IMAGING PARKINSON’S DISEASE:
Gray Matter Atrophy Associated With Motor Dysfunction

Student Author

Courtney Oare is a 2017 graduate of Purdue University who majored in Radiological Health Sciences with a concentration in Medical Physics. In the School of Health Sciences Honors Program, she partook in research for three years with an interest in imaging and evaluation of disease. Outside of coursework and research, she served as an Ambassador for the College of Health and Human Sciences, was a leader in the Health Physics Society, as well as other campus organizations. After graduation, she will be attending the University of Minnesota working toward a PhD in Medical Physics.

Mentors

Ulrike Dydak is Associate Professor of Health Sciences and Director of the Purdue Life Science MRI Facility. Her research is centered on the development of novel magnetic resonance imaging (MRI) and spectroscopy (MRS) techniques and their translation to clinical and life science studies – with a focus on movement disorders. Using cutting edge MRI and MRS techniques, her group is exploring the mechanism and associations of neurochemical, functional and structural changes in the brain with motor dysfunction as found in Parkinson Disease, as well as in manganese neurotoxicity leading to parkinsonism. For this research, she received the Outstanding New Environmental Scientist Award by NIEHS.

Chien-Lin Yeh is a fifth-year PhD student working with Dr. Ulrike Dydak in the School of Health Sciences and majoring in Medical Physics. She graduated with a master’s degree from Yang-Ming University in Taiwan before joining Dr. Dydak’s lab. Her research direction is focused on using the relaxometry property of MRI to assess deposition of manganese in the brain, with an additional focus on the occupational health of manganese-exposed welders. Besides research, she serves as a trainee member on International Society of Magnetic Resonance in Medicine and Society of Toxicology.
INTRODUCTION

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases with symptoms including tremor, bradykinesia (slowness of movement), rigidity, and impaired posture control (Miller & O’Callaghan, 2015). PD is characterized by the loss of dopaminergic neurons in the substantia nigra, but neurodegeneration is more widespread. While medication can alleviate certain PD symptoms, no treatment exists to slow the disease progression. Therefore, there is a great need for the development of a treatment method that can help slow down or reverse the neurodegeneration incurring among PD patients. Typically, a PD diagnosis is based on observed symptoms in the clinic, such as using the Unified Parkinson’s disease Rating Scale (UPDRS-III) which measures motor impairment. Yet, there is no objective biomarker that allows diagnosis or monitoring of disease progression for PD patients.

In recent years, medical imaging techniques have made advances as a potential solution to diagnose and monitor treatment strategies. In particular, Magnetic Resonance Imaging (MRI), which provides multiple contrasts and functional information, may provide more information regarding the pathological process of neurodegenerative diseases like PD.

Voxel-based morphometry (VBM) enables a whole-brain voxel-wise comparison of gray matter (GM) and white matter (WM) using MRI images. A voxel refers to a small volume of space, often used in imaging or three-dimensional modeling. VBM can help characterize and identify subtle changes in brain structures in a wide variety of neurologic and psychiatric dysfunction diseases. Since VBM measures the density of GM in the brain, that is, a measure of neuronal density, it should be a suitable tool to measure neurodegeneration and its progression in PD. All subcortical areas commonly associated with PD, including the caudate nucleus, the putamen, the globus pallidus, the subthalamic nucleus, and the substantia nigra, have been found to show significant atrophy using VBM (Lin et al., 2013). However, these changes have not been sensitive enough to serve as biomarker of progression for PD. Moreover, it has been shown that a high concentration of iron leads to incorrect classification of tissues in these subcortical structures (Lorio et al., 2016).

Recently, literature has also shown GM atrophy present in cortical brain areas that are not typically associated with PD, including the frontal lobe, intraparietal sulcus, the temporal lobe, parietal
stimulated by the environment. Figure 1 maps these two loops. Being able to noninvasively study progressive changes in GM density associated to these motor loops is therefore of particular interest in monitoring PD patients.

