonian syndromes

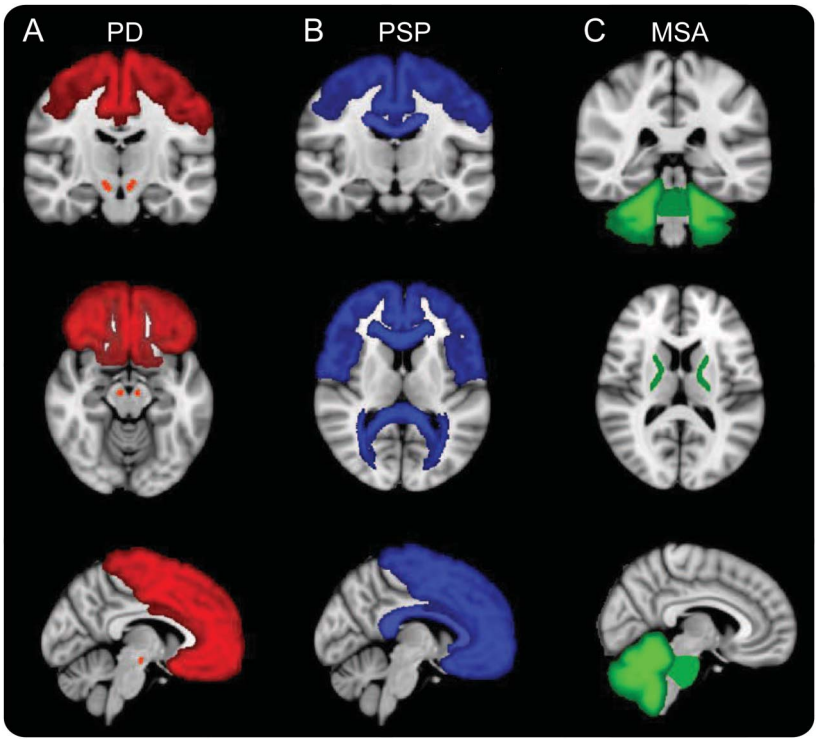
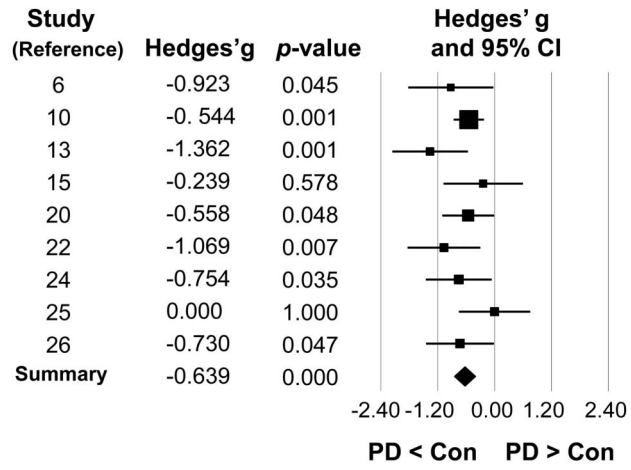


Illustration showing regions where ≥3 studies individually detected a significant ($p < 0.05$) alteration in fractional anisotropy (FA) in comparison with healthy controls. (A) Parkinson disease (PD): substantia nigra (n = 7 studies) and frontal lobe (n = 4). (B) Progressive supranuclear palsy (PSP): corpus callosum (n = 5) and frontal lobe (n = 3). (C) Multiple system atrophy (MSA): cerebellum (n = 5), middle cerebellar peduncle (n = 6), pons (n = 4), and internal capsule (n = 3). All alterations were reductions in FA apart from 1 instance of increase in PSP in the corpus callosum.

Development and validation of disease-specific biomarkers is increasingly important with the focus on developing targeted neuroprotective therapeutics for future at-risk populations and disease-modifying therapy. No published longitudinal studies investigating DTI measures in preclinical or early disease states or the effect of disease progression were identified in the current search. Interestingly, studies in rodent models of PD have detected early reduced FA in the SN.[50,51] Ideally, a correlation between FA reduction in SN and disease severity would be identified, suggesting that this measure may be used as a surrogate marker for monitoring disease progression and efficacy of treatment in neuroprotective trials. Findings, however, are mixed in current studies and it is premature to comment on whether this is feasible.

DTI and differential diagnosis. DTI results are limited and exploratory but provisionally promising for differentiating PD from atypical parkinsonian syndromes. Reductions in FA and elevations in MD in the cerebellum,

Figure 3 Meta-analysis for substantia nigra fractional anisotropy in Parkinson disease vs controls



CI = confidence interval; PD = Parkinson disease.

pons, and cerebellar peduncles may aid in distinguishing MSA from PD and also perhaps PSP. Infratentorial regional anisotropy and diffusivity changes were found in MSA, but these changes were absent in PD. The putamen also showed FA alterations and increased diffusivity in MSA compared with PD or controls. This is consistent with earlier studies, using diffusion-weighted imaging in MSA, showing that putaminal measures of diffusivity can be helpful in differentiating MSA-P from PD.[52] The CC is another early focus of interest.[12,17] It remains to be seen whether these techniques will offer sufficient sensitivity and specificity to be a valid tool in diagnosis. Current findings are encouraging but preliminary and there is not yet a robust way to differentiate these different diseases using DTI from studies.

