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# Data-driven approach to dynamic resting state functional connectivity in post-traumatic stress disorder: An ENIGMA-PGC PTSD study

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**Abstract**

Using functional magnetic resonance imaging (fMRI), symptoms of posttraumatic stress disorder (PTSD) have been associated with aberrations in brain networks in the absence of a given cognitive demand or task, called resting-state networks. Prior work has focused on disruption in the static functional connectivity (FC) among specific regions constrained by *a priori* hypotheses. However, dynamic FC, an approach that examines brain network characteristics over time, may provide a more sensitive measure to understand the network properties underlying dysfunction in PTSD. Further, using a data-driven analytic approach may reveal the contribution of other larger network disturbances beyond those revealed by hypothesis-driven examinations of ROIs or canonical networks. Therefore, the current study used group independent components analysis (ICA) and graph theory principles to identify, characterize, and subsequently compare brain network dynamics and recurrent connectivity states in a large sample of trauma exposed individuals (N=1,035) with and without PTSD from the ENIGMA-PGC PTSD workgroup. Neither static FC nor dynamic FC results showed robust differences between groups. There were also no group differences in dwell time or number of transitions of recurrent connectivity states. This multi-cohort sample with heterogenous trauma types and demographic features offers a significantly larger scale approach than prior literature with smaller homogenous trauma cohorts. Heterogeneity of PTSD, especially within diffuse brain networks, may not be captured by evaluating only diagnostic groups, further work should be done to evaluate brain network dynamics with respect to specific symptom profiles and trauma types.

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## Introduction

Globally, 70% of individuals are estimated to be exposed to trauma, and 40% are estimated to experience direct interpersonal violence (1). While the majority of individuals are resilient after trauma exposure, a substantial minority develop chronic posttraumatic stress disorder (PTSD) and related disorders (2–4). Symptoms of PTSD disrupt daily function and include re-experiencing the event through intrusive thoughts, nightmares, and flashbacks, avoiding trauma reminders, hyperarousal, and experiencing negative thoughts or emotions that begin or worsen after the event (5).

A growing body of literature has reported large-scale disruptions in resting state canonical networks in people suffering from PTSD (reviewed in (6,7). These canonical networks constitute correlated activity amongst neighboring and/or diffuse regions of the brain that robustly replicate across samples (8,9). Differential alterations in these networks have been associated with symptoms of PTSD (6,10–16) and many of the network "hubs" are regions commonly identified in ROI-based approaches (e.g., hippocampus, amygdala, frontal cortex).

Resting state functional magnetic resonance imaging (rs-fMRI) research has yielded robust results for canonical network analyses even within rather heterogeneous clinical disorders (e.g. PTSD; (11,17–19); however, one potentially limiting factor in this line of research is the use of static functional connectivity (FC) in which all brain activity during a resting state scan is condensed (i.e. averaged) into one metric. Though rs-fMRI scans consist of several minutes of undirected, task-independent activity, brain regions show time-invariant fluctuations in activity which can be captured via dynamic FC. Dynamic FC involves segmenting a resting state time series into smaller time bins, for example using a sliding window, so that network connectivity can be analyzed with greater temporal resolution (14,18,20–25).

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Relatively few studies have examined dynamic FC in those with PTSD (18,20–25); however, this method may be a more sensitive way of understanding network dysfunction in PTSD. In a sample of earthquake survivors using a network from a whole brain atlas, dynamic FC was a better predictor of PTSD than the more "traditional" static FC of the same network (20); those with PTSD had lower temporal variability across the distributed network compared to controls. Similar results have been reported in other small samples ($n < 100$) using various analytic approaches to identify the network evaluated in the dynamic FC analysis. For example, group differences in dynamic FC between individuals with and without PTSD have been reported for motor vehicle crash survivors using a voxel-wise approach (26) and in earthquake survivors using a structural connectome derived from diffusion tensor imaging (21). Though the direction of results (i.e., greater or lesser dynamic FC) between groups is reportedly mixed, these temporal dynamics would not have been identifiable by examining the full time series of resting state data (27,28). This emerging work has underscored that examining changes in functional connectivity across time may be more informative to understanding the properties of brain network function than simply the average strength of functional connections (29–31).

The current study builds upon the current literature by using a large and diverse sample of trauma exposed individuals from the large ENIGMA-PGC PTSD Neuroimaging workgroup database. The current study aimed to examine dynamic FC in a data driven manner, independent of *a priori* seed or canonical network, to 1) compare static and dynamic FC properties between trauma-exposed individuals who did and did not meet criteria for PTSD diagnosis, and 2) identify and compare dynamic FC connectivity states between groups. As demonstrated in the literature, a data-driven approach has the potential to identify new or additional regions or networks involved in the neurocircuitry underlying PTSD. The analysis and characterization of

connectivity states, or brain network states that reoccur over time, may describe, or explain the nuances and heterogeneity of PTSD symptomology more accurately than traditional analysis techniques. Use of a large database of trauma-exposed individuals ensures sufficient power for analyses as well as increases the potential for generalizability of findings across a diverse sample with various trauma exposures.

## Method

*Participants*

The current study utilized resting state fMRI scans, demographic and clinical data collected by the ENIGMA-PGC PTSD working group (https://pgc-ptsd.com/). Thirty international sites with resting state fMRI data in a sample of participants recruited to evaluate the effects of trauma on the brain were considered for analysis (N = 3,068). All study procedures were approved by respective site local institutional review boards (IRB), and participants provided written informed consent. The present analyses were granted exempt status by the University of Wisconsin-Milwaukee IRB. Given this consortium was organized and assembled in a post-hoc fashion, all contributing sites organized and conducted their respective studies using different study designs, clinical, and demographic features. Thus, a uniform set of data quality assurance checks were conducted on data from each site before analysis. Notably, a significant proportion of participants were dropped from final analysis such that the final sample was **N=1,035** (336 PTSD; Table 1). The drop in sample size was primarily due to the analysis exclusion criteria of variable TR length (only retained scans with TR = 2sec), sufficient duration for the dynamic rs-fMRI analysis, and poor data quality. See Supplemental Figure 1 for consort diagram and Supplemental Table 1 and 2 for sample characteristics and inclusion and exclusion criteria by site, respectively. All participants were trauma-exposed, and PTSD diagnosis was

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determined by DSM-IV and DSM-5 criteria within the respective clinical measure used at each site (see supplement for details). PTSD symptom severity is reported to support separability of PTSD diagnostic groups and due to scope, is included only as an exploratory analysis. Symptom severity was calculated using a harmonized total current PTSD severity score as the percentage of total points possible within each respective measure (normalized range = 0 – 1). Symptom severity was missing for 19% of the final sample and these cases were listwise removed from the correlational analyses (N = 834).

*Analytic Strategy Overview*

The current analysis involved many detailed steps, so a general overview of the analysis procedure is described here with full details in the supplementary material. Resting-state data were preprocessed using the standardized pipeline HALFpipe version 1.2.2 (32). Briefly, HALFpipe extends the utility of fMRIPrep with additional preprocessing and postprocessing steps and interactive quality assessment tools. See Supplemental Table 3 for scan acquisition parameters by site). Following preprocessing, the analysis pipeline followed the approach of previous work (31,33–35). First, the data-driven approach to brain network identification utilized a group independent component analysis (ICA) using the GIFT v4.0 toolbox (http://mialab.mrn.org/software/gift/) (36,37) to identify spatial regions within the brain that constitute the resting state brain network to be analyzed (see supplement for details). Group ICA was chosen over other methods of component derivation (i.e. spatio-temporal regression) due to its enhanced sensitivity to detect group differences (38) and was run on the whole sample. Resulting components from this approach represent components of a heterogenous sample of trauma-exposed individuals, which can be compared between those who did and did not meet diagnostic criteria for PTSD.

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To understand group differences in static FC across the whole network, graph metrics (i.e. global efficiency, local efficiency, clustering coefficient, connectivity strength, and characteristic path length) were calculated using the Brain Connectivity Toolbox in MATLAB (39). Metrics were calculated for the whole static-FC matrix (i.e. weighted graph of the correlations of the full time series for each component pair) yielding a single metric for each subject. Metrics were then averaged across subjects within diagnostic group and compared between groups. An FDR correction ($\alpha$=0.01) was applied to correct for multiple comparisons (40). As an exploratory analysis, Pearson's correlations were also run to examine associations between PTSD symptom severity and static FC graph metrics.

To evaluate dynamic FC of the network over time, a sliding window was used to segment the full resting state time series (120 TRs) into 101-time windows (window width=20TRs or 40 seconds and the window was advanced by 1 TR at each iteration). The decision to use a 20TR window width was made to balance the number of total windows in analysis (>100) with recommendations in the literature that suggest longer window widths yield more stable network dynamics (41,42). However, additional iterations of window length (5-30TRs in steps of 5TRs) were considered and results are included in the supplementary material. Importantly, patterns of results did not change with use of different window lengths. Pearson correlations between pairs of components were calculated for each time window and converted to a signed similarity measure (equation 1 in (31). Positive and negative correlations were included so that weighted graphs could be used to describe the magnitude and direction of correlations between regions. Graph theory metrics of interest were calculated for each time window across the whole network and compared between groups within each time window using t-tests and corrected for multiple comparisons ($FDR_{\alpha}$=0.01). For additional exploration and to reduce the number of comparisons,

the whole network time series was sectioned into three nonadjacent 24-window segments (i.e., time windows 1-25, 39-63, 77-101) to examine beginning, middle, and of scan FC without contamination effects (i.e. autocorrelation) between adjacent windows or segments, wherein groups were compared on average graph metrics within each segment.

