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Sensory overload and imbalance: Resting-state vestibular connectivity in PTSD and its dissociative subtype

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ABSTRACT

Background: The vestibular system integrates multisensory information to monitor one's bodily orientation in space, and is influenced by interoceptive awareness. Post-traumatic stress disorder (PTSD) involves typically alterations in interoceptive and bodily self-awareness evidenced by symptoms of hyperarousal, as well as of emotional detachment, including emotional numbing, depersonalization, and derealization. These alterations may disrupt vestibular multisensory integration between the brainstem (vestibular nuclei) and key vestibular cortical regions (parieto-insular vestibular cortex, prefrontal cortex). Accordingly, this study examined functional connectivity of the vestibular system in PTSD and its dissociative subtype.

Methods: Using resting-state fMRI data in SPM12 and PickAtlas, a seed-based analysis was employed to examine vestibular nuclei functional connectivity differences among PTSD (n = 60), PTSD dissociative subtype (PTSD + DS, n = 41) and healthy controls (n = 40).

Results: Increased vestibular nuclei functional connectivity with the parieto-insular vestibular cortex and the dorsolateral prefrontal cortex (dlPFC) was observed in PTSD and in controls as compared to PTSD + DS, and greater connectivity with the posterior insula was observed in controls as compared to PTSD. Interestingly, whereas PTSD symptom severity correlated negatively with dlPFC connectivity, clinical measures of depersonalization/derealization correlated negatively with right supramarginal gyrus connectivity.

Discussion: Taken together, decreased vestibular nuclei functional connectivity with key cortical vestibular regions in the PTSD + DS as compared to PTSD group, and its negative correlations with PTSD and dissociative symptoms, suggest that dysregulation of vestibular multisensory integration may contribute to the unique symptom profiles of each group. Further research examining disruption of vestibular system neural circuitry in PTSD and its dissociative subtype will be critical in capturing the neurophenomenology of PTSD symptoms and in identifying psychotherapeutic techniques that target dysfunction related to the vestibular system.

1. Introduction

The vestibular system operates subconsciously, consistently monitoring one's position in gravitational space and being influenced by one's own interoceptive awareness (Berthoz and Weiss, 2000; Day and Fitzpatrick, 2005; Heydrich and Blanke, 2013; Lopez, 2016; Lopez and Blanke, 2011; Zu Eulenburg et al., 2013). Most literature regarding the vestibular system emphasizes its role in bodily consciousness, where it is viewed as broadly integrating cognitive processes with multisensory input to maintain awareness of the bodily self, including physical balance (Blanke, 2012; De Waele et al., 2001; Hitier et al., 2014; Lenggenhager and Lopez, 2015; Pfeiffer et al., 2014). Maintenance of

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physical equilibrium relies upon continuous proprioceptive input used to respond to changes in one's gravitational balance, and it is derived from both exteroceptive signals, including tactile and visual external stimuli, as well as interoceptive signals stemming from more visceral sensations in the body (Aspell et al., 2013; Balaban and Thayer, 2001; Suzuki et al., 2013; Tsakiris et al., 2011). Taken together, the vestibular system plays a critical role in guiding the body through the physical world and in the interpretation of sensory stimuli. Accordingly, its disruption may signal profound alterations in key processes such as balance and sensory integration.

Neurobiologically, in non-human primates, vestibular multisensory input relating to one's position in the gravitational field travels through the vestibular nuclei of the brainstem and reaches its relevant cortical areas for multisensory processing, known as the parieto-insular vestibular cortex (PIVC; includes posterior insula, inferior parietal lobule – supramarginal and angular gyri), as well as somatosensory and motor areas (Akbarian et al., 1994; Boisacq-Schepens and Hanus, 1972; Guldin and Grüsser, 1998; Lopez and Blanke, 2011). The definition of the human PIVC is less concrete, as it is sometimes referred to broadly as the temporo-*peri*-Sylvian vestibular network; however, some areas of the non-human PIVC are thought to be overlap with its human homologue, such as the posterior insula and the temporoparietal junction (Dieterich et al., 2003; Kahane et al., 2003; Khan and Chang, 2013; Lopez and Blanke, 2011).

The cortical regions of the PIVC are critical for vestibular afferent processing, with each region playing an intricate role in organizing multisensory input to maintain vestibular function. Here, the posterior insula serves as a multisensory integration site to bring awareness to one's internal affective state, where it is critical to coordinating behavioral responses to exteroceptive vestibular input and contributes to one's own interoceptive awareness (Baier et al., 2013; Mazzola et al., 2014; Serino et al., 2013; Tsakiris et al., 2007). The entire insula is considered collectively the primary interoceptive cortex. Whereas the anterior insula plays a role in emotional regulation, the posterior insula is thought to be more involved with internal physiological homeostasis reactions to pain, cardiac signals and visceral sensations (Craig, 2002, 2003; Critchley et al., 2004). Importantly, the temporoparietal junction, which encompasses the supramarginal gyrus, as well as the posterior superior temporal gyrus/sulcus and angular gyrus, is also critical for receiving vestibular afferents and for integrating multisensory input related to bodily and visual spatial orientation relating to one's surroundings (Arzy et al., 2006; Blanke, 2012; Blanke and Arzy, 2005; Burgess et al., 2001; Decety and Lamm, 2007; Igelström et al., 2015).

Neurobiological models of PTSD suggest that physiological homeostasis is disrupted due to chronic stress, which may promote hyperarousal symptoms, such as hypervigilance or irritability observed in PTSD patients (Kendall-Tackett, 2000; Vieweg et al., 2006; Yehuda, 2002; Yehuda and LeDoux, 2007; Yehuda and McFarlane, 1995), or alternatively, hypoarousal symptoms associated with emotional detachment, including symptoms of depersonalization/derealization in patients with its dissociative subtype (Frewen and Lanius, 2006; Lanius et al., 2010; Pain et al., 2010; Van Der Kolk, 2006). Interestingly, depersonalization/derealization symptoms have been reported in vestibular disorders such as vertigo, where compromised sensorimotor processing can influence the relation between one's self and environment and affect negatively integration with other senses, particularly during acute episodes of severe stress (Yen Pik Sang et al., 2006). Moreover, aberrant functioning of the insula has been reported repeatedly in neuroimaging studies of PTSD and its dissociative subtype (Brown and Morey, 2012; Herringa et al., 2013; Hopper et al., 2007; Lanius et al., 2005; Nicholson et al., 2016; Simmons et al., 2009). Finally, altered activation of the temporo-parietal junction has been observed in patients with depersonalization disorder (Simeon et al., 2000), and is associated with dissociative symptoms observed in vestibular and psychiatric disorders, including dissociative PTSD (Ionta et al., 2011; Kennis et al., 2016; Lanius et al., 2005, 2002; Smith and Darlington, 2013; Steuwe et al., 2014; Voon et al., 2010). Critically, however, despite the close relationship between regions of the parieto-vestibular insular cortex and symptom profiles observed in PTSD and its dissociative subtype, the neural circuitry underlying the vestibular system in relation to PTSD has yet to be elucidated.

