Voxel-based analysis of brain microstructural diffusion indices changes in Parkinson disease with freezing of gait

Jing-Wu Chen[1], Fa-Ze Mai[2], Yong-Zhe Yang[3], Wan-Qun Yang[4], Li-Juan Wang[5], Kun Nie[5], Biao Huang[4]

[1]Department of Radiology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510260, China;
[2]Department of Radiology, Hainan General Hospital, Haikou, Hainan 570311, China;
[3]School of Medicine, South China University of Technology, Guangzhou, Guangdong 510006, China;
[4]Department of Radiology, Guangdong Academy of Medical Sciences, Guangdong Provincial People's Hospital, Guangzhou, Guangdong 510080, China;
[5]Department of Neurology, Guangdong Academy of Medical Sciences, Guangdong Provincial People's Hospital, Guangzhou, Guangdong 510080, China.

To the Editor: Freezing of gait (FOG) is a common disabling movement disorder in Parkinson disease (PD), affecting approximately 50% to 80% of PD patients in their late state. FOG can cause the patients to fall easily, seriously affects their quality of life and exerts both economic and emotional burdens. Unlike the common motor symptoms of PD (such as bradykinesia, tremor, or rigidity), FOG is seldom improved by dopaminergic medication therapy or deep brain stimulation. Moreover, FOG may be resistant to (or even worsened by) levodopa.[1] However, cognitive training has showed it can reduce the severity of FOG.[2] These findings imply that FOG may be caused not only by motor impairment but also by cognitive impairment. It is reasonable to hypothesize that FOG+ patients have impaired cognitive function and that the diffusion indices of the cerebral territories' microstructures associated with cognition are altered. To test this hypothesis, we applied whole-brain voxel-based analysis (VBA), a fully automated whole-brain analysis that uses voxel-wise statistics on diffusion metrics, to investigate the diffusion indices of brain microstructures changes in FOG+ patients, PD patients without FOG (FOG– patients), and healthy controls (HCs).

Twenty FOG+ patients were recruited from the Department of Neurology at Guangdong Provincial People's Hospital from January 2014 to December 2016. In addition, 23 FOG– patients and 20 age-, sex-, and educational-level-matched HCs were selected from our PD research database. The study was approved by the Institutional Ethics Committee of Guangdong Provincial People's Hospital. (No. GDREC2014029H[R1]) Written informed consent was obtained from all subjects before the magnetic resonance imaging (MRI) examination. All subjects were right-handed according to the Edinburgh Handedness Inventory. PD patients were diagnosed according to the UK Brain Bank criteria by two experienced neurologists. All patients were assessed in the "off" medication state (12 h after withdrawal of anti-Parkinsonian medication). Disease severity was based on the Hoehn and Yahr staging (H-Y). Global cognitive function was evaluated with the Mini-Mental State Examination (MMSE). The Unified Parkinson Disease Rating Scale (UPDRS)-III was used to assess the severity of motor symptoms. Patients were identified as FOG+ if they had a score of ≥1 on item 3 of the FOG Questionnaire[3] and either or both of the following: (a) the participant's verbal account of having experienced FOG; and (b) the patient's recognition of typical FOG when described to him or her by an experienced neurologist.[4] Patients who did not meet the above criteria were classified as FOG–. Diffusion tensor imaging (DTI) data of all subjects were collected on a 3.0T scanner (Signa Excite HD GE Healthcare, Milwaukee, WI, USA) and pre-processed using the Pipeline for Analyzing braiN Diffusion imAges (http://www.nitrc.org/projects/panda) software package based on MATLAB R2012a. Statistical analyses of clinical data were performed with the SPSS 21.0 statistical software (IBM Corp, Armonk, NY, USA). Differences with P values < 0.05 were considered significant. The exclusion criteria for all subjects and the neuroimaging analysis are shown in the Supplementary Materials, http://links.lww.com/CM9/A285.

