Brain Imaging and Behavior (2020) 14:2176–2186
https://doi.org/10.1007/s11682-019-00168-7

ORIGINAL RESEARCH

Altered spontaneous functional activity of the right precuneus and cuneus in patients with persistent postural-perceptual dizziness

Kangzhi Li[1] · Lihong Si[1] · Bin Cui[2] · Xia Ling[1] · Bo Shen[3] · Xu Yang[1]

Published online: 16 July 2019

Abstract

Persistent postural-perceptual dizziness (PPPD) is a functional vestibular disorder, and is the most common cause of chronic vestibular syndrome. However, the pathogenesis of PPPD is currently unclear. This study aimed to analyze the changes of brain spontaneous functional activities in PPPD patients during the resting state, and to explore the underlying pathogenesis of PPPD, particularly the abnormal integration of visual and vestibular information. Ten PPPD patients and 10 healthy controls were enrolled from January to June 2018, and baseline data were collected from all subjects. Videonystagmography (VNG), the vestibular caloric test, the video head impulse test (vHIT) and vestibular evoked myogenic potentials (VEMPs) were measured to exclude peripheral vestibular lesions. Functional MRI (fMRI) was conducted in PPPD patients and healthy controls. The amplitude of low frequency fluctuation (ALFF) and regional homogeneity (ReHo), and functional connectivity were calculated to explore changes in brain spontaneous functional activity during the resting state. Compared with healthy controls, ALFF and ReHo values in the right precuneus and cuneus were significantly lower in PPPD patients (both $P < 0.05$). Further seed-based functional connectivity analysis showed decreased functional connectivity between precuneus, cuneus and left precentral gyrus ($P < 0.05$). Our findings suggest that the spontaneous functional activity of cuneus and precuneus in PPPD patients were altered, potentially leading to abnormal integration of visual and vestibular information. Weakened functional connectivity between the precuneus and the precentral gyrus may be associated with aggravated symptoms during upright posture, active or passive movements.

Keywords PPPD · Resting state functional magnetic resonance imaging · Precuneus · Cuneus · Precentral gyrus

Introduction

Persistent postural-perceptual dizziness (PPPD) is a functional vestibular disease with clinical symptoms characterized by persistent dizziness and/or unsteadiness for more than 3 months. The symptoms of PPPD can be aggravated by upright posture, active/passive motion, and exposure to complex visual environments. PPPD is the most common cause of chronic vestibular syndrome.

PPPD diagnosis has evolved over a relatively long period, and was initially based on phobic postural vertigo (PPV) (Brandt 1996), space and motion discomfort (SMD) (Jacob et al. 2009), visual induced dizziness (VID) (Bisdorff et al. 2009; Bronstein 1995), and chronic subjective dizziness (CSD) (Staab et al. 2004). PPPD was officially defined by Barany in 2015 (Bisdorff et al. 2015), and its diagnostic criteria were formally presented in 2017 (Staab et al. 2017). PPV, SMD, VV, and CSD emphasize different focuses, but share a number of features. The differences between these diagnoses may reflect variation in perspectives on the potential pathogenesis of PPPD. To date, the precise pathogenesis of PPPD remains unclear.

The pathogenesis of PPPD has received much research attention from clinicians and researchers. In recent years, the development of functional magnetic resonance imaging (fMRI) has provided a valuable method for studying

✉ Xu Yang
yangxu2011@163.com

[1] Department of Neurology, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing 100049, People's Republic of China

[2] Department of Radiology, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing 100049, People's Republic of China

[3] Department of Neurology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou 121001, People's Republic of China

functional diseases, and a potential approach for exploring the pathogenesis of PPPD. fMRI is considered the preferred technique for studying the pathogenesis of PPPD because of its high temporal resolution, high spatial resolution, non-invasiveness and low cost. Van Ombergen et al. (2017) found that functional connectivity was decreased in the superior temporal gyrus and enhanced in the occipital lobe in VID patients using intrinsic connectivity contrast analysis. In addition, the superior temporal gyrus was found to be involved in processing vestibular information. Decreased functional connectivity in this region may adversely affect multi-sensory integration. Increased functional connectivity in the occipital lobe indicated that multisensory integration is mainly driven by visual information. Further seed-based analysis revealed increased functional connectivity between the visual cortex and middle frontal gyrus, precuneus. Van Ombergen et al. (2017) investigated the pathogenesis of VID using functional connectivity analysis, changes in functional connectivity between the visual cortex and the vestibular cortex could explain why dizziness occurs in VID patients following exposure to complex visual environments. Further analysis of the subjects included in the study revealed that nine subjects had peripheral lesions. Although there were significant differences in peripheral vestibular lesions, these findings require further verification (Van Ombergen et al. 2017). Indovina et al. (2015) conducted a task-based fMRI study in 18 patients with CSD using sound-evoked vestibular stimuli (a VEMP-type stimulus), and found that the activation of the posterior insula, anterior insula, prefrontal lobe, inferior frontal gyrus, hippocampus, and anterior cingulate cortex were reduced in CSD patients. Further functional connectivity analysis revealed reduced functional connectivity between the anterior insula and superior temporal gyrus, anterior insula and middle occipital gyrus, hippocampus and superior temporal gyrus, anterior cingulate cortex and superior temporal gyrus in CSD patients. Changes in functional connectivity between the anterior insula and the middle occipital gyrus may be associated with visual dependence in CSD patients. Using vestibular stimulation, the study revealed that the processing of vestibular information in the multisensory vestibular cortex was weakened in CSD patients. Further analysis revealed that all subjects included in the study had a history of peripheral vestibular lesions. Although the types of peripheral vestibular lesions varied greatly, no subgroup analysis of the types and sides of peripheral vestibular lesions was performed. Jin-Ok Lee et al. (2018) performed resting-state fMRI in 38 patients with PPPD. Whole brain and region of interest (ROI)-based functional connectivity analysis revealed that functional connectivity between the left hippocampus and bilateral central opercular cortices, left posterior opercular cortex, right insular cortex and cerebellum were decreased, indicating that functional connectivity among the vestibular cortex in PPPD patients was decreased. Functional connectivity between the subcallosal cortex, left superior lateral occipital cortex, and left middle frontal gyrus were increased, indicating that the interaction between the visual cortex and the vestibular cortex in PPPD patients was changed, and was more strongly driven by visual information. Nevertheless, whether changes in functional connectivity between the hippocampus and the vestibular cortex are sufficient to explain persistent dizziness and unsteadiness in PPPD patients remains unclear. Riccelli et al. (2017) performed task-based fMRI with visual stimulation in 15 patients with PPPD. The results revealed that the anterior bank of the central insular sulcus responded more strongly to vertical visual motion compared with horizontal visual motion in healthy controls, while no difference was found in patients with PPPD. The authors speculated that the difficulties of using visual information to identify the effects of gravity on self-motion in PPPD patients may have an adverse effect on balance control, particularly for individuals with a high level of visual dependence (Riccelli et al. 2017).

