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Brain metabolism in patients with freezing of gait after hypoxic-ischemic brain injury

A pilot study

Seo Yeon Yoon, MD[a,b], Sang Chul Lee, MD, PhD[c], Na Young Kim, MD[c], Young-Sil An, MD, PhD[d], Yong Wook Kim, MD, PhD[c,*]

Abstract

Movement disorders are 1 of the long-term neurological complications that can occur after hypoxic-ischemic brain injury (HIBI). However, freezing of gait (FOG) after HIBI is rare. The aim of this study was to examine the brain metabolism of patients with FOG after HIBI using F-18 fluoro-2-deoxy-D-glucose positron emission tomography (F-18 FDG PET).

We consecutively enrolled 11 patients with FOG after HIBI. The patients' overall brain metabolism was measured by F-18 FDG PET, and we compared their regional brain metabolic activity with that from 15 healthy controls using a voxel-by-voxel-based statistical mapping analysis. Additionally, we correlated each patient's FOG severity with the brain metabolism using a covariance analysis.

Patients with FOG had significantly decreased brain glucose metabolism in the midbrain, bilateral thalamus, bilateral cingulate gyri, right supramarginal gyrus, right angular gyrus, right paracentral lobule, and left precentral gyrus ($P_{FDR\text{-}corrected} < .01$, $k = 50$). No significant increases in brain metabolism were noted in patients with FOG. The covariance analysis identified significant correlations between the FOG severity and the brain metabolism in the right lingual gyrus, left fusiform gyrus, and bilateral cerebellar crus I ($P_{uncorrected} < 0.001$, $k = 50$).

Our data suggest that brain regions in the gait-related neural network, including the cerebral cortex, subcortical structures, brainstem, and cerebellum, may significantly contribute to the development of FOG in HIBI. Moreover, the FOG severity may be associated with the visual cortex and cerebellar regions.

Abbreviations: BG = basal ganglia, FOG = freezing of gait, HIBI = hypoxic-ischemic brain injury, PD = Parkinson disease, PET = positron emission tomography.

Keywords: brain metabolism, freezing of gait, hypoxic-ischemic brain injury

1. Introduction

Hypoxic-ischemic brain injury (HIBI) is a devastating condition, which frequently results in death or profound long-term neurological sequelae. Common etiologies of HIBI include sudden cardiac arrest, acute respiratory failure, and carbon monoxide intoxication.[1] As noted by Greer,[1] the anatomy, pathophysiology, and neurological complications of HIBI vary depending on the cause of the injury. Among the neurological complications, movement disorders including parkinsonism, dystonia, chorea, and myoclonus are estimated to occur in up to 40% of affected individuals.[2] Myoclonus is the most common movement disorder after HIBI, accounting for up to 30%.[2] Additionally, some patients suffer from parkinsonian symptoms for weeks or months after injury. Although studies suggest that the basal ganglia (BG) is especially vulnerable to hypoxia, with this vulnerability potentially being mediated by excitatory amino acid glutamate and N-methyl-D-aspartate receptors,[3] cases of isolated parkinsonism caused by HIBI are exceedingly rare[4]; thus, the precise mechanisms of parkinsonism after HIBI remain unclear.

Freezing of gait (FOG), a unique gait disorder in which patients are unable to initiate or continue locomotion, is 1 of the most disabling and least understood symptoms of advanced Parkinson disease (PD).[5] In FOG, patients have difficulty lifting their foot to step forward, making them feel as though their foot is glued or magnetized to the ground. FOG is very troublesome because of the high risk of falling, and FOG has a significant effect on the quality of life of patients with PD.[6] Unfortunately, the pathophysiological basis of FOG in these patients is not fully understood, although several not mutually exclusive hypotheses have been postulated.[7] For instance,[7] 1 potential explanation is that FOG is associated with dysfunctions in both the high-order cortical structures and brainstem regions that are involved in the dynamic and rhythmical control of gait.[7,8] However, clinical studies of FOG have focused mainly on PD, since FOG after HIBI

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[a] Department of Rehabilitation Medicine, Bundang Jesaeng General Hospital, Gyeonggi-do, [b] Department of Medicine, Graduate Program, Yonsei University College of Medicine, [c] Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, [d] Department of Nuclear Medicine and Molecular Imaging, Ajou University School of Medicine, Suwon, Republic of Korea.

[*] Correspondence: Yong Wook Kim, Department of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro Seodaemun-gu, Seoul 03722, Republic of Korea (e-mail: ywkim1@yuhs.ac).

