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Diffusion Tensor Imaging of Parkinson's Disease, Atypical Parkinsonism and Essential Tremor

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Summary

Diffusion tensor imaging could be useful in characterizing movement disorders because it non-invasively examines multiple brain regions simultaneously. We report a multi-target imaging approach focused on the basal ganglia and cerebellum in Parkinson's disease, parkinsonian variant of multiple system atrophy, progressive supranuclear palsy, essential tremor, and healthy controls. Seventy-two subjects were studied with a diffusion tensor imaging protocol at 3 Tesla. Receiver operating characteristics analysis was performed to directly compare groups. Sensitivity and specificity values were quantified for control vs. movement disorder (92% sensitivity, 88% specificity), control vs. parkinsonism (93% sensitivity, 91% specificity), Parkinson's disease vs. atypical parkinsonism (90% sensitivity, 100% specificity), Parkinson's disease vs. multiple system atrophy (94% sensitivity, 100% specificity), Parkinson's disease vs. progressive supranuclear palsy (87% sensitivity, 100% specificity), multiple system atrophy vs. progressive supranuclear palsy (90% sensitivity, 100% specificity), and Parkinson's disease vs. essential tremor (92% sensitivity, 87% specificity). The brain targets varied for each comparison, but the substantia nigra, putamen, caudate, and middle cerebellar peduncle were the most frequently selected brain regions across classifications. These results indicate that using diffusion tensor imaging of the basal ganglia and cerebellum accurately classifies subjects diagnosed with Parkinson's disease, atypical parkinsonism, and essential tremor and clearly distinguishes them from control subjects.

Keywords

DTI; Parkinsonism; essential tremor; basal ganglia; cerebellum

Introduction

The diagnosis of Parkinson's disease (PD) in the early stages can be challenging because symptoms often overlap with other movement disorders, such as the parkinsonian variant of multiple system atrophy (MSAp), progressive supranuclear palsy (PSP), and essential tremor (ET)^{1–3}. Advances in neuroimaging have led to a greater understanding of which brain regions are affected in these movement disorders⁴, with the basal ganglia and regions of the cerebellum commonly implicated. Using diffusion tensor imaging (DTI), several laboratories have confirmed that fractional anisotropy in the substantia nigra is reduced in subjects with PD compared with control subjects^{5–9}. ET and PD subjects have different fractional anisotropy patterns in the dentate nucleus and superior cerebellar peduncle¹⁰. DTI has also shown promise at differentiating PD from atypical parkinsonism. Diffusion-weighted imaging has been used to discriminate MSAp from PD and healthy controls based on putaminal^{11–13} and pallidal¹² diffusion coefficients. However, in other studies this same technique has shown mixed results for distinguishing subjects with PSP from MSAp^{14, 15}. In a recent study, regional apparent diffusion coefficients calculated from multiple brain regions, including the basal ganglia, thalamus, brainstem, and cerebellum, were shown to differentiate MSA (primarily the cerebellar subtype), PSP, PD, and healthy control subjects at the group level¹⁶, but receiver operating characteristic curves were not reported and apparent diffusion coefficients from multiple brain regions were not combined to help

improve group classification. Despite the promise that DTI has for understanding structural differences across movement disorders, the literature still lacks a robust method that distinguishes PD, MSAp, PSP, ET, and control subjects using the same technique in one study.

Rather than evaluating early-stage patients when the differential diagnosis may be challenging, the current study evaluated patients with PD, MSAp, PSP, and ET when the diagnosis reached probable criteria, with the future goal of evaluating patients using the methodology developed in this paper at an earlier disease stage. In particular, we extracted multiple DTI measures from multiple basal ganglia and cerebellar regions that are known to be affected in these movement disorders. We performed a series of analyses on these data to evaluate how well DTI distinguishes between movement disorders in comparisons that have clinical importance. The goal was to determine if DTI can distinguish: 1) movement disorder (PD/MSAp/PSP/ET) from control, 2) parkinsonism (PD/MSAp/PSP) from control, 3) PD from atypical parkinsonism (MSAp and PSP), 4) PD from MSAp, 5) PD from PSP, 6) MSAp from PSP, and 7) PD from ET.

