

# Altered resting-state functional connectivity of cerebellum in Parkinson's disease

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**Introduction:** Parkinson's disease (PD) is a neurodegenerative disease. The dopamine deficits in striatal subregions impair the function of parallel striatal-thalamo-cortical (STC) networks. The other important circuit, cerebello-thalamo-cortical (CTC) circuits, is known to influence cerebral cortical activity including motor control, higher cognitive and emotional processing. Thus, an improved understanding of the cerebellum, especially the CTC circuit in PD-related changes, is essential for a better understanding of the pathophysiology of the disorder. Schmahmann describes a relationship between the anterior lobe of the cerebellum and motor function, and between the posterior lobe and executive function. Accordingly, in this resting state fMRI study, we selected the anterior lobe and posterior lobe of cerebellum as regions of interest (ROIs). A method, which does not require a complicated task design, is able to detect very low frequency (<0.08 Hz) fluctuations (LFFs) in MR signal has been extensively employed to measure functional connectivity in resting brain<sup>[1]</sup>. In this study, using functional connectivity method we investigated PD-related modulation of functional connectivity of the cerebellum in the resting state.

**Methods:** MRI was performed on a 3.0-T scanner (GE HDxt, USA) after a minimum period of 12 h since the patients' last dose of anti-parkinson medication. The fMRI scanning was performed in darkness, and the participants were explicitly instructed to keep their eyes closed, relax, and move as little as possible. Functional images were collected using a gradient echo planar imaging (EPI) sequence sensitive to BOLD contrast: TR=3000 ms, TE=60 ms, FOV=24 cm×24 cm, flip angle=90°, matrix=64×64, slice thickness=3 mm, gap=0 mm, slices=60. No subject reported to have fallen asleep when routinely asked immediately after examination. The images were preprocessed using the following steps: slice timing, motion correction (translation<2 mm and rotation<2°), spatial normalization, followed by spatial smoothing with 6-mm full-width at half-maximum (FWHM) Gaussian kernel. To further reduce the effects of confounding factors, six motion parameters, linear drift and the mean time series of all voxels within the entire brain were removed from the smoothed data through linear regression. Then, the fMRI data were temporally band-pass-filtered (0.01–0.08 Hz).

The anterior lobe and posterior lobe of cerebellum-ROIs were defined by WFU\_PickAtlas and were resliced into Montreal Neurological Institute (MNI) space. Correlation analysis was carried out between the seed reference and the entire brain in a voxel-wise manner using the Resting-State fMRI Data Analysis Toolkit (REST, by Song Xiao-Wei et al., <http://www.restfmri.net>). Then, the correlation coefficients were transformed to z-values using the Fisher r-to-z transformation to improve normality. Within each group, individual z-values were entered into a one-sample t-test in a voxel-wise manner. A combined threshold of contrast maps was set at  $p < 0.005$  for each voxel and a cluster size of at least 702 mm<sup>3</sup>, which was equal to the corrected threshold of  $p < 0.05$ , determined by Monte Carlo simulation. In the second-level random effects analysis, direct comparisons were conducted to identify differences in functional connectivity between PD vs. HC. A combined threshold of contrast maps was set at  $p$  value <0.05 (AlphaSim corrected).

**Results and Discussion:** For the anterior lobe of cerebellum, regions showing significantly increased functional connectivity in PD group included superior temporal gyrus (voxels, peak MNI coordinate, peak intensity=54, (-39 -45 15), 4.5645) (Figure 1). For the posterior lobe of cerebellum, regions showing significantly increased functional connectivity in PD group included cerebellum (28, (-24 -33 -54), -5.015; 58, (-3 -60 -12), 5.4215) and superior temporal gyrus (129, (60 -48 15), 5.0707; 73, (-39 -39 12), 5.243). In contrast, areas showing significantly decreased functional connectivity in PD group included precuneus (82, (-21 -78 54), -4.1215; 35, (21 -54 42), -3.6816) and inferior parietal lobule (136, (42 -48 54), -5.4649) (Figure 2). The increased connectivity patterns of cerebellum were mainly located in posterior lobe in our study. Activations of the cerebellar posterior lobe have been ascribed to various cognitive tasks. Schmahmann and colleagues have described a schema in which the posterior lobe of the cerebellum is involved with cognitive or executive functions<sup>[2]</sup>. What's more, it has been postulated that compensatory activity in CTC circuits in PD patients may act as a compensatory mechanism to overcome the deficits in STC circuit<sup>[3]</sup>. Previous studies of PD subjects have shown increased recruitment of the cerebellum using a variety of tasks. Here we show that the same cerebellar alterations are also observable with resting-state functional connectivity. Thus it indicates that the presentation of increased functional connectivity of cerebellar posterior lobe may play an important role in cognitive or executive functions of PD patients.

**Conclusion:** In conclusion, we found that the increased connectivity of the cerebellum was mainly located in posterior lobe. This alteration may play a compensatory role in cognitive or executive functions of PD patients. Our findings of the cerebellar connectivity may improve our understanding of the pathophysiology of PD.

**References:** [1]Biswal B. et al., *Magn. Reson. Med.*, 34(4):537-41, 1995 [2]Schmahmann J.D. et al., *Brain*, 121(Pt4):561-79, 1998 [3]Cerasa A. et al., *Brain Res. Bull.*, 71(1-3):259-69, 2006.



Fig. 1 Changed functional connectivity of the anterior lobe of cerebellum in PD group.

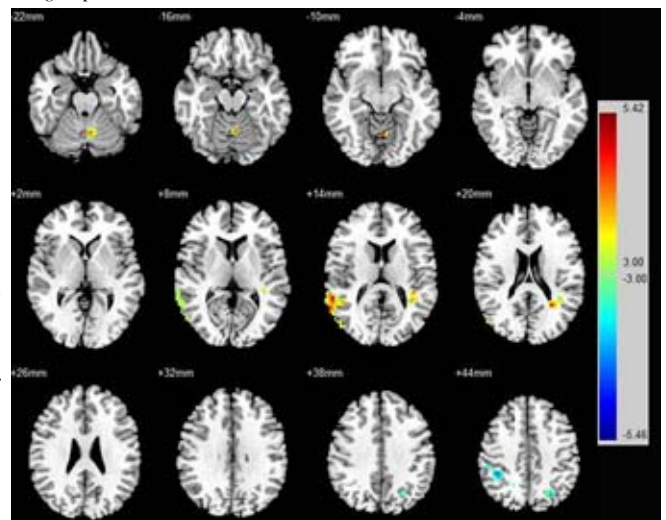


Fig. 2 Changed functional connectivity of the posterior lobe of cerebellum in PD group.