Accordingly, the objective of the current study was to examine functional connectivity of the vestibular system in PTSD, its dissociative subtype, and healthy controls. Using resting-state fMRI to determine the vestibular neural circuitry with key cortical regions overlapping with PTSD neurophenomenology, we performed a seed-based functional connectivity analysis of the vestibular nuclei with the whole-brain. Since the vestibular system operates subconsciously, continuous multisensory vestibular afferents monitoring one's position in the gravitational field are not dependent on conscious or localizable stimuli as employed in task-based paradigms; we thus predicted that changes in the neural circuitry of the vestibular system in PTSD would be detectable during rest. Given that brainstem-cortical functional connectivity is essential for multisensory processing, we hypothesized that as compared to PTSD, healthy individuals would demonstrate enhanced vestibular nuclei functional connectivity with relevant vestibular cortices (PIVC and prefrontal cortex) at rest. We further hypothesized that PTSD patient groups would differ in functional connectivity patterns. Specifically, we hypothesized that both PTSD groups would demonstrate altered multisensory integration patterns unique to the symptom profiles these groups experience. Moreover, we predicted that individuals with the dissociative subtype of PTSD would demonstrate significantly less vestibular nuclei functional connectivity with key vestibular cortices essential to understanding one's bodily self-awareness (e.g., supramarginal gyrus), due to their disposition to experiencing depersonalization/derealization symptoms.

2. Methods

2.1. Clinical and demographic information

The study consisted of one-hundred and forty-one participants, including 60 PTSD patients (PTSD), 41 PTSD patients with the dissociative subtype (PTSD + DS), and 40 healthy controls. London Health Sciences Center recruited participants from 2009 to 2016 via referrals from family physicians, mental health professionals, psychology/psychiatric clinics, community programs for traumatic stress, and posters/advertisements within the London, Ontario community.

Inclusion criteria for PTSD and its dissociative subtype was based on the CAPS interview, which assesses the frequency and intensity of PTSD symptoms [CAPS; versions IV and 5 (for 18 participants); CAPS IV cut-off score > 50, CAPS-5 uses a different scoring system with no definitive cut-off)] (Blake et al., 1995; Weathers et al., 2013). Individuals meeting criteria for the dissociative subtype scored at least two in frequency and intensity for depersonalization and/or derealization symptoms as per standard methods (Harricharan et al., 2016; Nicholson et al., 2015; Steuwe et al., 2014). For all participants, the SCID was administered (Structured Clinical Interview for DSM-IV Axis-I disorders) (First et al., 2002), along with a battery of questionnaires: Beck Depression Inventory (BDI) (Beck et al., 1997), Child Trauma Questionnaire (CTQ; 87% of all PTSD patients had histories of childhood trauma, confirmed if patient scored above the 'none/minimal' threshold for any trauma category according to the CTQ scoring manual) (Bernstein and Fink, 1998), as well as the Multiscale Dissociation Inventory (MDI) (Briere et al., 2005).

Clinical and demographic information are detailed in Table 1. Age differences were assessed via a one-way ANOVA, and a Pearson's chi-square was performed to calculate gender differences across all three participant groups. If Levene's test violated homogeneity of variance assumptions, a Kruskal-Wallis analysis followed by post-hoc Games-Howell comparisons was performed to assess the significance of non-parametric psychological measures (CAPS, BDI, CTQ, and averaged

Table 1
Participant Demographic and Clinical Characteristics.

Measure	PTSD	PTSD + DS	Controls
N	60	41	40
Age	37.8 ± 11.6	41.1 ± 13.7	35.0 ± 11.0
Sex	M = 25, F = 35	M = 8, F = 33	M = 14, F = 26
CAPS-IV Total (n = 123)	67.9 ± 13.4 (n = 53)	81.6 ± 12.7 (n = 30)	0.7 ± 3.1 (n = 40)
CAPS−5 Total (n = 18)	28.9 ± 6.9 (n = 7)	39.0 ± 8.2 (n = 11)	–
CTQ – Total	56.3 ± 24.7	68.2 ± 19.1	31.6 ± 8.6
BDI	22.8 ± 7.5	33.0 ± 10.3	1.2 ± 2.1
MDI – Total	54.1 ± 15.2	77.2 ± 22.0	33.7 ± 3.4
MDI – Depersonalization	6.6 ± 2.7	12.1 ± 5.3	5.2 ± 0.6
MDI – Derealization	8.6 ± 3.4	12.7 ± 4.0	5.2 ± 0.5
MDD	n = 11(24)	n = 23(9)	–
Panic Disorder/ Agoraphobia	n = 10(6)	n = 9(6)	–
Social Phobia	n = 2(2)	n = 6(0)	–
OCD	n = 3(2)	n = 0(2)	–
GAD	n = 1(0)	n = 0(0)	–

Age, gender, CAPS, and self-report questionnaires (CTQ, MDI, BDI) are reported as mean ± SD. Psychiatric disorders assessed via SCID-I (MDD, Panic Disorder/ Agoraphobia, Social Phobia, OCD and GAD) are reported in frequencies, as n = current (past) cases.

Abbreviations: PTSD, posttraumatic stress disorder; PTSD + DS, posttraumatic stress disorder with the dissociative subtype; M, Males; F, Females; CAPS, Clinician-Administered PTSD Scale; CTQ, Child Trauma Questionnaire; BDI, Beck Depression Inventory; MDI, Multiscale Dissociation Inventory; MDD, Major Depression Disorder; OCD, Obsessive Compulsive Disorder; GAD, Generalized Anxiety Disorder.

depersonalization and derealization MDI scores) across groups (Kruskal and Wallis, 1952).

