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Large-scale functional hyperconnectivity patterns in trauma-related dissociation: an rs-fMRI study of PTSD and its dissociative subtype

Saurabh B. Shaw

Braeden A. Terpou

Maria Densmore

Jean Theberge
The university of Western Ontario, jthberge@uwo.ca

Pau Frewen

See next page for additional authors

Large-Scale Functional Hyperconnectivity Patterns Characterizing Trauma-Related Dissociation: A rs-fMRI Study of PTSD and its Dissociative Subtype

Saurabh Shaw (saurabhshaw2006@gmail.com)
Western University https://orcid.org/0000-0002-9887-2856
Braeden Terpou
McMaster University, Hamilton, Canada https://orcid.org/0000-0002-6770-2715
Maria Densmore
Lawson Health Research Institute
Jean Theberge
Lawson Health Research Institute
Paul Frewen
Western University
Margaret McKinnon
McMaster University
Ruth Lanius
Western University

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Abstract

The dissociative subtype of post-traumatic stress disorder (PTSD) is a distinct PTSD phenotype characterized by trauma-related dissociation, alongside unique patterns of small and large-scale functional connectivity. However, disparate findings across these various scales of investigation have highlighted the need for a cohesive understanding of dissociative neurobiology. We took a step towards this goal by conducting the largest region of interest (ROI)-to-ROI analysis performed on a PTSD population to date. While modest functional connectivity differences were found between participants with PTSD and controls in the temporal regions and the right frontoparietal network, participants with the dissociative subtype demonstrated a markedly different pattern of widespread functional hyperconnectivity among subcortical regions, sensorimotor-related networks, and other intrinsic connectivity networks, when compared to controls. Furthermore, joint brain-behavior factor analysis identified two dissociative and one PTSD symptom-linked factor. These results advance our understanding of dissociative neurobiology, characterizing it as a divergence from normative small-world organization.

1. Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was released in 2012, introducing within it a newly formulated dissociative subtype of post-traumatic stress disorder (PTSD). Nearly a decade later, extensive clinical and neurobiological evidence on the dissociative subtype has revealed a psychophysiological profile, symptom pattern, and neurocircuitry that is markedly distinct from the traditional patterns in those with PTSD.[1,2] Differences in neural activity emerge at nearly every level of the brain between those with PTSD and its dissociative subtype, ranging from brainstem and midbrain regions all the way to higher-level, associative cortices. Moreover, these differences persist across various scales of investigation—from small-scale (i.e., node-based) to large-scale (i.e., network-level) functional connectivity. Importantly, these functional alterations seem to be consistent with patterns observed among complex dissociative disorders broadly.[3,4] However, an area that could benefit from further investigation would be the integration of these disparate node-based and network-related findings to identify brain-wide associations at the broadest of scopes, while also including behavioral and demographic factors to build toward a more cohesive understanding of dissociative neurobiology. Recent research suggests that approximately 40% of patients with PTSD fail to respond to psychotherapy and pharmacotherapy.[5–8] An overarching understanding of the dissociative subtype has the potential to improve treatment response rates by advancing neuroscientifically-informed therapies. The current study takes a step towards this goal by probing brain-wide patterns of functional connectivity underlying the dissociative subtype and trauma-related dissociation more broadly, while also examining its relationship with behavioral and demographic factors.

In general, the analyses used to study PTSD tradeoff regional specificity for a wider scoped analysis spanning longer range connections, or vice versa. For example, seed- and voxel-based analyses have

become a popular method of investigating node-based, resting-state functional characteristics.[9] These analyses involve extracting a signal time course from a selected region of interest (ROI) and correlating it across all remaining whole-brain voxels. Hence, these analyses allow region-specific functional connectivity patterns to be revealed with high sensitivity, but do not readily permit global or network-level inferences.[10] By contrast, an independent component analysis (ICA) broadens the scope to assess network-level functional connectivity based on a data-driven parcellation of co-activating brain regions.[11] However, participants with PTSD display widespread network-level alterations,[12] resulting in fundamentally different network topologies. This presents challenges when comparing patterns of within-network functional connectivity group-wise. A promising albeit underutilized alternative to these analyses is a whole-brain ROI-to-ROI analysis, which allows small-scale and large-scale functional connectivity patterns to be examined concurrently.[13] Similar to seed- and voxel-based analyses, this analysis involves conducting pair-wise correlations across a pre-defined set of network-related ROIs (e.g., intrinsic connectivity networks (ICNs)). However, despite these advantages, this analysis has never been performed at a whole-brain scale in participants with PTSD or its dissociative subtype, with its application consisting thus far of a few network-restricted approaches.[14–17]

Notwithstanding some of these limitations, considerable progress has been made toward identifying the neural underpinnings of PTSD. Seed- and voxel-based functional connectivity analyses have revealed extensive resting-state functional connectivity alterations in participants with PTSD and its dissociative subtype, with reports ranging from increased resting-state functional connectivity between brainstem,[18,19] midbrain,[20–24] and limbic regions[25–28] with frontal, temporal, and parietal regions, and decreased resting-state functional connectivity between key hubs of the ICNs with other regions implicated in those networks.[29–35] Moreover, ICAs have consistently demonstrated alterations among ICNs in participants with PTSD, with increased and decreased resting-state functional connectivity commonly revealed within the salience network and the default mode network (DMN), respectively.[12, 36–39] Generally, salience network-related alterations are thought to be mediating hypervigilance and hyperarousal symptoms, while DMN-related alterations are suggested to be mediating attention- and self-related processing disturbances. Although these relationships may hold true, they nonetheless discount the possibility that a more general explanation could be accounting for many of these neurobiological findings.

