Title page

Multilayer Analysis of Dynamic Network Reconfiguration in Pediatric Posttraumatic Stress Disorder

Xueling Suo[1,2,3,#], Huan Lan[1,2,3,#], Chao Zuo[1,2,3], Li Chen[1,2,3], Du Lei[4], Kun Qin[1,2,3], Lingjiang Li[5], Graham J Kemp[6], Song Wang[1,2,3], and Qiyong Gong[1,2,3,7*]

Affiliations:

[1] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu 610041, China

[2] Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu 610041, China

[3] Functional and Molecular Imaging Key Laboratory of Sichuan Province, West China Hospital of Sichuan University, Chengdu 610041, China

[4] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH 45227, United States

[5] Mental Health Institute, the Second Xiangya Hospital of Central South University, Changsha 410008, China

[6] Liverpool Magnetic Resonance Imaging Centre (LiMRIC) and Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L69 3GE, United Kingdom

[7] Department of Radiology, West China Xiamen Hospital of Sichuan University, Xiamen 361022, China

[#] Xueling Suo and Huan Lan contributed equally to this work.

***Corresponding Author:** Qiyong Gong, M.D., Ph.D., Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, PR China. Tel: 086-028 81812593; Fax: 086-028 85423503. E-mail: qiyonggong@hmrrc.org.cn

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82001800, 81621003, 81761128023, 81820108018, and 82027808), and Young Elite Scientists Sponsorship Program by CAST (No. 2021QNRC001).

Author contributions

QYG conceptualized the project. XLS designed the study and drafted the manuscript. XLS, HL, CZ, LC, DL, KQ, and LJL contributed to literature search, data collection and analysis, as well as data interpretation. GJK and QYG critically revised the paper. All authors approved the final version of the paper.

Data availability statement

The data that support the findings of present study are available from the corresponding author through reasonable request.

Conflict of interest

The authors have declared that no conflict of interest exists.

Abstract

Background: Neuroimage studies have reported functional connectome abnormalities in posttraumatic stress disorder (PTSD), especially in adults. However, these studies often treated the brain as a static network, and the time-variance of connectome topology in pediatric PTSD remain unclear.

Methods: To explore case-control differences in dynamic connectome topology, resting-state functional magnetic resonance imaging data were acquired from 24 treatment-naïve non-comorbid pediatric PTSD patients and 24 demographically matched trauma-exposed non-PTSD (TENP) controls. A graph-theoretic analysis was applied to construct time-varying modular structure of the whole-brain networks by maximizing the multilayer modularity. Network switching rate at the global, subnetwork and nodal levels were calculated and compared between PTSD and TENP groups, and their associations with PTSD symptom severity and sex interactions were explored.

Results: At the global level, PTSD patients showed significantly lower network switching rates than TENP, mainly in the default-mode and dorsal attention networks at the subnetwork level, and in the inferior temporal and parietal regions at the nodal level. PTSD symptom severity was negatively correlated with switching rate in the global network and the default mode network. There were no significant differences in diagnosis-by-sex interaction.

Conclusion: Pediatric PTSD is associated with dynamic reconfiguration of brain networks mainly involving the default mode and dorsal attention networks. This may provide insights into the biological basis of this disorder.

Keywords: Pediatric PTSD, resting-state fMRI, multilayer networks, dynamics analysis, network switching

1. Introduction

Posttraumatic stress disorder (PTSD) is a common and debilitating psychiatric disorder characterized by intrusive thoughts, avoidance, hyperarousal, and negative cognitions and mood. Pediatric PTSD affects an estimated 7% by the age of 18 [1], and brings psychological suffering and long-term harm including elevated lifetime risk of addiction, suicide and premature death [2]. Pediatric PTSD often co-occurs with other psychiatric conditions, most commonly anxiety, depression and attention deficit [3]. Treatment options are few [4], arguably limited by our relatively poor understanding of the pathophysiology. Novel neurobiological indicators may help here, especially those reflecting higher-level network processes. Graph theory-based connectivity analysis is particularly promising approach, building brain networks from the functional coupling between brain regions.

