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Characterising intra- and inter-intrinsic network synchrony in combat-related post-traumatic stress disorder

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ABSTRACT

Soldiers with post-traumatic stress disorder (PTSD) exhibit elevated gamma-band synchrony in left fronto-temporal cortex, and connectivity measures in these regions correlate with comorbidities and PTSD severity, which suggests *increased* gamma synchrony is related to symptomology. However, little is known about the role of intrinsic, phase-synchronised networks in the disorder. Using magnetoencephalography (MEG), we characterised spectral connectivity in the default-mode, salience, visual, and attention networks during resting-state in a PTSD population and a trauma-exposed control group. Intrinsic network connectivity was examined in canonical frequency bands. We observed *increased* inter-network synchronisation in the PTSD group compared with controls in the gamma (30–80 Hz) and high-gamma range (80–150 Hz). Analyses of connectivity and symptomology revealed that PTSD severity was positively associated with beta synchrony in the ventral-attention-to-salience networks, and gamma synchrony within the salience network, but also *negatively* correlated with beta synchrony within the visual network. These novel results show that frequency-specific, network-level atypicalities may reflect trauma-related alterations of ongoing functional connectivity, and correlations of beta synchrony in attentional-to-salience and visual networks with PTSD severity suggest complicated network interactions mediate symptoms. These results contribute to accumulating evidence that PTSD is a complicated network-based disorder expressed as altered neural interactions.

1. Introduction

Post-traumatic stress disorder (PTSD) is characterised by anxious and depressive symptoms that can develop after a traumatic episode, with emergent behavioural phenotypes that include re-experiencing, avoidance, emotional numbing, and hyperarousal (APA, 2013). The incidence of PTSD in the general population is thought to be around 5–10% (Kessler et al., 2005), although it is much higher in military populations returning from recent combat deployments (Richardson et al., 2011). Early imaging studies examined structural and functional segregation of brain regions and the contribution of individual areas to symptoms and cognitive deficits (Hull, 2002), but emerging evidence suggests that the disorder is one of atypical neuronal network communication, particularly that of disordered fronto–limbic interactions (Bremner et al., 2003; Shin et al., 2005; Etkin and Wager, 2007; Gold et al., 2011); there has been a gradual paradigm shift to thinking of the disorder as one of abnormal *integration*. Recent research supports this view and connectivity studies have shown that atypical synchronous network interactions characterise the disorder, in both task-free resting-state, and task-dependant, cognitive-behavioural paradigms (Dunkley et al., 2014, 2015).

Recent developments in the understanding of large-scale, resting-state networks and the brain's ongoing intrinsic functional connectivity within and amongst regions have led to numerous hypotheses regarding the significance of these circuits. Known as intrinsic connectivity networks (ICNs), several have been identified which are thought to be critical for perception and cognition (de Pasquale et al., 2012), and by extension, mental health and wellbeing (Menon, 2011). These include, but are not limited to, the default-mode network (DMN), ventral attention (VAN) and dorsal

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attention networks (DAN), the visual network (VIS), and the salience network (SAL). Regarding these ICNs, inter- and intra-network connectivity is flexible, and modified with current goal-directed behaviour and task demands, with each network contributing to the spatiotemporal organisation of information. The DMN is posited to be the cortical centre-piece of dynamic network integration (de Pasquale et al., 2012), as well as being implicated in self-referential thought and introspection (Buckner et al., 2008). Conversely, the putative DAN, VAN and SAL are *task-positive* networks, and these systems exhibit inverse activation patterns compared to the DMN and are involved in executive functions and attentional control (de Pasquale et al., 2012). The SAL network is implicated in goal-direction action and maintenance of the internal cognitive state and salience detection (Sridharan et al., 2008). The VIS network is heavily involved in visual processing (Laird et al., 2011), perhaps the most computationally-demanding of the perceptual modalities.

Alterations to the ongoing spatiotemporal interactions of ICN interplay have been found in PTSD (Hayes et al., 2012; Sripada et al., 2012; Tursich et al., 2015), but these findings have been limited to the domain of fMRI, which can only capture ultra-slow cortical dynamics. Little is known about the alterations to oscillations and synchrony in these networks at behaviourally-relevant time-scales, to which fMRI is blind (Hari and Salmelin, 2012). In particular, magnetoencephalography (MEG) has proven invaluable in this regard, and is sensitive to neurophysiological interactions which correspond to ICNs classically identified using MRI (Brookes et al., 2011), and can elucidate their frequency composition and dynamics (de Pasquale et al., 2012; Baker et al., 2014). Importantly, cortical oscillations and synchronisation are now known to subserve a variety of neurophysiological disorders, and characterising them provides new understanding of psychopathology (Tewarie et al., 2013), with studies of gamma abnormalities in autism (Wilson et al., 2007; Rojas et al. 2011, Ye et al., 2014), psychosis (Wilson et al., 2008; Ramyead et al., 2015), and schizophrenia (Light et al., 2006; Teale et al., 2008), as well as alpha and gamma aberrations in PTSD (Dunkley et al., 2014; Badura-Brack et al., 2015) and beta abnormalities in Parkinson's (Oswal et al., 2012; Heinrichs-Graham et al., 2014a, 2014b). Critically, MEG allows neuronal activity to be mapped with millisecond temporal resolution, elucidating functional brain changes on excellent time scales, as well as providing accurate localisation of activation.

