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Thalamic volume and related visual recognition are associated with freezing of gait in non-demented patients with Parkinson's disease

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ABSTRACT

Background: The pathophysiology of freezing of gait (FOG) in non-demented Parkinson's disease (PD) patients remains poorly understood. Recent studies have suggested that neurochemical alterations in the cholinergic systems play a role in the development of FOG. Here, we evaluated the association between subcortical cholinergic structures and FOG in patients with non-demented PD.

Methods: We recruited 46 non-demented patients with PD, categorized into PD with (n = 16) and without FOG (n = 30) groups. We performed neuropsychological test, region-of-interest-based volumetric analysis of the substantia innominata (SI) and automatic analysis of subcortical brain structures using a computerized segmentation procedure.

Results: The comprehensive neuropsychological assessment showed that PD patients with FOG had lower cognitive performance in the frontal executive and visual-related functions compared with those without freezing of gait. The normalized SI volume did not differ significantly between the two groups (1.65 ± 0.18 vs. 1.68 ± 0.31). The automatic analysis of subcortical structures revealed that the thalamic volumes were significantly reduced in PD patients with FOG compared with those without FOG after adjusting for age, sex, disease duration, the Unified PD Rating Scale scores and total intracranial volume (left: 6.71 vs. 7.16 cm^3, $p = 0.029$, right: 6.47 vs. 6.91 cm^3, $p = 0.026$). Multiple linear regression analysis revealed that thalamic volume showed significant positive correlations with visual recognition memory (left: $\beta = 0.441$, $p = 0.037$, right: $\beta = 0.498$, $p = 0.04$).

Conclusions: These data suggest that thalamic volume and related visual recognition, rather than the cortical cholinergic system arising from the SI, may be a major contributor to the development of freezing of gait in non-demented patients with PD.

Freezing of gait (FOG) is a unique and disabling symptom usually observed in 25% of early Parkinson's disease (PD) patients and 50% of patients with advanced PD [1]. FOG is an episodic inability to initiate gait and turning, in which the feet appear 'glued to the floor' [1]. It has been recognized that FOG is associated with motor dysfunction, cognitive processing and affective symptoms [2]. Although it definitely contributes to worsening the quality of life of patients with PD, the pathophysiology remains poorly understood. A recent review described that FOG induced by gait pattern generation disturbance, motor and cognitive automaticity failure, and frontal executive and perceptual malfunction [3]. And there are several evidences that structural and functional alteration may be involved in FOG. A volumetric analysis demonstrated that FOG is associated with frontal, temporal and inferoposterior parietal cortical atrophy [4]. Functional imaging studies showed that decreased coordinated neural connectivity, such as executive attention and visual network, is related to the development of FOG [5–7].

FOG is an independent motor symptom that is not correlated with parkinsonian motor symptoms of bradykinesia or rigidity, but is well correlated with frontal executive function, suggesting that distinct pathological or neurochemical changes in extra-dopaminergic system may underlie its pathogenesis [4]. Recent studies have suggested that neurochemical alterations in the cholinergic systems might play a role in the FOG development along with cognitive impairment [8,9]. There are two major sources

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of cholinergic projections in the brain. The nucleus basalis of Meynert located in the substantia innominata (SI) of the basal forebrain provides the principal cholinergic input of the cortical areas and the pedunculopontine nucleus provides the major cholinergic input to the thalamus [9]. In the present study, we hypothesized that cholinergic systems in the brain is related to the development of FOG and also influences cognitive performance in Parkinson's disease. To test our hypothesis, we performed region-of-interest-based volumetric analysis of the SI and automatic analysis of subcortical brain structures using computerized segmentation procedure in non-demented patients with PD to further elucidate the association between cholinergic structures and FOG. Additionally, we evaluated neuropsychological profiles and their associations with volumes of the SI and subcortical structures.

1. Patients and method

1.1. Subjects

In this study, 46 non-demented PD patients, who completed magnetic resonance imaging (MRI), comprehensive neuropsychological studies and FOG questionnaire [10], were recruited retrospectively from Apr 2009 to May 2011 at a university hospital by convenience sampling. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank [11]. The patients were categorized into two groups: PD with FOG ($n = 16$) and PD without FOG ($n = 30$) groups, depending on the presence of FOG. Patients who fulfilled the following conditions were categorized in the PD with FOG group: a) score >1 on the FOG Questionnaire item 3, b) observation of FOG by experienced neurologists (S.M.K and H.J.Y). Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part (UPDRS) III.

We used the Seoul Neuropsychological Screening Battery (SNSB) to determine the cognitive performance in both groups of patients [12,13]. The SNSB includes cognitive subsets of attention, language and related functions (reading, writing, comprehension, repetition, confrontational naming using the Korean version of the Boston Naming Test), visuospatial function (drawing an interlocking pentagon and the Rey Complex Figure Test), verbal memory (the Seoul Verbal Learning Test), visual memory (the RCFT; immediate recall, 20 min delayed recall and recognition), and frontal executive function (phonemic and semantic Controlled Oral Word Association Test and Stroop test). All patients showed no evidence of abnormal activities of daily living and scored above the 16th percentile for age and the educational-appropriate norm in the Korean version of the Mini Mental State Examination (K-MMSE). The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms in patients with PD [14]. Exclusion criteria included evidence of dementia compatible with the clinical diagnostic criteria for probable PD dementia [15], presence of focal brain lesions on brain MRI, or the presence of other neurodegenerative diseases that might account for parkinsonism. This study was approved by the Yonsei University Severance Hospital ethical standards committee on human experimentation for experiments using human subjects. Written informed consent was obtained from all subjects participating in this study.

