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Structural covariance network centrality in maltreated youth with posttraumatic stress disorder

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ABSTRACT

Childhood maltreatment is associated with posttraumatic stress disorder (PTSD) and elevated rates of adolescent and adult psychopathology including major depression, bipolar disorder, substance use disorders, and other medical comorbidities. Gray matter volume changes have been found in maltreated youth with (versus without) PTSD. However, little is known about the alterations of brain structural covariance network topology derived from cortical thickness in maltreated youth with PTSD. High-resolution T1-weighted magnetic resonance imaging scans were from demographically matched maltreated youth with PTSD (N = 24), without PTSD (N = 64), and non-maltreated healthy controls (n = 67). Cortical thickness data from 148 cortical regions was entered into interregional partial correlation analyses across participants. The supra-threshold correlations constituted connections in a structural brain network derived from four types of centrality measures (degree, betweenness, closeness, and eigenvector) estimated network topology and the importance of nodes. Between-group differences were determined by permutation testing. Maltreated youth with PTSD exhibited larger centrality in left anterior cingulate cortex than the other two groups, suggesting cortical network topology specific to maltreated youth with PTSD. Moreover, maltreated youth with versus without PTSD showed smaller centrality in right orbitofrontal cortex, suggesting that this may represent a vulnerability factor to PTSD following maltreatment. Longitudinal follow-up of the present results will help characterize the role that altered centrality plays in vulnerability and resilience to PTSD following childhood maltreatment.

1. Introduction

Childhood maltreatment is associated with increased risk for multiple forms of psychopathology (De Bellis and Zisk, 2014; McLaughlin et al., 2013). Children who have been maltreated exhibit difficulties in multiple forms of emotion regulation (De Bellis and Zisk, 2014; McCrory et al, 2011, 2013; McLaughlin et al., 2015) and social cognition (Kay and Green, 2016). About 20–30% of maltreated youth meet criteria for chronic posttraumatic stress disorder (PTSD) (McLeer et al., 1998; McLeer and Ruggiero, 1999), which is accompanied by heightened threat response and difficulty inhibiting fear response to traumatic reminders. We recently reported that maltreated youth with chronic PTSD, when compared to maltreated youth without PTSD, have smaller volumes in brain areas associated with fear extinction, emotion and memory processing, including left amygdala, right hippocampus and right ventromedial prefrontal cortex (Morey et al., 2016).

It has been widely accepted that the brain is organized into complex networks that evolve throughout postnatal and adolescent development (Di Martino et al., 2014; Zhang and Sejnowski, 2000). This brain development involves a highly choreographed process of neuronal growth and migration throughout the cortical mantle that may be derailed by exposure to various environmental insults (Evsyukova et al., 2013; Houston et al., 2014). Severe maltreatment may initially influence gray matter integrity by activating glutamate circuits and triggering pro-inflammatory processes that initiate a cascade of neural events, which manifest as reduced synaptic density and strength, as well as dendritic retraction and reduced arborization (Popoli et al., 2012). Indeed, prior work suggests that environmental threats such as childhood maltreatment may modify the development of brain networks (Hart and Rubia, 2012; Morey et al., 2015; Spielberg et al., 2015). However, knowledge about brain networks in maltreated youth with or without PTSD is scarce.

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Table 1
Demographic information.

TEST	Mean (SD)			Statistic (p-value)*		
	CONT (n = 67)	MALT (n = 64)	PTSD (n = 24)	PTSD vs MALT	MALT vs CONT	PTSD vs CONT
Age [years]	14.8 (2.7)	15.4 (2.8)	14.7 (2.7)	−1.011 (0.315)	1.138 (0.257)	−0.195 (0.846)
Sex [m(f)]	31 (36)	28 (36)	11 (13)	0.031 (0.861)	0.084 (0.772)	0.001 (0.971)
Parental Education	3.4 (0.8)	2.3 (1.2)	2.1 (1.2)	−0.824 (0.412)	−5.729 (< 0.001)	−5.806 (< 0.001)
CTQ Physical	5.1 (0.4)	7.9 (4.1)	11.3 (5.0)	3.294 (0.001)	5.582 (< 0.001)	10.142 (< 0.001)
CTQ Sexual	5.0 (0.4)	7.4 (4.6)	8.5 (6.1)	0.927 (0.356)	4.241 (< 0.001)	4.733 (< 0.001)
CTQ Emotional	6.1 (1.7)	9.3 (4.1)	12.1 (4.9)	2.722 (0.008)	5.847 (< 0.001)	8.637 (< 0.001)
Depression	−0.5 (0.8)	0.3 (1.0)	0.7 (1.0)	1.378 (0.172)	5.647 (< 0.001)	5.839 (< 0.001)
DISC	7.0 (5.4)	13.2 (7.9)	29.5 (9.2)	2.847 (0.007)	3.156 (0.003)	5.390 (< 0.001)
SCARED	12.4 (9.8)	22.5 (9.3)	31.0 (17.4)	2.221 (0.031)	4.354 (< 0.001)	5.628 (< 0.001)

Note: *, the statistical values for Sex are from Chi-Square tests, while others from t tests. CONT = Control, Malt = Maltreated youth without PTSD, PTSD = Maltreated youth with PTSD, m(f) = number of males (females), CTQ = Childhood Trauma Questionnaire, DISC = anxiety symptoms index from the Diagnostic Interview Schedule for Children Version IV, SCARED = Screen for Child Anxiety Related Disorders.