In PTSD studies, MEG has revealed abnormal local changes in neuronal function, including source amplitude, as well as atypical interactions among brain areas (Kolassa et al., 2007; Engdahl et al., 2010; Georgopoulos et al., 2010; Huang et al., 2014), and others have shown that pattern classification can differentiate those with the disorder from control groups (James et al., 2013). This evidence suggests brain oscillations contribute to symptoms of the disorder, and recently large-scale neuronal synchronisation in PTSD was found to be particularly informative. For example, the strength of ongoing high-frequency gamma synchrony in the left hippocampus, a brain region heavily implicated in episodic memory, was found to explain a significant degree of inter-subject variance in symptom severity (Dunkley et al., 2014), and was hypothesised to be related to the positive, clinical symptoms of the disorder, including the re-experiencing of traumatic episodic events and hyperarousal. In this previous study, we took an atlas-guided ROI approach to characterise these metrics and examined how *individual* regions and connections were atypical in their graph properties; in the present paper, we investigated how atypicalities in whole network-level connectomics are expressed in the disorder, and whether the connectivity between these intrinsic networks explains variability in severity of the primary and secondary symptoms of PTSD.

To investigate the role of neurophysiological interactions within and between ICNs in combat-related PTSD, we characterised frequency-specific inter-regional phase synchrony interactions in *a priori* defined ICNs, as well as determining how network-level interactions across various frequency-ranges differentiates soldiers with PTSD from trauma-exposed control soldiers. Moreover, we examined how these interactions are modulated by exposure to stressful, affective stimuli with a view to further elucidating the role of triggering images on brain dynamics, and if this can inform the ongoing connectivity in trauma-exposed control soldiers (Dunkley et al., 2014). Finally, we explored whether these interactions were associated with primary (PTSD severity) and secondary (anxiety and depression) symptoms. We predicted that veterans with PTSD would express atypical ICN synchrony, and that neurophysiological network connectivity would be associated with the severity of primary and secondary symptoms.

2. Materials and methods

2.1. Participants

MEG data were recorded from 48 Canadian Armed Forces (CAF) soldiers, who deployed in support of the Afghan mission. Of these, 21 were subsequently diagnosed with PTSD (all male, mean age = 37.10, SD = 7.06, age range 26–48), and 27 soldiers (all male, mean age = 34.00, SD = 5.27, age range 27–45) who did not develop PTSD were recruited as a trauma-exposed, matched control group. There was a small difference in age between the groups $t(46) = 2.13$, $p < 0.05$. The participants imaged here were a partial sample of those reported our previous resting-state paradigm (Dunkley et al., 2014).

PTSD group inclusion criteria were: a clinical diagnosis of combat-related PTSD from an operational trauma stress support centre (OTSSC); PTSD symptoms were present for at least 1 years, and less than 4 years prior to participation in the study; they were engaged in regular mental health follow-up; they had moderate or greater severity on the PTSD check list (Post Traumatic Stress Disorder Check List; PCL > 50). The diagnosis was determined by a psychiatrist or psychologist specializing in trauma-related mental health injuries and conducted through a comprehensive, semi-structured interview based upon DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2010), along with CAF standardized psychometric testing. All participants in the PTSD group were recruited from one of the CAF OTSSCs, which are centres of excellence for the diagnosis and treatment of trauma-related mental health injuries. There was usually more than one DSM-IV-TR 'A1' stressor-related criteria (American Psychiatric Association, 2010) identified as a traumatic event contributing to the development of PTSD (direct personal experience of an event that involves actual or threatened death or injury), with diagnosis related to operational exposure. Co-morbid diagnosis in these participants included depression (69.5%), substance-abuse (27.3%), and other anxiety disorders (18.2%). Control soldiers were matched on rank, education level, handedness and military experience, and were screened to exclude PTSD.

Additional inclusion criteria applied to both groups were: no history of a traumatic brain injury (TBI), screened by a psychiatrist through a review of their electronic health record, telephone interview, and administration of the Defence and Veteran's Brain Injury Centre (DVBIC) 3 item screening tool; English-speaking and able to understand task instructions and give informed consent. Exclusion criteria for both groups were: ferrous metal inside the body that might be classified as MRI contraindications or that might interfere with MEG data acquisition; presence of implanted medical devices; seizures or other neurological disorders, or active substance abuse; certain ongoing medications (anticonvulsants,

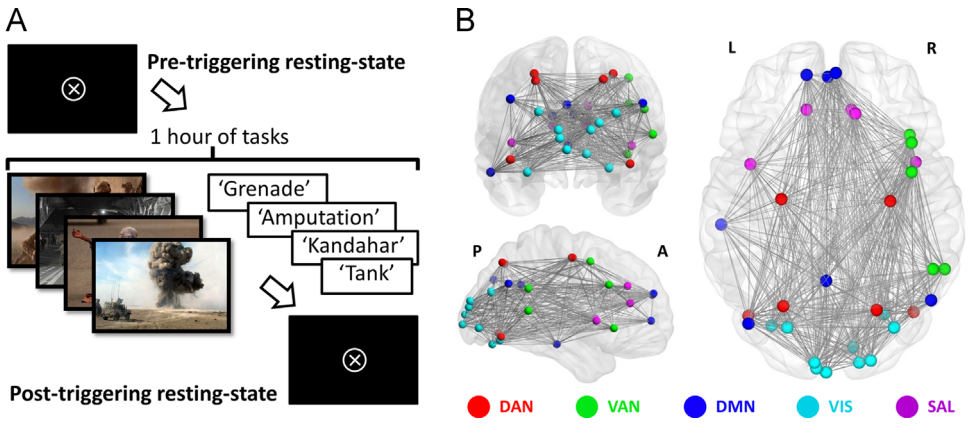

Fig. 1. Experimental schematic and intrinsic network seed locations. (A) Resting-state was acquired before participants completed a number of cognitive tasks that contained triggering images and words interspersed with neutral images and words. These examples are from a working memory paradigm (images) and an attentional blink (words) task. (B) Node locations that comprise the intrinsic networks are based on *a priori* seed coordinates.

benzodiazepines, and/or GABA antagonists) known to influence electroencephalographic (EEG) findings. As this was a naturalistic sample, however, PTSD patients were on evidenced-based psychotropic medication(s), such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and Prazosin.

