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Neural substrates of rapid eye movement sleep behavior disorder in Parkinson's disease

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ABSTRACT

Objectives: To investigate neural substrates of symptomatic rapid eye movement sleep behavior disorder (RBD) in Parkinson's disease (PD) by analyzing brain changes based on both hypothesis-free and hypothesis-driven neuroimaging analyses.
Methods: A total of 63 subjects (14 PDRBD−, 24 PDRBD+, and 25 age-matched healthy controls = HC) were enrolled in this study. RBD was defined by RBD screening questionnaire with video-polysomnographic confirmation. All subjects underwent volumetric and diffusion tensor imaging. The whole brain gray- and white-matter changes were analyzed and the central ascending cholinergic pathway involving the pedunculopontine nucleus and thalamus was compared with a region-of-interest analysis and probabilistic tractography.
Results: The PDRBD+ group showed decreased gray matter volume of the left posterior cingulate and hippocampus compared to the PDRBD− and additional gray matter decrease in the left precuneus, cuneus, medial frontal gyrus, postcentral gyrus and both inferior parietal lobule compared to the HC group (uncorrected $p < 0.001$, $k = 50$). There were no significant differences in white matter changes between the PDRBD− and PDRBD+ groups both by fractional anisotropy and mean diffusivities. However, both PD groups showed widespread changes by fractional anisotropy reductions and mean diffusivity increments compared to HC ($p < 0.05$ corrected). There were no significant differences in tract-based spatial statistics and the normalized tract volumes as well as the diffusion indices of both the thalamus and pedunculopontine nuclei among the study groups.
Conclusions: The appearance of RBD in PD may be related to regional gray matter changes in the left posterior cingulate and hippocampus but not localized to the brainstem.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal skeletal muscle atonia during REM sleep with dream enactment. It is common in patients with Parkinson's disease (PD), where it can either occur during the course of the disease or appear at the prodromal phase of PD [1].

There are continuing efforts to investigate possible neural substrates of RBD [2,3]. In several studies on idiopathic RBD patients, brainstem structures of the pedunculopontine nucleus (PPN), lateral dorsal tegmental nucleus (LDTN), and ceruleus/subceruleus complex, which serve as the sleep cycle control, have been suggested as possible neural substrates of RBD symptoms [4]. Pathological changes have also been reported in several white matter regions including the left temporal lobe, fornix, internal capsule, corona radiata, and right visual stream in idiopathic RBD patients

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by diffusion tensor imaging (DTI) analysis [5]. However, the neural substrates of RBD in PD patients remain to be elucidated especially in comparison to those PD patients who do not develop RBD symptoms despite a quite prolonged disease [6]. Clinically PD patients expressing RBD tend to have a poorer prognosis in terms of early development of dementia, postural instability, gait disturbance, and even an association with visual hallucination compared to those without RBD [7,8].

Despite the scarcity of clinical research, the neural substrates of RBD symptoms in PD might not be identical to those proposed in idiopathic RBD. In a recent study with PET using synaptic acetylcholinesterase binding ligands, cholinergic innervated regions of the neocortical, limbic, and thalamic areas as well as the basal forebrain were suggested as possible neural substrates of RBD symptoms in PD [9]. The brainstem structures were not significantly different according to the RBD symptoms in that study. A pathologic study also revealed that synucleinopathy, cholinergic depletion, and neuronal loss in the pontine tegmentum were not different according to the presence of RBD [10]. These observations have suggested that the involvement of brainstem structures, as it is suggested based on Braak's hypothesis on the pathological progression of PD, may not be sufficient to produce RBD symptoms in PD [11]. Alternately, some different nodes of the network were suggested to be disrupted for the appearance of RBD [10]. Thus, the aim of this study was to explore possible neural substrates for symptomatic RBD in PD by analyzing whole brain gray- and white-matter changes without a priori defined region of interest, and also by analyzing ascending cholinergic pathway from the brainstem.

2. Method

2.1. Subjects and clinical evaluations

Patients with PD were consecutively recruited from the neurology clinic at the Boramae Medical Center between September 2011 and August 2013. Diagnosis of PD was made by a movement disorders specialist (J.Y.L.) according to the UK PD brain bank society criteria [12]. Forty-five PD patients and 25 age-matched healthy controls were included as eligible subjects. The exclusion criteria included white matter changes, space occupying lesions, or structural lesions unrelated to PD revealed on brain imaging and significant psychiatric or cognitive illness which could affect RBD symptoms, dementia or significant cognitive impairment with a MMSE score <24, and a history of neurosurgical procedures including deep brain stimulation. Among 45 PD patients, two subjects were excluded due to image artifact, and 5 subjects due to low MMSE score (<24 points).

