Parkinsonism and Related Disorders 64 (2019) 169–174

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Involvement of cortical dysfunction in frequent falls in patients with Parkinson's disease

Hironori Otomune[a,b], Masahito Mihara[a,c,*], Noriaki Hattori[a,b], Hiroaki Fujimoto[a,b], Yuta Kajiyama[a], Kuni Konaka[a,d], Yukiko Mitani[a,c], Yoshiyuki Watanabe[e], Hideki Mochizuki[a,**]

[a] Department of Neurology, Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan
[b] Neurorehabilitation Research Institute, Morinomiya Hospital, Osaka, 536-0025, Japan
[c] Department of Neurology, Kawasaki Medical School, Kurashiki, Okayama, 701-0192, Japan
[d] Department of Physical Therapy, Faculty of Health Science, Osaka Yukioka College of Health Science, Osaka, 567-0801, Japan
[e] Department of Future Diagnostic Radiology, Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan

ARTICLE INFO

Keywords:
Parkinson disease
Accidental falls
Cerebral cortex
Gray matter

ABSTRACT

Introduction: Gait and balance disorders are common clinical features of Parkinson's disease (PD). Although falls significantly affect the activities of daily living (ADL) and quality of life (QOL) of patients with PD, the underlying neural mechanisms associated with frequent falls in PD patients are still unclear.
Methods: Hypothesizing that the cerebral cortex would contribute to frequent falls in PD, we obtained 3D T1-weighted images from 91 non-dementia patients with PD and performed voxel-based morphometric analysis (VBM). Gray matter volume was compared between patients with and without frequent falls to investigate the structural basis for frequent falls in PD. As an ancillary analysis, we also performed resting-state functional magnetic resonance analysis using data from 58 patients.
Results: Among the 91 patients, 36 had experienced frequent falls. Gray matter volume in the right superior temporal gyrus (STG) and the right inferior parietal lobule (IPL) of these patients was significantly lower than that of the non-frequent fallers. There was also a significant correlation between fall frequency and gray matter volume in these two regions. Additionally, resting-state functional analysis revealed lower connectivity in the right posterior perisylvian region, including in the IPL and STG, in frequent fallers than in non-frequent fallers.
Conclusion: Frequent falls in PD are associated with structural and functional abnormality of the cerebral cortex including the right IPL and STG.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive degenerative disorder of the central nervous system characterized by motor symptoms, including rigidity, bradykinesia, resting tremor, and postural instability. Although falls are also common in the general older population, previous studies have revealed that PD patients more often experience recurrent falls [1], resulting in a higher rate of hospital admissions due to injuries and fractures [2] and decreased physical activity [3]. Therefore, falls in PD patients have a significant impact on their activities of daily living (ADL) and quality of life (QOL) [4]. Based on clinical investigations, several risk factors for falling have been proposed, including a history of falling, severe disease symptoms, long disease duration, balance impairment, gait freezing, and cognitive decline [1]. However, falls in PD are associated with multiple factors and no single cause would usually result in all falls [5]. Although structural and functional changes in various cortical and subcortical regions may be involved in gait and balance impairments in PD patients [6], a previous study suggested the involvement of the cerebral cortex in gait and balance impairment in PD by demonstrating the positive effect of cortical facilitation on gait and postural control [7]. Another study also found that neocortical cholinergic function is associated with gait ability in PD [8]. The upward propagation of the degenerative process from the brainstem to the neocortex would suggest cortical involvement in gait and balance impairment in advanced PD [9]. However, an imaging study by Rosenberg-Katz et al. on frequent falls provided inconclusive findings. They demonstrated a relationship between reduced gray matter volume in the caudate head and fall history

** Corresponding authors. Department of Neurology, Osaka University Graduate School of Medicine2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan.
* Corresponding authors. Department of Neurology, Kawasaki Medical School 577 Matsushima, Kurashiki, Okayama, 701-0192, Japan.
E-mail addresses: mihara@med.kawasaki-m.ac.jp (M. Mihara), hmochizuki@neurol.med.osaka-u.ac.jp (H. Mochizuki).