Methods

Subjects

Seventy-two subjects participated between 2009 and 2011 (PD = 15, MSAp = 14, PSP = 12, ET = 14, Control = 17). Patients were diagnosed by movement disorders specialists at Rush University or Northwestern University using the following criteria: diagnosis of PD based on UK PD Society Brain Bank criteria¹⁷, probable MSAp based on American Academy of Neurology and American Autonomic Society¹⁸, probable PSP based on NINDS-PSP criteria¹⁹, and ET based on the Statement of the Movement Disorders Society²⁰. Diagnosis of all patients was reconfirmed 18 months after DTI by reviewing patient charts. Clinical features of the PSP patients were consistent with the Steele-Richardson-Olszewski subtype rather than the PSP-P subtype^{19, 21}. The controls were healthy volunteers who did not have a prior history of neurological or psychiatric disease. Patient and control group summary characteristics are in Table 1. PD, MSAp, and PSP subjects were matched at inclusion based on UPDRS-III scores. More detailed UPDRS motor scores are included in Appendix e-1 along with medications each subject was taking when enrolled in the study. Since the effects of medication on DTI are not known, we tested all patients after overnight withdrawal from anti-tremor and anti-parkinsonian medications. Subjects gave written informed consent approved.

DTI acquisition

Data were acquired on a GE 3.0-Tesla Signa HDx scanner using a customized DTI pulse sequence that corrects for eddy current-induced distortion^{5, 22, 23}. Images were acquired using an 8-channel phased-array head coil. The data acquisition parameters were: TR = 4,500 ms, TE = 82 ms, b values = 0, 1000 s/mm², diffusion gradient directions = 27, FOV = 200 mm², k-space matrix = 192 × 128, image space matrix = 256 × 256 (image interpolation was done using a homodyne reconstruction method²⁴), NEX = 4, slice thickness = 4 mm, slice skip = 1 mm, slice number = 15. Two scans were performed to cover the basal ganglia and cerebellum. In the first, the top slice was placed in the axial plane approximately 4 mm superior to the corpus callosum. In the second, the bottom slice was placed in the axial plane approximately 4 mm below the bottom of the cerebellum.

DTI analysis

All diffusion tensor calculations were carried out using DtiStudio²⁵. Images were inspected for artifacts related to eddy currents and motion. Eddy current distortion was properly

corrected in the customized pulse sequence. AFNI was used to quantify head motion, which was within 1 mm for all subjects. We did not exclude any data. We calculated four DTI measures to use in classification: 1) fractional anisotropy (FA), a measure of diffusion anisotropy, 2) radial diffusivity (RD), the average diffusivity of the two non-principal eigenvalues of the diffusion tensor, 3) longitudinal diffusivity (LD), diffusivity corresponding to the principal eigenvector, and 4) mean diffusivity (MD), the average of all three eigenvalues of the diffusion tensor^{26, 27}.

ROIs were selected based on previous pathological and neuroimaging findings in these movement disorders^{5, 10, 12, 28–32}. Figure 1 shows the B0 ($b = 0$) images and colormaps of relevant slices for the (A) basal ganglia and red nucleus and (B) cerebellum to illustrate the number and location of ROIs. All ROIs were circular and drawn bilaterally. Data were averaged across sides since we did not observe laterality effects. Since each structure has a unique size and subcomponents exist within the various structures, ROIs were drawn to match the size of each structure. Three ROIs of 5 voxels in diameter were drawn in the caudate, putamen, and globus pallidus. The FA image was used to visualize the external capsule, and the putaminal ROIs were placed immediately medial to it. In the red nucleus, one ROI (4 voxels in diameter) was placed, and in the substantia nigra three ROIs (4 voxels in diameter) were placed consistent with previous work⁵. In the cerebellum, ROIs were drawn with reference to the color map: two ROIs (3 voxels in diameter) were placed in the superior cerebellar peduncle, two (6 voxels in diameter) in the middle cerebellar peduncle, and one (3 voxels in diameter) in the inferior cerebellar peduncle. Three ROIs in the dentate nucleus (5 voxels in diameter) were drawn with reference to the B0 image³³. The combination of FA, RD, LD, and MD measures in each of the 21 ROIs yielded a total of 84 variables.

A standard noise threshold was set within DtiStudio to create a mask for the diffusion tensor calculations, and each image was visually inspected to ensure that signal loss did not occur in the ROIs or in surrounding tissue. All ROIs were drawn blinded to group status by an experienced investigator based on the methods described above. A separate individual, also blinded to diagnosis, extracted the DTI measures for each ROI. To determine inter-rater reliability, a third trained person, again blind to diagnosis, drew ROIs on five randomly selected subjects per group.