The findings of the PPPD-related fMRI studies described above are more consistent with dysfunction of the vestibular cortex and increased activity in visual cortex, while the integration of multisensory regions appears to be more strongly driven by visual cortex. However, there is substantial heterogeneity among studies regarding dysfunction of specific parts of the vestibular cortex. The heterogeneity between studies may be related to differences in the subjects enrolled in each study. Further analysis of the participants included in previous studies revealed that most participants in each study were affected by chronic dizziness after peripheral vestibular lesions. Several previous studies have reported changes in brain function and structure after acute peripheral vestibular lesions (Helmchen et al. 2014; Helmchen et al. 2011; Helmchen et al. 2009; zu Eulenburg et al. 2010). In studies of PPPD, it is difficult to define whether changes in PPPD patients are secondary to peripheral vestibular lesion, or reflect primary changes in PPPD. To explore the pathogenesis of PPPD, it is necessary to stratify and classify PPPD, enabling more reliable results. In addition, task-based fMRI emphasizes responses to a particular task. However, the symptoms of dizziness are persistent in patients with PPPD. Compared with task-based fMRI, resting-state fMRI may better reflect the essential changes involved in the disease.

Given this background, to exclude the effects of peripheral vestibular lesions on brain functional activity, we enrolled PPPD patients without a history of peripheral vestibular disease or peripheral vestibular lesions. Using resting state fMRI, we calculated the amplitude of low frequency fluctuation (ALFF), regional homogeneity (ReHo) and functional connectivity to explore essential changes of brain functional activity and elucidate the pathogenesis of PPPD.

Subjects and methods

Subjects

Ten PPPD patients were enrolled in this study between January and June 2018. All patients volunteered to participate in the study and provided written informed consent. This study was approved by the Ethics Committee of Peking University Aerospace School of Clinical Medicine. Detailed medical information was collected for all patients. Videonystagmography (VNG), the vestibular caloric test, the video head impulse test (vHIT), and VEMPs were measured to exclude peripheral vestibular lesions. MRI was further performed to exclude focal lesions and other neurological diseases. Other examinations, including blood pressure, blood routine test, and electrocardiography were conducted to exclude other diseases associated with chronic dizziness. Meanwhile, the subjective vestibular disability score (SVDS), clinical vestibular score (CVS), and dizziness handicap inventory (DHI) score (Helmchen et al. 2011; Jacobson and Newman 1990) were used to assess patients' symptoms. The 7-item Generalized Anxiety Disorder scale (GAD-7) and 9-item Patient Health Questionnaire depression scale (PHQ-9) were used to assess anxiety and depression levels in patients with PPPD. The diagnosis of PPPD refers to the diagnostic criteria proposed by the Bárány Society (2017 edition). In addition, we included 10 age- and gender-matched healthy controls (HC). All healthy controls had no history of headache or dizziness and no serious medical diseases. All subjects underwent peripheral vestibular function evaluation to exclude peripheral vestibular dysfunction. In addition, PPPD patients and healthy controls underwent fMRI scanning.

Image acquisition

The images were acquired using a 3.0-Tesla MR scanner (MAGNETOM Skyra syngo MR D13; Siemens, Germany) with a 32-channel head and neck coil. During image acquisition, subjects' heads were fixed using foam padding to reduce head movement, and earplugs were used to reduce scanner noise. Subjects were instructed to relax, keep eyes closed, and stay awake during scanning. Structural images were recorded using a 3-dimensional magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: repetition time (TR) = 1900 ms, echo time (TE) = 2.43 ms, flip angle = 8°, field of view (FOV) = 256 × 256 × 256 mm, voxel size: 1.0 × 1.0 × 1.0 mm, and a total of 192 slices were acquired. The functional images were recorded using an echo-planar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 222 × 222 × 222 mm, voxel size = 3.0 × 3.0 × 3.0 mm. A total of 200 volumes were collected with a scanning time of 6 min and 48 s. All subjects remained awake during the scan and no significant discomfort was reported during or after scan.

Data processing

fMRI data were processed with DPARSFA software on the MATLAB2013 platform (Chao-Gan and Yu-Feng 2010).

ALFF

We used the following process to calculate ALFF. (1) Data conversion: convert image data from DICOM format to NIFTI format; (2) deletion of the first 10 time points of the functional images: the first 10 time points were deleted to address the possible instability of the initial MRI signal and the need for participants to adapt to the scanning environment; (3) slice time correction: the 35th slice was chosen as the reference slice; (4) realignment: slight head motion of the subject between the time points during the scan was corrected. To ensure the accuracy of the position information, subjects who had more than 1.5 mm head translation in x, y, or z and 1.5° head rotation were removed; (5) regression: a linear regression model was used to remove the interference signal in the blood oxygen level dependent (BOLD) signal; (6) spatial normalization: to solve the problems related to differences in brain morphology among different subjects and inconsistencies in spatial position during scanning, fMRI images were spatially normalized to Montreal Neurological Institute space using DARTEL, and resampled at a resolution of 3 × 3 × 3 mm; (7) spatial smoothing: smoothing was performed with a Gaussian kernel of 8 × 8 × 8 mm to reduce registration errors and increase the normality of the data; (8) ALFF calculation: the power spectrum was obtained by transforming the time series of each voxel into frequency domain data using a fast-Fourier transform (FFT) algorithm. The average square root of the power spectrum across 0.01–0.08 Hz was calculated as the ALFF value. Each individual's ALFF value was then transformed to a Z-score to allow further comparison between groups.

ReHo

We calculated ReHo using the following process. (1) Data conversion; (2) deletion of the first 10 time points; (3) slice time correction; (4) realignment; (5) regression; (7) band-pass filtering: the time series for each voxel was temporally band-pass filtered (0.01–0.1 Hz) and linearly detrended to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise.; (8) spatial normalization; (9) ReHo calculation: ReHo calculation was performed using Kendall's coefficient of concordance (KCC) to measure the synchronicity of the time series between a given voxel with its 26 nearest neighbors in a voxel-wise way. The generated regional

homogeneity images were subsequently smoothed with 4 mm full-width-half-maximum; (10) spatial smoothing.

Functional connectivity

Functional connectivity was calculated using the following process. (1) Data conversion; (2) deletion of the first 10 time points; (3) slice time correction; (4) realignment; (5) regression; (6) band-pass filtering; (8) spatial normalization; (9) calculation of functional connectivity. After ALFF analysis, abnormal regions were selected as seeds to further explore changes in functional connectivity with other brain regions, particularly other vestibular cortex and visual cortex regions, between PPPD patients and healthy controls. The resulting r-values were normalized into Z values using Fisher's R-to-Z method for further comparison between groups; (10) spatial smoothing.

