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Annual Research Review: Pediatric posttraumatic stress disorder from a neurodevelopmental network perspective

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Background: Experiencing traumatic stress is common and may lead to posttraumatic stress disorder (PTSD) in a number of children and adolescents. Research using advanced imaging techniques is beginning to elucidate some of the neurobiological correlates of the traumatic stress response in youth. **Methods:** This paper summarizes the emerging network perspective of PTSD symptoms and reviews brain imaging research emphasizing structural and functional connectivity studies that employ magnetic resonance imaging techniques in pediatric samples. **Results:** Differences in structural connections and distributed functional networks such as the salience, default mode, and central executive networks are associated with traumatic and severe early life stress. The role of development has been relatively underappreciated in extant studies though there is evidence that critical brain regions as well as the structural and functional networks implicated undergo significant change in childhood and these typical developmental differences may be affected by traumatic stress. **Conclusions:** Future research will benefit from adopting a truly developmental approach that considers children's growth as a meaningful effect (rather than simply a covariate) interacting with traumatic stress to predict disruptions in the anatomical, functional, and connective aspects of brain systems thought to underlie the network of PTSD symptoms. Linking symptom networks with neurodevelopmental network models may be a promising avenue for future work. **Keywords:** Posttraumatic stress disorder; network analysis; brain development; structural connectivity; functional connectivity.

Introduction

Exposure to a traumatic events is common (Atwoli, Stein, Koenen, & McLaughlin, 2015). Experiencing or witnessing a life threatening, catastrophic, or otherwise traumatic event may lead to the development of posttraumatic stress disorder (PTSD) in a significant portion of children and adolescents, with rates varying by sample, assessment methods, and type of trauma (Fairbank, 2008). While such exposure is associated with diverse outcomes among youth such as anxiety disorders, depression, aggression, and even positive growth, or resilience (Hoven et al., 2005; Scott, Lapré, Marsee, & Weems, 2014; Scott & Weems, 2017; Weems & Graham, 2014), this review focuses primarily on pediatric PTSD. Research on PTSD has been facilitated by a common definition of the disorder provided in versions of the Diagnostic and Statistical Manual (DSM) of mental disorders (American Psychiatric Association [APA], 2013). In DSM-III-R (APA, 1987), pediatric PTSD had identical criteria to the adult diagnosis, while DSM-IV (APA, 1994) introduced some developmental modifications. Most recently, the DSM-5 (APA, 2013) relocated PTSD to a new chapter on trauma- and stressor-related disorders (it had been listed in the anxiety disorders group) and include a number of additional developmental modifications for PTSD.

DSM-5 PTSD diagnosis requires exposure to a traumatic stressor and defines traumatic stress as exposure to actual or threatened death, serious injury, or sexual violence. Exposure may involve directly experiencing the event, witnessing it happen to someone else, or learning it has happened to a loved one (APA, 2013). DSM-5 organizes PTSD symptoms into four categories (as compared to three in DSM-IV) with one or more symptoms required from each group. These groups are: (a) intrusion (one required), (b) avoidance (one required), (c) negative alterations in cognitions and mood (two required), and (d) altered arousal and reactivity (two required). Additionally, symptoms must persist for at least 1 month and cause clinically significant impairment in functioning (APA, 2013).

DSM-5 provides extensive description of developmental differences in symptom expression and for children aged 6 and younger, DSM-5 includes a separate set of developmentally sensitive criteria with three (not four), symptom groups (APA, 2013). Some symptoms, such as a 'sense of a foreshortened future' and the 'inability to recall an important aspect of the event' are not present in the young child criteria while other symptoms are differently defined, such as diminished interest in activities including constriction of play (APA, 2013). Although the DSM criteria provide consistency for research and practice, there remains disagreement in the field about the best way to conceptualize the constellation

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of symptoms that can present in the aftermath of traumatic experiences (Brewin & Holmes, 2003; Elhai & Palmieri, 2011; McNally, 2003; McNally et al., 2015).

Research using advanced brain imaging techniques is beginning to elucidate the neurobiological correlates of the traumatic stress response and PTSD in youth (Carrión & Weems, 2017). This paper reviews the network approach to PTSD symptoms (McNally et al., 2015; Russell, Neill, Carrión & Weems, 2017) and also structural and functional connectivity research using magnetic resonance imaging in pediatric samples to develop a neurodevelopmental network perspective. We begin with network models of PTSD symptom expression and their conceptual links to certain normative cognitive and emotional functions. Next, mechanisms whereby traumatic stress may affect the brain are discussed with research on the importance of a developmental approach to understanding the neurobiological response to traumatic stress emphasized. We then focus on reviewing the extant research into the effects of traumatic stress on the structural and functional connections amongst various brain regions, such as the regions of the prefrontal cortex (executive function), hippocampus (memory), and amygdala (emotion) implicated in distributed functional brain networks (Herringa, 2017; Menon, 2011). The research on pediatric neurobiological networks and the network symptom approach are summarized and the case is made for a truly developmental approach integrating symptom networks with brain networks and disentangling the role of chronological age, biological maturation, as well as the timing and type of trauma.

