Anatomical insights into disrupted small-world networks in pediatric posttraumatic stress disorder

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Advances in Knowledge

1. In brain MR images of pediatric patients with posttraumatic stress disorder (PTSD), we observed higher values of characteristic path length L_p (P=0.0248) and lower values of local efficiency E_{loc} (P=0.0498) and global efficiency E_{glob} (P=0.0274) relative to non-PTSD stress-exposed controls, indicating that the structural connectome of individuals with PTSD shifts toward 'regularization.'
2. We found decreased nodal centralities ($P < 0.05$, false discovery rate corrected) in the salience network (SN) (ventrolateral prefrontal cortex, insular, putamen and thalamus), the central executive network (CEN) (dorsolateral prefrontal cortex and superior parietal gyrus), visual regions (lingual gyrus and middle occipital gyrus) and angular gyrus; by contrast we observed increased nodal centralities in the anterior cingulate cortex and inferior temporal gyrus.
3. The PTSD-related subnetwork had 13 nodes and 21 edges, and the connections were mainly with the prefrontal-limbic-striatal, and ventral and dorsal visual systems.
4. Clinician-Administered PTSD Scale score, reflecting PTSD illness severity, was negatively correlated with nodal efficiency of left superior parietal gyrus (P=0.043).

Implications for Patient Care

The brain regions of the salience network (ventrolateral prefrontal cortex, insular, putamen and thalamus) may be potential targets for future therapeutic interventions for PTSD.

Summary statement

Using deterministic tractography combined with graph analysis to investigate topological organization of the brain in pediatric PTSD, we found that the structural connectome showed a shift toward to ‘regularization’, as we previously found in the functional connectome.

Abstract

Purpose: To use DTI and graph theory approaches to explore the brain structural connectome in pediatric posttraumatic stress disorder (PTSD).

Materials and Methods: This study was approved by the relevant research ethics committee, and all subjects' parents/guardians provided informed consent. Twenty-four pediatric PTSD patients and 23 trauma-exposed non-PTSD controls were recruited after the 2008 Sichuan earthquake. The structural connectome was constructed using diffusion tensor imaging tractography, by thresholding the mean fractional anisotropy of 90 brain regions to yield 90×90 partial correlation matrixes. Graph theory analysis was used to examine the group-specific topological properties, and nonparametric permutation tests were used for group comparisons of topological metrics.

Results: Both groups exhibited small-world topology. However, PTSD showed increase in the characteristic path length (L_p) (P=0.0248), and decrease in local efficiency (E_{loc}) (P=0.0498) and global efficiency (E_{glob}) (P=0.0274). Furthermore, PTSD showed reduced nodal centralities mainly in the default mode, salience, central executive and visual regions ($P < 0.05$, false discovery rate corrected). The Clinician-Administered PTSD Scale score was negatively correlated with nodal efficiency of left superior parietal gyrus (P=0.043).

Conclusion: The structural connectome showed a shift toward 'regularization', providing a structural basis for functional alterations of pediatric PTSD. These abnormalities suggest that PTSD can be understood by examining the dysfunction of large-scale spatially distributed neural networks.

Introduction

Brain structure can be interpreted as an integrated network using concepts of graph theory which quantify the whole brain as a single graph, comprising nodes linked by edges (1). Specifically, the small-world network pattern, which seems to have evolved to mediate high-efficiency parallel information transfer (2), has been used to define pathology in psychiatric disorders, including posttraumatic stress disorder (PTSD) (3-5).

PTSD is a trauma- and stressor-related disorder characterized by four symptom clusters: re-experience, avoidance, negative cognitions and mood, and arousal (6). Pediatric PTSD is not uncommon, the prevalence among children (12–17 years) being 3.7% for boys and 6.3% for girls (7). Childhood trauma is a severe stressor with multiple neurochemical and hormonal effects which can lead to lasting changes in brain structure and function (8). Children are particularly susceptible to PTSD (9), which may adversely influence brain development. Early interventions may help prevent brain changes.