To identify individual-level connectivity states, defined as reoccurring network states through time, modularity was assessed across all time windows for each subject. Time windows with high correlations of component strengths/connectivity measures were considered modular (39,43) and assigned to the same module. Each module was then considered an "individual-level connectivity state". The number of modules for each subject were counted so that quantities of connectivity states between groups could be compared.

To identify group-level connectivity states, the modules identified in the individual-level connectivity states analysis were submitted to a *k*-means clustering algorithm using the Python library *scikit-learn* (44–47). The elbow criterion was used to select the optimal number of clusters for the *k*-means solution (48). The cluster centroids, for a given cluster solution choice, were then used to predict cluster membership of each time window for each subject, based on Euclidean distance to the centroid (34,49). All time windows were assigned membership to a group-level connectivity state, which yielded a time series of connectivity states for each subject. From this time series, dwell time within each state was calculated by the sum of time windows assigned to a given state. Transitions between states were quantified by tallying the instances of state membership change between consecutive time windows (1-back) across the whole time series. As in the static FC analysis, exploratory Pearson's correlations were run to examine associations between PTSD symptom severity and individual and group-level connectivity state metrics.

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*Covariates of interest*

The covariates of interest when considering group comparisons were scanner site, PTSD diagnosis (Dx), age, gender, race, and major depressive disorder (MDD) Dx. Rather than including it as a categorical covariate in the group statistics, scanner site was accounted for directly in the analysis pipeline by applying *ComBat* to achieve fMRI data harmonization (see Supplement for details; (50,51). Gender and age were consistently reported with no missing data. During *ComBat* harmonization PTSD diagnosis, age, and gender were protected covariates during removal of site effects. Including all covariates of interest (age, gender, race, depression Dx) results in a final sample of n = 796 with 229 PTSD+ (n = 99 missing race, n = 143 missing depression Dx). Due to the 23% loss in sample size with inclusion of all covariates, all group-level analyses are presented with and without covariates. Covariates were compared across PTSD and Control groups, where available.

## Results

There was a significant group difference in age such that those in the PTSD group were older ($M_{Control}$ = 30.05, $M_{PTSD}$ = 32.80; $t(1033) = 3.61$, $p < .01$). There were marginally more men in the PTSD group ($\chi^2(1) = 4.21$, $p = .04$). Compared to the Control group, there were significantly fewer Black and significantly more White individuals in the PTSD group ($\chi^2(14) = 11.68$, $p < .001$). Compared to the Control group, there were more individuals in the PTSD group with depression ($\chi^2(1) = 85.97$, $p < .001$; Table 1). Those in the PTSD group had significantly higher PTSD symptom severity than the Control group ($M_{Control}$ = .45, $M_{PTSD}$ = .08; $t(832) = 36.64$, $p < .001$) suggesting robust separation of groups by diagnostic criteria.

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*Group ICA*

The 75 components output from the group ICA were visually inspected by two authors (CWT and JMF). Mutual agreement for component retention resulted in 41 components that comprised the final network carried forward in all analyses. Results of the reliability estimation (stability indices, $I_q$ ; average intra-cluster similarity over 10 runs of INFOMAX) indicated all 41 final components chosen were stable and reliable (all $I_q > 0.77$; (52). For ease of interpretation, final network components were broadly grouped into domains according to broad anatomical and functional properties i.e., cerebellar (CB), attention/cognitive control (COG), default-mode network (DMN), language and audition (L/A), sensorimotor (SM), subcortical (SC), and visual (VIS), with reference to previous research using similar methods (31,33,35,53,54) in conjunction with submitting peak coordinates for each component to NeuroSynth (https://neurosynth.org/) for confirmation with previous fMRI metanalytic studies. Domain grouping did not change the specific components derived from the group ICA step, but rather allowed for interpretation of how derived components may functionally relate to one another within domains/subnetworks. See Figure 1 for a composite image of components grouped by domain. See Supplemental Table 4 for brain regions, peak coordinates (RAI orientation; right-anterior-inferior), number of voxels, and stability indices for each of the final components organized by domain.

*Static Functional Connectivity*

For the whole network, there were no significant differences between PTSD and Controls in global efficiency, local efficiency, clustering coefficient, connectivity strength, or path length (Table 2). Results did not change after adjusting for covariates though males consistently had significantly higher global efficiency, local efficiency, clustering coefficient, connectivity strength and significantly lower path length than females ($p$'s < .001). There was no significant

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interaction of sex and diagnostic group in any models (*p*'s > .26). PTSD symptom severity was not correlated with whole network graph metrics (all *p*'s > .11; Supplemental Table 7).

Next, group comparisons were evaluated among components in the network using the average similarity index for each pair of static FC components. There was one significant group difference for a pair of regions in the visual (occipital pole) and sensorimotor networks (postcentral gyrus) such that those with PTSD had greater static FC between these regions than Controls though this effect did not hold with the inclusion of covariates. There were no other significant group differences in static FC in any pairwise components in the network (Figure 2).

*Dynamic Functional Connectivity*

Patterns of dynamic fluctuations in graph metrics for the whole network are shown by group in Figure 3. In both groups, there is a gradual ramping up of network efficiencies (i.e. increasing global and local efficiency, clustering coefficient, and connectivity strength and decreasing path length) from the beginning to the end of the scan. When each time window was examined individually, there were no significant group differences in network efficiencies before or after FDR correction. However, when examined by equal and nonadjacent thirds, the PTSD group had significantly higher network efficiencies in the first and last third of the time series compared to Controls, and significantly lower efficiencies in the middle third compared to Controls (all *p*'s < .01). Of note, differences in efficiencies are on the order of <1% (e.g. first third global efficiency: $M_{PTSD}$ = .675, $M_{Control}$ = .669; second third global efficiency: $M_{PTSD}$ = .675, $M_{Control}$ = .682; last third global efficiency: $M_{PTSD}$ = .686, $M_{Control}$ = .682). This same pattern of results held when examining cognition, DMN, sensorimotor, subcortical, and visual subnetworks (Supplemental Figure 5).

*Connectivity States*

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In either group, at most six connectivity states were identified for an individual across the whole scan. Results showed there were no significant differences in the number of individual-level connectivity states in any group comparisons, with or without covariates (Table 2; Supplemental Figure 7). PTSD symptom severity was not associated with individual-level connectivity states ($p$ = .33; Supplemental Table 7).

Based on results of the *k*-means clustering analysis, a 3-cluster solution was chosen. See Supplemental Figure 8 for heat maps of similarity indices across group state cluster centroids. Connectivity state #1 depicts a state with *low within and between* network connectivity, connectivity state #2 depicts *high within* and *high between* network connectivity, and connectivity state #3 depicts *moderate within and between* network connectivity (Supplemental Table 5). Across the whole scan in the whole sample, there were no significant differences in dwell time in either group connectivity state, or in number of transitions between states (Table 2; Supplemental Figure 9). Results did not change with the inclusion of covariates. PTSD symptom severity was not correlated with dwell times or transitions between states (all $p > .07$; Supplemental Table 7).

## Discussion

The current study utilized a data-driven approach to evaluate resting state brain network dynamics in a large global sample of individuals diagnosed with PTSD, and a control group of trauma exposed individuals without a diagnosis of PTSD. Differences between groups were tested for both static and dynamic FC graph-metrics within the resting-state networks identified via group ICA. Further, recurrent connectivity states identified through *k*-means clustering of time windows derived from the dynamic FC analysis were examined at the individual- and

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group-level. Neither static FC, dynamic FC analyses, nor connectivity states analysis showed robust differential patterns of graph dynamics between groups.

*Network Identification (Group ICA)*

First, the components extracted from the group ICA, especially after organization into six cognitive domains, closely resemble networks identified in many other samples using the same method (31,35,52,55–57). Relative consistency in the final components used within studies across researchers in several different fields lends support to the reliability of this data-driven approach to network identification in resting state fMRI analyses (30,38,55,58,59).

*Static Functional Connectivity*

A significant majority of seed-based and canonical network-based approaches reported reduced connectivity in those with PTSD compared to controls (30). On the other hand, studies using graph theory metrics to characterize seed-based or canonical networks reported lower graph metrics in those with PTSD relative to Controls (6,60). However, the current study saw little evidence of significant group differences in global network dysfunction and no correlations with PTSD symptom severity. There were some trending differences towards PTSD having lower connectivity within and between some subnetworks however these should not be over examined as the study was well powered to detect differences. Overall, these results do not align with the literature that routinely reports aberrations in specific regions of the default mode and salience networks in those with PTSD, such as the hippocampus and insula (6,60). Indeed, compromised structural integrity of the hippocampus in those with PTSD has been reported in a large overlapping portion of the current sample (17,61).

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*Dynamic Functional Connectivity and Connectivity States*

Closer examination of graph metrics in the dynamic FC analysis showed there were no robust group differences nor correlations with PTSD symptom severity in graph metric dynamics or connectivity states. Though there was a divergence between groups in efficiencies midway through the scan session, these differences were marginal (<1%). However, both groups showed a negligible ramping up of network efficiencies from the beginning to the end of the scan. There were some slight differences in these trends when examining each subnetwork, though group differences were still insignificant. These results do not align with the literature that has reported lower dynamic FC among regions such as the precuneus and insula and higher dynamic FC among frontal regions (18,20,21,58). The general trends observed in network dynamics across both groups may reflect trends unique to trauma exposure; however, the current study did not have a true "healthy control" group for comparison to support this claim. Future work should consider more targeted manipulation of brain states through task paradigms that may yield cognitively relevant neural signal related to PTSD symptoms and diagnosis.

