Default-Mode Network Abnormalities in Pediatric Posttraumatic Stress Disorder

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Objective: Resting-state functional magnetic resonance imaging (rs-fMRI) studies of adult posttraumatic stress disorder (PTSD) have identified default-mode network (DMN) abnormalities, including reduced within-network connectivity and reduced anticorrelation between the DMN and task-positive network (TPN). However, no prior studies have specifically examined DMN connectivity in pediatric PTSD, which may differ due to neurodevelopmental factors.

Method: A total of 29 youth with PTSD and 30 nontraumatized healthy youth of comparable age and sex completed rs-fMRI. DMN properties were examined using posterior cingulate cortex (PCC) seed-based connectivity and independent component analysis (ICA).

Results: Contrary to findings in adult studies, youth with PTSD displayed increased connectivity within the DMN, including increased PCC–inferior parietal gyrus connectivity, and age-related increases in PCC–ventromedial prefrontal cortex connectivity. Strikingly, youth with PTSD also displayed greater anticorrelation between the PCC and multiple nodes within salience and attentional control networks of the TPN. ICA revealed greater anticorrelation between the entire DMN and TPN networks in youth with PTSD. Furthermore, DMN and TPN connectivity strength were positively and negatively associated, respectively, with re-experiencing symptoms of PTSD.

Conclusion: Pediatric PTSD is characterized by heightened within-DMN connectivity, which may contribute to re-experiencing symptoms of PTSD and is consistent with the role of the DMN in autobiographical memory. At the same time, greater anticorrelation between the DMN and attentional control networks may represent compensatory mechanisms aimed at suppressing trauma-related thought, a notion supported by the inverse relationship between TPN strength and re-experiencing. These findings provide new insights into large-scale network abnormalities underlying pediatric PTSD, which could serve as biomarkers of illness and treatment response.

Key words: pediatric PTSD, DMN, rs-fMRI, connectivity

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Pediatric posttraumatic stress disorder (PTSD) affects an estimated 5% of youth by the age of 18 years.[1] Pediatric PTSD has high comorbidity with other mental illnesses including anxiety disorders, depression, and attention-deficit/hyperactivity disorder (ADHD).[2] Although there is a need to advance treatments for pediatric PTSD, progress remains hampered by an incomplete understanding of underlying brain mechanisms, which may differ from those in adult PTSD because of ongoing neurodevelopment.

Resting-state functional magnetic resonance imaging (rs-fMRI) allows assessment of intrinsic (i.e., task-free) functional networks[3] and is particularly suitable in pediatric populations. Resting state analyses consistently identify 2 main networks: the default mode network (DMN), involved in self-referential processes including autobiographical memory[4-6]; and the task positive network (TPN), involved in attentional control and behavioral response via the salience, dorsal attention, and ventral attention subnetworks.[7] In healthy adults, the DMN and TPN operate in an anticorrelated fashion, indicative of functionally competing brain systems that switch during the processing of internal versus external stimuli.[8-11] DMN hyperconnectivity and reduced DMN suppression/anticorrelation have been reported in psychopathology including schizophrenia and depression, suggesting that abnormal network strength and reciprocity may underlie difficulties in disengaging from internal stimuli such as delusional thought and depressive ruminations.[11,12]

Studies in adult PTSD suggest abnormal DMN function and connectivity, including decreased within-DMN intrinsic connectivity,[13-17] both decreased[13] and increased[16] DMN-TPN intrinsic anticorrelation, and reduced DMN suppression during task.[17] Together, these findings suggest that adult PTSD is characterized by both within- and between-network abnormalities of the DMN, which may contribute to difficulties disengaging from trauma-related thought. However, no prior study has specifically examined DMN properties, including its relationship to attentional control networks, in pediatric PTSD. Thus, it remains unknown whether similar DMN abnormalities are present in pediatric as in adult PTSD, and whether the normal developmental pattern of the DMN is disrupted. Notably, DMN-TPN anticorrelation develops with age, going from positive connectivity in childhood to negative or anticorrelated connectivity by adulthood.[18]

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To address these knowledge gaps, we examined intrinsic network properties in a sample of youth with severe PTSD relative to nontraumatized healthy youth. First, we assessed DMN connectivity using seed-based connectivity of the posterior cingulate cortex (PCC), a key node of the DMN. Next, we used group independent component analysis (ICA) to examine large-scale network differences within and between the DMN and TPN. Within these analyses, we examined age-related effects cross-sectionally as an indicator of altered neurodevelopment in pediatric PTSD. We hypothesized that pediatric PTSD would be associated with disrupted within-DMN connectivity, and reduced anticorrelation between the DMN and TPN, bearing similarity to adult PTSD. Finally, we examined the relationship of DMN/TPN network properties to symptom severity using a multidimensional symptom approach, incorporating PTSD, anxiety, and depressive symptoms in this highly comorbid sample.

