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A comparison of the functional connectome in mild traumatic brain injury and post-traumatic stress disorder

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Abstract

Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) often co-occur in the context of threat to one's life. These conditions also have an overlapping symptomatology and include symptoms of anxiety, poor concentration and memory problems. A major challenge has been articulating the underlying neurobiology of these overlapping conditions. The primary aim of this study was to compare intrinsic functional connectivity between mTBI (without PTSD) and PTSD (without mTBI). The study included functional MRI data from 176 participants: 42 participants with mTBI, 67 with PTSD and a comparison group of 66 age and sex-matched healthy controls. We used network-based statistical analyses for connectome-wide comparisons of intrinsic functional connectivity between mTBI relative to PTSD and controls. Our results showed no connectivity differences between mTBI and PTSD groups. However, we did find that mTBI had significantly reduced connectivity relative to healthy controls within an extensive network of regions including default mode, executive control, visual and auditory networks. The mTBI group also displayed hyperconnectivity between dorsal and ventral attention networks and perceptual regions. The PTSD group also demonstrated abnormal connectivity within these networks relative to controls. Connectivity alterations were not associated with severity of PTSD or post-concussive symptoms in either clinical group. Taken together, the similar profiles of intrinsic connectivity alterations in these two conditions provide neural evidence that can explain, in part, the overlapping symptomatology between mTBI and PTSD.

KEYWORDS
connectome, intrinsic connectivity, networks, post-traumatic stress, trauma, trauma

1 | INTRODUCTION

Mild traumatic brain injury (mTBI) is recognied as a major public health issue (Zatzick, 2010, p. 1) that can lead to a range of functional, emotional and cognitive problems (Bryant et al., 2015; Lippa et al., 2010; Zatzick et al., 2010). One of the main controversies in mTBI literature has been articulation of the causes of these post-concussive symptoms (PCS). Traditionally, they have been attributed to the neurological insult arising from mTBI. However, since mTBI often occurs in the context of psychological trauma, stress may be an important contributing factor (Meares et al., 2008; 2011). Reinforcing this possibility is the high degree of comorbidity between mTBI and post-traumatic

stress disorder (PTSD; Bryant, 2001, 2008). As PTSD symptoms overlap with those observed in mTBI, including emotional dysregulation, memory impairment and concentration difficulties (Bryant, 2011), a large number of studies suggest that the impairment observed following mTBI can be explained by PTSD (Hoge et al., 2008; Polusny et al., 2011; Schneiderman et al., 2008; Segev et al., 2016). Others argue that the constellation of emotional and cognitive symptoms is a unique clinical entity that is primarily associated with mTBI rather than being a more severe form of PTSD (Miller et al., 2016).

Examining the intrinsic functional connectivity of the brain is one potential mechanism to investigate the neural underpinnings of mTBI and PTSD. Unlike task-based functional magnetic resonance imaging (fMRI), that examines neural connectivity related to cognitive processes, examining task-free connectivity gives insight into the core intrinsic functional architecture of the brain underlying these processes (Buckner & Vincent, 2007). Altered intrinsic connectivity has been previously demonstrated in both PTSD and mTBI separately (Daniels et al., 2010; Kennis et al., 2015; Miller et al., 2017; Misaki et al., 2018; Palacios et al., 2017; Stevens et al., 2012). These studies showed that mTBI was associated with both connectivity reduction and enhancement across several large-scale brain networks, including visual, motor, limbic, executive control, default mode network (DMN), cingulo-opercular, cingulo-parietal and dorsal attention networks (Slobounov et al., 2011; Vakhtin et al., 2013; Vergara et al., 2017). These aberrant connectivity changes were also associated with PCS severity and predicted behavioural and cognitive outcomes at 6-month follow-up (Stevens et al., 2012). A reduced connectivity particularly in the DMN have been reported to be associated with neurocognitive dysfunction (Mayer et al., 2011; Zhou et al., 2012). While there have been mixed reports of both increase and decrease in salience network connectivity in mTBI (Amir et al., 2021; Palacios et al., 2017), it is suggested that the cognitive deficits observed in mTBI could be due to impaired coordination between the salience and DMN networks (Sharp et al., 2014).

Altered whole-brain connectivity has also been reported in PTSD. Studies have found that PTSD participants displayed hypoconnectivity among higher cortical areas and emotion regulation areas such as lateral frontal, supplementary motor area, salience network, DMN, executive control networks and between the parahippocampal and visual cortex areas (Bao et al., 2021; Breukelaar et al., 2021; Misaki et al., 2018; Ross & Cisler, 2020). A bias towards greater perceived saliency (reflected as a hyperactive salience network) has been proposed to underlie reduced cognitive capacity (impacting the cognitive control network) and disruptions in internal mentation and sense of self (impacting the default mode brain network) in PTSD (Akiki et al., 2017). These findings are consistent with the clinical profile of PTSD insofar as they have been associated with emotional dysregulation, re-experiencing and numbing or avoidance symptoms in PTSD (Breukelaar et al., 2021; Miller et al., 2017). On the other hand, chronic hyperconnectivity within hippocampal, thalamic, left frontal and temporal regions has been previously shown to be positively associated with PTSD severity (Dunkley et al., 2014, 2018). These findings are consistent with the hypervigilance theory of PTSD that is driven by rapid, bottom-up processing of threat (Dunkley et al., 2018).