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is extremely rare. Therefore, in this study, to investigate the pathophysiology of FOG caused by HIBI, we analyzed the differences in overall brain metabolism between healthy controls and patients with FOG after HIBI, and investigated which brain areas were correlated with the severity of FOG after HIBI using voxel-by-voxel-based statistical parametric mapping (SPM) analyses.

2. Methods

2.1. Subjects

From March 2009 to February 2015, we consecutively enrolled 11 patients who were diagnosed with FOG after HIBI. HIBI was determined by examining the brain magnetic resonance (MR) images acquired at the time of the initial injury and by reviewing the medical histories of the patients. The etiologies of HIBI in the 11 patients with FOG were sudden cardiac arrest in 7 patients, hypovolemia in 2 patients, acute respiratory failure in 1 patient, and carbon monoxide intoxication in 1 patient. All subjects underwent the Mini Mental State Examination (MMSE). Since an objective method for grading the FOG severity in patients with HIBI has not been established yet, we evaluated the severity using the FOG subscores of the Unified Parkinson Disease Rating Scale, which ranged from 0 (no freezing) to 4 (frequent falls from freezing). As controls, we recruited 15 age and sex-matched healthy individuals who were medically stable and who did not have any previous neurologic, orthopedic, or visual problems that might affect locomotion. All participants provided written informed consent, and the procedures were performed with the approval of the Yonsei Institutional Review Board for Clinical Studies (IRB No. 4-2015-1014).

2.2. Acquisition of F-18 fluoro-2-deoxy-D-glucose positron emission tomography images

Brain metabolism was assessed by acquiring images with F-18 fluoro-2-deoxy-D-glucose positron emission tomography (F-18 FDG PET) using a GE Advance PET scanner (GE). After fasting for at least 8 hours, subjects received 15 mCi (555 MBq) of F-18 FDG intravenously. All subjects rested, unstimulated, for 20 minutes, with their eyes closed and their ears unplugged, and then the scanning was started and continued for 15 minutes. To reduce head movement during scanning, the subjects were positioned and had their position maintained by an individually molded head holder. The in-plane and axial resolutions of the scanner were 4.8 mm full width at half maximum, respectively. F-18 FDG PET images were reconstructed using a transaxial, 8.5-mm Hanning filter and an 8.5-mm axial Ramp filter, and displayed in a $128 \times 128 \times 35$ matrix with a pixel size of $1.95 \times 1.95 \times 4.25$ mm.

2.3. Statistical analysis of F-18 FDG PET images

The PET images were analyzed using SPM2 (Institute of Neurology, University College London, UK). Before the statistical analysis, all of the subjects' PET images were averaged and spatially normalized to the Montreal Neurological Institute (MNI) standard PET template (MNI, McGill University, USA) using a nonlinear transformation in SPM2. The spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with a 12-mm full width at half maximum to increase the signal-to-noise ratio and to accommodate subtle variations in the anatomical structures. The effects of global metabolism were removed by normalizing the count of each voxel to the mean count of the brain.

After spatial normalization, we compared the overall brain metabolism of healthy controls with that of patients with FOG. The brain metabolism comparisons were performed on a voxel-by-voxel basis using a 2-sample *t* test. Statistical significance was determined using an extent threshold of 50 voxels. Correction for multiple comparisons was applied using false discovery rate (FDR) approaches, and the corrected threshold was set at $P < .01$. Additionally, using a covariance analysis model, we searched for brain areas in which the glucose metabolism was significantly correlated with the severity of FOG, covariated with age and the MMSE score. Regions with clusters of at least 50 continuous voxels that reached an uncorrected *P* value of .001 were considered significant. To visualize the *t*-score statistics, the significant voxels were projected onto 3-dimensional renderings of the brain provided by SPM2, thus allowing anatomic identification. Anatomic labeling of significant voxels was performed using the automated anatomic labeling program within the SPM toolbox, which was based on the anatomy provided by the MNI.

3. Results

Table 1 lists the baseline characteristics of the individuals in the FOG group. The FOG group consisted of 8 men and 3 women with a mean age of 35.92 ± 15.44 years (range 19–68 years), whereas the healthy control group consisted of 11 men and 4 women with a mean age of 37.36 ± 15.57 years (range 25–56

Table 1

General characteristics of HIBI patients with FOG.