Such studies have identified PTSD as a brain network disorder [5, 6], finding aberrant functional connectivity particularly in the default mode network [7], associated with individual clinical symptoms [8, 9] and treatment response [10, 11]. These studies have focused on static (i.e. time-invariant) connectivity patterns; but because the brain is a highly dynamic network system, in which temporal connectivity reconfiguration [12] allows integration of different neural subsystems across multiple time scales [13, 14], studying dynamic network properties could yield information inaccessible via traditional connectivity approaches.

To date, dynamic brain studies in PTSD have mainly been of adults, reporting e.g. abnormalities in variability [15-17] and transitions between connectivity states [18-20]. Few studies have been done in children and adolescents [21], who are known to have a

highly distinct variation of the disorder [22]. The topological features of dynamic brain networks in pediatric PTSD thus remain unclear.

To address this gap, we analyzed resting-state functional MRI data (rs-fMRI) using a multilayer network model [23] to characterize the topological dynamics of the functional connectome in treatment-naive pediatric PTSD patients without psychiatric comorbidity, compared with trauma-exposed non-PTSD (TENP) controls, and to explore associations with symptom severity. We hypothesized that: (i) PTSD patients would show significant alterations in brain connectome dynamics as compared to TENP e.g. in the default mode network; and (ii) these alterations in brain dynamics would be associated with individuals' PTSD symptoms. Finally, because being female increases the risk of developing PTSD [24], we (iii) analyzed sex/age-by-PTSD diagnosis interactions.

2. Materials and Methods

2.1 Participants

Individuals who survived the 8.0 magnitude earthquake in Sichuan in May 2008 were recruited between January and August 2009 and screened with the PTSD checklist-Civilian Version (PCL) [25]. At follow-up visits 8-15 months after the earthquake, PTSD diagnosis was established by Structured Clinical Interview for the DSM-IV Diagnosis (SCID) [26] and symptom severity was evaluated using the Clinician-Administered PTSD Scale (CAPS) [27]. Briefly, survivors scoring ≥ 35 on PCL and ≥ 50 on CAPS were included as PTSD if a diagnosis of PTSD was determined by SCID; those who scored < 35 on PCL without diagnosis of PTSD by SCID were considered TENP controls. See Supplementary Materials for detailed inclusion and exclusion criteria. Finally included were 24 treatment-

naive non-comorbid patients with PTSD and 24 demographically-matched TENP controls. This recruitment strategy ensured that participants with and without PTSD had similar earthquake experiences and demographic characteristics. The study protocol was reviewed and approved by the Sichuan University Research Ethics Committee. After receiving a complete explanation of study procedures, all child's guardian provided written informed consent.

2.2 Image acquisition

Resting-state functional MRI data were acquired on a 3 tesla Excite MR scanner (GE Healthcare, Milwaukee, Wisconsin USA) with an 8-channel phased-array head coil. The sequence parameters were: repetition time/echo time 2000 ms/30 ms; flip angle 90°; 30 axial sections per volume; 5 mm section thickness, no gap; 64 × 64 matrix; 240 × 240 mm field of view, voxel 3.75 × 3.75 × 5 mm. Participants lay still with eyes open and remain awake during the acquisition. All MR images were evaluated by an experienced neuroradiologist for gross pathology and image quality.

2.3 Image processing

Using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm) to pre-process fMRI image data. We deleted the first 10 time points to allow magnetic stabilization, then corrected slice timing for intra-volume acquisition delay and realigned the images for correction of head movement. We used echo-planar imaging templates (voxel size 3×3×3 mm) to normalize the images. We removed linear trends in the time series, and regressed out nuisance signals (including Friston 24-parameter head motion model, white matter signal, and cerebrospinal fluid signal). Finally, we detrended linearly and band-pass filtered to eliminate high-

frequency noise and maintain low frequency fluctuation 0.01–0.1 Hz, then smoothed the data with a 4 mm full-width at half maximum. We evaluate head motion during scanning using mean framewise-displacement (FD): no significant difference of mean FD was observed between TENP and PTSD (0.121±0.084 vs. 0.137±0.128, P = 0.615), and no participants showed excessive head motion (i.e. rotation > 3°, translation > 3 mm, or mean FD > 0.5 mm) .

2.4 Multilayer brain network switching rates

Figure 1 shows the overall flow of analysis.