*General Discussion*

The analysis and overall method of the current study was adopted from methodology applied to other clinical samples, including schizophrenia (31,35,56,57) and Alzheimer's Disease (62). The current study is the first to apply this method on a large, well-powered, diverse trauma sample (N=1,035). This method has been shown to yield highly reproducible and reliable results of network identification and FC properties (55). Despite the widespread use of dynamic FC approaches, there is significant criticism of the approach; for example, one study showed dynamic FC can be attributed to differences in how the brain organizes itself and may be tied to maintenance of functions that are derived from sleep states (63). These are complex processes,

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and our data suggest that DSM classification of PTSD status does not exhibit clear differences in these processes, again owing to heterogeneity of these processes within groups. Further, fMRI effect sizes in psychopathology are quite small and spurious findings in small samples (e.g. n = 100) have been shown to not replicate at larger sample sizes (e.g. n = 1,000; (64,65). Therefore, the results of the current study suggest previous PTSD diagnosis effects in dynamic FC at rest in smaller samples may fail to replicate in larger heterogenous samples. Though the greater heterogeneity in trauma exposure had the potential to increase generalizability of results, the degree of heterogeneity across sites and participant samples in addition to the numerous methodological differences between the current study and prior work may have impeded replication of prior literature.

Previous work by the ENIGMA-PGC PTSD workgroup, using the same method to standardize diagnosis of PTSD across study sites, has identified PTSD diagnosis group effects in structural volumes of the hippocampus, amygdala, and cerebellum suggesting sufficient power to detect group differences (17,61,66). By contrast, results herein suggest that those who met criteria for PTSD did not differ from trauma-exposed individuals who do not meet criteria in resting dynamic FC. Given the sample is trauma exposed there is certainly a question of how subthreshold clinical symptoms impact results; however, this was beyond the scope of the current study and future investigation should consider subthreshold symptoms.

*Limitations*

Given the retrospective design of the ENIGMA-PGC PTSD studies, there were many variables that could not be accounted for because they were either not collected at all sites or were measured in different ways. Variables that would have been pertinent to the aims and analysis but could not be included due to extreme missingness or were not reported to the

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consortium were index trauma timing and type, previous trauma history, anxiety disorder or other comorbidities, and substance and/or medication use. In addition, a large loss of sample size was necessary given the parameters of the analysis. Second, deriving components via group ICA using the full resting state time series may compromise the ability to detect dynamic changes in the network. Future work might consider applying group ICA to smaller time windows to evaluate changes in component identification over the course of the scan. Similarly, more fine-grained comparisons across time should be employed in analyzing dynamic FC and connectivity states to provide clarity as to when network connectivity patterns emerge during a resting state scan. However, given the immense heterogeneity of scan acquisition parameters among participants in the sample, smaller scale time comparisons were unreasonable. Finally, findings may generalize better than prior studies due to the variability in trauma type, though future work should account for previous trauma history and symptom presentation when possible.

*Conclusion*

While trauma exposure is a common global phenomenon, PTSD presentation is not (67). There are myriad combinations of symptoms that make PTSD a heterogenous disorder. The results of the current study suggest that in a diverse multi-site cohort of trauma exposed individuals, there were no differences in resting state-brain network organization that underlie PTSD diagnosis. Differences within the static dynamic and connectivity states analyses may be too nuanced to distinguish at the diagnostic group level; however, effects may emerge with closer examination of the context of trauma exposure and other unexamined comorbidities. Differences in resting-state networks in PTSD are often reported in smaller and homogenous trauma samples, and the current results provide additional support to studying PTSD as a disorder whose symptom presentation varies according to many factors. As such, continued

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investigation of the nuances of dynamic functional connectivity with respect to PTSD is warranted.

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**Author Contributions**

C.W. Tomas, J.M. Fitzgerald, C. Larson, and R.A. Morey made significant contributions to the conception and design of the analysis and interpretation of the work as well as drafting and revising of the manuscript. All authors contributed data to the analysis, reviewed and edited the manuscript, gave final approval of the version to be published, and accept accountability for all aspects of the work and its accuracy and integrity.

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**Competing Interests**

L.A.M. Lebois reports unpaid membership on the Scientific Committee for the International Society for the Study of Trauma and Dissociation (ISSTD), grant support from the National Institute of Mental Health, K01 MH118467, and spousal IP payments from Vanderbilt University for technology licensed to Acadia Pharmaceuticals unrelated to the present work. ISSTD and NIMH were not involved in the analysis or preparation of the manuscript. M.L. Kaufman reports unpaid membership on the Scientific Committee for the International Society for the Study of Trauma and Dissociation (ISSTD), grant support from National Institutes of Mental Health (R21MH112956, R01MH119227). ISSTD and NIMH were not involved in the analysis or preparation of the manuscript. W. El Hage reports affiliations with Air Liquide, Boehringer Ingelheim, CHUGAI, EISAI, Jazz Pharmaceuticals, Janssen, Lundbeck, Novartis, Otsuka, UCB of which none relate to the current manuscript. R.J. Davidson is the founder and president of, and serves on the board of directors for, the non-profit organization Healthy Minds Innovations, Inc, not related to the current manuscript. C.G. Abdallah has served as a consultant and/or on advisory boards for Douglas Pharmaceutical, Aptinyx, Genentech, Janssen, Psilocybin Labs, Lundbeck, Guidepoint, and FSV7. He also filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (Aug 20, 2018). None were involved in the preparation of the current manuscript. The remaining authors have nothing to disclose.

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**References**


1. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatology. 2017 Oct 27;8(sup5):1353383.

2. Bonanno GA. The resilience paradox. Eur J Psychotraumatology. 2021 Jan 1;12(1):1942642.

3. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. Eur J Psychotraumatology. 2014 Dec 1;5(1):25338.

4. Valiente C, Vázquez C, Contreras A, Peinado V, Trucharte A. A symptom-based definition of resilience in times of pandemics: patterns of psychological responses over time and their predictors. Eur J Psychotraumatology. 2021 Jan 1;12(1):1871555.

5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. 5 edition. Washington, D.C: American Psychiatric Publishing; 2013. 991 p.

6. Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. Curr Psychiatry Rep. 2017 Sep 19;19(11):81–4.

7. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011 Oct;15(10):483–506.

8. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007 Sep;8(9):700–11.

9. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011 Sep 1;106(3):1125–65.

10. Clausen AN, Francisco AJ, Thelen J, Bruce J, Martin LE, McDowd J, et al. PTSD and cognitive symptoms relate to inhibition-related prefrontal activation and functional connectivity. Depress Anxiety. 2017 May;34(5):427–36.

11. Ke J, Zhang L, Qi R, Li W, Hou C, Zhong Y, et al. A longitudinal fMRI investigation in acute post-traumatic stress disorder (PTSD). Acta Radiol Stockh Swed 1987. 2016 Nov 1;57(11):1387–95.

12. King AP, Block SR, Sripada RK, Rauch S, Giardino N, Favorite T, et al. Altered default mode network (dmn) resting state functional connectivity following a mindfulness-based exposure therapy for posttraumatic stress disorder (PTSD) in combat veterans of Afghanistan and Iraq. Depress Anxiety. 2016 Apr 1;33(4):289–99.

13. Spadoni AD, Huang M, Simmons AN. Emerging approaches to neurocircuits in PTSD and TBI: Imaging the interplay of neural and emotional trauma. Curr Top Behav Neurosci. 2018;38:163–92.

14. Yuan H, Phillips R, Wong CK, Zotev V, Misaki M, Wurfel B, et al. Tracking resting state connectivity dynamics in veterans with PTSD. NeuroImage Clin. 2018;19:260–70.

15. Zhang XD, Yin Y, Hu XL, Duan L, Qi R, Xu Q, et al. Altered default mode network configuration in posttraumatic stress disorder after earthquake: A resting-stage functional magnetic resonance imaging study. Medicine (Baltimore). 2017 Sep 1;96(37):e7826.

16. Zhang Y, Xie B, Chen H, Li M, Liu F, Chen H. Abnormal functional connectivity density in post-traumatic stress disorder. Brain Topogr. 2016;29:405–11.

17. Dennis EL, Disner SG, Fani N, Salminen LE, Logue M, Clarke EK, et al. Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults: results from the PGC-ENIGMA PTSD consortium. Mol Psychiatry. 2019 Dec 19;

18. Lei D, Li K, Li L, Chen F, Huang X, Lui S, et al. Disrupted functional brain connectome in patients with posttraumatic stress disorder. Radiology. 2015 Sep;276(3):818–27.

19. Spielberg JM, McGlinchey RE, Milberg WP, Salat DH. Brain network disturbance related to posttraumatic stress and traumatic brain injury in veterans. Biol Psychiatry. 2015;78(3):210–6.

20. Jin C, Jia H, Lanka P, Rangaprakash D, Li L, Liu T, et al. Dynamic brain connectivity is a better predictor of PTSD than static connectivity. Hum Brain Mapp. 2017 Sep;38(9):4479–96.

21. Li X, Zhu D, Jiang X, Jin C, Zhang X, Guo L, et al. Dynamic functional connectomics signatures for characterization and differentiation of PTSD patients. Hum Brain Mapp. 2014 Apr;35(4):1761–78.

22. Suo X, Lei D, Li K, Chen F, Li F, Li L, et al. Disrupted brain network topology in pediatric posttraumatic stress disorder: A resting-state fMRI study: Suo et al. Hum Brain Mapp. 2015 Sep;36(9):3677–86.

23. Xu J, Chen F, Lei D, Zhan W, Sun X, Suo X, et al. Disrupted functional network topology in children and adolescents with post-traumatic stress disorder. Front Neurosci. 2018;12:709.

24. Zhang Y, Liu F, Chen H, Li M, Duan X, Xie B, et al. Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. J Affect Disord. 2015 Nov;187:114–21.

25. Zhu H, Li Y, Yuan M, Ren Z, Yuan C, Meng Y, et al. Increased functional segregation of brain network associated with symptomatology and sustained attention in chronic post-traumatic stress disorder. J Affect Disord. 2019 Mar;247:183–91.