Statistics

We performed receiver operating characteristic (ROC) analyses for comparisons between groups³⁴ using custom C++ code based on the ROC analysis approach³⁵. We compared control vs. movement disorder (PD/MSAp/PSP/ET), control vs. parkinsonism (PD/MSAp/PSP), PD vs. parkinsonism (MSAp/PSP), PD vs. MSAp, PD vs. PSP, MSAp vs. PSP, and PD vs. ET.

The ROC analysis selected the top-ranked variables associated with the disease classification by maximizing the area under the curve (AUC measures the accuracy of a test in correctly identifying subjects with the targeted condition) using the classification probabilities estimated from the logistic regression as an input. A forward selection procedure was used examining one variable at a time. Selection was started with the variable that gave the highest AUC, and then each of the remaining variables were added into the logistic model to estimate the classification probabilities. The second variable selected was the variable that gave the highest AUC together with the first variable. The number of selected top-ranked variables was chosen to be less than 10% of the combined number of subjects for each model classification to ensure stable estimates³⁶. The number of variables for the comparisons were 7 (control vs. movement disorder), 6 (control vs. parkinsonism), 4 (PD vs. parkinsonism), 3 (PD vs. MSAp), and 2 (PD vs. PSP, MSAp vs. PSP, and PD vs.

ET). The set of DTI measures that gave the highest AUC are reported for each model. Sensitivity and specificity were quantified for each model for each comparison. Intraclass correlation coefficients were obtained from a two-way mixed model to quantify inter-rater reliability of experienced and novice ROI drawers.

Results

Comparing subject characteristics

Neither age of subjects nor proportion of males and females differed significantly across groups (Table 1). Years since first reported symptom differed significantly across the four patient groups. Since this variable was significant, we included this variable in the ROC analysis to determine if it was a predictor of disease group. The UPDRS-III scores were not different across groups with parkinsonism.

Distinguishing patients from healthy controls

Figure 2 and Table e-3 in the Appendix provide a summary of the classification models described below. The first step of the analysis was to determine how well the DTI measures identified the disease state from control. Subjects with PD, MSAP, PSP and ET were included as one group and DTI measures in this combined group were compared against DTI in the healthy control group. The AUC was 0.98 (sensitivity = 92%; specificity = 88%) in this comparison with seven diffusion variables identified in caudate, pallidum, substantia nigra, red nucleus, middle and inferior cerebellar peduncles. Comparing subjects with parkinsonism (PD, MSAP, and PSP) to healthy controls, the AUC increased to 0.99 (sensitivity = 93%; specificity = 91%) using DTI measures from the putamen, pallidum, substantia nigra, red nucleus, and middle cerebellar peduncle.

Distinguishing PD from atypical parkinsonism

To determine how well the DTI measures distinguished PD from atypical parkinsonism, MSAP and PSP were pooled and the DTI measures in this combined group were compared against DTI measures in the PD group. In this comparison, the AUC was 0.99 (sensitivity = 90%; specificity = 100%) using DTI measures from three ROIs: putamen, substantia nigra, and dentate nucleus.

Distinguishing between parkinsonian groups

The next step of analysis was to determine how well the DTI measures separated the three pairs of parkinsonism from each other: PD from MSAP, PD from PSP, and MSAP from PSP. The AUC was 0.99 (sensitivity = 94%; specificity = 100%) for PD vs. MSAP using DTI measures from substantia nigra and middle cerebellar peduncle. For PD vs. PSP, the AUC was 0.96 (sensitivity = 87%; specificity = 100%) using DTI measures from putamen and substantia nigra. To distinguish MSAP from PSP, the AUC was 0.97 (sensitivity = 90%; specificity = 100%) using DTI measures from caudate and middle cerebellar peduncle.

Distinguishing PD from ET

The final step of analysis was to determine how well the DTI measures distinguished PD from ET. The AUC was 0.96 (sensitivity = 92%; specificity = 87%) using DTI measures from the caudate and substantia nigra.

Inter-rater reliability

Intraclass correlations of FA values for the basal ganglia, red nucleus, and cerebellum, between the experienced ROI drawer and the novice ROI drawer were all above 0.90.

