NEUROLOGICAL RESEARCH
https://doi.org/10.1080/01616412.2019.1709141

Taylor & Francis
Taylor & Francis Group

ARTICLE

Resting-state fMRI reveals increased functional connectivity in the cerebellum but decreased functional connectivity of the caudate nucleus in Parkinson's disease

Oliver Kaut[a], Clemens Mielacher[b], René Hurlemann[b] and Ullrich Wüllner[a,c]

[a]Department of Neurology, University Clinic Bonn, Bonn, Germany; [b]Division of Medical Psychology, University Clinic Bonn, Bonn, Germany; [c]Department of Clinical Studies, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

ABSTRACT

Objective: Frequent falls are common in Parkinson's disease (PD). Resting-state fMRI (rs-fMRI) studies have found differences in functional connectivity between PD patients and healthy controls. However, whether functional connectivity in PD patients with frequent falls (PD-fallers) differs from those without falls (PD-non fallers) is unknown. Therefore, to elucidate the underlying mechanisms leading to postural instability in PD patients with frequent falls, we compared changes in functional connectivity between PD-fallers, PD-non fallers and healthy controls.

Methods: Thirteen healthy controls (70.7 ± 7.2 years) were compared to thirteen PD-fallers (70.6 ± 5.9 years) and 19 PD-non fallers (71.61 ± 5.8 years) without cognitive impairment. We performed 1.5T rs-fMRI scans and evaluated gait and balance, motor symptoms and cognitive functions.

Results: Cerebellar seed regions showed increased functional connectivity in PD-fallers compared to controls in two connections between the cerebellar cortex and vermis (p-value = 0.02). Conversely, in comparison to controls, functional connectivity between the precuneus and caudate nucleus was decreased in PD-non fallers (p-value = 0.015). A similar trend was also observed between controls and PD-fallers, although this difference did not reach statistical significance.

Discussion: We found increased functional connectivity among cerebellar structures in PD, which may reflect an adaptive (compensatory) mechanism through activation of additional brain structures to restore gait function. In contrast, a relative disconnection between the precuneus and caudate nucleus in PD patients might indicate an impaired brain network unrelated to the risk of falls. Cerebellar areas might thus be considered as future therapeutic targets for neuromodulatory treatment of postural instability in PD.

Abbreviations: DMN: default mode network; FC: functional connectivity; IPL: inferior parietal lobule; MMSE: Minimal Mental Status Examination; PD: Parkinson's disease; rs-fMRI: resting-state functional Magnetic Resonance Imaging; $UPDRS_{III}$: Unified Parkinson's disease ranking scale

ARTICLE HISTORY
Received 21 June 2019
Accepted 14 November 2019

KEYWORDS
Default mode network; resting state; connectivity; Parkinson's disease; postural instability

1. Introduction

Postural instability resulting in falls is common in individuals with PD. According to a retrospective study of 489 PD patients, approximately 60% of PD patients had at least 1 fall in 12 months [1]. In the Sydney multicenter 20-year follow-up study, falls occurred in 87% of advanced-stage PD patients [2]. The 3-month fall rate of PD patients in a meta-analysis of six prospective studies of falls in PD (n = 473) was 46% [3]. Recently, in a 4-year follow-up study of 1741 early treated PD subjects, it showed that 42% of them fell during the trial. For men, the probability of falling increased with age, especially after age 70, whereas this probability was not found in women [4].

The underlying pathophysiology leading to falls in PD is highly complex and still not fully understood. A multifactorial etiology, with contributions from both primary and secondary disease processes, as well as various compensatory mechanisms, is likely to be implicated [5]. Multi-sensory information, such as somatosensory, visual and vestibular sensation, is integrated in different areas of the brain to enable a delicate control of posture and gait. There are two levels of control involved: 1) an automatic process of gait control mediated by the descending pathways from the brainstem to the spinal cord, particularly the reticulospinal pathways arising from the lateral part of the mesopontine tegmentum and spinal locomotor network, 2) a cognitive process of postural control required when walking in unfamiliar surroundings or circumstances, located in the temporoparietal association cortex. In addition, the basal ganglia and cerebellum may modulate both the automatic and cognitive processes through reciprocal connections with the brainstem and cerebral cortex [6]. This interplay enables the regulation of muscle tone

CONTACT Oliver Kaut oliver.kaut@ukbonn.de Department of Neurology, University Clinic Bonn, Sigmund-Freud-Str. 25, Bonn 53105, Germany

and rhythmic limb movements [7]. Consequently, dysfunction at the level of cortex, basal ganglia, or cerebellum could impair posture and gait control and thereby induce falls [6].