Constructing the multilayer brain network: N nodes were defined by an atlas: we used the Brainnetome 246 atlas, which includes 210 cortical and 36 subcortical nodes [28] (so N = 246). The averaged signals of each N regions were extracted. From each participant's preprocessed rs-fMRI data, dynamic functional connectivity was calculated by a sliding windows method [12]; Hamming windows (window size 30, TR 60 s; window step 1, TR 2 s) were applied to obtain a series of W signal windows. Calculating Pearson correlations between each pair of region signals in each window yielded dynamic network matrices (N × N × W = 246 × 246 × 161) for each subject.

Detecting time-varying modular structures: We detected the time-varying modular network structures within each time window using a multilayer modularity algorithm [23] implemented in an open-source Matlab-based code package (https://github.com/GenLouvain/GenLouvain) with the default settings temporal coupling parameter ω = topological resolution parameter γ = 1 [29, 30]. As this only allows positive matrix values, all negative values in the connectivity matrices were set to zeros [30]. The

output is a module assignment matrix (N × W = 246 × 161) for each rs-fMRI scan, representing the temporal variation in module assignments for all 246 nodes.

Calculating network switching rates: From these multilayer module assignment matrices, the switching rate for a node i (f_i) was calculated as $f_i = n_i/(N-1)$, where n_i is the number of times its module assignment changed between consecutive layers, and N-1 is the maximum potential number of changes (here 161 - 1 = 160); the ranges from 0 to 1, a higher value indicating higher frequency of the node's transition between different functional modules, and thus lower temporal stability. Calculations used the Network Community Toolbox (http://commdetect.weebly.com) [31]. Switching rates for the global brain network were obtained by averaging all 246 nodes. Further, to explicitly characterize the contribution of each functional network, 210 cortical nodes corresponding to 7 different neural networks in the Yeo atlas (visual, somatomotor, dorsal and ventral attention, limbic, frontoparietal, and default mode network), and 36 subcortical nodes were defined as the subcortical nucleus network [32-35]. Switching rates for 8 subnetworks were obtained by averaging their constituent nodes.

2.5 Statistical analyses

Two-sample t tests (for continuous variables) and chi-square tests (for categorical variables) were used to test differences in demographic and clinical characteristics between PTSD and TENP, and two-sample t tests to test the between-group difference of brain network switching rates. Two-way analysis of variance (ANOVA) was used to analyze the interaction of PTSD diagnosis-by-sex and diagnosis-by-age (dividing the distribution into younger and older groups, 10–12 and 13–16 years); if statistically significant interactions were observed, *post hoc* contrasts assessed the simple main effects. Partial correlations

were performed between CAPS score and those network switching rates which showed significant between-group differences, with age, sex, years of education, and mean FD as covariates. All statistics were performed at the global, subnetwork, and nodal levels. False discovery rate (FDR) corrections were applied to control type I errors across the 7 subnetworks and 246 nodes. Results were visualized by the BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

2.6 Validation analyses

To minimise effects of head motion, we removed participants with excessive head motion (>2 mm translation or >2° rotation), carried out regression of 24-parameter head motion profiles [36] for each participant before building individual functional networks, and performed statistical analysis on network switching rates with mean FD as a covariate. To investigate effects of window length, we repeated the analysis with window length 50 TR = 100 s. To investigate effects of network analysis strategy, we repeated the multilayer analysis using $\omega = 0.5$ and 0.75, and $\gamma = 0.9$ [37].

3. Results

3.1 Demographic and clinical characteristics

Individuals with PTSD had significantly higher PCL scores than TENP ($P < 0.001$). The groups did not significantly differ by age, sex, years of education or time since trauma (all $P > 0.05$). See **Table 1.**

3.2 Group differences of switching rates at global, subnetwork, and nodal level

At the global level, individuals with PTSD had significantly lower brain network switching rates than TENP (P = 0.009). At the subnetwork level, individuals with PTSD had significantly lower switching rates than TENP in the dorsal attention network (P = 0.009, FDR corrected) and the default mode network (P = 0.005, FDR corrected). Differences falling short of statistical significance were observed in the limbic and frontoparietal networks. No significant differences were identified in the visual, somatomotor, ventral attention, or subcortical networks. See **Figure 2** and **Table 2**.