These studies suggest a potential overlap of large-scale network deficits in both PTSD and mTBI. However, only three studies to date have evaluated mTBI together with PTSD. One study evaluated individuals with PTSD and mTBI relative to those with PTSD alone and found that while resting-state connectivity within the hippocampal-striatal network was abnormally increased in both patient groups relative to healthy individuals, PTSD patients with mTBI demonstrated greater connectivity than patients with PTSD alone (Rangaprakash et al., 2017). They also found that neurobehavioural disturbances observed in individuals with PTSD and PCS were better explained by mTBI history than PTSD. Another study evaluating individuals with mTBI only relative to those with comorbid PTSD focussed on the DMN and demonstrated greater connectivity for the mTBI only group which was also associated with reduced PTSD symptoms (Santhanam et al., 2019). There is only one previous study that has directly compared resting-state connectivity between PTSD and mTBI without PTSD (Philippi et al., 2021). This study used data from military service personnel and employed a seed-based connectivity analysis; the results indicated connectivity for the DMN and the cognitive control (fronto-parietal) network was significantly reduced in the PTSD group compared with mTBI and also reduced for both clinical groups relative to controls. More studies that directly compare mTBI and PTSD-only groups, particularly civilian cohorts, and those that comprehensively evaluate the whole brain connectome are necessary to disentangle the true overlap in neural mechanisms between these conditions.

This study aims to fill this gap by profiling the intrinsic functional connectome in mTBI without PTSD in comparison to PTSD without mTBI, and healthy controls (HC) in a non-military cohort. This design allowed determination of the differential connectivity mechanisms underlying mTBI and PTSD. Additionally, by measuring PTSD symptoms and PCS, the study also permitted examination of the differential associations of PTSD symptoms and functional connectivity to PCS. Based on previous research our main hypothesis was that mTBI and PTSD would demonstrate some overlap in network connectivity deficits, particularly in the DMN and cognitive control networks (due to overlap of symptoms commonly observed in the two conditions; Philippi et al., 2021). We also hypothesised there would be a distinct connectivity profile between the two groups as our mTBI group did not have comorbid PTSD, for example related to the DMN (reduced for PTSD relative to mTBI; Philippi et al., 2021; Santhanam et al., 2019) and salience network (increased in PTSD relative to mTBI; Akiki et al., 2017). We also hypothesised that both mTBI and PTSD would demonstrate altered connectivity profiles in these networks compared with HC and these aberrations would be associated with PCS and PTSD symptoms, respectively.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was approved by the Western Sydney Area Health Service Human Research Ethics Committee. All participants provided informed consent before participation. The sample ($N = 175$)

comprised 42 (13 females) participants who had a history of mTBI without PTSD, 67 (46 females) participants with PTSD and 66 (22 females) HC who had never been diagnosed with a psychiatric disorder and never suffered a TBI.

All participants were recruited from the general community or were treatment seekers at the Traumatic Stress Clinic at Westmead Institute for Medical Research. Participants were interviewed regarding exposure to a traumatic event. Participants in PTSD and mTBI groups had experienced a psychologically traumatic event (as defined by the DSM-IV Criterion A stressor) and had experienced either abuse during childhood, a road accident, assault, death of a loved one, witnessed police violence, experienced domestic violence, or an industrial accident. Mild TBI was defined following participants' self-reported head injury, which involved loss of consciousness for <30 min, and post-traumatic amnesia of no >24 h. We defined PTSD as no history of head injury, exposure to a psychologically traumatic event, and meeting the DSM-IV criteria for PTSD. HC had no history of head injury, or any psychiatric disorder as indicated by responses on the Mini-International Neuropsychiatric Interview (MINI, version 5.5; Sheehan et al., 1998). Participant characteristics are presented in Table 1.

2.2 | Measures

PTSD was assessed using the Clinician-Administered PTSD Scale-IV (CAPS; Blake et al., 1995). PCS scores were assessed by adapting eight items on the 34-item Somatic and Psychological Health Report