https://doi.org/10.1016/j.parkreldis.2019.04.007
Received 25 September 2018; Received in revised form 4 April 2019; Accepted 7 April 2019
1353-8020/

but also showed increased functional connectivity between the left posterior parietal lobe and right inferior parietal lobe [10]. Based on these findings, we hypothesized that some specific cortical dysfunction may be associated with frequent falls in PD patients. In the present study, we conducted voxel-based morphometric (VBM) analysis using magnetic resonance imaging (MRI) data to determine the structural alterations in the brain associated with frequent falls in PD patients without dementia. In addition to the structural analysis, we also performed functional connectivity analysis using resting-state data as an ancillary analysis.

2. Methods

2.1. Study participants

We recruited 91 patients with PD (38 men and 53 women; age, 69.0 ± 8.8 y; Hoehn-Yahr [HY] stage, 2.6 ± 0.8) who were admitted to our hospital between March 2014 and June 2016. The inclusion criteria were as follows: (1) a clinical diagnosis of PD based on the UK brain-bank criteria [11], (2) an HY stage < 5 when on medication, (3) no contraindication for MRI, and (4) a Mini–Mental State Examination (MMSE) score ≥ 23 without severe cognitive deficiency that impaired ADL (determined by asking both patients themselves and their caregivers). As a baseline cognitive assessment to exclude dementia, we also measured digit span. Written informed consent was obtained from each patient and the study protocol was approved by the Ethics Review Board of Osaka University Hospital.

2.2. Clinical assessment

In addition to background characteristics (age, sex, handedness, disease duration, dominant side, cognitive status, and medication history), we evaluated motor symptoms in the on-drug condition using the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and the freezing of gait questionnaire (FOG-Q).

Study participants were divided into two groups, “frequent fallers” and “non-frequent fallers,” by assessing their fall frequency via interviews with them and their caregivers. Only approximately 20% of early PD patients experience falls more than once a week [12]. Moreover, in a study of falls among community-dwelling adults, in which fallers were defined as those who had fallen at least once a month on average during the past 12 months, many had difficulty recalling falls over a 12 month period [13]. Therefore, we defined frequent fallers as patients who had experienced more than five falls during the preceding 6 months. Likewise, patients who had fallen less than once a month in the preceding 6 months were defined as non-frequent fallers.

We compared baseline clinical characteristics between frequent and non-frequent fallers using a two-sample *t*-test for continuous variables and a chi-squared test for nominal variables and set the statistical significance threshold at $p < 0.05$.

2.3. Image acquisition and analysis for VBM analysis

Three-dimensional (3D) T1-weighted images were obtained for all study participants using a Discovery MR750 3.0T scanner (GE Healthcare, Milwaukee, WI, USA). For anatomical scans, a sagittal 3D fast-spoiled gradient recalled echo pulse sequence was used with the following parameters: echo time (TE) = 2.7 ms, repetition time (TR) = 7.0 ms, inversion time = 400 ms, matrix dimensions = 256 × 256, field of view (FOV) = 240 mm, slice thickness = 1.2 mm and slice number = 200. T2-weighted fast-spin echo and fluid-attenuated inversion-recovery axial scans were also acquired to enable better identification of possible vascular damage.

After converting images from DICOM to the NifTI format using DCM2Nii, we performed VBM analysis using Statistical Parametric Mapping 8 (SPM 8: http://www.fil.ion.ucl.ac.uk/spm/) on MATLAB R2015a (Mathworks, Natick, MA, USA) [14]. Pre-processing was performed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) with Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template. After the images were segmented into gray matter, white matter, and cerebrospinal fluid volumes, normalization was performed to align the individual images to a standard Montreal Neurological Institute space. Each volume was modulated with Jacobian determinants obtained in the process of normalization. During this process, they were corrected, with the total intracranial volume calculated from the sum of individual segment volumes. Finally, segments were smoothed using an 8-mm full-width-at-half-maximum parameter and gray matter volumes were compared between frequent fallers and non-frequent fallers.