Today, only a few large-scale, ROI-to-ROI analyses have been performed in participants with PTSD and, of these, all have opted for a network-restricted approach. Whereas Barredo and colleagues[15] investigated resting-state functional connectivity among networks involved in decision-making, Akiki and colleagues[14] investigated resting-state functional connectivity within the DMN using a combined structural, functional, and graph theoretic approach examining DMN-related connectivity and its relationship with PTSD symptom severity. Although informative, these studies have two key limitations: firstly, neither group used a set of ROIs that spanned the entire brain, restricting the discovery of patterns in global connectivity; and secondly, neither group referenced the dissociative subtype of PTSD. More recently, Lebois and colleagues[17] conducted a large-scale, ROI-to-ROI analysis among participants with PTSD with comorbid

dissociative symptoms and a history of childhood abuse. Thus far, their paper represents the best characterization of large-scale functional connectivity patterns underlying dissociative neurobiology. Their approach differs from the present approach in a few notable ways: firstly, they did not conduct group comparisons; secondly, they performed a subject-specific parcellation of each cortical lobe; and thirdly, they did not include subcortical regions among their set of ROIs.

In the present study, we sought to build on this prior work and address some of the remaining research gaps. We conducted the largest ROI-to-ROI analysis performed on a PTSD population to date, with a total of 132 ROIs and 197 participants, 134 of whom were diagnosed with PTSD. We implemented a whole-brain approach, comparing patterns of node-based, intra- and inter-network functional connectivity between participants with PTSD, its dissociative subtype, and non-traumatized, healthy controls. Among participants with PTSD, we conducted a joint factor analysis between the discovered patterns of functional connectivity with a battery of behavioral, demographic, and clinical scores to identify relationships between brain and behavior.

Based on the existing literature, we hypothesized observing enhanced resting-state functional connectivity among ROIs included in sensory- and motor-related networks and the salience network, as well as reduced resting-state functional connectivity among ROIs included in attention-related networks and the DMN in participants with PTSD as compared to healthy controls. Moreover, we hypothesized observing more profound differences among participants with the dissociative subtype of PTSD, given that these individuals generally display more severe symptoms relative to those with PTSD.[2,40,41] In particular, we hypothesized that the ventromedial prefrontal cortex, cerebellum, and fronto-orbital cortex would feature heavily in distinguishing the dissociative subtype of PTSD from controls based on recent findings from a prospective longitudinal biomarker study exploring persistent dissociation among at-risk trauma populations.[42]

Table 1: Participant Demographics and Clinical Scores.

Measure	Controls	PTSD	PTSD + DS
Number	63	84	50
Sex	45 Females; 18 Males	52 Females; 32 Males	40 Females; 10 Males
Age	36.7 ± 12.3	40.3 ± 12.0	40.6 ± 13.4
Ethnicity	49 Caucasian; 6 Asian; 1 African; 3 Hispanic; 4 Unknown	73 Caucasian; 2 Mixed; 1 Aboriginal; 2 Middle-Eastern; 1 Asian; 1 Hispanic; 4 Unknown	42 Caucasian; 2 Mixed; 1 African; 1 Middle-Eastern; 1 Hispanic; 3 Unknown
CAPS-IV Total	3.34 ± 6.98	66.8 ± 15.7	70.5 ± 24.9
CTQ Total	32.9 ± 8.94	55.7 ± 22.3	66.9 ± 19.1
MDI Total	36.3 ± 6.60	53.3 ± 15.0	79.6 ± 22.4
MDI Depersonalization + Derealization	5.47 ± 0.98	7.54 ± 2.64	12.8 ± 4.77

Abbreviations: CAPS: Clinician-Administered PTSD Scale (Normalized to CAPS-IV); CTQ: Childhood Trauma Questionnaire; MDI: Multiscale Dissociation Inventory

2. Results

2.1 ROI-to-ROI Analysis

FDR-corrected differences in ROI-to-ROI connectivity were observed for the PTSD > Controls and PTSD + DS > Controls contrasts, whereas no FDR-corrected differences were observed for the PTSD + DS > PTSD contrast.

2.1.1 PTSD > Controls

The differences in functional connectivity between PTSD and Controls were limited to changes in connectivity between two clusters, namely the inferior temporal gyrus (ITG) and the superior temporal gyrus (STG), and within the right frontoparietal network (FPN).