TABLE 1 Demographics and clinical characteristics

	PTSD ($n = 67$)	mTBI ($n = 42$)	Control ($n = 66$)
Age, years, *m* ± SD (range)	39.5 ± 11.4 (19–63)	43.5 ± 12.17 (18–62)	37.1 ± 12.0 (23–65)
Gender, female (%)*	46 (68.7)	13 (30.95)	22 (53.7)
CAPS, *m* ± SD (range)*	65.99 ± 20.7 (21–115)	12.51 ± 14.3 (0–65)	NA
CADDS, *m* ± SD (range)*	20.6 ± 13.17 (0–62)	4.62 ± 7.87 (0–46)	NA
BDI, *m* ± SD (range)*	31.72 ± 12.36 (4–58)	9.63 ± 7.6 (0–31)	NA
PCS*	15.30 ± 3.75 (8–22)	10.16 ± 2.34 (8–17)	N/A
Time since trauma, months*	20.51 ± 15.35 (0.75–51)	136.39 ± 130.51 (3–696)	NA
Trauma type, *n* (%)			
Child abuse	26 (38.81)	0	NA
Road accident	5 (7.46)	26 (60.5)	NA
Assault	13 (19.4)	11 (25.6)	NA
Death of loved one	4 (5.97)	1 (2.3)	NA
Witnessed violence/police	14 (20.9)	2 (4.7)	NA
Domestic violence	5 (7.46)	0	NA
Industrial accident current medication, *n* (%)*	0	1 (2.3)	NA
SNRI	11 (16.42)	2 (4.76)	NA
SSRI	15 (22.39)	3 (7.14)	NA
Antidepressant	13 (19.4)	0	NA
Antipsychotic	10 (14.93)	0	NA
Benzodiazepines	12 (17.91)	3 (7.14)	NA
Stimulant	1 (1.49)	0	NA
Comorbid diagnoses, *n* (%)*			
Major depressive episode	45 (67.16)	1 (2.38)	NA
Panic disorder	1 (1.49)	0	NA
Agoraphobia	22 (32.84)	2 (4.76)	NA
Social phobia	30 (44.78)	1 (2.38)	NA
OCD	11 (16.42)	0	NA
GAD	28 (41.79)	8 (19.04)	NA
Mean FD, *m* ± SD (range)*	0.08 ± 0.03 (0.04–0.14)	0.12 ± 0.07 (0.04–0.40)	0.07 ± 0.03 (0.03–0.16)

Note: * indicate statistically significant difference between groups at $p < .05$.

Abbreviations: BDI, Beck Depression Inventory; CADDS, Clinician-Administered Dissociative States Scale; CAPS, Clinician-Administered PTSD Scale; FD, framewise displacement; GAD, generalised anxiety disorder; OCD, obsessive-compulsive disorder; PCS, post-concussive symptoms; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

measure (McFarlane et al., 2008). This measure indexes a range of somatic symptoms, and we selected those that address core PCS, including headaches, dizziness, concentration deficits, memory problems, fatigue, nervousness, changing moods, tiredness, and irritability. These selected items had strong internal consistency in the current sample (Cronbach's $\alpha = .87$).

The MINI was used to assess Axis I psychiatric disorders. The MINI is a short, structured diagnostic interview based on the DSM-IV and the ICD-10 classification of mental illness. Participants with comorbid major depressive episode, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and generalised anxiety disorder were included in the study. Participants with alcohol abuse and dependence and marijuana abuse and dependence were excluded from the study.

The Beck Depression Inventory-2 (BDI) was used to assess severity of depressive symptoms (Beck et al., 1996), a 21-item self-report inventory measuring depressive symptoms in the past 2 weeks, and the Clinician-Administered Dissociative States Scale (Bremner et al., 1998); a 27-item scale with 19 subject-rated items and 8 clinician-rated items, was used to measure dissociative symptoms.

2.3 | Data acquisition

All fMRI data were acquired using an 8-channel phased-array head coil on a 3 T GE Signa Twinspeed HDxT MR Scanner (GE Healthcare, Milwaukee, Wisconsin). MRI protocol included five functional MRI tasks (Richard A. Bryant et al., 2021; Korgaonkar et al., 2013) and a T1-weighted structural image. The functional MRI tasks involved: (a) one run of a Go-NoGo response inhibition task—where participants were instructed to button press when the word "PRESS" was displayed in green (Go trials) and inhibit responses when the word "PRESS" was presented in red (NoGo trials). There were 240 total stimuli—180 Go trials and 60 No-Go trials each displayed for 500 ms with a 750 ms interstimulus interval and presented in pseudorandom order. (b) Conscious and nonconscious versions of facial emotion processing task—where participants passively viewed a block series of facial expressions depicting fear, anger, sad, happy, disgust, and neutral emotions (each emotion block presented for 10s comprising of 8 faces and repeated 5 times in a pseudorandom order). In the conscious version, each image was viewed for 500 ms with a 750 ms interstimulus interval. In the nonconscious version, the emotional face was presented for 16.7 ms, immediately followed by a neutral face for 150 ms thus backwardly masking the emotion face so that the participant is not consciously aware of the presented emotion. (c) Two runs of an cognitive re-appraisal task—where participants were presented three blocks (Think, Neutral, and Watch) in each run (order counterbalanced across the two runs). During the Neutral and Watch blocks, participants passively watched 10 neutral images or 10 negative image stimuli respectively. During the Think block, participants were presented 10 negative images but were instructed to down-regulate emotion responses to distressing stimuli using prior trained cognitive reappraisal techniques. Participants rated how negative the image made them feel after each stimuli.

Using a previously validated method (Korgaonkar et al., 2014), intrinsic functional connectivity data were derived from the concatenated residuals time series of the fMRI tasks. The acquisition, preprocessing and derivation of the intrinsic signal have been described previously (Goldstein-Piekarski et al., 2018; Korgaonkar et al., 2020). A detailed description is provided in the Supplementary Section.