At the nodal level, individuals with PTSD showed significantly lower switching rates than TENP in right inferior temporal gyrus (ITG) and left postcentral gyrus (PoCG) (P < 0.001, FDR corrected). See **Figure 3** and **Table 3**.

3.3 Interaction between groups and sex/age with respect to switching rate

Two-way ANOVA revealed no significant diagnosis-by-sex/age interaction in global brain network switching rate (P = 0.633 and 0.380), subnetwork switching rate in the dorsal attention network (P = 0.537 and 0.249) or default mode network (P = 0.276 and 0.701), or nodal switching rate in right ITG (P = 0.493 and 0.580) or left PoCG (P = 0.593 and 0.292).

3.4 Correlations between switching rate and symptom severity

In the PTSD group there was a significant negative correlation between CAPS score and the switching rates of the global network (r = -0.587, P = 0.013, FDR corrected) and the default mode network (r = -0.589, P = 0.013, FDR corrected). No significant correlations were found between CAPS scores and switching rates of the dorsal attention network, right ITG or left PoCG. See **Figure 4**.

3.5 Validation

To establish the robustness of our main findings, we assessed the influence of: testing for the head motion effects; different temporal coupling parameters (ω = 0.5 and 0.75) and topological resolution parameter (γ = 0.9); and different sliding window length (100s). The main results were largely the same (**Table S1**).

4. Discussion

To understand complex functional abnormalities we need appropriate tools, and the relatively new brain connectome dynamics approach holds particular promise. Using a time-varying multilayer network analysis of rs-fMRI data to quantify temporal switching among functional modules [38], we investigated brain modular dynamics in pediatric PTSD. Relative to TENP, pediatric PTSD showed significantly lower switching rates of functional brain network modules at global, subnetwork, and nodal levels, mainly in the dorsal attention and default-mode networks as well as temporal and parietal regions. These abnormal modularity metrics were associated with symptom severity, with no significant interactions between group and sex. These results give an insight into the dynamic network abnormalities of pediatric PTSD.

The lower switching rate at the global level in pediatric PTSD is consistent with findings in adult PTSD [16], and parallels reports in other paediatric psychiatric disorders [39, 40]. What do these abnormalities mean? In general a healthy biological system must be flexible in response to transient changes in the internal and external milieu [16, 41], and it is tempting to link slower module switching in children with PTSD to their impaired ability to adjust dynamically to changing conditions (in thoughts, stresses, behaviors, etc.), as

manifest in increased arousal and intrusive and negative thoughts. If so, these results reflect an important aspect of compromised brain health.

Can we be more specific? At the network level, children with PTSD had slower switching in the default-mode network (involved in internal mentation and self-directed thought, notably self-referential processing, emotion regulation and episodic memory retrieval [42, 43]) and the dorsal attention network (thought to be crucial for top-down orienting of attention [44]). Disruptions in both have been implicated in several neuropsychiatric disorders as well as adult and pediatric PTSD [5, 6, 45, 46]. Lower switching rates of these networks suggest discrete functional dysconnectivities, either reflecting or underpinning (because causality cannot yet be established) PSTD patients' reduced ability (e.g in rumination).to navigate away from internal emotional and cognitive states. At the nodal level, children with PTSD had slower switching in the right ITG and left PoCG. ITG is related to visual recognition of objects, and lesions in this region produce deficits in visual recognition memory [47]. Interestingly , flashback in PTSD is reportedly associated with smaller ITG volume [48]. The temporal and parietal lobes are also engaged in emotional and cognitive processes [49, 50]: ITG integrates perception and memory in women with PTSD related to early childhood sexual abuse [51]; and greater activations are reported in the ITG and posterior parietal cortex during classic and emotional Stroop interference in PTSD related to child abuse [52].

Taken together, these global, subnetwork and nodal alterations of the topological dynamics of the functional connectome show PTSD as a disorder of disrupted network integration. A strength of our study is comparison between treatment-naïve non-comorbid pediatric PTSD patients with similarly stressed TENP controls, demonstrating that

impaired switching rate at multiple levels is related to the clinical manifestations of PTSD beyond acute stress effects as experienced by the TENP. Notably, while we found no significant group-sex interaction with respect to switching rate, earlier neuroimaging studies of PTSD have reported sex differences in brain alterations [53-56]. However, others have not [57]. These divergent results may be due to differences in sample characteristics (e.g non-traumatized healthy controls vs. TENP), trauma type and severity, and study methods.