All participants completed brief cognitive-behavioural testing in additional to the MEG resting-state scan. These assessments included the Generalised Anxiety Disorder 7 test (GAD-7); Patient Health Questionnaire (PHQ9); and the PCL (PTSD group only).

2.2. Procedure and MEG data acquisition

Resting-state MEG data were collected in two separate runs (Fig. 1A). Participants were supine and instructed to rest with eyes open and maintain visual fixation on an X within a circle on the screen whilst maintaining a state of relaxed wakefulness. Following the first resting-state run, known as the 'Pre-triggering resting-state', participants completed a number of cognitive protocols, with a working memory and delayed recognition paradigm containing trigger images (Dunkley et al. 2015), such as scenes of traumatic events (e.g. battlefield casualties) intermixed with neutral images, an emotional faces task (Dunkley et al., 2015), and a verbal task that contained neutral as well as salient trigger words (such as 'Kandahar', 'grenade', etc.) (Todd et al., 2015). They then completed a second resting-state run, known as the 'Post-triggering resting-state'. The emotionally-salient, affective stimuli were predicted to induce increased arousal and attention, and differentially impact connectivity patterns in the PTSD group compared to the controls.

MEG data were collected inside a magnetically-shielded room on a CTF Omega 151 channel system (CTF Systems, Inc., Coquitlam, Canada) at The Hospital for Sick Children, at 600 Hz for 300 s per resting-state run. Throughout each run, head position was continuously recorded by three fiducial coils placed on the nasion, and left and right pre-auricular points. After the MEG session, anatomical MRI images were acquired using a 3T MRI Research scanner (Magnetom Tim Trio, Siemens AG, Erlangen, Germany) also at the Hospital for Sick Children, Toronto. Structural data were obtained as T1-weighted magnetic resonance images using resolution 3D MPRAGE sequences (repetition time [TR]=2300 ms; echo time [TE]=2.9 ms; flip angle [FA]=9°; Field-of-view [FOV]=28.8 × 19.2 cm; 256 × 256 matrix; 192 slices; 1 mm isovoxel) on a 12-channel head coil. MEG data were coregistered to the MRI structural images using the reference fiducial coil placements. A multi-sphere head model was constructed for each individual and their brain space was normalised to a standard Montreal Neurological Institute (MNI) brain using SPM2.

2.3. MEG data processing

2.3.1. Seed definition and virtual electrode recording

MEG data were band-pass filtered offline at 1–150 Hz, a notch filter applied at the 60 Hz powerline frequency (with 8 Hz bandwidth), and a third-order spatial gradient environmental noise-cancellation applied was to the recording. *A priori* sources (seeds) of interest in cortical and sub-cortical regions were identified using coordinates from de Pasquale et al (2012), (VAN, DAN, DMN, and VIS networks), and Brier et al. (2012) (SAL network). Fig. 1B shows the node locations, and region names and coordinates are listed in Table 1.

Time-series data were reconstructed from these seed locations using a vector beamformer for each subject and filtered into five canonical bandwidths for further analysis: Theta (4–7 Hz), Alpha (8–14 Hz), Beta (15–30 Hz), Gamma (30–80 Hz) and High-Gamma (80–150 Hz). The beamformer used here is a type of spatial filter used to suppress signals from unwanted noise sources, whilst being optimally sensitive to activity in a given brain location (in this particular case, the defined seed locations). Individual weight vectors are applied to each sensor measurement and summated to give estimated source activity to a particular cortical seed location, as used in prior work from our group (Leung et al., 2014; Schäfer et al., 2014; Ye et al., 2014; Dunkley et al., 2015). This type of spatial filter is also effective at suppressing ocular artefacts generated by eye movements, and non-ocular artefacts, such as cardiac and muscle activity (Muthukumaraswamy, 2013).

2.4. Assessing functional connectivity: weighted phase lag index

Each of the 5 band-pass filtered waveforms was then submitted to a functional connectivity analysis, using the *weighted phase lag index* (WPLI; Vinck et al. (2011)). The instantaneous phase of each sample from the filtered time-series was calculated using the Hilbert transform. The degree of phase synchronization between all pairwise combinations of the seeds was computed using the WPLI, which is based on the magnitude of the imaginary component of the cross-spectrum (Lau et al., 2012). Ranging between 0 and 1, these values quantify the phase synchrony between two cortical/sub-cortical sources, referred to as functional connectivity.

2.5. Statistical analysis

Adjacency matrices with WPLI values acting as edge weights for all sources pairs were constructed, which resulted in a matrix of weighted undirected graphs in each analysed frequency band for each participant. Connectivity weights between seeds that

Table 1
Definition of intrinsic networks by node location and MNI coordinates.

