

Title: Efficacy of diffusion tensor MR tractography in differentiating Parkinson's disease from Parkinson's-plus syndromes.

A. Study Purpose and Rationale

Parkinsonism constitutes a relatively well-established syndrome comprised of some combination of six cardinal features: rest tremor, rigidity, gait disturbances, bradykinesia-hypokinesia, flexed posture and loss of postural reflexes, and the freezing phenomenon.¹ Causes of parkinsonism are myriad, and the particular syndrome responsible for a patient's parkinsonism is often only discoverable (in life) through the demonstration of additional symptoms or a differential response to pharmacotherapy. Accurate and early determination of the etiology of parkinsonism presents a special challenge to neurologists: no blood, physiologic, or neuroimaging tests have yet been shown to provide definitive diagnosis of the root cause of a patient's parkinsonism. In particular, no highly sensitive and specific test exists to distinguish between idiopathic primary parkinsonism (Parkinson's Disease; PD) and the so-called Parkinson-plus syndromes (PPS), which include multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), among others.^{2,3}

Diagnosis of PD and Parkinson-plus syndromes can only be conclusively provided with post-mortem neuropathologic examination. Current practice thus relies on clinical examination to differentiate among the causes of parkinsonism, with PD defined as the presence of at least two of the cardinal PD symptoms (rest tremor, bradykinesia, or rigidity). Several additional clinical parameters are frequently assessed in distinguishing between PD and a PPS. In general, PD is associated with symptoms beginning unilaterally and, even with eventual bilateral involvement, remaining asymmetrical. Furthermore, PD patients almost all manifest a rest tremor.^{2,3} In contrast, MSA tends to strike at a younger age, begin symmetrically, and to lack a rest tremor. MSA can present with rest tremor and asymmetric symptoms, however, reducing the confidence with which physicians can distinguish it from PD clinically.⁴ Response to levodopa is currently the single most reliable method to distinguish PD from a PPS. PD patients almost always respond to levodopa initially, while patients with a PPS tend to be unresponsive or only minimally responsive. While non-responsiveness to levodopa strongly suggests a non-primary form of parkinsonism, a positive response to levodopa

¹ Rowland, L.P. Merritt's Neurology, 11th Edition. 2005: Lippincott Williams & Williams, Philadelphia, PA.

² Lang, A.E., Lozano, A.M., 1998a. Parkinson's disease. First of two parts. N. Engl. J. Med. 339, 1044 – 1053.

³ Lang, A.E., Lozano, A.M., 1998b. Parkinson's disease. Second of two parts. N. Engl. J. Med. 339, 1130 – 1143.

⁴ Quinn, N.P., Marsden, C.D., 1993. The motor disorder of multiple system atrophy. J. Neurol. Neurosurg. Psychiatry 56, 1239 – 1242.

does not conclusively indicate the presence of PD, as PPS patients too can demonstrate a response to levodopa, particularly in the early stages.¹⁻⁴

MSA is a diagnosis that encompasses four previously distinct syndromes: striatonigral degeneration (SND; Parkinson-type), olivopontocerebellar degeneration (OPCD), Shy-Drager syndrome, and parkinsonism-amyotrophy syndrome. Of these four syndromes, only SND presents with purely parkinsonian characteristics; Shy-Drager syndrome is associated with autonomic dysfunction, OPCD is associated with atypical (for PD) cerebellar signs, and the amyotrophic variant involves pathology of the anterior horn cells of the spinal cord.^{1,4} Neuropathologically, MSA is relatively well-characterized. Neuronal loss and gliosis are typically found in the substantia nigra, globus pallidus, neostriatum, cerebellum, inferior olives, basis pontine nuclei, intermediolateral horn cells, anterior horn cells, and corticospinal tracts.^{1,4} This is in contrast to PD proper, in which cellular loss primarily takes place in the substantia nigra.¹⁻³ The observation that all four MSA syndromes demonstrate oligodendroglial cytoplasmic inclusions containing α -synuclein, ubiquitin, and *tau* protein (among others), raised the possibility of using magnetic resonance spectroscopy (MR-S) as a testing modality.⁵ In addition, MR volumetry has been used to attempt to distinguish between PD and MSA based on gliosis and neuronal loss in key areas (e.g. caudate/putamen vs. substantia nigra).⁶ While each of these methods met with some limited success, a convenient and rapid method for differentiation between PD and MSA (particularly early-stage MSA, prior to the manifestation of clinically distinct features), still remains elusive, and a highly sensitive/specific test remains to be demonstrated.^{7,8}