Recent studies have emphasized the role of the cerebellum in PD [8]. Functional magnetic resonance imaging (fMRI) studies have found support for the long-held notion that relatively intact cerebellar circuits may compensate for impaired basal ganglia function and that cerebellar activity is increased in PD patients compared to healthy subjects [9]. To assess neural activity, resting-state fMRI [rs-fMRI] has been widely used over the last decade in various neurodegenerative disorders. The objective of resting-state experiments is to assess the statistical properties of endogenously generated neural activity, while the subject is at 'rest', which is defined as a constant condition without external stimuli or tasks [10]. In comparison to task-based fMRI, rs-fMRI is not biased by compliance or task performance [11].

Many studies have evaluated resting-state activity in PD; however, the results have been largely inconsistent, likely due to different preprocessing protocols. A recent meta-analysis across rs-fMRI studies found the presence of intrinsic functional disturbances in the bilateral inferior parietal lobule (IPL) and in the supramarginal gyrus to be one of the few consistent features in PD patients [11]. This study also focused on the DMN in PD, which was characterized by deactivation of cortical areas (i.e. medial prefrontal cortex, posterior cingulate cortex, precuneus, lateral parietal cortex, and medial temporal cortex) during the performance of executive tasks [12, 13, 14]. This analysis also showed that convergent aberrations in PD formed an interconnected network, mainly with DMN, in a task-independent functional connectivity (FC) analysis [11]. And it was based on patterns across the whole brain, whereas studies using a seed-based approach were not included.

A decreased FC in rigidity-dominant PD patients was found particularly in the posterior DMN, whereas FC was increased in the anterior DMN and left medial prefrontal regions [15]. In addition, a recent 1.5-year follow-up study demonstrated that the connectivity in PD remains altered in the same regions as identified at baseline [16].

Despite alternations in FC in PD patients, the relation with disturbances of gait and posture control remains unclear. Therefore, in order to elucidate the underlying pathophysiology of falls in PD patients, the objective of our study was to assess the association between changes in FC and disturbances of gait and posture control in PD patients by comparing patients with frequent falls (PD-fallers) to those without falls (PD-non fallers) as well as healthy controls using a seed-based approach.

2. Methods

2.1. Characterization of study cohort

Thirteen healthy individuals (70.7 ± 7.2 years) were compared to 13 PD-fallers (70.6 ± 5.9 years) and 19 PD-non fallers (71.61 ± 5.8 years). In the PD-fallers group, we included patients with at least 2 or more falls during the last 12 months; the rate of falls in the PD-fallers group was 6.2 ± 5.1/year. We evaluated gait and balance, motor symptoms and cognitive functions using the Unified Parkinson's Disease Ranking Scale ($UPDRS_{III}$), Timed Up and Go (TUG) Test, 8-m walk (8 MW), and Mini-Mental State Examination (MMSE) (Table 1). Medication was continued unchanged and patients were assessed in ON state during the study.

2.2. Ethics statement

The study protocol was approved by the Ethics Committee (no. 15/015) of the University Clinic of Bonn, Germany. All subjects were volunteers, and they provided a written informed consent prior to their participation in the study, in accordance with the Declaration of Helsinki.

2.3. Neuroimaging acquisition

Magnetic resonance imaging (MRI) data were acquired using a 1.5 Tesla Avanto MRI system (Siemens, Erlangen, Germany), which was equipped with a 12-channel standard head coil and was performed at the University Clinic Bonn. A high-resolution structural image of the whole brain was acquired using a T1-weighted 3D MRI sequence (voxel size = 1 × 1 × 1 mm; TR = 1660 ms; TE = 3.09 ms; flip angle = 15°; matrix size = 256 × 256, no interslice gap). Subsequently, one resting-state run (10 min, 200 volumes, eyes closed) was obtained using a T2*-weighted gradient-echo planar image (EPI) sequence (voxel size = 3 × 3 × 3 mm; TR = 3000 ms; TE = 45 ms; flip angle = 90°; FoV = 192 mm; matrix size = 64 × 64; 37 slices; interleaved slice order with