Most early structural neuroimaging studies investigating the impact of childhood trauma on white matter (WM) integrity in children (10, 11) used manual tracing or volumetric morphometry. Diffusion tensor imaging (DTI) has since emerged as a powerful technique to assess WM tracts by exploiting the diffusion of tissue water. Using DTI we identified whole-brain WM microstructural abnormalities in pediatric PTSD (12), but we did not explore the neurocircuitry directly using connectivity analyses. We also applied graph theory to functional magnetic resonance imaging (MRI) data, finding that the functional connectome in pediatric PTSD is shifted toward ‘regularization’ (from a small-world to a more regular network) (4). As functional

interaction is constrained by brain cortical anatomy (13), to fully understand function one must study its structural substrate directly. Based on our findings in the functional connectome (4), we hypothesized that in pediatric PTSD the structural connectome would show a similarly disrupted topological organization.

Our purpose was to use DTI and graph theory approaches to explore the brain structural connectome in pediatric posttraumatic stress disorder (PTSD).

Materials and Methods

Participants

This study was approved by the local research ethics committee. Each child's parent/guardian was given a detailed information sheet, and then gave written consent. A total of 4,200 earthquake survivors were screened by M.W. and X.W. 8-15 months after the 8.0 magnitude earthquake in Sichuan in May 2008. Each participant was interviewed and screened using the PTSD checklist (PCL) (14); those scoring >35 on PCL were given the Clinician-Administered PTSD Scale (CAPS) (15) by a psychiatrist (L.L., 31 years' experience), of which those scoring >50 on CAPS were diagnosed with PTSD; those scoring <30 on PCL were considered non-PTSD trauma-exposed controls and were not assessed using CAPS (16). Inclusion criteria for all participants were: personal experience of the earthquake; personal witness of death, serious injury, or building collapse; age <18 years; IQ >80. This identified 161 PTSD patients and 99 trauma-exposed non-PTSD controls with similar demographic characteristics, lifestyle and earthquake experiences. Exclusion criteria were: psychiatric co-morbidities assessed using the Structured Clinical Interview for DSM-IV (17); history of psychiatric or neurological

disorders (n=42); MRI contraindication (n=30); recent medication that might affect brain function (n=24); unavailability of key data (n=12); left-handedness (n=10); CAPS score >35 but <50 (n=8); history of or current brain injury (n=7). Twenty-eight drug-naïve first-episode PTSD patients and 26 trauma-exposed non-PTSD controls underwent MRI scanning. Head-motion artifacts excluded data from 4 PTSD and 3 controls. MRI data from 24 PTSD and 23 controls went forward for analysis. We have reported elsewhere some other MR data from some of these subjects. In (4) we reported resting state functional MRI data of 24 PTSD and 24 controls: that work investigated the brain functional connectome, while our current work explores the brain structural connectome. In (12) we reported DTI data of 27 PTSD and 24 controls: that work investigated the microstructural networks using voxel-based analysis, while our current work explores the structural network directly using connectivity analyses.

Data Acquisition

MRI data were acquired on a 3T MRI system (EXCITE; General Electric) using a single-shot spin-echo echo planar image (SE-EPI) sequence, and included one high-resolution T1 scan and one DTI data scan. Foam padding was used to minimize head motion. A whole-brain high-resolution T1-weighted image was acquired using a sagittal three-dimensional spoiled gradient recall (SPGR) sequence with repetition time (TR) = 8.5 ms, echo time (TE) = 3.4 ms, inversion time (TI) = 400 ms, slice thickness = 1 mm, no inter-slice gap, 156 axial slices, matrix size = 256×256, field of view (FOV) = 24×24 cm^2 and flip angle = 12°. The diffusion sensitizing gradients were applied along 15 non-collinear directions (b-value = 1000 s/mm^2) together with an acquisition without diffusion weighting (b = 0). Imaging parameters were TR = 12000 ms, TE

= 71.6 ms, number of excitations (NEX) = 2, slice thickness = 3 mm, 50 slices, 128×128 matrix and 24×24 cm^2 FOV. The protocol included susceptibility-weighted imaging (SWI) which will be analyzed in a future study and fluid attenuated inversion recovery (FLAIR) sequences which were evaluated for clinical abnormalities by a neuroradiologist. A radiologist (L.S., with 3 years experience) evaluated and verified image quality.

