Parkinsonism and Related Disorders 20 (2014) 622–626

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Subcortical grey matter changes in untreated, early stage Parkinson's disease without dementia

Hye Mi Lee [a], Kyum-Yil Kwon [a], Min-Jik Kim [a], Ji-Wan Jang [a], Sang-il Suh [b], Seong-Beom Koh [a], Ji Hyun Kim [a,*]

[a] Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Guro-dong Ro 148, Guro-gu, Seoul 152-703, Republic of Korea
[b] Department of Radiology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 3 July 2013
Received in revised form
5 March 2014
Accepted 10 March 2014

Keywords:
Parkinson's disease
Subcortical grey matter
Voxel-based morphometry
Regional volumetry
Shape analysis

ABSTRACT

Background: Previous MRI studies have investigated cortical or subcortical grey matter changes in patients with Parkinson's disease (PD), yielding inconsistent findings between the studies. We therefore sought to determine whether focal cortical or subcortical grey matter changes may be present from the early disease stage.
Methods: We recruited 49 untreated, early stage PD patients without dementia and 53 control subjects. Voxel-based morphometry was used to evaluate cortical grey matter changes, and automated volumetry and shape analysis were used to assess volume changes and shape deformation of the subcortical grey matter structures, respectively.
Results: Voxel-based morphometry showed neither reductions nor increases in grey matter volume in patients compared to controls. Compared to controls, PD patients had significant reductions in adjusted volumes of putamen, nucleus accumbens, and hippocampus (corrected $p < 0.05$). Vertex-based shape analysis showed regionally contracted area on the posterolateral and ventromedial putamen bilaterally in PD patients (corrected $p < 0.05$). No correlations were found between cortical and subcortical grey matter and clinical variables representing disease duration and severity.
Conclusions: Our results suggest that untreated, early stage PD without dementia is associated with volume reduction and shape deformation of subcortical grey matter, but not with cortical grey matter reduction. Our findings of structural changes in the posterolateral putamen and ventromedial putamen/nucleus accumbens could provide neuroanatomical basis for the involvement of motor and limbic striatum, further implicating motor and non-motor symptoms in PD, respectively. Early hippocampal involvement might be related to the risk for developing dementia in PD patients.

1. Introduction

Recent advances in computational analysis of structural MRI allow in vivo identification of macroscopic cerebral atrophy, thereby contributing greatly to the understanding of structural changes associated with widespread pathologic processes in Parkinson's disease (PD). Voxel-based morphometry (VBM) is the method most extensively used to evaluate structural changes of both cortical and subcortical grey matter (GM). A number of VBM studies have shown relatively consistent findings of GM reduction in multiple cortical areas and hippocampus in PD patients, especially those with dementia [1–5]. In contrast, VBM investigations have not yielded uniform results with respect to cortical or subcortical GM changes in non-demented PD. Previous studies reported GM reduction in various regions, such as frontal cortex [4,5], temporal lobe [2], or caudate nucleus, whereas others found no significant changes in either cortical or subcortical GM in non-demented PD [6,7].

A few studies addressed the issue of whether PD is associated with subcortical GM changes, yielding variable findings [8–11]. Vertex-based shape analysis is another fully automated method that provides useful information about the location and pattern of morphological changes of the subcortical GM [12]. Because it can precisely localize regional shape deformation of the subcortical GM and detect changes that are not found in VBM, shape analysis is now increasingly used to study subcortical GM in a variety of neurological and psychiatric disorders.

* Corresponding author.
E-mail address: jhkim.merrf@gmail.com (J.H. Kim).

http://dx.doi.org/10.1016/j.parkreldis.2014.03.009
1353-8020/

The two aims of this study were to determine whether focal cortical or subcortical GM changes may be present from the early disease stage and to elucidate their relationships with clinical factors. To minimize confounding factors that are known to possibly affect GM changes, we only recruited untreated, early stage PD patients without dementia. Specifically, VBM was used to evaluate cortical GM changes, automated volumetry to assess volume changes of the subcortical GM, and shape analysis to assess regional shape deformation of the subcortical GM.