No.	Age	Sex	Etiology of CPR and HIBI	Duration, mos	Subtype of FOG	MMSE	FOG grading	H&Y stage
1	41	M	Sudden cardiac arrest	3	Start/turning	13	4	4
2	26	M	Sudden cardiac arrest	4	Start/turning/destination	21	3	4
3	29	M	Sudden cardiac arrest	37	Start/turning	28	2	3
4	19	M	Sudden cardiac arrest	37	Turning/destination	13	4	3
5	28	M	Acute massive bleeding after accident	18	Turning/destination	25	4	3
6	30	F	Sudden cardiac arrest	5	Start/turning	19	3	4
7	32	F	Respiratory failure after suicidal hanging	1	Tight quarter	25	1	3
8	68	F	Severe carbon monoxide intoxication	4	Turning	5	1	4
9	36	M	Sudden cardiac arrest	4	Start/turning/destination	21	4	3
10	37	M	Sudden cardiac arrest	10	Start/turning/destination	25	4	3
11	65	M	Massive bleeding after stabbing injury	6	Start/turning/destination	25	4	4

F = female, FOG = freezing of gait, H&Y = Hoehn and Yahr, HIBI = hypoxic-ischemic brain injury, M = male, MMSE = Mini Mental State Examination.

Table 2

Brain areas showing decreased brain metabolism in patients with FOG after HIBI compared with normal controls ($P_{FDR\text{-}corrected} < .01$, $k = 50$).

Side	Area	Coordinate			T score	Z score	Cluster size
		x	*y*	*z*			
Right	Thalamus	12	−30	4	8.27	5.58	2019
	Midbrain	20	−10	16	6.90	5.03	2019
Left	Thalamus	−12	−22	10	6.76	4.97	2019
Left	Cingulate gyrus	−8	−22	36	6.80	4.98	5612
Right	Cingulate gyrus	12	−20	34	6.50	4.85	5612
Bilateral	Cingulate gyrus	0	−20	32	6.22	4.71	5612
Right	Supramarginal gyrus	70	−24	38	6.27	4.74	177
	Midline paracentral lobule	4	−30	78	4.95	4.04	286
Right	Angular gyrus	38	−80	46	5.16	4.16	118
Left	Postcentral gyrus	−56	−4	48	5.10	4.13	79
Left	Precentral gyrus	−50	10	44	4.11	3.53	79

FOG = freezing of gait, HIBI = hypoxic-ischemic brain injury.

years). No significant differences were observed between the 2 groups with respect to age or sex ($P > .05$). The mean duration from onset was 11.73 ± 13.30 months and the mean freezing subscore from the Unified Parkinson Disease Rating Scale, which reflects the severity of freezing, was 3.09 (grading scale range 1–4) at the time of evaluation. The MMSE score (FOG group: 20.00 ± 7.00, control group: 29.27 ± 1.49, $P < .05$) was significantly different between the 2 groups, indicating that the FOG group had severely impaired cognitive function compared with the healthy control group.

Table 2 and Fig. 1 demonstrate the differences in brain metabolism between the healthy control and FOG groups. The SPM analysis of the F-18 FDG PET images demonstrated that compared with healthy controls, patients with FOG had significantly decreased brain metabolism in the midbrain, bilateral thalamus, bilateral cingulate gyri, right supramarginal gyrus, right angular gyrus, right paracentral lobule, and left precentral gyrus ($P_{FDR\text{-}corrected} < .01$, $k = 50$). No significant increases in brain metabolism were noted in patients with FOG when compared with healthy controls ($P_{FDR\text{-}corrected} < .01$, $k = 50$). The covariance analysis identified significant correlations between the FOG severity and the decreases in brain metabolism in the right lingual gyrus, left fusiform gyrus, and bilateral cerebellar crus I ($P_{uncorrected} < .001$, $k = 50$; Fig. 2, Table 3).

4. Discussion

This F-18 FDG PET study is the first to elucidate the differences in brain metabolic activity between healthy subjects and patients with FOG after HIBI. The major findings of the present study were as follows: compared with healthy controls, patients with FOG after HIBI exhibited decreased brain metabolism in the thalamus, paracentral lobule, cingulate, sensory association cortices, and midbrain; and the decreased brain metabolism that was identified in the visual cortex and cerebellum of the patients was correlated with the FOG severity. These data suggest that the brain regions within walking-related neural networks, including the cerebral cortex, subcortical structures, brainstem, and cerebellum, may significantly contribute to the development of FOG in patients after HIBI.

