IMAGING PARKINSON'S DISEASE:

Gray Matter Atrophy Associated With Motor Dysfunction

Student Author

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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.

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder with common symptoms including rigidity, tremors, and bradykinesia. While current medication can alleviate symptoms, no treatment exists to stop or slow neuronal cell death and disease progression. There is an unmet need for a biomarker associated with progression that could aide in development of treatments by monitoring disease progression. Since Magnetic Resonance Imaging (MRI) allows for the measure of gray matter (GM) density in the human brain noninvasively, this study was designed to investigate the association between brain atrophy, measured by MRI, and motor dysfunction in PD subjects, as a biomarker.

MRI and voxel-based morphometry methods were used to investigate GM atrophy and the association with motor impairment in 43 PD and 59 control subjects. T1-weighted whole-brain MRI images were acquired in collaborative studies in Germany and at Indiana University on 3T MRI scanners. Group differences in GM density between PD and control subjects were examined voxel by voxel with SPM12 using cluster-corrected two-sample t-tests. Among PD subjects, associations of GM density with motor dysfunction (measured by UPDRS-III) were analyzed by multiple regression.

Compared to controls, PD subjects show significant GM atrophy in the supplementary motor cortex ($p < 0.005$). This is a critical brain region, linking cognition to action. Among PD subjects, there is a significant association ($p < 0.001$) of GM atrophy with motor dysfunction (high UPDRS-III) bilaterally in the superior parietal lobules of the motor cortex. These findings agree with the hypothesis that motor dysfunction is associated with GM atrophy in the motor cortex, and that imaging GM density by MRI is a good display of neurodegenerative progression in PD.

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Keywords

Parkinson's disease, neurodegeneration, motor impairment, MRI, voxel-based morphometry

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, 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

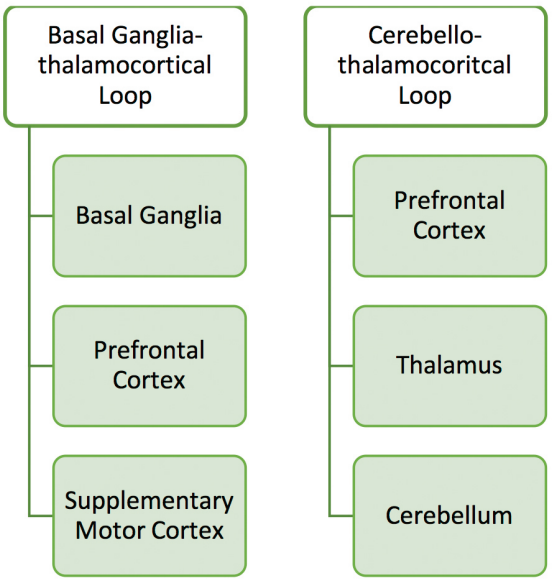

Figure 1. Summary of motor loops, connecting cortical and subcortical brain regions.

lobe, and occipital lobes (Burton, McKeith, Burn, Williams, & O'Brien, 2004; Lee et al., 2014; Weintraub et al., 2012; Melzer et al., 2012; Sterling et al., 2017). However, results were inconsistent. The discrepancies across studies may be due to inhomogeneous subjects, such as the heterogeneity amongst different subtypes of parkinsonism, displaying different types of symptoms.

Since PD is classified as a movement disorder, most damage has been found in motor loops of the central nervous system (Draganski & Bhatia, 2010). These motor loops connect the subcortical brain regions commonly associated with PD to cortical brain regions executing movement and cognition. First, the basal ganglia-thalamocortical loop interconnects the structures of the basal ganglia (including the substantia nigra), the prefrontal cortex, and the supplementary motor cortex (Ash et al., 2011). This loop and associated brain regions are very important for motor behavior. An additional pathway to consider is the cerebello-thalamocortical loop connecting the prefrontal cortex, the thalamus, and the cerebellum. This pathway plays a key role to regulate actions 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

Study	Scanner	Subjects	Median Age (Years)	Median UPDRS-III
Ruhr University, Bochum, Germany	3T Philips Achieva	PD $n = 24$	62	30
		Controls $n = 43$	59	1
Indiana University, Indianapolis, Indiana	3T Siemens Trio	PD $n = 19$	63	31
		Controls $n = 16$	58	3

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 mm^3. 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.