2.1.2 PTSD + DS > Controls

The differences in functional connectivity between the PTSD + DS and the healthy controls were markedly different from that observed for the PTSD > Controls contrast. Firstly, many more ROI pairs showed abnormal connectivity in those with PTSD + DS as compared to controls. Secondly, most of the abnormal connections indicated a pattern of hyperconnectivity in those with PTSD + DS. Finally, these differences in connectivity spanned a wider range of ROI clusters, including sensorimotor (primary visual, motor, auditory), cerebellar, thalamic, and behavioural and cognitive networks (salience, DMN, FPN, DAN).

The connections showing the greatest level of hyperconnectivity included those between the fronto-orbital regions and the DAN, the anterior DMN and the auditory network, FPN and salience network, salience (specifically anterior cingulate cortex) and motor networks, and finally cerebellar and subcortical brain regions (thalamus, caudate and nucleus accumbens). A detailed results table is provided in the supplementary materials (S-Table 1).

2.2 Dynamic ROI-to-ROI Connectivity

The PTSD group showed greater temporal variance in dynamic connectivity, compared to controls, while the PTSD + DS group did not show significantly different temporal variance in any ROI-to-ROI connections (shown in supplementary Figure 1). This implies that the pattern of increased hyperconnectivity seen in the PTSD + DS group could be “rigid” in its temporal dynamics, without significantly increased temporal variance when compared to controls.

2.3 Joint Brain-Behaviour Factor Analysis

Among the identified joint brain-behavior latent factors, three factors were observed to show high correlation with the brain connectivity and behavioural variables (Figure 3).

The first factor showed the highest positive scores for MDI total, accompanied by some DERS subscales, age, and CTQ. Notably, CAPS-IV appeared with a negative score within this factor, alongside BDI, some MDI subscales, employment status, and sex. The first factor was also characterized by high positive scores for the connections between the medial frontal gyrus (subregion of the anterior DMN) and the insular cortex and central operculum.

The second factor also showed the highest positive scores for the MDI total, and was accompanied by some DERS subscales, sex, CTQ, and employment status, while most of the MDI subscales appeared to have negative scores. In contrast to the first factor, the second factor showed strong positive scores for the connections between the medial frontal cortex and the bilateral central operculum, medial frontal cortex and the left insular cortex, and the medial frontal gyrus and the planum polare/temporale. Notable connections with negative scores included connectivity between the anterior cingulate and the right post-central gyrus, and the connection between the middle frontal gyrus and left central operculum (both opposite to Factor 1 results).

Finally, the third factor was characterized by a maximally positive score for CAPS-IV, with MDI total appearing as the second most negative score. This was accompanied by a positive score for the

connections between the sub-callosal cortex and central operculum, right ITG and anterior ITG, and fronto-orbital regions and anterior STG/temporal poles. Most of the other connections between the anterior DMN and the insular and opercular brain regions showed negative scores.

3. Discussion

We conducted a large-scale, ROI-to-ROI analysis among participants with PTSD and non-traumatized, healthy controls, revealing significant small-scale and large-scale functional connectivity differences, especially among those with the dissociative subtype of PTSD. Interestingly, functional connectivity patterns specific to the dissociative subtype bring to mind that of a hyperconnected and rigid brain: hyperconnected on the basis of the profound increases in functional connectivity, and rigid in terms of the similar temporal variability to that of nominally connected controls. Notably, these functional connectivity patterns align with what we would expect based on the existing literature, namely that participants with PTSD display increased functional connectivity between sensory-based networks and the salience network, and decreased functional connectivity within higher-level, ICNs. Moreover, many of these functional connectivity patterns covaried with patient scores on the CAPS, MDI, and CTQ, appearing together in the brain-behaviour factors, with the top three factors roughly corresponding to two dissociative symptom factors and a PTSD symptom factor. Here, we suspect that early childhood maltreatment—a known risk factor for the development of PTSD and dissociative symptomatology[60–62]—alters the developmental trajectory of the ICNs, leading to a breakdown in the efficient, small-world organization of the brain.[63] In order to preserve global brain functioning, the dissociative brain might require more node-based functional connectivity to make up for the lack of small-world organization. In the following paragraphs, we look to explore these findings in greater detail.

