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Neurofunctional differences and similarities between persistent postural-perceptual dizziness and anxiety disorder

Maximilian Maywald [a,*,1], Oliver Pogarell [a,1], Susanne Levai [a], Marco Paolini [b], Nadja Tschentscher [a], Boris Stephan Rauchmann [a,b], Daniela Krause [a], Sophia Stöcklein [b], Stephan Goerigk [a], Lukas Röll [a], Birgit Ertl-Wagner [b], Boris Papazov [b], Daniel Keeser [a,b], Susanne Karch [a,1], Agnieszka Chrobok [a,1]

[a] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
[b] Department of Radiology, University Hospital, LMU Munich, Munich, Germany

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ABSTRACT

Introduction: Persistent postural-perceptual dizziness (PPPD) (ICD-11) and anxiety disorders (ANX) share behavioural symptoms like anxiety, avoidance, social withdrawal, hyperarousal, or palpitation as well as neurological symptoms like vertigo, stance and gait disorders. Furthermore, previous studies have shown a bidirectional link between vestibulo-spatial and anxiety neural networks. So far, there have been no neuroimaging-studies comparing these groups.

Objectives: The aim of this explorative study was to investigate differences and similarities of neural correlates between these two patient groups and to compare their findings with a healthy control group.

Methods: 63 participants, divided in two patient groups (ANX = 20 and PPPD = 14) and two sex and age matched healthy control groups (HC-A = 16, HC-P = 13) were included. Anxiety and dizziness related pictures were shown during fMRI-measurements in a block-design in order to induce emotional responses. All subjects filled in questionnaires regarding vertigo (VSS, VHQ), anxiety (STAI), depression (BDI-II), alexithymia (TAS), and illness-perception (IPQ). After modelling the BOLD response with a standard canonical HRF, voxel-wise t-tests between conditions (emotional-negative vs neutral stimuli) were used to generate statistical contrast maps and identify relevant brain areas (pFDR < 0.05, cluster size >30 voxels). ROI-analyses were performed for amygdala, cingulate gyrus, hippocampus, inferior frontal gyrus, insula, supramarginal gyrus and thalamus ($p \leq 0.05$).

Results: Patient groups differed from both HC groups regarding anxiety, dizziness, depression and alexithymia scores; ratings of the PPPD group and the ANX group did differ significantly only in the VSS subscale 'vertigo and related symptoms' (VSS-VER). The PPPD group showed increased neural responses in the vestibulo-spatial network, especially in the supramarginal gyrus (SMG), and superior temporal gyrus (STG), compared to ANX and HC-P group. The PPPD group showed increased neural responses compared to the HC-P group in the anxiety network including amygdala, insula, lentiform gyrus, hippocampus, inferior frontal gyrus (IFG) and brainstem. Neuronal responses were enhanced in visual structures, e.g. fusiform gyrus, middle occipital gyrus, and in the medial orbitofrontal cortex (mOFC) in healthy controls compared to patients with ANX and PPPD, and in the ANX group compared to the PPPD group.

Conclusions: These findings indicate that neuronal responses to emotional information in the PPPD and the ANX group are comparable in anxiety networks but not in vestibulo-spatial networks. Patients with PPPD revealed a stronger neuronal response especially in SMG and STG compared to the ANX and the HC group. These results might suggest higher sensitivity and poorer adaptation processes in the PPPD group to anxiety and dizziness related pictures. Stronger activation in visual processing areas in HC subjects might be due to less emotional and more visual processing strategies.

* Corresponding author.
E-mail address: maximilian.maywald@med.uni-muenchen.de (M. Maywald).
[1] Authors contributed equally to this publication.

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1. Introduction

As early as the 19th century a connection between vertigo symptoms and anxiety disorders was discussed among European neurologists. "Phobic postural vertigo" (PPV) was defined as a separate clinical illness including disturbances in balance and gait, a reduced body sway, a connection to visual perception, e.g. visual moving scenes inducing unsteadiness and character traits such as perfectionism or an obsessive personality structure (Brandt et al., 1994; Querner et al., 2002). Different nomenclatures like "chronic subjective dizziness (CSD)", "functional dizziness and vertigo" or "primary/secondary somatoform dizziness" referring to the same clinical construct (Dieterich and Eckhardt-Henn, 2004; Staab et al., 2017; Staab, 2012). The Bárány Society published new diagnose guidelines for this syndrome 2017 (Staab et al., 2017). In 2019, the WHO included this clinical entity as a new diagnosis in ICD-11, in the chapter 10 "diseases of inner ear/ AB32.0 chronic vestibular syndrome" termed "persistent postural–perceptual dizziness" (PPPD), but clear diagnostic criteria were omitted (WHO, 2019).

Several retrospective analyses of patients with dizziness and vertigo with cohorts of up to 21,000 patients found PPPD to be the second most commonly diagnosed condition at approximately 20 % (Kim et al., 2020; Xue et al., 2018). In further retrospective analyses it was the first most diagnosed illness in the age group 19–64 years (Kim et al., 2020). Overall, the number of patients diagnosed with PPPD in vertigo outpatient clinics was estimated to be 15–20 % (Staab et al., 2017). An average duration of the disease of 4.5 years was assumed. In patients with CSD the most common comorbidity was anxiety disorders with about 60 % (Staab, 2012). Dizziness symptoms are also very common in patients with agoraphobia and panic disorder (Schneier et al., 1991; Telch et al., 1989). Furthermore, there is evidence that especially in agoraphobia and panic disorder balance functions can be impaired (Jacob et al., 1996, 1997).

A meta-analysis of neuro functional activation examining induced (e.g. emotional pictures) and pathological anxiety (e.g. social anxiety or panic disorder) found an increased activation in the left and right insula and in the cingulate cortex/medial prefrontal cortex as overlapping areas. Furthermore, the following brain areas were reported to be involved in pathological anxiety: bilateral middle and superior temporal gyrus, left amygdala, thalamus, left hippocampus, bilateral parahippocampal gyrus, bilateral fusiform and lingual gyrus, anterior and mid cingulate gyrus, superior medial frontal gyrus, left middle occipital, left postcentral gyrus, left and right caudate, left and right calcarine fissure, left and right precuneus, right supramarginal, left and right superior parietal and superior occipital gyri, middle frontal gyrus, supplemental motor area (Chavanne and Robinson, 2021).

In a meta-analysis about the representation of the human vestibular cortex the retroinsular-cortex was revealed as the only common key region in the context of caloric, galvanic and auditory stimulation methods (Lopez et al., 2012). The retroinsular cortex was found to correspond with the parietal-insular vestibular cortex (PIVC) in non-human primates. However, one does not dare to speak of a "primary vestibular cortex" in analogy to the primary visual cortex in humans, because many regions in the brain are involved in the processing of vestibular information: for example, in the pre-processing (cerebellum, thalamus, nucleus vestibularis) and primary processing (somatosensory cortex 2v, 3av). Additional structures involved in the processing of vestibular information are the intraparietal sulcus, posterior parietal cortex, cingulate, hippocampus, medial superior temporal region, inferior parietal lobes, angular and supramarginal gyrus and precuneus (Lopez and Blanke, 2011).

Based on the findings of Lopez and Blank, Indovina et al. (2015) compared 18 healthy control subjects (HC) with 18 patients with CSD using loud short tone bursts in a fMRI-study. They discovered an overlapping of anxiety and vestibular information processing, especially in the insula and the hippocampus. Their results revealed a reduction of neural activity in the PIVC, the anterior and posterior insula, the hippocampus and the anterior cingulate cortex (ACC). Contrary to expectations, they found a reduced neuronal response in the vestibular processing areas in the CSD group. The authors interpreted their results as long-term effects of CSD.

These long-term effects of patients with PPPD are also associated with a reduced local gyrification index in posterior insular cortices, supramarginal gyri, and posterior superior temporal gyri (Nigro et al., 2019), as well as with decreased grey substance in the left middle temporal gyrus, the right anterior insular cortex, the secondary visual cortex, the right superior temporal gyrus, the cerebellum, different areas of the prefrontal cortex, the left posterior hippocampus, and the left anterior cingulate cortex (Wurthmann et al., 2012).

Indovina and Riccelli et al. (2015) found a reduced connectivity in patients with CSD compared to a healthy control group between the left anterior insula/inferior frontal gyrus (IFG) and the right superior temporal gyrus (STG), between the left IFG and the right middle occipital gyrus, between the right STG and the hippocampus, and between the right STG and the ACC. Riccelli et al. (2017) found an increased connectivity between the right amygdala and the left PIVC in patients with CSD, with high anxiety-related personality traits (high neuroticism, high introversion) compared to HC group during a virtual reality rollercoaster task. The researchers presented novel evidence suggesting that anxiety-related personality traits are associated with changes in functional connectivity patterns in visuo-vestibular and anxiety processing brain structures. A resting-state study on 10 patients with PPPD and 10 healthy controls found a decreased functional connectivity in PPPD compared to the HC group between the cuneus, the precuneus and the precentral gyrus. The findings were interpreted as aggravated symptoms during upright posture, active or passive movements (Li et al., 2019).