AIMS/PURPOSE

There is an unmet need for an objective biomarker associated with progression of disease—in particular with worsening motor function. If sensitive enough, such a biomarker could even allow intervention at the onset of disease before severe symptoms appear. It could also help with early diagnosis of atypical parkinsonism, which requires different treatment, or help to monitor disease modifying therapy (Miller & O’Callaghan, 2015).

Therefore, the purpose of this present study was to evaluate the relationship between GM atrophy in PD patients compared to control subjects, and how it relates to motor dysfunction. VBM was used to: (1) assess the difference in GM density between PD patients and control subjects and (2) investigate differences in GM density with decreased motor function across PD patients.

METHODS

Voxel-Based Morphometry (VBM)

MRI is used to study structural changes in the brain. VBM is a neuroimaging analysis technique that allows the investigation of structural changes in the brain using statistical parameter mapping. In this study, VBM was used to investigate changes in GM density in PD patients and associations with motor impairment in PD.

Subjects

A total of 43 PD patients and 59 controls were used in this analysis. All patients and controls in the study were male. MRI data was obtained from two collaborative PD studies: 24 PD patients and 43 controls were recruited at Ruhr University in Bochum, Germany. Nineteen PD patients and sixteen controls were

<table>
<thead>
<tr>
<th>Study</th>
<th>Scanner</th>
<th>Subjects</th>
<th>Median Age (Years)</th>
<th>Median UPDRS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruhr University, Bochum, Germany</td>
<td>3T Philips Achieva</td>
<td>PD ( n = 24 )</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls ( n = 43 )</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Indiana University, Indianapolis, Indiana</td>
<td>3T Siemens Trio</td>
<td>PD ( n = 19 )</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls ( n = 16 )</td>
<td>58</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1. PD and control subject demographics.
studied at Indiana University School of Medicine (IUSM) in Indianapolis, Indiana. Demographics of subjects are summarized in Table 1.

Motor Dysfunction Assessment

To assess individual motor function, all subjects were scored by certified neurologists using the motor part of the Unified Parkinson Disease Rating Scale (UPDRS-III), which assesses the ability to perform various motor tasks. A higher UPDRS-III score indicates increased motor impairment. It should be noted that PD patients from Bochum were taking medication, which may influence their UPDRS-III scores, whereas patients in the study at IUSM were either medication-naïve or withheld medication for at least 12 hours prior to their UPDRS-III evaluation and MRI scans.

MRI

High resolution T1-weighted magnetic resonance images (MPRAGE) were acquired on 3.0 Tesla whole-body MRI systems for all subject groups. T1-weighted MRI’s provide tissue contrast, which is useful when distinguishing GM, WM, and cerebrospinal fluid (CSF). Data was acquired on a Philips Achieva MRI system at Bochum and on a Siemens TIM Trio system at IUSM. Imaging parameters included TR/TE = 8.3/2.7 milliseconds and an acquisition matrix of 240x240x240, yielding a resolution of 1x1x1 mm³. Each complete whole-brain MRI scan contained 220 slices.

Data Analysis

To determine GM density, Statistical Parameter Mapping (SPM12) Functional MRI software was used in conjunction with MATLAB to determine GM density. The flowchart in Figure 2 outlines the process. The T1-weighted images acquired in Bochum and Indianapolis were first coregistered into the same imaging plane, which places all images in the same orientation. Next, images were segmented into GM, WM, and CSF on a voxel-by-voxel basis, analyzing image contrast. As a result, a probability map is created proportional to the density of GM, WM, and CSF in each voxel. Images are then normalized to a standard brain atlas, retaining individual GM, WM, and CSF probabilities. Finally, an 8mm full-width-at-half-maximum (FWHM) Gaussian kernel filter was applied. This spatial smoothing is set to remove noise and random signal, increasing the validity of SPM12. Figure 3 exemplifies the transition of the original T1-weighted image before and after processing.
volume. A significance threshold of $p < 0.001$ with a
cluster size $> 200$ voxels was used.