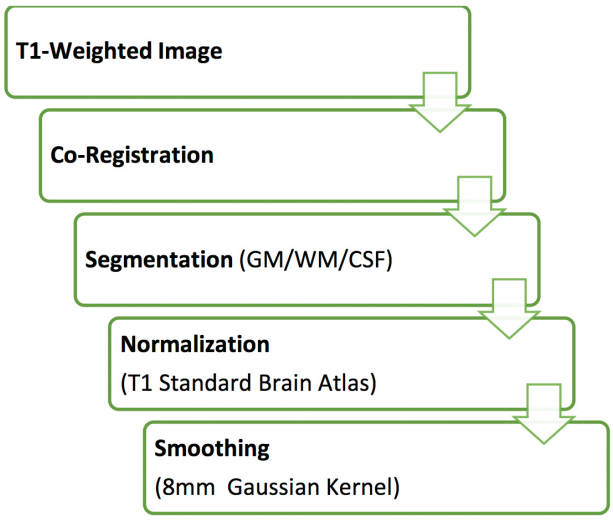

Figure 2. SPM12 processing sequence.

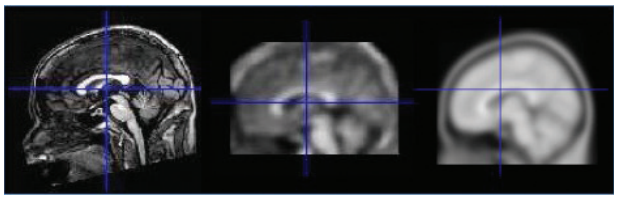

Figure 3. Left: Original sagittal T1-weighted MRI; **Middle:** T1-weighted MR image after segmentation, normalization, and smoothing; **Right:** T1 template image.

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. 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 differences on a T1-weighted overlay.

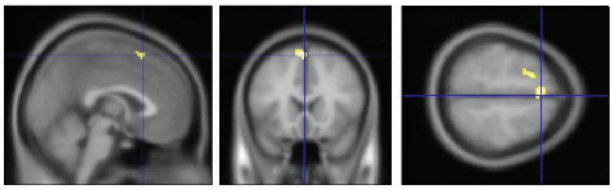

Figure 4. Group differences: Compared to controls, significant GM atrophy is seen in the left supplementary motor cortex of PD patients (p-value < 0.005, cluster size > 200).

Regression with Motor Dysfunction

Among PD subjects there is a significant ($p < 0.001$, cluster size > 200) association of GM atrophy with increased UPDRS-III scores in the right and left superior parietal lobules of the motor cortex as shown in Figure 5.

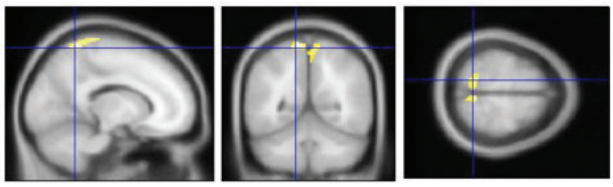

Figure 5. Regression with motor function: Within PD subjects lower motor performance (higher UPDRS-III score) correlated with lower GM density in the left and right superior parietal lobes of the motor cortex (p-value < 0.001, cluster size > 200).

DISCUSSION

Our analysis revealed differences among PD and control subjects in the supplementary motor cortex. The supplementary motor cortex is a critical brain region that works to link cognition to action (Nachev, Kennard, & Husain, 2008). These findings are in line with previous literature showing GM atrophy in the frontal lobe and supplementary motor cortex across PD patients (González-Redondo et al., 2014).

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.

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

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