Based on the anxiety diathesis one study used negative-emotional pictures to test threatening in general in 16 patients with PPPD and with 16 age and sex matched recovered patients with PPPD as control group. Compared to the HC group patients with PPPD demonstrated decreased neural activity in ACC and increased activity in the left angular gyrus (AG) (negative vs positive pictures). ACC activity was interpreted as anxiety related response, and AG activity as response to spatial information. Typical anxiety-activation patterns could not be observed (von Söhsten Lins et al., 2021).

Chrobok (2017) induced panic symptoms in patients with phobic postural vertigo (PPV) with cholecystokinin-tetrapeptide (CCK-4) and compared their results with those of the HC group. The results indicated increased dizziness, depression and anxiety scores in patients with PPV, but contrary to previous studies no differences in personality traits (NEO Personality Inventory) (Chrobok, 2017; Indovina et al., 2014; Riccelli et al., 2017). CCK-4 induced higher cardiovascular reactions in both groups, but the PPV group had higher breath rates at injection time which was interpreted as a kind of somatosensoric amplification (Barsky et al., 1988; Chrobok, 2017). Additionally, patients showed significantly higher scores on a DSM-IV-derived panic symptom scale – as already used by Bradwejn et al. (1990) and Zwanzger et al. (2001) in former studies - before CCK-4 injection, along with a feeling of losing balance and vertigo (Chrobok, 2017). Similar to anxiety patients, patients with PPV seemed to show anticipatory anxiety. This result was congruent with the neural activation patterns in the PPV group. Patients with PPV showed a significantly increased BOLD-signal in emotion-processing brain-structures, such as amygdala, insula and hippocampal gyrus before the bolus. Further increased brain activation was found in motor regions (putamen, globus pallidus, precentral and postcentral gyrus) and vestibular processing structures, such as cuneus, precuneus, AG and supramarginal gyrus (SMG) (Chrobok, 2017).

Apparently, there are possible overlapping areas of neuronal activation patterns across patients with anxiety and PPPD such as insula, STG, precuneus, AG, SMG, or hippocampus.

Evidence of altered neuronal responses in anxiety-processing brain structures as well as anxiety disorders as the highest comorbidity in

patients with PPPD give reason for a comparative study between patients with anxiety disorders (ANX) and with PPPD in order to find neurobiological and functional differences or similarities. The second aim of this study was to compare their findings with those of a healthy control group.

Firstly, it was hypothesised that the PPPD and the ANX group show stronger activation patterns of anxiety- and vestibulo-spatial networks in the fMRI measurements than healthy control subjects (H1).

Secondly, it was hypothesised that the PPPD and the ANX group share commonalities in the activation patterns of anxiety- and vestibulo-spatial networks in the fMRI measurements (H2).

Thirdly, it was hypothesised that patients with PPPD show stronger activation patterns of vestibulo-spatial networks in the fMRI measurements than patients with anxiety disorders and healthy control subjects (H3).

Fourthly, it was hypothesised that the ANX group shows stronger fMRI activation patterns related to anxiety-networks than the PPPD group and healthy control subjects (H4).

2. Methods

2.1. Sample

This explorative study comprised the investigation of 63 participants aged between 18 and 58 years, 20 patients with anxiety disorder (ANX, sex: ♀=13, ♂=7; age: M = 34.85, SD = 12.38; 1x agoraphobia, 3x panic disorder, 12x agoraphobia with panic disorder, 4x social phobia) and 14 patients with PPPD (sex: ♀=6, ♂=8; age: M = 37.21, SD = 9.96) with and without an otological disease in their history (s. also Table 1 for comorbidity), plus 29 sex and age matched healthy control subjects (sex: ♀=16, ♂=13; age: M = 34.29, SD = 9.83), 16 participants in a HC-A group (sex: ♀=12, ♂=4; age: M = 33.56, SD = 10.78) as control group for patients with anxiety disorder and 13 participants in HC-P group (sex: ♀=4, ♂=9; age: M = 34.85, SD = 8.52) as control group for patients with PPPD. The ANX and the PPPD group were balanced regarding depression and secondary comorbid anxiety disorder, but not in medication. All participants were recruited between October 2017 and February 2020 at the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich in cooperation with local neurologists and psychiatrists. Guidelines of the Bárány Society were followed. Recruitments were stopped with the first corona lockdown in Germany. Key inclusion criteria were age between 18 and 67 years and the ICD-10 diagnosis of an anxiety disorder with a focus on panic disorder or agoraphobia with or without panic disorder (F41.0, F40.01, F40.00) as well as PPPD/other somatoform disorders (F45.8). Exclusion criteria were neuro-otological illnesses, which could solely explain dizziness symptoms such as benign paroxysmal positional vertigo, Meniére's disease, etc., structural brain pathologies associated with prior head injury or neoplasm, a lifetime diagnosis of psychosis or substance dependence disorder, pregnancy, lactation or typical MRI contraindications like claustrophobia or ferromagnetic implants. The study received approval from the local ethics committee of the Medical Faculty of LMU Munich and was designed in accordance with the Declaration of Helsinki and subsequent revisions. Participants were compensated with €70. 13 participants had to be excluded from the MRI-analysis because of technical problems (4xANX, 3xHC, 1xPPPD), claustrophobia (2xANX, 1xPPPD) permanent make-up (1xANX), or contraceptive spiral (1xHC).

Table 1
Sample characteristics.

	PPPD (n = 14)	ANX (n = 20)	HC-P (n = 13)	HC-A (n = 16)
Age at entry, M (SD)	37.21 (9.96)	34.85 (12.38)	35.25 (8.77)	33.56 (10.78)
male, n (%)	8 (57.1)	7 (35)	9 (69.2)	4 (25)
female, n (%)	6 (42.9)	13 (65)	4 (30.8)	12 (75)
Psychiatric diagnosis, n (%)				
comorbid anxiety disorder	6 (42.9)	8 (40)		
comorbid depression	7 (50)	11 (55)		
comorbid other	1 (7.1)	2 (5)		
Antidepressant, n (%)				
SSRI	1 (7.1)	6 (30)		
NaSSA		1 (5)		
subsided otolithic/ neurological disease				
BPPV	1 (7.1)			
vestibular neuritis	1 (7.1)			
vestibular migraine	1 (7.1)			

Abbreviations: M: mean, SD: standard deviation, BPPV: benign paroxysmal positional vertigo.

2.2. Psychometric questionnaires

Various psychometric tests were used in order to screen for dizziness, anxiety, depression, alexithymia, and illness perception. We assessed anxiety with the State Trait Anxiety Inventory (STAI), dizziness with the Vertigo Handicap Questionnaire (VHQ-D) and the Vertigo Symptom Scale (VSS) (Laux et al., 1981; Tschan et al., 2008, 2010). Depression symptomatology of participants was determined using the Beck Depressions Inventory II (BDI-II) (Beck et al., 1996). Furthermore, participants filled in the Toronto Alexithymia Scale (TAS) and the Illness Perception Questionnaire (IPQ) (Kupfer et al., 2000; Moss-Morris et al., 2002). All questionnaires were validated in German.

2.3. Statistical analysis of psychometric data and regions of interest (ROIs)

Statistical analysis of the questionnaire ratings and ROIs of patients and the HC group were calculated via SPSS version 26 with a level of significance $p < 0.05$. Kruskal-Wallis tests were used to compare the results between groups. A non-parametric test was used because of the following three reasons: the Kolmogorov-Smirnov-test showed no normal distribution, the Leven's test showed significant variance for BDI, IPQ, VSS, and the sample size was small, especially of the dizziness group and the corresponding control group (PPPD: N = 14; HC-P = 13). Six pairwise comparisons (Dunn's method) were performed in each case. Due to multiple testing, a Bonferroni correction was applied resulting in a significance level of $p < 0.05$. Due to the small sample size as consequence of the pandemic, we had to conduct also a one-way independent ANOVA with bootstrapping to overcome the problem of lack of power between the ANX and PPPD group. For correlations between questionnaires and ROIs a spearman-correlation coefficient was calculated within each group.

Confounding factor in the PPPD group

The ANX group and the PPPD group were balanced with regard to the comorbidity depression, so that depression could be excluded as a confounding factor. Since only one patient with PPPD received SSRI medication, this factor was neglected. Theoretically, it would be conceivable that patients with PPPD with high vertigo symptom severity (VSS-Ver) would have higher scores in anxiety (STAI-S), depression (BDI-II), or greater social impairment (VHQ). Thus, anxiety, dizziness and depression would no longer be independent factors. Including these factors as covariates in the statistical model would therefore - due to the shared variance of covariate and treatment - remove too much explained variance from the model, making type II (false negative) errors more likely. Moreover, sex differences in the HC group might become visible. Hence, we chose the Field (2009) approach of forming subgroups and examining them in terms of symptom expression.

A Mann-Whitney-*U* test was computed to examine whether sex/comorbidity/vertigo symptom severity (VSS-Ver) was confounded with anxiety, depression, and vertigo (results see supplementary information).

2.4. MRI and fMRI data acquisition

Imaging was performed in a 3 Tesla Siemens Skyra scanner with echo planar capability and a 20-channel phased array head coil. We acquired a T1-weighted high-resolution 3D data set for each subject for anatomical referencing (spatial resolution 0.9 mm isotropic) in the anterior commissure posterior commissure plane. For functional BOLD imaging an *EPI* sequence was acquired in the same position as the anatomical images (repetition time: 2500 ms; echo time (TE): 30 ms; 43 transversal slices; slice thickness: 3 mm; gap: 0.4 mm, number of volumes: 450; 2 dummy volumes, field of view: 448x448, matrix: 64x64, isotropic voxel-size: 1 mm^3).