Statistical analysis

Clinical baseline data were analyzed using SPSS22. Functional data were analyzed using a statistical module in SPM12. The two-sample t-test was applied to analyze differences in ALFF, ReHo and functional connectivity between PPPD patients and healthy controls with regressing covariates such as age and gender. We used family-wise error (FWE)-corrected values for multiple comparisons, and $P < 0.05$ was considered to indicate statistical significance. The results were presented using xjview and Brainnetview (Xia et al. 2013).

Results

Clinical data

In terms of clinical baseline data, four males and six females were included. All participants were right-handed. The mean age was 47.70 ± 12.37 years. Mean SVDS was 9.10 ± 5.43. Mean CVS was 4.56 ± 3.57. Mean GAD7 score was 8.90 ± 2.40. Mean PHQ9 score was 3.40 ± 2.07. Mean DHI score was 52.33 ± 9.51. Mean DHI-P score was 15.33 ± 3.46. Mean DHI-E score was 15.78 ± 6.36. Mean DHI-F score was 21.56 ± 4.67 (Table 1). Analysis of the three sub-scores of the DHI revealed a significant difference among DHI-P, DHI-E and DHI-F ($P = 0.01$, $P < 0.05$). Further pairwise comparisons indicate that DHI-F was significantly higher than DHI-P ($P = 0.02$) and DHI-E ($P = 0.03$). There were no significant differences between DHI-F and DHI-P ($P = 0.96$; $P > 0.05$) (Fig. 1).

In terms of clinical features, all 10 patients showed persistent dizziness and postural instability. Only one patient (1/10) showed non-spinning vertigo. In terms of exacerbating/releasing factors, eight (8/10) patients' symptoms were exacerbated by upright posture, active or passive movement, and exposure to a complex visual environment, and all patients (10/10) were exacerbated by active or passive movement, and exposure to a complex visual environment. Patients showed fewer symptoms when they awoke, with aggravation over the course of the day. Sitting or lying alleviated the severity of symptoms. In terms of precipitating factors of PPPD, PPPD was precipitated by autonomic disorders, headache, anxiety, autonomic disorders and whiplash injuries in six patients; however, the specific precipitants of PPPD were not identified in four patients with longer disease duration. Among the 10 patients, five had a history of motion-sickness, and nine had a history of fear of heights (Table 2).

fMRI data

ALFF

Comparison of healthy controls vs. PPPD patients revealed that ALFF values in the right precuneus and cuneus (X = 24, Y = −81, Z = 42) was significantly lower in PPPD patients than in healthy controls ($P = 0.002$, FWE-corrected) (Fig. 2). Significantly decreased ALFF in the right precuneus and cuneus of PPPD patients suggests a decrease in spontaneous activity in this area.

ReHo

The difference in ReHo between PPPD patients and healthy controls was further compared to explore whether ReHo changes matched ALFF changes in PPPD patients. Comparison of healthy controls vs. PPPD patients revealed that ReHo values in the right precuneus and cuneus (X = 12, Y = −90, Z = 36) were significantly lower in PPPD patients than among healthy controls ($P = 0.029$, FWE-corrected) (Fig. 3). Regions with abnormal ReHo included areas with significantly reduced ALFF and adjacent areas. ReHo changes matched changes in ALFF, indicating dysfunction of the precuneus and cuneus.

Functional connectivity

The functional connectivity of areas with abnormal ALFF was further analyzed to explore changes of functional connectivity with other brain areas. Comparison of healthy controls vs. PPPD patients revealed that functional connectivity of this area with surrounding areas (X = 21, Y = −75, Z = 45, $P < 0.001$, FWE-corrected) was decreased (Fig. 4). Functional connectivity between precuneus and surrounding areas was decreased, matching the change of ReHo, indicating dysfunction of the precuneus in patients with PPPD. Functional connectivity with left precentral gyrus (X = −36, Y = −9, Z = 48, $P = 0.0047$, FWE-corrected) was also

Table 1 Clinical baseline data of PPPD patients

NO.	Age (year)	Duration (month)	DHI	DHI-P	DHI-E	DHI-F	SVDS	CVS	GAD7	PHQ9
P01	67	120	36	16	8	12	11	9	10	2
P02	35	6	40	12	10	18	5	2	8	1
P03	34	3	58	18	14	26	5	0	5	5
P04	57	8	62	14	26	24	6	8	7	1
P05	62	120	65	18	20	28	12	9	8	6
P06	46	156	52	20	12	20	22	5	6	3
P07	55	36	56	12	22	22	3	3	7	1
P08	32	12	50	18	10	22	8	0	10	5
P09	40	6	52	10	20	22	8	5	13	6
P10	49	7	64	18	20	26	11	4	6	4

decreased in PPPD patients (Fig. 5). The weakened functional connectivity between the precuneus and precentral gyrus indicated a weakened ability to adjust posture and movement using vestibular and visual information in PPPD patients.

Discussion

PPPD is a functional vestibular disease with severe subjective symptoms. However, positive identification of PPPD is difficult with current clinical examination methods, and there is often a mismatch between clinical examination and subjective symptoms. Because PPPD patients often exhibit dizziness and postural instability, patients typically exhibit high DHI scores based on subjective symptoms. The DHI was proposed by Gary in 1990. This scale consists of DHI-P, DHI-E, and DHI-F, which evaluate the physical, mood, and functional effects, respectively, of dizziness and instability (Jacobson and Newman 1990). This study revealed that DHI-F scores were significantly higher than DHI-P and DHI-E scores in PPPD patients, indicating that the clinical symptoms of PPPD patients were largely functional (Jacobson and Newman 1990). Thus, high DHI-F scores may aid the identification of PPPD. PPPD patients often suffer from anxiety and depression in varying degrees. In the present study, GAD-7 and PHQ-9 scales were used to assess anxiety and depression levels in patients with PPPD. We found that all patients had no severe anxiety or depression. Anxiety and depressive symptoms may represent complications of PPPD rather than its main pathogenic factors.