Hypoxic-ischemic insult and following reperfusion process can lead to brain damage, and certain brain regions appear to be more commonly affected than other regions. For example, areas with higher metabolic and oxygen demands are particularly vulnerable.[9] Mild-to-moderate HIBI usually results in watershed zone damage, whereas severe HIBI additionally affects the cerebral cortices and subcortical structures.[10] During reperfusion process, inhibition of protein synthesis in selective vulnerable areas such as hippocampus and cortex, re-oxygenation injury, and hypoxia-induced decreases in cellular antioxidant enzymes can also cause reperfusion injury, resulting in neurologic sequelae.[11] In the present study, the MR images of patients with FOG after HIBI showed diffuse neural damage in the bilateral cerebral cortices, BG, thalamus, and deep white matter. Based on these findings, we hypothesize that the pathophysiology of FOG in patients with HIBI may be different from that in patients with PD.

Normal human locomotion requires the activation of 3 processes.[12] The first process is locomotion initiation, which derives from volitionally elicited locomotor commands arising from the cerebral cortex. The second process is locomotion regulation, in which the neural circuits of the cerebral cortex, BG, thalamus, and cerebellum play major roles. Lastly is the locomotion execution process, which occurs in the brainstem and spinal cord, and automatically controls the movement. Likewise, locomotion control mechanisms are complex and involve various subcortical and cortical control areas. Functional neuroimaging studies investigating brain activity during normal gait found increased activation in the BG, thalamus, frontal cortex, posterior parietal cortex, occipital cortex, and cerebellum.[13,14] However, patients with PD and FOG had decreased brain metabolism in the frontal cortex, parietal cortex, and BG.[15,16] A dorsal pathway via the parietal cortex is involved in the integration of sensory and visual information during locomotion and postural control.[17] Indeed, the posterior parietal cortex receives both visual and locomotor-related information from the somatosensory cortex. Spatial information can then be converted into spatially directed movements through the frontal area. Thus, the fronto-parietal pathway disruptions noted in our patients may underlie their gait disturbances and FOG.[18]

Because patients with injuries to the premotor cortices, including the supplementary motor area (SMA), exhibit FOG, it is likely that this area plays an important role in gait initiation. Gait requires the ability to initiate movement and to maintain rhythmic stepping, both of which are associated with the SMA.[19] Indeed, the SMA is activated during complex voluntary motor movements and is thought to be involved in the planning

