Introduction

- Parkinson’s Disease (PD) is one of the most common neurodegenerative diseases with symptoms including tremor, bradykinesia, rigidity, and impaired posture control[1]. While medication can alleviate certain symptoms, no treatments exist to slow the disease progression. Therefore, there is an unmet need for a biomarker associated with progression. A biomarker could allow intervention at the onset of disease to stop or slow progression to aid in development of disease modifying treatments[2].

- PD is characterized by the loss of dopaminergic neurons in the substantia nigra, but neurodegeneration is more widespread. Recent data indicates that grey matter (GM) atrophy in the thalamus is a correlate of global disease severity[3].

- The purpose of this study is to investigate the association between GM atrophy and motor dysfunction in PD patients.

Methods

- Subjects: MRI data were obtained from PD studies in Bochum, Germany (24 PD patients, 19 controls) and Indiana University (19 PD, 16 controls). Subject demographics are given in Table 1.

- Motor Function: The motor function of all subjects was scored using the Unified Parkinson Disease Rating Scale (UPDRS-III), assessing the patient’s ability to perform various motor tasks. A high UPDRS-III score indicates low motor function.

- MRI: High-resolution T1-weighted whole-brain images (MPRAGE, resolution: 1x1x1 mm³) were acquired on a 3T Philips Achieva scanner (Bochum) or 3T Siemens Tim Trio (IL). Part of the data was acquired by our collaborators at the IPA, Ruhr University Bochum, Germany.

- Image Analysis: Voxel-based morphometry (VBM) is a quantitative MRI approach that is widely used in neurological disorders to show structural changes in the brain. GM Density was calculated with SPM12 normalization.

- Statistical Analysis: 1. Multiple regression analysis was used to compare GM density versus motor function (UPDRS-III score). 2. A two sample T-test was used to compare GM densities in PD patients versus the healthy controls. All comparisons were corrected for both intracranial volume and age as additional covariates in the analysis.

Results

Part I: Regression of GM loss with Motor Function (UPDRS-III score)

- As shown above in Figure 2, there is a significant association with increased UPDRS-III scores (reflecting “parkinsonism”) in the left and right superior parietal lobes of the motor cortex.

- Compared to normal subjects, previous studies show PD patients have less neural activity in the superior parietal lobes[4-6].

- Our results are also in line with previous studies that have shown reduced GM density in the motor cortex being associated with disease severity as indicated by the UPDRS[7].

- Findings agree with the hypothesis that severity of PD symptoms can be associated with GM atrophy.

Part II: Group Differences

- As shown in Figure 3, there appears to be significant GM atrophy in PD patients versus healthy controls in the Left Supplementary Motor Cortex of the frontal lobe.

- The supplementary motor cortex is a critical brain region that works to link cognition to action[8,9], and an important consideration for PD patients.

- Previous studies have repeatedly shown GM atrophy in the frontal lobe and supplementary motor cortex across PD patients[10].

- Findings agree with the hypothesis that PD patients see more GM atrophy compared to healthy controls.

Table 1: Demographics of PD patients and control subjects for respective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Scanner</th>
<th>n</th>
<th>Mean Age</th>
<th>Mean UPDRS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bochum</td>
<td>Philips Achieva</td>
<td>24</td>
<td>61.77 yrs</td>
<td>30 ±12</td>
</tr>
<tr>
<td>Controls</td>
<td>n=43</td>
<td>58.59 yrs</td>
<td>0.8 ±2.2</td>
<td></td>
</tr>
<tr>
<td>Indiana University</td>
<td>Siemens Trio</td>
<td>19</td>
<td>63.89 yrs</td>
<td>32 ±9</td>
</tr>
<tr>
<td>Controls</td>
<td>n=15</td>
<td>59.10 yrs</td>
<td>4.9 ±3.4</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Main Conclusions:
  - Analysis revealed differences between PD and control subjects in the motor cortex.
  - Findings agree with the hypothesis that motor dysfunction is associated with GM atrophy in the motor cortex in PD.

- About our Experimental Design
  - The 16 controls from the Indiana University study have a relatively high mean UPDRS-III score.
  - Healthy controls ideally should have a very low UPDRS score.
  - This scoring discrepancy could alter the group difference analysis.

- Limitations
  - Limited number of PD patients and healthy control subjects.
  - Increasing the sample sizes could lead to more accurate results.

- Bochum PD patients were currently taking medication to relieve symptoms.

- Effects on UPDRS-III scores.

- Bochum Control subjects were not matched in socioeconomic background and education, due to recruitment via newspaper ads. Alcohol and substance abuse may be a confounder.

- About Voxel-Based Morphometry (VBM)
  - Many different studies show variable results. In order to determine a biomarker, data must be reproducible across several studies.
  - With further validation, VBM could be a useful biomarker tool.

- Overall, non-invasive MRI could be a useful tool to find a biomarker in PD patients in the future to improve treatment at the onset of disease and to help stop or slow progression.

References


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Grey Matter Atrophy Associated with Motor Dysfunction in Parkinson’s Disease

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