3.1 PTSD

In participants with PTSD, we revealed cluster-level functional connectivity differences within the right frontoparietal network (FPN) and between the inferior temporal gyrus (ITG) and the superior temporal gyrus (STG). The FPN, also known as the central executive network, mediates sustained attention, complex problem-solving, and working memory.[64–66] Altered FPN-related functional connectivity has been reported elsewhere in PTSD,[12,67–69] with impaired inhibitory control cited as a possible symptom associated with these alterations.[70,71] With respect to the temporal gyri, it has been suggested that the STG might be particularly vulnerable to the effects of childhood maltreatment, with maltreated children and adolescents found to have significantly greater gray matter volumes in the STG.[72] Within these temporal clusters, we found increased node-based functional connectivity between the fronto-orbital cortex and the temporal poles in participants with PTSD. The uncinate fasciculus provides a bidirectional path between these frontolimbic regions, with the temporal poles suggested to serve as a convergence zone where semantic representations of people and places are imbued with emotional significance.[73] In turn, these semantic representations are proposed to guide fronto-orbital cortex-mediated decision-marking. Decreased white matter integrity of the uncinate fasciculus has been reported in participants

with PTSD,[74,75] and correlated with PTSD symptom severity.[76] Perhaps these reported increases in frontolimbic functional connectivity function to compensate for these white matter alterations in PTSD, a question requiring more direct investigation.

3.2 Dissociative Subtype of PTSD

By contrast, participants with the dissociative subtype of PTSD revealed considerably more cluster-level functional hyperconnectivity, especially among subcortical networks, sensorimotor-related networks, and other ICNs. The strongest of these patterns of functional hyperconnectivity was found between the dorsal attention network (DAN) and the ITG, which was also found to positively covary with the PTSD symptom factor (Factor 3) of the joint factor analysis, and negatively covary with the other two dissociative symptom factors (Factor 1 and 2). Whereas the DAN mediates externally-directed attention, the ITG underlies higher-level, visual processing and associated semantic representations.[77,78] Although these results reflect resting-state data, they could be taken to suggest that participants with the dissociative subtype allocate greater attentional resources to the processing of visual information, perhaps as a means to compensate for blunted executive functions facilitating semantic memory processing and retrieval.[79]

Interestingly, some of the strongest results featured the cerebellum. Specifically, cerebellar lobules 4, 5, 6, and 10, and cerebellar vermes 4, 5, 6, 7, and 9 were hyperconnected with thalamic and striatal regions in the dissociative subtype. Moreover, these thalamic and striatal regions were significantly more functionally connected with other regions of the cerebellum, the brainstem, and the parahippocampal gyrus, pointing to a general pattern of hyperconnectivity among subcortical regions critically involved in sensory, motor, and memory-related processing. These findings were also supported by the joint factor analysis, which found that the functional connectivity between the vermes 4 and 5 and the nucleus accumbens positively covaried with the dissociative factors (Factors 1 and 2) and negatively covaried with the PTSD symptom factor (Factor 3). Although promising, more research is needed to better understand how cerebellar and striatal functional connectivity patterns contribute to PTSD symptomatology.

Conversely, higher-level ICNs also demonstrated alterations in the dissociative subtype, with patterns of functional hyperconnectivity revealed between the left FPN and the salience network, and between the anterior DMN and the auditory network. These findings converge with those of Lebois and colleagues[17] who found FPN- and DMN-related functional connectivity alterations to be the strongest predictors of dissociative symptomatology among participants with PTSD. Furthermore, we found that the anterior cingulate cortex and insular cortex nodes of the salience network were hyperconnected with the motor network and the anterior DMN in participants with the dissociative subtype, respectively. Moreover, the pattern of hyperconnectivity between the insular cortex and the anterior DMN was most strongly associated with the joint factor for dissociative symptomatology (Factor 1), perhaps suggesting that dissociative symptomatology is disproportionately rooted in salience- and DMN-related functional alterations. Interestingly, a recent systematic review on the biomarkers of pathological dissociation found

results convergent to this, namely that dissociation as a transdiagnostic construct is associated with altered functional connectivity among key hubs of the salience network and the DMN.[4] Taken together, these findings reveal a common pattern of global hyperconnectivity between higher-level, ICNs with lower-level, sensory- and motor-related networks, deviating from what we might expect based on a small-world organization of the brain.

3.3 Limitations and Future Directions

Next, we offer a few limitations to consider, as well as future directions that extend from these considerations. Firstly, we used a non-traumatized, healthy control group as opposed to a trauma-exposed, healthy control group. Hence, we cannot say with certainty that the observed responses are specific to the etiology of PTSD, since they may have resulted from trauma exposure more generally. Secondly, we did not assess for complex dissociative disorders among the patient sample. A recent study found that nearly half of those with the dissociative subtype of PTSD additionally meet criteria for one or more of the dissociative disorders,[80] highlighting the importance of considering comorbid dissociative disorders in future investigations.[81] Thirdly, the ROIs used span the cortex and certain subcortical regions, but do not include many parcels of the brainstem and midbrain, leaving these regions underrepresented. Replicating these analyses with atlases that parcellate the brainstem and midbrain would yield a much richer description of subcortical–cortical interactions.[82] Lastly, pathological dissociation often involves transitioning between different biopsychosocial states (also known as, 'parts') at varying time intervals, underscoring the importance of considering the temporal dynamics of these patterns of functional connectivity.[83,84] While our approach to assessing dynamic connectivity is effective at estimating temporal dynamics, it would stand to benefit from a shorter repetition time (TR) and a more detailed investigation of the stability of the observed abnormal connections.