Author Manuscript

26. Fu S, Ma X, Wu Y, Bai Z, Yi Y, Liu M, et al. Altered Local and Large-Scale Dynamic Functional Connectivity Variability in Posttraumatic Stress Disorder: A Resting-State fMRI Study. Front Psychiatry. 2019 Apr 12;10:234.

27. Zhang J, Kucyi A, Raya J, Nielsen AN, Nomi JS, Damoiseaux JS, et al. What have we really learned from functional connectivity in clinical populations? NeuroImage. 2021 Nov;242:118466.

28. Greene AS, Horien C, Barson D, Scheinost D, Constable RT. Why is everyone talking about brain state? Trends Neurosci. 2023 Jul;46(7):508–24.

29. Fornito A, Zalesky A, Bullmore E. Fundamentals of brain network analysis. London: Academic Press; 2016.

30. Ross MC, Cisler JM. Altered large-scale functional brain organization in posttraumatic stress disorder: A comprehensive review of univariate and network-level neurocircuitry models of PTSD. NeuroImage Clin. 2020;27:102319.

31. Yu Q, Erhardt EB, Sui J, Du Y, He H, Hjelm D, et al. Assessing dynamic brain graphs of time-varying connectivity in fMRI data: application to healthy controls and patients with schizophrenia. NeuroImage. 2015 Feb 15;107:345–55.

32. Waller L, Erk S, Pozzi E, Toenders YJ, Haswell CC, Büttner M, et al. ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based data. Hum Brain Mapp. 2022 Jun 15;43(9):2727–42.

33. Allen EA, Erhardt EB, Damaraju E, Gruner W, Segall JM, Silva RF, et al. A baseline for the multivariate comparison of resting-state networks. Front Syst Neurosci. 2011;5:2.

34. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD. Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex N Y N 1991. 2014 Mar;24(3):663–76.

35. Damaraju E, Allen EA, Belger A, Ford JM, McEwen S, Mathalon DH, et al. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. NeuroImage Clin. 2014;5(C):298–308.

36. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group infer- ences from functional MRI data using independent component analysis. Hum Brain Mapp. 2001;14(140):151.

37. Erhardt EB, Rachakonda S, Bedrick EJ, Allen EA, Adali T, Calhoun VD. Comparison of multi-subject ICA methods for analysis of fMRI data. Hum Brain Mapp. 2011 Dec 1;32(12):2075–95.

38. Salman MS, Du Y, Damaraju E, Lin Q, Calhoun VD. Group information guided ICA shows more sensitivity to group differences than dual-regression. In: 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017) [Internet]. Melbourne, Australia: IEEE;

Author Manuscript

2017 [cited 2023 Feb 8]. p. 362–5. Available from: http://ieeexplore.ieee.org/document/7950538/

39. Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage. 2010;52:1059–69.

40. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol. 1995;57(1):289–300.

41. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex. 2012;22(1):158–65.

42. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, et al. Dynamic functional connectivity: promise, issues, and interpretations. NeuroImage. 2013 Oct 15;80:360–78.

43. Telesford QK, Burdette JH, Laurienti PJ. An exploration of graph metric reproducibility in complex brain networks. Front Neurosci. 2013 May 13;7:67.

44. Forgy EW. Cluster analysis of multivariate data: efficiency vs interpretability of classification. Biometrics. 1965;21:768–9.

45. Hartigan JA, Wong MA. Algorithm AS 136: A K-means clustering algorithm. 1979;28:100–8.

46. Lloyd SP. Least squares quantization in PCM. IEEE Trans Inf Theory. 1982;28:128–37.

47. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: Machine learning in Python. J Mach Learn Res. 2011;12:2825–30.

48. Ketchen DJ, Shook CL. The application of cluster analysis in strategic management research: An analysis and critique. Strateg Manag J. 1996 Jun 1;17(6):441.

49. Aggarwal C, Hinneburg A, Keim D. On the surprising behavior of distance metrics in high dimensional space. Database Theory ICDT. 2001;420–34.

50. Fortin JP, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, et al. Harmonization of multi-site diffusion tensor imaging data. NeuroImage. 2017 Nov;161:149–70.

51. Fortin JP, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, et al. Harmonization of cortical thickness measurements across scanners and sites. NeuroImage. 2018 Feb;167:104–20.

52. Ma S, Correa NM, Li XL, Eichele T, Calhoun VD, Adalı T. Automatic identification of functional clusters in FMRI data using spatial dependence. IEEE Trans Biomed Eng. 2011 Dec;58(12):3406–17.

Author Manuscript

53. Allen EA, Erhardt EB, Wei Y, Eichele T, Calhoun VD. Capturing inter-subject variability with group independent component analysis of fMRI data: A simulation study. NeuroImage. 2012 Feb 15;59(4):4141–59.

54. Yao Z, Shi J, Zhang Z, Zheng W, Hu T, Li Y, et al. Altered dynamic functional connectivity in weakly-connected state in major depressive disorder. Clin Neurophysiol. 2019 Nov;130(11):2096–104.

55. Abrol A, Damaraju E, Miller RL, Stephen JM, Claus ED, Mayer AR, et al. Replicability of time-varying connectivity patterns in large resting state fMRI samples. NeuroImage. 2017;163:160–76.

56. Salman MS, Du Y, Lin D, Fu Z, Fedorov A, Damaraju E, et al. Group ICA for identifying biomarkers in schizophrenia: 'Adaptive' networks via spatially constrained ICA show more sensitivity to group differences than spatio-temporal regression. NeuroImage Clin. 2019;22:101747.

57. Yu Q, Plis SM, Erhardt EB, Allen EA, Sui J, Kiehl KA, et al. Modular organization of functional network connectivity in healthy controls and patients with schizophrenia during the resting state. Front Syst Neurosci [Internet]. 2012 [cited 2020 Oct 22];5. Available from: http://journal.frontiersin.org/article/10.3389/fnsys.2011.00103/abstract

58. Fu Z, Tu Y, Di X, Du Y, Pearlson GD, Turner JA, et al. Characterizing dynamic amplitude of low-frequency fluctuation and its relationship with dynamic functional connectivity: An application to schizophrenia. NeuroImage. 2018 15;180(Pt B):619–31.

59. Rashid B, Damaraju E, Pearlson GD, Calhoun VD. Dynamic connectivity states estimated from resting fMRI identify differences among schizophrenia, bipolar disorder, and healthy control subjects. Front Hum Neurosci. 2014;8:897.

60. Breukelaar IA, Bryant RA, Korgaonkar MS. The functional connectome in posttraumatic stress disorder. Neurobiol Stress. 2021 May;14:100321.

61. Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, et al. Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. Biol Psychiatry. 2018 Feb;83(3):244–53.

62. Fu Z, Caprihan A, Chen J, Du Y, Adair JC, Sui J, et al. Altered static and dynamic functional network connectivity in Alzheimer's disease and subcortical ischemic vascular disease: shared and specific brain connectivity abnormalities. Hum Brain Mapp. 2019 01;40(11):3203–21.

63. Laumann TO, Snyder AZ, Mitra A, Gordon EM, Gratton C, Adeyemo B, et al. On the Stability of BOLD fMRI Correlations. Cereb Cortex. 2016 Sep 2;cercor;bhw265v1.

Author Manuscript

64. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. Nature. 2022 Mar 24;603(7902):654–60.

65. Ioannidis JPA. Correction: Why Most Published Research Findings Are False. PLOS Med. 2022 Aug 25;19(8):e1004085.

66. Huggins AA, Baird CL, Briggs M, Laskowitz S, Hussain A, Fouda S, et al. Smaller total and subregional cerebellar volumes in posttraumatic stress disorder: a mega-analysis by the ENIGMA-PGC PTSD workgroup. Mol Psychiatry. 2024 Mar;29(3):611–23.

67. Galatzer-Levy IR, Bryant RA. 636,120 ways to have posttraumatic stress disorder. Perspect Psychol Sci J Assoc Psychol Sci. 2013 Nov;8(6):651–62.

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*Table 1.* Final sample characteristics by diagnostic group **(N=1,035)**

| | **PTSD (N=336)** | **Control (N=699)** |
|---|---|---|
| **Gender** | 137 female / 199 male | 334 female / 365 male |
| **Age,** M (SD) | 32.80 (10.99) | 30.05 (11.67) |
| **Race**, N=937; % | | |
| Asian | <5 | <5 |
| American Indian | <5 | 0 |
| Black/African American | 19 | 26 |
| Latino | <5 | <5 |
| Multiracial | 12 | <5 |
| Pacific Islander | <5 | 0 |
| Unknown | <5 | <5 |
| White | 59 | 45 |
| **Depression Dx,** N=892 | 185 + / 91 - | 206 + / 410 - |
| **PTSD Severity*,** N = 834; M (SD) | .45 (.17) | .08 (.12) |

*Note:* M, mean; SD, standard deviation; Dx, diagnosis; N, sample size. *PTSD severity scores have been normalized across measures as the percentage of total points possible in each respective measure (normalized range = 0 - 1).