This study has some limitations. First, it was cross-sectional; how brain network dynamics after major life stress evolve and predict PTSD conversion must be addressed in longitudinal studies. Second, the participants are earthquake-exposed children without psychiatric comorbidity, so it remains to be established whether the findings apply to adult PTSD, PTSD caused by other types of trauma, or patients with psychiatric comorbidities. Third, we characterized brain network dynamics that distinguish stressed individuals who do and do not develop PTSD; a parallel control group of non-traumatized individuals would be needed to identify how major life stress itself impacts brain network dynamics. Fourth, our patients did not have any cognitive assessments, and this will need to be addressed. Fifth, our relatively small sample size limited statistical power. Finally, not all confounding factors can be excluded, and the effects of e.g. socioeconomic status need to be explored separately.

In conclusion, this study demonstrates lower network switching rates in PTSD at global, subnetwork and nodal levels, which showed some association with severity of PTSD symptoms. The effects mainly involved the dorsal attention and default-mode networks, as well as temporal and parietal regions. Our findings suggest a disruption of dynamic

network construction in children with PTSD, which provides a new perspective on understanding the neural mechanisms. This study is a contribution to the developing clinical subspecialty of psychoradiology [58-60], which aims to guide diagnostic and therapeutic decision making in patients with neuropsychiatric disorders.

References

1. Danese A, Widom CS. Objective and subjective experiences of child maltreatment and their relationships with psychopathology. *Nat Hum Behav*.2020;4:811-818.
2. Shalev I, Moffitt TE, Braithwaite AW, Danese A, Fleming NI, Goldman-Mellor S*, et al.* Internalizing disorders and leukocyte telomere erosion: a prospective study of depression, generalized anxiety disorder and post-traumatic stress disorder. *Mol Psychiatry*.2014;19:1163-1170.
3. Lamberg L. Psychiatrists explore legacy of traumatic stress in early life. *JAMA*.2001;286:523-526.
4. Morina N, Koerssen R, Pollet TV. Interventions for children and adolescents with posttraumatic stress disorder: A meta-analysis of comparative outcome studies. *Clin Psychol Rev*.2016;47:41-54.
5. Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*.2012;36:2130-2142.
6. Bao W, Gao Y, Cao L, Li H, Liu J, Liang K*, et al.* Alterations in large-scale functional networks in adult posttraumatic stress disorder: A systematic review and meta-analysis of resting-state functional connectivity studies. *Neurosci Biobehav Rev*.2021;131:1027-1036.
7. Akiki TJ, Averill CL, Wrocklage KM, Scott JC, Averill LA, Schweinsburg B*, et al.* Default mode network abnormalities in posttraumatic stress disorder: A novel network-restricted topology approach. *Neuroimage*.2018;176:489-498.

8. Miller DR, Logue MW, Wolf EJ, Maniates H, Robinson ME, Hayes JP*, et al.* Posttraumatic stress disorder symptom severity is associated with reduced default mode network connectivity in individuals with elevated genetic risk for psychopathology. *Depress Anxiety*.2017;34:632-640.
9. Suo X, Lei D, Li W, Yang J, Li L, Sweeney JA*, et al.* Individualized Prediction of PTSD Symptom Severity in Trauma Survivors From Whole-Brain Resting-State Functional Connectivity. *Front Behav Neurosci*.2020;14:563152.
10. Korgaonkar MS, Chakouch C, Breukelaar IA, Erlinger M, Felmingham KL, Forbes D*, et al.* Intrinsic connectomes underlying response to trauma-focused psychotherapy in post-traumatic stress disorder. *Transl Psychiatry*.2020;10:270.
11. Sheynin J, Duval ER, King AP, Angstadt M, Phan KL, Simon NM*, et al.* Associations between resting-state functional connectivity and treatment response in a randomized clinical trial for posttraumatic stress disorder. *Depress Anxiety*.2020;37:1037-1046.
12. Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex*.2014;24:663-676.
13. Calhoun VD, Miller R, Pearlson G, Adali T. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron*.2014;84:262-274.
14. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M*, et al.* Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage*.2013;80:360-378.