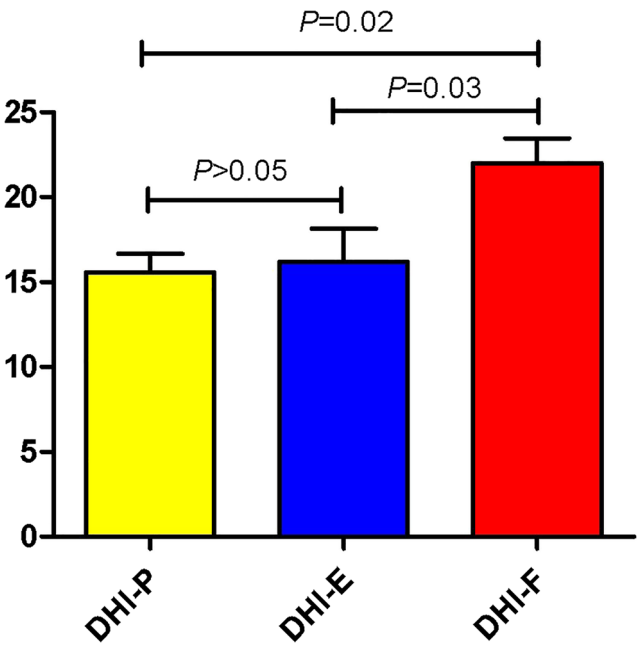

Fig. 1 DHI sub-scores revealed significant differences among DHI-P, DHI-E and DHI-F scores ($P = 0.01$, $P < 0.05$). Further pairwise comparisons (Tukey's method) revealed no significant differences between DHI-P and DHI-E scores ($P = 0.96$, > 0.05); DHI-F scores were significantly higher than DHI-P scores ($P = 0.02$, < 0.05); DHI-F scores were significantly higher than DHI-E scores ($P = 0.03$, < 0.05). Significantly higher DHI-F scores may improve the identification of PPPD

ALFF refers to the amplitude of spontaneous functional activity of the brain (Zang et al. 2007). The greater the amplitude, the stronger the brain activity. ReHo is a voxel-based measure of brain activity that evaluates synchronization between the time-series of a given voxel and its nearest neighbors (Zang et al. 2004). Decreased ReHo in this area suggests a decrease in the consistency of regional functional activity in PPPD patients. In the present study, we found that ALFF and ReHo values in the right precuneus and cuneus were decreased, and functional connectivity with the precentral gyrus was decreased in PPPD patients, indicating that the spontaneous functional activity of the precuneus and cuneus were impaired. A previous study reported that electrical stimulation of the precuneus can lead to vestibular symptoms, suggesting that the precuneus participates in the processing of vestibular information (Kahane et al. 2003). Studies using fMRI with galvanic vestibular stimulation, VEMP-type stimulation and

Table 2 Clinical characteristics of PPPD patients

NO.	Precipitating factors	Core vestibular symptoms			Increased as the day progressed	Exacerbating factors			Motion sickness	Fear of heights
		Dizziness	Unsteadiness	Non-spinning vertigo		Upright posture	Active or passive motion	Complex visual environment		
P01	–	√	√		√	√	√	√	√	√
P02	Autonomic disorders	√	√	√	√	√	√	√		√
P03	Headache	√	√		√	√	√	√		√
P04	–	√	√		√		√	√		√
P05	–	√	√		√	√	√	√	√	
P06	–	√	√		√	√	√	√		√
P07	Anxiety	√	√		√	√	√	√	√	√
P08	Autonomic disorders	√	√		√		√	√		√
P09	Headache	√	√		√	√	√	√	√	√
P10	Whiplash injuries	√	√		√	√	√	√	√	√

the caloric stimulation have also reported that the precuneus participates in the processing of vestibular information, operating as part of the multisensory vestibular cortex (Klingner et al. 2013; Lopez et al. 2012). The precuneus,

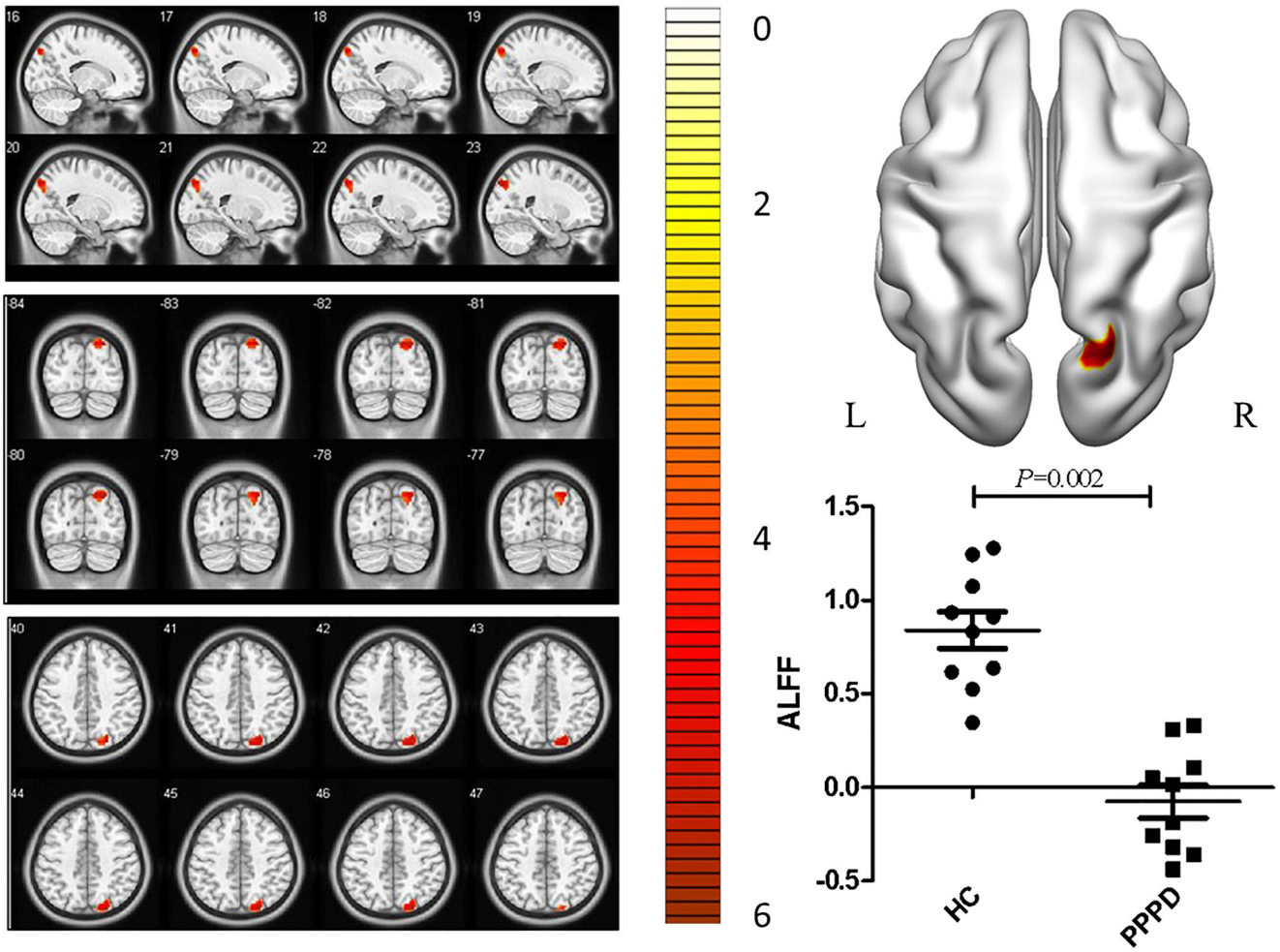

Fig. 2 ALFF in the right precuneus and cuneus (X = 24, Y = −81, Z = 42) was significantly higher in healthy controls than in PPPD patients ($P = 0.002$, FWE-corrected), suggesting that spontaneous functional activity was weakened in these areas in PPPD patients