4. Conclusion

In the largest ROI-to-ROI analysis performed on a PTSD population to date, we revealed widespread small-scale and large-scale functional connectivity differences among participants with PTSD and its dissociative subtype. These findings were generated with conservative significance thresholds, which speaks to the magnitude of these differences. In the dissociative subtype of PTSD, we found evidence of a general pattern of hyperconnectivity, especially among subcortical regions, sensory- and motor-related networks, and other ICNs. These patterns seem to reflect a deviation from the small-world organization of the brain, which might suggest a pattern of hyperconnectivity serves a compensatory function to preserve global brain functioning. Although these hypotheses demand more direct investigation, they provide a neurobiological framework to understand the dissociative subtype of PTSD and trauma-related dissociation more generally. These findings also have important clinical implications, especially for neuroscientifically-guided treatments that look to normalize large-scale functional connectivity patterns (e.g., neurofeedback, neurostimulation). In closing, it cannot be lost that these patterns likely served an

adaptive function at some critical juncture in development, helping these individuals to cope with adversity early in life, a perspective that will be useful to keep in mind when guiding future research.

5. Detailed Materials and Methods

5.1 Participant Information

Data from a total of 197 participants (Healthy Controls: N=63; PTSD: N=84; Dissociative Subtype of PTSD (PTSD+DS): N=50) were included in this study (Table 1). These participants were recruited through a combination of referrals from healthcare workers and advertisements within the London, Ontario community over a period of 12 years (2009–2022). The recruited participants belonged to a wide range of ethnicities (given in Table 1). All participants provided written informed consent, adhering to the study protocol approved by the Research Ethics Board at Western University, London, ON, Canada. The age, sex and ethnic distributions of the groups did not differ significantly.

5.1.1 Inclusion Criteria

Participants were included in either of the PTSD groups based on a primary diagnosis of PTSD, as determined using the Clinician-Administered PTSD Scale[43,44] (CAPS). Notably, CAPS Version-IV[43] was used for 76 participants, while CAPS Version-5[44] was used for 58 participants after it's update, to assess participants with the most updated diagnostic criteria. To maintain compatibility with previously collected data, the total scores from the CAPS-5 scale were normalized to match that of CAPS-IV using a procedure similar to that performed in Nicholson and colleagues.[45,46]

Inclusion in the PTSD + DS group additionally required a score ³ 2 for both frequency and intensity of either depersonalization or derealization symptoms within the CAPS-IV scale, or a symptom severity ³ 2 for the depersonalization or derealization symptoms within the CAPS-5 scale, as per standard procedure.[45,47,48]

5.1.2 Exclusion Criteria

Participants were excluded from the PTSD and PTSD + DS groups if they had comorbid alcohol or substance abuse/dependencies that were not in sustained full remission, and if they were diagnosed with bipolar disorder or schizophrenia. Participants were excluded from the control group on the basis of any lifetime Axis-I psychiatric disorder, determined using SCID and CAPS. Finally, participants were excluded if they did not meet MR safety standards, were pregnant, had a previous head injury involving loss of consciousness.

5.1.3 Clinical Questionnaires

In addition to the CAPS, a battery of questionnaires probing behavioural, demographic, and clinical data was collected, including the Childhood Trauma Questionnaire[49] (CTQ), Beck Depression Inventory[50] (BDI),

Multiscale Dissociation Inventory[51] (MDI), and Difficulties in Emotion Regulation Scale[52] (DERS). MDI and DERS total scores and subscales were analyzed. Finally, age, biological sex, highest education level, and employment status were also collected.

5.2 Imaging Protocol and Preprocessing

All MRI scanning was performed using a 3T Siemens Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany), and a 32-channel head coil. Each scan included an axial 3D MPRAGE scan (TI/TR/TE=900/2000/4.2ms, FA=9^{o}, 192x256x256, thickness=1mm), followed by a 6-minute fMRI resting-state scan, acquired using a 2D GRE EPI sequence (TR/TE=3000/20ms, FA=90^{o}, 120x128x128x62, thickness=2mm). The participants were instructed to let their minds wander freely without thinking of anything in particular during the resting-state scan.

All preprocessing and further analysis used SPM12 and the CONN toolbox (version 21a)[53], including realignment and unwarping, 12-DOF motion correction, frequency-domain phase shift slice timing correction (STC), ART-based outlier scrubbing, simultaneous normalization to the MNI152 atlas and segmentation[54], spatial smoothing (6mm Gaussian), and band-pass filtering (0.008Hz-0.09Hz).

