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Patterns of grey matter loss associated with motor subscores in early Parkinson's disease

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ABSTRACT

Classical motor symptoms of Parkinson's disease (PD) such as tremor, rigidity, bradykinesia, and axial symptoms are graded in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III. It is yet to be ascertained whether parkinsonian motor symptoms are associated with different anatomical patterns of neurodegeneration as reflected by brain grey matter (GM) alteration. This study aimed to investigate associations between motor subscores and brain GM at voxel level. High resolution structural MRI T1 scans from the Parkinson's Progression Markers Initiative (PPMI) repository were employed to estimate brain GM intensity of PD subjects. Correlations between GM intensity and total MDS-UPDRS III and its four subscores were computed. The total MDS-UPDRS III score was significantly negatively correlated bilaterally with putamen and caudate GM density. Lower anterior striatal GM intensity was significantly associated with higher rigidity subscores, whereas left-sided anterior striatal and precentral cortical GM reduction were correlated with severity of axial symptoms. No significant morphometric associations were demonstrated for tremor subscores. In conclusion, we provide evidence for neuroanatomical patterns underpinning motor symptoms in early PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by rigidity, tremor, bradykinesia and loss of postural stability (Gibb, 1988). There is however, significant heterogeneity in the clinical presentation and course of the disease (Thenganatt and Jankovic, 2014; van Rooden et al., 2011; Marras and Chaudhuri, 2016). A number of MRI brain imaging methods (Brooks, 2010; Garg et al., 2015; Pyatigorskaya et al., 2014; Politis, 2014) have been applied to study the grey matter (GM) and white matter changes, and their association with clinical features of PD (Cochrane and Ebmeier, 2013; Gattellaro et al., 2009; Koshimori et al., 2015). GM density loss (Burton et al., 2004; Nagano-Saito et al., 2005; Beyer et al., 2007; Melzer et al., 2012; Koshimori et al., 2015) and atrophy (Melzer et al., 2012; Rosenberg-Katz et al., 2013; Mak et al., 2015; Delgado-Alvarado et al., 2016) in PD patients have been extensively studied using voxel-based morphometric methods. In contrast, relatively little attention has been paid to study the relation between MRI GM intensity changes and clinical motor measures as assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III (Goetz et al., 2007). This is important because analysis of morphometric association of GM with clinical (sub)domain scores is a logical and powerful method to identify functionally meaningful brain structural patterns that may inform on PD biotypes.

Previous findings for the correlation between GM structural changes and MDS-UPDRS III were inconsistent. For example, one study based on brain image segmentation and cortical surface reconstruction found that there was a significant negative correlation between the MDS-UPDRS III score and the volume of the left caudate, but not with cortical thickness (Zarei et al., 2013). However, another study (Apostolova et al., 2010) did not show significant associations between MDS-UPDRS III subscale scores and caudate radial distance mapping an intuitive measure of the cortical thickness. Nevertheless, there are also several potential drawbacks with these earlier studies as they used relatively small sets of data (< 100 PD subjects). Moreover, none of the studies looked at the correlation between MDS-UPDRS III score and MRI GM intensity. This is likely to have limited the studies' sensitivity as previous experiments (Rosenberg-Katz et al., 2013; Mak et al., 2015; Delgado-Alvarado et al., 2016) showed that GM intensity was an arguably more reliable approach to investigate subcortical atrophy. Although significant correlation between GM concentration in the right middle frontal gyrus and a previous version of the UPDRS III score

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(Fahn and Elton, 1987) was observed (Melzer et al., 2012), MRI GM intensity associations with MDS-UPDRS III motor subscores have not been attempted. It thus remains to be shown which of the MDS-UPDRS III subscales best reflects symptoms arising from specific patterns of GM deficit. This would be an important step toward better understanding links between progression of the GM changes and clinical progression in PD (Vingerhoets et al., 1997). In this study, a T1 weighted sequence was adopted as the most popular method used to study brain structural changes in neurodegenerative disorders. It offers detailed, validated structural information including cortical thickness and GM density, which can inform on structural macroscopic disease effects and their patterns, and has been extensively used for PD morphometric studies (Pan et al., 2012). Diffusion tensor imaging (DTI) is also commonly used to study neurodegenerative disease based on its detailed characterisation of subtle white matter changes, but it is less well established to study neurodegenerative GM changes.

The purpose of this study was twofold. First, we used voxel-based correlational analyses to investigate the correlation between GM density and MDS-UPDRS III scores and its four main subscores (tremor, rigidity, bradykinesia, and axial symptoms) (Berganzo et al., 2016). This allowed us to identify regional patterns of neurodegeneration underpinning specific motor symptoms based on our hypothesis that GM intensity reduction may be a suitable index of early neurodegenerative pathology leading to reduced neuronal density before overt atrophic volume reduction. We postulated that mapping motor domains separately would reveal distinct GM patterns pointing to potential neural biotypes in PD.