2.4 | Generation of whole-brain functional connectomes

For each participant, the average residual time series across the 600 concatenated fMRI volumes were extracted from 307 cortical regions and 36 subcortical regions (Gordon et al., 2016; Tian et al., 2020). These brain regions are based on a high-resolution template that used resting-state functional connectivity patterns to define brain parcels that represent putative, functionally coherent, brain areas and categorises each region into established large-scale functional brain networks. The 36 subcortical regions were included due to previously shown important of subcortical areas, in particular the amygdala and thalamus to stress-related disorders (Breukelaar et al., 2021; Rabinak et al., 2011). The blood oxygen level dependent (BOLD) time-series within each of these regions was then correlated pair-wise with every other regions and Fisher-Z transformed to create a 343×343 inter-regional functional correlation matrix for each participant. Since the interpretation of negative connectivity remains controversial (Qian et al., 2018), negative connections within these matrices were removed.

2.5 | Statistical analysis

We used the network-based statistic (NBS; Zalesky et al., 2010) to analyse whole-brain resting-state connectivity differences between groups. The NBS is a non-parametric statistical approach that addresses the multiple comparison problem by testing the null hypothesis based on interconnected subnetworks or components rather than individual connections.

First, for each connection, NBS compares groups using a two-sample *t*-test and assigns a significant *t*-statistic to each. These values are then compared against a predefined threshold and only those above this threshold are used to form a network. We used a *t*-statistic threshold of three corresponding to $p < .001$. Group membership is then randomly permuted (total of 1000 permutations performed) and the size of the largest component detected is stored. A corrected *p*-value is determined for each component and only those in the top 5% (family wise corrected [FWE] $\alpha < .05$) are deemed to be significant. For the identified significant connections, we computed an average connectivity estimate and labelled it as an intrinsic functional network pair using the functional network definitions for the joined parcels, that is, intra-network connections if both brain regions are associated with the same functional network or inter-network connections if regions are associated with different networks. We further computed an average *t*-score for intra-network and inter-network connection