Participants were excluded if they could not adhere to the safety regulations required for the 3.0T scanner, including metal implants, previous head trauma associated with a period of unconsciousness, current or past history of neurological disorders, significant untreated medical illness, and/or pervasive developmental mental disorders. Additional exclusion criteria for PTSD patients included current or past history of bipolar or psychotic disorders, or if patients had alcohol/ substance dependency or abuse for at least six months prior to participation in the study, as determined by the SCID. Control participants were screened for prior trauma exposure and were excluded if lifetime criteria were met for any DSM-IV Axis-I psychiatric disorder. Approximately 35 patients (PTSD, n = 20; PTSD + DS, n = 15) were using psychotropic medications at the time of the study. The medications included antidepressants (n = 32: SSRIs, n = 13; SNRIs, n = 7; NDRIs, n = 9; MAOI, n = 1; SARIs, n = 4; tricyclics, n = 1; tetracyclics, n = 2), atypical antipsychotics (n = 9), and sedative drugs (n = 13: benzodiazepines, n = 11; cyclopyrrolone, n = 2). Moreover, 89% of participants were right-handed (n = 126), while 11 participants were left-handed (Controls, n = 2; PTSD, n = 5; PTSD + DS, n = 4) and 4 participants' handedness were unknown. If eligible, subjects provided written informed consent to participate in the study. All scanning was conducted in London, Ontario, Canada at either Robarts Research Institute's Center for Functional and Metabolic Mapping or Lawson Health Research Institute. The study was approved by the Research Ethics Board at Western University of Canada.

2.2. Data acquisition

Whole-brain fMRI (functional magnetic resonance) data were collected in a 3.0T scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased array head coil. BOLD (blood oxygen level dependent) fMRI data were collected using a manufacturer's standard gradient-echo planar imaging (EPI) pulse sequence (single-shot, blipped-EPI) with an interleaved slice acquisition order per the following specifications: Time Resolution (TR) = 3000 ms, Echo Time (TE) = 20 ms, voxel size = 2 × 2 × 2 mm^3, Field of View (FOV) = 192 × 192 × 128 mm^3 (94 × 94 matrix, 64 contiguous slices), and Flip Angle (FA) = 90°. High-resolution T1-weighted anatomical images were also collected (MPRage: 192 slices, voxel size = 1 × 1 × 1 mm3). To obtain resting-state data, subjects were asked to close their eyes and let their minds wander without focusing on anything in particular for 6 minutes as per standard methods (Bluhm et al., 2009; Fransson, 2005; Harricharan et al., 2016), with follow-up post-scan clinical state measures, including the State-Trait Anxiety Inventory (STAI) (Spielberger, 2010) and the Responses to Script-Driven Imagery Scale (RSDI) (Hopper et al., 2007) to assess the participants' state clinical symptoms during the scan.

2.3. fMRI preprocessing

Image preprocessing and statistical analyses were performed using statistical parametric mapping software (SPM12, Wellcome Trust Center for Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm; RRID: SCR_007037) within MATLAB 8.6 (R2015b, Mathworks Inc., MA; RRID: SCR_001622). The functional images for each subject were realigned to the first functional image, after four dummy scans were omitted to allow magnetization to reach steady state, to correct for motion in the scanner and were resliced. The resulting mean functional image was co-registered to the T1-weighted anatomical image to spatially realign BOLD data with the subject's anatomical space. The co-registered images were segmented using the "New Segment" method implemented in SPM12, which uses T2-weighted and PD-weighted scans when generating tissue probability maps. The functional images were registered to a MNI template using the forward deformation field, with additional visual inspection of precise brainstem normalization in each subject, and were subsequently smoothed with a three-dimensional isotropic Gaussian kernel of 6 mm full-width half maximum [FWHM; as guided by previous fMRI vestibular nuclei studies which range from 4 to 8 mm FWHM smoothing kernels (Kirsch et al., 2016; Miller et al., 2008)]. The images were further motion corrected with ART software (version 2015-10; Gabrieli Lab, McGovern Institute). The means of the total motion outliers per subject in each group were compared to assess any potential influence on the results of the present study and did not vary significantly across groups (p = 0.327, *ns*). Physiological denoising of the data was done through bandpass filtering of the smoothed functional volumes to isolate frequencies of interest and reduce respiratory and other physiological noises, ranging from 0.012 to 0.1 Hz. Bandpass filtering isolates low frequencies associated with spontaneous fluctuations within the grey matter of the brain at rest, while adjusting for proper sampling of cardiac and respiratory noise for frequencies of physiological interest (Fox et al., 2005; Zuo et al., 2010). While low frequencies are associated with low MR scanner noise (i.e. slow scanner drifts), high frequencies are thought to correspond to white matter, as well as cardiac and respiratory signals (Cordes et al., 2000; van de Heuvel et al., 2008).

2.4. fMRI seed-based functional connectivity statistical analysis

2.4.1. Within-subject analysis

A within-subject general linear model was used to assess resting-state functional connectivity patterns for each subject. The model included the mean signal intensity time course for the resting-state scan, with ART motion outliers used as regressors. The left and right vestibular nuclei (LVN and RVN) [***x***: ± 16, ***y***: −36, ***z***: −32] were used as spherical (5 mm radii) seed regions-of-interest (Fig. 1), in concordance with previous studies (Kirsch et al., 2016; Miller et al., 2008), and generated using PickAtlas software (WFU Pickatlas, version 3.0.5 (Maldjian et al., 2003); http://fmri.wfubmc.edu/software/pickatlas; RRID: SCR_007378). The mean signal intensity time course was created via in-house software, developed by co-author Jean Théberge, which

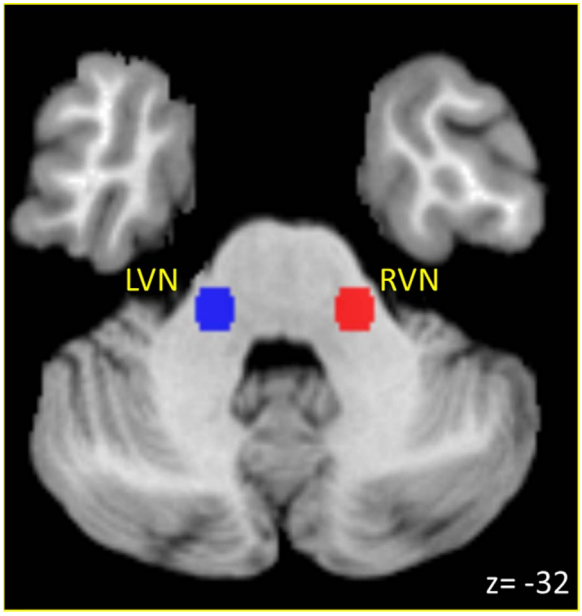

Fig. 1. Left (LVN) and right (RVN) vestibular nuclei regions-of-interest [MNI: *x*: ± 16 y: −36 *z*: −32; 5 mm sphere] used to generate seed time courses for within-subject analysis.

read LVN and RVN seed activity from PickAtlas in each resting-state functional volume per subject. A voxel-wise approach was used to calculate positive and negative correlations between LVN and RVN signal time courses with other voxels of the brain.