Discussion

This is the first study to combine multiple DTI measures and target regions in the basal ganglia, red nucleus, and cerebellum to provide accurate classification of individual subjects with PD, MSAP, PSP, and ET. Figure 2 provides a roadmap differentiating the movement disorders based on specific brain regions and dependent measures needed in each group classification. This multi-target approach yielded consistent targets in the caudate, putamen, globus pallidus, substantia nigra, red nucleus and middle cerebellar peduncle across the different subject group comparisons. A key point is that the pattern of DTI targets and measures that yielded the highest AUC for differentiating these movement disorders was unique for each classification. It is also important to emphasize that we were interested in which combination of brain areas and DTI measures provided the best classification of the groups. Therefore, areas beyond those that provided the best classification could still be affected by the diseases.

Pathologically, there is substantial cell loss in the substantia nigra of PD as well as MSAP and PSP^{21, 29, 32}, but not ET³⁷. We showed that fractional anisotropy, radial diffusivity, and longitudinal diffusivity from the substantia nigra were DTI measures that were essential in most group classifications. The administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a murine model of PD demonstrated that these same measures derived from DTI increased (radial diffusivity and longitudinal diffusivity) or decreased (fractional anisotropy) within 7 days following MPTP administration³⁸. The findings (Table e-3) confirm prior studies from various laboratories that fractional anisotropy is reduced in the substantia nigra of PD when compared with control subjects^{5-9, 39}. Most importantly, the findings demonstrate that DTI of the substantia nigra is insufficient to differentiate PD from these other movement disorders, even though it was a critical variable that was included in all but one of the classifications of Figure 2. Additional regions that improved the classification model in Figure 2 were the caudate, putamen, globus pallidus, red nucleus, superior, middle, and inferior cerebellar peduncles, and dentate nucleus.

Instead of combining measures across multiple targets, most prior studies have focused on selected regions when comparing atypical parkinsonism to PD. Three areas that have shown promise are the putamen, pallidum, and pons, which are known to degenerate in MSAP³². Trace values from the putamen and pallidum have been shown to be increased and FA values in the pons decreased in MSAP compared to controls and subjects with PD¹². When distinguishing nine MSAP subjects from nine PD subjects trace values (equivalent to mean diffusivity) from the putamen revealed an AUC of 1.0¹³. Further, sensitivity and specificity for FA values were 70% and 100% in the pons and 70% and 87.5% in the putamen to differentiate 10 MSAP patients from 21 PD patients⁴⁰. Importantly, these authors suggest that FA values and apparent diffusion coefficients considered together provided better classification than just one measure alone. Our results support this. Although the present study did not identify the putamen as a region for distinguishing MSAP from PD, our results identified the putamen as an important ROI when comparing control vs. PD/MSAP/PSP, PD vs. MSAP/PSP, and PD vs. PSP. Also, measures from the pallidum were included in our classification for control vs. PD/MSAP/PSP/ET and control vs. PD/MSAP/PSP, which is in agreement with prior work, indicating the importance of DTI measures from the pallidum¹².

The aforementioned analyses were performed in gray matter regions, including substantia nigra, putamen and globus pallidus. Although these areas are not the typical targets for DTI studies, gray matter diffusion anisotropy changes have been reported in brain maturation⁴¹, aging⁴², and other neurological disorders⁴³. The underlying mechanism for such change has not been understood as thoroughly as white matter changes, and future studies are needed to explore this important area.

In this study, we have also examined changes of diffusion parameters in white matter. Within the cerebellum, diffusion-weighted imaging has shown that the apparent diffusion coefficient from the superior cerebellar peduncle provides accurate classification between PSP vs. PD^{15, 44} and between PSP vs. MSAP¹⁵. Our analytic approach examined all four DTI measures from all ROIs. At each iteration, the brain target and measure with the strongest classification was included based on the AUC. With this approach, a promising ROI may be left out because another region had a slightly greater AUC. This was the case for the superior cerebellar peduncle in the comparison of PD vs. PSP. In this contrast, the first variable was fractional anisotropy from the substantia nigra and the second variable was longitudinal diffusivity from the putamen providing an AUC of 0.96. If we included fractional anisotropy from both substantia nigra and superior cerebellar peduncle, the AUC would have been equal to 0.94, which although still good, was not the highest AUC possible. Our findings are consistent with post-mortem studies that demonstrate that the basal ganglia and superior cerebellar peduncle are affected by neurodegeneration in PSP^{30, 31}. To maintain stability in the parameter estimates in the logistic regression, the number of variables was constrained to be 10% of the number of subjects in each comparison³⁶. Thus, future work with larger sample sizes could identify additional brain targets and DTI measures using this approach. In addition, the multi-parametric approach can be further extended to other diffusion imaging parameters obtained from not only the diffusion tensor model but also other advanced diffusion models for brain tissue.