Data Pre-Processing and DTI-Based Structural Network Construction

All the image preprocessing and analyses were implemented using a pipeline tool for diffusion MRI (PANDA) (18). We (X.S. and D.L.) extracted the fractional anisotropy (FA) map of each subject in 3 steps: BET (skull removal), eddy correct and DTIFIT (building diffusion tensor models). We then registered the FA maps with the FMRIB FA template in standard MNI space using nonlinear registration.

The automated anatomic labeling atlas (90 regions) was used to define the nodes of the WM network. PANDA uses the procedure proposed by Gong et al (19). Briefly, each of the individual FA images in native space was co-registered to its corresponding T1-weighted image using an affine transformation. Then the transformed T1-weighted images were non-linearly registered to the MNI space. The inverse transformations were obtained to the above two steps to transform the automated anatomic labeling atlas from MNI space to DTI native space. Thus, the individual cerebrum in native space was divided into 90 nodes corresponding to the automated anatomic labeling atlas. Each node represents a region of the DTI-based structural brain network. Deterministic tractography was performed to reconstruct whole brain WM tracts using the Fiber Assignment by Continuous Tracking algorithm (20). A tract was terminated if the turn angle

was >45° or the fiber entered a voxel with FA <0.2 (21). We defined the averaged FA of the linking fibers for each connection. For each individual, we generated a symmetric 90×90 network matrix in which each row/column represents a brain node/region and each element represents the averaged FA of the linking fibers between nodes.

Using the GRETNA toolbox we investigated the topological properties of brain networks at both the global and nodal level. The global level properties were of two kinds: small-world parameters [for definitions see (2)], including the clustering coefficient C_p, characteristic path length L_p [calculated as the harmonic mean distance between all possible pairs of regions to address the disconnected graphs dilemma(22)], normalized clustering coefficient γ, normalized characteristic path length λ, and small-worldness σ; and network efficiency parameters [for definitions see (23)], including the local efficiency E_{loc} and global efficiency E_{glob}. The nodal level properties were the nodal degree, nodal efficiency, and nodal betweenness.

For each network metric we calculated the area under the curve (AUC) over the sparsity range from S1 to Sn with an interval of ΔS, where S1 = 0.10, Sn = 0.34 and ΔS = 0.01. The AUC provides a summarized scalar for the topological characterization of brain networks independent of a single threshold selection. This approach uses a subject-specific correlation coefficient threshold to normalize all networks to the same number of nodes and edges, minimizing the effects of discrepancies in the overall correlation strength between groups, thereby enabling exploration of between-group differences in relative network organization (24), which is sensitive to topological alterations in brain disorders (4, 5, 24).

Subdivision of the whole brain network

Each submatrix of PTSD comprised nodes that exhibited significant between-group differences in at least one of the three nodal centralities, and edges that linked between any two of these altered nodes, which were individually extracted from the original 90×90 matrix. For each binary (0 and 1) submatrix, the edges connecting every pair of regions were counted. Note that edges were used only to indicate the existence (1) or absence (0) of connections, not to represent the connectivity strength. Finally, we summarized the edges of all the PTSD patients to constitute the PTSD-related subnetwork.

Statistical Analysis

For comparing clinical characteristics, statistical analyses were carried out using SPSS, version 16.0 (http://www.spss.com). Independent-sample t tests were used to compare quantitative variables. Qualitative variables were compared using a chi-squared test. The threshold for these statistical analyses was set at $P < 0.05$. All tests were two-tailed.

Between-group differences of structural connectome were compared using nonparametric permutation tests, which had been described in detail previously (4).

After significant between-group differences were identified in the network metrics, partial correlations were computed to examine relationships between these metrics and the CAPS scores in the PTSD group, using age and gender as covariates.

Results

Demographic and Clinical Comparisons

There were no significant differences in age, gender, education or time since the trauma between PTSD and controls ($P > 0.05$) (Table 1).

Global Topological Organization of the Structural Connectome

In the defined threshold range, both the PTSD and the control group showed small-world topology: compared with controls, PTSD showed significantly increased L_p (P=0.0248), with no significant differences in C_p (P=0.5947), γ (P=0.1074), λ (P=0.1940) or σ (P=0.1052). With regards to network efficiency, PTSD showed significantly decreased E_{loc} (P=0.0498) and E_{glob} (P=0.0274) (Figure 1).