Network	Area	X	Y	Z
DAN	LpIPS	−25	−67	48
	RpIPS	23	−69	49
	LFEF	−26	−12	53
	RFEF	30	−13	53
	LMT	−43	−72	−8
	RMT	42	−70	−11
VAN	RMFG	41	17	31
	RPCS	41	2	50
	RSMG	52	−48	28
	RSTG	58	−48	10
	RVFC	40	21	−4
DMN	LAG	−43	−76	35
	RAG	51	−64	32
	PCC	−3	−54	31
	vMPFC	−2	51	2
	dMPFC	−13	52	23
	RMPFC	2	53	24
	LITG	−57	−25	−17
VIS	LV1	−3	−101	−1
	RV1	11	−88	−4
	LV2d	−8	−99	7
	RV2d	14	−96	13
	LV3	−9	−96	13
	RV3	20	−95	18
	LV4	−31	−77	−17
	RV4	27	−71	−14
	LV7	−23	−78	26
	RV7	32	−78	25
SAL	rPGACC	12	32	30
	lPGACC	−13	34	16
	rSGACC	10	34	16
	Lins	−42	6	4
	Rins	43	7	2

DAN – Dorsal attention network, VAN – Ventral attention network, DMN – Default mode network, VIS – Visual network and SAL – Salience network.

comprised *within* or *between* intrinsic networks were averaged to characterise the magnitude of spontaneous intra-and inter network synchronisation. These adjacency matrices were then divided into the respective groups and inferential statistics investigating group differences for mean edge weights were implemented using non-parametric permutation testing, which do not require the data distributions to be normal. False positives due to multiple comparisons were controlled for using Bonferroni-correction within frequency-bands given assumed independent mechanistic roles of these rhythmic interactions (uncorrected – $p=0.034$ is equivalent to adjusted/corrected – $p=0.05$). Cognitive-behavioural correlation analyses were conducted using MATLAB Statistics Toolbox (The Mathworks, Inc.).

3. Results

3.1. Cognitive-behavioural outcomes

Measures for the cognitive-behavioural test outcomes for soldiers with and without PTSD are presented in Table 2. Soldiers with PTSD exhibited increased incidence of comorbid anxiety and depression.

3.2. Pre- and post-triggering intra- and inter-ICN communication

Between-groups contrasts of intrinsic network connectivity in the pre-triggering resting-state revealed significant differences in gamma (30–80 Hz) synchrony (Fig. 2), with hyperconnectivity characterising the PTSD group as increased inter-network interactions in the DMN-VAN, and DMN-SAL networks ($^{**}p<0.05$ corrected). High-gamma (80–150 Hz) synchrony was also found to be significantly different in PTSD ($^{**}p<0.05$ corrected), with inter-network interactions between the DMN-VIS networks. A trend for increased intra-DMN connectivity was also found ($^{*}p<0.01$ uncorrected). Finally, a trend was also found in the alpha band for intra-network synchrony in the VIS-SAL network synchrony for the PTSD group ($^{*}p<0.01$ uncorrected).

Following provocation and exposure to triggering images, the majority of these networks differences were attenuated and significant effects were no longer observed in these ICNs between soldiers with PTSD and matched controls. However, triggering altered DMN-DAN connectivity in the gamma range, and found to be significantly higher in the PTSD group ($^{**}p<0.05$ corrected).

Table 2
Cognitive-behavioural assessment measures for PTSD and Control participants.

	PTSD	Control	Test statistic
n	21	27	
GAD7	15.67 (5.00)	2.25 (2.29)	$t=12.57$, $df=47$, $p<0.001$
PHQ9	17.09 (5.29)	2.18 (2.48)	$t=13.15$, $df=47$, $p<0.001$
PCL	64.38 (7.73)	NA	

GAD7 – Generalised Anxiety Disorder 7; PHQ9 – Patient Health Questionnaire; PCL – Posttraumatic Stress Disorder Check List.

3.3. Spontaneous inter-ICN visual alpha synchrony correlates with comorbid anxiety and depression

Combined-group correlations were performed to investigate network-level connectivity with associated comorbidities in the sample of all soldiers. We combined both groups and then ran correlational analyses across each network edge (either the *within* or *between* mean edge weight), with post-hoc Bonferroni correction for multiple comparisons. Associations of clinical scores with connectivity are summarised in Fig. 3, where all significant correlations were observed in the alpha band, with a negative relation to comorbid symptoms. Specifically, we found that resting alpha synchrony in the VIS-VAN was negatively associated with anxiety (Fig. 3A; rho$=-0.43$, $^{**}p<0.05$ corrected), while VIS-VAN (rho$=-0.48$, $^{**}p<0.05$ corrected), VIS-DMN (rho$=-0.43$, $^{**}p<0.05$ corrected), and VIS-SAL (rho$=-0.45$, $^{**}p<0.05$ corrected) alpha synchrony were found to be negatively correlated with depression (Fig. 3B).

3.4. Spontaneous beta and gamma synchrony correlates with PTSD symptom severity

Finally, we employed a single-group (PTSD) correlational approach to characterise the relation between ICN inter- and intra-communication, and PCL scores (PTSD symptom severity). Fig. 4A highlights the findings, with a strong, significant positive correlation being observed in the beta-band VAN-SAL network connectivity (rho$=0.71$, $^{**}p<0.05$ corrected). High correlations approaching significance were also observed for the within VIS network resting connectivity (rho$=-0.58$, $^{*}p<0.01$ uncorrected), and in the gamma range for the within SAL network synchrony (rho$=0.56$, $^{*}p<0.01$ uncorrected). The relation between ongoing resting synchrony within and between these networks, and the PCL outcome scores are schematically represented in Fig. 4B.