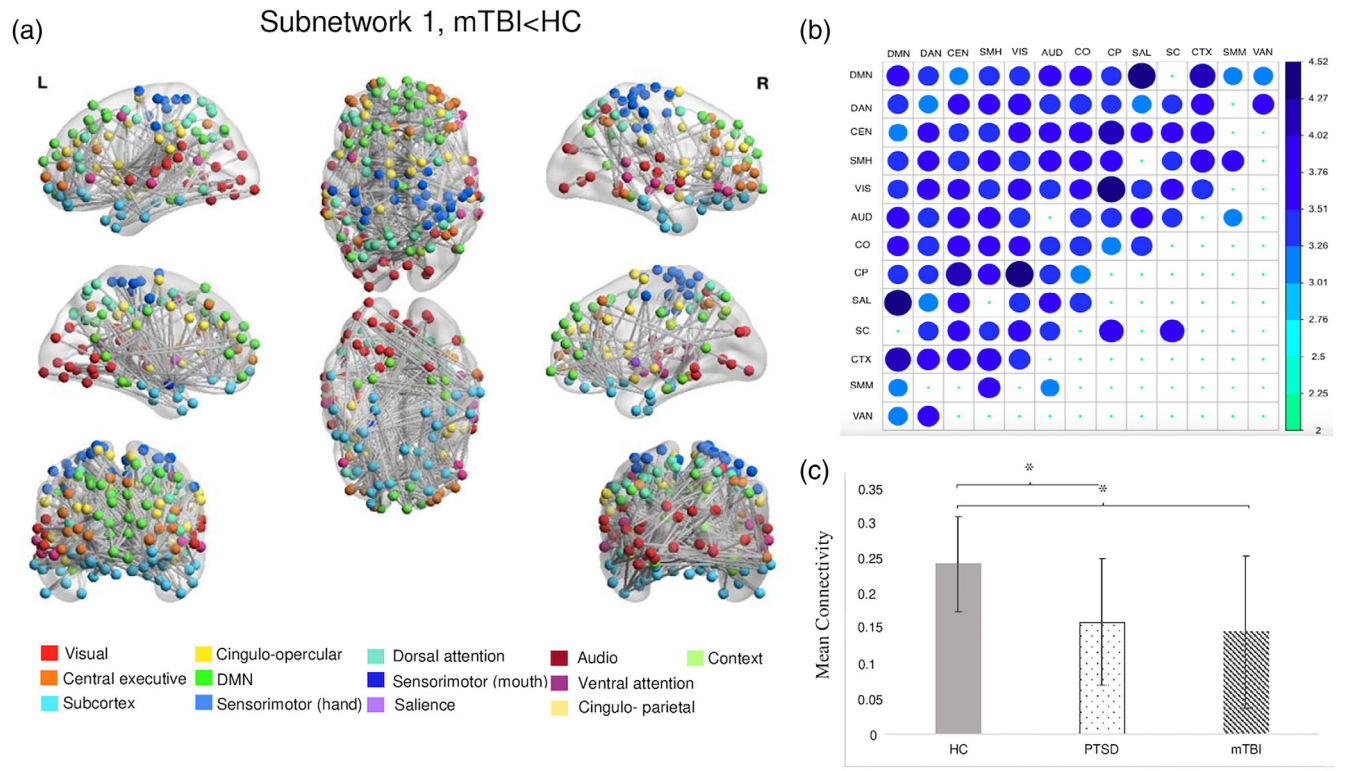

FIGURE 1 (a) Subnetwork (subnetwork 1) of decreased connectivity in mild traumatic brain injury (mTBI) compared with controls. Whole network superimposed on the surface of the brain using BrainNet viewer. (b) Heatmap of the mean *t*-statistic of significant between and within network connections. Diagonal middle row corresponds with intra-network connections, all other rows correspond with inter-network connections. Larger size and darker colour of the circle correspond to a greater mean *t*-statistic for between group differences. (c) Difference in mean connectivity for this network between groups. *indicates significant difference at $p < .05$. AUD, auditory; CEN, central executive network; CO, cingulo, opercular; CP, cingulo, parietal; CTX, context; DAN, dorsal attention network; DMN, default mode network; HC, healthy controls; PTSD, post-traumatic stress disorder; SAL, salience; SC, subcortex; SMH, sensorimotor (hand); SMM, sensorimotor (mouth); VAN, ventral attention network; VIS, visual

pairs to indicate their contribution to the significant results (presented in Figures 1b and 2b,e).

As the primary analysis of this study was to determine differences between PTSD and mTBI, we first ran an NBS analysis directly comparing mTBI and PTSD groups to identify differences between the two clinical groups. Then, we identified connections where mTBI were different from HC. We then tested if the significant connections from this analysis were also altered in PTSD relative to HC to identify these alterations in connectivity were also present in PTSD.

Using significant connections from these analyses, we also tested correlations between connectivity and clinical measures (mTBI and PTSD symptom scores and time since trauma) within the mTBI and PTSD groups, separately. A false discovery rate (FDR) corrected $p < .05$ was used to control for multiple comparisons.

3 | RESULTS

3.1 | Participant characteristics

Participant characteristics are presented in Table 1. There were no significant differences between the three groups on age ($p = .175$) but there were gender differences ($\chi^2 = 2.45$, $p < .001$) with lower percentage of females in the mTBI cohort compared with both PTSD and HC groups (both $p < .001$; PTSD had similar gender distribution as HC). PTSD participants also had significantly higher CAPS, BDI, PCS and CADDS scores than mTBI participants (all $p < .05$). More time had elapsed since trauma for mTBI participants than PTSD participants ($p < .001$).

3.2 | Whole-brain connectivity differences related to mTBI

There were no significant differences in the whole-brain connectome between mTBI and PTSD identified with NBS with or without controlling for demographic (gender) and symptom (CAPS, BDI, PCS and CADDS) differences between the two groups as well as differences in the number of individuals on medication. For mTBI versus HC, the NBS analysis identified one subnetwork (mTBI < HC) comprised of 374 connections across 207 nodes where the mTBI group had significantly lower functional connectivity than HC ($p < .001$, FWE-corrected $\alpha < .05$; Figure 1a). This subnetwork was comprised of inter-network connections among all the primary brain networks and

