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Advancements in Functional Magnetic Resonance Imaging for Persistent Postural-Perceptual Dizziness

Mengchun Zhou, Lan Zhang*, Tao Yang*, Qiang Tu, Tingting Hu

Department of Neurology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: *lanzhang_516@163.com, *yangtao9819@163.com

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Abstract

Persistent postural-perceptual dizziness, defined in 2017, is a chronic functional vestibular disorder. Which is characterized by persistent dizziness, unsteadiness, and/or non-spinning vertigo. However, the exact mechanisms remain unclear. In recent years, FMRI studies have provided key insights into the pathogenesis of PPPD. This review summarized functional imaging studies of persistent postural dizziness and its predecessors in recent years and found changes in the activity and functional connectivity of important areas of visual processing, multisensory vestibular and spatial cognition in patients with PPPD. In addition, factors such as stimulation mode, personality traits, mental comorbidities and external vestibular lesions have important effects on brain functional activities and connectivity patterns, and further stratified studies on these factors are needed in the future to further clarify and draw exact conclusions on the pathological mechanism of PPPD.

Keywords

Persistent Postural Dizziness, Functional Imaging, Magnetic Resonance Imaging

1. Introduction

Persistent postural-perceptual dizziness (PPPD) [1] is a very common chronic dizziness and one of the most common diagnoses of dizziness in the elderly, with a prevalence rate of 15% - 20% of all patients with vestibular disorders, second only to BPPV. Chronic vestibular dysfunction, which has long been considered to have certain psychological factors and is not simply classified as a

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*Lan Zhang is the first corresponding author, Tao Yang is the second corresponding author.

psychiatric category, was re-classified in 2017. It unites the core traits of the precursors including "phobic postural vertigo (PPV) [2]" "space motion discomfort" (SMD) [3] "visual vertigo (VV) [4]" and "chronic subjective dizziness (CSD) [5]". It is mainly characterized by persistent non-rotating dizziness and/or instability. As the symptoms persist and do not cure, the quality of life of patients is significantly reduced [6] [7], which brings no small financial burden to patients. Some previous studies have shown that sleep disorders [8], mood disorders dominated by anxiety and depression [9] [10], neuroticism and introverted personality traits [11], central sensitization [12], vestibular complications [13] [14] and other factors may induce or aggravate PPPD symptoms. Changes in postural strategy [15] [16], visual deterioration [17] [18], decreased spatial navigation [19] [20], decreased vestibular perception threshold [21], changes in multisensory integration [22], and heightened anxiety and hypervigilance in acute somatic symptoms [23] have been identified as possible pathophysiological mechanisms of PPPD. But the mechanism of PPPD is still unclear, functional magnetic resonance imaging (fMRI) based on blood-oxygen-level dependent (BOLD) [24] can identify functional abnormalities at an early stage. In recent years, scholars have used FMRI Chen methods to explore the pathogenesis of PPPD, providing key insights, and this review summarizes FMRI studies conducted in recent years to better understand the specific pathogenesis behind PPPD.

2. PPPD's Task State Functional Magnetic Resonance Imaging

Task-state fMRI involves having subjects perform set experimental tasks or receive external stimuli, such as visual, motor, language, attention, and sensory function tasks, performing BOLD imaging to observe changes in the subjects' brain regions.