Nonmotor symptoms can be particularly problematic in PD, with up to 80% of older patients eventually developing associated dementia.[53] A study[9] comparing PDD with PD detected bilateral posterior cingulate FA reduction in PDD, an interesting finding suggesting that the posterior cingulate may have an important role in dementias associated with Lewy bodies but one that requires further verification and direct comparison with Alzheimer disease for which this is also an early area of change.[54] LBDs, PDD, and LBD share common clinical and neurobiological features. Differences among these diseases are gradually being elucidated and they may form part of a continuous spectrum of Lewy body disease. The study[44] comparing PDD and LBD found generally similar regions of reduced FA in both diseases, with more severe white matter abnormalities in LBD. It is possible that in such studies, patients may have a degree of overlap with another dementia pathology, especially Alzheimer disease, which could diminish the differences detected between the 2 diseases. Whether DTI has the capacity to reliably differentiate PDD and LBD or to detect the impending onset of cognitive impairment in PD remains unknown.

Future directions. Future studies could explore whether preclinical DTI findings can be identified to predict development of parkinsonian syndromes and related dementias. The prospect of a sensitive, specific MRI biomarker is clinically highly desirable and further studies are required to target this. Longitudinal studies on large cohorts will be particularly informative and allow measurements of the effect of disease progression. Multimodal imaging, integrating different techniques such as quantification of SN iron, may enhance diagnostic sensitivity and is an important developing research direction. Longitudinal studies may lead to methods to identify those susceptible to developing cognitive dysfunction and subsequent PDD, enabling earlier intervention, as well as delineating the differences between PDD and LBD. There is also a need to investigate the effects in trials of antiparkinsonian medications on diffusion tensor measures. The higher field strengths of ≥3 tesla could yield clinically exciting DTI findings by providing increased signal sensitivity and thus increased image resolution.

Limitations. There are some methodology and data limitations to be considered for this review. The number of studies and the size of studies are modest, limiting the generalizability of the results. No publication bias was detected for the meta-analysis but this cannot be excluded. Although no significant statistical heterogeneity was detected in the meta-analysis of SN in PD, there were differences among the total 43 studies in data acquisition, data analysis, and subject details, with associated limitations. First, interplay between selected image acquisition parameters and factors including signal-to-noise ratio, image resolution, and image distortion influences the accuracy of the diffusion tensor and thus the results derived. Although certain image parameters, such as increasing diffusion-encoding direction number, may be expected to be associated with higher-quality results from first principles, our data did not allow us to confirm this. Second, for data analysis, ROI techniques can fail to detect important differences occurring outside the selected ROIs and may be subject to user bias when manually locating the intended ROI. VBA techniques, conversely, by performing, essentially, voxel-by-voxel statistical comparisons throughout the brain, can be biased toward errors due to multiple comparisons, and issues with smoothing and spatial normalization may lead to inaccuracies.[55] Third, clinical diagnostic criteria were used for patient selection without neuropathologic verification in the studies, thus misdiagnosis cannot be excluded. The stage of a patient's disease, either early or advanced, may influence DTI findings. Patients with early disease were underrepresented in the studies, most likely because clinical

diagnostic accuracy is higher in the later stages. Such early-stage cases would be particularly interesting because this reflects a situation in which a potential DTI diagnostic tool would have clear utility. Studies are similarly lacking that use undifferentiated cases with diagnostic uncertainty to explore whether imaging predicts subsequent clinical diagnosis. Patient groups also often included those who were already initiated on therapy, and antiparkinsonian medications are another factor that may modulate DTI findings. The limited number and size of studies precluded meaningful investigation of the effects of these additional study variables.

CONCLUSION DTI may prove valuable in supporting the diagnosis in parkinsonian syndromes and could have a role in detecting premanifest disease and monitoring progression and drug therapeutic impact. Studies using DTI on larger cohorts of patients with parkinsonian syndromes, particularly longitudinal studies including at-risk and early-disease populations, are needed to investigate some encouraging preliminary findings. Future research will be facilitated by the increasing availability of higher field and multimodal neuroimaging and would benefit from greater congruity in MRI protocols. The complexity of the parkinsonian syndromes, illustrated by the increasing recognition of different phenotypes of PD,[56] suggests it is likely that DTI would be used not in isolation but in combination with other relevant biomarkers.

AUTHOR CONTRIBUTIONS

Dr. Cochrane: drafting/revising the manuscript, study concept or design, acquisition of data, analysis or interpretation of data. Dr. Ebmeier: revising the manuscript, study concept or design, acquisition of data, analysis or interpretation of data.

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