For comparison between the gray matter volume change between the two patient groups, we used a two-sample *t*-test. To eliminate possible confounding effects of several clinical features related to frequent falls, we included age, MDS-UPDRS part III, and freezing severity as covariates. The statistical significance threshold was set at an uncorrected $p < 0.001$ at the initial voxel level with a false discovery rate adjusted $p < 0.05$ at cluster level and an extent threshold of $k_E = 250$ voxels. We also performed Spearman's correlation analysis between fall frequency and gray matter volume reduction of regions detected in VBM analysis. In the correlation analysis, we also considered $p < 0.05$ as statistically significant.

2.4. Imaging acquisition and analysis for resting state functional MRI

As an ancillary analysis, we also performed resting-state connectivity analysis using resting-state fMRI (rsfMRI) data. rsfMRI was performed with spin-echo echo-planar imaging under the following conditions: time points = 240, TR = 2500 ms, TE = 30 ms, flip angle = 80°, matrix = 64 × 64, FOV = 220 mm, slice thickness = 3.5 mm and slice number = 40 at the same time as the anatomical imaging acquisition. During rsfMRI scans, we instructed participants to lay still with their eyes open and to look at the fixation cross without thinking about anything for 10 min. Because our institutional resting-state fMRI protocol was changed during our study, rsfMRI data using the above protocol were only obtained from 58 patients. We compared baseline clinical characteristics between frequent and non-frequent fallers using a two-sample *t*-test for continuous variables and a chi-squared test for nominal variables and set the statistical significance threshold at $p < 0.05$ (Table S1).

To investigate differences in whole-brain functional connectivity between the two groups, we used the CONN-fMRI Functional Connectivity toolbox v17 (http://www.nitrc.org/projects/conn). After pre-processing (i.e., normalized, segmented, and smoothed) the structural and functional MRI images using the default preprocessing pipeline of the CONN-toolbox, we eliminated the first 10 vol to assure that the MR signal reached stability and then excluded outlier scans in which head motion was > 0.9 mm. Datasets were de-noised and bandpass filtered (0.009–0.08 Hz) for blood-oxygen-level-dependent (BOLD) signals, which are blood oxygenation indicators. Because we focused on functional connectivity among supratentorial regions, we excluded cerebellar regions of interest (ROIs), thereby obtaining 106 ROIs (91 cortical and 15 subcortical ROIs from the FSL Harvard-Oxford Atlas) for further ROI-to-ROI analysis. As for the VBM analysis, we included age, MDS-UPDRS part III, and freezing severity as covariates to eliminate possible confounding effects. In the ROI-to-ROI analysis, a false discovery rate adjusted $p < 0.05$ at the seed level was considered statistically significant.

Table 1
Demographics and clinical evaluation results of PD patients with and without frequent falls.

	Non-frequent fallers	Frequent fallers	Total
Number of subjects	55	36	91
Sex (M/F)	24/31	14/22	38/53
Age (y)	67.8 ± 7.8	70.8 ± 9.9	69.0 ± 8.8
Handedness (right/left)	54/1	36/0	90/1
Disease duration*	3.3 ± 2.8	7.4 ± 5.2	4.9 ± 4.4
Dominant side of symptom (right/left/none)	26/29/0	14/19/3	40/48/3
Medication (Levodopa equivalent daily dose)	274.6 ± 236.1	437.8 ± 426.3	345.1 ± 336.4
Hoehn-Yahr*	2.2 ± 0.5	3.2 ± 0.8	2.6 ± 0.8
MDS-UPDRS part III*	27.1 ± 12.2	33.0 ± 12.2	29.5 ± 12.5
FOG-Q*	6.9 ± 5.7	15.4 ± 4.9	10.2 ± 6.8
MMSE	27.4 ± 3.6	26.5 ± 3.3	27.1 ± 3.5
Digit span forward (n = 90)	5.6 ± 1.2	5.6 ± 1.0	5.6 ± 1.1
Digit span backward (n = 90)	4.1 ± 1.0	3.9 ± 0.7	4.0 ± 0.9

Abbreviations: PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; FOG-Q, Freezing of Gait Questionnaire; MMSE, Mini-Mental State Examination.
*$p < 0.05$.