Regional Topological Organization of the Structural Connectome

We identified the brain regions showing significant between-group differences in at least one nodal metric (P<0.05, FDR corrected). Compared with controls, PTSD showed decreased nodal centralities in the dorsolateral prefrontal cortex [left superior frontal gyrus, dorsolateral], ventrolateral prefrontal cortex [left inferior frontal gyrus, opercular part and right inferior frontal gyrus, orbital part], right insular cortex, left lingual gyrus, left middle occipital gyrus, left superior parietal gyrus, bilateral angular gyrus, left putamen, left thalamus. Increased nodal centralities were found only in the left anterior cingulate cortex and left inferior temporal gyrus (Figure 2, Table 2).

PTSD-related subnetwork

The PTSD-related subnetwork had 13 nodes and 21 connections (Figure 2), and the edges were mainly associated with the prefrontal-limbic-striatal, and ventral and dorsal visual systems.

Relationships between Network Metrics and Clinical Variables

An outlier analysis by excluding one subject whose CAPS score was not in the range of $\bar{x}\pm2SD$ showed that CAPS was negatively correlated with nodal efficiency of left superior

parietal gyrus (P=0.043) (Figure 3), but not with the other global and nodal metrics.

Discussion

Deterministic tractography based on DTI confirmed small-world architecture in both groups, but PTSD showed a variety of differences relative to stress-exposed non-PTSD controls: at the global level, increased characteristic path length L_p and decreased local and global network efficiency, E_{loc} and E_{glob}; and regionally, decreased nodal centralities in the salience network (ventrolateral prefrontal cortex, insular, putamen, thalamus), central executive network (dorsolateral prefrontal cortex and superior parietal gyrus), visual regions (lingual gyrus and middle occipital gyrus) and default mode network (angular gyrus), and increased nodal centralities in the anterior cingulate cortex and inferior temporal gyrus. Furthermore, some key abnormalities are related to clinical severity: CAPS score was negatively correlated with nodal efficiency of left superior parietal gyrus. What do these abnormalities mean, and how do they affect function?

At the global level, decreased E_{loc} makes the network less fault-tolerant: damage or disconnection of one region will dramatically affect connections with linked regions. Decreased E_{glob} may impair ability to combine specialized information from distributed brain regions affected by the loss of long-range connections (23). Furthermore, increased L_p represents a shift toward 'regularization', in line with what we found in the functional connectome of pediatric PTSD (4) Previous studies have suggested that global brain network topology is mediated by myelination degree in children (25). Traumatic stress during childhood have adverse effects on brain maturation (11). Our evidence of alterations in structural connectome might therefore possibly

implicate reduced myelination in pediatric PTSD. However, our previous and current connectome studies of pediatric PTSD reveal something different from the 'small-worldization ' in the functional connectome of adult PTSD (5). It is unclear why the transformation direction of brain network differs between adults and children. One possibility is that the neurobiological effects of stress vary at different developmental periods. For example, meta-analyses suggest that adult PTSD is associated with reduced hippocampal volume (26), while structural studies of pediatric PTSD reported no reduction of hippocampal volume, which may not become fully apparent until adulthood (27). Another alternative is that neuropsychological function of pediatric PTSD reveals a different pattern from adult PTSD (28). These hypotheses clearly require further testing in future studies, including longitudinal examination of children with PTSD into adulthood.

Turning to regional abnormalities, we found decreased nodal centrality mainly in the salience, central executive, and default mode networks (29). Several structural studies have focused on the corpus callosum following childhood trauma (30, 31), but by examining predefined regions of interest may have missed other important alterations in WM microstructure. Based on whole-brain analysis, Patel et al. invoke a ‘triple network’ model of PTSD, focusing on intrinsic connectivity networks (29). Our recent study of pediatric PTSD found that most of the abnormal brain regions belonged to two important networks: the default mode and salience networks (12). However, it did not directly explore the neurocircuitry using connectivity analyses, as the present study does. Recent graph analysis studies in PTSD also found abnormalities in the intrinsic connectivity network (3-5). These seem to play a role in the pathophysiology. For example,

comparing remitted and persistent PTSD, a significant interaction effect in the pallidum (part of the salience network) suggests that treatment can alter network topology (32); furthermore, in functional MRI studies activation of lateral prefrontal cortex and insular cortex (components of the salience network) predicts response to PTSD treatment (33, 34). Alongside our own findings, this evidence suggests that the salience network could be a target for therapeutic intervention in pediatric PTSD.