Network approach to pediatric PTSD symptoms

As noted, and evident in the change from three to four symptom groups in DSM-5, researchers continue to debate the organization of PTSD symptoms (Bennett, Kerig, Chaplo, McGee, & Baucom, 2014; McNally et al., 2015). While factor analytic studies report models of three, four, or five factors (Elhai & Palmieri, 2011), comparison of these models often suggests relatively equivalent performance (e.g., only slight differences in fit to the data; Bennett et al., 2014). Network-based analyses are an emerging alternative to traditional factor-models. The network systems approach emphasizes broad patterns of associations between symptoms, with the aim of identifying 'central' symptoms and critical between-symptom associations. According to Borsboom and Cramer (2013), symptoms in a network may be considered 'mutually interacting, often reciprocally reinforcing, elements in a complex network' (p. 96). Within a symptom network, some symptoms may be more critical or 'central' to the network, in that they are related to or influence a larger number of other symptoms. Theoretically, these central symptoms hold critical influence over the network at large (Martel, Levinson, Langer, & Nigg, 2016).

To foreshadow a later point, network analysis of symptoms offers researchers the opportunity to identify related subgroups of symptoms (or specific, central symptoms) that may share a common neurological origin in the brain's functional and structural networks. For example, within a neurobiological network, some regions may be more critical to traumatic stress response, thereby demonstrating comparatively more centrality or connectivity within related brain networks. These regions may link or influence a larger number of stress response regions, and differences in their connections may then represent a critical influence over risk or resilience to experiencing certain pediatric PTSD symptoms or explain symptom associations.

McNally et al. (2015) conducted the first study applying network methodology to PTSD symptoms in a sample of adult disaster survivors and reported a strong connection between sleep problems, anger/irritability, and concentration difficulties. McNally et al. theorized that this interrelatedness might stem from a common impairment in cognitive executive function systems. Russell, Neill, Carrión, and Weems (2017) conducted the first network analysis of pediatric PTSD symptoms among youth exposed to disaster-related traumatic stress. While results suggest developmental differences in the PTSD symptom network, a similar clustering emerged between symptoms linking to executive function and emotion regulation. For example, meaningful links were revealed between sleep disturbances, concentration difficulties, anger/irritability, exaggerated startle, and hyperarousal.

Russell et al. (2017) also observed interconnectedness between symptoms related to recall and memory. Shared association with the underlying processes of learning and memory formation may help account for the pattern of links seen by Russell et al., specifically between: nightmares, acting or feeling as if the event was recurring (i.e., flashbacks or 'recurrence'), intrusive thoughts, psychological and physiological reactivity, and avoiding thoughts and activities related to the trauma. A third group was centered on symptoms driven by emotional constriction accompanying posttraumatic stress. In the aftermath of traumatic experiences, individuals may exhibit blunted affect, or emotional numbing – broadly, an inability to experience strong negative or positive emotions (Weems, Saltzman, Reiss, & Carrión, 2003). Relatedly, anhedonia may be responsible for a general loss of interest in previously enjoyed activities (Kashdan, Elhai, & Frueh, 2006), as well as an experience of detachment or interpersonal distance, both symptoms of PTSD. Empirical research suggests that the content and emotional salience of trauma memories may be jointly consolidated (Weems et al., 2014). It may be that a limited ability to experience certain types of emotions

inhibits the ability to recall experiences with similar affective valence. Such an effect may be an important area for future research, and is suggested by the results from PTSD network studies in adults showing that amnesia and emotional numbing symptoms cluster together (Fried et al., 2017). Some key developmental differences also emerged when networks were compared across older (>13 years.) and younger participants. Numbing of negative emotions exhibited a strong link to amnesia in children, but not teens, while irritability and loss of interest were meaningfully associated in teens, but not children (Russell et al., 2017).

The network approach to symptoms is not without limitations. Researchers disagree over the reliability and replicability of network models of psychopathology (Borsboom et al., 2017; Forbes, Wright, Markon, & Krueger, 2017; Steinley, Hoffman, Brusco, & Sher, 2017). However, there appears to be agreement that network approaches to symptoms hold promise in complementing existing categorical or factor analytic models (Borsboom & Cramer, 2013; Forbes et al., 2017). Moreover, connections within memory, emotion, and executive function related symptoms are supported by conceptual links within these broad functional concepts via their theoretical origins in brain structures and functions related to memory, emotion, and executive function. Similar to the cascade of symptoms that may evolve following trauma (underscored by a network model of symptoms), there may be a cascade of neurodevelopmental changes that may occur following traumatic stress. In the next section, we discuss some of the mechanisms thought to underlie the neurobiological response to stress and present data to underscore the idea that the neurobiological effects of traumatic stress seen in pediatric PTSD need to be understood in the context of typical brain development.

Mechanisms: damage, altered development, or both

Much of the research on stress-affected brain regions is driven by the idea that traumatic stress may damage regions of the brain. For example, in the hippocampus, glucocorticoids secreted during stress may cause atrophy or apoptosis in pyramidal cells, or suppress neurogenesis of granule cells (Sapolsky, 1993; Sapolsky, Uno, Rebert, & Finch, 1990). Such a view can appear to assume that severe stress is pathological to an unchanging brain – initiating processes that accumulate to produce structural effects. However, for many regions of the brain, the direction of this effect (larger or smaller volumes) remains unclear. Stress is known to activate both inflammatory *and* anti-inflammatory mechanisms in brain tissue, which may alternately contribute to larger or smaller volumes (García-Bueno, Caso, & Leza, 2008). Activation of these mechanisms in response to stress may be region specific or, more importantly, may depend on the developmental timing of stress exposure. Empirical data suggest both cell growth and regional atrophy in areas of the brain such as the hippocampus (Gould & Tanapat, 1999). Large-scale investigations of the normative trends in brain development suggest both normative increases (e.g., amygdala, hippocampus) and decreases (e.g., nucleus accumbens) in regional brain structures (Albaugh et al., 2017; Goddings et al., 2014). Despite the increasing knowledge of normative trends in regional brain development, a truly developmental approach to the neurobiological effects of traumatic stress has not been the norm (Weems, 2017).