2.1. Sound-Evoked Vestibular Stimulation in Functional Magnetic Resonance Studies of PPPD

In 2015 Indovina I *et al.* [25] studied changes in brain functional regions under sound-induced vestibular stimulation in patients with CSD and matched on standardized measures of neuroticism, introversion, anxiety, and depression. Then they found that, compared to controls, patients with CSD had reduced activity in the parietal vestibular cortex, the anterior insula, the inferior frontal gyrus, the hippocampus, and the anterior cingulate gyrus cortex, as well as reduced connectivity in the left anterior insula and right superior temporal gyrus, the left inferior frontal gyrus and the right middle occipital cortex, the left hippocampus and the right superior temporal gyrus, and the left anterior cingulate cortex and the right superior temporal gyrus. This study suggests that CSD patients showed reduced activity and fewer patterns of functional connectivity in key areas of the vestibular (parietal insular vestibular cortex), visual cortex (medial occipital cortex), and potentially interacting brain regions of the vestibular and anxiety systems (hippocampus, anterior insular, inferior frontal gyrus, anterior cingulate cortex) in response to sound-induced vestibular stimulation. Changes in the functional connectivity between the parietal insula vestibular cortex (vestibular cortex center) and the hippocampus (spatial-motor environmental information processing) may be related to the persistent sensation of unsteadiness, dizziness symptoms, postural changes and physical alertness. The altered functional connectivity between frontal and visual areas may further impair the sensory system, leading to visually induced dizziness. And functional connectivity of the anterior insula, anterior cingulate cortex (which plays a major role in anxiety regulation) and the parietal insula vestibular cortex is associated with postural changes and maintenance of dizziness symptoms. This may provide a basis for the mechanism of visual dependence and anxiety-induced physical hypervigilance in CSD. While another study [26] investigated the effects of anxiety-related personality traits (neuroticism, introversion) on brain activity and functional connectivity in PPPD patients in response to sound-evoked vestibular stimulation. It showed that neuroticism was positively correlated with activity in the pontine bridge, vestibulocerebellum, and parastriate cortex (visual association area), and negatively correlated with activity in the superior limbic gyrus. Neuroticism was also positively correlated with pons and amygdala, cerebellar vestibule and amygdala, inferior frontal gyrus and superior marginal gyrus, inferior frontal gyrus and paramystriate cortex. Whereas introversion was positively correlated with the activity of the amygdala, and negatively correlated with the amygdala and the inferior frontal gyrus. This research suggests that neuroticism and introversion influence activity and connectivity in cortical and subcortical vestibular, visual, and anxiety systems, and that these personality-related changes in brain activity may be related to threat sensitivity in postural and gaze control mechanisms in normal individuals.

2.2. Visual Stimulation in Functional Magnetic Resonance Studies of PPPD

In 2017 Riccelli *et al.* [27] used functional magnetic resonance imaging to test brain activity of vertical and horizontal visual motor stimulation in PPPD patients during a visual virtual reality roller coaster. They found that activity in vestibular stimulation areas (insula centrale sulcus) was reduced in PPPD patients, whereas activity in the visual system [visual cortex (V1, V2, V3)] was increased, who found that increased activity in the visual cortex (V1, V2, V3) in PPPD patients was positively correlated with the severity of dizziness disorder. The authors speculated that using visual information to identify the effects of gravity on self-movement in patients with PPPD may adversely affect balance control, especially in individuals with a high degree of visual dependence. These results suggest that complex alterations in the connectivity between the primary visual cortex, visual association areas, and brain regions that process and regulate responses to multimodal spatial motion information may underlie visually induced dizziness as well as responses to the visual motor and visual orientation cues in patients with PPPD. This may provide a mechanistic explanation for postural control problems and greater sensitivity to visual stimuli in PPPD patients. In 2018 Passamonti *et al.* [28] investigated the effect of neuroticism and introversion on functional network changes in PPPD patients subjected to roller coaster virtual reality simulations of vertical and horizontal visual stimuli. Then they found that, relative to controls, PPPD patients had more brain activity during the vertical period, and neuroticism was positively correlated with activity in the inferior frontal gyrus, with enhanced connections between the inferior frontal gyrus and the occipital area. These results suggested that neuroticism increases the activity and connectivity of neural networks in PPPD patients, and that mediated attention to visual motor cues during vertical movement, thereby mediating balanced visual control in neurotic PPPD patients and increasing the risk of postural control.