2.5. MRI and fMRI data pre- and post-processing

Functional and anatomical recordings were analysed using BrainVoyager™ version 21.4 software for Windows (Brain Innovation, Maastricht, Netherlands). For further analysis, raw-data in a DICOM-format were converted into a NIfTI-format using MRIConvert (Version 2.0.7 build 369, University of Oregon, Lewis Center for Neuroimaging, 2013) and analysed with the freeware programme FSL (FMRIB Software Library v6.0, Analysis Group, FMRIB, Oxford, UK). The first two images were excluded from any further analysis due to relaxation time effects.

The pre-processing of functional data included temporal high-pass filtering (GLM approach with Fourier basis set with two cycles) to low frequency signal drifts inherent in echo planar imaging, a slice scan time correction (cubic spline), spatial smoothing (Gaussian filter with FWHM 8.0 mm), and 3D motion correction (trilinear/sinc interpolation). 20 datasets had to be corrected using independent component analysis (ICA), because of a special motion artefact (spin-history effect) (Zaitsev et al., 2017). This was done according to the principles of Salimi-Khorshidi et al. (2014). In addition, functional images were transferred to a standard Talairach brain. We used a general linear model (GLM) to detect the variation in blood oxygen level dependent (BOLD) signal associated with blocks of anxiety/dizziness and neutral images and their time derivatives. Furthermore, we used a fixed effects model to account for variability between subjects, because of the small sample size. Fixed effects analyses allow assumptions about effects within the existing sample, but do not allow generalizations about the underlying population (McNeish and Kelley, 2019). Voxelwise t-tests were calculated to identify those brain areas where the average BOLD signal change was significantly different within each group for each block type and for block differences. Then, we used the *t*-test for independent samples to compare differences between groups. We used the false-discovery-rate (FDR) correction method at a threshold of $p < 0.05$ to counteract the problem of multiple testing. Its better suitable for clusters than for single voxels, therefore only clusters with a voxel number of >30 were reported and visualised (Benjamini and Heller, 2007). For the emotion-associated task, we calculated the contrast anxiety/dizziness minus neutral pictures for each group separately.

Based on the current state of the art, specific **ROIs** were selected for analysis. Amygdala, hippocampus, thalamus, cingulate gyrus and inferior frontal gyrus were selected because they are involved in the processing of emotional processes such as fear, SMG and the insula for the processing of vestibular stimuli (Chavanne and Robinson, 2021; Lopez et al., 2012). For this purpose, predefined general anatomical ROI templates of the BrainVoyager were used for the subcortical structures: amygdala, hippocampus and thalamus; in addition, individual ROIs for the cortex were created using the "AtlasCortex template" of BrainVoyager: amygdala, hippocampus, inferior frontal gyrus, insula, cingulate gyrus, supramarginal gyrus thalamus.

2.6. Paradigm

FMRI measurements took place at the Department of Radiology, Ludwig Maximilians University Munich. Before the fMRI session participants filled in depression, anxiety, dizziness and alexithymia questionnaires. The visual stimulation consisted of 80 neutral and 40 negative emotional pictures. The compilation of the image set was retrieved from several online databases: International Affective Picture System (IAPS) (Lang et al., 1999), "The Nencki Affective Picture System" (NAPS) (Marchewka et al.s, 2014), "The Set of Fear Inducing Pictures" (SFIP) (Michałowski et al., 2017) and "The Geneva affective picture database" (GAPED) (Dan-Glauser & Scherer, 2011).

In addition, royalty-free images were selected via internet searches and validated according to the methods of the IAPS (Lang et al., 1999). In this study 60 images, 20 neutral and 40 negative (https://www.pixabay.com), were rated by 51 healthy subjects (♂ = 19, 37 %; ♀ = 32, 68 %) aged 18–65 years using an online survey (Google forms). As in the original study (Lang et al., 1999) the 'Self-Assessment Manikin Scale', a visual rating system, was used to rate the images on a Likert scale of 1–5 on the three dimensions of valence, arousal and dominance. Of the original 60 images only one image was excluded due to lack of valence.

Negative emotional pictures showed anxiety-related pictures such as armed persons or dangerous animals and dizziness-related pictures such as rollercoasters or people in heights, the neutral pictures presented e.g. landscapes or objects like a pencil.

The following measurements were acquired during the fMRI sessions:

Emotion-associated task: Based on the assumption that both anxiety and dizziness symptoms can occur in both patient groups, we mixed emotional and vertigo pictures and tested the general emotional reaction to neutral and negative-related images. For this purpose, the images were presented in a pseudo-randomised order and in a block-design using the software programme "Presentation" (version 20.0, neurobehavioralsystems, https://www.neurobs.com). First, a test block with five neutral images was shown followed by a fixation cross. Then, five neutral images and five fear and dizziness images were presented alternately, with an interruption of five seconds by a white fixation cross on a black background. Each image was shown for 5 s, consequently a block of images lasted 25 s, 33 blocks were shown. Patients were encouraged to look at the images and let them sink in.

3. Results

3.1. Comparison of psychometric data between the HC, the ANX and the PPPD group

Significant differences between groups were found in all questionnaires (STAI, VSS, VHQ, BDI-II, TAS and IPQ), only the subscales *IPQ-personal control* and *IPQ-Illness coherence* did not show any significant difference (s. Table 2).

Table 2
Kruskal-Wallis test of psychometric data between HC-A, HC-P, PPPD and ANX.

Questionnaire	H	df	p-value
STAI-S	20.82	3	<0.001*
STAI-T	14.51	3	<0.002*
VSS-AA	31.38	3	<0.001*
VSS-VER	37.88	3	<0.001*
VHQ	11.66	2	0.003*
BDI-II	30.17	3	<0.001*
TAS - overall	18.85	3	<0.001*
TAS - Difficulty Identifying Feelings	27.10	3	<0.001*
TAS - Difficulty Describing Feelings	14.80	3	0.002*
IPQ - Timeline acute/chronic	16.19	3	0.001*
IPQ - Timeline cyclical	10.06	3	0.018*
IPQ - Consequences	24.38	3	<0.001*
IPQ - Personal control	2.24	3	0.524
IPQ - Illness coherence	9.694	3	0.073
IPQ - Emotional Representation	22.87	3	<0.001*

H: Bonferroni corrected test statistic, df: degrees of freedom, p: two-tailed significance, *: sig.

The evaluation of the pairwise comparison did not show any difference between the PPPD and the ANX group or between the HC-P and the HC-A group. There was a significant difference between the PPPD and the HC-P group in STAI-S VSS-AA, VSS-VER, VHQ, BDI-II, TAS-Difficulty Identifying Feelings, IPQ-Timeline acute/chronic, IPQ-Consequences, IPQ-Emotional Representation (s. Table 3). Both ANX and HC-A group did show in all questionnaires a significant difference except in IPQ-Timeline cyclical (s. Table 4). After conducting a one-way independent ANOVA with bootstrapping there was a significant difference between the PPPD and the ANX group in the VSS-VER subscale, $F(1,32) = 10.93$, $p = 0{,}002$. In all other subscales there was no such difference between these two groups.

3.2. Neural responses during the emotion-associated task between PPPD vs HC-P

During the emotion-associated task, patients with PPPD demonstrated increased neuronal responses (negative emotional pictures minus neutral pictures) compared to HC-P subjects, especially in brain regions, which are related, among others, to the processing of vestibular information (e.g., retroinsular cortex, superior temporal gyrus), emotional information (e.g., hippocampus, insula, lentiform nucleus/amygdala, inferior frontal gyrus/OFC [BA47]) and motor information (pyramis, substantia nigra, nucleus ruber, precentral gyrus) (Fig. 1 & Fig. 2). HC-P subjects revealed higher neural activations in brain areas, which are associated, among others, with visual information processing (e.g., middle occipital gyrus, cuneus, fusiform gyrus) (Fig. 1 & Fig. 2). Both groups showed an increased BOLD-signal in brain structures related to higher cognitive control functions, such as the dlPFC (BA9, BA8) and in the supramarginal gyrus, which is related to vestibular, emotional and proprioception information processing (Table 5) (Fig. 1 & Fig. 2).

3.3. Neural responses during the emotion-associated task between ANX vs HC-A

During the emotion-associated task (negative emotional pictures minus neutral pictures), patients with ANX demonstrated increased neural responses compared to the HC group, especially in brain regions which are associated, among others, with the processing of emotional (e.g. insula) and vestibular information (e.g. retroinsular cortex, supramarginal gyrus [BA40]) (Fig. 1 & Fig. 2). HC-A subjects revealed a higher neural activation in brain areas, which are, among others, associated with visual information processing (e.g. middle occipital gyrus, fusiform gyrus) (Table 6) (Fig. 1 & Fig. 2).

Table 3
Pairwise comparison of psychometric data between HC-P and PPPD.