RESULTS

Group Differences

Compared to normal controls, a significant
($p < 0.005$, cluster size $> 200$) GM atrophy was found
in PD patients in the left supplementary motor cortex
of the frontal lobe. Figure 4 highlights the GM differ-
ences on a T1-weighted overlay.

Additionally, our findings agreed with the hypoth-
esis that motor dysfunction is associated with GM
atrophy in the motor cortex in PD patients. Our
results are in line with a previous study that has seen
significant GM atrophy in the motor cortex being as-
associated with disease severity (Wu & Hallett, 2005).
Atrophy in these brain regions could also explain
that, compared to normal subjects, PD patients have
been shown to have less neural activity in the parietal
lobules of the motor cortex (Zhang et al., 2015).

As previously discussed, the supplementary motor
cortex is a part of the basal ganglia-thalamocortical
loop. Activation of this loop is important for volun-
tary movement. With a loss of neuronal function in
the supplementary motor cortex due to GM atrophy
(i.e., loss of neurons), these findings indicate that GM
atrophy could be related to voluntary motor control
in PD. Therefore, these findings agree with the hy-
pothesis that severity of PD motor symptoms can be
associated with GM atrophy.

Limitations of our Study: Experimental Design

In order to increase the sample size for statistical
comparison, we pooled two studies, which bears its
own limitations. For example, the 16 healthy controls
from the IUSM study had a relatively high median
UPDRS-III score of 3, as was noted in Table 1. Ide-
ally, a healthy control should have a very low rating
(less than 2) on a UPDRS-III scale, which might
slightly increase with age. The difference could be
due to a scoring inconsistency between the raters of
the two studies which could alter the group differ-
ence analysis. In future studies, the same rater should
be scoring all subjects to avoid such inconsistencies.
Furthermore, the Bochum PD patients were not with-
holding medication at the time of the study, as did
the IUSM PD patients. This may have an effect on
their UPDRS-III scores, which could have an impact
on the regression with motor dysfunction findings.
Additionally, the Bochum control subjects were not
matched in socioeconomic background and education
due to recruitment via newspaper advertisements.
Alcohol and substance abuse may additionally have
been a confounding variable.

Finally, the sample size in this study was relatively
limited. Increasing the sample size could improve the
accuracy and validity of the results.

Limitations of Voxel-Based Morphometry

With respect to the use of VBM, many studies show
variable results. Despite the potential of using VBM
as a biomarker of progression of neurodegeneration,
there are numerous drawbacks that may impede its usefulness in the clinic at this time. For example, GM atrophy in PD patients is very small, less than a few percent difference at onset of disease (Ash et al., 2011). More progressed disease may see more advanced degeneration. For this reason, it is essential to improve accuracy and reduce sources of error in volumetry techniques to produce reliable conclusions.

Moreover, the coherence across VBM studies is lacking, especially in neurodegenerative diseases like PD. Some studies have shown a wide range of GM atrophy across several brain regions, while others find no significant differences. The large range in findings is not unexpected, as long as PD patients are not stratified for their diverse symptoms (for example, with or without dementia, etc.) and potential for atypical PD. These different clinical symptoms rely on many different brain regions associated with motor control and cognitive processing of voluntary movement and may thus affect these brain regions differently in these subpopulations.

If obstacles such as these are overcome, VBM may prove to become a successful biomarker in PD and other neurodegenerative diseases, helping in the development of treatment options by being able to objectively monitor progression of the disease, irrespective of medication status.

CONCLUSION

Overall, noninvasive MRI can be a useful tool to identify GM atrophy in PD patients and changes in GM density that are associated with specific symptoms, such as motor impairment, to serve as marker of disease progression. Congruence among several studies will validate results observed in this study as well as previous literature. Our study is one step toward this validation.

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REFERENCES


Figure 6. 2017 Dydak lab group in the new Purdue MRI Facility. Photo courtesy of Ulrike Dydak.