We also found decreased nodal centrality in visual areas, which might be related to 're-experience' symptoms. This decreased nodal centrality, which has been demonstrated to be a reliable index of network integrity (35), may reflect disruption of white matter integrity in the current structural connectome, perhaps partially accounting for the disruption in the functional connectome (4). Specifically, the nodal centrality of left superior parietal gyrus was negatively correlated with CAPS. As the parietal regions are related to the fear response (36), impaired microstructural integrity of this region may contribute to arousal in PTSD.

Unexpectedly, we observed increased nodal centrality in anterior cingulate cortex and inferior temporal gyrus. As Du et al. found significantly greater anterior cingulate cortex activation in PTSD (37), we speculate that the nodal centrality increase in anterior cingulate cortex may be compensatory. The inferior temporal gyrus is the last cortical area along the ventral visual pathway (38), and our observation may be related to the hypervigilance and hyperprosexia that are characteristic of PTSD.

We identified a PTSD-related subnetwork composed of 13 brain regions with 21 connections, mainly involving the prefrontal-limbic-striatal, and ventral and dorsal visual pathways. This

might be related to dysfunctional emotional and visual processing. Interestingly, the findings were mainly in the left hemisphere. Brain imaging studies have not shown consistent lateralized changes in PTSD. However, childhood trauma may set the stage for lateralized responses (10). Additional research will be needed to delineate the potential role of lateralized hemispheric deficits in PTSD.

This study has several limitations. Deterministic fiber tractography was used to define the edges of the structural connectome. The tracking procedure stops when it reaches regions with fiber crossings (20), which tends to reduce sensitivity. Probabilistic tractography, which requires a DTI sampling scheme at least 30 unique encoding directions (39), may be helpful to address this. A technical limitation is the comparatively low number (N=15) of gradient directions (chosen for practical reasons of patient comfort), which limits the quality of the available data. Future advanced DTI studies with more gradient directions are needed to improve the accuracy of tractography. The study is cross-sectional; longitudinal studies will be needed to define the gradual remodeling of the WM network in PTSD. The automated anatomic labeling template defines regions with a variety of sizes, which may bias nodal centrality; further studies are needed to determine which brain parcellation strategy is most appropriate for the characterization of network topology in PTSD. To control for possible stress-related brain alterations, we chose as controls the population who were also exposed to the earthquake but did not develop PTSD; non-traumatized healthy controls will need to be evaluated to provide more comprehensive insights into the pathology of PTSD. The P value of the negative correlation between the CAPS and nodal efficiency of left superior parietal gyrus was close to 0.05, so this analysis should be

considered exploratory. Future studies with large sample size are needed.

In summary, the structural connectome of pediatric PTSD patients showed a shift toward 'regularization', supporting the idea that this is a general pattern in pediatric PTSD. The widespread abnormalities were compatible with the notion that PTSD can be understood by investigating the dysfunction of large-scale, spatially distributed neural networks. This study provides a structural basis for the alterations of brain function in pediatric PTSD and might help to define early interventions which may attenuate adverse brain development.

References

1. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC. Organization, development and function of complex brain networks. Trends Cogn Sci. 2004;8(9):418-25.

2. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature. 1998;393(6684):440-2.

3. Long Z, Duan X, Xie B, et al. Altered brain structural connectivity in post-traumatic stress disorder: a diffusion tensor imaging tractography study. J Affect Disord. 2013;150(3):798-806.

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

5. Lei D, Li K, Li L, et al. Disrupted Functional Brain Connectome in Patients with Posttraumatic Stress Disorder. Radiology. 2015;276(3):818-27.

6. Association AP. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlingtion: American Psychiatric Association, 2013.

7. Kilpatrick DG, Ruggiero KJ, Acierno R, Saunders BE, Resnick HS, Best CL. Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: results from the National Survey of Adolescents. J Consult Clin Psychol. 2003;71(4):692-700.

8. Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Front Hum Neurosci. 2012;6:52.