Questionnaire	HC-P		PPPD		p-value
	M	SD	M	SD	
STAI-S	33.69	9.53	47.71	12.08	0.030*
STAI-T	45.85	3.13	49.36	3.61	0.134
VSS-AA	7.15	4.69	26.29	26.50	0.001*
VSS-VER	2.46	2.07	27.93	27.00	<0.001*
VHQ	11.00	13.94	43.92	19.53	0.004*
BDI-II	2.69	3.38	14.43	8.37	0.030*
TAS - overall	53.15	7.71	60.64	8.42	0.166
TAS - Difficulty Identifying Feelings	13.92	3.93	20.93	5.43	0.006*
TAS - Difficulty Describing Feelings	11.62	3.10	13.36	3.69	1.000
IPQ - timeline acute/chronic	11.62	4.31	17.29	3.77	0.008*
IPQ - Timeline cyclical	10.15	2.41	13.14	3.01	0.055
IPQ - Consequences	11.15	4.38	17.00	2.86	0.005*
IPQ - Emotional Representation	12.85	3.69	19.00	5.32	0.002*

M: mean, SD: standard deviation, p: two-tailed Bonferroni corrected significance values, *: sig.

Table 4
Pairwise comparison of psychometric data between HC-A and ANX.

Questionnaire	HC-A		ANX		p-value
	M	SD	M	SD	
STAI-S	33.38	8.56	47.95	10.69	0.008*
STAI-T	46.81	3.35	50.60	3.82	0.033*
VSS-AA	8.31	9.96	24.50	10.67	<0.001*
VSS-VER	3.88	4.46	12.85	11.15	0.010*
BDI-II	3.25	3.89	16.95	13.03	0.001*
TAS – overall	50.88	9.38	63.80	9.02	0.001*
TAS – Difficulty Identifying Feelings	14.13	4.10	22.25	6.21	<0.001*
TAS – Difficulty Describing Feelings	10.50	3.39	15.60	3.82	0.002*
IPQ – timeline acute/chronic	12.63	5.23	16.50	2.87	0.032*
IPQ – Timeline cyclical	10.63	2.99	12.75	2.95	0.458
IPQ – Consequences	12.31	4.24	17.50	3.46	0.002*
IPQ – Emotional Representation	12.81	4.87	17.95	4.83	0.008*

M: mean, SD: standard deviation, p: two-tailed Bonferroni corrected significance values, *: sig.

3.4. Neural responses during the emotion-associated task between ANX vs PPPD

During the emotion-associated task (negative emotional pictures minus neutral pictures), patients with PPPD showed increased neural responses compared to patients with ANX, especially in brain regions which are, among others, associated with the processing of vestibular (e.g. supramarginal gyrus, superior temporal gyrus, precuneus) and motoric information (pyramis, cerebellar tonsil), as well as in brain structures, which are, among others, related to higher cognitive control functions, such as the dlPFC (BA9, BA8) (Fig. 3). The ANX group revealed higher neural activations in brain structures, which are, among others, related to emotional (e.g. medial prefrontal cortex/orbitofrontal cortex [OFC, BA10]), and visual information processing (e.g. middle occipital gyrus, cuneus, fusiform gyrus) (Table 7) (Fig. 3).

3.5. ROI-analysis

The group comparison between the HC subjects and patients with PPPD and with ANX resulted in a significant difference only in the inferior frontal gyrus ($H(3) = 9.158$, $p \leq 0.05$). However, the pairwise comparison remained without significance.

3.6. Correlations between ROIs and questionnaires

The vertigo patients showed no significant correlation between questionnaire scores and BOLD activation measured during the presentation of anxiety and vertigo inducing images. In contrast, hippocampal BOLD activity of patients with anxiety significantly correlated with anxiety as state and as trait measure (STAI-S: $r = 0.635$, $p = 0.020$; STAI-T: $r = 0.654$, $p = 0.015$). In addition, the correlation of amygdala and STAI-T reached trend level ($r = 0{,}528$, $p = 0{,}064$). Furthermore, there was a significant negative correlation between BDI-II and the insula ($r = -0{,}414$, $p = 0{,}049$).

4. Discussion

To the best of our knowledge, this study is the first to compare the neurobiological basis of emotion processing in patients with persistent postural-perceptual dizziness, patients with anxiety disorders, and healthy control subjects. Based on the findings of Chrobok (2017), the study was designed to explore the neurobiological and psychometric differences between PPPD, ANX, and HC. We here focussed on the activity of brain regions, which are typically associated with anxiety, vestibulo-spatial and motor networks.

For the first time, we have shown that patients with PPPD and with

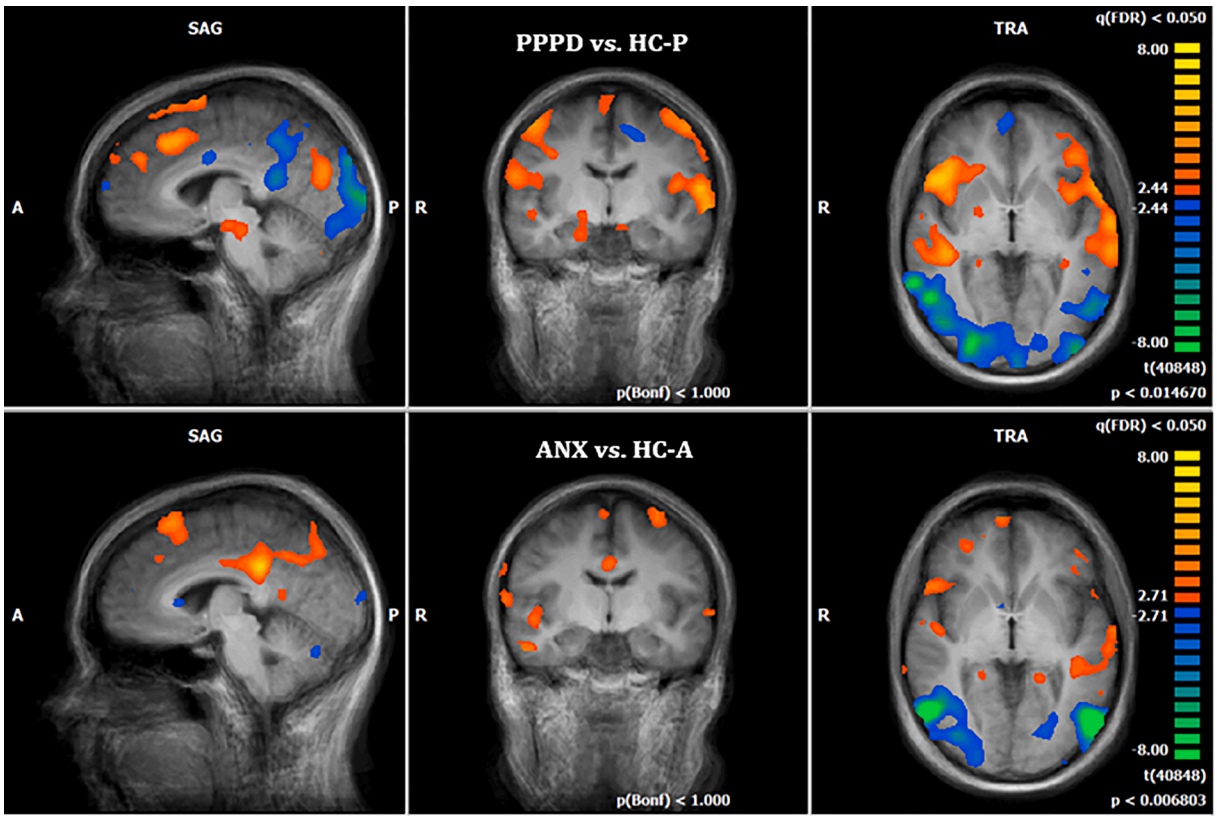

Fig. 1. Neural responses of the emotion-associated patients with PPPD minus HC-P group (1st row)/ ANX minus HC-A group (2nd row) [negative emotional pictures > neutral pictures; q(FDR) < 0.05, *T*-score: −8 to 8, fixed-effects-analysis], in orange: increased responses of patients with PPPD/ANX compared to HC-P/HC-A group; PPPD group: anterior insula, right amygdala, superior temporal gyrus, brainstem, mid cingulate gyrus, bilateral supramarginal gyrus; ANX group: anterior/posterior insula, left supramarginal gyrus in blue: increased activations of HC compared to the PPPD group, e.g. middle occipital cortex, cuneus (1st, 2nd row: x = -5; y = -9; z = 0; 3rd, 4th row: x = -60; y = -20; z = 15). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ANX showed comparable neuronal emotional information processing to threating stimuli, whereby the PPPD group revealed stronger neuronal responses to emotional stimuli compared to the ANX and the HC group.

4.1. *Clinical outcome of psychometric data*

Regarding the results of the questionnaires, it was noticeable that the PPPD and the ANX group did not differ significantly from each other with regard to **depression** and **anxiety**. However, in comparison with the respective matched control groups, the latter values became significant. This is consistent with results of previous studies examining predecessors of PPPD (Chrobok, 2017; Eckhardt-Henn et al., 2009). These results indicate that patients with PPPD express increased anxiety and elevated depression scores as a consequence of the disorder (state). In addition, we agree with previous studies examining CSD that individuals with more anxious or depressed traits or higher neuroticism scores are more likely to develop CSD symptoms and comorbidities, although we were unable to replicate these findings in patients with PPPD (Chiarella et al., 2016; Chrobok, 2017; Indovina and Riccelli et al., 2014; Zaback et al., 2015). We assume that patients with PPPD focus more intensively on physical symptoms in terms of somatosensory amplification than healthy people, and that vertigo symptoms trigger anxiety and do so more easily the more pronounced the trait anxiety pre-exists in the sense of vulnerability. This may lead to marked anticipatory anxiety and, in certain patients to a comorbid anxiety disorder (Chrobok, 2017).