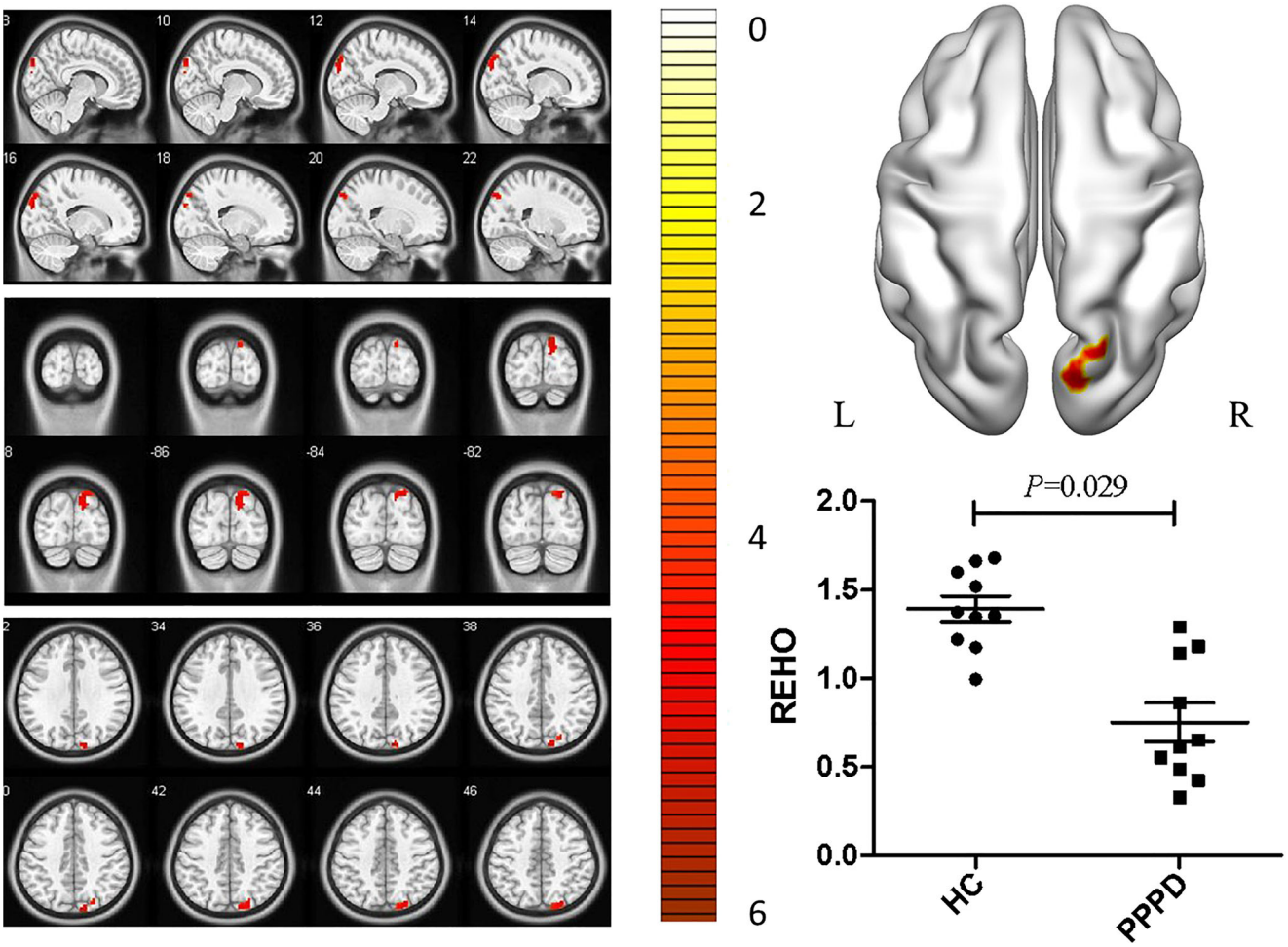

Fig. 3 ReHo in the right precuneus and cuneus (X = 12, Y = −90, Z = 36) was significantly higher among healthy controls compared with PPPD patients ($P = 0.029$, FWE-corrected), suggesting a decrease in the consistency of regional functional activity of these regions in PPPD patients

located in Brodmann area 7, is a part of the parietal association cortex, which participates in the integration of visual information and vestibular information, and plays an important role in spatial positioning and spatial perception (Cavanna and Trimble 2006). The cuneus, located in Brodmann area 19, is part of the visual association cortex and participates in the processing of visual spatial information (Waberski et al. 2008; Fortin et al. 2002). Abnormal spontaneous functional activity in PPPD patients has been found in an area in the parieto-occipital junction, which is involved in the integration of visual and vestibular information. Dysfunction of this area may cause abnormal integration of visual and vestibular information.

In the resting state, the precuneus, which is one of the brain regions with the highest metabolic rate (Zhu et al. 2012; Gusnard et al. 2001a, 2001b), is an important component of the default network, and directly interacts with other nodes of the default network (Fransson and Marrelec 2008). The default network is activated mainly in the resting state, and plays an important role in monitoring the external environment by collecting and evaluating the information generated in the internal and external environment (Gusnard et al. 2001a, 2001b; Hahn et al. 2007). Healthy people can typically maintain body balance and spatial perception without requiring extra attention. In contrast, PPPD patients show persistent dizziness and unsteadiness in the resting state. The precuneus is an important network hub in the brain (Gusnard et al. 2001a, 2001b; Buckner et al. 2008), but functioning of the precuneus is impaired in PPPD patients. We speculate that hypofunction of the precuneus may lead to default network dysfunction, which cannot effectively evaluate internal and external environment information, and cannot achieve clear spatial perception. Moreover, if this abnormality persists in the resting state, it would be expected to cause persistent dizziness and unsteadiness.