Table 1. Clinical characteristics of study cohort.

	control $n = 13$	PD-non fallers $n = 19$	PD-fallers $n = 13$
Age	70.7 (±7.2)	70.6 (±5.9)	71.5,8 (±5.8)
Gender (female/male)	6/7	15/4	4/9
MMSE	27.9 (±1.8)	28.3 (±2.0)	28.7 (±2.6)
$UPDRS_{III}$	–	18.3 (±7.1)	23.5 (±13.3)
H&Y	–	1.8 (±0.37)	3.1 (±0.3)
Timed up and Go-Test	5.6 (±6.3)	9.2 (±4.0)	14.0 (±7.1)
8MW	4.9 (±0.62)	5.8 (±1.5)	8.3 (±2.4)
Disease duration (years)	–	6.58 (±4.25)	7.5 (±3.8)
Levodopa daily dose	–	272.0 (±143.6)	532.7 (±174.8)
Dopaminagonists, yes/no	–	13/6	8/13

All values are expressed in mean (SD).
H&Y = Hoehn and Yahr stages; MMSE = Mini-Mental State Examination; $UPDRS_{III}$ = Unified Parkinson's disease Rating scale, Motor Score

interslice gap of 1 mm). Slices were oriented parallel to the intercommissural plane (AC-PC line). During the study, the participants wore earplugs, and foam padding was used to reduce head motion.

2.4. Preprocessing and FC analysis

Resting-state data were analyzed using the CONN toolbox for SPM (v17, www.nitrc.org/projects/conn, RRID: SCR_009550). The first five images were discarded to eliminate T1-equilibration artifacts from the time-series. Subsequently, preprocessing was conducted using the CONN preprocessing pipeline. Images were motion-corrected using realignment and unwarping followed by slice-time correction. Functional images were then co-registered to the structural T1 image, spatially normalized to 2 mm Montreal Neurological Institute (MNI) space, and smoothed with an 8 mm full width at half maximum Gaussian kernel. To address the impact of head motion and physiological confounders, we created a linear regression model for each subject and added volumes that showed more than 0.5 mm head motion, realignment parameters and nuisance components derived from blood oxygen level-dependent (BOLD) signal time courses extracted from white matter (WM, 16 dimensions) and cerebrospinal fluid (CSF, 16 dimensions) masks using the anatomical component-based noise correction method (CompCor) as regressors [17]. Additionally, a 0.008–0.09 Hz band-pass filter was applied to the data.

Furthermore, we ran seed-to-seed connectivity analyses using the regions of interest (ROIs) that were anatomically defined by the FMRIB Software Library (FSL) Harvard-Oxford and the Automated Anatomical Labeling (AAL) atlases. We analyzed three sets of seeds that are either relevant to the pathophysiology of PD or have shown to discriminate PD patients from healthy controls. The first set consisted of the bilateral cerebellar areas, vermis, and brain stem; the second set consisted of the posterior cingulate cortex, precuneus, and bilateral caudate nuclei [18]; the third set consisted of basal ganglia encompassing the canonical direct pathway, the thalamus, caudate nucleus, putamen, pallidum and precentral gyrus [19]. Moreover, all the bilateral seeds in the left and right hemisphere were analyzed separately. For each subject, correlational analyses were performed by extracting the Blood Oxygenation Level Dependent (BOLD) time-course from each seed region, and by computing separately the correlation coefficients between the time-series of each seed and all other ROIs of the same set. Additionally, to compare FC across subjects, correlation coefficients were converted using the Fisher's *r*-to-*Z* transformation. At the second level, group differences were tested using the two-sample *t*-test with the threshold for significance set to $p < .05$. All seed-to-seed analyses were corrected at the set level using false-discovery rate correction.

3. Results

Given that the main focus of our study was on the dysfunctional brain network organization in PD patients with frequent falls, we applied a targeted approach by analyzing brain structures that are known to be critically involved in gait and stance control, including the cerebellum, brain stem and basal ganglia.