Concerning the **vertigo** questionnaires it can be assumed that in both patient groups an increased (somatic) anxiety and vertigo symptomatology exists. Patients with PPPD showed significantly higher vertigo symptoms than the ANX group. Furthermore, the PPPD group reported significantly more physical and psychosocial impairments due to vertigo symptoms than the HC-P group. These results are congruent with those of others studies examining conditions similar to PPPD (Holmberg et al., 2006; Limburg et al., 2021; Chrobok, 2017).

Both patient groups were also similar with regard to **alexithymia**, while differing significantly in some subscales when compared with the control group. Alexithymia is considered either a normally distributed personality construct or an adaptation to difficult developmental conditions (Franz and Schäfer, 2009; Franz et al., 2008). It is assumed that difficult developmental conditions can be measured with the "Toronto Alexithymia Scale" (TAS) (Taylor et al., 1990; Taylor et al., 1985). In the TAS, especially patients with ANX had difficulties in describing feelings, while both patient groups had trouble with identifying feelings. Overall, these findings are consistent with previous studies, which showed that individuals who had difficulties identifying and describing feelings tended to experience psychological distress as somatic symptoms and attributed them less to emotions (Von Rimscha et al., 2013). This is a possible indication for often-protracted courses of the disease. Anxiety patients do also sometimes classify their symptoms as physical illness, e.g., they misinterpret their panic attack for a heart attack.

In the **perception of their illness** (IPQ), both patient groups assumed that it was a chronic course of their disease having a significant impact on their lives. In addition, patients also scored significantly higher in emotional representations, e.g., illness makes one angry, afraid, or depressed. Overall, a negative illness perception has been shown to delay recovery from that very illness (Petrie and Weinman, 2006; Trinidade et al., 2021).

Altogether, it can be assumed that the PPPD and the ANX group do not differ regarding the psychometric data except vertigo symptom

Table 5
Neuronal responses during the emotion-associated task PPPD vs HC-P (negative emotional-associated pictures minus neutral pictures; clusters of > 30 voxels, q(FDR) < 0.05, *T*-score: 8 to −8).

			Center of gravity			Size	*t*-score	
Brain region	**side**	**BA**	**x**	**y**	**z**		**Ø**	**max**
PPPD > HC-P								
precentral gyrus	R	6	43.83	−3.24	43.17	6311	3.85	6.65
medial frontal gyrus	L	6	−0.74	16.11	45.14	3129	2.88	4.46
frontal superior gyrus	L	9	−28.05	43.29	31.76	9734	3.80	7.53
middle frontal gyrus	L	9	−45.32	6.64	36.24	7405	3.65	7.09
	R	9	30.13	40.5	33.02	13,003	4.04	6.98
inferior frontal gyrus	L	46	−39.52	36.41	7.7	5651	3.36	5.72
	R	47	33.79	17.67	−21.64	977	3.60	5.17
inferior parietal lobule/supramarginal gyrus	L	40	−51.2	−49.62	29.35	3129	2.88	4.46
	R	40	48.18	−41.2	28.41	1219	2.85	3.96
cuneus / precuneus	L	18/31	−3.77	−72.37	24.15	4755	3.43	5.40
superior temporal gyrus	L	22	−59.2	−22.17	4.67	6725	3.55	5.58
	R	38	33.79	17.67	−21.64	977	3.60	5.17
	R	22	45.9	−26.69	−0.12	5456	3.29	5.68
insula	R	13	44.46	10.45	7.37	20,645	3.64	6.92
	L	13	−46.64	5.86	6.56	11,454	3.62	6.38
	L	13	−47.81	−18.15	23.42	5232	3.15	4.99
hippocampus	R	28	17.98	−10.24	−17.04	606	2.77	3.43
uncus	R	28	26.78	3.36	−18.28	2231	3.07	4.19
lentiform nucleus/amygdala	R	LGP	19.02	−5.18	−5.1	835	2.76	3.44
pyramis	R	*	9.64	−74.65	−29.18	2280	3.23	4.83
mesencephalon/substantia nigra/red nucleus	*	*	−3.86	−19.34	−13.95	1882	2.86	3.88
HC-P > PPPD								
cingulate gyrus	L	31	−16.95	−20.66	44.24	3679	2.89	3.90
	L	24	−1.2	−0.37	30.51	1011	3.33	5.12
posterior cingulate gyrus	L	29	−11.16	−45.03	18.29	1135	3.36	5.46
middle frontal gyrus	R	46	41.67	30.18	19.54	2069	3.59	6.11
medial frontal gyrus	R	10	5.82	55.83	12.24	4172	3.21	5.77
superior frontal gyrus	R	8	20.95	16.08	45.07	5309	3.36	5.47
	L	6	−21.18	13.34	47.17	1137	2.78	3.41
inferior parietal lobule	R	40	52.58	−28.27	35.8	2656	3.69	6.39
precuneus	R	31	10.97	−48.19	32.13	20,319	3.85	7.58
	R	19	26.69	−77.16	32.32	16,747	5.36	12.86
	L	7	−18.49	−48.24	41.52	2810	3.20	5.28
middle temporal gyrus	L	39	−47.89	−55.56	7.72	9413	3.74	8.51
	R	39	49.71	−56.88	6.93	18,763	4.95	10.78
fusiform gyrus	L	37	-33.3	−42.9	−13.76	7597	3.59	7.67
middle occipital gyrus/ lingual gyrus/ cuneus	R	18	1.96	−85.28	2.68	49,868	4.37	9.38
cuneus	L	19	−27.65	−78.0	27.29	8311	4.07	9.15
declive	R	*	24.77	−72.92	−16.11	1766	3.62	5.54
	R		24.01	−58.0	−15.17	7614	4.53	7.79
	L		−24.69	−77.84	−16.55	6310	3.71	7.79
cerebellar tonsil	R		25.43	−36.11	−34.33	837	2.96	4.08
culmen	R		47.3	−50.59	-22.09	935	3.07	4.75

Abbreviations: BA: Brodmann area; side: hemisphere; L: left; R: right; max: maximal *t*-score; Ø: average *t*-score; size: cluster size; voxels: number of activated voxels; x: Talairach coordinate x-axis; y: Talairach coordinate y-axis; z: Talairach coordinate z-axis).

severity. Patients of the PPPD and ANX group differed significantly from the healthy control group in terms of depression, anxiety, vertigo symptomatology and alexithymia. Although there was no confound between comorbidities and questionnaires, this assumption is based on a small sample size (type-I error).

4.2. Functional imaging data

4.2.1. Differences in vestibular processing brain regions

Across all three contrasts, two structures demonstrated to be important in the PPPD group, which could indicate a difference from both patients with anxiety disorder and healthy subjects: bilateral supramarginal gyrus and bilateral posterior superior temporal gyrus.

As key area identified in previous studies for processing of vestibular information (Dieterich and Brandt, 1993; Lopez and Blanke, 2011) the left **SMG** (BA 40) showed an increased activity in the PPPD group compared to the ANX group and the healthy control group. This supports our third hypothesis (H3) that patients with PPPD show stronger activation patterns in structures associated with the vestibulo-spatial network in the fMRI measurements than patients with ANX and healthy control subjects. The SMG is part of the somatosensory association cortex which mainly processes tactile stimuli and is involved in the perception of one's own body in space (Ruben et al., 2001). SMG overlaps with the **retroinsular cortex,** a key brain area processing vestibular information extending above and below the Sylvian fissure, mainly inside SMG/BA40, BA22 (Kahane et al., 2003). In addition, the SMG is part of the mirror neuron system, which is responsible for identifying and interpreting posture as well as gestures and facial expressions of other persons (Cattaneo and Rizzolatti, 2009). Thus, the supramarginal gyrus has an additional central role in empathy (Silani et al., 2013). We hypothesize that the PPPD group is more sensitive to spatial and movement information of people presented in the pictures, which could trigger their own vestibular symptoms. The ANX group also showed increased neuronal activity in the retroinsular cortex compared to the HC group, so we assume that anxiety subjects in our study also suffered from pronounced vertigo sensitivity, which is an accordance with the literature (Jacob et al., 1996, 1997). Another hypothesis could be that especially the left part of the activated area of the PPPD group in