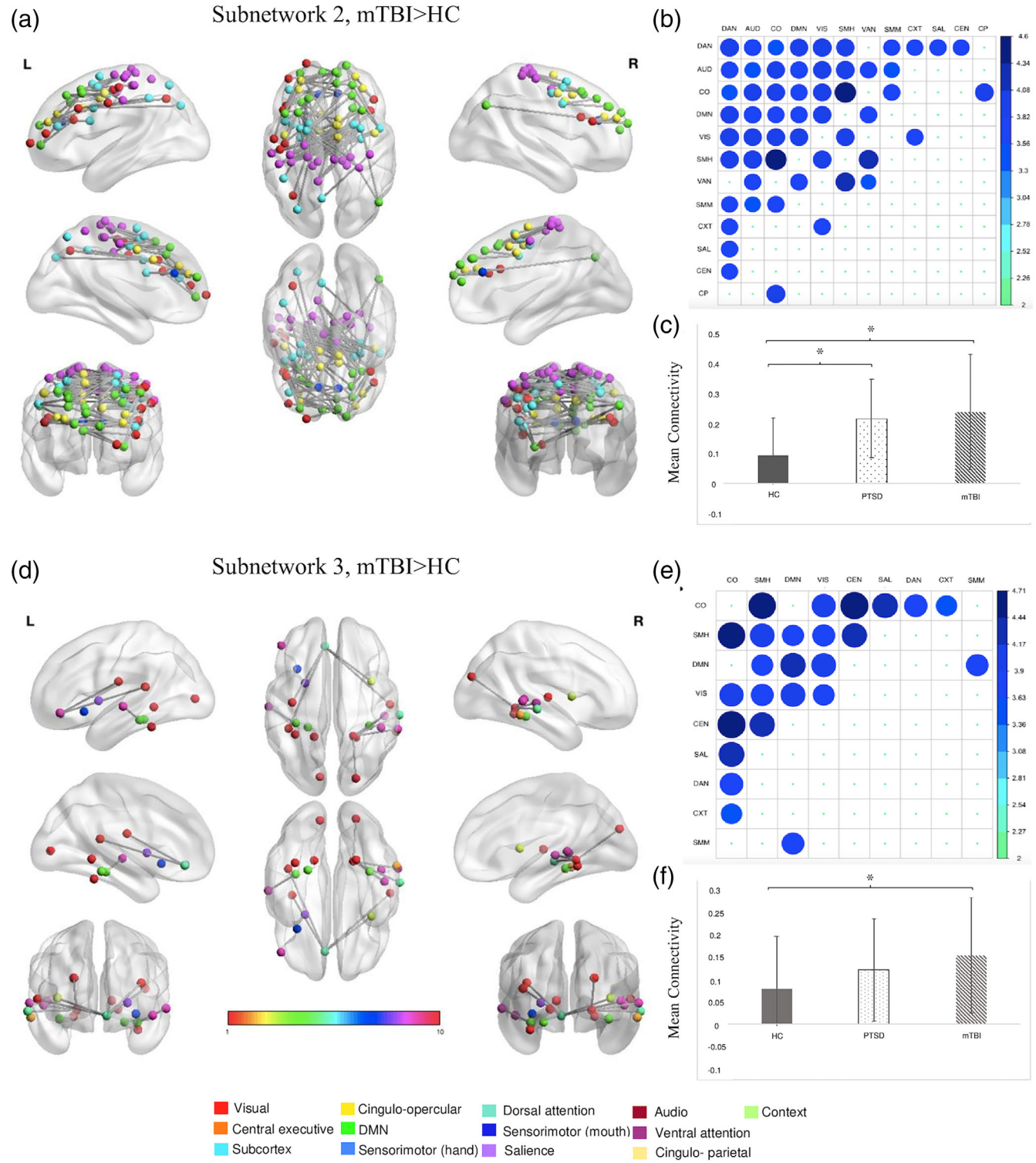

FIGURE 2 Subnetworks of increased connectivity in mild traumatic brain injury (mTBI) compared with controls. (a–c) Refer to subnetwork 2, (d–f) refer to subnetwork 3. (a,d) Whole network superimposed on the surface of the brain using BrainNet viewer. (b,e) Heatmap of the mean *t*-statistic of significant between and within network connections. Diagonal middle row corresponds with intra-network connections, all other rows correspond with inter-network connections. Larger size and darker colour of the circle correspond to a greater mean *t*-statistic for between group differences. (c,f) Difference in mean connectivity across the significant subnetwork between groups. *indicates significant difference at $p < .05$. AUD, auditory; CEN, central executive network; CO, cingulo, opercular; CP, cingulo, parietal; CXT, context; DAN, dorsal attention network; DMN, default mode network; HC, healthy controls; SAL, salience; SC, subcortex; SMH, sensorimotor (hand); SMM, sensorimotor (mouth); VAN, ventral attention network; VIS, visual

intra-network connections within the DMN, dorsal attention, sensorimotor, visual, central executive and cingulo-opercular networks. The greatest number of connections with significantly lower connectivity in the mTBI group were related to the DMN, followed by dorsal attention, visual, executive, and sensorimotor, then cingulo-opercular, auditory, cingulo-parietal, salience, context and ventral attention network connections (Figure 1b). Overall, connections between the cingulo-parietal and visual network demonstrated the greatest significant difference ($t = 4.52$) between the groups (Table S1).

The NBS analysis also identified two subnetworks (mTBI > HC) of 106 and 40 connections across 70 and 35 nodes, respectively, where the mTBI group displayed significantly higher functional connectivity than HC ($p < .001$, FWE-corrected $\alpha < .05$). Within the first of these subnetworks, mTBI showed increased connectivity compared with controls primarily between dorsal attention, auditory, cingulo-opercular, DMN and visual networks (Figure 2a,b and Table S2). The second subnetwork included cingulo-opercular, sensorimotor, DMN, visual and central executive networks (Figure 2d,e, Table S3).

As there were differences in gender between mTBI and HC groups, we evaluated the significance of the findings above controlling for gender and found the connectivity differences between the mTBI and HC groups to be unchanged.

3.3 | Connectivity comparisons for mTBI versus PTSD and PTSD versus HC

As there were no connectome level differences between PTSD and mTBI, we used the significant connections found for the mTBI versus HC contrast (i.e., HC > mTBI—subnetwork 1; and mTBI>HC—subnetworks 2 and 3 described above) to further compared PTSD with mTBI. There were no significant differences between mTBI and PTSD cohorts in mean connectivity (Figure 1c, 2c, and 2f) with or without controlling for demographic (gender) and symptom (CAPS, BDI, PCS and CADDS) differences between the two groups.