Weems (2017) presented a model of traumatic stress effects on the brain, in particular the amygdala, which posits age/maturation as the critical driver of variation in amygdala volumes with traumatic stress acting as a moderator of normal developmental trends. The model is consistent with an evolutionary account wherein severe stress may serve to delay, accelerate, or prolong normal developmental processes, depending on the adaptive value of such changes (see e.g., Del Giudice, Ellis, & Shirtcliff, 2011). Research into stress-related effects on normal brain development suggests that differences in regional volumes, functional connectivity, or structural connective pathways may be predicted by an interaction between age or maturation (e.g., pubertal development) and indices of stress (such as continuous or dichotomous assessment of exposure to severe stress or presence of PTSD symptoms). Specifically, the potential for maturational differences in regions of the brain (such as the amygdala) among different patient populations with high or traumatic stress exposure (Mehta et al., 2009; Tottenham, 2012; Tottenham & Sheridan, 2009) suggests that exposure to traumatic stress may moderate the association between age and amygdala volumes.

Weems (2017) summarized fourteen studies that have examined normal developmental variation in amygdala volumes or otherwise correlated age with amygdala volumes in various patient and control samples. The review notes that while findings about the direction of the effect of trauma on amygdala volumes (larger, smaller, no difference) is inconclusive, 13 of the 14 studies reported a statistically significant association with chronological age (or longitudinal growth) in a community or control sample. Moreover, a curvilinear association appears to best define the relationship between age and amygdala volumes across broad age ranges such as from infancy to early adulthood (e.g., Østby et al., 2009; Uematsu et al., 2012). Evidence from at least two samples specifically support the notion that this normal maturational variation in the amygdala may be altered by exposure to traumatic stress (Weems, Klabunde, Russell, Reiss, & Carrión, 2015; Weems, Scott, Russell, Reiss, & Carrión, 2013) and is

consistent with other age-related structural findings in trauma and severe stress exposed pediatric samples (Weems, 2017; see also Teicher & Samson, 2016, who emphasize the developmental timing of traumatic stress).

While traumatic stress has been linked to particular areas (e.g., the amygdala, hippocampus), the brain is a complex network of regions with essential structural and functional connections. Researchers have identified several key functional networks that may play a role in psychopathology, such as traumatic stress. For example, the salience network is a collection of regions (with nodes anchored in the dorsal anterior cingulate cortex and frontoinsular cortex, see Menon, 2011 for fuller anatomical descriptions), thought to be involved in detecting behaviorally relevant stimuli and coordinating neural resources in response. The default mode network (anchored in the posterior cingulate cortex and medial prefrontal cortex) is active when an individual is at wakeful rest (i.e., active 'by default' when not involved in a task). The central executive network (anchored in the dorsolateral prefrontal cortex and lateral posterior parietal cortex) is responsible for 'executive' cognitive functions such as emotion regulation, decision making, and the control of attention (Menon, 2011). As Menon (2011) noted, linking 'dysfunctional cognitive and psychological processes associated with psychiatric disorders onto individual brain areas is now widely considered implausible. This is not surprising given that most psychiatric conditions are syndromes or 'disorders' encompassing multiple, heterogeneous, behavioral phenotypic features' (p. 484).

In a review of the adult PTSD literature, Akiki, Averill, and Abdallah (2017) argued that PTSD can be characterized by a weak and hypoactive default mode network and an executive network that is overwhelmed by a hyperactive and strongly connected salience network. Theoretically, this leads to a low threshold for perceived saliency and inefficient executive and default network control. In the case of pediatric PTSD, the prefrontal (executive function), hippocampus (memory) and amygdala (emotion) have particular salience as their functions appear to underlie certain PTSD symptoms and their connectivity may be particularly important. An emerging area of research seeks to investigate the interwoven patterns of structural and functional connections in pediatric samples exposed to severe and traumatic stress (Herringa, 2017).

Traumatic and severe stress links to structural and functional brain networks

Table 1 summarizes seven studies found in a literature search (conducted to 11-10-17 using Medline, PsycINFO, Google Scholar, and a review of references in previous publications) that have used diffusion tensor imaging (DTI) to examine structural connectivity differences in samples of youth (we focused on samples under age 18) exposed to severe or traumatic stress. Overall, a picture of reduced structural connectivity between limbic system structures (e.g., hippocampus, amygdala) and regions of the frontal cortex emerges – areas linked by a white matter tract known as the uncinate fasciculus. For example, Eluvathingal et al. (2006) found weaker structural integrity (i.e., decreased fractional anisotropy values – a measure of connectivity strength) along this tract among orphanage-reared youth with histories of early deprivation, compared with typically developing controls. In a follow-up study using a larger sample of adoptees, Kumar et al. (2014) reported that compared to normative controls, the early deprivation group presented with reduced microstructural integrity of multiple limbic and paralimbic pathways including the uncinate fasciculus, cingulum, and arcuate fasciculus (see also Govindan, Behen, Helder, Makki, & Chugani, 2009).