In a multimodal imaging study, Popp *et al.* [29] analyzed changes in brain functional activity in patients with fearful postural vertigo (PPV) during a task-based fMRI visuomotor experiment without controlling psychological and psychiatric factors. They found that, compared to controls, patients had increased activation, especially in the anterior cingulate gyrus subpatella. In PPV patients, the connections between the inferior anterior cingulate gyrus and left inferior frontal gyrus, prefrontal cortex, lingual gyrus, posterior central gyrus, thalamus and cerebellar lobules were enhanced. The functional connectivity between the prefrontal cortex and thalamus, anterior insula, parahippocampal gyrus, anterior cingulate cortex, amygdala and posterior front medial gyrus increased, while the functional connectivity between the prefrontal cortex and posterior cerebellar, left superior limbic gyrus and middle temporal gyrus was lower. In addition, the orbitofrontal cortex had increased connections with the anterior central gyrus, talar sulci and superior parietal lobe, and decreased functional connections with the inferior frontal gyrus, vermis and posterior lobe. In sum, compared with controls, PPV patients had increased functional connectivity between prefrontal cortical areas and associated thalamic projection areas and primary motor cortex, and reduced connectivity between visual and vestibular areas and frontal pole cortex without controlling for psychological and psychiatric factors. These results suggest that disease-specific mechanisms of PPV are related to networks involved in emotion regulation, fear generalization, internal feelings, and cognitive control.

And in 2020 Huber J *et al.* [30] used graph theory analysis to study and analyze the whole-brain network properties of functional magnetic resonance imaging under static visual stimulation and visuomotor stimulation in the same cohort of PPV patients. They found that the brain network connectivity of PPV patients differed between static and visuomotor stimulation. During static visual stimulation, the default mode network and cerebellar network had stronger connectivity, while the sensorimotor network had lower connectivity. In response to visual motor stimulation, the sensorimotor networks in PPV patients became more tightly knit, while the cerebellar networks became less tightly knit.

These results suggest that altered visuomotor processing in PPV patients may stem from altered connectivity status of sensory and cerebellar networks. Without controlling for psychological and psychiatric factors, these results may have some limitations, and the changes in network levels found in PPV patients may not be specific to functional dizziness, but may also be seen in depression or anxiety. In 2021 von *et al.* [31] compared differences in brain activity between female PPPD patients and healthy subjects using immobile but emotionally charged (positive, neutral, negative) visual stimuli. They found that PPPD patients had reduced anterior cingulate cortex activity and increased left angular gyrus activity when faced with negative and positive stimuli compared with healthy groups. At the same time, the in-group analysis found that PPPD patients showed increased activity in visuospatial regions (paravail gyrus, medial parietal sulcus) in negative images relative to neutral and positive stimuli, while the healthy group showed increased activity in anxious regions (amygdala, orbitofrontal cortex). PPPD patients may be more sensitive to visuospatial elements relative to emotional visual stimulus content.

In task state functional magnetic resonance imaging studies, several studies have demonstrated the presence of functional brain changes in the parietal vestibular cortex, insula, inferior frontal gyrus, hippocampus and anterior cingulate gyrus cortex, cerebellum, temporal gyrus, and amygdala in patients with PPPD. But there are some differing conclusions, e.g., Indovina I, von *et al.* found a decrease in the activity of the anterior cingulate cortex in contrast to the study of Popp *et al.* which may be related to the fact that Popp *et al.* did not control for psychological and psychiatric factors. In some studies of personality traits associated with anxiety (neuroticism, introversion) neuroticism was found to be associated with activity in the pons, vestibulo-cerebellar and parastriate cortex (visual association area), and inferior frontal gyrus, and introversion was associated with amygdala activity. In conclusion, PPPD patients showed changes in brain activity and functional connectivity in visual, vestibular, spatial cognition, and anxiety-related areas. Combined with the studies on controlling mental factors and non-controlling mental factors and the studies on the effects of anxiety-related personality traits (neuroticism and introversion) on brain activity and functional connectivity in PPPD patients, the effects of psycho-psychological and personality trait factors on PPPD are accurate, but more research data are needed on how to regulate and affect the brain network and regions of PPPD.