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*Table 2.* Static functional connectivity and connectivity states graph metric comparisons by group (N=1,035)

| | | Mean PTSD | Mean Control | *t* | *p*-value | 95% CI |
|---|---|---|---|---|---|---|
| **Static functional connectivity** | **Global Efficiency** | .689 | .688 | -.22 | .82 | (-.008, .007) |
| | **Local Efficiency** | .683 | .682 | -.30 | .76 | (-.009, .006) |
| | **Clustering Coefficient** | .683 | .682 | -.30 | .76 | (-.009, .006) |
| | **Connectivity Strength** | 27.54 | 27.51 | -.23 | .81 | (-.362, .284) |
| | **Path Length** | 1.51 | 1.52 | .27 | .78 | (-.01, .02) |
| **Connectivity States** | **# Individual CS** | 3.31 | 3.27 | .71 | .47 | (-.06, .14) |
| | **CS #1 Dwell Time** | 39.19 | 38.25 | .46 | .88 | (-4.87, 2.99) |
| | **CS #2 Dwell Time** | 21.75 | 21.11 | .37 | .70 | (-4.00, 2.72) |
| | **CS #3 Dwell Time** | 40.05 | 41.62 | -1.08 | .28 | (-1.28, 4.44) |
| | **Transitions** | 7.80 | 7.90 | .38 | .70 | (-.41, .60) |

*Note*. *t*, *t*-statistic; *p*, *p*-value (uncorrected); CI, confidence interval; CS, group-level connectivity state.
* $p < .05$.

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**Figures**

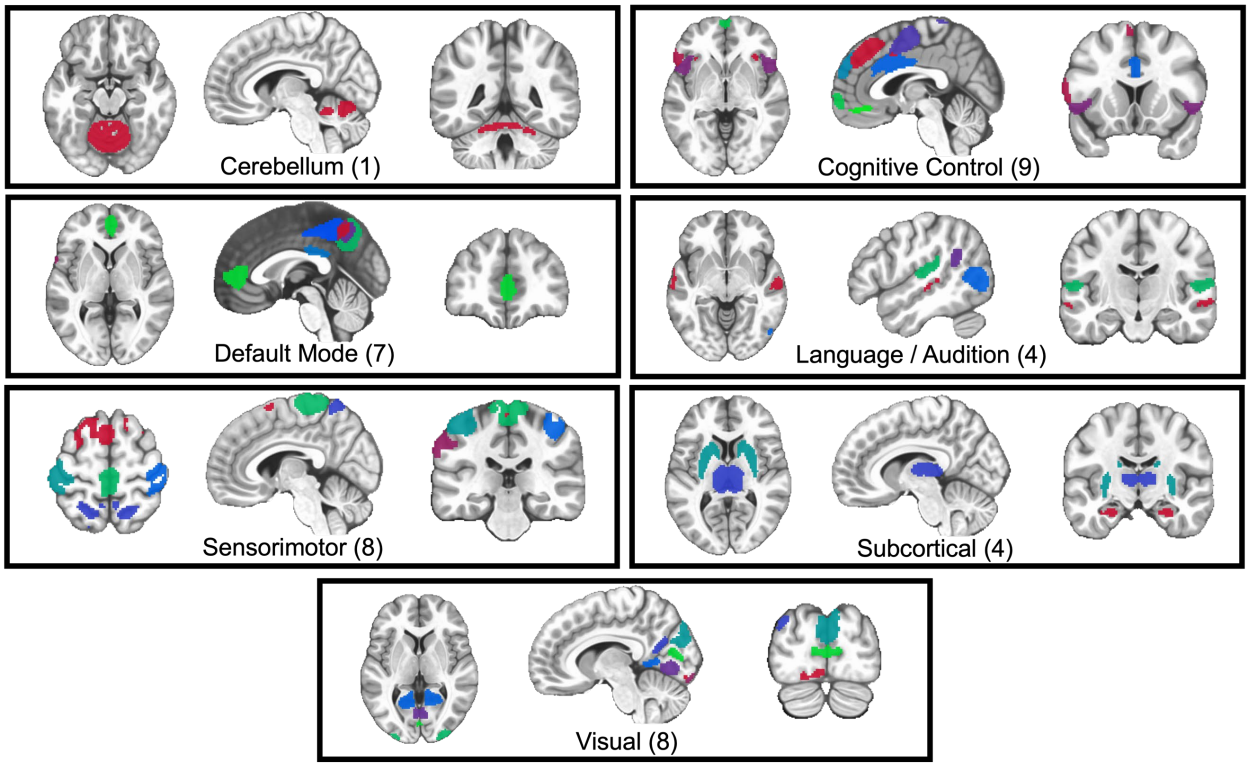



*Figure 1.* Composite images of final 41 components grouped into domains.

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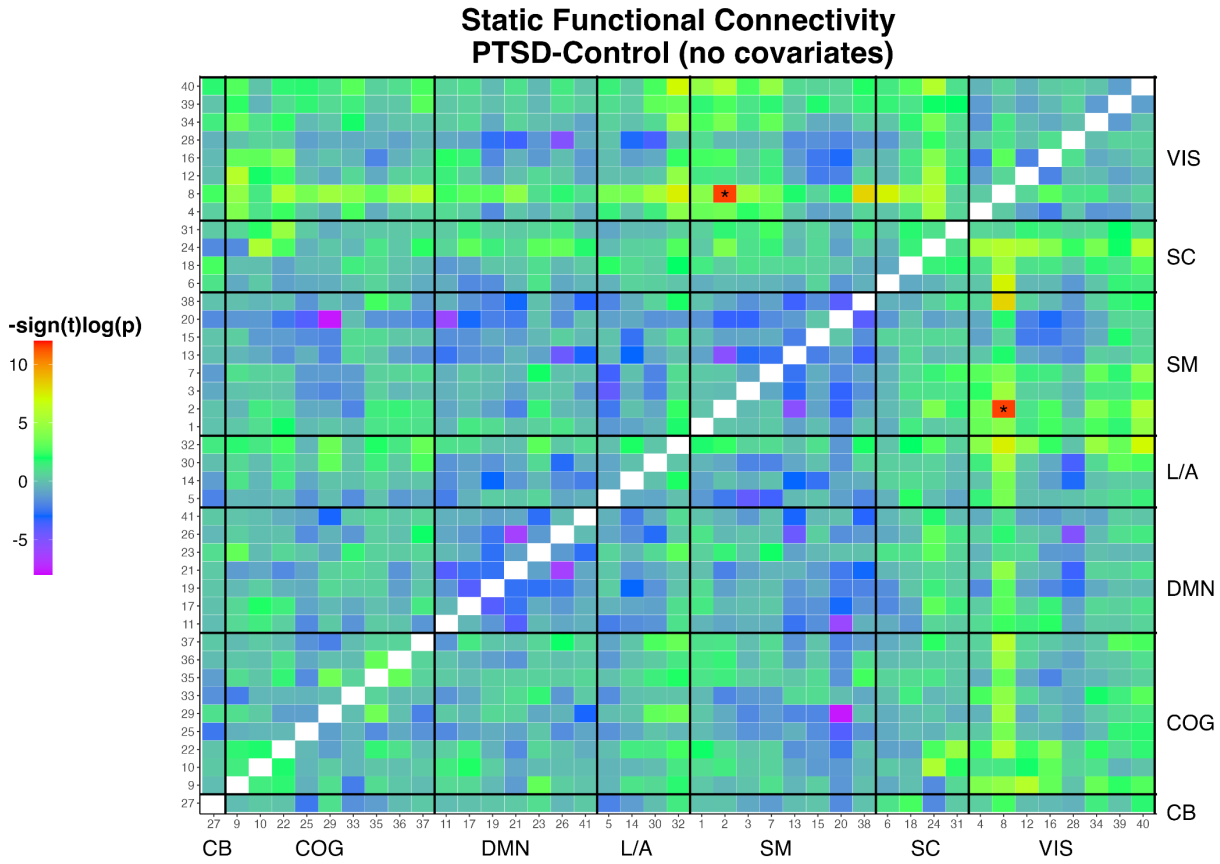



*Figure 2.* Heat map of group differences between PTSD and Control of static functional connectivity correlations for all pairwise components (N=1,035). Values are plotted as sign(*t*)*-log(*p*) where *t* and *p* values were obtained from the group diagnosis term of the *t*-test model. Results are presented this way to simultaneously indicate the strength and direction of the group effect for each comparison. Heat map is symmetrical with respect to the diagonal. Black horizontal and vertical lines indicate organization of components into broad cognitive domains: CB=cerebellar, COG=attention/cognitive control, DMN=default mode network, L/A=language/audition, SM=sensorimotor, SC=subcortical, VIS=visual.



