Diffusion Tensor Imaging: Image Processing & Analysis

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Dr. Yu Zhang (UCSF)
Shannon Buckley (UCSF)
Susan Mendick (IND)
Karen Crawford (LONI, USC)
Objectives

• Data Processing
  – Quantitative quality control
  – Alignment of DTI to anatomical MRI
  – Computations of DTI and tractography maps

• Data Analyses
  – Measure DTI alterations in PD
  – Identify DTI changes as marker of PD progression
  – Explore novel analysis strategies
    • Tractography
    • Network analysis
    • Individual predictions from DTI using machine learning
# Received/Processed (as of 4/25/2014)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Control</th>
<th>PD</th>
<th>SWEDD</th>
<th>Total Received</th>
<th>% Processed</th>
<th>Total Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>76</td>
<td>171</td>
<td>39</td>
<td>286</td>
<td>94.8%</td>
<td>15</td>
</tr>
<tr>
<td>12m</td>
<td>63</td>
<td>134</td>
<td>11</td>
<td>208</td>
<td>93.3%</td>
<td>3</td>
</tr>
<tr>
<td>24m</td>
<td>7</td>
<td>52</td>
<td>3</td>
<td>62</td>
<td>82.2%</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>146</td>
<td>357</td>
<td>53</td>
<td>556</td>
<td>92.8%</td>
<td>18 (3%)*</td>
</tr>
</tbody>
</table>

* Percent of total received

- Note: most subjects have 2 DTI scans per session. Thus the number of processed scans is nearly double the number of subjects
Objectives

• Data Processing
  – Perform quantitative QA
  – Align DTI to anatomical MRI
  – Compute DTI and tractography maps

• Data Analyses
  – Measure DTI alterations in PD
  – Identify DTI changes as marker of PD progression
  – Explore novel analysis strategies
    • Tractography
    • Multivariate whole brain analyses using machine learning
PPMI Site Quality
(DTI Signal-to-Noise over time)

Cutoff
SNR=30
LONI Uploads: DTI & T2 Maps

Control

PD

T2

Directional DTI

Substantia nigra

T2

Directional

FA
Baseline Paper

Objectives:
1. Characterize baseline DTI
2. Replicated previous findings of reduced nigral FA in PD in a large cohort
3. Determine correlation between variations in nigral FA and
   - PD severity
   - DAT deficits (novel)
# Demographics

<table>
<thead>
<tr>
<th>Measure</th>
<th>PD</th>
<th>Control</th>
<th>Difference</th>
<th>P-value (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>153</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male [%]</td>
<td>63</td>
<td>66</td>
<td>-3</td>
<td>0.7</td>
</tr>
<tr>
<td>Age [years]</td>
<td>61 ± 10</td>
<td>60 ± 11</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Side of Onset [L:R:S] (a)</td>
<td>65:85:3</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn-Yahr (b)</td>
<td>1.6 ± 0.5</td>
<td>0</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS total (c)</td>
<td>36 ± 14</td>
<td>6 ± 4</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS-III (d)</td>
<td>22 ± 9</td>
<td>1 ± 1</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MOCA (e)</td>
<td>28 ± 2</td>
<td>28 ± 1</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>minDAT (f)</td>
<td>0.7 ± 0.3</td>
<td>1.9 ± 0.4</td>
<td>-1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Group Differences in Nigra FA

Ipsi

Contra

FA

Caudal Middle Rostral Caudal Middle Rostral

p = 0.04

T2w DTI

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research
Correlations Between DAT – DTI

FA versus DAT by nigral ROI

Radial Diffusivity versus DAT by nigral ROI

Axial Diffusivity versus DAT by nigral ROI

\[ \lambda_1 = \text{longitudinal (axial) diffusivity (AD)} \]
\[ \frac{\lambda_2 + \lambda_3}{2} = \text{radial diffusivity (RD)} \]
\[ \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \text{mean diffusivity (MD)} \]
Baseline: Voxelwise Group Differences In FA*

154 PD and 67 HC
*anatomical left/right

No increased FA in PD

Reduced FA in PD

HC > PD

HC < PD

covariates: age, sex

FWE-corr

no suprathreshold clusters

Height threshold: T=3.13, p=0.001 (0.998)

FDR-corr

0.168

p_FWE-corr 0.035

p_uncorr 0.000

q_FDR-corr

Play a Part in Parkinson’s Research
Executive loop: DLPFC – anterior ventral vertex of PUT