3. PPPD with Resting-State Functional Magnetic Resonance Imaging

Compared to task state fMRI resting-state functional magnetic resonance imaging (rs-fMRI) is not only easy to acquire signals and has a high signal-to-noise ratio, but also can easily identify functional regions in different patient groups. In recent years, researchers have explored brain function and brain network changes in diseases through data analysis methods such as resting-state amplitude of low-frequency oscillations (ALFF) analysis, local coherence (ReHo) analysis, functional connectivity, graph theory analysis, and seed-point-based analysis.

3.1. Based on Seed Point Analysis

In 2018 Lee *et al.* [32] used whole brain and regions of interest to analyze resting whole brain networks in PPPD patients. In a whole-brain functional connectivity analysis, they found increased connectivity in the subcallosal cortex with the left lateral occipital cortex and the left middle frontal gyrus, and decreased connectivity in the left hippocampus with the bilateral central cortex, the left parietal cortex, the right insular cortex, and the bilateral cerebellar lobe VI, the right cerebellar lobe V, and the left cerebellar peduncle I in PPPD patients, as compared with the control group. In their seed-point analysis centered on vestibular and visual brain regions, they found that patients with PPPD had enhanced connectivity between the left parietal cortex and the left lateral occipital cortex, and also between the left visual cortex and the left temporal pole, whereas connectivity was reduced between the left hippocampus and the left cerebellar lobule VI and cerebellar peduncle I. After controlling for anxiety and depression as covariates, PPPD patients still exhibited reduced connectivity between the left hippocampus and the right inferior frontal gyrus, bilateral temporal lobes, bilateral insular cortex, bilateral central temporal cortex, left parietal cortex, bilateral occipital lobes, and cerebellum. Individuals with PPPD exhibit decreased connectivity between regions involved in multisensory vestibular processing and spatial cognition, but increased connectivity in networks linking visual and emotional processing. The patient person may have a significant reduction in the cortical integration of multisensory spatial-motor information and have spatial cognition deficits. In another study [33], researchers investigated changes in functional connectivity in patients with PPPD who underwent resting-state fMRI before and after visually stimulated task-based fMRI. They performed seed-to-somatosensory resting-state FC analyses using vestibular, visual, somatosensory, and spatial cognitive centers as seed points. Then they found that functional connectivity between visual and spatial cognitive areas, and between visual and prefrontal areas, was increased in patients with PPPD after stimulation compared to before stimulation. There were no brain regions that showed significant differences between the HC and PPPD groups during all five visual stimuli. However, prior to stimulation, functional connectivity between visuospatial and spatial cognitive areas and somatosensory areas was elevated in PPPD relative to controls, while functional connectivity between vestibular cortex and visual areas was lower. These findings suggest that vestibular inputs in the vestibular-visual-somatosensory network are not fully utilized and that somatosensory and visual inputs compensate for vestibular inputs, leading to the maintenance of visual and somatosensory dependence of spatial orientation in PPPD. Functional connectivity between visual and spatial cognitive regions and between visual and prefrontal regions is increased in PPPD after stimulation compared to before stimulation. This increased functional connectivity from visual areas to spatial cognition and prefrontal areas following visual stimulation may account for the visual deterioration and prolonged symptoms following anxiety states in PPPD.

3.2. Graph Theory Analysis

In 2019 Indovina *et al.* [34] Graph-theoretic analysis of resting-state functional magnetic resonance images of agoraphobic patients was used to assess the interactive effects of neuroticism and introversion on brain features in agoraphobia. Compared to controls, patients with subclinical agoraphobia had lower global clustering, efficiency, and transmissibility in response to lower overall integrative functioning across the brain. Specifically, patients with agoraphobia had reduced connectivity in the visuospatial-emotional and vestibular-navigational networks, with introversion further decreasing visuospatial-emotional connectivity and having no effect on the vestibular-navigational network. But neuroticism had no effect on any of the networks No effect.