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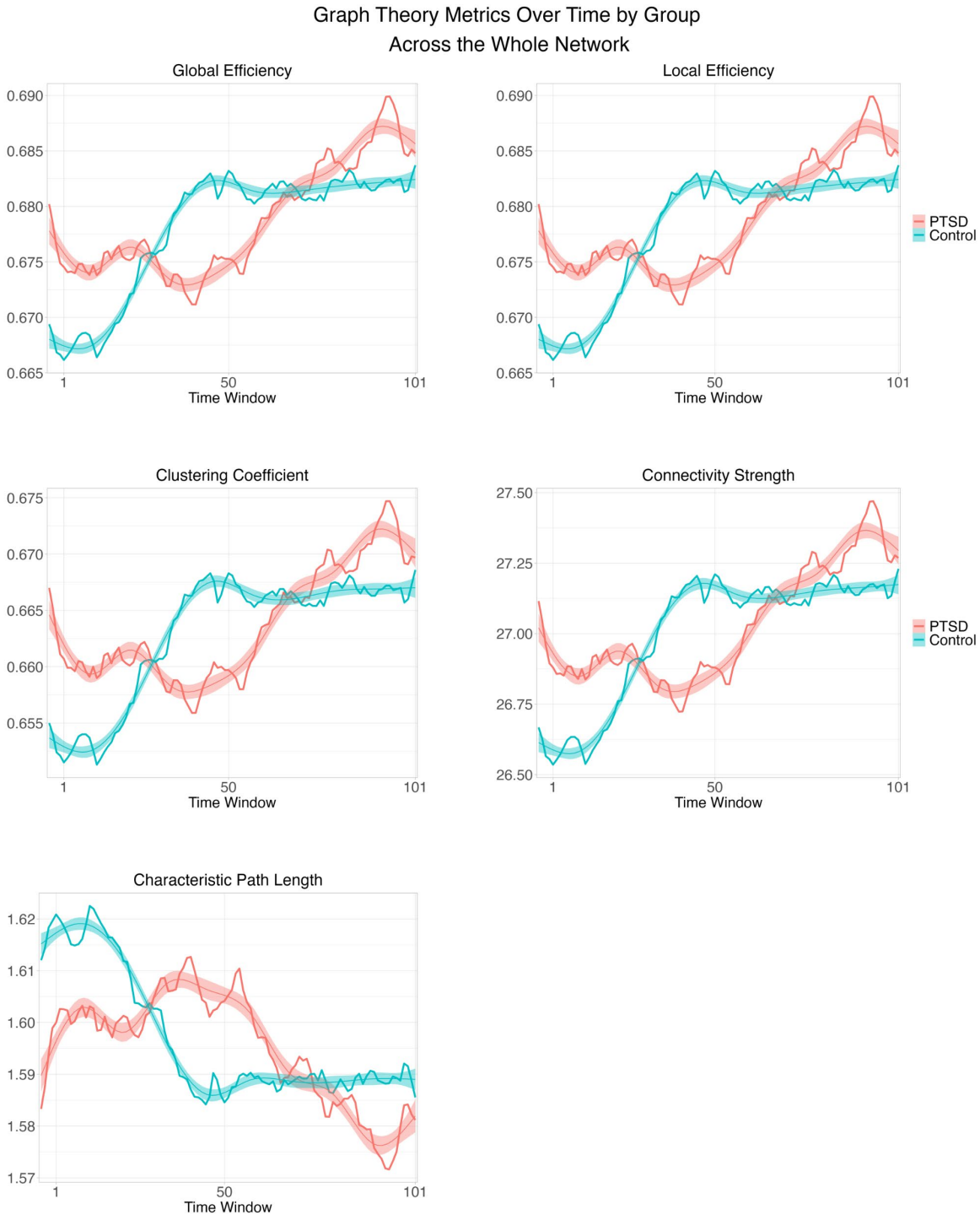



*Figure 3.* Graph metrics averaged across the whole network plotted over 101-time windows (window length = 20TRs) for each group. Red lines represent the PTSD group, and teal lines represent the Control group. The smoothed time series with error bands depict a fitted gamma function with 95% confidence interval (N=1,035). There were no significant group differences in graph metrics over time across the whole network.

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Graphical Abstract Text

In a large global sample of people with trauma exposure, we utilized a data-driven approach to evaluate resting state brain network dynamics. Neither static nor dynamic functional connectivity dynamic analyses showed robust differential patterns of graph dynamics between those with posttraumatic stress disorder and those without.

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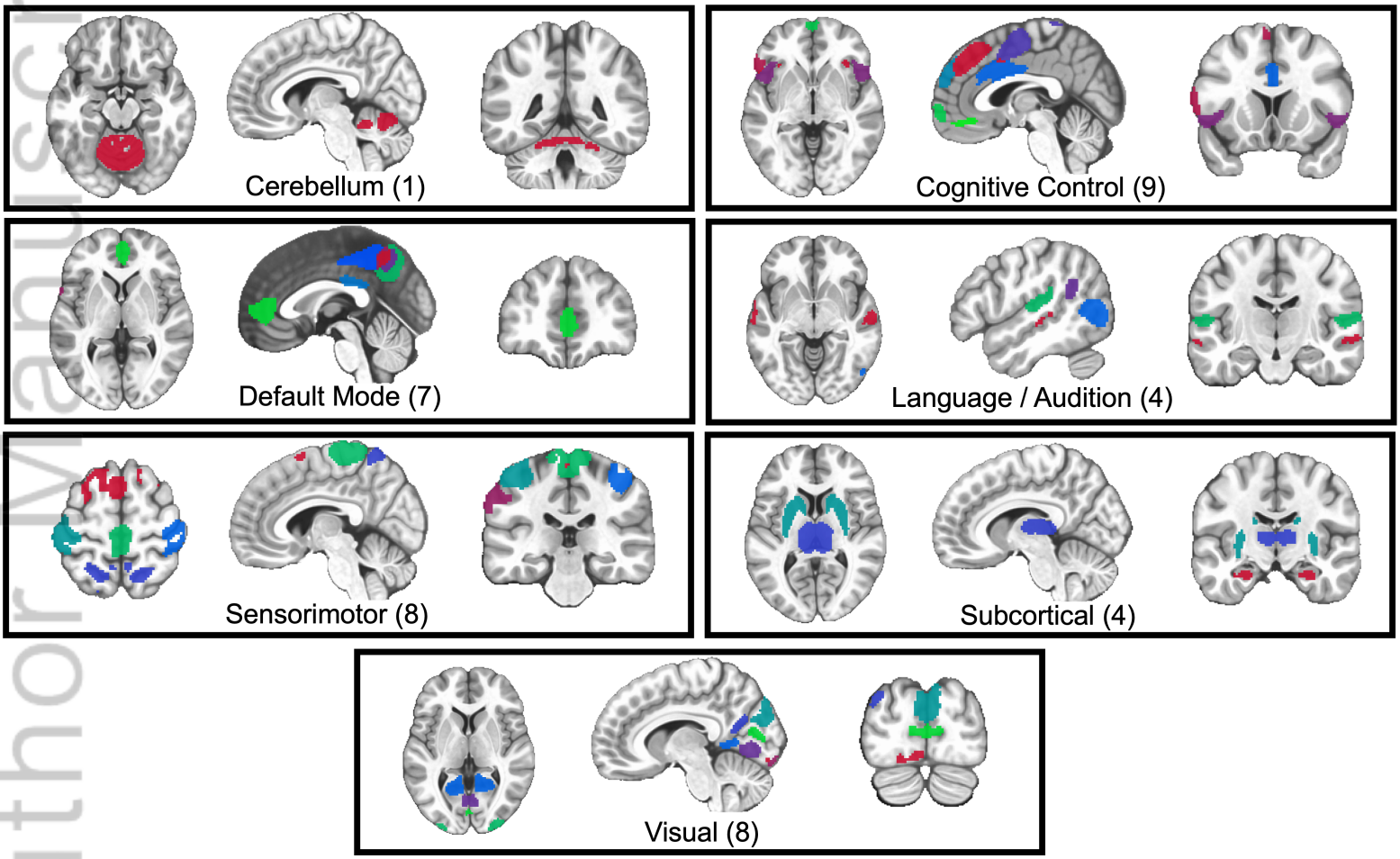