Behen et al. (2009) found that a group of 15 youth with histories of early life deprivation had reduced probability of striatal connection to the right frontal pole compared to normative controls. The striatum is a principal part of the basal ganglia and receives direct input from multiple regions in the cerebral cortex as well as limbic structures including the amygdala and hippocampus. The DTI literature has also begun to examine differences in structural connections among components of the aforementioned functional networks. Lei et al. (2015) reported microstructural abnormalities in components of the default-mode network (including the precuneus and angular gyrus), and the salience network (including the insula, putamen, and thalamus) in 24 youth exposed to a natural disaster when compared to a control sample. To date, the structural connectivity literature is limited in number but the extant data suggest a picture of traumatic stress effects on structural connections in and across regions important to emotion processing, memory, and executive function.

Table 2 summarizes 15 studies found as a part of the same literature search that used functional MRI (fMRI) to examine the functional connectivity in pediatric samples exposed to severe or traumatic stress. As in the structural studies, a picture of differential connectivity between limbic structures and frontal cortex regions emerges, with both increased and decreased connectivity found for traumatized youth. For example, Aghajani et al. (2016) investigated resting-state fronto-amygdalar functional connectivity across 19 PTSD-diagnosed adolescents, and a control sample. Anatomical comparison revealed smaller amygdala volumes among the PTSD group relative to controls. Moreover, the PTSD group showed relative diminished right amygdala connectivity with dorsal and ventral portions of the anterior cingulate and medial prefrontal cortex, but *increased* connectivity between the left amygdala

Table 1 Summary of structural connectivity studies using diffusion tensor imaging

Study	Mean age (T/C)	Age effect	*N* (T/C)	Trauma type	Compared to controls, trauma exposed group presented with
Behen et al. (2009)	10.2/12.1	NT[a]	15/12	ED	• Increased probability of connections for striatal projections terminating in the cortex and reduced probability of connection to the frontal pole in the right hemisphere
Eluvathingal et al. (2006)	9.7/10.7	NT/CON	7/7	ED	• Decreased fractional anisotropy values in the left uncinate fasciculus
Govindan et al. (2009)	10.9/11.7	NT/CON	17/15	ED	• Decreased fractional anisotropy in bilateral uncinate fasciculus and bilateral superior longitudinal fasciculus
Kumar et al. (2014)	10.5/10.6	NT/CON	36/16	ED	• Increased mean diffusivity and decreased fractional anisotropy in the left and right uncinate fasciculus and cingulum
Lei et al. (2015)	13.0/13.2	NT/CON	24/27	ND/WD/WSI	• Various microstructural abnormalities in regions of the default mode network (precuneus, angular gyrus) and salience network (insula, putamen, thalamus)
Puetz et al. (2017)	10.6/10.4	NT/CON	25/24	DV/PA/N/ABND	• Decreased connectivity strength across entire connectome • Lower connectivity strength in regions within the ventromedial prefrontal cortex
Suo et al. (2015)	13.0/13.2	NT/CON	24/23	ND/WD/WSI	• Decreased nodal centralities in the salience network (ventrolateral prefrontal cortex, insula, putamen, and thalamus), central executive network (dorsolateral prefrontal cortex and superiorparietal gyrus)

T, Trauma/Maltreated; C, Controls; NT, Differential age effect not tested; CON, Age controlled as covariate; ED, Early Deprivation; ND, Natural Disaster; WD, Witnessed Death; WSI, Witnessed Serious Injury; PA, Physical Abuse; DV, Domestic Violence; N, Neglect; ABND, Abandonment.
[a]Discussion section indicated no association/no results presented.

and orbitofrontal and subcallosal cortices. Additional results suggested that connectivity may vary across amygdala sub-regions (e.g., centro-medial, basolateral).

There seems to be a general trend toward *reduced* connectivity in PTSD youth (Table 2); however, the findings presented by Aghajani et al. (2016) suggest that this effect may not be global in nature, in that some areas of the brain may exhibit increased connectivity as well. Thomason et al. (2015) reported decreased connectivity between the corticomedial amygdala and subgenual anterior cingulate cortex but increased connectivity between the centromedial/ basolateral amygdala and components of the default mode network (precuneus, posterior cingulate cortex) compared to controls. Similarly, Keding and Herringa (2016) report decreased connectivity between the dorsal anterior cingulate cortex and dorsomedial prefrontal cortex, amygdala and dorsomedial prefrontal cortex, and the amygdala and ventrolateral prefrontal cortex, in response to angry faces, but increased connectivity in response to happy faces compared to the control sample.

While the extant pediatric PTSD imaging research has identified connectivity differences amongst specific limbic and frontal regions, studies have also investigated the effects of traumatic stress on the broader functional networks described by Menon (2011). Cisler, Scott Steele, Smitherman, Lenow, and Kilts (2013) used independent component analysis to distinguish a fronto-cingulate (salience) network, frontoparietal (central executive) network, and default mode network. Cisler et al. (2013) reported greater activation of the fronto-cingulate network for fearful (vs. neutral) faces among adolescent girls ages 12–16 (n = 15) with a history of experiencing physical and/or sexual assault. Within the fronto-cingulate network, there was weakened functional connectivity between the left amygdala and the perigenual anterior cingulate cortex for fearful (vs. neutral) faces, the latter being associated with affective experiences and directly engaged in autonomic regulation each of these findings in comparison to a control sample (Cisler et al., 2013). The cingulate cortex is considered as a part of the limbic system and is involved with emotion formation and processing.