5.3 ROI-to-ROI Analysis

A total of 132 ROIs were used in the large-scale ROI-to-ROI analysis, combining 106 cortical and subcortical ROIs from the Harvard-Oxford atlas,[55] and 26 cerebellar ROIs from the AAL atlas[56]. This set of ROIs were chosen for the current study due to their extensive use in the literature where whole-brain coverage is needed for ROI-to-ROI analyses, and its integration with the CONN toolbox [53]. Such a well validated set of ROIs was deemed critical for the current study, given the lack of whole-brain ROI-to-ROI analysis performed on a PTSD population to date. This inevitably excluded more detailed parcellations of the midbrain and brainstem regions, which should be investigated in future studies. Pairwise bivariate correlation coefficients were computed between each pair of ROIs using their preprocessed BOLD timeseries, followed by Fisher transformation to allow inter-subject comparisons. Between-group ANOVA analyses were performed, estimating the PTSD > Controls, PTSD + DS > Controls, and PTSD + DS > PTSD contrasts. All results were corrected for multiple comparisons at the cluster level, using a two-sided threshold of *p*-FDR<0.05. The *a priori* grouping of the 132 ROIs provided within the CONN toolbox was used to define the clusters. The F-statistic and T-statistic values, estimates of effect sizes (h^2 for the F-statistic and Cohen's d_z for the T-statistic), uncorrected p-values and FDR-corrected p-values are given in supplementary table 1. The h^2 and d_z were computed as follows [86],

$$\eta 2 = \frac{F \times df_{effect}}{F \times df_{effect} + df_{error}}$$

$$d_z = \frac{T}{\sqrt{n}}$$

where F and T were the F-statistic and T-statistic values, respectively, df_{error} was the degrees of freedom of the effect, df_{error} was the degrees of freedom of the error, and *n* was the number of participants.

5.4 Dynamic ROI-to-ROI Connectivity

To determine if the between-group differences observed were a result of a shift in static connectivity or from a change in dynamic connectivity between these ROIs, dynamic connectivity was estimated using 32 sliding windows of length 45 seconds (spaced 10 seconds apart). A dynamic connectivity graph was then created using the variance of connectivity strength between each pair of ROIs as the edge weight, followed by a between-group ANOVA, with similar contrasts as the previous analysis.

5.5 Joint Brain-Behaviour Factor Analysis

Finally, to assess the behavioural implications of the observed group differences in ROI-to-ROI connectivity, joint brain-behaviour factor analysis was performed using the pool of the participants from the two PTSD groups. The ROI-to-ROI connections surviving FDR corrections were analyzed alongside 20 behavioural, demographic, and clinical variables using canonical correlation analysis (CCA) to identify joint brain-behaviour latent factors.[57–59] This analysis was performed in MATLAB R2022a (MathWorks Inc., Natick, MA), utilizing the built-in implementation of the CCA algorithm. To ensure stability of the identified factors, the CCA analysis was repeated 10 times with a random subset of the participants for each run. The top three factors with the highest joint correlation (>0.9) were extracted and analyzed.

Declarations

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Disclosures

S.B. Shaw, B. Terpou, M. Densmore, J. Théberge, P. Frewen, M. McKinnon, and R. Lanius do not have any financial disclosures or conflicts of interest to disclose.

Data Availability Statement

The group data (SPM files) from the ROI-to-ROI large scale analyses reported in this manuscript will be made available upon request and are not openly available due to ethical and privacy concerns. Please direct any such request to the corresponding author via email.

Code Availability Statement

All analysis used standard SPM12, CONN (version 21a) analysis pipelines, and MATLAB R2022a implementations of some algorithms. Hence, no custom code was used in this study.