3. Results

3.1. Clinical characteristics

Among the 91 patients, 36 were classified as frequent fallers. Compared with non-frequent fallers, frequent fallers exhibited significantly more severe freezing, longer disease duration, higher HY stages, and higher MDS-UPDRS part III scores. Age, handedness, dominant side, levodopa equivalent dose, MMSE, and both digit span forward and backward did not significantly differ between the two groups (Table 1). T2-weighted images did not reveal severe vascular damage in any of the patients. Among the 58 patients for whom resting-state fMRI scans were obtained, 15 were frequent fallers (Table S1).

3.2. Voxel-based morphometry (VBM) analysis

After adjusting for the effects of age, MDS-UPDRS part III score, and freezing severity, frequent fallers showed significantly lower gray matter volume in the right superior temporal gyrus (STG; $p_{\text{-FDR}} = 0.009$, $k_E = 362$), the right supramarginal gyrus, and part of the inferior parietal lobule (IPL; $p_{\text{-FDR}} = 0.024$, $k_E = 258$), compared with non-frequent fallers (Fig. 1). Furthermore, there were significant linear correlations between fall frequency and gray matter volume reduction in the right IPL (Fig. 2(A), $R = -0.496$, $p < 0.001$) and right STG (Fig. 2(B), $R = -0.416$, $p < 0.001$).

3.3. Functional connectivity analysis

As shown in Fig. 3, functional connectivity analysis revealed the resting-state connectivity between the left pallidum and right perisylvian cortical area of frequent fallers was lower than that of non-frequent fallers. This network included the right planum temporale, the right anterior STG, and the right parietal operculum, which is part of the IPL. Further, resting-state connectivity between the left paracingulate gyrus (PaCiG) and the posterior middle temporal gyrus (MTG) of frequent fallers was lower than that of non-frequent fallers.

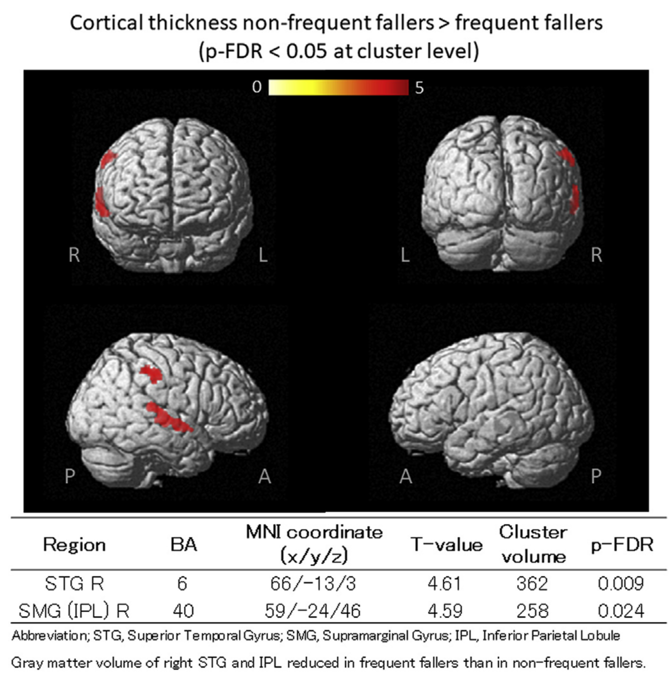


Fig. 1. Voxel-based morphometry (VBM) analyses. VBM analysis for 91 patients. Significantly reduced gray matter volume can be seen in the right inferior parietal lobule and superior temporal gyrus in frequent fallers.