2.4.2. Full factorial analysis

A full-factorial analysis of variance (ANOVA) was performed to examine the 3 × 2 interaction between participant group (PTSD, PTSD + DS and controls) and regions-of-interest (left and right vestibular nuclei; L/R VN) as well as main effects. Separate ANOVAs were performed using either MDD diagnosis (determined via SCID assessment; see Methods; Table 1) or participants on medications as covariates. Post-hoc one-sample *t*-tests and two-sample *t*-tests were used to assess functional connectivity patterns within and between each group and region-of-interest, respectively. Correlations between PTSD seed-based analysis and psychological measures (CAPS, CTQ and averaged depersonalization and derealization MDI scores) and post-scan clinical state measures (STAI and averaged depersonalization and derealization RSDI scores) were assessed. Subsequent ROI analyses of key parieto-vestibular cortical areas [posterior insula (***x:*** −42, ***y:*** −12, ***z:*** 10) and supramarginal gyrus (***x:*** 59, ***y:*** −36, ***z:*** 30)] based on anatomical data from a previous vestibular-related resting-state neuroimaging study (Göttlich et al., 2014) were performed to look at results from the full-factorial analysis and regression analyses of clinical correlations with seed-based analysis. Brain regions were identified using the AAL atlas (Tzourio-Mazoyer et al., 2002) via xjview software (http://www.nitrc.org/projects/xjview), the MNI2Tal atlas available online via the Bio-Image Suite at Yale University (http://bioimagesuite.yale.edu/mni2tal/) (Lacadie et al., 2008) and visually inspected using an additional anatomical atlas (Montemurro and Bruni, 1988).

In order to determine significant clusters, the FWE-corrected alpha was set to p = 0.05, resulting in a calculated FWE corrected cluster size of k = 10 based on random field theory in SPM (Friston et al., 1994; Hayasaki and Nichols, 2003; Lui et al., 2011; Nicholson et al., 2015). Significant clusters identified in ROI analyses were adjusted for multiple comparisons at a voxel-wise FWE-corrected threshold set at $p \leq 0.025$, k = 10.

3. Results

3.1. Overview

Overall, the present study revealed altered vestibular nuclei functional connectivity patterns across PTSD, PTSD + DS and healthy control groups. More specifically, bilateral vestibular nuclei functional connectivity with the parieto-vestibular insular cortex (posterior insula, supramarginal gyrus) and the dorsolateral prefrontal cortex was observed in both PTSD and healthy controls whereas the PTSD + DS group in contrast showed minimal functional connectivity with these areas. Interestingly, the PTSD group showed greater vestibular nuclei functional connectivity with the right angular and supramarginal gyri than both the PTSD + DS and healthy control groups. Conversely, healthy controls demonstrated greater RVN connectivity with the left posterior insula than the PTSD group. Finally, PTSD symptom severity negatively correlated with vestibular nuclei functional connectivity with the prefrontal cortex, while averaged depersonalization/derealization MDI and RSDI scores negatively correlated with vestibular nuclei connectivity with the right supramarginal gyrus.

3.2. Clinical and demographic statistical results

ANOVA analysis did not reveal significant differences in ages across all three participant groups ($p = 0.073$, df = 2), and a Pearson's chi-square test failed to reveal a statistically significant association between gender and participant group ($p = 0.066$, df = 2). Kruskal–Wallis analysis of variance yielded significant values for all psychological test measures, including CTQ, CAPS, MDI, and BDI, as well as resting-state clinical measures RSDI and STAI (all $p < 0.001$). Post-hoc Games-Howell comparisons revealed no significant differences between PTSD + DS and PTSD groups for CAPS-IV ($p = 0.794$) and BDI scores, but did reveal significantly higher CTQ and MDI (averaged depersonalization and derealization) scores in PTSD + DS individuals ($p < 0.05$). For resting-state clinical measures, Games-Howell comparisons revealed no significant differences between PTSD + DS and PTSD for STAI scores ($p = 0.064$), but did reveal significantly higher RSDI (averaged depersonalization and derealization score) in PTSD + DS as compared to PTSD ($p < 0.05$) during the scan. All psychological measures and resting-state clinical measures revealed significantly higher scores in both PTSD patient groups as compared to controls (all $p < 0.01$).

4. Seed-based functional connectivity analysis

4.1. 3 × 2 full factorial ANOVA

The 3 × 2 full factorial ANOVA conducted for the seed-based analysis revealed an interaction between participant group (PTSD + DS, PTSD, healthy controls) and region-of-interest (left and right vestibular nuclei; LVN, RVN, respectively) as well as main effects for each factor; results are shown in the supplementary material. Post-hoc one-sample and two-sample *t*-tests were used to assess group and region-of-interest differences [all results are reported as FWE-voxel corrected, $p < 0.05$, $df = (1, 276)$]. Separate full-factorial analyses using either MDD diagnosis or patients on medications as a covariate did not change the results of the original full-factorial ANOVA analysis.

4.2. Within group functional connectivity

Fig. 2 depicts vestibular nuclei functional connectivity patterns with previously identified key vestibular cortical regions (posterior insula, supramarginal gyrus) and the dorsolateral prefrontal cortex within each participant group. A more comprehensive explanation of within group vestibular nuclei functional connectivity patterns are detailed in the supplementary material.