Diffusion-weighted magnetic resonance imaging (DWI), wherein directional restrictions on the Brownian motion of water molecules in tissue are assessed, can reveal areas of edema and neuronal loss in living brain. Clinically, DWI is primarily used to investigate suspected infarctions. DWI allows measurement of fractional anisotropy (FA) – the relative non-randomness of water diffusion – as well as mean diffusivity (MD) – an index of the medium in which the water is diffusing – for every given voxel of the brain.⁹ A number of studies have been performed to investigate the use of these measures in assessing parkinsonism, working on the assumption that FA will correlate with the health of a given region. Some of these studies have met with encouraging results,

⁵ Federico, F., Simone, I.L., Lucivero, V., Iliceto, G., De Mari, M., Giannini, P., Mezzapesa, D.M., Tarantino, A., Lamberti, P., 1997. Proton magnetic resonance spectroscopy in Parkinson's disease and atypical parkinsonian disorders. *Mov. Disord.* 12, 903–909.

⁶ Schulz, J.B., Skalej, M., Wedekind, D., Luft, A.R., Abele, M., Voigt, K., Dichgans, J., Klockgether, T., 1999. Magnetic resonance imaging-based volumetry differentiates idiopathic Parkinson's syndrome from multiple system atrophy and progressive supranuclear palsy. *Ann. Neurol.* 45, 65–74.

⁷ Schrag, A., Kingsley, D., Phatouros, C., Mathias, C.J., Lees, A.J., Daniel, S.E., Quinn, N.P., 1998. Clinical usefulness of magnetic resonance imaging in multiple system atrophy. *J. Neurol. Neurosurg. Psychiatry* 65, 65 – 71.

⁸ Litvan, I., 1999. Recent advances in atypical parkinsonian disorders. *Curr. Opin. Neurol.* 12, 441–446.

⁹ Hajnal, J.V., Doran, M., Hall, A.S., Collins, A.G., Oatridge, A., Pennock, J.M., Young, I.R., Bydder, G.M., 1991. MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic, and pathologic considerations. *J. Comput. Assist. Tomogr.* 15, 1–18.

demonstrating highly reliable efficacy in distinguishing between PD and MSA.¹⁰ Diffusion tensor imaging (DTI), a relatively young imaging modality that is currently not used outside of laboratories, measures MD and FA as well, but, rather than examining each voxel's water diffusion from just three orthogonal directions as in DWI, DTI assesses diffusion in a voxel from many directions (the PICS facility in the Neurological Institute uses 56 directions). The resultant data provides quantitative information about the diffusion of water in a voxel in each measured direction. Since the primary cause of restricted diffusion in living brain is cell membranes, DTI data can be used to perform tractography: probabilistic mathematical algorithms are applied to the data to extrapolate the most likely layout and orientation of white matter tracts based on directional diffusion parameters.^{11,12}

FA and MD provide information about diffusion in a single voxel; if pathologic change has not occurred in such a way as to alter the FA or MD, no abnormality will be detected. DTI tractography, on the other hand, can assess the integrity of axonal tracts even if they are distant from the site of a lesion. Cell death in the putamen, for example, may not be detectable via changes in FA, but subsequent Wallerian degeneration of projections from the putamen will be detectable as tract disruptions via DTI. We propose to use DTI tractography to examine the brains of parkinsonian patients to distinguish those with PD from those with MSA or other Parkinson-plus syndromes. Our hypothesis is that, because MSA involves lesions of sites beyond merely the substantia nigra, tractography should reveal a difference between PD and MSA in the health of the tracts projecting from the substantia nigra (primary lesion in PD) and projecting from the striatum (primary lesion in MSA). We further hope to show that DTI tractography is superior to using FA and MD alone in drawing this distinction, and that tractographic changes are detectable at an earlier stage in the disease process.

B. Methods

Study Design:

This study will be a case-control study of patients recruited from the Neurological Institute's Center for Parkinson's Disease and Other Movement Disorders. The study will involve patients with known diagnoses of PD, MSA, and other Parkinson's-plus disorders as well as normal controls from the PICS facility database. These patients will be scanned using DTI, and tractography will be performed to assess the integrity of nerve tracts projecting from the substantia nigra and from the striatum. FA and MD values will also be recorded at these two locations and compared across groups.

Analysis of the subject data will further involve stratification of subjects according to illness, time since diagnosis, medication history, and symptomatology.

¹⁰ Schocke, M.F., Seppi, K., Esterhammer, R., Kremser, C., Jaszke, W., Poewe, W., Wenning, G.K., 2002. Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. *Neurology* 58, 575 – 580.