15. 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;10:234.
16. 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;38:4479-4496.
17. 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;19:260-270.
18. Kundu S, Ming J, Stevens J. Developing Multimodal Dynamic Functional Connectivity as a Neuroimaging Biomarker. *Brain Connect*.2021;11:529-542.
19. Ou J, Xie L, Jin C, Li X, Zhu D, Jiang R*, et al.* Characterizing and Differentiating Brain State Dynamics via Hidden Markov Models. *Brain Topogr*.2015;28:666-679.
20. 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;35:1761-1778.
21. Cisler JM, Herringa RJ. Posttraumatic Stress Disorder and the Developing Adolescent Brain. *Biol Psychiatry*.2021;89:144-151.
22. Scheeringa MS. Developmental considerations for diagnosing PTSD and acute stress disorder in preschool and school-age children. *Am J Psychiatry*.2008;165:1237-1239.
23. Mucha PJ, Richardson T, Macon K, Porter MA, Onnela JP. Community structure in time-dependent, multiscale, and multiplex networks. *Science*.2010;328:876-878.

24. Tang B, Deng Q, Glik D, Dong J, Zhang L. A Meta-Analysis of Risk Factors for Post-Traumatic Stress Disorder (PTSD) in Adults and Children after Earthquakes. *Int J Environ Res Public Health*.2017;14.

25. Weathers FW, Litz BT, Herman D, Huska J, Keane T. The PTSD checklist-civilian version (PCL-C). *Boston, MA: National Center for PTSD*.1994.

26. First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for Axis I DSM-IV disorders. *New York: Biometrics Research*.1994.

27. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS*, et al.* The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*.1995;8:75-90.

28. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L*, et al.* The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cereb Cortex*.2016;26:3508-3526.

29. Bassett DS, Porter MA, Wymbs NF, Grafton ST, Carlson JM, & Mucha PJ Robust detection of dynamic community structure in networks. *Chaos*.2013;23:013142.

30. Pedersen M, Zalesky A, Omidvarnia A, Jackson GD. Multilayer network switching rate predicts brain performance. *Proc Natl Acad Sci U S A*.2018;115:13376-13381.

31. Bassett DS, Wymbs NF, Porter MA, Mucha PJ, Carlson JM, Grafton ST. Dynamic reconfiguration of human brain networks during learning. *Proc Natl Acad Sci U S A*.2011;108:7641-7646.

32. Baltruschat S, Candido A, Megias A, Maldonado A, Catena A. Risk proneness modulates the impact of impulsivity on brain functional connectivity. *Hum Brain Mapp*.2020;41:943-951.

33. Jiang R, Zuo N, Ford JM, Qi S, Zhi D, Zhuo C*, et al.* Task-induced brain connectivity promotes the detection of individual differences in brain-behavior relationships. *Neuroimage*.2020;207:116370.

34. Zhu Y, Li X, Qiao Y, Shang R, Shi G, Shang Y*, et al.* Widespread plasticity of cognition-related brain networks in single-sided deafness revealed by randomized window-based dynamic functional connectivity. *Med Image Anal*.2021;73:102163.

35. Wang Q, Hu K, Wang M, Zhao Y, Liu Y, Fan L*, et al.* Predicting brain age during typical and atypical development based on structural and functional neuroimaging. *Hum Brain Mapp*.2021;42:5943-5955.

36. Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A*, et al.* A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage*.2013;76:183-201.

37. Lei T, Liao X, Chen X, Zhao T, Xu Y, Xia M*, et al.* Progressive Stabilization of Brain Network Dynamics during Childhood and Adolescence. *Cereb Cortex*.2022;32:1024-1039.

38. Liao X, Cao M, Xia M, He Y. Individual differences and time-varying features of modular brain architecture. *Neuroimage*.2017;152:94-107.

39. Cai W, Chen T, Szegletes L, Supekar K, Menon V. Aberrant Time-Varying Cross-Network Interactions in Children With Attention-Deficit/Hyperactivity Disorder and the Relation to Attention Deficits. *Biol Psychiatry Cogn Neurosci Neuroimaging*.2018;3:263-273.