Table 2 Summary of functional connectivity studies using fMRI

Study	Mean age (T/C)	Age effect	*N* (T/C)	Task	Trauma type(s)	Compared to controls, trauma exposed group presented with
Aghajani et al. (2016)	16.2/15.5	NT/COV	19/23	RS	SA	• Decreased connectivity between right basolateral amygdala and dorsal, ventral anterior cingulate, as well as medial prefrontal cortex • Increased connectivity between left centromedial amygdala and orbitofrontal and subcallosal cortices
Cisler et al. (2013)	15.1/14.3	NT	15/15	FEP	PA/SA	Salience Network (fronto-cingulate): • Greater activation overall in response to fearful faces (vs. neutral). Increased connectivity between right amygdala and left middle frontal gyrus • PTSD severity linked to decreased connectivity between left amygdala and perigenual anterior cingulate cortex, pre-supplementary motor area Central Executive Network (fronto-parietal): • Decreased connectivity between right premotor region and right posterior middle frontal gyrus • PTSD severity linked to decreased connectivity between left parietal and right premotor region; left anterior middle frontal gyrus and left premotor region Default Mode Network: • Increased connectivity between left parahippocampal gyrus and ventromedial prefrontal cortex; left motor cortex and precuneus, right parietal cortex • PTSD severity linked to decreased connectivity between right parahippocampal gyrus and left middle frontal gyrus
Cisler, Sigel, Steele, et al. (2016)	13.9/—	NT	20/—	CR	PA/SA/WV	• Increased connectivity between right amygdala and bilateral insula when viewing negative images linked to symptom reduction following treatment for PTSD • Increased connectivity between right amygdala and bilateral insula when reappraising negative images linked to worse outcomes following treatment
Cisler, Sigel, Kramer, et al. (2016)	13.8/14.3	NT/COV	20/15	FEP	PA/SA/WV	• Whole-brain functional connectivity network during FEP task is comprised of six modular networks • Greater within versus between module connectivity (modularity) when viewing neutral faces (vs. fearful) at pre-treatment predicted poorer posttreatment outcomes
Cisler (2017)	15.2/14.7	NT/COV	26/30	RS	PA/SA/WV	• Weaker connectivity between amygdala and prefrontal cortex • Connectivity between amygdala and prefrontal cortex less predictive of connectivity between encompassing limbic and default mode networks, respectively

(continued)

Table 2 (continued)

Study	Mean age (T/C)	Age effect	*N* (T/C)	Task	Trauma type(s)	Compared to controls, trauma exposed group presented with
Cisler et al. (2018)	14.6/15.0	NT/COV	59/29	FEP	PA/SA	• Increased network modularity, assortativity, but decreased efficiency • For all, network modularity predicted greater amygdala activation during FEP task • For all, network modularity inversely related to functional connectivity between amygdala and medial prefrontal cortex
Gee et al. (2013)	12.1/10.8	Yes	41/48	FEP	ED	• Decreased amygdala and medial prefrontal cortex connectivity in younger, but not older, children during fearful affect processing
Keding and Herringa (2016)	14.3/14.2	NT/COV	25/28	FEP	ACC/PA/SA/TG/WV	• Decreased connectivity between dorsal anterior cingulate cortex and dorsomedial prefrontal cortex, amygdala and dorsomedial prefrontal cortex, amygdala, and ventrolateral prefrontal cortex, in response to angry faces, but increased connectivity in response to happy faces
Lee et al. (2015)	16.1/—	NT/COV	31/—	FEP	VA	• Decreased connectivity between amygdala and anterior cingulate cortex in response to sad faces
Marusak, Martin, Etkin, and Thomason (2015)	12.7/12.8	NT/COV	14/16	FEC	DV/N/PA	• Reduced negative connectivity (i.e., down-regulation) between perigenual anterior cingulate cortex and amygdala in response to 'emotional conflict' trials where face emotion did not match overlaid emotion text
Marusak, Etkin, and Thomason (2015)	12.6/12.1	NT/COV	14/19	FEC/RS	DV/N/PA/SA/WV	• Altered intrinsic connectivity in components of the salience network Increased in left amygdala, left middle insula Decreased in right dorsal anterior cingulate cortex • Connectivity between salience network components and left insula mediated link between exposure severity and reward sensitivity • Altered connectivity between salience network and default-model network Decreased connectivity between right dorsal anterior cingulate cortex and components of salience network
Patriat, Birn, Keding and Herringa (2016)	14.6/14.0	Yes	29/30	RS	ACC/PA/SA/TG/WV	• Increased connectivity between default mode network regions: posterior cingulate cortex and left inferior parietal gyrus • Decreased connectivity between parietal-cingulate cortex and several regions involved in attentional control • Increased connectivity between posterior cingulate cortex and ventromedial prefrontal cortex with age (decreased in controls)

(continued)

Table 2 (continued)