9. Fletcher KE. Childhood posttraumatic stress disorder. In: Mash EJ, Barkley RA, eds. Child psychopathology, 2nd ed. New York, NY: Guildford Press, 2003; p. 330-71.

10. De Bellis MD, Keshavan MS, Clark DB, et al. A.E. Bennett Research Award.

Developmental traumatology. Part II: Brain development. Biol Psychiatry. 1999;45(10):1271-84.

11. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry. 2002;52(11):1066-78.

12. Lei D, Li L, Li L, et al. Microstructural abnormalities in children with post-traumatic stress disorder: a diffusion tensor imaging study at 3.0T. Sci Rep. 2015;5:8933.

13. Honey CJ, Sporns O, Cammoun L, et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009;106(6):2035-40.

14. Weathers F, Litz B, Herman D, Huska J, Keane T. The PTSD checklist-civilian version (PCL-C). Boston, MA: National Center for PTSD, 1994.

15. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8(1):75-90.

16. VA National Center for PTSD. Using the PTSD checklist for DSM-IV (PCL). http://www.ptsd.va.gov/professional/pages/assessments/assessment-pdf/PCL-handout.pdf. Accessed January 19, 2014.

17. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Patient Edition (SCID-I/P, 2/2001 revision). Washington, D.C: American Psychiatric Press, 1997.

18. Cui Z, Zhong S, Xu P, He Y, Gong G. PANDA: a pipeline toolbox for analyzing brain diffusion images. Front Hum Neurosci. 2013;7:42.

19. Gong G, He Y, Concha L, et al. Mapping anatomical connectivity patterns of human cerebral

cortex using in vivo diffusion tensor imaging tractography. Cereb Cortex. 2009;19(3):524-36.

20. Mori S, van Zijl PC. Fiber tracking: principles and strategies - a technical review. NMR Biomed. 2002;15(7-8):468-80.

21. Yang S, Hua P, Shang X, et al. A significant risk factor for poststroke depression: the depression-related subnetwork. J Psychiatry Neurosci. 2015;40(4):259-68.

22. Newman ME. Mixing patterns in networks. Phys Rev E Stat Nonlin Soft Matter Phys. 2003;67(2 Pt 2):026126.

23. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett. 2001;87(19):198701.

24. Zhang J, Wang J, Wu Q, et al. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biol Psychiatry. 2011;70(4):334-42.

25. Hagmann P, Sporns O, Madan N, et al. White matter maturation reshapes structural connectivity in the late developing human brain. Proc Natl Acad Sci U S A. 2010;107(44):19067-72.

26. Kuhn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol Psychiatry. 2013;73(1):70-4.

27. Keding TJ, Herringa RJ. Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. Neuropsychopharmacology. 2015;40(3):537-45.

28. Beers SR, De Bellis MD. Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. Am J Psychiatry. 2002;159(3):483-6.

29. 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(9):2130-42.

30. Jackowski AP, Douglas-Palumberi H, Jackowski M, et al. Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. Psychiatry Res. 2008;162(3):256-61.

31. Rinne-Albers MA, van der Werff SJ, van Hoof MJ, et al. Abnormalities of white matter integrity in the corpus callosum of adolescents with PTSD after childhood sexual abuse: a DTI study. Eur Child Adolesc Psychiatry. 2015.

32. Kennis M, van Rooij SJ, van den Heuvel MP, Kahn RS, Geuze E. Functional network topology associated with posttraumatic stress disorder in veterans. Neuroimage Clin. 2016;10:302-9.

33. Roy MJ, Francis J, Friedlander J, et al. Improvement in cerebral function with treatment of posttraumatic stress disorder. Ann N Y Acad Sci. 2010;1208:142-9.

34. van Rooij SJ, Kennis M, Vink M, Geuze E. Predicting Treatment Outcome in PTSD: A Longitudinal Functional MRI Study on Trauma-Unrelated Emotional Processing. Neuropsychopharmacology. 2016;41(4):1156-65.

35. Wang JH, Zuo XN, Gohel S, Milham MP, Biswal BB, He Y. Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. PLoS One. 2011;6(7):e21976.

36. Bremner JD, Vermetten E, Vythilingam M, et al. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. Biol Psychiatry.