There were no significant differences among the FOG+ patients, FOG– patients, and HCs in age, sex, or education time ($P > 0.05$). The MMSE scores were significantly lower ($P < 0.05$), and UPDRS-III ($P < 0.05$) and H-Y ($P < 0.05$) scores significantly higher, in the FOG+ patients than those in the FOG– patients. The mean disease duration

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Jing-Wu Chen and Fa-Ze Mai contributed equally to this work.

Correspondence to: Biao Huang, Department of Radiology, Guangdong Academy of Medical Sciences, Guangdong Provincial People's Hospital, #106 Zhongshan 2nd Road, Guangzhou, Guangdong 510080, China
E-Mail: huangbiao@gdph.org.cn

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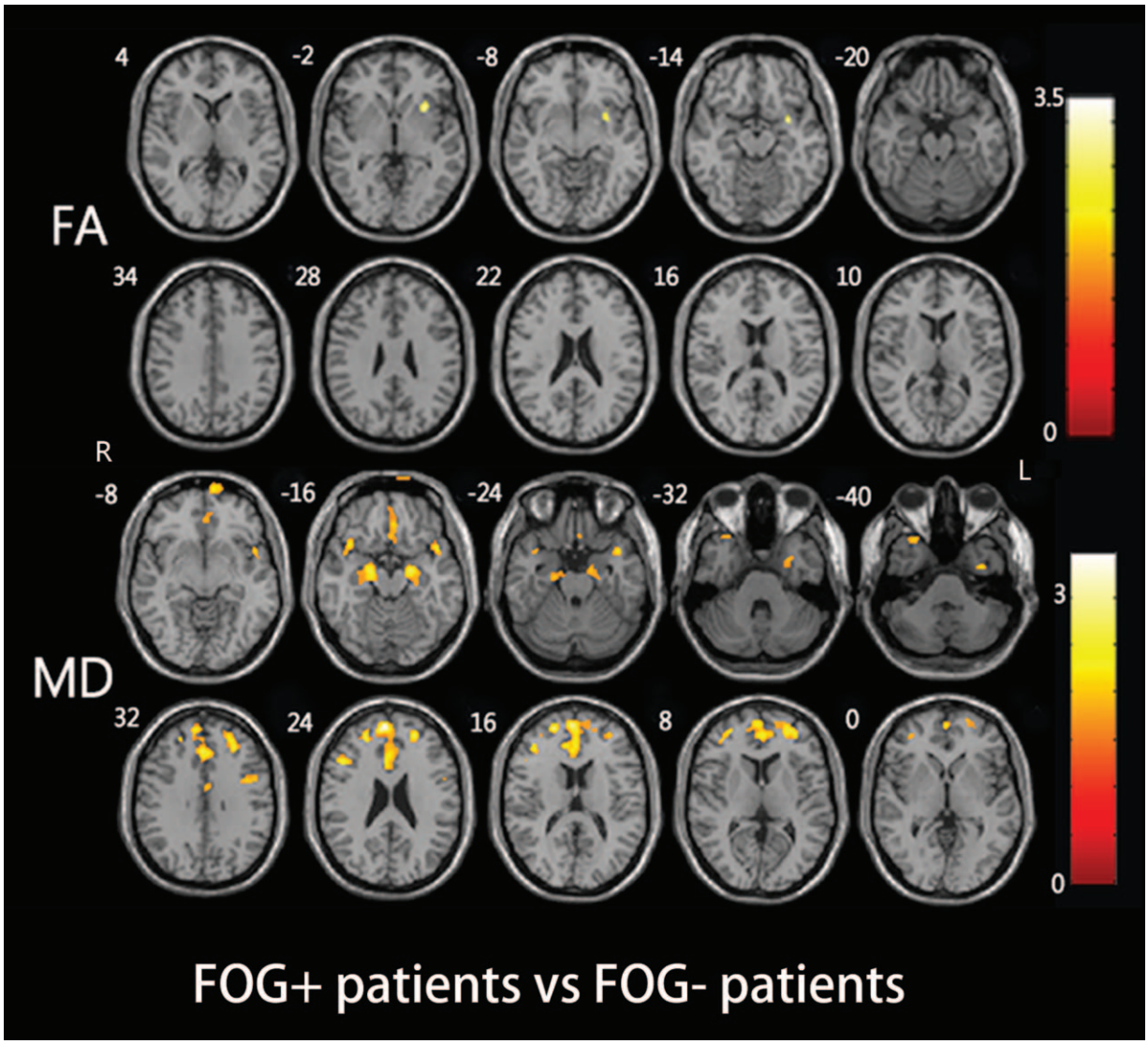