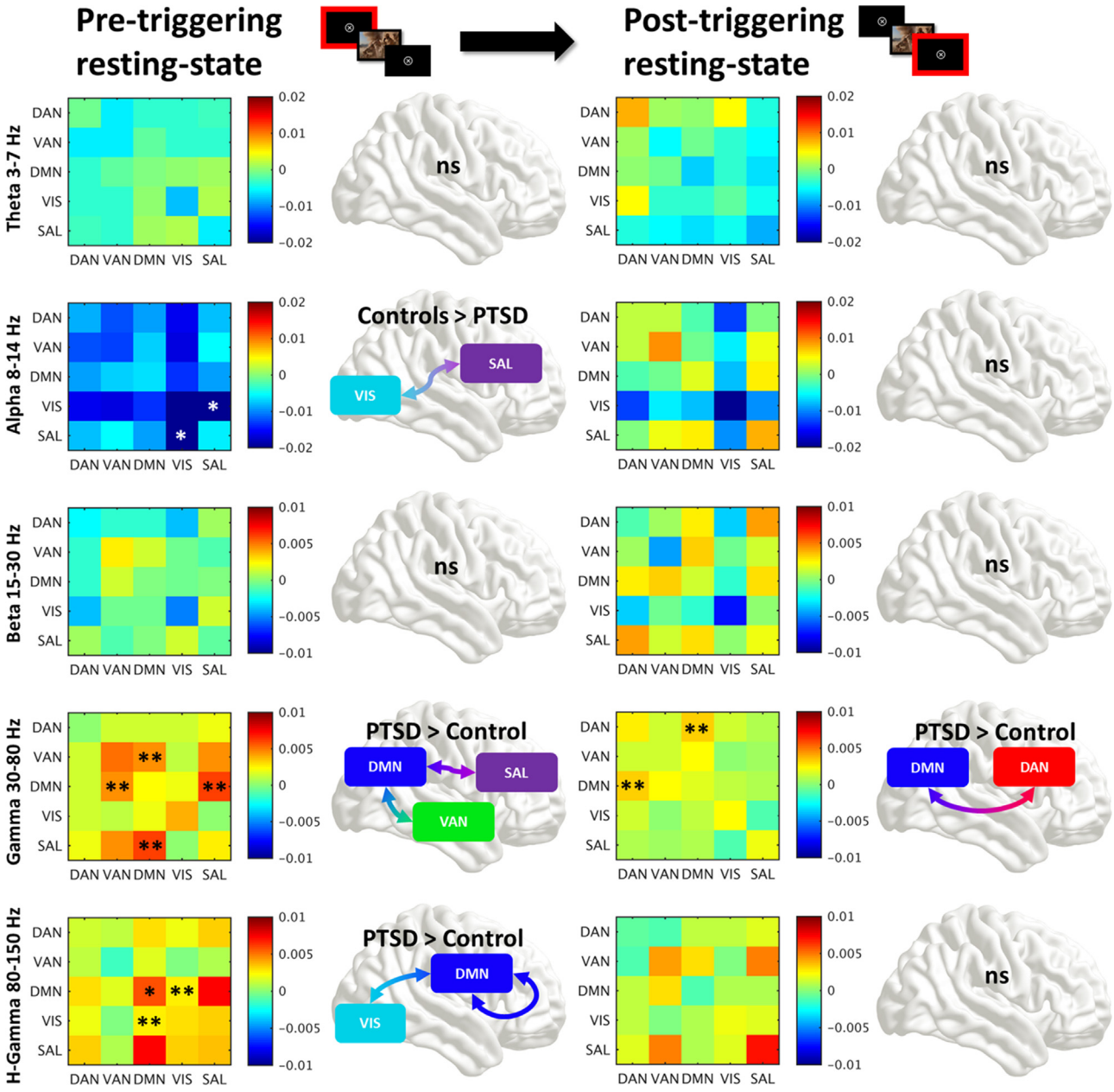

Fig. 2. Frequency-specific intra- and inter-network communication in the pre-triggering and post-triggering resting-state for PTSD minus control soldiers. Warm colours indicate increased connectivity in the PTSD cohort, whilst cool colours indicate decreased connectivity. $^{*}p < 0.01$ uncorrected, $^{**}p < 0.05$ corrected.

4. Discussion

This is the first study, to our knowledge, to examine neurophysiological synchrony in Intrinsic Connectivity Networks (ICNs) in PTSD. We investigated frequency-specific interactions in functional ICNs in soldiers with combat-related PTSD and a matched combat-experienced-exposed control group. First, we found that the PTSD group exhibited elevated high-frequency (gamma and high-gamma) synchronisation in interconnected networks linking to the DMN. Second, we found that triggering images modified spontaneous ICNs such that the previous differential connectivity was attenuated in those formerly-identified circuits, and DMN-DAN connectivity was now enhanced in the PTSD group. Third, using a correlational approach to explore associations of secondary symptoms in a combined, trauma-exposed soldier sample, we found that visual network alpha synchrony with other networks appeared inversely related to these symptoms. Finally, we applied the same analysis to characterise inter-subject variability of symptom severity in the PTSD group and its relation to ICN topology, and showed that beta synchrony demonstrated a bidirectional relation with symptomology, differentially expressed within and between distinct networks. We observed a negative correlation of PCL scores with intra-VIS network connectivity, but a positive relationship with SAL-VAN connectivity, as well as intra-SAL network gamma, which accounted for a significant portion of the variance of our PTSD group PCL scores.