40. Marchitelli R, Paillere-Martinot ML, Bourvis N, Guerin-Langlois C, Kipman A, Trichard C*, et al.* Dynamic Functional Connectivity in Adolescence-Onset Major

Depression: Relationships With Severity and Symptom Dimensions. *Biol Psychiatry Cogn Neurosci Neuroimaging*.2022;7:385-396.

41. Rangaprakash D, Dretsch MN, Katz JS, Denney TS, Jr., Deshpande G. Dynamics of Segregation and Integration in Directional Brain Networks: Illustration in Soldiers With PTSD and Neurotrauma. *Front Neurosci*.2019;13:803.
42. Andrews-Hanna JR, Saxe R, Yarkoni T. Contributions of episodic retrieval and mentalizing to autobiographical thought: evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. *Neuroimage*.2014;91:324-335.
43. Raichle ME The brain's default mode network. *Annu Rev Neurosci*.2015;38:433-447.
44. Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. *Neuroscientist*.2014;20:150-159.
45. Patriat R, Birn RM, Keding TJ, Herringa RJ. Default-Mode Network Abnormalities in Pediatric Posttraumatic Stress Disorder. *J Am Acad Child Adolesc Psychiatry*.2016;55:319-327.
46. Niu R, Lei D, Chen F, Chen Y, Suo X, Li L*, et al.* Disrupted grey matter network morphology in pediatric posttraumatic stress disorder. *Neuroimage Clin*.2018;18:943-951.
47. Peelen MV, He C, Han Z, Caramazza A, Bi Y. Nonvisual and visual object shape representations in occipitotemporal cortex: evidence from congenitally blind and sighted adults. *J Neurosci*.2014;34:163-170.
48. Kroes MC, Whalley MG, Rugg MD, Brewin CR. Association between flashbacks and structural brain abnormalities in posttraumatic stress disorder. *Eur Psychiatry*.2011;26:525-531.

49. Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. *Trends Cogn Sci*.2003;7:77-83.

50. Herold D, Spengler S, Sajonz B, Usnich T, Bermpohl F. Common and distinct networks for self-referential and social stimulus processing in the human brain. *Brain Struct Funct*.2016;221:3475-3485.

51. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Staib LH*, et al.* Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol Psychiatry*.2003;53:879-889.

52. Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, Elzinga BM, van Balkom AJ*, et al.* Treatment effects on insular and anterior cingulate cortex activation during classic and emotional Stroop interference in child abuse-related complex post-traumatic stress disorder. *Psychol Med*.2012;42:2337-2349.

53. Helpman L, Zhu X, Zilcha-Mano S, Suarez-Jimenez B, Lazarov A, Rutherford B*, et al.* Reversed patterns of resting state functional connectivity for females vs. males in posttraumatic stress disorder. *Neurobiol Stress*.2021;15:100389.

54. Luo Y, Liu Y, Qing Z, Zhang L, Weng Y, Zhang X*, et al.* Sex Differences in Re-experiencing Symptoms Between Husbands and Wives Who Lost Their Only Child in China: A Resting-State Functional Connectivity Study of Hippocampal Subfields. *Front Hum Neurosci*.2021;15:655044.

55. Luo Y, Qi R, Zhang L, Qing Z, Weng Y, Wang W*, et al.* Functional brain network topology in parents who lost their only child in China: Post-traumatic stress disorder and sex effects. *J Affect Disord*.2019;257:632-639.

56. Shvil E, Sullivan GM, Schafer S, Markowitz JC, Campeas M, Wager TD*, et al.* Sex differences in extinction recall in posttraumatic stress disorder: a pilot fMRI study. *Neurobiol Learn Mem*.2014;113:101-108.

57. Woon F, Hedges DW. Gender does not moderate hippocampal volume deficits in adults with posttraumatic stress disorder: a meta-analysis. *Hippocampus*.2011;21:243-252.

58. Lui S, Zhou XJ, Sweeney JA, Gong Q. Psychoradiology: The Frontier of Neuroimaging in Psychiatry. *Radiology*.2016;281:357-372.

59. Gong Q. Clinical Aims of Psychoradiology. *Neuroimaging Clin N Am*.2020;30:xvii-xviii.

60. Li F, Sun H, Biswal BB, Sweeney JA, Gong Q. Artificial intelligence applications in psychoradiology. *Psychoradiology*.2021;1:94-107.