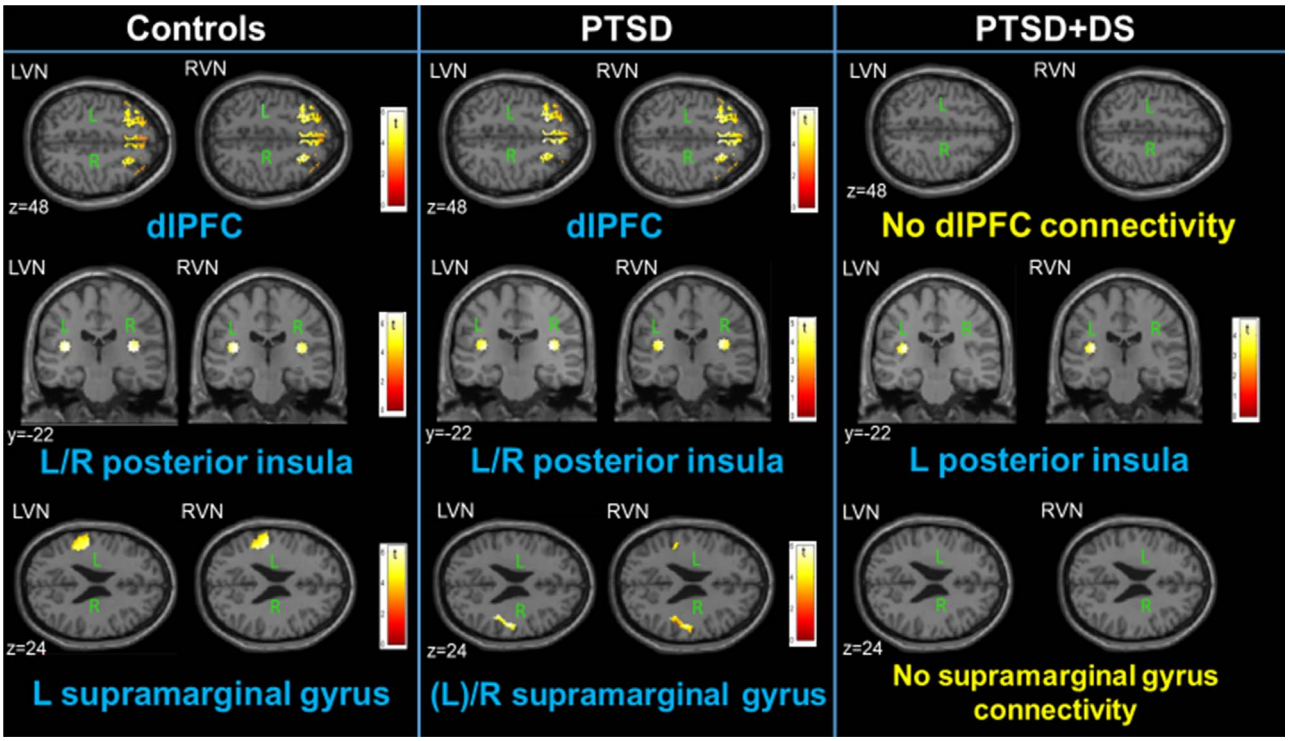

Fig. 2. Left and right vestibular nuclei functional connectivity patterns with key cortical regions relevant to the vestibular system based on seed-based analysis within all three participant groups (controls, PTSD and PTSD + DS), including the parieto-insular vestibular cortical regions (posterior insula, supramarginal gyrus), and the dorsolateral prefrontal cortex. Notably, healthy controls and PTSD demonstrated connectivity with all three brain regions shown (dlPFC, posterior insula, supramarginal gyrus), whereas PTSD + DS demonstrated neither LVN nor RVN functional connectivity with neither the dlPFC nor the supramarginal gyrus. Abbreviations: PTSD posttraumatic stress disorder patients non-subtype; PTSD + DS, PTSD patients with the dissociative subtype; LVN, left vestibular nuclei; RVN, right vestibular nuclei; L, left hemisphere; R, right hemisphere; dlPFC, dorsolateral prefrontal cortex.

4.3. Functional connectivity differences between patient groups

4.3.1. PTSD > PTSD + DS or healthy controls

PTSD demonstrated greater bilateral vestibular nuclei connectivity with the right angular and supramarginal gyri, as well as the right middle temporal gyrus as compared to PTSD + DS, with additional increased LVN connectivity with the superior and middle frontal gyri (BA 9,10), the medial orbitofrontal cortex, the right fusiform and the right inferior occipital gyrus as compared to PTSD + DS (Table 2). Moreover, the PTSD group demonstrated greater LVN connectivity with the right angular gyrus and greater RVN connectivity with the right supramarginal gyrus as compared to healthy controls (Table 2).

4.3.2. PTSD + DS > PTSD or HEALTHY Controls

The PTSD + DS group did not demonstrate greater bilateral vestibular nuclei connectivity with any area as compared to PTSD and healthy controls.

4.3.3. Healthy controls > PTSD or PTSD + DS

Healthy controls demonstrated increased LVN connectivity with the middle temporal gyrus as compared to the PTSD group, as well as increased RVN connectivity with the left posterior insula upon subsequent ROI analyses as compared to PTSD (Table 2). In addition, controls demonstrated greater bilateral vestibular nuclei connectivity with the left precuneus as compared to PTSD + DS, with additional increased LVN connectivity with the left supramarginal gyrus, precentral gyrus, middle temporal gyrus and middle frontal gyrus as compared to PTSD + DS (BA 6).

4.4. Functional connectivity differences between LVN and RVN

Functional connectivity patterns between region-of-interest differences demonstrated greater PTSD + DS RVN connectivity with the bilateral superior frontal gyrus (BA 10), middle frontal gyrus (BA 8), and the inferior frontal triangularis as compared to LVN functional connectivity patterns (Table 3). In addition, greater RVN functional connectivity was observed with the left middle temporal gyrus and the superior temporal pole as compared to LVN in PTSD + DS (Table 3). LVN and RVN regions-of-interest differences were not observed in PTSD and controls.

4.5. Clinical measure correlations with functional connectivity analysis

CAPS-IV total scores correlated negatively with the middle frontal gyrus in all PTSD patients (both PTSD and PTSD + DS groups) for both LVN [(***x:*** 44, ***y:*** 40, ***z:*** 30), $k = 320$, $p\text{FWE} = 0.013$) and RVN [(***x:*** 42, ***y:*** 42, ***z:*** 30), $k = 319$, $p\text{FWE} = 0.017$] functional connectivity patterns. In addition, averaged depersonalization/derealization RSDI and MDI scores correlated negatively with the right supramarginal gyrus upon ROI analysis for the LVN [(***x:*** 54, ***y:*** −28, ***z:*** 30), $k = 162$, $p\text{FWE} = 0.009$] and RVN [(***x:*** 62, ***y:*** −38, ***z:*** 34), $k = 188$, $p\text{FWE} = 0.002$] connectivity patterns, respectively. There were no correlations with functional connectivity analyses observed with other psychological test scores (CTQ, BDI) and clinical state measure (STAI).