The current results revealed that visual stimuli and complex visual environments aggravated symptoms of dizziness and instability, which is a characteristic manifestation of PPPD and an important factor in differential diagnosis with other diseases (Staab et al. 2017). In the current study, dizziness and unsteadiness were aggravated in all patients (10/10) when exposed to visual stimuli or a complex visual environment. When presented with visual stimuli or complex visual

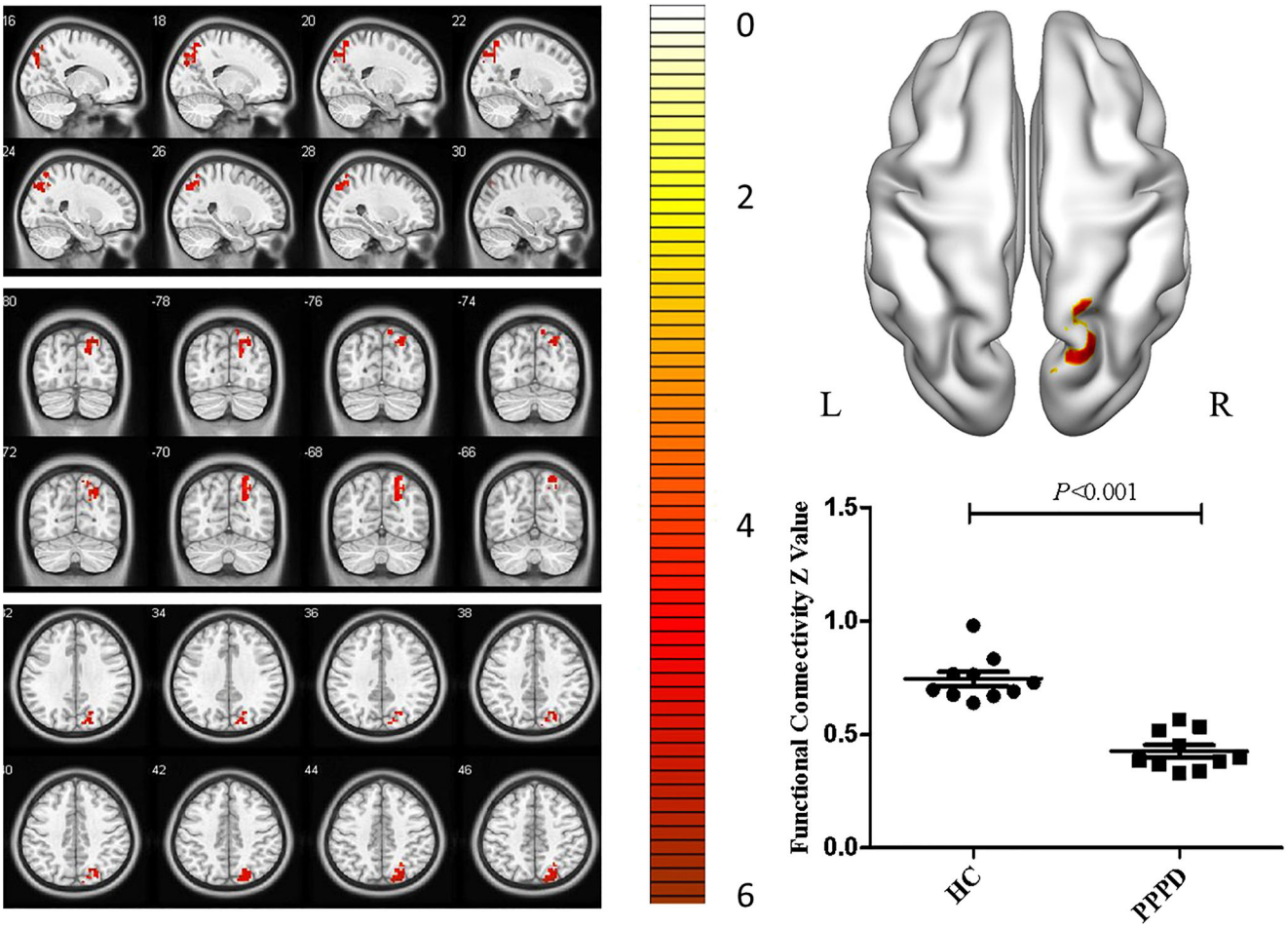

Fig. 4 Functional connectivity between the area with abnormal ALFF and surrounding area (X = 21, Y = −75, Z = 45) was decreased ($P < 0.001$, FWE-corrected). This result indicates that the short-range functional connectivity of the area with abnormal ALFF was abnormal. Changes of ALFF, ReHo and functional connectivity were matched, suggesting that precuneus and cuneus function were impaired

environments, incoming complex visual information aggravates the impaired integration of visual and vestibular information, resulting in aggravation of dizziness and unsteadiness.

The weakened functional connectivity between the precuneus and precentral gyrus in PPPD patients may be associated with aggravation of dizziness and unsteadiness induced by upright posture, and active/passive motion. There are extensive functional and structural connections between the precuneus and adjacent areas, as well as more distant areas (Lopez et al. 2012). Previous studies have confirmed that the precuneus has connections with the precentral gyrus and supplementary motor area (Leichnetz 2001; Wise et al. 1997). The precentral gyrus is the motor center, and participates in the regulation of body movement and posture. In the current study, decreased functional connectivity between the precuneus and precentral gyrus in PPPD patients suggested a weakened ability to adjust posture and movement using vestibular and visual information. Furthermore, the integration of vestibular and visual information in patients with PPPD is abnormal, further exacerbating the abnormality of posture and movement regulation using vestibular information. A previous study demonstrated that the gait of PPV patients changed (i.e., the speed decreased, the pace decreased, and the time of contact between the feet and the ground increased) (Schniepp et al. 2014). Further in-depth postural analysis revealed that PPV patients increased postural swing during normal posture through joint contractions of leg flexors and extensors, and this high-demand postural control strategy was activated only in the event of danger or falling (Wuehr et al. 2013). The present results may help to elucidate the underlying mechanisms of posture and gait changes in PPPD (and PPV). We found that functional connectivity of the precuneus and precentral gyrus was weakened, with a reduced ability to adjust body movement and posture using vestibular-visual information, causing patients to adopt a high-risk posture control strategy to maintain balance. In the upright posture, active/passive motion, particularly during fast movement, further exacerbate the impaired ability to adjust movement and posture, resulting in aggravation of dizziness and unsteadiness.