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Figures

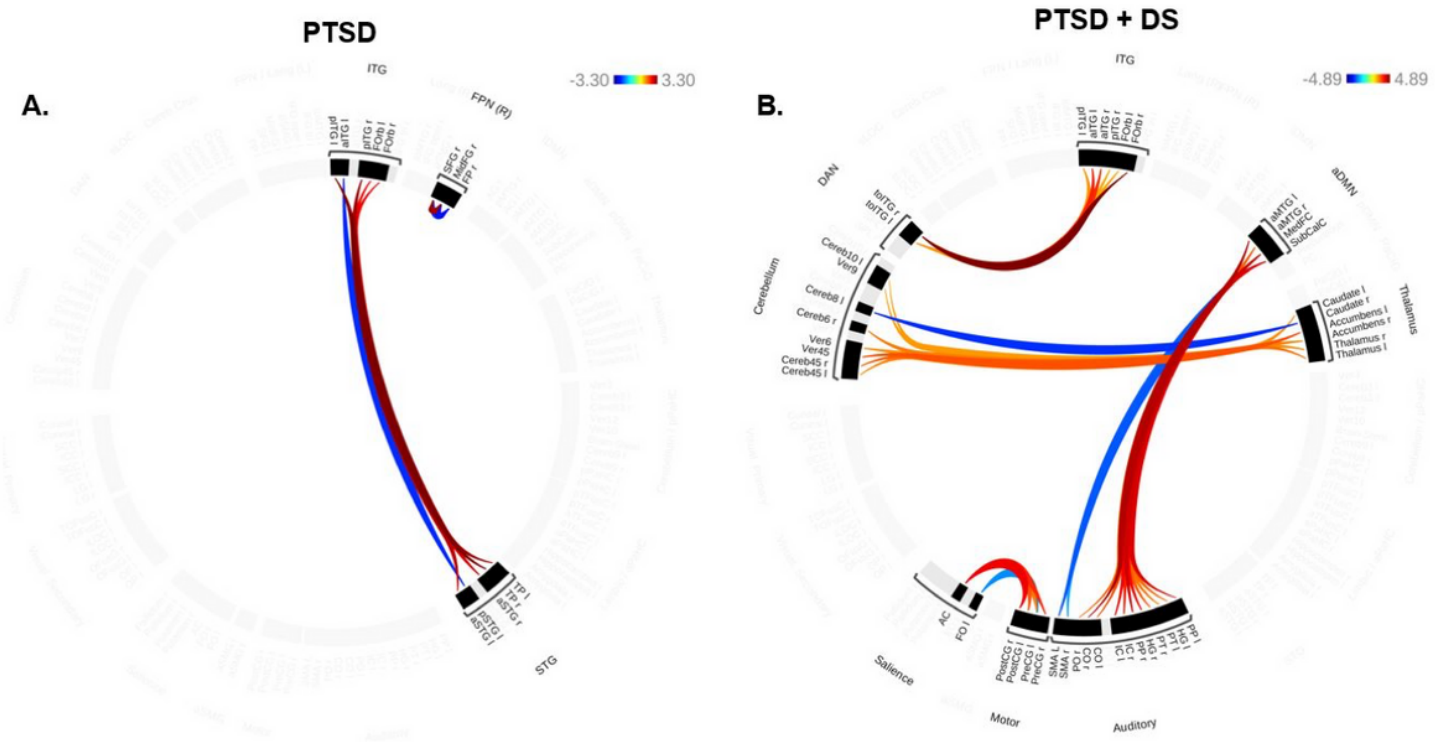

Figure 1

ROI-to-ROI connectivity differences between A). PTSD > Controls; and B). PTSD + DS > Controls. Results are FDR-corrected at the cluster level. Note the markedly higher number of abnormal connections in PTSD + DS > Control as compared to the PTSD > Control contrast, with most connections being hyperconnected. The colormap represents the T-value for the relevant contrast. See supplementary Table 1 for full results table.

