Progression of White Matter Degeneration in Early Parkinson’s Disease: A Multicenter Evaluation Using Diffusion Tensor Imaging

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Faculty Disclosure

Speaker Name: Yu Zhang

I have no conflicts of interest to disclose with regard to the subject matter of this presentation.
Background

PPMI (*Parkinson's Progression Markers Initiative*): An observational multi-center study to identify markers of Parkinson’s disease progression

Longitudinal Diffusion Tensor Imaging (DTI):
- DTI measures directionality of tissue water diffusion
- Fractional Anisotropy (FA) quantifies the degree of directionality
- Reduced FA of white matter is generally considered a marker of microstructural degeneration
- Few earlier longitudinal DTI studies of PD, suggesting:
  - A trend of FA reduction over time
  - Rates of changes in DTI are associated with changes in UPDRS
Objectives

1) To determine whether PD is associated with
   (i) DTI changes over time in white matter
   (ii) Greater DTI changes than in normal aging

2) To determine whether DTI changes of white matter in PD correlate with:
   (i) Clinical progressions, i.e. motor, cognitive symptoms
   (ii) Biological progressions, i.e. dopamine deficiency (DAT binding ratios).
Study Protocols

DATA sharing:
- PPMI allows standardized data acquisition protocols for imaging, clinical, laboratory and genetic assessments in multiple sites
- Following with quality control, all data from multi-sites are uploaded to a database: LONI (http://www.loni.usc.edu/)
- PPMI Data are shared publicly

MRI acquisitions:
- T1: 3D MPRAGE, 1 mm$^3$ resolution
- T2: 3D double spin echo, 1 mm$^3$ resolution
- DTI: cardiac-gated 2D single-shot echo-planar sequence, 2 mm$^3$ resolution
  - 64 directions
  - $B_{\text{max}} = 1000s/mm^2$
  - 2-fold acceleration
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>HC baseline</th>
<th>HC Follow-up</th>
<th>PD baseline</th>
<th>PD Follow-up</th>
<th>PD vs. HC (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>50</td>
<td>—</td>
<td>122</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>60.6 ± 11</td>
<td>60.5 ± 9</td>
<td>0.92</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex [M : F]</td>
<td>32M : 18 F</td>
<td>79 M : 43 F</td>
<td>0.92</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Scan Interval [months]</td>
<td>12.7 ± 1</td>
<td>12.6 ± 1</td>
<td>0.90</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Side of Onset Symptom</td>
<td>—</td>
<td>51 L : 70 R : 1 sym</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. of medication [Off : On]</td>
<td>—</td>
<td>34 Off : 88 On</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>total MDS-UPDRS</td>
<td>2.6 ± 2.9</td>
<td>3.6 ± 3.9</td>
<td>29.3 ± 13</td>
<td>34.9 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MDS-UPDRS-III</td>
<td>0.6 ± 1.5</td>
<td>1.0 ± 1.9</td>
<td>20.4 ± 9</td>
<td>22.6 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hoehn-Yahr</td>
<td>0 ± 0</td>
<td>0 ± 0.3</td>
<td>1.6 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Putamen DaT (minimum side)</td>
<td>1.8 ± 0.3</td>
<td>—</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>total MoCA</td>
<td>28.3 ± 1</td>
<td>27.3 ± 2</td>
<td>27.5 ± 2</td>
<td>26.9 ± 3</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Longitudinal DTI Processing Flow

Native space

Subject #1
- Baseline
- Follow-up

Intra-subject space

Subject #2
- Baseline
- Follow-up

MNI space

JHU_MNI_DTI
Brain Region & Tract Atlas

Whole brain WM atlases (JHU_MNI_DTI):

(1) WM Tracts (58 ROIs)

(2) WM regions adjacent to the cortices (42 ROIs)

(3) Basal ganglia / midbrain (18 ROIs)
Statistical Modeling

Linear mixed-effect models for longitudinal changes:
- time / time*group as fixed effect
- subject random effect

1. Test FA change is larger than zero in each group.
2. Test FA change in PD is larger than in normal aging
3. Post-hoc whether FA change is related to dominant side of symptom at onset

Significance:
- Adjusted for multiple comparisons, i.e. FDR
- $p = 0.05$
Annual FA Rates As Percent from Baseline Value

% FA per year vs. HC for various brain regions:
- Temporal WM
- Occipital WM
- Parietal WM
- Frontal WM
- Limbic Tracts
- Corpus Callosum
- Long Assoc. Tracts
- Projection Tracts
- Midbrain/Braintem
- Basal ganglia

HC

PD

PD vs. HC
Rates Of Regional FA Reduction In PD vs HC

Ipsilateral vs Contralateral

Annual rate of FA reduction (%)

$P_{FDR\text{-adjusted}} < 0.05$
Other DTI Scalars

• **Lower FA:**
  Impaired coherence or connectivity of the WM microstructure

• **Higher rD:**
  Demyelination or changes in the axonal diameters or density

• **Higher aD**
  Vary in neurological conditions, increase in chronic WM degeneration
Rates Of Regional rD Increase In PD vs HC

Annual rate of rD increase (%)

$P_{FDR\text{-}adjusted} < 0.05$
Rates Of Regional aD Increase In PD vs HC

Annual rate of aD increase (%)

$P_{FDR\text{-adjusted}} < 0.05$
## Pearson’s Correlations Between Rates Of Regional FA And Rates Of Clinical Measures