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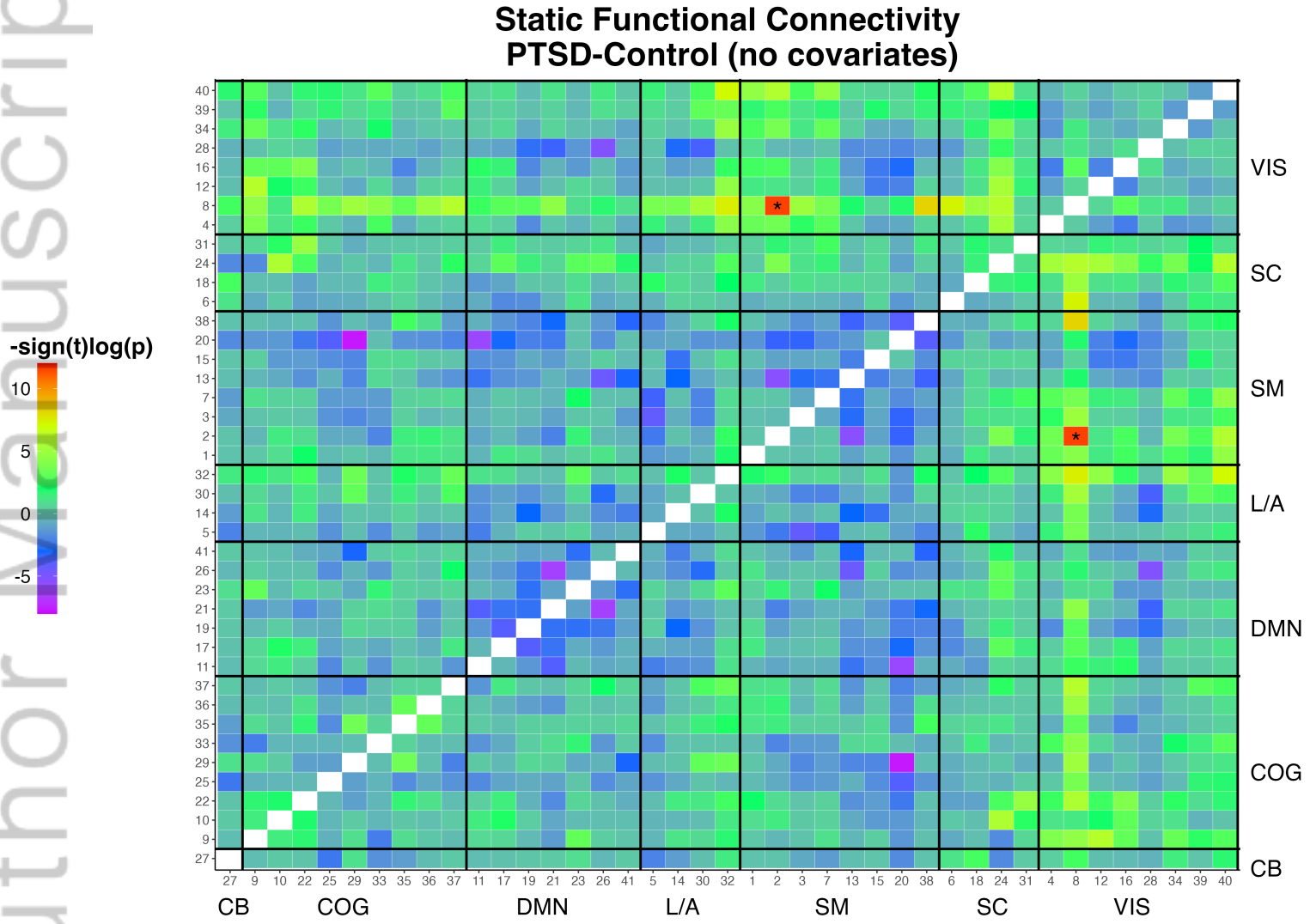
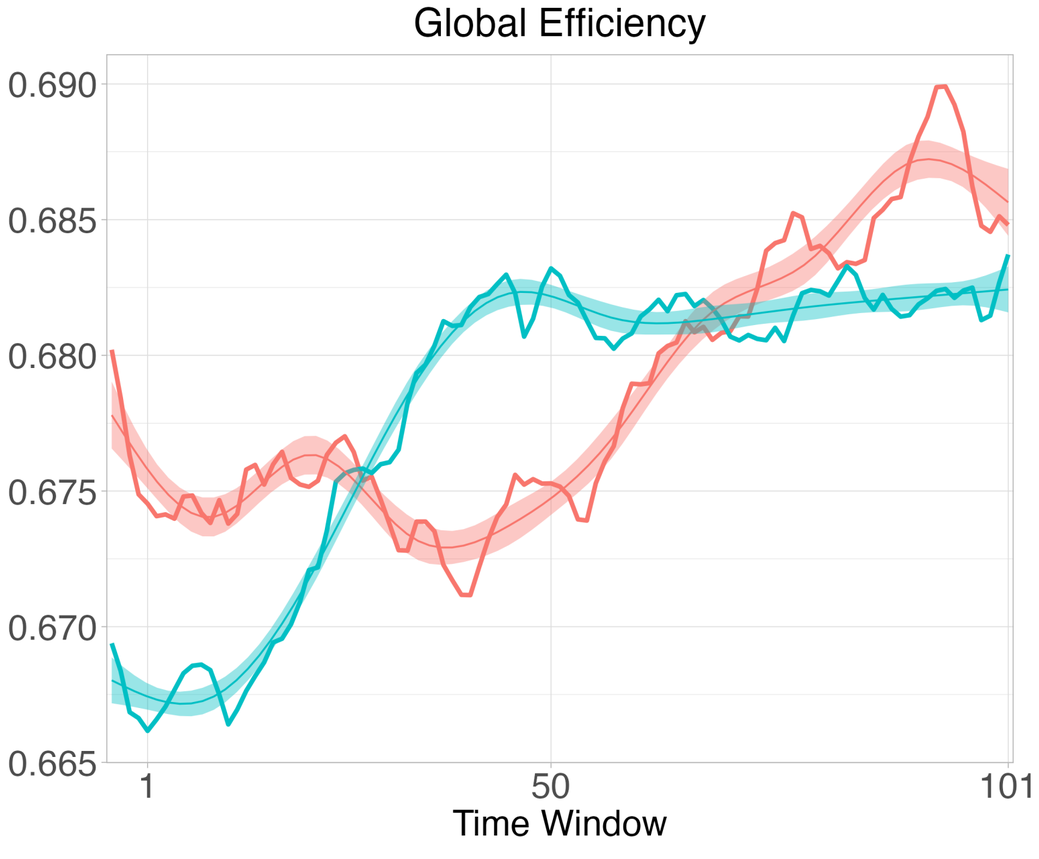
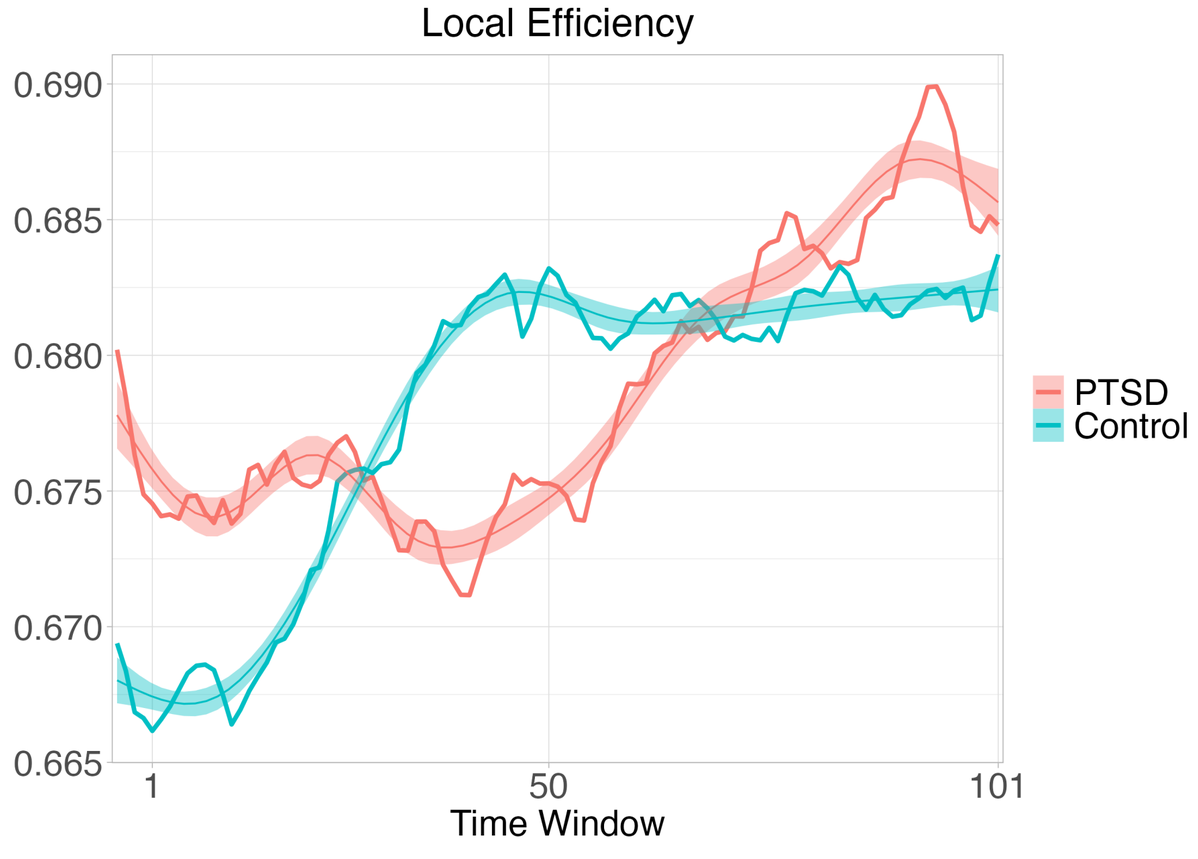