Motor Loop: SMA – inner posterior PUT

Nigrostriatal: SN – GP and ventral PUT
## Group Differences in Tracts FA, Cognitive and Motor Functions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Number</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Executive Scale (SD)</td>
<td>0.10 (0.7)</td>
<td>-0.04 (0.9)</td>
</tr>
<tr>
<td>Memory Scale (SD)</td>
<td>0.23 (0.7)</td>
<td>-0.09 (0.7)</td>
</tr>
<tr>
<td>Attention Scale (SD)</td>
<td>0.44 (0.8)</td>
<td>-0.18 (1.0)*</td>
</tr>
<tr>
<td>MDS-UPDRS-III total</td>
<td>—</td>
<td>21.4 (8)</td>
</tr>
<tr>
<td>FA executive loop [MAS(^{(1)})]</td>
<td>0.42 (0.03)</td>
<td>0.42 (0.04)</td>
</tr>
<tr>
<td>FA executive loop [LAS(^{(2)})]</td>
<td>0.43 (0.03)</td>
<td>0.43 (0.04)</td>
</tr>
<tr>
<td>FA motor loop [MAS]</td>
<td>0.45 (0.05)</td>
<td>0.48 (0.05)</td>
</tr>
<tr>
<td>FA motor loop [LAS]</td>
<td>0.47 (0.04)</td>
<td>0.48 (0.04)</td>
</tr>
<tr>
<td>FA dopaminergic fiber [MAS]</td>
<td>0.45 (0.05)</td>
<td>0.41 (0.04)**</td>
</tr>
<tr>
<td>FA dopaminergic fiber [LAS]</td>
<td>0.45 (0.04)</td>
<td>0.41 (0.05)**</td>
</tr>
</tbody>
</table>

* 0.01 ≤ p < 0.05; ** p<0.01

(1) [MAS] = most affected side, contralateral to the symptomatic side at onset.
(2) [LAS] = least affected side, ipsilateral to the symptomatic side at onset.
Correlation between Tract FA and Cognitive or Motor Functions in 37 PD patients

<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th>Executive</th>
<th>Attention</th>
<th>UPDRS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA executive loop [MAS(^{(1)})]</td>
<td>0.04</td>
<td>0.44(^{**})</td>
<td>0.45(^{**})</td>
<td>-0.10</td>
</tr>
<tr>
<td>FA executive loop [LAS(^{(2)})]</td>
<td>0.25</td>
<td>0.30</td>
<td>0.35(^*)</td>
<td>0.10</td>
</tr>
<tr>
<td>FA motor loop [MAS]</td>
<td>0.33(^*)</td>
<td>0.28</td>
<td>0.31</td>
<td>-0.03</td>
</tr>
<tr>
<td>FA motor loop [LAS]</td>
<td>-0.07</td>
<td>0.04</td>
<td>-0.16</td>
<td>-0.06</td>
</tr>
<tr>
<td>FA dopaminergic fiber [MAS]</td>
<td>0.17</td>
<td>0.24</td>
<td>0.09</td>
<td>-0.50(^{**})</td>
</tr>
<tr>
<td>FA dopaminergic fiber [LAS]</td>
<td>0.20</td>
<td>0.33(^*)</td>
<td>0.25</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

\(^*\) \(0.01 \leq p < 0.05\); \(^{**}\) \(p < 0.01\)

(1) [MAS] = most affected side, contralateral to the symptomatic side at onset.
(2) [LAS] = least affected side, ipsilateral to the symptomatic side at onset.
Longitudinal DTI Processing

Native Space

Subject_1_Tp1
Subject_1_Tp2
Subject_1_Tp3

Transformation

Individual
Mean Space

Transformation

Mean Subject_1

Transformation

Atlas Space

JHU_mni
Brain labels

All Subjects _Tp1
All Subjects _Tp2
All Subjects _Tp3

Voxelwise
or ROI
analysis

* use “optimal thresholding” to keep binary ROI
Rates of FA Reduction in PD

HC=41, PD=52

126 Brain wm regions = 50 wm regions + 58 tract regions + 18 basal ganglia regions

Lme fix-effects: regional FA ~ dx * interval; Lme random effects: subjects; weights = regional WMD
Prediction of DAT Change From DTI Baseline
Summary & Conclusion

I. DTI findings from previous studies not replicated, though there is a weak PD signal in SN

II. Tract-based DTI seems more sensitive than ROIs for capturing a PD signal

III. PD is associated with FA reduction over time in primary frontal lobe regions

IV. Baseline FA predicts DAT decline over time

V. DTI carries a PD signal including disease progression
Plans

I. Additional Baseline Papers
   I. Tract-based results
   II. Voxelwise results
   III. Methods multicenter DTI QC and reproducibility
   IV. Relationship between DTI and volumetric brain changes
   V. Relationship between DTI and CSF biomarkers

II. Analyses
   I. Longitudinal FA change
   II. Predictions of DAT change from baseline DTI, and vice versa
   III. Relationship between DTI and atrophy rates

IV. Other analysis approaches
   I. Machine learning
   II. DTI connectome (network analysis)
Extra Slides
Regional Reduction Of FA In SWEDD vs PD*

153 PD and 37 SWEDD  (*) accounting for differences in motor severity and age

**SWEDD < PD**
- covariates: age, sex, UPDRSIII
- \( p_{\text{FWE-corr}} = 0.001 \)
- \( p_{\text{uncorr}} = 0.000 \)
- \( q_{\text{FDR-corr}} = 0.001 \)

Height threshold: \( T=3.13, p=0.001 \) (0.998)

**SWEDD > PD**
- covariates: age, sex, UPDRSIII
- \( p_{\text{FWE-corr}} \) no suprathreshold clusters
- \( p_{\text{uncorr}} \) no suprathreshold clusters
- \( q_{\text{FDR-corr}} \) no suprathreshold clusters

Height threshold: \( T=3.13, p=0.001 \) (0.998)
Brain Region & Tract Atlas

• Four atlases:
  – GM (60 rois)
  – WM (50 rois)
  – Tracts (58 rois)
  – Basal ganglia (18 rois)