Second, to test for potential confounding age effects we undertook repeat regression analysis controlling for age but limited to the striatum based on widely documented structural and diffusional alterations of the striatal nuclei in PD (Péran et al., 2010; Fioravanti et al., 2015). We hypothesised that there would not have significant age and striatal GM intensity correlation in PD.

2. Materials and methods

2.1. MRI dataset

Three hundred and ninety-two PD MRI T1 structural images were initially used in this study. All MRI image data were obtained from the PPMI website (http://www.ppmi-info.org/) on 13/10/2015 as previously published (Li et al., 2017). Also, the UPRDS III scores for these subjects were obtained from the PPMI database. Diagnosis of PD was performed by movement disorder specialists according to the PD UK Brain Bank Criteria. This excluded atypical Parkinsonism, concomitant vascular load, history of cognitive impairment, psychiatric disorders or other neurodegenerative disorders other than PD and any factors that would preclude MRI scanning. Tremor, rigidity, bradykinesia, and axial subscores were calculated according to the table in the supplementary material section (Supplementary Table). Table 1 shows the demographics and clinical details of the data used in the study.

Table 1
Demographics and clinical details of 364 subjects with PD (235 male) derived from PPMI repository.

	PD (mean ± SD)
Age	62.12 ± 9.77
Total MDS-UPDRS III score	21.63 ± 9.85
Sum of axial subscore	2.08 ± 1.48
Sum of bradykinesia subscore	9.68 ± 5.56
Sum of rigidity subscore	4.12 ± 2.89
Sum of tremor subscore	5.76 ± 3.42
Hoehn and Yahr Stage score	1.62 ± 0.52
Duration of disease (month)	6.70 ± 6.65
Number of patients on PD medication	117

SD: Standard deviation.

2.2. MDS-UPDRS III subscores

We divided the MDS-UPDRS III score into 4 subgroups according to motor symptoms in PD (Berganzo et al., 2016; Jankovic, 2008). MDS-UPDRS III scores were then subdivided into tremor (sum of items 15–18), rigidity (item 3), bradykinesia (sum of items 2, 4–9 and 14) and axial (sum of items 1 and 9–13) (Supplementary_Table). Group means of the total UPDRS III scores and the sums of items of the 4 subscores are displayed in Table 1.

2.3. Software packages for MRI data analysis

In the present study we employed several software packages/languages. The FSL-VBM package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) was adopted for image registration, image segmentation, GM modulation and image smoothing. The image registration toolkit (IRTK) (https://github.com/BioMedIA/IRTK) was also applied for image registration (Rueckert et al., 1999) if FSL failed for the image registration. MATLAB (www.mathworks.com) was used for MRI GM correlation analysis. In addition, Python language (https://www.python.org) was implemented to extract patient information from the clinical table, including age and total MDS-UPDRS III scores and subscores. To help localize GM differences, the 120 regions specified in the Automated Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002) were used to label regions in the resultant statistical maps. Visual inspection was carried out at each step of image and clinical data processing.

2.4. MRI GM image processing

The MRI GM image was obtained using the FSL software package. First, structural T1 images were registered to the Montreal Neurological Institute (MNI) template using the FSL Linear Image Registration Tool (FLIRT) (Jenkinson and Smith, 2001) function. If the images failed to be registered, then the IRTK package with a manual registration was carried out to obtain the initial value for a rigid registration. A large head mask, as part of the MNI template, was employed to exclude shoulder and neck in the PPMI T1 brain image. This was done by multiplying the registered images with the head mask using FSL-maths functions. The Brain Extract Tool (BET) method (Smith, 2002) was employed to extract the brain (removing the skull from the whole image) for each of the 392 image sessions. Next, non-uniformity correction was carried out, and the FSL Automated Segmentation Tool (FAST v.4) (Zhang et al., 2001) was adopted to segment tissues according to their type. The segmented GM partial volume images were then aligned to the MNI standard space (MNI152) by applying the affine registration tool FLIRT (FMRIB's linear image registration tool) and nonlinear registration FNIRT (FMRIB's nonlinear image registration tool) methods, which use a B-spline representation of the registration warp field. The registered images (before smoothing), were averaged to create a study specific template, and the native GM images were then nonlinearly re-registered to the template image. The registered GM partial volume images were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The segmented and modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation (sigma = 3 mm), and the final smoothed image (with sigma = 3 mm) was employed for the correlation analysis between brain GM and MDS-UPDRS III scores.

2.5. Correlation analysis and statistical inference

For GM and MDS-UPDRS III correlation analyses, 26 subjects were removed from the study due to GM segmentation problems, and two subjects had to be excluded due to missing MDS-UPDRS III scores