The current study has several important caveats. Each subject was diagnosed by neurologists who specialize in movement disorders using probable diagnostic criteria, the highest level of diagnostic certainty short of autopsy confirmation. Although studies indicate that such a diagnosis for PD and atypical parkinsonism have high sensitivity and specificity when performed by a neurologist specializing in movement disorders¹, the current findings may have been different if we could base the diagnosis on future neuropathology. Further, our sensitivity and specificity findings may not apply when the diagnosis is less certain, and this is a focus of future studies. Finally, the current study focused on the basal ganglia and cerebellum. Including targets in the pons could prove useful for classifying MSAP, and including targets in the cortex could prove important for differentiating MSAP, PD, PSP, and ET, particularly in later stages. Although not the same technique, recent network approaches with metabolic imaging have proven beneficial by combining data from the cortex in distinguishing PD, MSA, and PSP⁴⁵.

In summary, the current findings demonstrate that multiple DTI measures from multiple targets in the basal ganglia, red nucleus, and cerebellum accurately classify control subjects and patients with PD, MSAP, PSP, and ET. If these findings are replicated in a larger cohort across multiple sites, this readily available approach may have utility outside of specialized research centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain*. 2002; 125(Pt 4):861–870. [PubMed: 11912118]
2. Michell AW, Lewis SJ, Foltynie T, Barker RA. Biomarkers and Parkinson's disease. *Brain*. 2004; 127(Pt 8):1693–1705. [PubMed: 15215212]
3. Lang AE, Mikulis D. A new sensitive imaging biomarker for Parkinson disease? *Neurology*. 2009; 72(16):1374–1375. [PubMed: 19129504]
4. Mahlknecht P, Hotter A, Hussl A, Esterhammer R, Schocke M, Seppi K. Significance of MRI in diagnosis and differential diagnosis of Parkinson's disease. *Neurodegener Dis*. 2010; 7(5):300–318. [PubMed: 20616565]
5. Vaillancourt DE, Spraker MB, Prodoehl J, et al. High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease. *Neurology*. 2009; 72(16):1378–1384. [PubMed: 19129507]
6. 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(1):90–97. [PubMed: 21850668]
7. Du G, Lewis MM, Styner M, et al. Combined R2* and diffusion tensor imaging changes in the substantia nigra in Parkinson's disease. *Mov Disord*. 2011; 26(9):1627–1632. [PubMed: 21618607]
8. Rolheiser TM, Fulton HG, Good KP, et al. Diffusion tensor imaging and olfactory identification testing in early-stage Parkinson's disease. *J Neurol*. 2011; 258(7):1254–1260. [PubMed: 21287185]
9. Peran P, Cherubini A, Assogna F, et al. Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. *Brain*. 2010; 133(11):3423–3433. [PubMed: 20736190]
10. Nicoletti G, Mannes D, Novellino F, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. *Neurology*. 2010; 74(12):988–994. [PubMed: 20308683]
11. Schocke MF, Seppi K, Esterhammer R, et al. Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. *Neurology*. 2002; 58(4):575–580. [PubMed: 11865135]
12. Schocke MF, Seppi K, Esterhammer R, et al. Trace of diffusion tensor differentiates the Parkinson variant of multiple system atrophy and Parkinson's disease. *Neuroimage*. 2004; 21(4):1443–1451. [PubMed: 15050569]
13. Kollensperger M, Seppi K, Liener C, et al. Diffusion weighted imaging best discriminates PD from MSA-P: A comparison with tilt table testing and heart MIBG scintigraphy. *Mov Disord*. 2007; 22(12):1771–1776. [PubMed: 17579357]
14. Seppi K, Schocke MF, Esterhammer R, et al. Diffusion-weighted imaging discriminates progressive supranuclear palsy from PD, but not from the parkinson variant of multiple system atrophy. *Neurology*. 2003; 60(6):922–927. [PubMed: 12654954]
15. Nicoletti G, Tonon C, Lodi R, et al. Apparent diffusion coefficient of the superior cerebellar peduncle differentiates progressive supranuclear palsy from Parkinson's disease. *Mov Disord*. 2008; 23(16):2370–2376. [PubMed: 18816803]
16. Tsukamoto K, Matsue E, Kanasaki Y, et al. Significance of apparent diffusion coefficient measurement for the differential diagnosis of multiple system atrophy, progressive supranuclear palsy, and Parkinson's disease: evaluation by 3.0-T MR imaging. *Neuroradiology*. 2012; 54(9):947–955. [PubMed: 22274571]
17. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. 1992. *Neurology*. 2001; 57(10 Suppl 3):S34–38. [PubMed: 11775598]
18. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci*. 1999; 163(1):94–98. [PubMed: 10223419]
19. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996; 47(1):1–9. [PubMed: 8710059]
20. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee *Mov Disord*. 1998; 13 (Suppl 3):2–23.