However relative to HC, the PTSD group also demonstrated significantly lower mean connectivity in subnetwork 1 (Figure 1c) and higher mean connectivity in subnetwork 2 (Figure 2C). There were no differences in mean connectivity in subnetwork 3 between PTSD and HC (Figure 2f). In the supplementary section, we report comparisons (PTSD vs. mTBI and PTSD vs. HC) for specific inter-network and intra-network connections within the three subnetworks; however, none of these survive significance after correction for multiple comparisons.

3.4 | Association of connectivity and clinical measures

Finally, to evaluate whether the clinical symptoms measures (PCS and PTSD symptoms) in the mTBI group could explain connectivity alterations associated with mTBI, and to evaluate any confounds of duration since experienced trauma, we evaluated correlations of PCS and CAPS symptom scores and time since trauma with the significant patterns of connectivity within the mTBI group. There were no significant correlations between mean connectivity in the mTBI group and any of the clinical measures at the corrected level (uncorrected findings are presented in the supplementary section). We also tested these correlations independently in the PTSD group and found no significant associations. Further, there were no differences in mean connectivity in the mTBI group based on whether participants were taking medication.

4 | DISCUSSION

This is the first study to date to directly compare intrinsic connectivity between mTBI and PTSD using a connectome-wide approach. Our primary objective was to understand the overlap and distinction in neural mechanisms between mTBI and PTSD. While there were no differences in intrinsic connectivity between the two groups, both mTBI and PTSD demonstrated reduced and increased connectivity relative to HC. As the mTBI cohort did not have comorbid PTSD, and vice versa, these findings suggest that the overlapping symptomatology in the two conditions is a result of a shared neural connectivity profile rather than due to co-occurrence of the two conditions.

Similar to previous reports of connectivity alterations in mTBI, global hypoconnectivity observed in mTBI in our study was primarily driven by the DMN, as well as attention and control networks–such as the central executive, cingulo-opercular and cingulo-parietal networks. Zhou et al. (2012). showed that in mTBI *reduced* connectivity in the posterior DMN was associated with neurocognitive dysfunction, whereas *increased* connectivity in the anterior DMN negatively correlated with PCS symptoms. Bonnelle et al. (2011) further showed that mTBI is characterised by structural disconnection within the DMN. The DMN is thought to interact with cognitive control networks, such as executive control and cingulo-opercular networks, to achieve emotion regulation (Delgado et al., 2008). Consequently, reduced connectivity between these networks has been observed in PTSD, generalised anxiety disorder and high trait anxiety where emotional dysregulation is one of the core clinical features (Daniels et al., 2010; Kennis et al., 2015; Miller et al., 2017; Misaki et al., 2018; Modi et al., 2015; Sylvester et al., 2012). Thus, emotional dysregulation and increased anxiety that is commonly observed in PCS could be due to reduced connectivity related to cognitive control networks and DMN and could be a common mechanism in both PTSD and mTBI underlying PCS features. While we did not observe correlations with PCS symptom scores with connectivity after correcting for multiple comparisons, we did observe trend level (uncorrected) correlations with connectivity related to both the cingulo-opercular (with dorsal attention) and DMN (with salience) brain networks. It is possible that these effects are enhanced in cohorts with comorbid mTBI and PTSD (Zhou et al., 2012).

Han and colleagues further proposed that this disconnection could be the underlying mechanism of goal-directed cognition deficits, such as poor concentration and memory, seen in PCS (Han

et al., 2016). van der Horn et al. (2017) also observed PCS-mediated decreased connectivity between DMN and control networks. They proposed that network switching might contribute to PCS complaints where stronger top-down control of DMN by task-positive networks may be required to switch from internal thoughts to externally directed processing (van der Horn et al., 2016). In line with these findings, greater PCS symptoms have been previously associated with reduced connectivity within both DMN and some of the task-positive networks (Stevens et al., 2012). While some of the connectivity features were correlated with PCS symptoms in our study, they did not survive after controlling for multiple comparisons (see Supplementary Section).

When compared with HC, both mTBI and PTSD groups also displayed reduced connectivity between the DMN, dorsal attention and central executive networks and perceptual networks, namely visual and auditory networks. Disrupted connectivity between these networks has been previously hypothesised to result in attentional control deficits in highly anxious individuals (Modi et al., 2015). PTSD is known to be characterised by a weakly connected DMN and central executive network, which is primarily driven by an over-reactivity to salience processing (reflected as a hyperconnected salience network; Akiki et al., 2017). In addition, these connectivity alterations between the visual brain regions with the DMN and executive brain networks have been observed in mTBI patients with lower connectivity between these networks associated with poor cognitive performance—highlighting a link between visual processing problems and executive processes (Gilmore et al., 2016). Hence, individuals with mTBI may have difficulty processing perceptual stimuli which might be related to cognitive dysfunction. This might suggest that although the impacted neural mechanism may be similar in both mTBI and PTSD, the cause driving this mechanism could possibly be different in the two disorders; for example, PTSD may be impacted by salience over-reactivity versus cognitive dysfunction for mTBI.