5. Discussion

The aim of the present study was to delineate the neural circuitry of the vestibular system by examining functional connectivity patterns of the brainstem vestibular nuclei in PTSD and its dissociative subtype, as well as in healthy controls during resting-state. The cortical areas implicated in the vestibular system neural circuitry overlap with areas identified as aberrant during resting-state in previous PTSD literature. We therefore predicted that altered neural circuitry in PTSD would be detectable at resting-state as vestibular function relies on continuous multisensory input for awareness of one's own position in the

Table 2
LVN and RVN functional connectivity between participant groups.

Contrast	LR	BA	Region	k	vFWE	Z	MNI Coordinates		
							x	y	z
PTSD > PTSD + DS LVN	R	40	Angular Gyrus	1970	< 0.001	5.88	56	−62	28
	R	40	Supramarginal Gyrus		< 0.001	5.67	64	−28	28
	R	39	Middle Temporal Gyrus		< 0.001	5.66	52	−70	18
	R	37	Inferior Occipital Gyrus		0.002	5.16	50	−66	−14
	R	37	Fusiform Gyrus		0.006	4.89	52	−58	−18
	L	10	Middle Frontal Gyrus	104	0.005	4.90	−42	54	14
	R	10	Middle Frontal Gyrus	364	0.007	4.83	38	54	20
	R	9	Superior Frontal Gyrus		0.013	4.70	28	48	38
	L	40	Supramarginal Gyrus	44	0.010	4.75	−62	−28	42
	R	10	Medial Orbitofrontal Cortex	16	0.011	4.74	6	68	−4
PTSD > PTSD + DS RVN	R	40	Angular Gyrus	1099	0.001	5.40	58	−60	28
	R	40	Supramarginal Gyrus		0.001	5.29	66	−28	28
	R	39	Middle Temporal Gyrus		0.024	4.56	56	−64	18
PTSD > Ctrl LVN	R	39	Angular Gyrus	175	0.048	4.38	56	−62	28
PTSD > Ctrl RVN	R	40	Supramarginal Gyrus	187	0.004	4.96	66	−28	30
PTSD + DS > PTSD LVN			None						
PTSD + DS > PTSD RVN			None						
PTSD + DS > Ctrl LVN			None						
PTSD + DS > Ctrl RVN			None						
Ctrl > PTSD LVN	L	22	Middle Temporal Gyrus	81	0.014	4.68	−68	−22	−4
Ctrl > PTSD RVN	L	41	*ROI Analysis** Posterior Insula	51	0.02	3.04	−52	−12	10
Ctrl > PTSD + DS LVN	L	40	Supramarginal Gyrus	330	0.006	4.87	−52	−26	42
	L	6	Precentral Gyrus	964	0.008	4.81	−26	−20	74
	L	6	Middle Frontal Gyrus		0.014	4.69	−34	8	62
	L	21	Middle Temporal Gyrus	92	0.016	4.65	−68	−34	−8
	L	5	Precuneus	252	0.023	4.56	−2	−36	56
Ctrl > PTSD + DS RVN	L	5	Precuneus	3612	0.023	4.57	−4	−36	−56

Post-hoc two-sample *t*-tests based on full-factorial analysis (reported at family-wise error whole-brain voxel-corrected at $p < .05$, $k = 10$). Pea*k* coordinates without *k* (cluster size) values listed are subpeaks of the nearest *k* value listed above. *ROI analysis is adjusted for multiple comparisons and is reported at vFWE $p \leq 0.025$, $k = 10$.
Abbreviations: PTSD posttraumatic stress disorder; PTSD + DS, posttraumatic stress disorder with the dissociative subtype; Ctrl, healthy controls; LVN, left vestibular nuclei; RVN, right vestibular nuclei; L, left hemisphere; R, right hemisphere; BA, Brodmann Area; *k*, Cluster Size; vFWE, family-wise error voxel-corrected.

gravitational field. Moreover, given the role of the vestibular system in integrating proprioceptive input based on both interoceptive and exteroceptive multisensory information to inform bodily experience, we predicted that PTSD and its dissociative subtype would display unique sensory processing patterns based on their distinctive symptom profiles. On balance, this proved the case. Specifically, as compared to PTSD patients with the dissociative subtype, PTSD patients without the dissociative subtype and healthy controls demonstrated increased functional connectivity with key vestibular cortical brain regions identified in previous literature [parieto-insular vestibular cortex (PIVC) and dorsolateral prefrontal cortex]. Interestingly, whereas controls demonstrated increased vestibular nuclei connectivity with the posterior insula as compared to PTSD, the PTSD group demonstrated greater connectivity with the right temporoparietal junction as compared to both controls and PTSD + DS. These findings suggest PTSD patients may display differing multisensory integration patterns that influence uniquely vestibular function in PTSD based on the presence of the dissociative subtype during resting-state. We discuss these findings in turn.

Table 3
LVN versus RVN Functional Connectivity Within Participant Group.

Contrast	LR	BA	Region	k	pFWE	Z	MNI Coordinates		
							x	y	z
PTSD LVN > RVN			None						
PTSD RVN > LVN			None						
PTSD + DS LVN > RVN			None						
PTSD + DS RVN > LVN	R	10	Superior Frontal Gyrus	249	0.001	5.30	30	66	0
	R	38	Superior Temporal Pole	87	0.016	4.58	34	16	−30
	L	21	Middle Temporal Gyrus	194	0.027	4.44	−58	−30	−18
	L	8	Middle Frontal Gyrus	249	0.032	4.40	−38	16	58
	L	44	Inferior Frontal Triangularis		0.042	4.33	−56	24	26
	L	10	Frontal Gyrus	37	0.046	4.31	−12	68	6
Ctrl LVN > RVN			None						
Ctrl RVN > LVN			None						

Post-hoc two-sample *t*-tests based on full-factorial analysis (reported at family-wise error whole-brain voxel-corrected at $p < .05$, $k = 10$). Pea*k* coordinates without *k* (cluster size) values listed are subpeaks of the nearest *k* value listed above.
Abbreviations: PTSD, posttraumatic stress disorder; PTSD + DS, posttraumatic stress disorder with the dissociative subtype; Ctrl, healthy controls; LVN, left vestibular nuclei; RVN, right vestibular nuclei; L, left emisphere; R, right hemisphere; BA, Brodmann Area; *k*, Cluster Size; vFWE, family-wise error voxel-corrected.