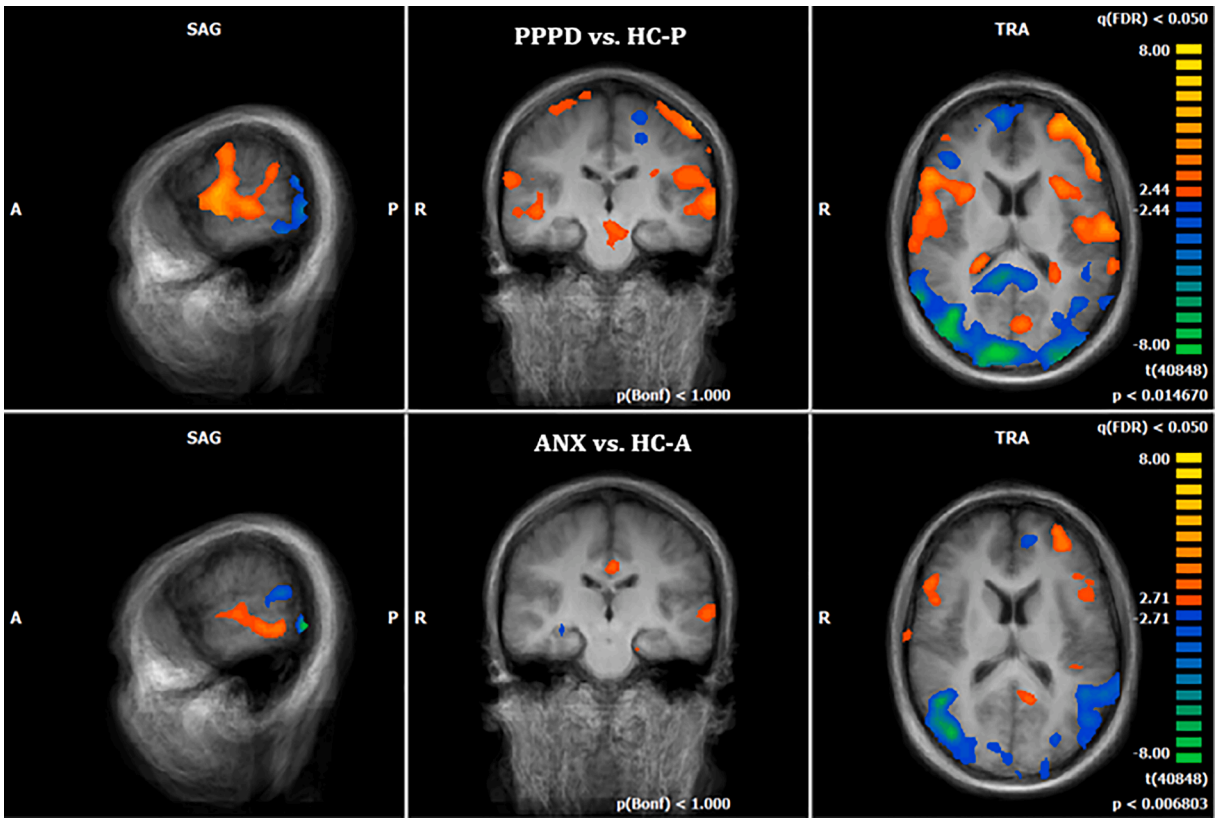

Fig. 2. Neural responses of the emotion-associated PPPD minus HC-P group (1st row)/ANX minus HC-A group (2nd row) [negative emotional pictures > neutral pictures; q(FDR) < 0.05, *T*-score: −8 to 8, fixed-effects-analysis], in orange: increased responses of patients with PPPD/ANX compared to HC-P/HC-A group; PPPD group: anterior insula, right amygdala, bilateral superior temporal gyrus, brainstem, bilateral inferior frontal gyrus, bilateral supramarginal gyrus; ANX group: bilateral inferior frontal gyrus. middle/superior temporal gyrus in blue: increased activations of HC compared to the PPPD group, e.g. middle occipital cortex, posterior temporal gyrus, precuneus (1st, 2nd row: x = -5; y = -9; z = 0; 3rd, 4th row: x = -60; y = -20; z = 15). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

our study could be considered as part of the **temporoparietal-junction** (TPJ), which plays a major role in functional neurological disorders (FND). This finding is congruent with other studies examining PPPD and FND (Demartini et al., 2021; von Söhsten Lins et al., 2021). Brandt and Dieterich (1986) hypothesized that the sway vertigo and stance unsteadiness in PPV is due to a disruption of the mechanism of spatial constancy due to a partial decoupling of the efference copy for head and body movements, i.e., a discrepancy between the actual sensory feedback and the predicted feedback. This discrepancy creates the feeling of an abnormal sense of agency in patients with FND (Demartini et al., 2021).

The **STG** can be assigned to the nonspecific vestibular network (Kahane et al., 2003; Lopez et al., 2012; Stephan et al., 2005). It is also related to the anxiety-network, because of its strong functional connectivity to the amygdala (Zhao et al., 2014). There is evidence for its involvement in patients with CSD as well: Indovina and Riccelli et al. (2015) found an increase of functional connectivity between the insula and the STG, and between the hippocampus and the STG. We found a stronger activation in the STG in the PPPD group in comparison to both ANX and HC group, which we interpret as an increased neural response to vestibular and emotional stimuli. The HC and the ANX group also demonstrated an increased BOLD signal in this area. Therefore, we assume that this is a brain region involved in general processing of emotional and vestibular information.

4.2.2. Differences in brain regions associated with emotion processing

In direct comparison with the corresponding HC group, the PPPD group revealed enhanced responses in several brain regions that have been related to emotion processing, such as the amygdala, lentiform nucleus, hippocampus and brainstem (Basile et al., 2021; Chavanne and Robinson, 2021). The PPPD group showed stronger responses in multiple brain regions than the ANX group. This could indicate that the emotional stimuli had a greater provocative effect on a neuronal basis in the PPPD than in the ANX group.

However, there was no such difference in the direct comparison between the ANX and the PPPD group, supporting hypothesis 2 that patients with PPPD activate similar neural networks as patients with anxiety disorder. On the other hand, only the ANX group showed a trend-level in the correlations between amygdala and STAI-T and a significant correlation between the hippocampus ROI and STAI-T and STAI-S, which supports our forth prediction (H4), that patients with ANX show stronger activation patterns of anxiety-associated neuronal networks in the fMRI measurements than the PPPD and the HC group.

Lesion studies on animals and humans focusing on anxiety have identified the **amygdala** as a key region for conditioning processes (LeDoux et al., 1988; Wilensky et al., 2006). These conditioning processes are used as an explanatory model in both disorders, in PPPD and its related predecessors, especially when preceded by a somatic disease, such as Menières disease or vestibular migraine (Best et al., 2006; Schaaf et al., 1999).

Chrobok (2017) also found an increased amygdala response under anticipatory anxiety and the CCK-4 paradigm, comparing patients with PPV and HC groups. In a block-design it could mean, that provoking stimuli also creates anticipatory anxiety between neutral picture block and expected emotional picture block. Furthermore, there is evidence that an increased amygdala activation plays a major role in functional movement disorders (Demartini et al., 2021). In patients with PPPD this could mean that anticipatory fear of certain movements, which may

Table 6
Neuronal responses during the emotion-associated task ANX vs HC-A (negative emotional-associated pictures minus neutral pictures; clusters of >30 voxels, q(FDR) < 0.05, *T*-score: 8 to −8).

			Centre of gravity			Size	*t*-score	
Brain region	**side**	**BA**	**x**	**y**	**z**		**Ø**	**max**
ANX > HC-A								
superior frontal gyrus	L/R	6	−0.44	12.53	57.97	4811	3.44	4.97
middle frontal gyrus	L	10	−30.54	49.32	11.68	1956	3.57	5.27
	L	6	−34.79	5.37	52.91	3819	3.40	4.71
	R	6	28.67	12.2	51.13	1945	3.45	5.17
	R	10	39.95	34.84	24.33	1299	3.20	4.38
inferior frontal gyrus	R	45	50.0	17.29	7.37	5214	3.59	6.23
	L	45	−45.48	19.14	13.28	859	2.90	3.47
inferior parietal lobule	R	40	45.56	−56.33	42.22	3442	3.17	4.63
precuneus	L	7	−15.27	−53.13	39.28	22,498	3.54	7.22
superior temporal gyrus	R	22	54.91	−6.49	2.55	2126	3.21	4.71
middle temporal gyrus	L	21	−56.5	−31.53	−1.99	4700	3.23	4.52
insula	L	13	−48.64	−34.01	22.71	1191	3.15	4.19
HC-A > ANX								
inferior frontal gyrus	R	9	40.5	7.33	29.84	3430	3.62	6.34
precuneus	R	7	40.5	7.33	29.84	1839	3.14	4.15
	L	7	−24.21	−49.59	51.86	2250	3.52	5.39
superior temporal gyrus	L	22	−52.19	−51.31	14.53	5101	3.54	5.98
middle temporal gyrus	R	9	44.42	−55.38	−1.36	9816	5.12	12.64
	R	39	42.42	−54.64	20.13	3719	4.23	7.48
fusiform gyrus	L	37	−42.04	−44.2	−12.93	1705	3.59	5.51
	L	19	−42.43	−64.58	−8.42	10,427	5.90	16.18
	L	18	−20.82	−86.15	−12.18	2836	3.48	4.95
middle occipital gyrus	R	19	35.34	−75.32	8.33	26,739	4.52	11.71
	L	19	−38.77	−73.78	13.35	8142	4.17	9.91
	L	18	−20.84	−93.12	8.88	1654	3.47	4.74
cerebellar tonsil	R	*	30.84	−41.9	−32.44	1937	3.38	4.64
	L		−28.26	−40.11	−32.78	1615	3.36	4.26
declive	R		35.73	−58.38	−20.31	3225	3.96	7.50
culmen	R		39.43	−42.31	−16.27	1471	3.74	5.38
pyramis	L		−13.57	−71.42	−25.58	2226	3.25	4.36

Abbreviations: BA: Brodmann area; side: hemisphere; L: left; R: right; max: maximal *t*-score; Ø: average *t*-score; size: cluster size; voxels: number of activated voxels; x: Talairach coordinate x-axis; y: Talairach coordinate y-axis; z: Talairach coordinate z-axis).

cause dizziness, could lead to increased amygdala activity and to compensatory mechanisms in postural control (Dieterich and Staab, 2017; Im et al., 2021).