The cerebellar seed regions showed significantly increased FC in PD-fallers compared to controls in the two connections spanning between the vermis and both the left ($T(24) = 3.51$, $p\text{-value} = 0.041$) and right ($T(24) = 3.65$, $p = 0.041$) cerebellar cortex (Figure 1). In comparison to controls, we also noted an increased FC in PD non-fallers, although the difference failed to reach statistical significance ($p = 0.366$). However, with regard to laterality, the brain regions showed no functional differences between the left and right cerebellar hemisphere. Moreover, a direct comparison between PD-fallers and PD non-fallers revealed no statistically significant differences (all $p > 0.583$).

Furthermore, the connectivity between the precuneus, and left ($T(30) = -3.26$, $p = 0.017$) and right caudate nucleus ($T(30) = -2.56$, $p = 0.048$) was decreased in PD-non fallers as compared to controls ($p = 0.015$). A similar trend was also observed in PD-fallers compared to controls, but again without reaching statistical significance ($p = 0.10$). In the PD-fallers group, the difference in FC in this region with respect to controls was greater in the right caudate nucleus as compared to the left caudate nucleus. Moreover, the strength of the FC of the right caudate nucleus was similar to that observed in the non-fallers group. A direct comparison between PD-fallers and PD-non fallers revealed no statistically significant differences (all $p > 0.685$).

Lastly, no significant changes were found within the basal ganglia encompassing the canonical direct pathway, while multivariate regression analysis also revealed no association between FC measures and levodopa dosage or dopamine agonist therapy (data not shown).

4. Discussion

We investigated the resting state profiles of PD patients with frequent falls, PD patients without falls as well as age-matched healthy controls. The results were as follows: 1) PD patients exhibited higher functional connectivity within the cerebellum, and 2) the functional connectivity between the precuneus and caudate nucleus was decreased in PD patients.