Tables

Table 1. Demographic and clinical characteristics of PTSD and TENP participants [a]

Variables	TENP (n=24)	PTSD (n=24)	*P*
Age (years) [b]	13.0±1.4 (11-16)	13.2±1.8 (10-16)	0.65 [c]
Gender (male/female)	10/14	8/16	0.77 [d]
Duration of education (years) [b]	7.8±2.2 (6-14)	7.9±2.0 (6-12)	0.97 [c]
Time since trauma (months) [b]	12.3±1.9 (9-15)	11.3±1.9 (9-15)	0.09 [c]
PTSD checklist score	23.4±1.8 (19-27)	54.8±5.3 (40-65)	<0.001 [c]
CAPS score	-	65.8 ±6.7 (60-86)	

[a] Data are presented as mean ± SD (minimum-maximum) unless noted. [b] Age, years of education and time since trauma were defined relative to the time of MRI scanning. [c] *P* value using two sample two-tailed t test. [d] *P* value using two-tailed Chi-squared test.

Abbreviations: PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD control; CAPS, Clinician-administered PTSD scale.

Table 2. Network switching rate at global and subnetwork level in PTSD and TENP

Network switching rate	TENP (n=24)	PTSD (n=24)	*P(T)*
Global	0.052±0.007	0.047±0.007	**0.009** (2.707)
Subnetwork			
Visual network	0.051±0.010	0.048±0.010	0.205 (1.286)
Somatomotor network	0.047±0.011	0.043±0.012	0.226 (1.228)
Dorsal attention network	0.054±0.009	0.046±0.010	**0.009** (2.711)
Ventral attention network	0.050±0.009	0.045±0.011	0.111 (1.625)
Limbic network	0.056±0.008	0.051±0.008	0.030 (2.240)
Frontoparietal network	0.054±0.010	0.049±0.008	0.044 (2.073)
Default mode network	0.051±0.008	0.044±0.009	**0.005** (2.964)
Subcortical network	0.053±0.011	0.049±0.012	0.225 (1.230)

Abbreviations: PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD control. Subnetworks were considered abnormal in PTSD if they exhibited significant between-group differences ($P < 0.05$, FDR corrected, shown in bold).

Table 3. Regions showing lower nodal switching rate in PTSD compared with TENP.

Label ID	Regions	MNI (x, y, z)	TENP	PTSD	*P(T)* value
90	ITG_R_7_1	46, -14, -33	0.063±0.015	0.043±0.016	<0.001 (4.357)
159	PoG_L_4_3	-46, -30, 50	0.057±0.020	0.039±0.015	<0.001 (3.587)

Abbreviations: PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD control; ITG, inferior temporal gyrus; PoG, postcentral gyrus, MNI, Montreal Neurological Institute; L, left; R, right.

Figure legends

Figure 1. The analysis strategy. Individual images were preprocessed, and the mean values of each region in the Brainnetome 246 atlas were extracted to build a dynamic functional matrix for each subject. An iterative ordinal Louvain sliding windows algorithm was used to track dynamic network modulation over time. Finally, network switching rate was calculated and compared between the participant groups at the global, sub-network, and nodal levels. Abbreviations: Rs-fMRI, resting-state functional magnetic resonance imaging.

Figure 2. Between-group differences in global and subnetwork-level switching rates.

The bar-charts compare the switching rates (means with standard error bars) in the two groups, with P values (asterisks denote $P < 0.05$), for 9 different network levels as labelled. Abbreviations: PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD control.

Figure 3. Between-group differences in nodal-level switching rates. The figure shows a bar-chart comparison of switching rates (means with standard error bars) in the two groups, with P values, in ITG (left panel) and postcentral gyrus (right panel), whose locations are shown in the middle panel. Abbreviations: PTSD, post-traumatic stress disorder; TENP, trauma-exposed non-PTSD control; L, left; R, right; ITG, inferior temporal gyrus, PoG, postcentral gyrus.

Figure 4. Relations of network switching rates to CAPS scores in PTSD. The figure shows the relationship between the individual patients' switching rates at the global level

(left panel) and in the default-mode network (right panel) and individual CAPS scores Abbreviations: PTSD, post-traumatic stress disorder; CAPS, Clinician-administered PTSD scale.