The **lentiform nucleus** as part of the basal ganglia comprising the putamen and the globus pallidus, plays a role in motor, cognitive and emotional functions, as well as in emotional motor responses (Badgaiyan, 2010; Badgaiyan et al., 2007; Ell et al., 2011; Schunck et al., 2008). Increased neural activation was found in an anticipatory anxiety paradigm in healthy volunteers and patients with PPPD (Chrobok, 2017; Schunck et al., 2008). This result could indicate an increased emotional or motor response in PPPD patients.

In comparisons between PPPD and HC, an increased neuronal activation of the **hippocampus** was shown. The hippocampus is involved in content links between spatial vision and navigation, in episodic memory, as part of declarative long-term memory which enables conscious recall of experiences in the past, but also in rumination as part of depression (Aminoff et al., 2013; Cooney et al., 2010; Ward et al., 2014). A transdiagnostic meta-analysis of patients (e.g., depression, anxiety disorder) showed an increased neuronal response in the amygdala and the hippocampal/parahippocampal gyri, mostly during processing of unpleasant stimuli compared to controls. An increase of activity in this area might be associated with an increased emotional reaction in patients with PPPD. Another assumption could apply, e.g., an increased activity in the PPPD group may be due to vestibular related processes (Indovina et al., 2015). However, due to the multi-functionality of the hippocampus and selected neuroimaging methods, it is uncertain whether this activation pattern is due to their role in processing anxiety or vestibulo-spatial information. The ANX group showed a significant correlation between the hippocampus ROI and STAI-T and STAI-S supporting our forth prediction, that patients with ANX show stronger activation patterns of anxiety-associated neuronal networks in the fMRI measurements than the PPPD group and healthy control subjects (H4).

Increased **brainstem** activity in patients with PPPD compared with HC subjects might suggest an increased fear response on the one hand, and an increased vestibular response on the other, because this part of the brain is involved in both functions (Angelaki and Cullen, 2008; Lueken et al., 2014; Tuescher et al., 2011). The **nucleus ruber** in particular influences motor control, e.g., limb movements, but also acquisition and execution of conditioned reflexes (Basile et al., 2021), and seems to be integrated in the fear network (Linnman et al., 2011). Resting-state studies found a strong functional connection with anxiety related structures such as insula, hippocampus, and basal ganglia, but also with structures involved in vestibular information processing like the precuneus and the SMG (Nioche et al., 2009; Zhang et al., 2015). Another difference, which we found, was a stronger deactivation in the **medial orbitofrontal cortex** (mOFC) in the PPPD group compared to the ANX or the HC group. The orbitofrontal cortex has reciprocal connections with areas processing emotions like insula, amygdala, ACC and hippocampus (Carmichael and Price, 1995; Cavada et al., 2000; Kringelbach and Rolls, 2004). The OFC plays an important role in multimodal stimulus-reinforcement association learning, and also in the area of reward and punishment (Rolls, 2004). While the lateral OFC (lOFC) is associated with negative emotions and obsessions, the mOFC is related to fear extinction and positive emotions (Milad and Quirk, 2012; Milad and Rauch, 2007). Decreased reactivity in mOFC was found for example in patients with depression and anxiety disorder compared to a healthy control group (Eshel and Roiser, 2010; Fischer et al., 1998; Milad et al., 2014; Whitton et al., 2015); Fischer et al., 1998; Milad et al., 2014; Whitton et al., 2015). In the present study, the decrease in neuronal activation in the mOFC can be interpreted as an increased emotional response in the PPPD group compared with the HC and the ANX group, or as a poorer adaptation process to provoking stimuli, respectively.

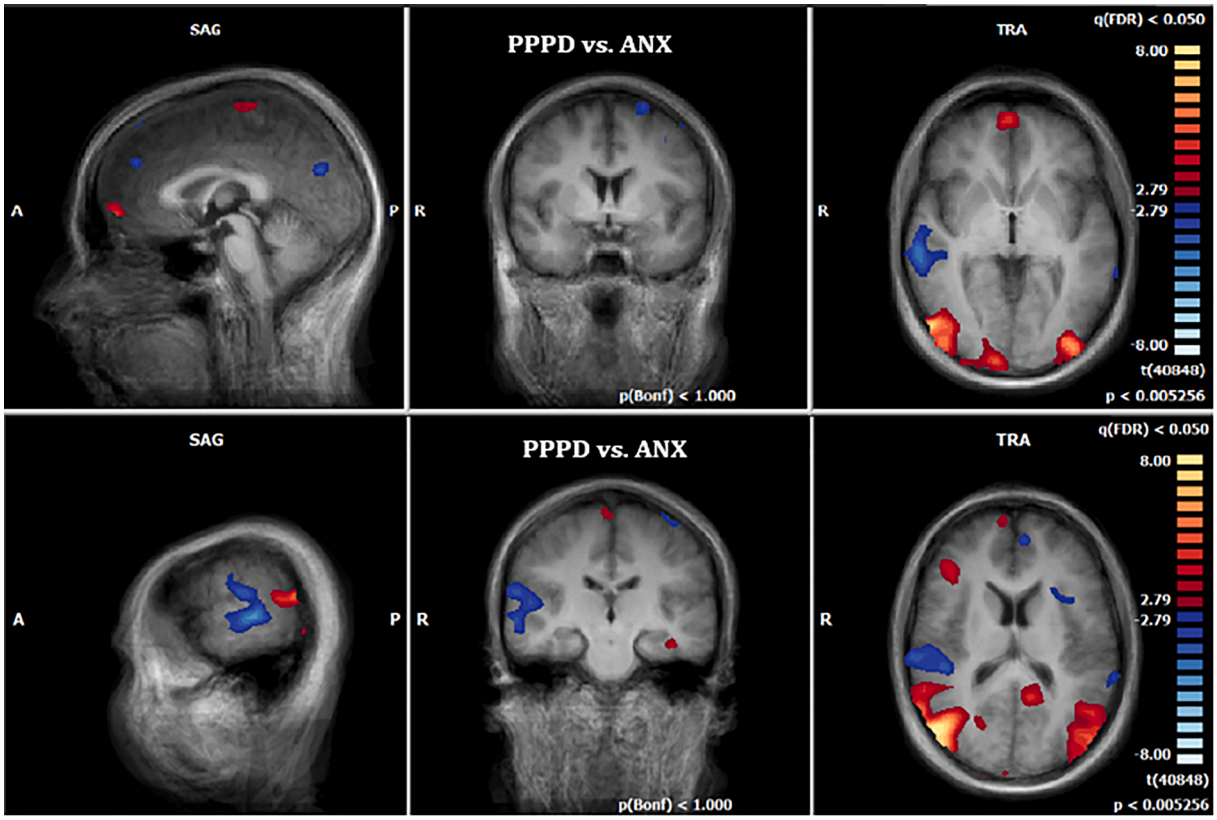

Fig. 3. Neural responses of the emotion-associated in the ANX group minus the PPPD group [negative emotional pictures > neutral pictures; q(FDR) < 0.05, *T*-score: −8 to 8, fixed-effects-analysis], in orange: increased responses of patients with ANX compared with PPPD, e.g. medial prefrontal cortex [BA10], and visual processing areas (e.g. middle occipital gyrus, cuneus, fusiform gyrus); in blue: increased activations of the PPPD group compared to the ANX group, e.g. right supramarginal gyrus/retroinsular cortex, superior temporal gyrus, left anterior insula (1st row: x = 0; y = 0; z = 0; 2nd row: x = 60; y = -20; z = 15). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

These results are in contrast to von Söhsten and colleagues (2020), whose results showed an increased sensitivity for visual and spatial but not for emotional information in PPPD patients. However, they compared patients with PPPD to patients with remitted PPPD symptoms and not to a healthy control group. Furthermore, they did not include vestibular pictures only emotional ones. It is conceivable that vestibular stimuli can trigger not only dizziness but also an anxiety response, especially if the stimulus is not strong enough to directly induce dizziness.

4.2.3. *Differences in visual processing brain structures*

Compared to the ANX and the HC-P group, the PPPD group showed a deactivation in brain regions, which are associated with processing visual information, such as fusiform gyrus, cuneus and middle occipital gyrus. The ANX group demonstrated the same pattern compared to the HC-A group.

If we assume that healthy control subjects react less emotionally to emotional stimuli than patients, then greater activation of the visual processing areas could indicate the use of visual processing strategies. We suggest that motivational factors control attention and gaze behaviour (Sabatinelli et al., 2004; van Reekum et al., 2007). These findings are congruent with other studies using pictures as stimulation method (Maywald et al., 2022; von Söhsten Lins et al., 2021).