21. Hardman CD, Halliday GM, McRitchie DA, Cartwright HR, Morris JG. Progressive supranuclear palsy affects both the substantia nigra pars compacta and reticulata. *Exp Neurol*. 1997; 144(1): 183–192. [PubMed: 9126169]
22. Poonawalla, AH.; Zhou, XJ. Correction of eddy currents in EPI-based diffusion tensor imaging. *Proc Intl Soc Magn Reson Med*; 2001; Glasgow, Scotland. 2001. p. 736
23. Vaillancourt DE, Spraker MB, Prodoehl J, Zhou XJ, Little DM. Effects of aging on the ventral and dorsal substantia nigra using diffusion tensor imaging. *Neurobiology of aging*. 2012; 33(1):35–42. [PubMed: 20359780]
24. Noll DC, Nishimura DG, Macovski A. Homodyne detection in magnetic resonance imaging. *IEEE Trans Med Imaging*. 1991; 10(2):154–163. [PubMed: 18222812]
25. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*. 2004; 230(1):77–87. [PubMed: 14645885]
26. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J*. 1994; 66(1):259–267. [PubMed: 8130344]
27. Hasan KM, Narayana PA. Retrospective measurement of the diffusion tensor eigenvalues from diffusion anisotropy and mean diffusivity in DTI. *Magn Reson Med*. 2006; 56(1):130–137. [PubMed: 16755537]
28. Axelrad JE, Louis ED, Honig LS, et al. Reduced Purkinje cell number in essential tremor: a postmortem study. *Archives of neurology*. 2008; 65(1):101–107. [PubMed: 18195146]
29. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain*. 1991; 114 (Pt 5):2283–2301. [PubMed: 1933245]
30. Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol*. 1999; 246(Suppl 2):II6–15. [PubMed: 10525997]
31. Tsuboi Y, Slowinski J, Josephs KA, Honer WG, Wszolek ZK, Dickson DW. Atrophy of superior cerebellar peduncle in progressive supranuclear palsy. *Neurology*. 2003; 60(11):1766–1769. [PubMed: 12796528]
32. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord*. 1997; 12(2):133–147. [PubMed: 9087971]
33. Nicoletti G, Mannens D, Novellino F, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. *Neurology*. 74(12):988–994. [PubMed: 20308683]
34. Zhou, X.; Obuchowski, NA.; McClish, DK. Statistical methods in diagnostic medicine: Wiley Series in Probability and Statistics. 2002.
35. Li J, Fine JP. ROC analysis with multiple classes and multiple tests: methodology and its application in microarray studies. *Biostatistics*. 2008; 9(3):566–576. [PubMed: 18304996]
36. Agresti, A. An Introduction to categorical data analysis: Wiley Series in Probability and Statistics. 2007.
37. Louis ED, Faust PL, Vonsattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain*. 2007; 130(Pt 12):3297–3307. [PubMed: 18025031]
38. Boska MD, Hasan KM, Kibuule D, et al. Quantitative diffusion tensor imaging detects dopaminergic neuronal degeneration in a murine model of Parkinson's disease. *Neurobiol Dis*. 2007; 26(3):590–596. [PubMed: 17428671]
39. Yoshikawa K, Nakata Y, Yamada K, Nakagawa M. Early pathological changes in the parkinsonian brain demonstrated by diffusion tensor MRI. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004; 75(3):481–484.
40. Ito M, Watanabe H, Kawai Y, et al. Usefulness of combined fractional anisotropy and apparent diffusion coefficient values for detection of involvement in multiple system atrophy. *J Neurol Neurosurg Psychiatry*. 2007; 78(7):722–728. [PubMed: 17353258]
41. Mukherjee P, Miller JH, Shimony JS, et al. Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *AJNR Am J Neuroradiol*. 2002; 23(9):1445–1456. [PubMed: 12372731]
42. Pfefferbaum A, Adalsteinsson E, Rohlfing T, Sullivan EV. Diffusion tensor imaging of deep gray matter brain structures: effects of age and iron concentration. *Neurobiology of aging*. 2010; 31(3): 482–493. [PubMed: 18513834]