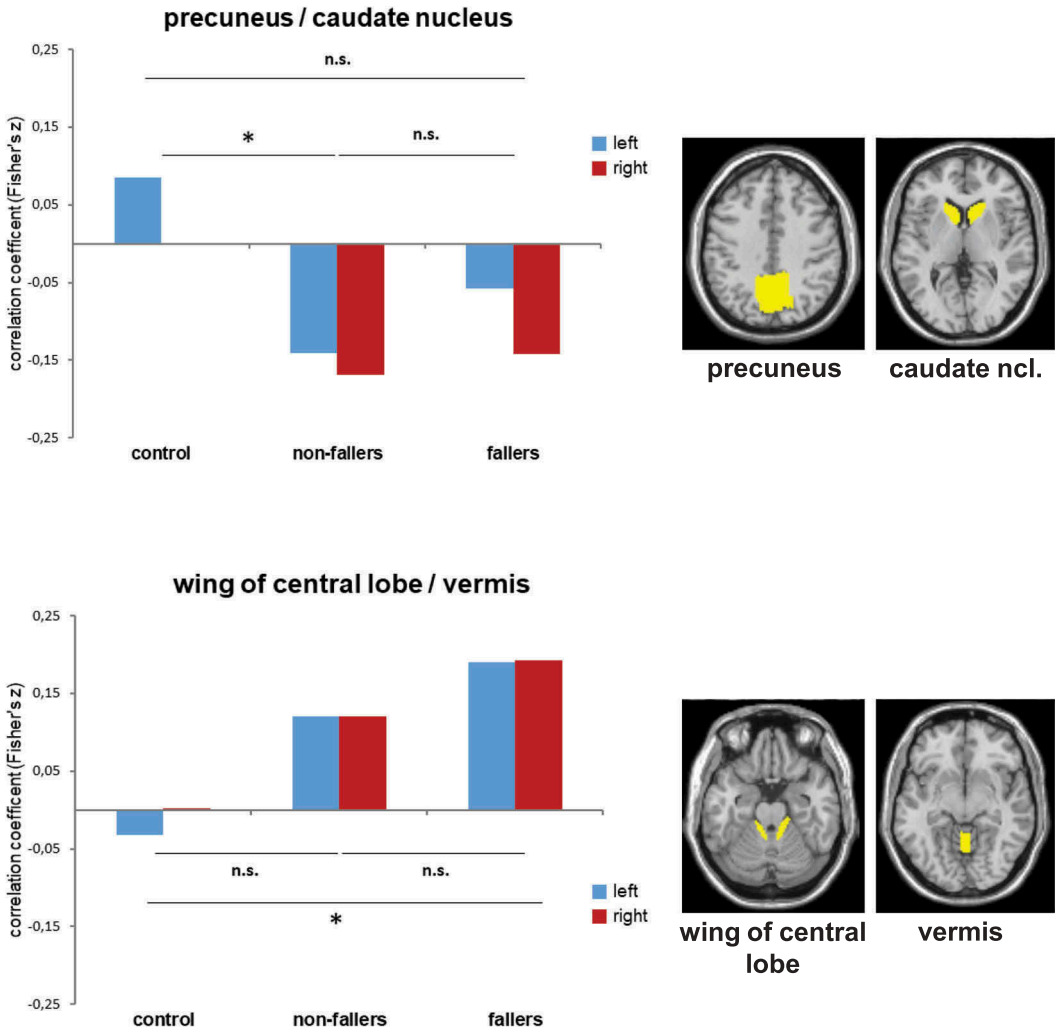

Figure 1. Correlation coefficient (Fisher's z) demonstrates in PD non-faller patients reduced connectivity between precuneus and caudate nucleus compared to healthy controls (above), and hyperconnectivity between the wing of central lobe and vermis of the cerebellum in PD faller compared to healthy controls (below). P-values are corrected for multiple comparisons. Panels on the right exhibit MNI brain templates.

4.1. Increased connectivity within the cerebellum

In line with previous studies [16, 20], we demonstrated a significantly increased connectivity within the cerebellum in PD patients in comparison to healthy individuals. However, in contrast to these, we recruited and analyzed two distinct subgroups of PD patients, i.e. fallers and non-fallers, and found a trend towards cerebellar hyperconnectivity in PD-fallers as compared to PD non-fallers. This finding suggests that there is an association between cerebellar hyperconnectivity and postural instability in PD-fallers. Tuovinen et al. used a mixed study cohort encompassing 16 PD patients of whom 6 suffered from postural instability, suggesting that the cerebellar changes they observed could be caused by this subgroup of patients.

Intact function of the vermis is essential for stance and gait control. Typically, the vermis is part of the spinocerebellum, and receives somatic sensory input related to the head and proximal parts of the body from ascending spinal pathways [21]. In addition, it is also a target of projections from motor areas of the cerebral cortex [22]. The vermis triggers and adaptively modifies the anticipatory postural adjustments in gait control [23], and it is involved in the fine-tuning of the sensorimotor integration. Accordingly, lesions or functional inactivation of the vermis lead to deficits in whole-body posture and locomotion [24]. Thus, our finding of cerebellar hyperconnectivity in the vermis of PD-fallers supports its relevance in the context of postural control in PD.

Our results are unlikely to be biased by other confounders like age, cognitive deficits, or disease duration, as the distribution of these potential confounders was similar between the groups. However, in this study, the group of PD-fallers had a higher levodopa dosage daily intake than the non-fallers' group. As dopaminergic medication might also induce cerebellar hyperconnectivity [25], we would also have expected to see cerebellar hyperconnectivity in the PD-non fallers group as the intergroup difference in daily levodopa dosage intake was rather small. Interestingly, PD

patients without levodopa medication had increased levels of cerebellar-cerebellar connectivity, whereas continuing the medication intake induced a decreased connectivity [26]. In any case, we found no correlation between levodopa dosage and FC in our cohort.

Using regional cerebral blood flow measurements with H(2)(15)O positron emission tomography (PET), PD patients showed a greater cerebellar activation than healthy individuals, and a lesser activation in the supplementary motor cortex. Thus, PD patients might have activated the cerebellar pathways to compensate for the basal ganglia dysfunction. However, this was not seen in patients with other diseases that affect the cerebellum like multiple system atrophy (MSA) [27]. This may be an adaptive mechanism that bypasses the dysfunctional basal ganglia in PD [28, 29]. We postulate that the observed cerebellar hyperconnectivity in our patient cohort also may represent a compensatory mechanism reflecting activation of additional brain structures to restore gait function in PD patients with postural instability.