Figure 1: Differences of MD and FA between FOG+ patients and FOG– patients. The MD values in the frontal lobe (bilateral medial frontal gyrus, right superior frontal gyrus, bilateral inferior frontal gyrus, right middle frontal gyrus, and pre-central gyrus) and limbic areas (including the hook, right amygdala, and bilateral parahippocampal gyrus, hippocampus, and cingulate gyrus) and bilateral temporal lobe (right middle temporal gyrus, left inferior temporal gyrus and bilateral superior temporal gyrus) were significantly higher in the FOG+ patients than FOG– patients, while the differences in FA values were not significant. Conversely, the FOG+ patients showed reduced FA values in the left insula compared to those in the FOG– patients. FA: Fractional anisotropy; FOG: Freezing of gait; MD: Mean diffusivity.

was significantly longer in FOG+ patients than that in the FOG– patients ($P < 0.05$). Diffusion indices analyses showed that the mean diffusivity (MD) values in the frontal lobe, limbic areas, and bilateral temporal lobe were significantly higher in the FOG+ patients than FOG– patients, while the differences in fractional anisotropy values were not significant [Figure 1]. In addition, our study analyzed the diffusion indices between FOG+ patients and HCs, FOG– patients and HCs. The higher MD values in the frontal lobe also were found in FOG+ patients than HCs, but no changes between FOG– patients and HCs [Supplementary Materials, http://links.lww.com/CM9/A285].

The main finding of our study was that FOG+ patients had impaired cognitive function and microstructural changes in the bilateral frontal lobe. In the present study, FOG+ patients showed a lower MMSE score compared with that in FOG– patients. For the diffusion indices of whole-brain microstructures, the FOG+ patients demonstrated higher MD values in the bilateral frontal lobe using VBA. MD values represent a parameter of average molecular motion, which can reflect on the microstructural changes of neural tissue in patients. Based on our results, we suggest that the changes in the frontal lobe microstructures associated with cognition are closely related to FOG. Impairments in cognitive flexibility are a widely recognized "cognitive signature" associated with FOG. Most of the previous functional MRI studies in FOG+ patients have revealed abnormal functional activation and connectivity in brain regions responsible for frontal executive and attention abilities.[5] Together with recent findings, our results substantiate the importance of frontal lobe areas in the pathophysiology of FOG in patients with PD. The frontal lobe area dysfunction may lead to a decreased ability to focus attention on a motor performance which resulted as FOG. Moreover, we also found the limbic areas and temporal lobe areas were affected in FOG+ patients. A decrease in

dopamine levels in the limbic system is suggested to be associated with pathological changes of PD.[6] Mood disorders implicated limbic system may also be more common in FOG+ patients, with the incidence positively correlated with the severity of cognitive impairment. Therefore, we speculate that dysfunctional limbic areas may involve the occurrence of FOG in PD. In addition, we observed significant microstructural changes in temporal lobe areas including the middle temporal gyrus and inferior temporal gyrus. Recent evidence reveals that visuospatial integration related to the middle temporal area is more severely impaired in FOG.[7]

In summary, we have shown that the FOG+ patients had impaired cognitive function and that the diffusion indices of the frontal lobe microstructures associated with cognition were altered. Our study provides evidence that the dysfunction of the frontal lobe microstructures may point to the key role of the occurrence of FOG in PD patients, which supports cognitive training therapy for FOG+ patients.

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Conflicts of interest

None.

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