3.3. ALFF Analysis

2020 Li *et al.* [35] recruited patients with PPPD without a history of peripheral vestibular disease or peripheral vestibular lesions. They found significantly lower ALFF and ReHo values in the right precuneus and cuneus lobes of patients with PPPD compared to controls, and that the altered spontaneous functional activity of the cuneus (which plays an important role in visuospatial information processing) and the precuneus (which plays an important role in the integration of visual and vestibular information) might result in abnormal integration of visual and vestibular information. Weakened functional connectivity between the precuneus and precentral gyrus was also found, which may be associated with symptom exacerbation during upright posture, and active or passive movement. Further independent component analysis and seed-based functional connectivity analysis [36] found that patients with PPPD had reduced intra-network functional connectivity in the right precuneus within the post-default mode network, reduced intra-network functional connectivity between the right precuneus and bilateral precuneus, left premotor cortex, and enhanced intra-network functional connectivity with bilateral corpus callosum. These results reflect the altered visual-vestibular-auditory integration in patients with PPPD. In another study [37] that used low-frequency fluctuation fractional amplitude (fALFF) and voxel-mirror-homotopic connectivity (VMHC) to analyze resting-state fMRI in patients with PPPD, functional changes in the precuneus were also found. And the study demonstrated an elevated fALFF in the right precuneus and a decreased VMHC in the bilateral precuneus. Moreover, precuneus fALFF values were positively correlated with Dizziness Handicap Inventory (DHI) scores and VMHC values were negatively correlated with disease duration in PPPD patients. The altered function of the precuneus in PPPD patients suggests that the integration of visual and vestibular information is aberrant, leading to resting dizziness and exacerbation of dizziness due to visual stimuli or a complex visual environment.

In resting-state functional magnetic resonance imaging studies, some researchers have found functional changes in these core brain regions in patients with PPPD in the insula, frontal lobe, hippocampus, parietal cortex, cerebellum, temporal lobe, and thalamus by performing whole-brain functional connectivity analyses using vestibular, visual, somatosensory, and spatial cognitive centers as the seed points. They used graph-theoretic analysis to discover changes in the connectivity of visuospatial, affective, and vestibular navigation networks. What's more, multiple studies have also identified changes in the functional activity of the precuneus (involved in multisensory interactions between vestibular and visual areas). The discovery of these changes in the activity of brain regions involved in the integrated regulation of cognitive, emotional networks, visual, and vestibular loops will undoubtedly provide additional neuroimaging evidence for us to further explore the pathomechanisms of PPPD.

4. Summarize

Functional magnetic resonance studies of PPPD are still relatively scarce, and scholars have done a lot of research on the use of task-based fMRI and resting-state fMRI to explore the activity and functional connectivity of brain regions in PPPD. And although some of the results have been inconsistent and even contradictory, several studies have observed changes in the PIVC, visual cortex, frontal cortex, hippocampus, precuneus, superior temporal gyrus, precentral gyrus, and cerebellum, from which changes in activity and functional connectivity in regions important for visual processing, multisensory vestibular and spatial cognition have been identified. It was shown that PPPD patients are more dependent on visual stimuli than on vestibular stimuli and that different modalities of visual stimulation and content formation (static or motion, horizontal or vertical, positive or negative) can cause different changes in the brain regions of PPPD patients. The various factors, including personality traits, psychiatric comorbidities, and peripheral vestibular pathology, play an important role in the brain's functional activity and connectivity patterns. However, more research evidence is needed on how these factors regulate and affect the brain networks and regions of PPPD. Most of these studies are biased by small sample sizes, so future they may need to further validate the large sample size and further stratify the triggers such as different visual stimulation modalities, personality traits, psychiatric comorbidities, and vestibular comorbidities, in order to further elucidate and draw definitive conclusions about the pathomechanisms of PPPD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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