5.1. Vestibular nuclei-parieto-insular vestibular cortex connectivity

5.1.1. Posterior insula

Both groups of PTSD patients, as well as healthy individuals, demonstrated bilateral vestibular nuclei functional connectivity with the left posterior insula; however, only PTSD patients without the dissociative subtype and healthy controls showed bilateral functional connectivity with the right posterior insula. Moreover, the control group showed increased RVN connectivity with the posterior insula as compared to the PTSD group. Here, the posterior insula is critical to one's interoceptive awareness as multimodal sensory integration of afferent stimuli is essential for physiological homeostasis to maintain one's affective state in response to external environmental cues and sensory-evoked emotions (Baier et al., 2013; Craig, 2003; Critchley et al., 2004; Flynn, 1999; Wager and Barrett, 2004). Direct brainstem vestibular nuclei connectivity with the posterior insula observed in PTSD and healthy controls reflects this, as sensory processing can subconsciously integrate both exteroceptive and interoceptive information to maintain physiological homeostasis. However, decreased RVN connectivity with the left posterior insula observed in PTSD as compared to the healthy controls may suggest deficient sensory integration of exteroceptive and interoceptive cues, as exteroceptive information relayed from the vestibular nuclei to the posterior insula may be subject to the influence of additional neural networks involving the posterior insula in relation to PTSD symptomatology. Interestingly, Nicholson et al. (2016) observed increased posterior insula connectivity with the basolateral amygdala in PTSD patients during rest and postulated its association with increased sensory processing during hyperarousal and hypervigilant symptoms, which exist irrespective of the presence of a threat, and would thus be detectable during resting-state (Kimble et al., 2014). Aberrant sensory integration in the PTSD group can trigger physiological dysregulation, which may contribute to increased sympathetic tone observed in PTSD patients as well as alter a patient's ability to appraise threat (Lipov and Kelzenberg, 2012; Révész et al., 2014; Sbarra and Hazan, 2008; Tsigos and Chrousos, 1994).

PTSD + DS did not demonstrate vestibular nuclei functional connectivity with the right posterior insula, perhaps suggesting weakened interoceptive awareness in these patients as well, given that additional depersonalization symptoms render one more prone to experience emotional detachment and to developing an altered sense of bodily self-consciousness that can alter the ability to navigate the physical world and integrate sensory stimuli (Frewen et al., 2008; Heydrich and Blanke, 2013; Lanius et al., 2010; Lopez, 2013). Interestingly, state depersonalization/derealization symptoms (RSDI) were elevated during the resting state scan in PTSD + DS as compared to PTSD. It is therefore possible that the emotional detachment these individuals experience may re-direct or stagnate overwhelming sensory/emotional input associated with their interpretation of surroundings, thus obstructing the vestibular nuclei connectivity with the posterior insula (Frewen and Lanius, 2006).

5.1.2. Supramarginal gyrus

The temporoparietal junction, which encompasses the supramarginal gyrus, is critical for multisensory processing; specifically, the right temporoparietal junction is thought to be critical for discriminating between one's self versus non-self, thereby contributing to feelings of body ownership (Blanke and Arzy, 2005; Igelström et al., 2015; Tsakiris et al., 2008). Both PTSD and healthy controls demonstrated vestibular nuclei functional connectivity with the supramarginal gyrus as compared to PTSD + DS, which did not demonstrate any connectivity.

Given the role of the supramarginal gyrus in integrating multisensory information in terms of bodily orientation, brainstem vestibular nuclei functional connectivity with the supramarginal gyrus observed in healthy individuals aligns with the observation that they are less susceptible than patients with PTSD with the dissociative subtype to feelings of disembodiment and are thus better able to maintain adequate integration of tactile and proprioceptive external cues, a pattern similar to that observed in PTSD patients without the dissociative subtype (Blanke, 2012; Lopez, 2016; Lopez et al., 2008; Vieweg et al., 2006). Interestingly, the PTSD group demonstrated increased vestibular nuclei functional connectivity with the right supramarginal gyrus as well as the right angular gyrus, also part of the temporoparietal junction, as compared to healthy individuals and PTSD + DS. Recruitment of additional areas of the right temporoparietal junction may reflect a greater effort required for PTSD patients to process tactile and proprioceptive sensory information pertaining to external cues because of their hypervigilance symptoms, which may heighten one's concern for knowledge of his/her own position in gravitational space to fulfill the need to consistently evaluate one's own safety in relation to his/her environment (Engel-Yeger et al., 2013; McFarlane et al., 1993; Porges, 2011). In contrast, the depersonalization/derealization symptom profile observed in PTSD + DS may be responsible for altered processing of tactile and proprioceptive sensory information, as deficient functional connectivity between the vestibular nuclei and the supramarginal gyrus can compromise proper assessment of one's own bodily orientation in space. This may also contribute to elevated RSDI -depersonalization/derealization symptoms observed during the resting-state scan in PTSD + DS patients, as compared to PTSD and controls (Blanke, 2012; Serino et al., 2013), where previous studies have also linked altered right supramarginal gyrus function to provocation of out-of-body experiences, which may be related to depersonalization experiences in the dissociative subtype of PTSD (Blanke et al., 2002; Lopez et al., 2008; Lopez, 2013; De Ridder et al., 2007). Additional clinical resting-state measures also revealed significantly higher state anxiety clinical measures in PTSD + DS as compared to healthy controls during the resting-state scan, which itself has been suggested to intensify depersonalization/derealization symptoms in those with vestibular dysfunction (Kolev et al., 2014). Future research is warranted to principally investigate the role of anxiety on vestibular function and its relation to symptoms of depersonalization/derealization.

5.2. Vestibular nuclei-dorsolateral prefrontal cortex functional connectivity

PTSD and healthy individuals demonstrated significant functional connectivity with the prefrontal cortex, particularly with the dorsolateral prefrontal cortex (BA 8, 9, 46). De Waele et al. (2001) suggested that vestibular nerve stimulation leads to egomotion processing at the level of the prefrontal cortex thus facilitating planning for motor responses in response to disruptions in balance (both voluntary and involuntary) and contributing to knowledge of one's own physical equilibrium. Here, PTSD seed-based functional connectivity correlations also revealed that increased CAPS-IV scores negatively correlated with prefrontal cortex functional connectivity, as increased PTSD symptom severity may compromise one's ability to properly integrate exteroceptive and interoceptive information relating one's own position in gravitational space (see Fig. 3). Critically, within group, PTSD + DS did not demonstrate connectivity with *any* area of the prefrontal cortex, and PTSD demonstrated greater LVN connectivity with the dorsolateral prefrontal cortex (BA 9) as compared to PTSD + DS. Symptoms of disembodiment and vestibular dysfunction may therefore hinder the ability to conduct ego-motion processing and may contribute to gait unsteadiness reported previously in dissociative conversion disorders (Holmes et al., 2005; Janet, 1907). Interestingly, Janet (1889) proposed that following intense trauma, psychological disorganization ("*déagréation psychologique*") can lead to altered states of consciousness that manifest as somatic symptoms (Gottlieb, 2003; Janet, 1889), which may not be limited to feelings of disembodiment as have been discussed in relation to altered states of consciousness associated with PTSD (Frewen and Lanius, 2015).