* No significant differences between ipsilateral and contralateral hemisphere in association with clinical progression

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Hemisphere*</th>
<th>Statistic</th>
<th>UPDRS-total&lt;sup&gt;a&lt;/sup&gt;</th>
<th>UPDRS-III&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Putaminal DAT&lt;sup&gt;b&lt;/sup&gt; (min side)</th>
<th>Putaminal DAT&lt;sup&gt;b&lt;/sup&gt; (ave side)</th>
<th>MOCA total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantia Nigra</td>
<td>Contra-</td>
<td>Coefficient</td>
<td>-0.09</td>
<td>-0.09</td>
<td>0.27</td>
<td>0.15</td>
<td>0.02</td>
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<tr>
<td></td>
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<td>p-value</td>
<td>0.4</td>
<td>0.3</td>
<td>0.005</td>
<td>0.1</td>
<td>0.8</td>
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<tr>
<td></td>
<td>Ipsi-</td>
<td>Coefficient</td>
<td>-0.03</td>
<td>-0.04</td>
<td>0.10</td>
<td>0.03</td>
<td>0.10</td>
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<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.8</td>
<td>0.7</td>
<td>0.3</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>MidBrain</td>
<td>Contra-</td>
<td>Coefficient</td>
<td>-0.08</td>
<td>-0.08</td>
<td>0.12</td>
<td>0.10</td>
<td>0.09</td>
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<tr>
<td></td>
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<td>p-value</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
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<tr>
<td></td>
<td>Ipsi-</td>
<td>Coefficient</td>
<td>-0.01</td>
<td>-0.02</td>
<td>0.07</td>
<td>0.08</td>
<td>0.17</td>
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<td>p-value</td>
<td>0.9</td>
<td>0.8</td>
<td>0.5</td>
<td>0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Contra-</td>
<td>Coefficient</td>
<td>-0.07</td>
<td>-0.07</td>
<td>0.26</td>
<td>0.19</td>
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<tr>
<td></td>
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<td>p-value</td>
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<td>0.5</td>
<td>0.006</td>
<td>0.05</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Ipsi-</td>
<td>Coefficient</td>
<td>-0.04</td>
<td>-0.05</td>
<td>0.08</td>
<td>0.11</td>
<td>0.09</td>
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<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.7</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> 18 missing values;  <sup>b</sup> 14 missing values;  <sup>c</sup> 6 missing values
### Pearson’s Correlations Between Rates Of Regional rD And Rates Of Clinical Measures

<table>
<thead>
<tr>
<th>Region of Interest</th>
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<th>MOCA total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantia Nigra</td>
<td>Contra-</td>
<td>Correlation</td>
<td>0.02</td>
<td>0.02</td>
<td><strong>-0.21</strong></td>
<td>-0.14</td>
<td>0.03</td>
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<tr>
<td></td>
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<td>p-value</td>
<td>0.9</td>
<td>0.9</td>
<td><strong>0.03</strong></td>
<td>0.2</td>
<td>0.7</td>
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<tr>
<td></td>
<td>Ipsi-</td>
<td>Correlation</td>
<td>0.00</td>
<td>0.02</td>
<td><strong>-0.08</strong></td>
<td>-0.03</td>
<td>-0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.9</td>
<td>0.9</td>
<td>0.4</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>MidBrain</td>
<td>Contra-</td>
<td>Correlation</td>
<td>0.05</td>
<td>0.06</td>
<td><strong>-0.08</strong></td>
<td>-0.11</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Ipsi-</td>
<td>Correlation</td>
<td>0.02</td>
<td>0.06</td>
<td><strong>-0.02</strong></td>
<td>-0.07</td>
<td>-0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.8</td>
<td>0.6</td>
<td>0.9</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Contra-</td>
<td>Correlation</td>
<td>0.09</td>
<td>0.04</td>
<td><strong>-0.010</strong></td>
<td>-0.09</td>
<td><strong>-0.33</strong></td>
</tr>
<tr>
<td></td>
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<td>p-value</td>
<td>0.4</td>
<td>0.7</td>
<td>0.3</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Ipsi-</td>
<td>Correlation</td>
<td>0.06</td>
<td>0.06</td>
<td><strong>-0.09</strong></td>
<td>-0.14</td>
<td><strong>-0.27</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>0.6</td>
<td>0.5</td>
<td>0.3</td>
<td>0.1</td>
<td><strong>0.003</strong></td>
</tr>
</tbody>
</table>

* No significant differences between ipsilateral and contralateral hemisphere in association with clinical progression
\(^a\) 18 missing values; \(^b\) 14 missing values; \(^c\) 6 missing values
Summary

• PD was associated with greater rates of FA reduction, rD and aD increases predominantly in the basal ganglia regions, without ipsilateral and contralateral asymmetries.

• Among these regions, substantia nigra had the highest rate of ~3%/year FA reduction; and the basal ganglia regions had 4-6%/year increases of radial diffusivity.

• Rates of FA reduction of the contralateral substantia nigra and thalamus correlated with the rates of putaminal dopamine deficiency; rates of increased diffusivities in thalamus were associated with cognitive decline.
Conclusion

White matter degeneration over time in PD is detected by DTI, and this degeneration is consistent with clinical progression of PD.

Rates of white matter degeneration is a potential marker of PD progression.
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