2. Methods

2.1. Subjects

This was a retrospective study and the local ethics committee approved the study protocol. De novo patients with idiopathic PD were carefully selected through the Parkinson's Disease Registry of Korea University Guro Hospital between September 2010 and March 2012. All patients fulfilled the UK Parkinson's Disease Society Brain Bank diagnostic criteria for PD. In our movement disorder clinic, it is recommended that all patients with newly diagnosed PD undergo MRI scanning which includes high-resolution 3D volumetric images in addition to clinical MR images. In order to recruit early stage PD patients without dementia, we only included patients with a modified Hoehn and Yahr (H–Y) staging score of 3 or less and Mini-Mental State Examination (MMSE) score of 26 or more [13]. Exclusion criteria were the following: (1) history of neurological disorders other than PD; (2) history of visual hallucinations; (3) presence of major medical illnesses; (4) history of proven major psychiatric disorders (e.g., major depressive disorder, bipolar disorder, schizophrenia) and history of taking anti-depressants, mood stabilizers, or anti-psychotics; (5) history of severe head injury, drug abuse, or chronic alcoholism; (6) presence of vascular lesions, hydrocephalus, marked cortical atrophy, or white matter abnormalities outside the normal range on visual inspection of the clinical MR images; and (7) appearance of any atypical parkinsonian features suggesting an alternative diagnosis of atypical parkinsonism (e.g., poor levodopa responsiveness, myoclonus, cerebellar signs, supranuclear gaze palsy, Babinski sign, early severe dysautonomia, early severe dementia with disturbances of memory, language, and praxis) during the follow-up period (mean = 25.5 ± 6.9 months). Clinical data such as age of symptom onset and disease duration were obtained through reviews of medical records. The Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale was used for the evaluation of motor symptoms.

For group comparison, 53 right-handed control subjects matched for age and gender were randomly selected from the pool of MRI database. All control subjects underwent neurological examination and a detailed interview to ensure that they had (1) no neurological abnormality and global cognitive impairment (MMSE score $\geq$ 26); (2) no history of neurological, psychiatric, or systemic disorders; and (3) no history of severe head injury, alcohol and drug abuse.

2.2. Magnetic resonance imaging acquisition

All participants were scanned on a Siemens Trio 3T scanner (Erlangen, Germany) with a 12-channel head coil. For volumetric analysis, high-resolution 3D MP-RAGE sequence was acquired with the following parameters: TR = 1780 ms, TE = 2.34 ms, matrix = 256 × 256, voxel size = 1 mm^3. For identification of structural abnormalities, the following MR images were acquired: axial T2-weighted and fluid-attenuated inversion recovery images (4 mm thickness), coronal T2-weighted image (4 mm thickness), gadolinium-enhanced axial and coronal T1-weighted images (5 mm thickness). The clinical MR images were re-evaluated for any structural abnormalities and reported as normal in all subjects.

2.3. Voxel-based morphometry

Data preprocessing and VBM analysis were carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Briefly, the volumetric T1-weighted images were segmented into GM and white matter (WM) using the New Segment module with default settings. Segmentations were produced with rigid alignment to standard MNI space and resampled to 1.5 mm^3 isotropic voxels for use with Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) [14]. DARTEL then iteratively registered the GM and WM segments to an evolving estimate of their group-wise average. The native space tissue segments were then normalized to MNI space using the DARTEL transformations and modulated to account for volume changes using the Jacobian determinants. Finally, the modulated GM volumes were smoothed with a Gaussian kernel of 8-mm FWHM.

The GM maps were analyzed using the framework of General Linear Model on a voxel-wise comparison across the entire brain. First, regionally specific differences in GM volume between patients and controls were assessed using an analysis of covariance (ANCOVA) with total intracranial volume (TIV), age, and gender as nuisance variables. An absolute GM threshold of 0.2 was used to avoid possible edge effects around the border between GM and WM. Second, multiple regression analysis was performed to assess the relationships between GM volume and disease stage (modified H–Y stage), disease duration (years), and motor impairment (UPDRS motor subscale score) in patients, with TIV, age, and gender as nuisance variables. All results were considered as significant at $p < 0.05$, corrected for multiple comparisons using family-wise error (FWE).