¹¹ Behrens, T.E.J., Johansen-Berg, H., Woolrich, M.W., et. al., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience* Vol. 6, Num. 750-757.

¹² Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. *Radiology* 201, 637 – 648.

The goal of the study is to test the null hypothesis that tractography and FA/MD values in the substantia nigra and striatum will be similar between PD and PPS patients. Secondly, the stratification scheme will allow us to investigate correlations between FA/MD/tractographic integrity and disease progression, medication exposure, and specific presentations.

Power Analysis:

There is no pilot data yet for using tractography to detect significant difference between study groups of this type. Assuming that tractographic measures are normally distributed, we can use a t-test to estimate that for every 20 patients scanned, we will be able to detect one standard deviation of effect difference at 80% power and with $p = 0.05$. Ideally, since the standard deviations are unknown, our group size will exceed 20 and hopefully will approach 80, which would provide us with power to detect an effect of one-half standard deviation. Once pilot data is acquired and standard deviations are known, we will be able to estimate minimum effect sizes.

Statistical Analysis:

Detection of disruptions in tracts originating from the substantia nigra and the striatum will be compared to clinical diagnosis to determine odds ratios of having a particular illness given certain tract characteristics. Correlations between FA/MD values, tract integrity, and clinical diagnosis will be assessed via multiple regression.

C. Study Procedures

Study procedures to be performed on each patient for this study include only DTI scanning, which is non-invasive and requires no injectable contrasts or radiation exposure. T1- and T2-weighted structural scans may be performed at the discretion of the managing neurologists. Aside from the DTI scan, the study requires no interventions or tests outside of those normally performed in the care of these types of patients at the Center.

D. Study Drugs N/A

E. Medical Device

Scans will be performed in the PICS center with the Philips 3T closed-tube MRI. No IV contrast or radioactive isotopes will be used. The device will be operated by a skilled technician. All scans will be assessed by an experienced neuroradiologist to ascertain whether there are any unknown abnormalities that require the patient's attention and disqualify from the study.

F. Study Questionnaires N/A

G. Study Subjects

Inclusion Criteria: Patients at the Center for Parkinson's Disease and Other Movement Disorders carrying diagnoses of PD, MSA, or other Parkinson's-plus syndromes.

Exclusion Criteria: Patients with neurological comorbidities (e.g. Alzheimer's disease), patients who have had neurosurgical procedures, patients who have experienced traumatic brain injury, any patient with metallic implants.

H. Recruitment of Subjects

Study subjects will be identified by Center neurologists with whom we will be collaborating. As the neurologists will already be the patient's primary neurological caregiver, they will be able to approach the patients for recruitment into the study.

I. Confidentiality of Study Data

All study data will be coded to eliminate personal identifiers and stored in a secure location.

J. Potential Conflicts of Interest N/A

K. Location of Study

Columbia University, Neurological Institute, Center for Parkinson's Disease and Other Movement Disorders, Program for Imaging and Cognitive Science.

L. Potential Risks

No risks have been demonstrated to be associated with magnetic resonance imaging at the time of this writing. Some individuals who have claustrophobia have been known to find MRI distressing. Individuals with metallic implants cannot be placed in an MRI machine.

M. Potential Benefits

There is no tangible benefit to study participants from enrolling in the study. Establishing a non-invasive, highly sensitive and specific method for distinguishing between PD and PPS, however, could impact management of these diseases for future patients and, furthermore, could help to increase understanding of the separate pathophysiologies underlying each of them, which in turn could lead to interventions in the future.

N. Alternative Therapies N/A

O. Compensation to Subjects N/A

P. Costs to Subjects

The only cost to subjects in this study will be time spent in the scanner, which will not exceed an hour.

Q. Minors as Research Subjects N/A

R. Radiation or Radioactive Substances N/A

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- ⁸ Litvan, I., 1999. Recent advances in atypical parkinsonian disorders. *Curr. Opin. Neurol.* 12, 441-446.
- ⁹ Hajnal, J.V., Doran, M., Hall, A.S., Collins, A.G., Oatridge, A., Pennock, J.M., Young, I.R., Bydder, G.M., 1991. MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic, and pathologic considerations. *J. Comput. Assist. Tomogr.* 15, 1-18.
- ¹⁰ Schocke, M.F., Seppi, K., Esterhammer, R., Kremser, C., Jaschke, W., Poewe, W., Wenning, G.K., 2002. Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. *Neurology* 58, 575-580.
- ¹¹ Behrens, T.E.J., Johansen-Berg, H., Woolrich, M.W., et. al., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience* Vol. 6, Num. 750-757.
- ¹² Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. *Radiology* 201, 637-648.