Diffusion Tensor Imaging: Parkinson’s Disease and Atypical Parkinsonism

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Characteristics of Parkinson’s disease

- **Prevalence rate PD** (Moghal et al., 1994)
  - general population = 0.3%
  - 50-70 = 1%
  - > 65 = 3%

- **Primarily a motor disorder**
  - Tremor, bradykinesia, and rigidity
  - Affects activities of daily living such as eating, cooking, grooming
  - Also affects cognition, depression, anxiety, sense of smell

- **Structural and physiological changes**
  - Loss of neurons in SNc (McGeer et al., 1977)
  - PET studies show reduced dopamine uptake in the striatum (Brooks, 1990)
Major problems for current research

- There is no definitive diagnosis for PD, PSP, MSA, and ET while the person is alive.
- It can be difficult to diagnose these diseases early.
- Important to diagnose these diseases early and accurately because the prognosis is different.
- Symptomatic treatments for PD, PSP, MSA, and ET are already different.
- Disease modifying treatments could be different.
What to focus on today

- Diffusion tensor imaging of the substantia nigra:
  - Early stage drug naïve Parkinson’s disease
  - Healthy aging
  - Atypical Parkinsonism and Essential Tremor
Cell Loss in PD

Caudate Nucleus

Putamen

Cell Loss in Substantia Nigra

Dopamine cell loss correlates with DTI in mouse model of PD

Boska et al. Neurobiology of Disease, 2007
Ventrolateral tier of the substantia nigra most depleted in PD

Figure 2.9. Cell loss in subregions of the substantia nigra (a) normal anatomy; PL, pars lateralis; DL, dorsolateral tier; DM, dorsomedial tier; VL, ventrolateral tier; VI, ventrointermediate tier; VM, ventromedial tier; (b) ageing (20–90 years), (c) incidental Lewy body cases, (d) Parkinson’s disease [10].

Differs from age related neuron loss which has a sparing of ventral lateral tier with aging

Sawle, Movement Disorders in Clinical Practice, 2000
Study design

- 14 early stage, de novo PD patients
  - Average age: 57 years
  - UPDRS motor range = 4 to 32
  - UPDRS mean 17
- 14 age and sex matched control subjects
- DTI sequence
  - 3T GE; 8-channel head coil; matrix = 256x256; 4mm slices; 15 slices; NEX = 4; b = 0, 1000; TR = 4500 ms; TE = 82 ms; 27 directions;
A  Dorsal B0 Image

Red Nucleus
Rostral to caudal degeneration pattern

![Bar chart showing fractional anisotropy across rostral, middle, and caudal regions for control and PD groups.](Image)

![ROC Curve showing sensitivity vs. 1-specificity.](Image)

Vaillancourt et al., Neurology, 2009
Individual patients have reduced FA

*Caudal regions provide 100% sensitivity and 100% specificity

Vaillancourt et al., Neurology, 2009
Combined DTI and R2* MRI based imaging

- 30 patients with PD
- 22 control subjects
- DTI and R2*
- Used voxel-based and ROI methods
- Increased R2* in SN
- Reduced FA in SN and thalamus

Peran et al., Brain, 2010
Combined DTI and R2* MRI based imaging has high sensitivity

Also supported by Du et al. (In press) in Movement Disorders

Peran et al., Brain, 2010
**Dorsal tier of the substantia nigra most depleted in aging**

**Figure 2.9.** Cell loss in subregions of the substantia nigra (a) normal anatomy; PL, pars lateralis; DL, dorsolateral tier; DM, dorsomedial tier; VL, ventrolateral tier; VI, ventrointermediate tier; VM, ventromedial tier; (b) ageing (20–90 years), (c) incidental Lewy body cases, (d) Parkinson’s disease [10].
Healthy aging affects dorsal SN

**Could be different for ages greater than 71 years**

Vaillancourt et al., Neurobiology of Aging, 2010
Thalamus and PD

Adapted from Wichmann and Delong, Arch Neurol, 2007
Thalamus and PD

A. Seed Voxel Placement

AN

VA

DM

VL

VPM/VPL

PU

B. Fiber Tracking

AN

VA

DM

VL

VPM/VPL

PU

*ICCs for two raters above 0.83
Thalamus and PD

The bar chart illustrates the mean FA (+/- 1 SEM) for various thalamic nuclei (AN, VA, DM, VL, VPM/VPL, PU) comparing controls (black bars) and PD (white bars). The asterisks (*) indicate statistically significant differences between the two groups.
fMRI and De Novo PD

Spraker et al., Human Brain Mapping, 2010
Prodoehl et al., Movement Disorders, 2010
Trait and state biomarkers

Trait biomarkers
- separating a disease from health
- separating a disease from other diseases

State biomarkers
- tracking progression of neurodegeneration
- tracking the efficacy of a drug acutely or chronically over time
Hypothesis: diffusion tensor imaging will differentiate PD from MSA, PSP, and ET.

Recruitment Goal: recruit 60 well diagnosed patients with these four movement disorders.
DTI in PD, MSA, PSP, and ET

**What is involved:**
- One morning session (few hours)
  - Tested off DA therapy (patients do not take morning dose)
- Structural imaging using T1 and T2
- Diffusion tensor imaging of **basal ganglia**
- Diffusion tensor imaging of **cerebellum**
- Diffusion tensor imaging of **whole brain**
- Rating scales for movement and cognition
Regions of Interest Analysis

- Basal ganglia: hand-drawn
  - Putamen, caudate, globus pallidus, substantia nigra

- Cerebellum: hand-drawn
  - Dentate, superior cerebellar peduncle (CP), middle CP, inferior CP

- Frontal and Cortical: standard ROIs

- Two raters blinded to patient status
Example ROIs for BG

- Caudate
- Putamen
- Globus Pallidus
- Substantia nigra
Example ROIs for Cerebellum

- Dentate
- Superior Cerebellar Peduncle
- Middle Cerebellar Peduncle
- Inferior Cerebellar Peduncle
Substantia nigra of autopsied brains

- Alpha-synuclein accumulation greater in MSA and PD compared to PSP (Tong et al. 2010)
- Alpha-synuclein accumulation greater in MSA compared to PD (Tong et al. 2010)
- Reactive astrocytes greater in PSP and MSA compared to PD (Song et al. 2009)

Suggests that SN microstructure is fundamentally different in PD relative to atypical Parkinsonism
Summary

- Have demonstrated that FA values from DTI in the ventral SN has high sensitivity for early stage, de novo PD

- Combined DTI and iron imaging has high sensitivity for PD (Peran et al. 2010)

- AN, DM, and VA thalamic nuclei impaired in early PD

- DTI in substantia nigra shows promise in preliminary data for differentiating PD from MSA, PSP, and ET
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