4. Discussion

Consistent with our hypothesis, gray matter volume in the right IPL and STG of frequent fallers was significantly lower than that of non-frequent fallers. There were also significant linear correlations between fall frequency and gray matter volume reduction in these areas. It is well-known that the IPL receives input from the visual and somatosensory cortex and plays an essential role in multimodal sensory integration and processing [15]. Previous studies have found that various areas of the IPL may be involved in vestibular information processing. The involvement of the supramarginal gyrus in maintaining an upright posture in healthy subjects has also been suggested [16]. In PD patients, gray matter loss in the IPL has been associated with freezing of gait [17] and the postural instability gait difficulty (PIGD) subtype [18]. These results indicate that the IPL is involved in gait and balance control in PD patients. Along with the IPL, the STG has been implicated in the processing of vestibular information and postural function [19]. A previous study found that vestibular dysfunction, including abnormalities in subjective visual vertical in PD patients, resulted in an increased risk of falls [20]. It has been reported that the perception of subjective visual vertical was impaired due to lesions in the right perisylvian [21,22]. In addition, a recent study found that neuromodulatory inhibition of the right STG led to impaired self-motion perception [23]. These findings suggest an essential role of the STG in postural control.

Consistent with VBM analysis, functional connectivity analysis revealed reduced resting-state connectivity between the left pallidum and the right perisylvian region and postcentral gyrus in frequent fallers;

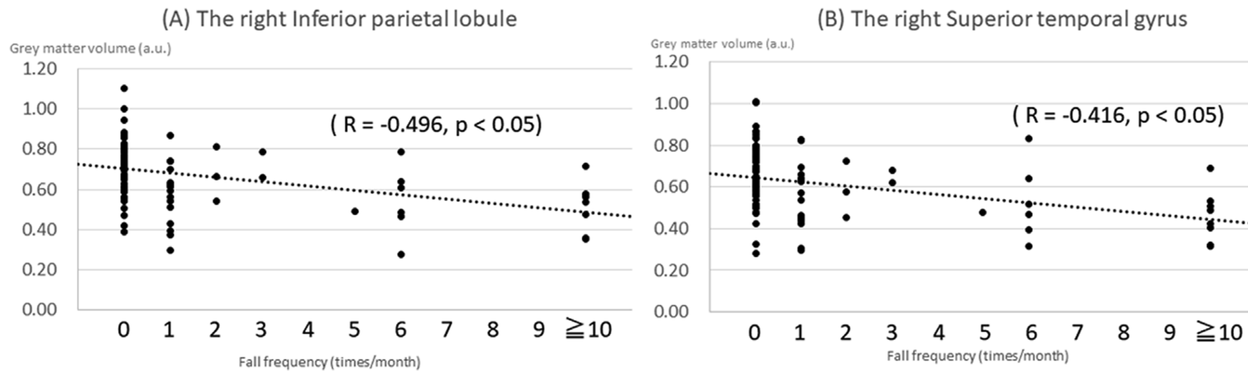
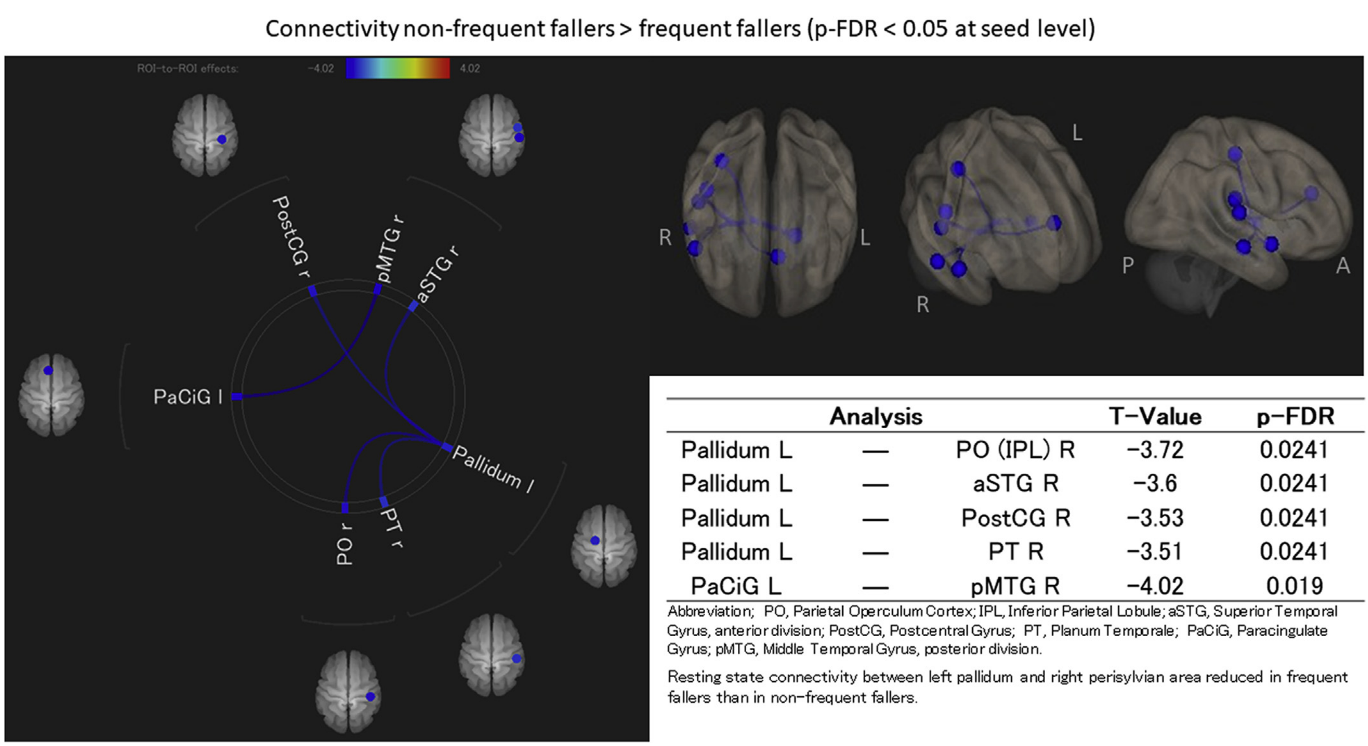