Study	Mean age (T/C)	Age effect	*N* (T/C)	Task	Trauma type(s)	Compared to controls, trauma exposed group presented with
Puetz et al. (2014)	10.6/10.3	NT/COV	25/26	SE	DV/N/PA	• Decreased connectivity between dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, and left temporoparietal junction during social exclusion • Increased connectivity between dorsal anterior cingulate cortex, right retrosplenial cortex, and subcortical ventral tegmental area during social exclusion
Suo et al. (2017)	13.0/13.0	NT/COV	24/24	RS	ND/WD/WSI	• Increased nodal clustering, local normalized characteristic path length and local (though not global) efficiency • Decreased connectivity in a network consisting of dorsolateral prefrontal cortex, thalamus, and regions of the parietal and occipital lobes
Thomason et al. (2016)	12.8/12.3	NT/COV	21/21	RS	DV/EA/N/PA/SA/WV	• Decreased connectivity between corticomedial amygdala and subgenual anterior cingulate cortex • Increased connectivity between centromedial and basolateral amygdala and components of the default mode network (precuneus, posterior cingulate cortex)
Wolf and Herringa (2013)	14.5/13.8	Yes	24/24	TIP	ACC/TG/SA/WV	• Decreased connectivity between left amygdala and rostral anterior cingulate cortex, dorsomedial prefrontal cortex (bilateral). Connectivity negatively related to avoidance symptoms • Increased connectivity between left amygdala and ventromedial prefrontal cortex with age (decrease in controls)

T, trauma exposed; C, controls; NT, no test of differential age effects; COV, age controlled as covariate; CR, Cognitive reappraisal; FEP, facial emotions processing task; FEC, faces-emotions conflict task; RS, resting state; SE, social exclusion; TIP, threatening image processing; ACC, accident; DV, domestic violence; EA, emotional abuse; ED, early deprivation; N, neglect; ND, natural disaster; PA, physical abuse; SA, sexual abuse; TG, traumatic grief; VA, verbal abuse; WD, witnessed death; WSI, witnessed serious injury; WV, witnessed violence.

In both the structural and functional connectivity studies (Tables 1 and 2), it is common for researchers to control for age by matching traumatized groups and/or controlling for age in the analyses as a covariate. To date, research examining the effects of development (age or index of development, such as Tanner stage) and neural connectivity is quite uncommon. In our review (i.e., papers in Tables 1 and 2), we found that no structural studies and only three functional studies reported testing for such effects. Of the three functional studies that did analyze and report developmental effects, differential patterns emerged in all three (others may have tested this effect and not reported non-significant results). Wolf and Herringa (2016) examined youth engaged in a threat processing task, and found that left amygdala to bilateral ventromedial prefrontal cortex connectivity increased with age in controls, but decreased with age in the trauma-exposed group. Patriat, Birn, Keding, and Herringa (2016) reported that resting state posterior cingulate cortex to ventromedial prefrontal cortex connectivity decreased with age in controls, but increased with age in traumatized youth. Finally, Gee et al. (2013) reported reduced amygdala-medial prefrontal cortex connectivity during an affective processing task among younger, but not older youth with histories of early deprivation relative to controls.

Drawing from the idea that stress and traumatic stress may influence normal developmental trajectories of particular regions (Weems, 2017), the extant data suggest a similar effect may exist on functional connections. Theoretically, age/maturation is likely also a critical driver of variation in structural and functional connections with stress altering normal developmental trends, particularly in emotion

processing regions. Di Martino et al. (2014) has theorized that emotional disorders can be conceptualized as developmental mis-wiring, in that the maturational changes in the connectome (a theoretical map of neural connections) may be accelerated, 'precocious', or delayed. There is evidence that the connections between the amygdala and prefrontal cortex continue developing through adolescence and early adulthood, and that the connectivity of the amygdala becomes stronger and more differentiated from late childhood to early adulthood (see Tottenham & Galván, 2016). For example, Kumar et al. (2014) found that age was negatively correlated with mean diffusivity values in the left and right uncinate fasiculi, cingulum, and left arcuate fasciculus. Similarly, Gabard-Durnam et al. (2014) found that while resting state functional connectivity of the amygdala with other subcortical and limbic regions was largely stable across development (ages 4–23 years), the amygdala's connectivity with the medial prefrontal cortex increased, while the strength of connectivity to the insula, superior temporal region, parahippocampal gyrus, and posterior cingulate decreased. Such evidence further demonstrates the importance of testing the interactive effects of age and trauma on connectivity strength.

Age, puberty, and time

The extant research using chronological age begs the question, 'what are the biological factors associated with amygdala growth (and/or the end of growth/pruning) and true developmental change in volumes?' Chronological age (or time in study, in longitudinal designs) is, however, an imprecise proxy for indexing actual biological change. While these changes do unfold across time, they are not necessarily *driven* by time's passage. Blakemore, Burnett, and Dahl (2010) have argued for the need to examine neural maturation in the context of pubertal development, which may more closely reflect the activity of underlying biological processes. Goddings et al. (2014) conducted a longitudinal investigation of neurodevelopmental change across puberty, using data from the NIMH longitudinal brain imaging project. The sample was derived from the larger project data bank and included 275 typically developing youth (42% female), who, (a) were scanned two or more times between the ages of 7–20, (b) provided age and pubertal status (Tanner stage) at each scan. Mixed effects modeling to examine the growth process of several subcortical structures across pubertal development suggested that the amygdala and hippocampus were generally larger at later Tanner stages (with some evidence of a tapering off in stages 4 and 5), whereas the caudate, globus pallidus, nucleus, accumbens, and putamen were smaller.