4.2. Decreased FC of caudate nucleus and precuneus

In PD-non-fallers, we found a significantly decreased FC between the precuneus and caudate nucleus. However, this was not found in PD fallers. Others also demonstrated decreased connectivity of the precuneus to the motor system networks in PD [30] and decreased FC of the precuneus and amygdala in tremor-dominant PD. Furthermore, a decreased connectivity in occipital lobule and precuneus was seen in akinetic/rigid-dominant PD [31]. In addition, the study revealed that lower DMN functional connectivity correlated with a lower gray matter volume in the posterior cingulate and precuneus in PD [1].

The precuneus is a region involved in the DMN which is active during rest and is related to cognitive processes. In PD, motor sequence learning is associated with bilateral activation of the precuneus, dorsal premotor cortex, pre-supplementary motor area and cerebellar hemispheres [32]. So, the relative disconnection between precuneus and caudate nucleus in PD patients might demonstrate an impaired brain network resulting in motor dysfunction.

4.3. Conclusions

Our findings suggest that the relative disconnection between precuneus and caudate nucleus is not associated with frequent falls in PD. On the other hand, functional hyperconnectivity within the cerebellum of PD patients supports the idea of an ongoing compensatory mechanism to restore impaired gait control. Given that the clinical management of falls in PD patients is still inadequate, further interventional studies targeting this debilitating symptom of the disease are warranted. In this regard, our findings indicate that cerebellar areas might be considered as promising future therapeutic targets for neuromodulative treatment of postural instability in PD.

Acknowledgments

Special thanks to Kaeli Zimmermann for performing rs-fMRI. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Oliver Kaut (MD, PhD) works as neurologist at the University of Bonn, Germany. He has publish many papers in peer-reviewed journals with a focus on Parkinson's disease, also including epigenetic studies about DNA methylation in neurological disorders. Since over 10 years we cares for PD patients in an in- and out-patient clinic of the University of Bonn.

Clemens Mielacher is a member of the NEMO research group of René Hurlemann. He has a Master of Science title and his research focuses on functional imaging in depression using MRI. He also published a paper about methods of neuromodulation using rTMS and has expertise in functional connectivity analyses and rTMS.

René Hurlemann is psychiatrist and works at the University of Bonn, Germany. His clinical and research interests are as follows: Affective spectrum disorders, predictive biotypes, personalized brain stimulation, Neuromodulation of Emotion (NEMO). He has widespread clinical research experience: Involved in multicenter clinical trials, including MOOD-HF, PRONIA. And has many board memberships: WPA Section on Personalized Psychiatry, Personalized Medicine in Psychiatry. His Honors (excerpt) are Ph.D. with distinction 2008: Gerd-Huber-Award for advances in neuroimaging of schizophrenia 2013: Helen C. Levitt Visiting Professor, University of Iowa (USA) 2013: Visiting Faculty, California Institute of Technology (Caltech), Pasadena (USA) 2014: Member of the American College of Neuropsychopharmacology.