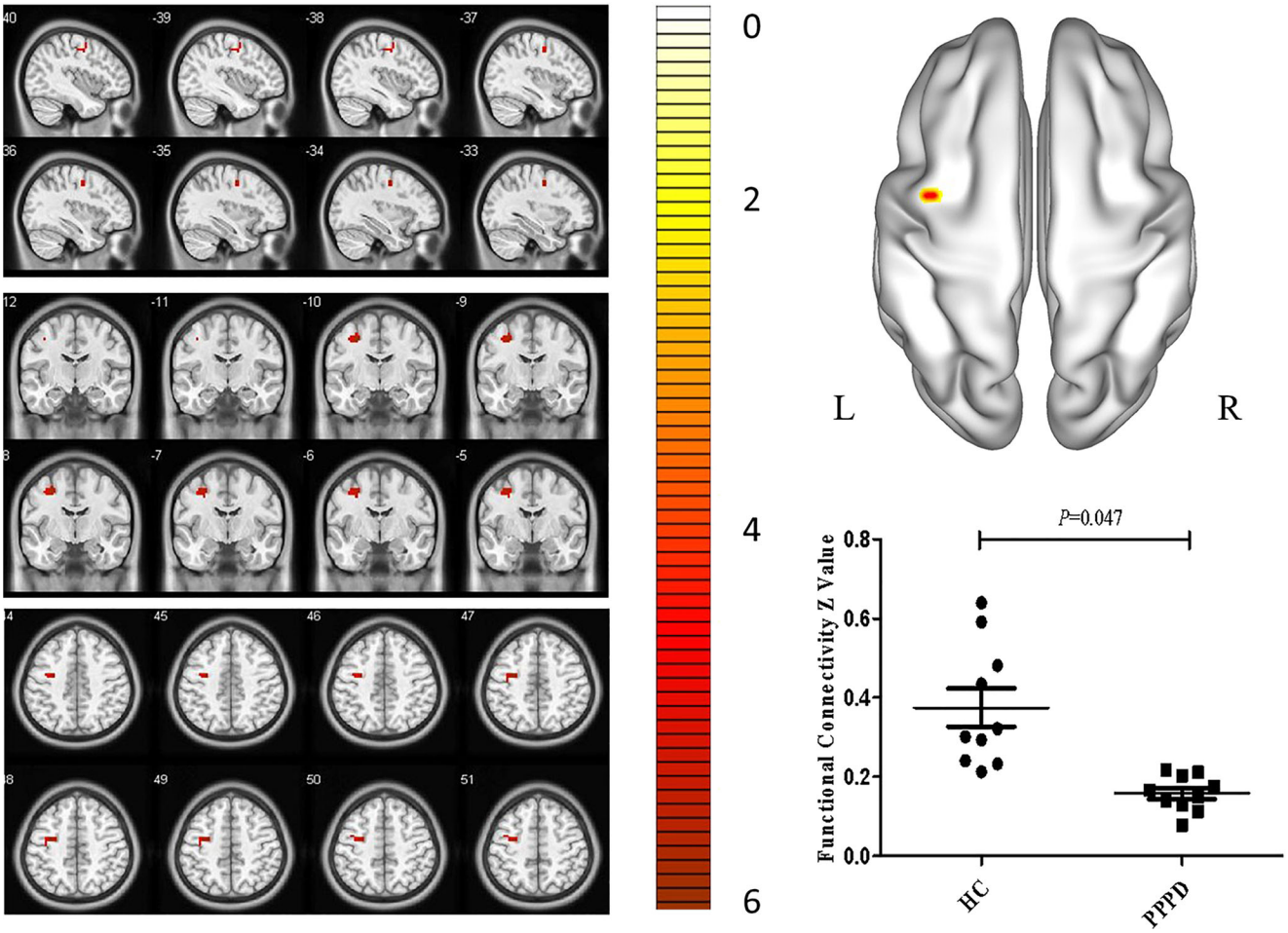

Fig. 5 Functional connectivity between left precentral gyrus (X = −36, Y = −9, Z = 48) and the abnormal ALFF region was significantly decreased in PPPD patients compared with healthy controls ($P = 0.049$, FWE-corrected), indicating that information exchange between the precentral gyrus and both the precuneus and cuneus was weakened in PPPD patients

Importantly, no changes of spontaneous functional activity in other vestibular and visual cortical areas were found in PPPD patients without peripheral vestibular lesions in the current study. Most subjects in previous PPPD functional imaging studies had peripheral vestibular lesions, or the triggering factor was peripheral vestibular lesions (Helmchen et al. 2011; zu Eulenburg et al. 2010; Hong et al. 2014), and those studies have reported that functional activity of the vestibular cortex of PPPD patients is decreased, functional activity of the visual cortex is enhanced, and the integration of multiple sensations is more strongly driven by visual information. These changes are similar to changes of brain functional activity caused by peripheral vestibular lesions. It is difficult to define whether functional changes of the vestibular and visual cortex are primary changes of PPPD or secondary changes of peripheral vestibular lesions. In the current study, we enrolled PPPD patients without a history of peripheral vestibular disease or peripheral vestibular lesions. The precipitating events of PPPD included autonomic disorders, headache, anxiety, autonomic disorders and whiplash injuries, however, the specific precipitants of PPPD cannot be identified in all patients, especially those with longer disease duration, but these patients did not have peripheral vestibular lesions, such as benign paroxysmal positional vertigo, vestibular neuronitis, and Meniere's disease before onset. The results showed that no abnormal changes of other vestibular cortical areas were found after excluding the confounding factors of peripheral vestibular lesions. Changes of brain functional activity in PPPD patients may reflect impaired integration of visual-vestibular information caused by dysfunction of the precuneus and cuneus. Therefore, we speculate that brain functional changes of PPPD patients with a history of peripheral vestibular lesions differ from those of patients with no history of peripheral vestibular lesions, and may have a different pathogenesis.

In the current study, we investigated the possible pathogenesis of PPPD by analyzing spontaneous functional brain activity in PPPD patients. The results suggested that abnormal changes of spontaneous functional activity and functional connectivity in the precuneus and cuneus may explain persistent dizziness, instability and aggravating factors in patients

with PPPD. However, several limitations involved in this study should be considered: 1) Because the sample size of this study was relatively small, the results should be further verified with a larger sample size. 2) All patients included in the study had no severe anxiety or depression. However, anxiety and depressive symptoms are commonly comorbid with PPPD. Therefore, further analyses of PPPD patients with and without comorbid conditions are desirable. 3) Classified and stratified studies in future are needed to investigate the differences in the changes of brain functional activity between PPPD patients with and without peripheral vestibular lesions, and to extend understanding of the pathogenesis of PPPD.

Conclusions

In patients with PPPD, precuneus and cuneus function are impaired, potentially leading to abnormal integration of visual and vestibular information and resulting in persistent dizziness and unsteadiness. The weakened functional connectivity between the precuneus and the precentral gyrus may be associated with aggravated symptoms in the upright position and during active or passive motion.

Funding The study was supported by Aerospace Center Hospital (Grant No. YN201802).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of Peking University Aerospace School of Clinical Medicine, and all procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Bisdorff, A., Von Brevern, M., Lempert, T., & Newman-Toker, D. E. (2009). Classification of vestibular symptoms: Towards an international classification of vestibular disorders. *Journal of Vestibular Research, 19*, 1–13.