1.2. Volumetric determination of SI

The SI volumes were determined by manually delineating the boundaries of this structure with MRIcro software [16] on the coronal T1-weighted MRI scans. The delineation of the SI on the MRI was based on the method reported previously [17,18]. Briefly with the first section at the level of the crossing of the anterior commissure, the ventral aspect of the globus pallidus demarcated the dorsal border of the SI, whereas the ventral border was the base of the brain containing the anterior perforated space. The medial border of the SI was operationally defined by a vertical line extending from the ventrolateral border of the stria terminalis to the base of the brain. The lateral border extended to the medial aspect of the putamen. In the second section traced, the anterior commissure might be uncrossed. The third section evaluated was at the level of the emergence of the anterior commissure from the temporal lobe. The anatomical landmarks used to define the SI borders were applied to all three consecutive sections. The total SI volume calculated included both the right and left hemispheres. Normalized SI volume was defined by the following formula: total SI volume (mm3)/intracerebral volume (mm^3) ×10,000. Tracings were performed blindly (by S.M.K and L.J.E), and the expressed correlation coefficients of intra- and inter-rater reliability were 0.79 and 0.82, respectively.

1.3. Segmentation and volumetric analysis for subcortical structure

Volumetric analysis for subcortical structures was performed with FMRIB's Software Library (FSL)—FMRIB's Integrated Registration and Segmentation Tool (FIRST, version 5.0). The method is the automated model-based registration and segmentation tool, which is optimized for segmentation of deep subcortical structures including caudate nucleus, putamen, pallidum, thalamus, hippocampus [19].

The T1-weighted MR inputs are registered to MNI (Montreal Neurological Institute) 152 standard space with 12 DOF (degree of freedom) affine transformation. Secondly, each structure was segmented, based on shape models using another 12 DOF registration with application of a subcortical mask. Then, boundary correction was applied with FSL's FAST tool, which re-classifies boundary voxels by determining whether these voxels belong to each structure according to their intensity. After the registration and segmentation, output with each structure from the procedure was manually checked and no gross error was revealed. Finally, summary of segmented volumes of bilateral caudate, putamen, palladium and thalamus were acquired using routine FSL command: FSLstats (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils).

For estimation of total brain volume adjusted for individual skull sizes, SIENAX [20], part of FSL was used [21]. After extraction of skull images from the whole-head input data, brain images are registered to the MNI152 standard space, using skull image to determine the registration scaling. Finally, tissue-type segmentation with partial volume estimation is performed to calculate volume of brain (including separate estimates of volumes of gray and white matter).

1.4. Statistical analysis

Data were expressed as the mean ± SD. The chi-square and independent *t*-tests were used to evaluate categorical and continuous variables, respectively. Analysis of covariance was used to compare the difference of cognitive performance and deep gray matter volume between PD patients with and without FOG adjusted for the effects of confounders (age, sex, disease duration, BDI, UPDRS scores and total intracranial volume). Multiple linear regression analysis was calculated for the correlation between volumes of the SI and subcortical structures and each cognitive subsets adjusted for age, sex, BDI and disease duration. Statistical analyses were performed using commercially available software (SPSS, V.18.0), and a two-tailed $p < 0.05$ was considered significant.

2. Result

2.1. Demographic characteristics

Demographic characteristics of the patients are presented in Table 1. No significant differences in age, sex, education, parkinsonism duration, clinical dementia rating, and levodopa equivalent dose were observed. K-MMSE scores were significantly lower in PD patients with FOG than in those without FOG (26.1 vs. 27.4, $p = 0.035$). UPDRS motor score (30.7 vs. 18.7, $p < 0.01$) and BDI scores (23.07 vs. 13.09, $p < 0.01$) were higher in PD patients with FOG than in those without FOG. The detailed neuropsychological test results are shown in Table 2. The PD with FOG group showed more severe cognitive deficits in the visuoconstructional (27.3 vs. 32.1, $p = 0.020$), total COWAT (40.1 vs. 52.3, $p = 0.041$) compared with the PD group without FOG. Additionally, the PD with FOG group had lower scores in RCFT recognition domain (17.9 vs. 19.1,

Table 1
Demographic characteristics between PD with FOG and PD without FOG.

	FOG (+) ($n = 16$)	FOG (−) ($n = 30$)	*p*-value
Age (yr)	66.7 (4.8)	68.8 (3.7)	NS
Gender (number of men, %)	7 (43.8%)	14 (46.7%)	NS
Education durations (yrs)	7.8 (5.4)	9.8 (4.2)	NS
Parkinsonism duration (yrs)	4.2 (1.9)	3.3 (1.7)	NS
UPDRS motor score	30.7 (14.5)	18.7 (7.4)	<0.001
K-MMSE	26.1 (2.4)	27.4 (1.8)	0.035
BDI	23.1 (5.9)	13.1 (7.75)	<0.001
Levodopa equivalent dose (mg)	554.7 (168.7)	507.5 (239.1)	NS
Total intracranial volume (mm^3)	1328730.0 (108532.4)	1353502.9 (86198.7)	NS

K-MMSE: the Korean version of the Mini-Mental State Examination, BDI: Beck Depression Inventory, Values are expressed as mean (standard deviation), NS; not significant.