Ullrich Wüllner is a neurologist at the University clinic of Bonn, Germany. Since 2014 he is head of the movement disorder section. He also is affiliated with the German Center of Neurodegenerative Diseases (DZNE), Germany and works as the leader of the biomarker research group. His neurobiology lab investigates the aetiology of Parkinson's disease and related disorders. His lab identified the transcriptional repressor activity of ataxin3, the disease protein in SCA3. Epigenetics is a key research topic: a concealed promoter in the a-synuclein gene was found hypomethylated in PD and genome-scale methylation analysis of PD are ongoing.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Sources of support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Lucas-Jiménez O, Ojeda N, Peña J, et al. Altered functional connectivity in the default mode network is associated with cognitive impairment and brain anatomical changes in Parkinson's disease. Parkinsonism Relat Disord. 2016;33:58–64.
[2] Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23:837–844.
[3] Pickering RM, Grimbergen YA, Rigney U, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. Mov Disord. 2007;22:1892–1900.
[4] Chou KL, Elm JJ, Wielinski CL, et al. NINDS NET-PD Investigators. Factors associated with falling in early, treated Parkinson's disease: the NET-PD LS1 cohort. J Neurol Sci. 2007;377:137–143.
[5] Bloem BR, Hausdorff JM, Visser JE, et al. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord. 2004;19:871–884. Review.
[6] Takakusaki K. Functional trol. J Mov Disord. 2017;10:1–17.
[7] Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. Mov Disord. 2013;28:1483–1491.
[8] Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain. 2013;136:696–709.
[9] Appel-Cresswell S, de la Fuente-fernandez R, Galley S. Imaging of compensatory mechanisms in Parkinson's disease. Curr Opin Neurol. 2010;23:407–412.
[10] Snyder AZ, Raichle ME. A brief history of the resting state: the Washington University perspective. Neuroimage. 2012;62:902–910. Review.
[11] Tahmasian M, Eickhoff SB, Giehl K, et al. Resting-state functional reorganization in Parkinson's disease: an activation likelihood estimation meta-analysis. Cortex. 2017;92:119–138.
[12] Hampson M, Driesen NR, Skudlarski P, et al. Brain connectivity related to working memory performance. J Neurosci. 2006;26:13338–13343.
[13] Esposito F, Bertolino A, Scarabino T, et al. Independent component model of the default-mode brain function: assessing the impact of active thinking. Brain Res Bull. 2006;70:263–269.
[14] Raichle ME, MacLeoc AM, Snyder AZ, et al. A default mode of brain function. Proc Natl Acad Sci USA. 2001;98:676–682.
[15] Hou Y, Luo C, Yang J. Default-mode network connectivity in cognitively unimpaired drug-naïve patients with rigidity-dominant Parkinson's disease. J Neurol. 2017;264:152–160.
[16] Tuovinen N, Seppi K, de Pasquale F, et al. The reorganization of functional architecture in the early-stages of Parkinson's disease. Parkinsonism Relat Disord. 2018;50:61–68.
[17] Behzadi Y, Restom K, Liau J, et al. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage. 2007;37:90–101.
[18] van Eimeren T, Monchi O, Ballanger B, et al. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. Arch Neurol. 2009;66:877–883.
[19] Purves D, Augustine GJ, Fitzpatrick D, et al. Neuroscience. 3rd. Sunderland (MA): Sinauer Associates; 2004.
[20] Cerasa A, Novellino F, Quattrone A. Connectivity changes in Parkinson's Disease. Curr Neurol Neurosci Rep. 2016;16:91.
[21] Kandel ER, Schwartz JH, Jessel TM. Principles of neural science. New York: McGraw-Hill; 2000.
[22] Coffman KA, Dum RP, Strick PL. Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. PNAS. 2011;108:16068–16073.
[23] Cordo PJ, Nashner LM. Properties of postural adjustments associated with rapid arm movements. J Neurophysiol. 1982;47:287–302.
[24] Colnaghi Colnaghi S, Honeine JL, Sozzi S, et al. Body sway increases after functional inactivation of the cerebellar vermis by cTBS. Cerebellum. 2017;16:1–14.
[25] Jech R, Mueller K, Schroeter ML, et al. Levodopa increases functional connectivity in the cerebellum and brainstem in Parkinson's disease. Brain. 2013;136:e234.
[26] Festini SB, Bernard JA, Kwak Y. Altered cerebellar connectivity in Parkinson's patients ON and OFF L-DOPA medication. Front Hum Neurosci. 2015;9:214.
[27] Payoux P, Brefel-Courbon C, Ory-Magne F, et al. Motor activation in multiple system atrophy and Parkinson disease: a PET study. Neurology. 2010;75:1174–1180.
[28] Palmer SJ, Li J, Wang ZJ, et al. Joint amplitude and connectivity compensatory mechanisms in Parkinson's disease. Neuroscience. 2010;166:1110–1118.
[29] Mentis MJ, Dhawan V, Feigin A, et al. Early stage Parkinson's disease patients and normal volunteers: comparative mechanisms of sequence learning. Hum Brain Mapp. 2003;20:246–258.
[30] Thibes RB, Novaes NP, Lucato LT, et al. Altered functional connectivity between precuneus and motor systems in Parkinson's Disease patients. Brain Connect. 2017;7:643–647.
[31] Guan X, Zeng Q, Guo T, et al. Disrupted functional connectivity of basal ganglia across tremor-dominant and akinetic/rigid-dominant Parkinson's Disease. Front Aging Neurosci. 2017;9:360.
[32] Carbon M, Reetz K, Ghilardi MF, et al. Early Parkinson's disease: longitudinal changes in brain activity during sequence learning. Neurobiol Dis. 2010;37:455–460.