We are aware of no longitudinal studies that examined the differential effect of traumatic stress on diverse brain region development among youth at different stages of puberty. However, Weems et al. (2013), using a small longitudinal sample of 15 youth exposed to traumatic stress, reported a Tanner stage by time interaction predicting change in amygdala volumes. Less developed youth (earlier Tanner) showed increases in amygdala volumes across time, whereas more developed youth decreases. True explication of traumatic stress effects requires longitudinal investigation into neuroanatomical development. Cohort-sequential (accelerated longitudinal) designs may offer an ideal design by testing development using 'cohorts' of youth spread across a nearly continuous distribution of chronological age or Tanner stage at study entry (Baltes, Reese, & Nesselroade, 1977; Hoffman, 2015) with longitudinal follow-ups to examine growth over time. Our theory suggests developmental stage by time by exposure to trauma (or PTSD) interactions. Specifically, differential longitudinal volumetric growth or structural connectivity among youth in earlier age or Tanner stage cohorts than at later developmental stages. Theoretically, traumatic stress may show differential effects on growth of specific brain regions, or structural/functional networks depending on when participants are assessed, and/or when participants experienced trauma. This means that (a) age and/or tanner stage at study entry or age of the trauma (b) repeated measurement over time (i.e., the longitudinal change effect), and (c) assessment of exposure to traumatic stress/trauma type and PTSD symptoms are all important design elements.

Brain structure, function, and connectivity are all nested within normal development. Our review suggests differential structural or functional connectivity (within and between various distributed networks and between limbic system structures and prefrontal regions) among youth exposed to traumatic stress. These differences may stem from adaptive differences in the brain development which nonetheless may foster a cascade of PTSD symptoms leading to clinically significant impairment in functioning. A truly developmental approach is needed in future research which tests age and/or indices of maturation as moderators of traumatic stress' effect on brain growth, connectivity, and broader links to symptomatology. Traumatic stress moderating the effect of age and time implies their use as interactions rather than covariates (or a control variable). In fact if a variable such as age interacts with another variable (such as PTSD group vs. controls), it violates of the homogeneity of regression assumption of a covariate in ANCOVA models (Tabachnick & Fidell, 2013). While cross-sectional designs can be improved by including age as an interactive effect, elucidating the true nature of these effects will require rigorous longitudinal and experimental designs involving youth at diverse stages of development, but also reporting diverse timings of trauma experiences.

Timing of the trauma refers to when the trauma occurs relative to development (i.e., what age, or pubertal status) and/or the time elapsed between trauma and assessment. A related concept, dosage, refers to the duration and intensity of the traumatic experience. These two variables – timing and dosage – are also critical to clarifying linkages between trauma, pre-existing risk, and outcomes of traumatic stress. Interpretation of effects in studies examining these constructs is often limited by the use of nonexperimental and cross-sectional study designs, as well as low statistical power resulting from small sample sizes. Developmental cognitive neuroscientists could address these challenges by harmonizing data sets (increasing sample size by using similar collection protocols in studies focusing on normative and clinical samples) or designing studies from the outset with sufficient power to detect hypothesized moderator effects. In addition, inclusion of imaging data in intervention studies may further elucidate the effects of stress on the brain in that intervention designs allow experimental manipulation of factors (e.g., social support, emotion regulation skills) that theoretically may alleviate the effects of stress on brain development.

Directions for future research

A network approach to symptoms may foster understanding the links among traumatic experiences, structures and networks of the brain, and the expression of PTSD symptoms (Sun, Haswell, Morey, & De Bellis, 2018). PTSD is a complex disorder, with over 600,000 different ways to meet the diagnostic criteria (Galatzer-Levy & Bryant, 2013). Attempting to identify the neurological basis of a disorder with such a diverse presentation may be an impossible task. However, identifying the neurological basis for differential associations amongst symptoms, or why certain symptoms are more central to a network, may be more readily attainable. That is, brain network functions are theoretically more specifically connected to specific symptoms (or symptom sets) than the amazingly heterogeneous 'PTSD' diagnosis. To date, studies have reported links between functional connectivity patterns and general PTSD severity (Cisler, 2017) and symptom-specific connections have also been reported (e.g., hyperarousal symptoms to prefrontal cortex-hippocampus connectivity see Keding & Herringa, 2016). Employing a network symptom approach, while speculative at this point, may enhance our understanding of the differential associations amongst symptoms and the centrality of certain symptoms in pediatric PTSD. To the extent that traumatic stress alters more or less of the functional connections/networks, one may expect to see differential symptom centrality or symptom connections across time and across samples differing in dosage or time since the trauma. Moreover, recent evidence suggests that exposure severity is predictive of global changes across large-scale brain networks (e.g., modularity, assortativity; Cisler, Privratsky, Smitherman, Herringa, & Kilts, 2018).

Promising next steps in research involve testing the impact of stress exposure on age-related changes in structural or functional connectivity, linking these connectivity effects to the network of symptom expression, and clarifying the role of cumulative stress (dose) and the timing of the trauma on connectivity. While research that links functional networks of the brain to symptom networks of pathology is an alluring next step, it will be a challenge for research to resolve the difficulty in linking subject-level networks of regional activation with sample-level networks of symptoms. Seed-based correlation analysis (SBA) and independent components analysis (ICA) constitute two common approaches to identifying functional connectivity networks between brain regions. Briefly described, SBA involves computation of the correlation between the time series blood oxygen level dependent (BOLD) signal in a pre-selected reference area of the brain or 'seed' (i.e., a voxel), and respective signal series in regions across the brain. ICA is a data-driven approach that decomposes the BOLD time-series of many voxels into orthogonal spatial and temporal components (Van den Heuvel & Hulshoff Pol, 2010). Each of these popular approaches ultimately output covariance matrices at the participant level, as functional links between regions in the individual brain. In contrast, network analyses of symptom expression produce covariance matrices that define the dynamic interplay between symptoms at the sample level. Unifying these approaches into a mutually informative model may require novel methodology that can link results across different levels of analysis.