Fig. 2. Correlation analysis between fall frequency and gray matter volume in Voxel-based morphometry (VBM). The scatter plot represents the mean gray matter volume in each region. There were significant correlations between fall frequency and gray matter volume reduction (A) in the right inferior parietal lobule and (B) the right superior temporal gyrus.

this finding supports the possible involvement of these cortical areas in frequent falls in PD patients. In addition to the perisylvian region, including the STG and IPL, the involvement of the parietal operculum has also been proposed in a study of patients with chronic vestibular impairment [24]. Taken together, cortical functional networks involved in vestibular information processing and postural control would be more impaired in frequent fallers than in non-frequent fallers with PD. One possible interpretation is that the degenerative process propagated to the cerebral cortex would result in cortical volume reduction and reduced functional connectivity [9]. Another possibility is that severe dopaminergic deficiency in frequent fallers results in excessive cortical inhibition via the basal ganglial network. However, a simple physiological model could not fully explain our findings, suggesting a *trans*-hemispheric alteration of the cortico-basal ganglial network. Nonetheless, our findings indicate a close relationship between fall tendency and a functional brain network including the basal ganglia and the cortical center for somesthetic graviception. In addition, although a connection between the left PaCiG and the right MTG was not expected, the right MTG has been reported to be associated with a sense of body verticality in patients with pusher syndrome [25], which is consistent with our interpretation above.

In the present study, reduced gray matter volume and resting-state connectivity were apparent on the right side of the brain, although neither handedness nor the dominant side differed significantly between the two groups. In general, the two hemispheres differ in their capacity for information processing, with the left hemisphere being dominant for language processing and the right for processing visuospatial relations [26]. A previous study found that vestibular information processing is also performed largely by the non-dominant hemisphere [27]. These findings support the likelihood that right-dominant anatomical and functional alterations could lead to impaired integration of multimodal sensory information in frequent fallers.