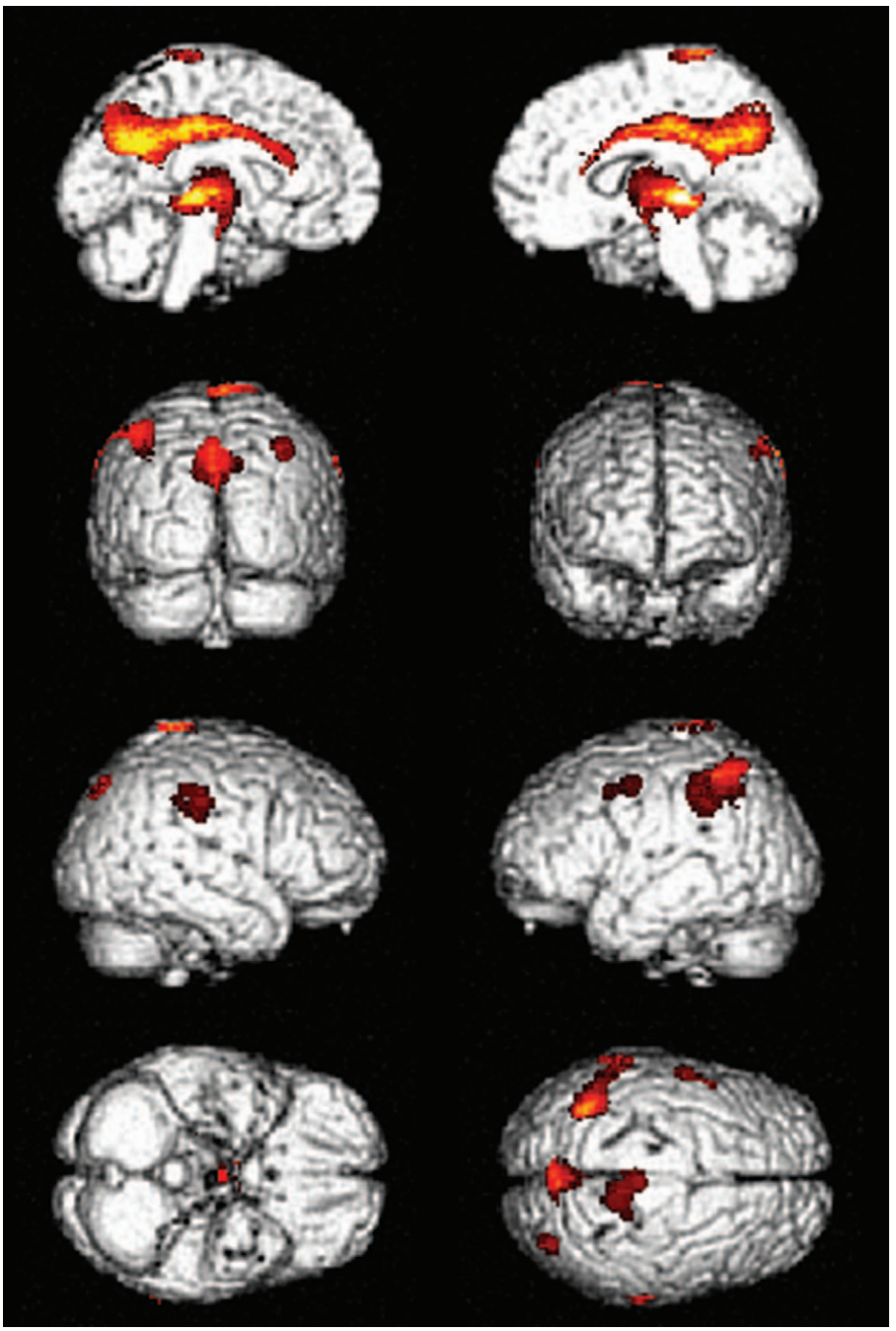

Figure 1. Voxel-by-voxel-based statistical parametric maps showing the spatial distributions of the significant decreases in cerebral glucose metabolism in patients with freezing of gate after hypoxic-ischemic brain injury compared with normal controls. Displayed voxels are significant at $P_{FDR\text{-}corrected} < .01$, $k = 50$.

or programming of voluntary movement and postural control. A previous study demonstrated that performing a motor sequence test with the foot increased the regional cerebral blood flow in the SMA, whereas simple sustained flexion of the foot failed to activate the SMA.[20] Additionally, stronger event-related potentials were found for the SMA during a gait initiation task than during a simple foot dorsiflexion task in a previous electroencephalography study,[21] and SMA lesions have been shown to cause severe hypokinetic movement in gait.[22] In an animal study, muscimol injections into the trunk/leg regions of the SMA disturbed postural control during walking without limb paralysis.[23] Thus, we assumed that in our patients, SMA alterations after HIBI deteriorated the patients' ability to prepare their posture before gait initiation.

In the locomotion control network, the cerebellum is considered dispensable for steady-state locomotion, but crucial for avoiding obstacles and adapting to novel conditions.[24] Furthermore, high-level gait processing may occur in the systems between the BG, cerebellum, and brainstem in the absence of conscious awareness.[12] During walking, the cerebellar crus I plays a role in visuomotor control by receiving information from the frontal eye fields.[25] The observed relationship between the FOG severity and the impaired metabolism in the cerebellum and visual cortices in the present study may explain why disturbances