4.1. Resting-interactions and triggering

Our results demonstrate that connectivity of spontaneous ICNs in a combat-related PTSD cohort is distinct from a combat-exposed control group, and that the interplay between frequency-mediated

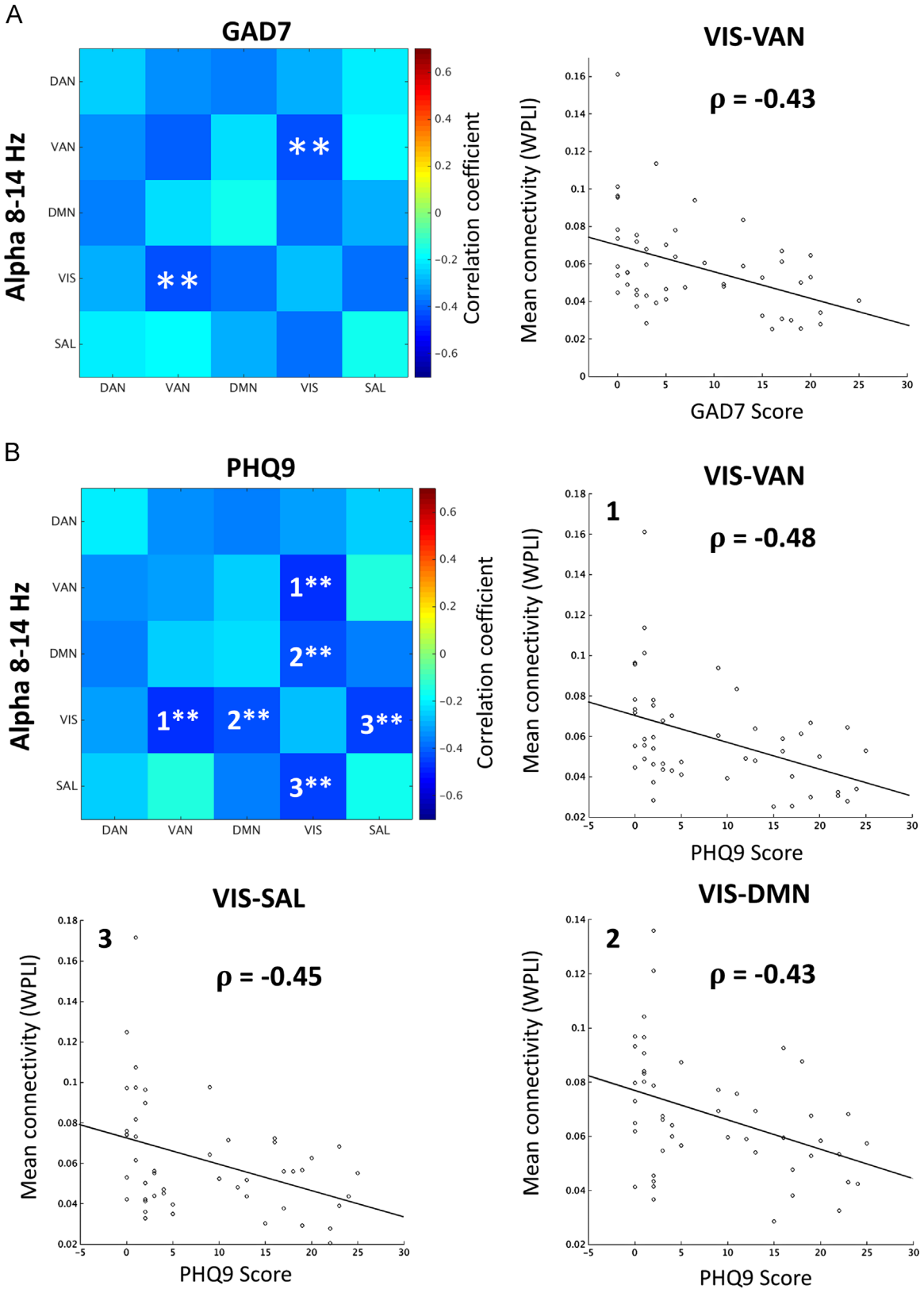

Fig. 3. Correlation matrices of associated symptomology for combined groups of soldiers (PTSD plus control) versus alpha synchronisation. (A) Associations of GAD7 scores (anxiety) versus alpha connectivity. Cool colours indicate negative correlations. Visual-to-ventral attention connectivity was associated with decreased anxiety symptoms. (B) PHQ9 scores (depression) were negatively correlated with intrinsic alpha in the visual-to-ventral attention, visual-to-salience, and visual-to-default-mode networks.

networks, expressed across a variety of inter- and intra-ICN relations, is complex. However, it was clear that these significant differences were concentrated within the gamma (30–80 Hz) and high-gamma range (80–150 Hz), and strongly involved DMN connectivity to the VAN, SAL and VIS networks. These results extend our previous findings, which suggest soldiers with PTSD are