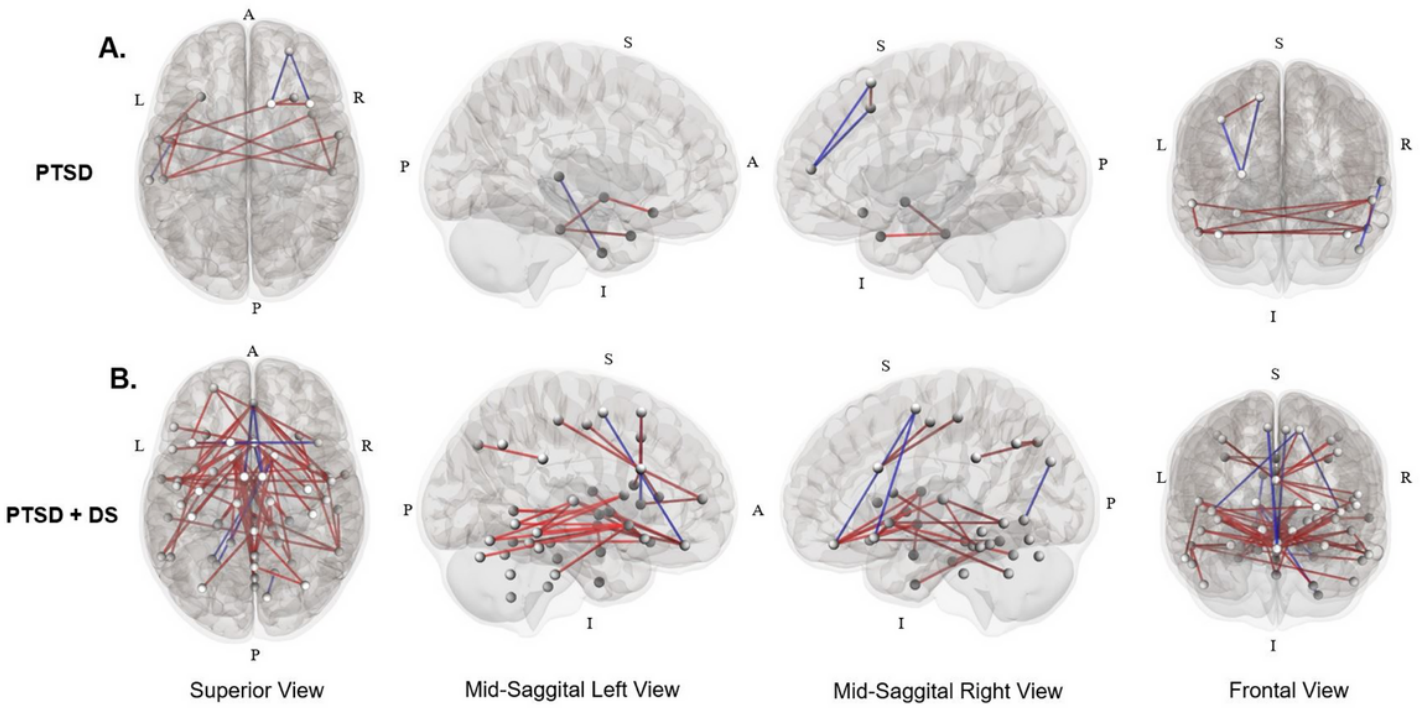

Figure 2

ROI-to-ROI connectivity differences from Figure 1, visualized on the brain for the contrast A). PTSD > Controls; and B). PTSD + DS > Controls. These are shown across different views (left to right – superior view, mid-saggital left view, mid-saggital right view and frontal view). The anterior (A), posterior (P), superior (S), inferior (I), left (L) and right (R) directions are also shown.

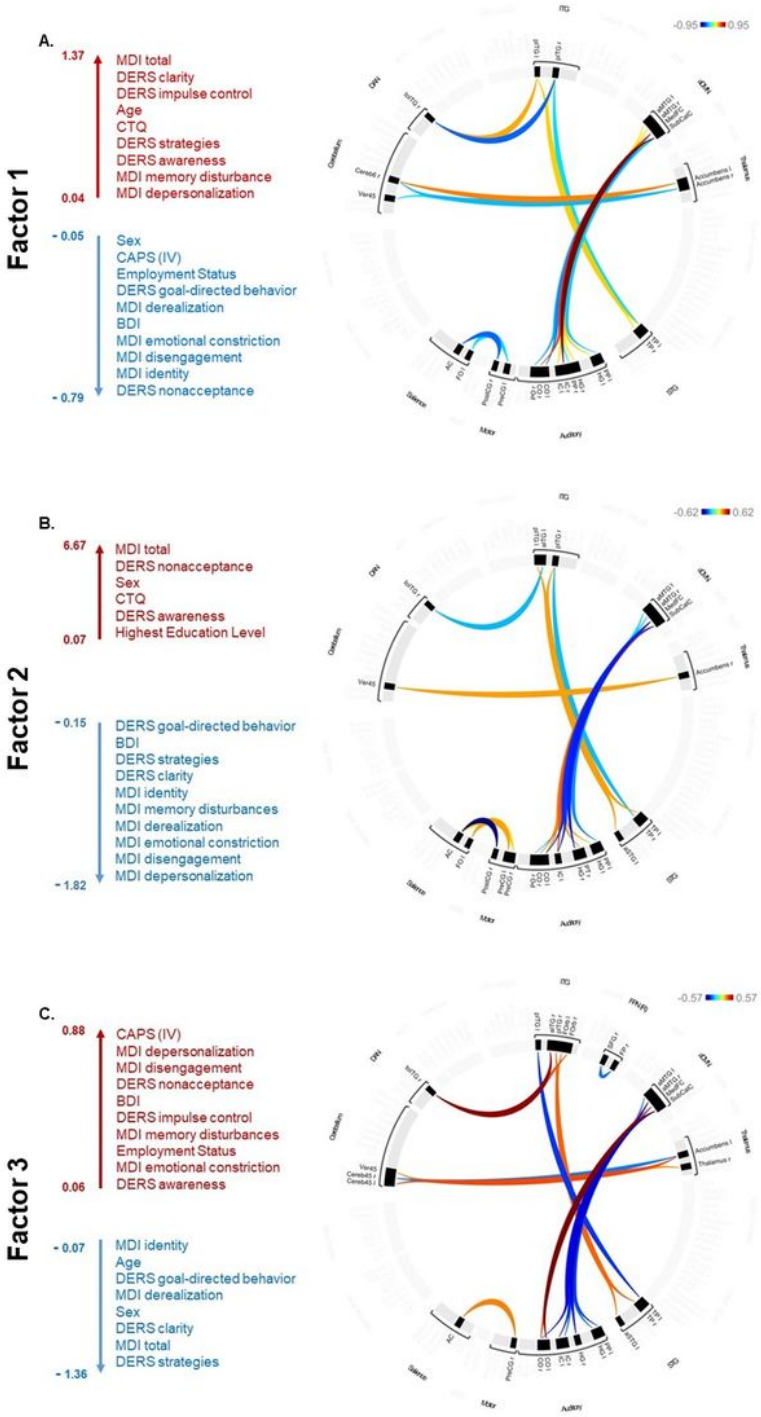

Figure 3

Composition of the top three joint factors with maximal correlation across the brain connectivity results shown in Figures 1 & 2, and behavioral, clinical, and demographic data. The weights of the variables and connections to each factor are shown in red if they positively contribute to the factor, or in blue if they negatively contribute to the factor.

Supplementary Files

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