43. Bozzali M, Cercignani M, Sormani MP, Comi G, Filippi M. Quantification of brain gray matter damage in different MS phenotypes by use of diffusion tensor MR imaging. *AJNR Am J Neuroradiol*. 2002; 23(6):985–988. [PubMed: 12063230]
44. Rizzo G, Martinelli P, Manners D, et al. Diffusion-weighted brain imaging study of patients with clinical diagnosis of corticobasal degeneration, progressive supranuclear palsy and Parkinson's disease. *Brain*. 2008; 131(Pt 10):2690–2700. [PubMed: 18819991]
45. Tang CC, Poston KL, Eckert T, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol*. 2010; 9(2):149–158. [PubMed: 20061183]

Figure 1.

Regions of interest (ROI) drawings for the basal ganglia and cerebellum. **A**, shows three images from the DTI analysis: B0 ($b = 0$) image (analogous to T2-weighted image), fractional anisotropy (FA) map, and color map. These images were used to draw ROIs in the caudate nucleus (red circles), putamen (white circles), globus pallidus (yellow circles), substantia nigra (green circles), and red nucleus (blue circles). The ROIs were always placed on the image where the structure can be viewed. All four DTI measures were extracted from each ROI. **B**, shows the same image type as in part A including B0 image, FA map, and colormap. ROIs are shown in the superior cerebellar peduncle (red circles), middle cerebellar peduncle (white circles), inferior cerebellar peduncle (yellow circles), and dentate nucleus (green circles). Note that the ROIs for the peduncles were drawn on the color map, whereas the dentate ROIs were drawn on the B0 image.

Group analysis	AUC	Sen	Spec	Caudate	Putamen	GP	SN	RN	SCP	MCP	ICP	Dentate
Control vs. ET/PD/MSAp/PSP	0.98	92%	88%	FA ₂		RD ₂	FA ₁ FA ₃	LD ₁		RD ₁	RD ₁	
Control vs. PD/MSAp/PSP	0.99	93%	91%		FA ₃	RD ₂ LD ₃	RD ₃	MD ₁		RD ₂		
PD vs. MSAp/PSP	0.99	90%	100%		LD ₁ LD ₃		FA ₃					MD ₁
PD vs. MSAp	0.99	94%	100%				FA ₃		RD ₂	RD ₁		
PD vs. PSP	0.96	87%	100%		LD ₁		FA ₃					
MSAp vs. PSP	0.97	90%	100%	FA ₃						RD ₂		
PD vs. ET	0.96	92%	87%	FA ₃			FA ₃					

Figure 2.

Findings from the logistic regression and receiver operating characteristic analyses. Area under the curve (AUC) was the primary outcome variable in the study and is reported for each comparison. Sensitivity (Sen) and specificity (Spec) are also shown. The dark gray indicates the regions of the brain included in each comparison. The dependent measures included for each comparison are listed in each dark gray box. Subscript identifies the ROI number for each region (1 = anterior, 2 = middle, 3 = posterior). FA is fractional anisotropy, RD is radial diffusivity, LD is longitudinal diffusivity, and MD is mean diffusivity.

Table 1

Subject Characteristics

	PD n=15	MSAp n=14	PSP n=12	ET n=14	Control n=17	p-value
Age	62.7 (7.7)	64.3 (8.9)	70.7 (5.6)	61.6 (11.0)	62.9 (9.0)	p > .05 ANOVA
UPDRS-III	30 (8.9)	39.2 (14.6)	33.1 (15.5)	na	na	p > .05 ANOVA
Female Sex	2 (13%)	6 (43%)	7 (58%)	8 (53%)	7 (41%)	p > .05 Chi-square
First reported symptoms	10.5 (7.3)	7.4 (4.0)	10.5 (2.5)	28.2 (21.0)	na	**p < .001 ANOVA