The present study had several limitations. First, we investigated the frequency of falls solely via interviews, which may have underestimated the number of falls. Second, we observed significant differences in background characteristics between patients with and without



Analysis			T-Value	p-FDR
Pallidum L	—	PO (IPL) R	−3.72	0.0241
Pallidum L	—	aSTG R	−3.6	0.0241
Pallidum L	—	PostCG R	−3.53	0.0241
Pallidum L	—	PT R	−3.51	0.0241
PaCiG L	—	pMTG R	−4.02	0.019

Fig. 3. Functional connectivity analysis. Functional connectivity analysis for 58 patients. Significantly reduced functional connectivity can be seen in the right perisylvian region in frequent fallers.

frequent falls. Although we attempted to reduce confounding effects by including the above factors in our statistical model, it is possible that these or other factors not chosen as confounders might have affected the results of the VBM and connectivity analysis. Third, we only screened gross cognitive status using MMSE. Domain-specific cognitive impairment evaluation was incomplete so we could not exclude patients with mild cognitive impairment [28,29]. Declined cognitive status, especially executive, attentional, and visuospatial domains have been associated with impaired gait and increased risk of falling [30]. Previous postural-cognitive dual-task studies revealed that impaired ability to divide sufficient attentional resources between multiple postural tasks in PD patients can result in falling [31]. Therefore, we could not exclude the possibility that a mild cognitive decline in fallers might be associated with reduced cortical volume. A previous study suggested the positive correlation between gray matter volume and MMSE score in the temporal gyrus including the STG [32], but our study showed no group difference in MMSE scores between frequent fallers and non-frequent fallers. In addition, although cognitive decline is associated with increased fall risk in PD, falls may occur in patients with or without cognitive impairment [33]. Future studies should focus on investigating the association between falls in PD and individual cognitive and postural ability. Fourth, the resting-state fMRI could not be performed in all patients and our results might not be reflective of the study population. Finally, although we suspected that multimodal sensory information and vestibular information processing were associated with frequent falls, specific clinical assessments, including subjective visual vertical analysis, were not performed.

5. Conclusions

We found that anatomical and functional alterations in brain networks, including the right perisylvian region, are associated with frequent falls in PD patients. Our findings suggest that impaired processing and integration of multimodal sensory information, especially vestibular information, might relate to postural impairments in PD patients. Our findings also support the possibility that the right perisylvian region, including the IPL and STG, is a potential target for early detection and neuromodulatory intervention to address falls in PD patients.

Author contribution statement

H.O., M.M., and H.M designed the study. H.O., M.M., H.F., Y.K., K.K., and Y.M. assessed and collected patient clinical data. Y.W. performed the MRI. H.O., M.M., and N.H. analyzed and interpreted the data. H.O., M.M., and H.M. wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Declarations of interest

None.

Acknowledgments

We appreciate the meaningful suggestions and support from Dr. G. S. Revankar, and other laboratory members.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.04.007.

Financial disclosures of all authors

M. Mihara. Grants: Health and Labour Sciences Research Grants for Comprehensive Research on Persons with Disabilities (JP15652696) from the Japan Agency for Medical Research and Development (AMED), Grant in aid for Scientific Research (C) (Kakenhi: JP16717091) from the Japan Society for the Promotion of Science (JSPS), and a grant from the Japan Foundation for Neuroscience and Mental Health.

H. Mochizuki. Grants: Health and Labour Science Research Grants for research on rare and intractable diseases, from the Ministry of Health, Labour, and Welfare of Japan, and a grant for the Practical Research Project for Rare/Intractable Diseases from AMED.

Y. Kajiyama. Grants: Grant in aid for Scientific Research (C) (Kakenhi: JP16717091) from JSPS.

Kuni Konaka. Grants: Grant in aid for Scientific Research (C) (Kakenhi: JP16717091) from JSPS.

Funding

This work was supported by the Grant in aid for Scientific Research (C) (Kakenhi: JP16717091) from JSPS.

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