Bisdorff, A. R., Staab, J. P., & Newman-Toker, D. E. (2015). Overview of the international classification of vestibular disorders. *Neurologic Clinics, 33*, 541–550.

Brandt, T. (1996). Phobic postural vertigo. *Neurology, 46*, 1515–1519.

Bronstein, A. M. (1995). Visual vertigo syndrome: Clinical and posturography findings. *Journal of Neurology, Neurosurgery, and Psychiatry, 59*, 472–476.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1–38.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain, 129*, 564–583.

Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience, 4*, 13.

Fortin, A., Ptito, A., Faubert, J., & Ptito, M. (2002). Cortical areas mediating stereopsis in the human brain: A PET study. *Neuroreport, 13*, 895–898.

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage, 42*, 1178–1184.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001a). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*, 4259–4264.

Gusnard, D. A., Raichle, M. E., & Raichle, M. E. (2001b). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews. Neuroscience, 2*, 685–694.

Hahn, B., Ross, T. J., & Stein, E. A. (2007). Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cerebral Cortex, 17*, 1664–1671.

Helmchen, C., Klinkenstein, J., Machner, B., Rambold, H., Mohr, C., & Sander, T. (2009). Structural changes in the human brain following vestibular neuritis indicate central vestibular compensation. *Annals of the New York Academy of Sciences, 1164*, 104–115.

Helmchen, C., Klinkenstein, J. C., Krüger, A., Gliemroth, J., Mohr, C., & Sander, T. (2011). Structural brain changes following peripheral vestibulo-cochlear lesion may indicate multisensory compensation. *Journal of Neurology, Neurosurgery, and Psychiatry, 82*, 309–316.

Helmchen, C., Ye, Z., Sprenger, A., & Münte, T. F. (2014). Changes in resting-state fMRI in vestibular neuritis. *Brain Structure & Function, 219*, 1889–1900.

Hong, S. K., Kim, J. H., Kim, H. J., & Lee, H. J. (2014). Changes in the gray matter volume during compensation after vestibular neuritis: A longitudinal VBM study. *Restorative Neurology and Neuroscience, 32*, 663–673.

Indovina, I., Riccelli, R., Chiarella, G., Petrolo, C., Augimeri, A., Giofrè, L., Lacquaniti, F., Staab, J. P., & Passamonti, L. (2015). Role of the insula and vestibular system in patients with chronic subjective dizziness: An fMRI study using sound-evoked vestibular stimulation. *Frontiers in Behavioral Neuroscience, 9*, 334.

Jacob, R. G., Redfern, M. S., & Furman, J. M. (2009). Space and motion discomfort and abnormal balance control in patients with anxiety disorders. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*, 74–78.

Jacobson, G. P., & Newman, C. W. (1990). The development of the dizziness handicap inventory. *Archives of Otolaryngology – Head & Neck Surgery, 116*, 424–427.

Kahane, P., Hoffmann, D., Minotti, L., & Berthoz, A. (2003). Reappraisal of the human vestibular cortex by cortical electrical stimulation study. *Annals of Neurology, 54*, 615–624.

Klingner, C. M., Volk, G. F., Flatz, C., Brodoehl, S., Dieterich, M., Witte, O. W., & Guntinas-Lichius, O. (2013). Components of vestibular cortical function. *Behavioural Brain Research, 236*, 194–199.

Lee, J. O., Lee, E. S., Kim, J. S., Lee, Y. B., Jeong, Y., Choi, B. S., Kim, J. H., & Staab, J. P. (2018). Altered brain function in persistent postural perceptual dizziness: A study on resting state functional connectivity. *Human Brain Mapping, 39*, 3340–3353.

Leichnetz, G. R. (2001). Connections of the medial posterior parietal cortex (area 7m) in the monkey. *The Anatomical Record, 263*, 215–236.

Lopez, C., Blanke, O., & Mast, F. W. (2012). The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis. *Neuroscience, 212*, 159–179.

Riccelli, R., Passamonti, L., Toschi, N., Nigro, S., Chiarella, G., Petrolo, C., Lacquaniti, F., Staab, J. P., & Indovina, I. (2017). Altered insular

and occipital responses to simulated vertical self-motion in patients with persistent postural-perceptual dizziness. *Frontiers in Neurology, 8*, 529.

Schniepp, R., Wuehr, M., Huth, S., Pradhan, C., Brandt, T., & Jahn, K. (2014). Gait characteristics of patients with phobic postural vertigo: Effects of fear of falling, attention, and visual input. *Journal of Neurology, 261*, 738–746.

Staab, J. P., Eckhardt-Henn, A., Horii, A., Jacob, R., Strupp, M., Brandt, T., & Bronstein, A. (2017). Diagnostic criteria for persistent postural-perceptual dizziness (PPPD): Consensus document of the committee for the classification of vestibular disorders of the Bárány society. *Journal of Vestibular Research, 27*, 191–208.

Staab, J. P., Ruckenstein, M. J., & Amsterdam, J. D. (2004). A prospective trial of sertraline for chronic subjective dizziness. *Laryngoscope, 114*, 1637–1641.

Van Ombergen, A., Heine, L., Jillings, S., Roberts, R. E., Jeurissen, B., Van Rompaey, V., Mucci, V., Vanhecke, S., Sijbers, J., Vanhevel, F., Sunaert, S., Bahri, M. A., Parizel, P. M., Van de Heyning, P. H., Laureys, S., & Wuyts, F. L. (2017). Altered functional brain connectivity in patients with visually induced dizziness. *Neuroimage Clin, 14*, 538–545.

Waberski, T. D., Gobbelé, R., Lamberty, K., Buchner, H., Marshall, J. C., & Fink, G. R. (2008). Timing of visuo-spatial information processing: Electrical source imaging related to line bisection judgements. *Neuropsychologia, 46*, 1201–1210.

Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: Corticocortical connectivity and combinatorial computations. *Annual Review of Neuroscience, 20*, 25–42.

Wuehr, M., Pradhan, C., Novozhilov, S., Krafczyk, S., Brandt, T., Jahn, K., & Schniepp, R. (2013). Inadequate interaction between open- and closed-loop postural control in phobic postural vertigo. *Journal of Neurology, 260*, 1314–1323.

Xia, M., Wang, J., & He, Y. (2013). BrainNet viewer: A network visualization tool for human brain connectomics. *PLoS One, 8*, e68910.

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Sui, M. Q., Liang, M., Tian, L. X., Jiang, T. Z., & Wang, Y. F. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev, 29*, 83–91.

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *Neuroimage, 22*, 394–400.

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. *Biological Psychiatry, 71*, 611–617.

zu Eulenburg, P., Stoeter, P., & Dieterich, M. (2010). Voxel-based morphometry depicts central compensation after vestibular neuritis. *Annals of Neurology, 68*, 241–249.