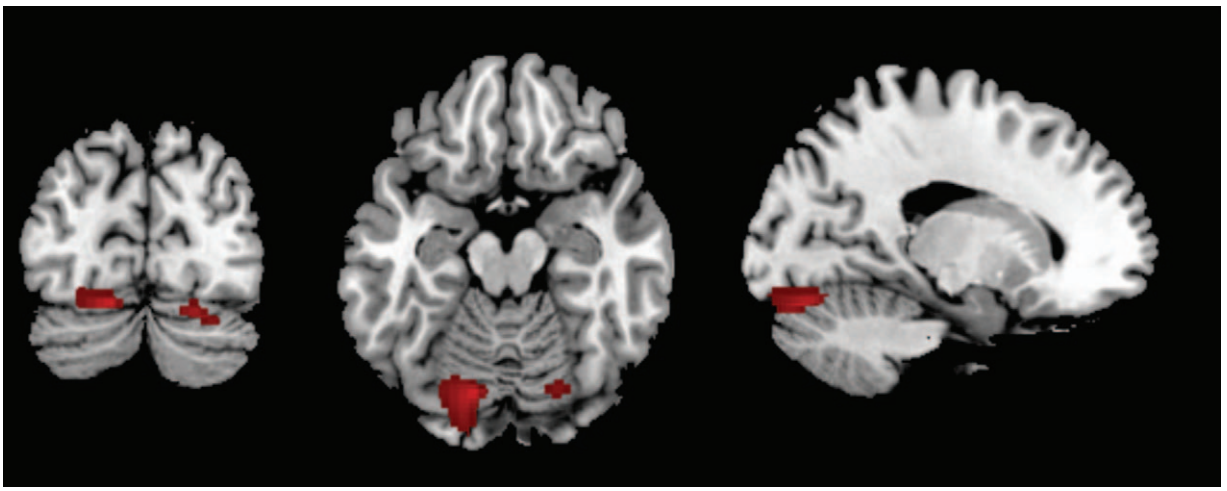

Figure 2. Voxel-by-voxel-based statistical parametric maps showing the regions with decreased cerebral glucose metabolism that were correlated with the freezing of gate severity in patients with freezing of gate after hypoxic-ischemic brain injury. Displayed voxels are significant at $P_{uncorrected} < .001$, $k = 50$.

in visuomotor control in adaptive and novel environments can exacerbate the gait freezing. Our results are concordant with the results of a recent study comparing patients with PD and FOG to patients with PD without FOG and healthy controls, which demonstrated that the FOG in patients with PD was associated with abnormalities in their corticopontine-cerebellar pathways and visual temporal areas.[26] Functional neuroimaging studies performed during mental imagery or virtual reality conditions may improve our understanding of the role of the cerebellum in the development of FOG after HIBI.

In patients with PD, the pathophysiology of gait disorders, particularly the cerebral mechanisms that lead to FOG, are insufficiently understood, as FOG responds poorly to L-dopa therapy.[27] Thus, nondopaminergic mechanisms of gait control such as cholinergic system-mediated, high-level processing areas including the pedunculopontine nucleus (PPN) have been explored. A previous neuroimaging study found that the thalamic volume was significantly decreased in patients with PD and FOG[28]; moreover, Bohnen et al[29] demonstrated that acetylcholine esterase activity in the thalamus, which represents PPN cholinergic output, plays an important role in gait and postural control. A diffusion tensor imaging study of the FOG in patients with PD and patients with HIBI revealed alterations in the PPN,[30,31] whereas Thevathasan et al[32] demonstrated that bilateral PPN stimulation in patients with FOG improved their FOG symptoms. Previous animal model studies also suggested the relationships between FOG and reticulospinal system including PPN and mesencephalic locomotor region.[33] Our results are consistent with these previous data and support that the cholinergic pathway, including the thalamus and PPN, is an important factor leading to the noted postural control and gait dysfunctions in patients with FOG.

This study has several limitations, with the primary limitation being the small number of patients. During the 6-year study period, we only enrolled 11 patients with HIBI patients with FOG owing to the low incidence of FOG after HIBI. Hence, studies with a larger sample size are recommended. The second limitation is that we compared patients with HIBI and FOG to healthy controls, which made it difficult to definitively conclude whether the decreased metabolism in the patient group was associated with FOG, HIBI, or both. Therefore, further studies that perform a 3-group comparison among patients with HIBI and FOG, patients with HIBI without FOG, and healthy controls are warranted.

5. Conclusions

In conclusion, patients with FOG after HIBI showed decreased brain metabolism in the thalamus, paracentral lobule, cingulate, sensory association cortices, and midbrain. In addition, the correlation analysis identified significant correlations between the decreased metabolism in the visual cortex and cerebellum, and the severity of FOG. These data suggest that regions within the walking-related neural networks including the cerebral cortex, subcortical structures, brainstem, and cerebellum may significantly contribute to the development and severity of FOG in individuals with HIBI, and it is somewhat different from that of FOG in PD. Further research utilizing larger sample sizes and more detailed group comparisons are needed.

Table 3

Brain areas negatively correlated with the patients' FOG severity ($P_{uncorrected} < .001$, $k = 50$).

Side	Area	Coordinate			T score	Z score	Cluster size
		x	*y*	*z*			
Right	Cerebellum crus I	16	−80	−20	10.00	4.02	341
Right	Lingual gyrus	12	−60	−8	6.01	3.30	341
Left	Cerebellum crus I	−24	−86	−26	9.35	3.93	146
Left	Fusiform gyrus	−22	−76	−22	7.77	3.67	146

FOG = freezing of gait.

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