2.4. Subcortical grey matter volumetry

Cortical reconstruction and volumetric segmentation were performed by using Freesurfer software (version 5.1.0, http://surfer.nmr.mgh.harvard.edu/). Image preprocessing procedures include removal of non-brain tissue, automated Talairach transformation, intensity normalization, segmentation of subcortical WM and deep GM structures, tessellation of the GM/WM boundary, automated topology correction, and surface deformation to detect GM/WM and GM/CSF boundaries. The automated procedures for volumetric measurements of the subcortical GM structures were described in detail previously [15]. Briefly, this procedure automatically provided segments and labels for up to 40 unique structures, and assigned a neuroanatomical label to each voxel in an MRI volume based on probabilistic information estimated automatically from a manually labeled training set. A Bayesian segmentation procedure was then performed, and the maximum a posteriori estimate of the labeling was computed. All segmentations were visually inspected for accuracy prior to inclusion in the analysis.

Regional volumes of 7 GM structures (thalamus, caudate, putamen, globus pallidus, nucleus accumbens, hippocampus, amygdala) were automatically measured. As most patients had bilateral motor symptoms, and volumes of the left and right subcortical GM were highly correlated, the left and right GM volumes were combined together to further reduce the variables to the smallest possible set. The adjustment was performed on each GM volume via a formula based on ANCOVA approach: adjusted volume = raw volume $- b \times$ (TIV − mean TIV), where b is the slope of regression of a GM volume on TIV. Group differences in TIV-adjusted GM volumes were assessed by using multivariate analysis of covariance (MANCOVA) adjusting for the effects of age and gender. The resulting p values from MANCOVA were multiplied by 7 and the statistical significance was set at $p < 0.05$, corrected for multiple comparisons using Bonferroni correction. Relationships between subcortical GM volumes and clinical factors were further explored. Specifically, correlations between TIV-adjusted GM volumes and UPDRS motor subscale score were assessed using Pearson partial correlation analysis after controlling for the effect of age ($p < 0.05$). Correlations between TIV-adjusted GM volumes and disease duration and modified H–Y stage, where the assumption of normality was not met (Kolmogorov–Smirnov test, both $p < 0.05$), were assessed using Spearman partial rank-order correlation analysis after controlling for the effect of age ($p < 0.05$). Statistical analyses were conducted with SPSS (version 19.0; IBM, Armonk, New York) and SAS (version 9.3; SAS Institute Inc., Cary, NC).

2.5. Shape analysis of subcortical grey matter

Automated segmentation of the subcortical GM was carried out using FIRST, part of FMRIB's Software Library (FSL 4.1, http://www.fmrib.ox.ac.uk/fsl), that uses Bayesian probabilistic approach [12]. Registration in FIRST comprises an affine transformation (12 degrees of freedom) of the volumetric T1-weighted images to MNI 152 standard space. After subcortical registration, a subcortical mask was applied to locate the different subcortical GM structures, followed by segmentation based on shape models and voxel intensities. The shape models used in FIRST are constructed from a library of manually segmented T1-weighted MRI datasets. FIRST then created a surface mesh for each subcortical structure using a deformable mesh model. The mesh is composed of a set of triangles and the apex of adjoining triangles is called a vertex. The number of vertices per mesh was fixed for a GM structure and the correspondence between vertices was enforced during the fitting so that corresponding vertices can be compared across individuals and between groups. The shape and appearance model is based on multivariate Gaussian assumptions, and shape is then expressed as its mean and modes of variation. Default options were used for boundary correction allowing determination of whether boundary voxels belong to the structure or not (z-value = 3, corresponding to a 99.998% certainty that the voxel belonged to the respective structure). A detailed description of FIRST can be found elsewhere [12].

Group comparisons of vertices were carried out using F-statistics. The effects of TIV, age, and gender were regressed out. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons using false discovery rate (FDR). The associations between regional shape changes of subcortical GM and clinical variables (modified H–Y stage, disease duration, UPDRS motor subscale score) were also explored (FDR-corrected $p < 0.05$).

3. Results

Clinical data and brain volumes for 49 right-handed PD patients (27 women, mean age = 65.0 years) and 53 control subjects (32 women, mean age = 63.1 years) are presented in Table 1. The two groups did not differ in age, gender, education years, MMSE score, total GM volume, total WM volume, CSF volume, and TIV (all $p > 0.05$). Mean modified H–Y stage of the patients was 2.0 ± 0.5