One possibility for structural analysis is suggested by Sun et al. (2018) who examined brain structural covariance network (using analyses similar to the symptom network analysis in Russell et al., 2017) centrality in maltreated youth with PTSD and in maltreated youth resilient to PTSD. Intraregional correlations in measures of cortical thickness in 148 cortical regions (nodes) and network centrality of the cortical regions within the network architecture were calculated for each group (maltreated youth with PTSD (n = 31), without PTSD (n = 32), and nonmaltreated controls (n = 57). Greater centrality was reported in the right frontal pole in maltreated youth resilient to PTSD compared to both youth with PTSD and controls. Conversely, reduced centrality was found in the left posterior cingulate cortex and right inferior frontal cortex in both groups of maltreated youth compared to controls. Sun et al. conclude with a suggestion to link the brain and symptom network literature in large multisite longitudinal studies investigating age and PTSD symptoms along with brain networks. The idea here would be to include symptoms in the same network analysis of regional

brain volume (e.g., conduct the analyses in Russell et al., 2017, and include regional brain volumes in the network). This analysis would be most meaningful for a trauma-exposed group, where it might reveal the networked associations between symptoms and certain regions of the brain.

Teicher and Samson (2016) suggests that different types of trauma may have different effects on different brain structures. A network approach to symptom expression that includes an understanding of the structural and functional brain networks affected by traumatic stress may help elucidate specific 'trauma type' effects, while also helping to clarify apparent inconsistencies in the PTSD symptom network modeling literature. For example, Forbes et al. (2017) reviewed eight network analysis studies of adult PTSD symptoms and highlighted salient differences in the symptoms that were deemed 'central' to the diagnosis (see their tables 2 and 3). However, samples in each of these studies reviewed varied widely in terms of the type of traumas experienced. Potentially, a differential effect of trauma type on brain networks could provide a functional neurological basis for inconsistency in the symptom networks across samples of varying trauma types. For example, a hyper-active salience network may be a more common result of stress associated with chronic sexual or physical abuse.

Our understanding of the traumatic stress response and PTSD may be expanded by investigation of broader response networks that incorporate other cognitive, emotional, and memory-domain 'symptoms' (e.g., focusing only on PTSD symptoms in a network analysis limits understanding to the existing definition of PTSD). Future studies, could consider including other factors besides traditional PTSD symptoms in the network theoretical approach. Indeed, research has already begun exploring neural connectivity as a predictor of positive adaptation to childhood adversity, such as exposure to traumatic stress (e.g., Herringa et al., 2016). An individual's susceptibility or resilience to the impact of traumatic stress depends on temporal factors, such as the developmental timing of the event (Teicher & Samson, 2016), pre-exposure functioning (Weems & Graham, 2014), socioeconomic context and social support (Jaffee, 2017), and genetic susceptibility to environmental influences (Belsky, 2005). From this, Weems (2015) developed a model of risk and resilience to traumatic stress, describing three critical components predicting an individual's response. The first represents qualities of exposure, such as subjective judgments of the intensity and/or negativity of the experience(s), as well as mitigating or positive components of the event (e.g., individuals were evacuated successfully from a disaster, community worked together for common good). The second represents the genetic susceptibility to environmental influences, which may involve age-related critical periods (i.e., developmental timing of the trauma). The third is the degree to which the trauma is enduring/chronic, coupled with how positive versus negative the posttrauma environment was for the individual, family, community, or broader society. Each of the three components may differentially relate to the neurological response in terms of connectivity structural development and function. For example, a child with high negative exposure, but low genetic susceptibility may experience little change in network connections linking the frontal (executive) to limbic/salience (emotion) regions (i.e., show resilience to trauma), whereas another with high susceptibility may experience large changes in structural or functional connectivity of salience or executive networks. These two individuals' posttrauma experience will further influence the strength and nature of those changes, as will the degree to which earlier life experiences have primed the stress related networks toward risk or resilience.

Assessing the large samples of trauma exposed youth needed for such studies while simultaneously addressing the timing of the traumatic event might be facilitated by deploying research teams to assess youth in the immediate aftermath of large scale traumatic events such as disasters (Weems, 2015). Studying the neurodevelopmental response to trauma using a natural disaster event offers a methodological advantage with regard to the accurate timing of the initial trauma (e.g., date for a disaster and the age at that time can be objectively known). Both timing and dose of trauma (measures that assess level and extent of exposure) are both important characteristics of natural disasters. Finally, while this review has emphasized age/development, recent work suggests there may be gender-based differences in the effect of stress on neurological structures such as the insula (Klabunde, Weems, Raman, & Carrion, 2017). Future research would benefit from testing both gender and age/maturation interactions with traumatic stress exposure on the brain and its structural and functional connections.

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Key points

- Traumatic stress is an important influence on normal brain development.
- Network models of PTSD symptoms may complement the neurodevelopmental understanding the effects of traumatic stress.
- Changes in the structural and functional connections among brain networks have been implicated particularly from the prefrontal (executive function), to limbic regions such as the hippocampus (memory) and amygdala (emotion).
- Differences in structural connections and distributed functional networks such as the salience, default mode, and central executive networks are associated with traumatic and severe early life stress.
- A truly developmental approach is needed in future research which tests age and indices of maturation as interacting with exposure to traumatic stress (not just controlling for age) as predictors of brain connectivity.

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