We recognised an increased neural response in the PPPD group in the **frontal eye field** (FEF, BA8, BA6) compared to the ANX and the HC-P group, and also in patients with ANX compared to HC-A subjects. The FEF is responsible for triggering voluntary eye movements and plays a role in visuo-spatial attention, spatial-memory, visual perception, visual awareness and top-down influences on visual areas and visual performance (Vernet et al., 2014). This result could indicate an increase in visual attention to external stimulus or visual compensation strategies in the PPPD and the ANX group, similar to findings in other vestibular illnesses (Dieterich et al., 2007). If patients with fear of heights were exposed to heights, less eye movement was detected. This finding was interpreted as an impairing factor in visual stabilisation of balance function (Kugler et al., 2014). We suppose that this finding could be associated with a decreased activation of the FEF. In contrast, especially patients with PPV and high levels of discomfort showed a shorter fixation duration compared to healthy controls when walking along a crowded hospital hallway. This might suggest that they explored the surrounding for suitable auxiliary means for potential postural support (Penkava et al., 2020). This finding could be associated with an increase in the FEF and may be an explanation for the increased activation of the FEF in our study. Furthermore, the FEF is supposed to play a role in top-down processes (Fukushima et al., 2004). Therefore, visual-compensation strategies may be a top-down process.

4.2.4. *Similarities in activation between the PPPD and the ANX group*

Both the PPPD and the ANX group showed stronger activity in the insula than the respective matched control group; the PPPD group in the bilateral anterior, the right middle and the left posterior, the ANX group in the right posterior. This result supports our first and second prediction, i.e. that patients show a stronger activation pattern of anxiety-associated structures than healthy control subjects (H1). It also suggests that patients with PPPD and with ANX share commonalities in anxiety neuronal networks, as shown by fMRI measurements in the current study (H2).

As part of the limbic system, the **insula** is involved in cognitive and social-emotional, in different sensorimotor and olfacto-gustatory processes while having an integrative function (Kurth et al., 2010; Pugnaghi

Table 7
Neuronal responses during the emotion-associated task ANX vs PPPD (negative emotional-associated pictures minus neutral pictures; clusters of >30 voxels, q(FDR) < 0.05, *T*-score: 8 to −8).

			Center of gravity			Size	*t*-score	
Brain region	**side**	**BA**	**x**	**y**	**z**		**Ø**	**max**
PPPD > ANX								
frontal superior gyrus	L	6	−17.19	6.25	62.09	1714	3.71	5.55
		8	−20.21	43.98	39.03	5405	3.99	7.33
middle frontal gyrus	R	8	26.73	36.49	36.91	12,613	3.60	5.65
	L	9	−43.29	8.1	39.04	9601	3.68	8.76
inferior parietal lobule/ supramarginal gyrus/ angular gyrus	L	40/39	−43.1	−57.06	40.46	2554	3.33	5.03
precuneus	R	31	3.36	−71.74	24.31	1355	3.49	5.14
	L	31	−11.22	−49.41	28.96	880	3.43	5.01
superior temporal gyrus	R	41/22	54.85	−25.2	8.31	10,125	3.42	5.36
	L	22	−62.7	−34.0	7.57	1663	3.34	4.74
pyramis	R	*	19.62	−76.51	−28.48	1478	3.19	4.22
	L	*	−25.12	−71.47	−27.51	1030	3.16	4.14
cerebellar tonsil	L	*	−30.24	−42.26	−31.81	2479	3.78	5.74
ANX > PPPD								
middle frontal gyrus	R	46	39.42	29.06	19.36	2190	3.89	5.77
medial frontal gyrus	R	10	4.8	59.13	5.39	1780	3.52	4.90
	L	6	0.8	−24.8	66.5	1048	3.05	3.67
precuneus	R	7	27.26	−48.94	38.05	1004	3.14	4.16
superior parietal lobule	R	7	20.38	−63.91	54.63	2050	3.70	5.62
middle occipital gyrus	R	19	35.44	−75.74	6.18	22,010	4.37	9.33
	L		−41.79	−74.62	9.57	13,568	4.30	7.21
cuneus	R	19	19.76	−77.85	31.32	4250	3.94	6.48
fusiform gyrus	R	20	39.66	−39.02	−13.11	3574	3.74	6.77
	R	19	25.45	−57.19	−11.86	1898	3.31	4.97
	L	20	−30.99	−36.22	−13.13	4089	3.35	5.22
posterior cingulate	L	29	−11.99	−47.63	13.85	1448	3.48	4.90
declive	L	*	−42.76	−63.57	−15.8	2508	4.02	6.66

Abbreviations: BA: Brodmann area; side: hemisphere; L: left; R: right; max: maximal *t*-score; Ø: average *t*-score; size: cluster size; voxels: number of activated voxels; x: Talairach coordinate x-axis; y: Talairach coordinate y-axis; z: Talairach coordinate z-axis).

et al., 2011). In subjects in the study by Carlson and colleagues (2011) the insula responded during the presentation of neutral and aversive stimuli. No habituation effect occurred, particularly in the anterior insula, leading Craig and colleagues (2009) to hypothesise that the anterior insula responds to anticipated interoceptively linked emotions that can be repeatedly triggered. Previous studies also found similar changes in patients with PPV (Chrobok, 2017). In line with Indovina and Riccelli et al. (2015), we suggest that this area is part of the anxiety and the vestibulo-spatial network and stands for an increased fear response in the PPPD and ANX group alike. This supports our second prediction, i.e., that patients with PPPD and patients with ANX share commonalities in the activation patterns of anxiety networks in the fMRI measurements (H2). There is evidence that activation of the anterior insula is increased by the emotion disgust (Wicker et al., 2003; Wright et al., 2004). This might be another explanation for the increased activation of the anterior insula.

Furthermore, both patient groups showed increased neuronal activity in the **IFG** compared to the HC subjects, the ANX group bilateral [BA45] and the PPPD group in the right hemisphere [BA47]. In a fear conditioning task, Lueken et al. (2014) found that patients with panic disorder reacted with enhanced neural responses in bilateral IFG, compared to a healthy control group. They interpreted their result as an increased inhibitory response to a threatening stimulus, in the sense of a modified top-down processing. Contrary to that, Indovina et al. (2015) found a decrease in IFG in patients with chronic subjective vertigo, but their stimulation paradigm was different. We here assume that the neuronal activation depends on the provocation paradigm, but might also depend on comorbidity. A meta-analysis of the left IFG (BA44/45/47) demonstrated its involvement in empathy, language processing, working memory, motor- or impulse-control (Aron et al., 2014; Liakakis et al., 2011). It is also assumed that the IFG internally creates a representation of motion sequences, since it is simultaneously involved in motion perception and in the evaluation of action intentions (Liakakis et al., 2011). Another study suggests that the right IFG has a more general detection role for relevant cues, not only for the inhibition of motor responses. In patients with PPPD, this could mean that after a dizziness-inducing involuntary movement, this movement is voluntarily stopped in order to prevent a recurrence of dizziness. Alternatively, an evaluation process, which identifies potentially harmful movements, preventively or retrospectively, could also be considered a putative interpretation. However, due to the multi-functionality of the IFG and selected neuroimaging methods, it is uncertain whether this activation pattern is due to their role in processing vestibulo-spatial information.

5. Limitations

The following limitations must be considered in this study: firstly, statistical power has to be taken into account, as our study comprises a small sample size per group due to the corona pandemic situation. Hence, generalisations should be made with caution. Future studies should take this aspect into account. Nevertheless, the hemodynamically abnormal brain areas in our study have also been identified in previous studies as being involved in the pathophysiology of PPPD. Secondly, no randomisation was performed which carries the risk of overestimating the measured effects (Ioannidis, 2005). Thirdly, no distinction was made between female and male subjects, or between right- and left-handed subjects. Unfortunately, this was not possible due to the small sample size in this study. However, the examination of gender and the psychometric test variables did not show any confound. Furthermore, FMRI studies have shown that emotion processing differs between genders to some extent (McRae et al., 2008; Sabatinelli et al., 2004). Furthermore, an ANCOVA was not calculated because anxiety and depression as potential covariates are confounded with PPPD, e.g., people who suffer from PPPD are more likely to develop depressive and anxiety symptoms (Staab, 2012). The occurrence of depressive symptoms was balanced between ANX and PPPD group, but anxiety disorders, and medication was not. This problem could only be solved with a different study-design, which will be considered in future projects.

Also, a subdivision of the images into general anxiety-inducing and specific dizziness-inducing could provide further insights into the specific response of anxiety and dizziness patients to general anxiety-inducing and, in particular, dizziness-inducing images. Finally, visual attention was not examined with eye-tracking methods. This could be included in future studies to investigate gaze-behaviour in patients with PPPD.

6. Conclusion

Overall, dysfunctional neural processing of fear and vestibular-associated stimuli seems to be present in the PPPD group compared to the HC group. Additionally, patients with PPPD showed deviated neuronal activation patterns, especially in two brain regions compared to ANX and HC group: the supramarginal gyrus and the superior temporal gyrus. These results may indicate higher sensitivity and poorer adaptation processes in the PPPD group to emotional stimuli. Stronger activation in visual processing areas in HC subjects could be due to the use of little emotional but rather visual processing strategies. Neurobiological findings are consistent with psychometric data and revealed potential risk factors in patients with PPPD and ANX.

Author contributions

MM, SL, OP, SK, DK, and AC conceived and designed the experiments. The experiments were performed by MM, SL, BP, DK and AC. Data analysing was done by MM, SL, SK, DK, SG, LR and AC. MM, SL, SK, BR, NT, MP, SS, BEW, DK, OP and AC contributed in the writing of this manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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Further reading

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