2004;55(6):612-20.

37. Du X, Wei D, Ganzel BL, Kim P, Zhang Q, Qiu J. Adolescent earthquake survivors' show increased prefrontal cortex activation to masked earthquake images as adults. Int J Psychophysiol. 2015;95(3):292-8.

38. Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DL, Goodale MA, Mansfield RJW, eds. Analysis of Visual Behavior. Cambridge, MA: MIT Press, 1982; p. 549-86.

39. Jones DK. The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study. Magn Reson Med. 2004;51(4):807-15.

Table 1. Demographics and clinical characteristics of the subjects [a]

Variables	PTSD(n=24)	Non-PTSD(n=23)	*P* value
Age (years) [b]	13.0±1.7 (10-16)	13.2±1.3 (11-16)	0.77
Gender (male/female)	10/14	11/12	0.53
Years of education [b]	7.7±2.1 (6-12)	8.1±2.2 (6-14)	0.49
Time since trauma (months)[b]	10.1±1.5 (8-12)	13.4±1.2 (10-15)	0.10
PTSD checklist	54.9±5.6 (40-65)	23.9±3.0 (19-35)	-
CAPS	65.5±6.4 (60-86)	-	-

[a] Data are presented as mean±SD (minimum-maximum) unless noted.

[b]Age, years of education and time since trauma were reported by participants' parents/guardians at the time of MR scanning.

Abbreviation: PTSD, post-traumatic stress disorder; CAPS, Clinician-administered PTSD scale.

Table 2. Regions showing altered nodal centralities in the pediatric PTSD group compared with the trauma-exposed non-PTSD control group

Brain regions	*P* Values		
	Nodal Degree	Nodal Efficiency	Nodal Betweenness
PTSD < non-PTSD			
Left superior frontal gyrus, dorsolateral	0.0266	0.0250	0.0848
Left inferior frontal gyrus, opercular part	0.5059	0.3043	0.0490
Right inferior frontal gyrus, orbital part	0.2679	0.0840	0.0180
Right insular cortex	0.2376	0.0258	0.8068
Left lingual gyrus	0.0162	0.0182	0.0736
Left middle occipital gyrus	0.2024	0.0402	0.5635
Left superior parietal gyrus	0.0520	0.0484	0.2421
Left angular gyrus	0.1858	0.0392	0.8780
Right angular gyrus	0.0812	0.0168	0.2206
Left putamen	0.4061	0.0450	0.3551
Left thalamus	0.0344	0.0062	0.0800
PTSD > non-PTSD			
Left anterior cingulate cortex	0.1420	0.3055	0.0444
Left inferior temporal gyrus	0.1156	0.7181	0.0124

Regions were considered abnormal in the pediatric PTSD patients if they exhibited significant between-group differences ($P<0.05$, FDR corrected) in at least one of the three nodal centralities (shown in bold font).

Abbreviation: PTSD, posttraumatic stress disorder.

Figure legends

Figure 1. The differences in topological properties of the brain structural connectome between pediatric PTSD and trauma-exposed non-PTSD controls (nonparametric permutation test, $P < 0.05$). Significant differences were found in L_p ($P = 0.0248$), E_{glob} ($P = 0.0274$) and E_{loc} ($P = 0.0498$) in PTSD. PTSD: posttraumatic stress disorder; E_{glob}: global efficiency; E_{loc}: local efficiency; L_p: characteristic path length; C_p: clustering coefficient; λ: normalized characteristic path length; γ: normalized clustering coefficient; σ: small-worldness.

Figure 2. The pediatric PTSD-related subnetwork. Every node denotes a brain region and every line denotes a connection. Different colored nodes represent different brain regions: purple, salience network; dark blue, central executive network; blue, default mode network; yellow, visual regions. L, left; R, right; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; PUT, putamen; THA, thalamus; INS, insular; AG, angular gyrus; SPG, superior parietal gyrus; LG, lingual gyrus; MOG, middle occipital gyrus; ITG, inferior temporal gyrus.

Figure 3. Scatter plots of nodal efficiency of left SPG against CAPS scores in pediatric PTSD. PTSD: posttraumatic stress disorder; CAPS: Clinician-Administered PTSD Scale; SPG, superior parietal gyrus.