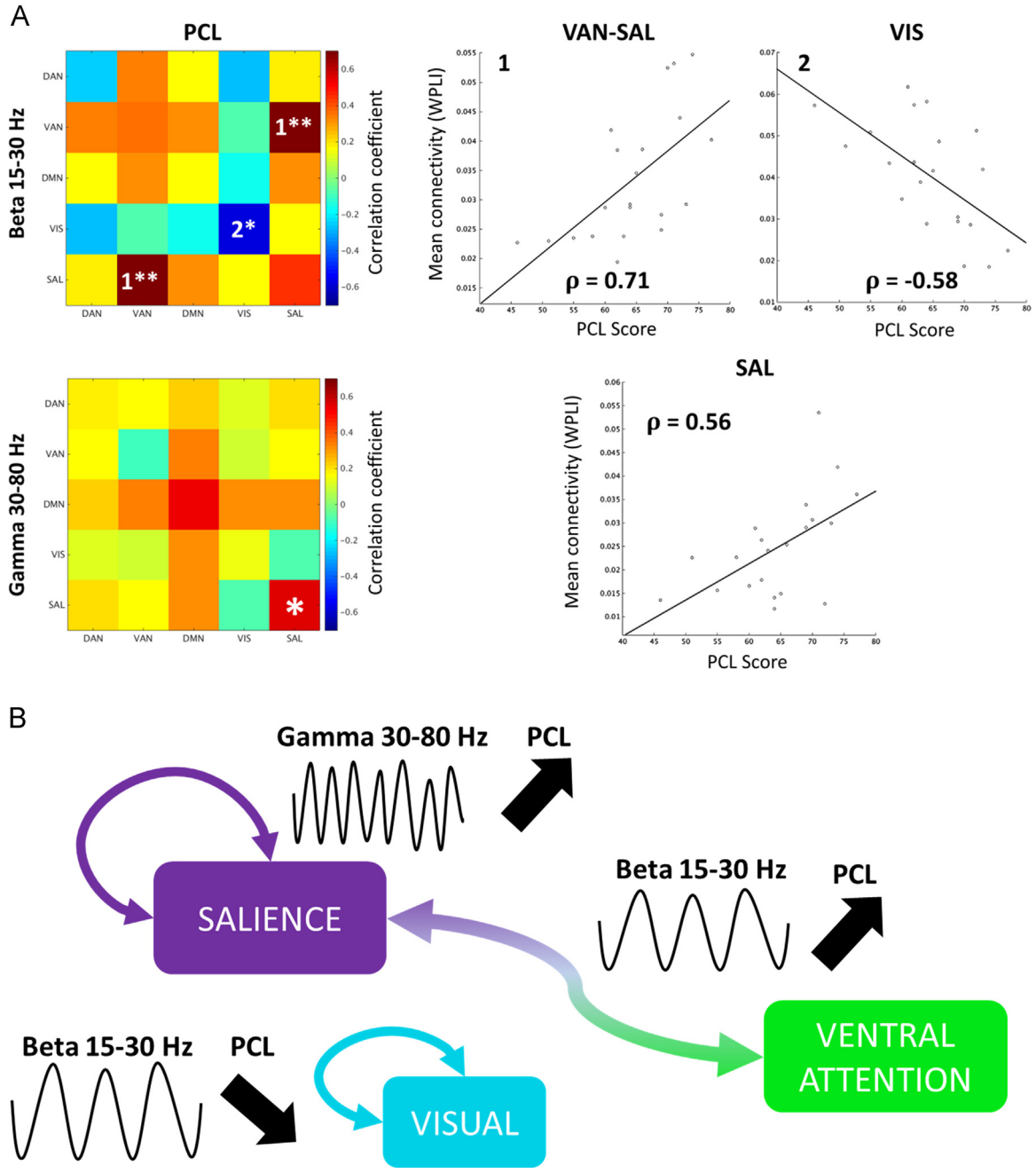

Fig. 4. (A) Correlations of intrinsic beta and gamma synchrony versus symptom severity in PTSD participants, and (B) summary schematic illustration of those correlations within and between networks in opposing directions in the beta frequency band that mediate PCL scores. VAN-SAL network interconnectivity was *positively* associated with PTSD symptom severity (i.e, increasing PCL scores). Intra-VIS network resting synchrony was *negatively* correlated with PCL scores, whereas gamma synchrony within the salience was positively associated with this measure of PTSD severity.

hypersynchronous in the gamma frequency range (Dunkley et al. 2014), brain rhythms that are posited to be active in the formation and retrieval of autobiographical memories (Canolty et al., 2006), conscious perception (Doesburg et al., 2005), and the regional integration of information-carrying activity (Fries, 2009; Lisman and Jensen, 2013). We have further expanded on the prior report by examining whole network-level connectomics, based on previously reported and pervasive intrinsic, spontaneous networks that show remarkable inter-individual homogeneity, and how these differ in PTSD. Furthermore, rather than analysing the regions that differed most between groups and seeing how measures from these regions correlated with PTSD, here we have shown that interactions *within* and *between* these networks also explain much of the variability in primary and secondary PTSD symptoms.

In the present study, we found that these increased gamma and high-gamma interactions in the PTSD group were in connections linking to the DMN, a network involved in episodic memory and self-referential thought (Qin and Northoff, 2011), and structures within this specific network have shown altered connectivity patterns in PTSD (Bluhm and Williamson, 2009). The DMN is also proposed to facilitate easy toggling between networks, as it is known to anti-correlated with task-positive networks (Buckner et al., 2008), and this atypical DMN activity in PTSD may be related to a breakdown in the efficient integration and segregation of distributed networks required for healthy brain function in

cognitive processes such as attentional control and mental flexibility (Dunkley et al. 2015).