METHOD

Participants

Youth with PTSD and healthy youth were recruited from area mental health clinics and the community, respectively. Healthy participants were free of any history of trauma or mental illness. Exclusion criteria for all participants included IQ<70, unstable medical condition, MRI contraindication, and possibility of pregnancy. Additional exclusion criteria for the group with PTSD included active suicidality, history of psychotic disorder, bipolar disorder, obsessive-compulsive disorder, recent (past 4 weeks) substance abuse or dependence, or use of psychotropic medication (past 4 weeks; 6 weeks for fluoxetine). A total of 119 youth were screened for study inclusion. Of these, 44 were excluded at initial assessment (subthreshold for PTSD, n = 29; exclusionary diagnosis, n = 7; active substance/medication use, n = 3; no child memory of a traumatic event, n = 3; MRI contraindication, n = 1; other, n = 1). Three additional youth met study criteria but were unable to complete MRI. In all, 72 participants completed the study, including 35 youth with PTSD and 37 healthy youth. Of these, 12 were excluded based on data quality described below. The final sample includes 29 youth with PTSD (18 female and 11 male; mean age = 14.6 years) and 30 healthy youth (18 female and 12 male, mean age = 14.0 years). All participants provided written consent, or assent with caregiver consent when applicable. All procedures were approved by the University of Wisconsin Health Science Internal Review Board.

Clinical and Behavioral Assessment

Clinical assessments for this study have been previously described.[19,20] A board-certified child and adolescent psychiatrist interviewed and screened all participants, incorporating both caregiver and youth reports. Psychiatric diagnoses and trauma exposure were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS).[21] PTSD was diagnosed using *DSM-IV* criteria by combination of the K-SADS and the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA).[22,23] A PTSD diagnosis required at least 5 *DSM-IV* symptoms, including at least 1 from each symptom cluster following Cohen *et al.*[24] These criteria are slightly modified from adult criteria and were chosen to allow greater likelihood of study inclusion yet maintain a relatively high symptom severity. Furthermore, youth fulfilling 2 versus 3 symptom clusters have been reported not to differ in overall clinical impairment or distress.[25] Using these criteria, most youth in the group with PTSD (n = 24 or 83%) met full standard *DSM-IV* criteria for PTSD. Of the remaining 5 participants with PTSD, 3 met criteria for 2 symptom clusters, and 2 met criteria for 1 symptom cluster. With regard to *DSM-5* criteria, an estimated 22 participants (76%) met the full diagnosis of PTSD using conservative criteria based on extrapolation from *DSM-IV* symptoms.[26] Of the remaining 7 participants, 5 met criteria for 3 symptom clusters, and 2 met criteria for 2 symptom clusters. PTSD severity was additionally examined using the University of California, Los Angeles (UCLA) PTSD Reaction Index (PTSD-RI).[27] Because the CAPS-CA was not acquired for the first 7 participants with PTSD, PTSD-RI scores were used in lieu of CAPS-CA for secondary analyses. Here, the greater of youth and caregiver report for each item was used,[19,20] as this was most strongly correlated with CAPS scores, which represent the gold standard for PTSD assessment (r = 0.85, 0.74, and 0.60 for greater of youth/caregiver report, youth only, and caregiver only, respectively). Depressive symptoms (past 2 weeks) were quantified with the Mood and Feelings Questionnaire (MFQ).[28] Anxiety symptoms (past 3 months) were quantified with the Screen for Child Anxiety Related Emotional Disorders (SCARED).[29] MFQ and SCARED scores were calculated using the average of youth and caregiver reports. Pubertal stage was assessed by self-report using the Tanner picture-based rating scale.[30] IQ was estimated using the Full-Scale IQ-2 component of the Wechsler Abbreviated Scale of Intelligence–II.[31]

Data Acquisition

Each participant underwent 2 mock scan sessions to familiarize them to the scanning environment and reduce motion. High-resolution T1 and rs-fMRI data were acquired using a 3.0T GE Discovery MR750 scanner with an 8-channel head coil (General Electric Medical Systems, Waukesha, WI). High-resolution T1 images were acquired using a BRAVO pulse sequence (with axial orientation, TE =3.18 milliseconds, TR = 8.16 milliseconds, TI = 450 milliseconds, voxel size = 1 × 1 × 1 mm^3, 156 slices, flip angle = 12 degrees, field of view [FOV] = 25.6 cm, and matrix size = 256 × 256). rs-fMRI was acquired using an echo-planar imaging (EPI) pulse sequence (with sagittal orientation, TE = 22 milliseconds, TR = 2150 milliseconds, flip angle = 79 degrees, slice thickness = 3 mm, gap = 0.5 mm, 41 slices, FOV = 224 mm, and matrix size = 64 × 64, number of volumes = 147 [5 minutes 16 seconds]). For rs-fMRI, participants were instructed to remain still with their eyes fixed on a cross.

rs-fMRI Preprocessing

Preprocessing was carried out using AFNI.[32] Figure S1, available online, shows the preprocessing pipeline used for each research participant. The steps were: deletion of the first 3 volumes; despiking of rs-fMRI data; slice-timing correction; co-registration of T1 and EPI images; realignment of EPI volumes and normalization to Montreal Neurological Institute (MNI) template in a single step (final resolution 2 mm isotropic for visualization with template underlay); spatial smoothing (6 mm full width at half maximum [FWHM]); anatomy segmentation; and nuisance regression (eroded white matter and cerebrospinal fluid masks, 6 motion parameters and their derivatives) and temporal filtering (0.01–0.1Hz) along with motion censoring in a single step. Volumes were motion censored using a threshold of 0.25 mm based on framewise displacement calculated using the Euclidean norm. Participants having 37 or more volumes (25%) flagged by the censoring algorithm were excluded from the study, resulting in 12 exclusions (6 PTSD and 7 healthy participants). The average motion in all directions was calculated and compared across groups; no difference in motion was observed (Table S1, available online).

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