Patients were evaluated for the presence of probable RBD based on a questionnaire (RBD screening questionnaire, cut-off value > 5) during the follow-up visit [13]. To confirm RBD, video polysomnographic evaluation (PSG) was conducted by a sleep specialist (H.W.N.) in a video PSG monitoring room of our hospital for documentation of objective muscle activity during REM sleep along with aberrant motor behavior. We classified subjects as PDRBD+ when the patients met both criteria of PD and RBD simultaneously (n = 24), and those subjects who had never experienced symptoms suggestive of RBD were classified as a PD control (PDRBD−) (n = 14). PSG confirmation was completed in 85.7% of PDRBD− (12/14) and 79.2% of PDRBD+ patients (19/24).

Demographics and clinical information including the Movement Disorder Society task force revised-unified PD rating scale (MDS-UPDRS; permission obtained; name of certified rater, J.Y.L.) scores, Hoehn & Yahr stages, duration of PD and mini-mental status examination (MMSE) scores at the time of the evaluation were also collected from the medical records. RBD screening questionnaire and MMSE were instructed and given by trained nurse (D.H.K.), and all participants have finished filling in the questionnaire with the assistance of supervisor (D.H.K.).

This study was approved by Institutional Review Board at Seoul National University Boramae Medical Center (IRB No. 06-2011-128, 26-2014-115), and informed consent was obtained from all the participating subjects. Brain image data with the same study protocol from healthy control subjects who were age-matched to our PD patients were included in the analysis.

2.2. Image acquisition and preprocessing

A 3.0-Tesla magnetic resonance imaging scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands) was used in this study. The acquisition parameters for the volumetric T1 images were repetition time, 9.9 ms; echo time, 4.6 ms; slice thickness, 1 mm; intersection gap, 1 mm; matrix, 224 × 224; flip angle 8°. The detailed protocols for DTI acquisition were matrix, 112 × 112; repetition time, 6598.2 ms; echo time, 66 ms; slice thickness, 2 mm; intersection gap, 2 mm; flip angle, 90°; 1 T2-weighted image with no diffusion sensitization (b0 images); 15 diffusion-weighted images (b = 800 s/mm^2).

2.3. Assessment of gray matter structural changes: voxel-based morphometry (VBM)

Preprocessing steps for VBM were performed with Statistical Parametric Mapping 8 (SPM8, www.fil.ion.ac.uk/spm) implemented on MATLAB (http://www.mathworks.com). The images for gray matter, white matter and cerebrospinal fluids were identified and segmented using tissue probability maps included in SPM. Intersubject alignments of gray and white matter images were performed by nonlinear deformations with the DARTEL (diffeomorphic anatomical registration using exponentiated lie algebra) toolbox in SPM8 [14]. The segmented and modulated gray matter images were then spatially normalized to MNI (Montreal Neurological Institute) space and smoothed with a Gaussian kernel of 10 × 10 × 10 mm. The smoothed gray matter images were globally normalized by total intracranial volume, and a masking threshold of 0.1 was applied. Image data were entered for group comparisons adjusted for age, gender, PD duration and Hoehn and Yahr stage. The statistical thresholds were set at $p < 0.001$ uncorrected for multiple comparisons and an extent threshold k of 50 voxels.

2.4. Assessment of white matter structural changes: tract-based spatial statistics (TBSS)

DTI processing steps were performed with FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl). DTI images were corrected for eddy currents and motion using the B0 image of each subject. Subsequently, DTI-derived maps of the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated and further processed for TBSS. The DTI-derived maps were non-linearly registered to a FMRIB58_FA template and projected to a precalculated FA skeleton based on the FA data from the study subjects. Then, a skeleton mask of FA > 0.2 was applied to eliminate non-white matter tissues and misalignment issues. Voxel-wise statistics were done for all skeletonized DTI measures across subjects using a general linear model with threshold-free cluster enhancement methods and 10,000 permutations. A statistical threshold for group comparisons was set at $p < 0.05$ corrected for multiple comparisons.