Using triggering images with high-emotional salience to these groups, these ICNs were shown to be amendable to trauma-related cues, particularly in the combat-exposed non-PTSD soldiers. Triggering was found to modify connectivity in the PTSD group to a lesser extent than the control soldiers, which suggests a highly-synchronised level of spontaneous connectivity that is close to ceiling, and in turn, inefficient for the coordination of cognitive contents. In other words, those with PTSD may already be ruminating on previous traumatic experiences and/or be in an associated state of hyperarousal during the initial pre-triggering scan, and this mental state is characterised by high-frequency synchrony; on the other hand, the veterans without PTSD would not be in such a frame-of-mind until the salient pictures triggered some of those memories and the associated state of elevated synchrony. This might explain the findings in the post-triggering resting-state, and would be interesting to study longitudinally (e.g., has the induced high-frequency hypersynchrony returned to baseline levels in the control soldiers some time later post-trigger, and is the initial difference in ICN interactions present again?).

Overall, these findings are congruent with our prior report using an atlas-guided beamforming approach (Dunkley et al., 2014). However, we did find that DMN-DAN connectivity was enhanced in the PTSD group following provocation, which may relate to internally-focused attention and introspection. The evidence for modulation of spontaneous phase synchrony in the brain opens the possibility of studying PTSD-like brain states in trauma-exposed, but resilient, populations.

4.2. Secondary symptoms and alpha interactions

In contrast to the distinguishing high-frequency signature network synchrony in PTSD soldiers, a secondary analysis revealed that spontaneous alpha synchrony between VIS and other networks was significantly negatively associated with two common comorbid traits of PTSD, anxiety and depression (Hayes et al., 2012). We observed VIS-VAN connectivity that was negatively associated with anxiety, and VIS-DMN, VIS-SAL and VIS-VAN that were related to depression. Whilst other network interactions were not found to be significantly correlated with these outcome scores, *all* of the correlations within the alpha band displayed identical directionality, which perhaps suggests a generic, whole-brain, or at least multi-ICN, association with alpha synchrony.

Two theories propose neurophysiological functional roles of alpha oscillations that differ by spatial scale. Local amplitude increases in alpha are thought to be related to the inhibition of task-irrelevant regions (Jensen and Mazaheri, 2010), whilst large-scale network alpha synchrony is believed to play an active role in the integration of information between subpopulations of neurons (Palva and Palva, 2007). This rhythmicity at the global level is understood to play a mechanistic role, and modulate ongoing neuronal excitation and inhibition at the local level (Palva and Palva, 2011), particularly within primary sensory cortices (Voytek et al., 2010). Other theories have proposed more specific psychophysiological roles related to top-down attentional control mediated by alpha (Jensen et al., 2014), and a mechanism utilised by regions to communicate and maintain the contents of visual working memory (Palva et al., 2010), and more generally, cognitive performance (Klimesch, 1999; Sadaghiani et al., 2012). Given our task-free observations, and the lack of a correlation between alpha synchrony and PCL scores, we propose that these large-scale alpha-symptom relations are likely non-specific, being related to the more generic, associated cognitive and memory difficulties seen in PTSD.

4.3. Primary PTSD symptoms and synchronised ICNs

We observed strong intra- and inter-network beta synchrony correlations with PTSD severity: VIS network synchrony being inversely related to symptoms, and VAN-SAL coupling being positively associated with PCL scores. In regards to the putative functional role of beta band-limited oscillation and synchrony, a unifying theory has remained relatively obscure (except perhaps for their role in motor function (Pogosyan et al., 2009) and Parkinson's disease (Toledo et al., 2014)), but beta synchrony is hypothesised to have an integrative role in higher-level cognition (Donner and Siegel, 2011). Studies have shown that top-down attention is known to enhance beta oscillations in striate cortex (Grothe et al., 2012), and those with PTSD often exhibit comorbid deficits in the visual domain (Mueller-Pfeiffer et al., 2013), which might explain why soldiers with greater symptom severity show reduced beta synchrony.

It is interesting to note that beta resting synchrony showed ICN-specific associations with symptoms, with correlations that differed in directionality; VAN-SAL connectivity in this band was also highly positively correlated with PCL symptom scores, in contrast to the VIS network synchrony. Other theories of beta propose that it acts as a maintenance mechanism, sustaining the ongoing 'status-quo' of the internal current sensory-cognitive state (Engel and Fries, 2010), which we propose could reflect the integration of introspective thoughts held in the salience network and internally-focused attention driven by the ventral attention network.

In addition to the bidirectional beta correlations observed, PCL score was highly correlated with SAL network gamma synchrony, a network that includes the bilateral anterior cingulate cortex and insula. Abnormal activation in this network is noted in a number of psychiatric disorders (Menon, 2011; Palaniyappan and Liddle, 2012), as well as PTSD (Sripada et al., 2012), with increases in insula activation consistent with elevated levels of interception and awareness of arousal which could be related to symptoms of PTSD such as withdrawn and hypervigilant states (Shin and Liberzon, 2010).

5. Conclusion

Our results demonstrate atypical neurophysiological interactions within and between intrinsic resting networks, often involving increased high-frequency synchrony in networks connected to the DMN, in a combat-related PTSD population. These distinguishing markers may prove a reliable neurophysiological phenotype that typify the disorder. Furthermore, variability in the severity of symptoms was observed in a number of distinct networks and across canonical frequency scales. Thus, these results contribute to the accumulating knowledge-base that PTSD is expressed as network-level atypicalities, which can be detected using macroscopic neurophysiological imaging, and that primary symptomology, as well as associated cognitive and emotional dysfunction, is related to aberrant large-scale integration subserved by cortical synchrony. This may assist in the development of candidate biomarkers for diagnosing the disorder and tracking intervention efficacy, as well as contributing to increasing evidence that PTSD is a complicated network-based disorder expressed as altered neural interactions.

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The authors declare no competing financial interests or potential conflicts of interest.

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