Apart from hypoconnectivity, this study also observed hyperconnectivity in the mTBI group compared with controls. Hyperconnectivity was primarily observed within the anterior DMN, central executive, cingulo-opercular and sensorimotor networks. Enhanced connectivity within DMN and executive control networks is thought to represent compensatory mechanisms in response to a reduced capacity to maintain neural activation profiles and hence the ability to appropriately mediate behaviour (Stevens et al., 2012). Previous studies have also observed increased connectivity within the sensorimotor network and between this network and the DMN in the context of attentional deficits in mTBI (Shumskaya et al., 2017; Vergara et al., 2017). It could be hypothesised that this relationship could be mediated by the DMN (referred to in the field as the DMN interference hypothesis) due to the observed greater connectivity between the sensorimotor network and the DMN in this study and based on previous work that has shown increased connectivity within the DMN with attention deficits in mTBI (Bonnelle et al., 2011).

Our PTSD cohort showed altered mean connectivity compared with HC in the same connectome features that characterised mTBI. This is consistent with previous studies that have also found alterations in intrinsic connectivity in PTSD compared with controls (Akiki et al., 2018; Breukelaar et al., 2021; Jung et al., 2016; Lei et al., 2015; Rabinak et al., 2011; Sripada et al., 2012; Zhang et al., 2017), particularly in the networks found in our study. There were, however, no differences in mean connectivity between mTBI and PTSD in all features that characterised mTBI from controls. This is consistent with the recent evidence that suggests that mTBI is characterised by a neural profile that involves regions that are implicated in chronic stress reactions and could explain some of the overlapping symptoms observed in PCS and PTSD (Klimova et al., 2019; Korgaonkar et al., 2021; Sydnor et al., 2020).

4.1 | Limitations

There are several procedural limitations in our study that should be considered. First, we were not able to classify mTBI according to medical records that could provide objective documentation regarding loss of consciousness and post-traumatic amnesia; replication studies should attempt to validate the self-reported mTBI status and severity of participants. In hindsight, the study could have also benefitted from a standard assessment of TBI symptoms (e.g., using the neurobehavioural symptom inventory) which was not included in our protocol. Second, previous research suggests that history and nature of trauma exposure is an important variable that should be controlled for. The underlying sources of trauma were different between our mTBI and PTSD groups and previous work even in PTSD has shown differences in symptomatology of PTSD dependent on the nature of trauma (Litz et al., 2018). Third, we did not classify mTBI based on chronicity due to sample size limitations and instead used time since trauma as a continuous measure. It is possible that acute mTBI is characterised by a distinct connectivity profile compared with a more chronic illness. Although we did not observe any significant association between time since trauma and mTBI connectivity, the effects of adaptive processes and remodelling cannot be ruled out. Fourth, we did not compare mTBI participants with and without PCS as all participants in our cohort exhibited PCS symptoms. Similarly, our PTSD cohort had individuals with a higher number of comorbidities, such as depression and anxiety disorders, compared with the mTBI cohort and were taking on average more medication in line with the increased severity of the illness. Previous work has demonstrated neural circuitry differences in PTSD with and without comorbid depression (Kennis et al., 2013) and the impact of medication on neural circuitry differences is not completely understood (Lanius et al., 2010). Future work should evaluate how the presence of comorbidities and medication could influence connectivity differences between PTSD and mTBI. Finally, we did not include PTSD participants with comorbid mTBI as our focus was to disentangle the true overlap in neural mechanisms between these conditions which required including participants without comorbid mTBI and PTSD conditions. However, including this cohort could potentially help tease out any additive effects that mTBI might have on PTSD symptom severity and connectivity. It could also help to control for the underlying source of trauma.

4.2 | Summary

This study provides new insight into intrinsic connectivity alterations in mTBI and their overlap with PTSD. The aberrant functional connections observed in mTBI are known to be involved in symptoms (such as emotion dysregulation, increased anxiety) often observed in PTSD which could suggest that mTBI in itself could be a risk factor for severe PTSD. In addition, this study has several clinical implications. It identifies neuroimaging markers that could be used to monitor mTBI recovery and aid in predicting symptom prognosis. We also identified several neural features that are important for emotion regulation. Although this relationship remains to be confirmed in future work, this mechanism could be a potential target for treatment of PCS. For example, repetitive transcranial magnetic simulation of the dorsolateral prefrontal cortex (a key region of the executive control network and involved in cognitive reappraisal strategies of emotion regulation) has been trialled in PCS and shows promising results (Moussavi et al., 2019). The overlap of neural features also opens up possibilities of treating mTBI using treatment strategies commonly used in PTSD. Overall, the current findings provide neural evidence partially explaining some of the clinical overlap between mTBI and PTSD and provide an analytic framework to further understand the interplay between these two potentially debilitating conditions.

AUTHOR CONTRIBUTIONS

Aleksandra Klimova contributed to the design, data collection, analysis, interpretation and wrote first draft of the article. Isabella Breukelaar contributed to the analysis, interpretation and revision of the article. Richard A. Bryant acquired funding and contributed to the design, acquisition, interpretation and revision of the article. Mayuresh S. Korgaonkar contributed to the design, development of analysis methodology, interpretation and drafting and revision of the work. All authors approved the current version to be published.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data presented in the article is available on request by contacting the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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