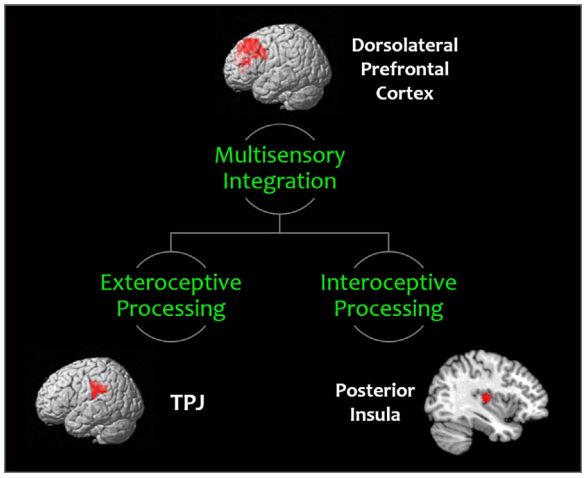

Fig. 3. Multisensory Integration. Multisensory integration is dependent upon exteroceptive and interoceptive processing, where vestibular multisensory input pertaining to one's awareness in gravitational space requires an understanding of both the physical and mental self in order to navigate through the physical world with appropriate context of one's surroundings. Here, as compared to healthy controls, PTSD patients with and without the dissociative subtype display unique sensory processing patterns based on their distinctive symptom profiles. Decreased vestibular nuclei connectivity with the posterior insula in PTSD patients as compared to healthy controls points towards a weakened interoceptive awareness, where a limited understanding of one's own internal affective state can alter one's interpretation of the context of his/her surroundings and may cause physiological dysregulation. This pattern aligns with the hypervigilance and hyperarousal symptoms observed in PTSD patients. Moreover, PTSD patients with the dissociative subtype show no vestibular nuclei connectivity with the temporoparietal junction, which may limit exteroceptive processing, as depersonalization/derealization symptoms appear to alter one's bodily self-consciousness and compromise proper assessment of one's own bodily orientation in space. Overall, these factors weaken multisensory integration at the level of the prefrontal cortex, where symptom severity in PTSD patients correlates negatively with dorsolateral prefrontal cortex connectivity. Increased PTSD symptom severity may compromise one's ability to integrate exteroceptive and interoceptive information relating to one's own position in gravitational space, and can ultimately facilitate disengagement from one's own environment.

5.3. Limitations and future directions

Several limitations of this study need to be considered. First, previous studies have reported gender-related differences during resting state in healthy individuals (Gur et al., 1995; Tian et al., 2011), but see also (Damoiseaux et al., 2006; Weissman-Fogel et al., 2010). Future studies should therefore explore the gender-specific neural circuitry of the vestibular system in relation to trauma. Secondly, although the data has been corrected for general effects of heart rate through filtering grey matter frequencies, this may not fully account for the physiological influence on the BOLD signal [e.g., EEG, COMPCOR (Behzadi et al., 2007), RETROICOR (Glover et al., 2000)]. Future studies investigating the brainstem should therefore explore optimal methods of correcting for physiological noise as the brainstem is comprised of a unique grey and white matter distribution. Thirdly, this study was only powered to examine brainstem vestibular nuclei functional connections with the whole brain; however, further investigation of the influence of the parieto-insular vestibular cortex on its neural correlates and vice-versa, is required to eventually assist in delineating the neural circuitry underlying the vestibular system in PTSD using dynamic causal modelling. In addition, we intend to further explore the effect of task-based fMRI paradigms on the vestibular network in post-traumatic stress disorder to delineate how conscious multisensory information processing affects vestibular function. Moreover, future research is warranted to explore other aspects of the vestibular system, such as the vestibular link with anxiety symptoms, and its role in autonomic regulation addressed in previous studies (Balaban, 1999; Biaggioni et al., 1998). Finally, the present study did not identify a right-dominant hemispheric laterality component to the vestibular system as described in previous studies (Bottini et al., 2001; Fasold et al., 2002). Future studies should therefore investigate whether this absence of laterality is more pronounced in PTSD patients, or, alternatively, whether hemispheric laterality is greater under experimental conditions as compared to resting-state conditions.

6. Conclusions

On balance, the current findings lay the groundwork for future studies examining the vestibular system in PTSD and its dissociative subtype, where alterations in one's interoceptive awareness and sense of bodily orientation can compromise multisensory integration of vestibular signals critical for understanding one's relationship with his/her surroundings. Moreover, PTSD symptom severity negatively correlated with prefrontal cortex functional connectivity, as well as between clinical dissociative measures and the right supramarginal gyrus connectivity. Taken together, these findings suggest altered multisensory integration patterns in PTSD patients may distort the intricate relationship between one's surroundings, interoceptive awareness and bodily self-consciousness. This disruption may, in turn, compromise vestibular function and contribute to the neurophenomenology of the unique symptom profiles observed in PTSD and its dissociative subtype. Decreased vestibular functional connectivity with the posterior insula in PTSD patients as compared to healthy individuals suggest a weakened interoceptive awareness, which may impair one's attunement with his/her surroundings and promote hypervigilance symptoms to consistently evaluate one's own safety in his/her environment. Moreover, limited vestibular functional connectivity with key vestibular cortical regions (parieto-insular vestibular cortex, dorsolateral prefrontal cortex) in the PTSD dissociative subtype as compared to PTSD and healthy controls suggests that depersonalization/derealization and emotional numbing symptoms may further intensify vestibular dysfunction. This dysfunction may, in turn, hinder one's cognitive capability to integrate multisensory information and, ultimately, facilitate disengagement from one's environment. Hence, there is an urgent need to study the neural circuitry of the vestibular system in PTSD patients, an effort that may be critical not only to further delineating the neural underpinnings of PTSD symptomatology but to identifying psychotherapeutic interventions that target symptoms of interoceptive awareness and disembodiment related to vestibular dysfunction.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.09.010.

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