Graph theoretical measures have been recently employed to investigate structural and functional brain networks in patients with various neuropsychiatric disorders (Bassett et al., 2008; Bernhardt et al., 2008; He et al., 2008, 2009; Yao et al., 2010). Cortical morphometric network analyses (Bassett et al., 2008; He et al., 2008; He and Evans, 2010; Lerch et al., 2006; Sporns, 2011) are based on structural inferences made between specific pairings of cortical regions that vary in tandem with respect to cortical thickness or gray matter volume (Gong et al., 2012; Lerch et al., 2006). Although the neurobiological interpretation of the covariance in cortical thickness across regions is yet unclear, it has been proposed that the correlation strength increases between regions that are concurrently affected by common factors, and decreases between regions that are differentially affected by such factors (Mueller et al., 2015). The structural covariance network method based on cortical thickness/gray matter volume is relatively insensitive to the noisy components that accompany task-based and resting-state functional magnetic resonance imaging (fMRI). Thus it is posited that the structural covariance network may reflect the current state of the highly choreographed developmental processes of neuronal growth and migration throughout the cortical mantle (Gong et al., 2012; Lerch et al., 2006; Marin et al., 2010).

The supra-threshold structural covariance between anatomically delineated brain regions may be treated as a connection in the brain network and further quantified with graph theoretical measures, although there may be no direct connections between regions. Previous studies have also indicated that cortical thickness covariance partly reflects underlying fiber connections where 35–40% of thickness correlations showed convergent diffusion connections, but should not be taken as a proxy measure of fiber connections (Gong et al., 2012). Centrality is an indicator of the importance of a region within a network of interconnected nodes. Graph theory suggests that nodes with high centrality play a crucial role in controlling network information transfer and neural communication (He et al., 2008).

Structural covariance network analyses based on cortical thickness have shown that adults previously exposed to childhood maltreatment exhibited lower brain network centrality than adults without childhood maltreated in left anterior cingulate gyrus, and increased centrality in right precuneus and right anterior insula (Teicher et al., 2014). Moreover, military veterans with PTSD demonstrated decreased centrality in left orbitofrontal cortex and anterior cingulate cortices (ACC), and increased centrality in left insula and right orbitofrontal cortex (Mueller et al., 2015). However, these studies are focused on PTSD in adults, often decades after exposure to childhood maltreatment, and were not able to uncover the brain network alterations associated with acute effects of child maltreatment and subsequent PTSD. Here, we examined the brain structure covariance network of maltreated youth with and without PTSD.

We were specifically interested in orbitofrontal cortex (OFC) and ACC (Kelly et al., 2013; Kringelbach, 2005), which are consistently related to emotion processing, safety signal learning, and decision-making processes that may be disrupted by childhood maltreatment (McLaughlin et al, 2014b, 2015) and PTSD (James et al., 2014; Morey et al., 2012). Previous research has also shown structural and functional disruptions to OFC and ACC in survivors of childhood maltreatment (Kelly et al., 2013; Lim et al., 2014; Teicher et al., 2014) and those with PTSD (Morey et al., 2016; Mueller et al., 2015; Spielberg et al., 2015). We hypothesized that maltreatment would be broadly associated with altered centrality in OFC and in the ACC, particularly children with PTSD as disruptions in these neural networks may increase their vulnerability to the disorder. Specifically, we predicted that these areas would show lower centrality in maltreated youth with PTSD than maltreated youth without PTSD and non-maltreated controls. Based on findings from previous studies of brain structural covariance network architecture in adults exposed to maltreatment (Teicher et al., 2014) or with PTSD (Mueller et al., 2015), we also anticipated between-group differences in insula/inferior frontal cortex (Ins/IFC) and temporal pole (TP).

2. Methods

2.1. Participants

Study participants were drawn from three neuroimaging cohorts of childhood maltreatment: one cohort of maltreated adolescents (aged 13-20) completed in Boston (Boston Children's Hospital) and two cohorts of maltreated children (aged 8-19) completed in Seattle (University of Washington). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and was approved by the local institutional review board. Written informed consent was obtained from each participant after the nature of the procedures had been fully explained. The combined sample consisted of all participants who completed an MRI and included maltreated youth with chronic PTSD (N = 24), without PTSD (N = 64), and non-maltreated controls (n = 67). As shown in Table 1, there were no between-group differences in age and sex. However, maltreatment (both with and without PTSD) was associated with lower parental education. Exclusion criteria included psychiatric medication use (with the exception of stimulant medications for attention-deficit/hyperactivity disorder [ADHD], which were discontinued 24 h before the scan), dental braces, claustrophobia, active substance dependence, pervasive developmental disorder, inability to speak English, and presence of active safety concerns.

2.2. Measures

Maltreatment was assessed using the Childhood Trauma