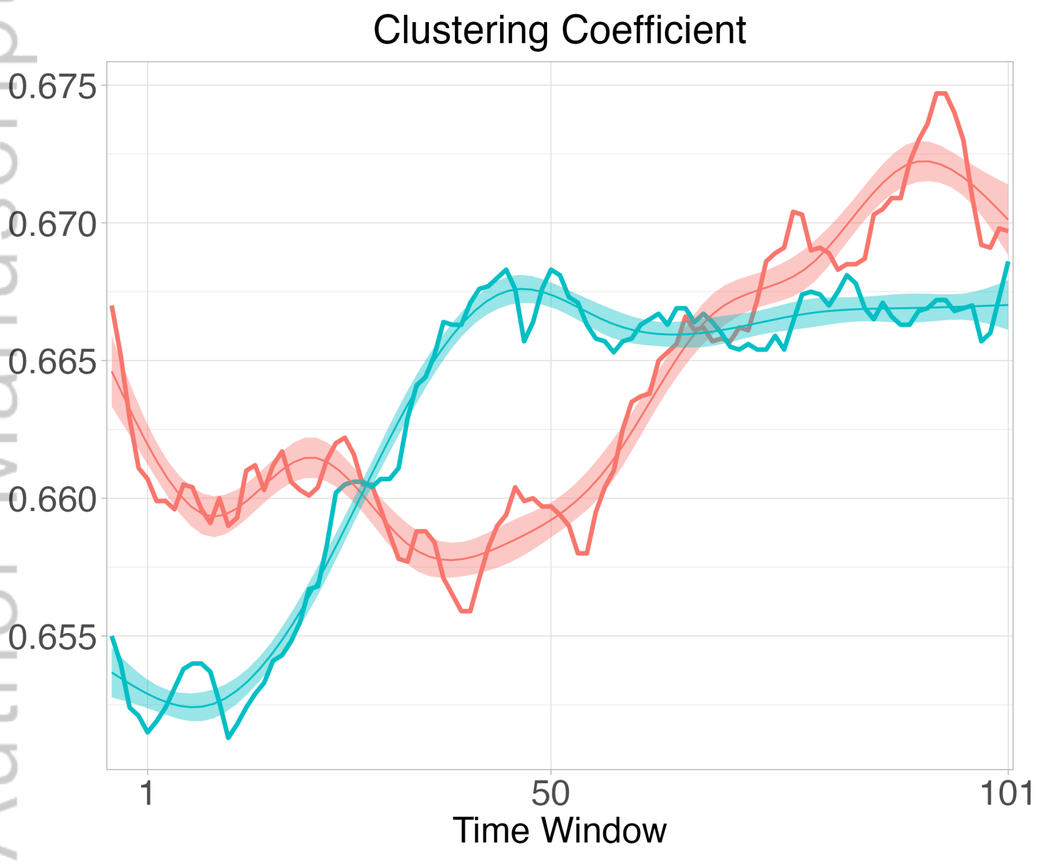

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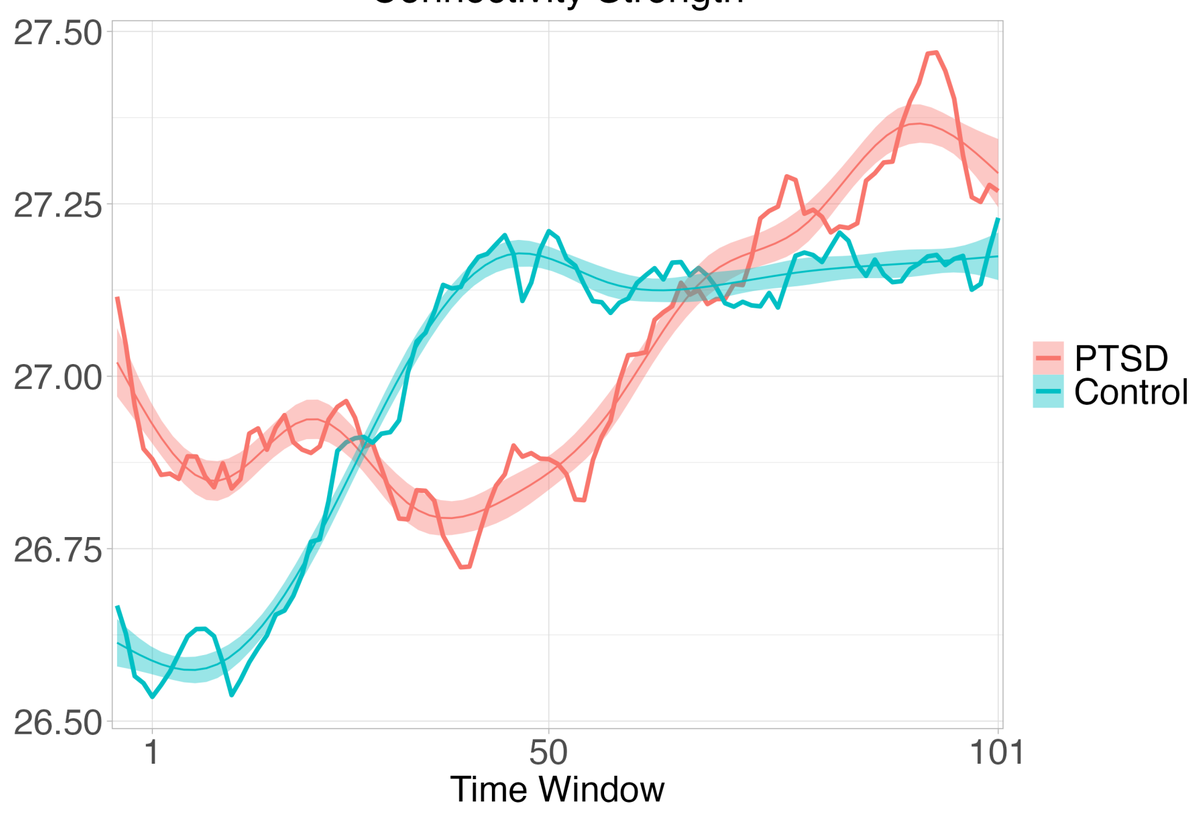
# Graph Theory Metrics Over Time by Group Across the Whole Network

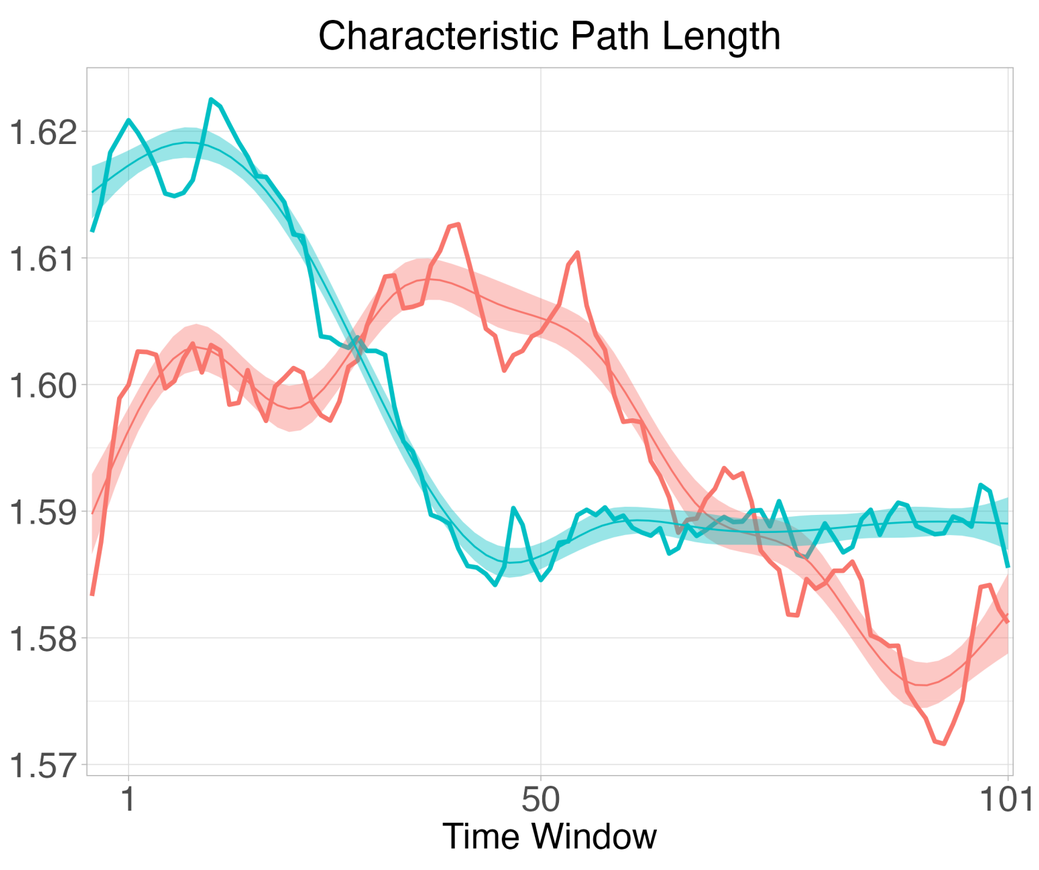



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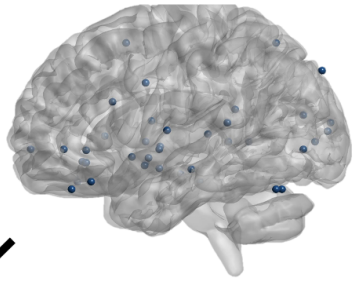



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Psychiatric Genomics Consortium for PTSD

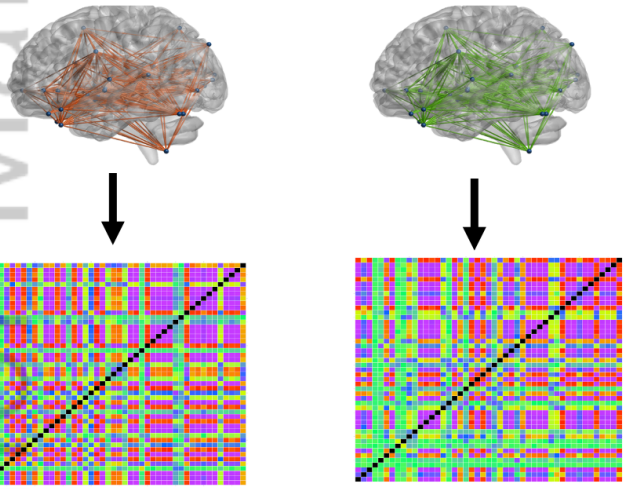
1,035 trauma exposed with resting state scans from ENIGMA-PGC-PTSD Workgroup

Group ICA to identify network nodes



**Static functional connectivity**

Pairwise correlations among nodes for full time series



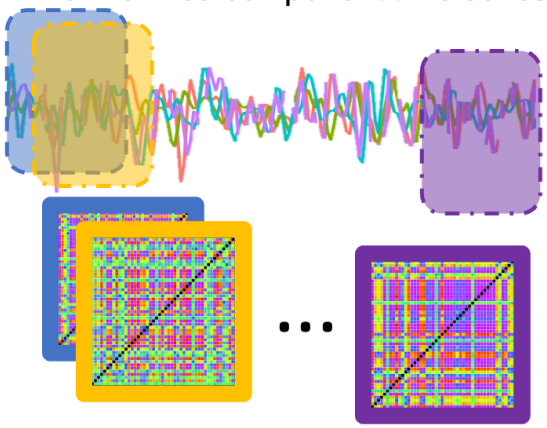
PTSD+ (N = 336)

PTSD- (N=699)

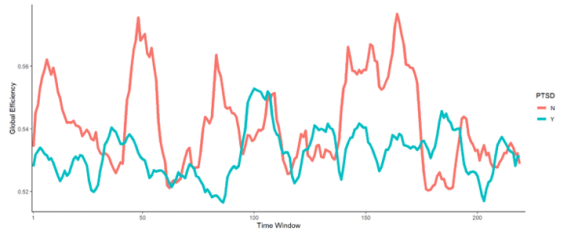
Compare pairwise connectivity across entire scan between groups

**Dynamic functional connectivity**

Sliding window to segment full harmonized component time series



Calculate pairwise connectivity for all nodes within each time window




Graph theory in each time window to compare changes through time across groups

Identify **connectivity states** for each individual and across whole group

GraphicalAbstract.png

In a large global sample of people with trauma exposure, we utilized a data-driven approach to evaluate resting state brain network dynamics. Neither static nor dynamic functional connectivity dynamic analyses showed robust differential patterns of graph dynamics between those with posttraumatic stress disorder and those without.

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