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.

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.

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.

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

Student Author

Mentors

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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><em>Ruhr University, Bochum, Germany</em></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>1</td>
</tr>
<tr>
<td><em>Indiana University, Indianapolis, Indiana</em></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.
Imaging Parkinson's Disease

The SPM output is given as spatial x, y, z coordinates of voxels, each associated with a proportional density of GM within the voxel. This method allows a voxel-by-voxel statistical comparison across a large sample of MR images. SPM12 also allows the display of neuromorphometric regions in which the user can identify a coordinate-based brain region related to significant findings as part of the statistical analysis.

Statistical Analysis

An SPM12 significance map is created to identify and highlight areas of statistical significance depending on the user-defined threshold. To analyze GM differences between 43 PD patients and 59 normal control subjects, a two-sample t-test was performed with age and intracranial volume as covariates. For the group difference, the significance was set to \( p < 0.005 \). To account for multiple comparisons across the many voxels, a cluster size threshold of > 200 voxels was set.

To investigate an association between GM atrophy and motor dysfunction, a multiple regression analysis was completed across the 43 PD subjects and their UPDRS-III scores, correcting for age and intracranial volume.
Additionally, our findings agreed with the hypothesis 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 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 voluntary 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 hypothesis 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. Ideally, 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 difference analysis. In future studies, the same rater should be scoring all subjects to avoid such inconsistencies. Furthermore, the Bochum PD patients were not withholding 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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