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Does Development Moderate the Effect of Early Life Assaultive Violence on Resting-State Networks? An Exploratory Study

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Abstract

Current neurocircuitry models of PTSD do not account for developmental effects, despite that early life assaultive violence is a potent risk factor for PTSD. Here, we preliminarily evaluated developmental stage as a moderator of the effect of early life assaultive violence on resting-state connectivity amongst regions associated with emotion generation and regulation using fMRI. Participants were adult women ($n = 25$) and adolescent girls ($n = 36$) who had or had not experienced early life assaultive violence. We found significant interactions between developmental stage and trauma exposure on resting-state functional connectivity (FC). Left amygdala connectivity with the left ventral anterior cingulate gyrus (BA 32) was reduced among trauma-exposed compared to control adolescents, but increased among trauma-exposed compared to control adults. A corresponding pattern of results was identified for FC between rostral anterior cingulate gyrus seed region and a similar right ventral anterior superior frontal gyrus cluster. Increased FC in both regions for assaulted adult women scaled positively with self-reported emotion regulation difficulties. Our results should be viewed tentatively due to sample limitations, but provide impetus to examine whether neurocircuitry models of PTSD may be strengthened by accounting for developmental stage.

Keywords

Assaultive violence; Trauma; Resting State Networks; Emotion Regulation; Development; PTSD

1. Introduction

Exposure to assaultive violence confers significant risk for the development of posttraumatic stress disorder (PTSD) (Betts et al., 2013; Breslau et al., 1998), which is characterized by re-

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experiencing, avoidance, hyperarousal, and negative alterations in cognition and mood (American Psychiatric Association, 2013). Importantly, trauma exposure can have both proximal and distal effects. Individuals who experience early life trauma are more likely to experience additional trauma in adulthood (Werner et al., 2015), and are at an increased risk for developing PTSD both during childhood and in response to adulthood trauma (Breslau et al., 2008; Breslau and Peterson, 2010; Cogle et al., 2009). Early life trauma and/or the experience of PTSD might therefore alter normative development in ways that increase risk of additional violence exposure and/or PTSD.

Fear conditioning models of PTSD, which conceptualize PTSD as a disorder of fear regulation (i.e., one characterized by persistently elevated fear responses and deficits in fear extinction to trauma cues), have dominated existing research (Etkin and Wager, 2007; Garfinkel et al., 2014; Milad et al., 2009; Rauch et al., 2006). However, recent work has begun to also emphasize broader changes in individuals' abilities to regulate emotions following trauma given that emotion deficits are not limited to fear (Chang et al., 2017; Fitzgerald et al., 2018a, 2018b; McLean and Foa, 2017). Therefore, one possibility, supported by preliminary evidence, is that development might moderate the core neural mechanisms implicated in PTSD – particularly, those associated with implicit emotion regulation. The ability to upregulate, downregulate, and maintain emotions in response to contextual demands (Campos et al., 2004; Gross, 2015), referred to as emotion regulation, is strongly linked to PTSD (Badour and Feldner, 2013; Lilly et al., 2014; Tull et al., 2007) and overlaps with fear extinction models (Schiller and Delgado, 2010). In healthy samples, the neurocircuitry of emotion regulation also partially overlaps with the neurocircuitry of PTSD, and generally involves the coordinated activity between sub-circuits related to processing salient/emotional stimuli, executive control/task switching, and emotion inhibition/down-regulation. Recent neurocircuitry models that attempt to explain risk for PTSD following trauma exposure (Admon et al., 2013; Patel et al., 2012; Pitman et al., 2012; Rauch et al., 2006) generally posit dysfunction within neural circuits related to emotion processing and regulation. Consistent with these models, decades of research have demonstrated that trauma exposure and PTSD are associated with increased activation of the amygdala, dorsal anterior cingulate cortex (dACC), and insular cortices in response to salient stimuli, as well as decreased activation of the hippocampus and medial prefrontal cortex during emotion processing and regulatory tasks (Patel et al., 2012; Rauch et al., 2000; Shin et al., 2005, 2001; Stark et al., 2015).

Although most studies have examined neural activation subsequent to external stimuli/task demands, resting-state network analyses are necessary to increase understanding of the intrinsic organization of functional networks and of stimulus-independent functional connectivity (FC; Deco et al., 2011). These methods are also in line with examining implicit emotion regulation. Examinations of FC in adult PTSD patients have evidenced some consistencies, such as hyperconnectivity between the amygdala and insula (Rabinak et al., 2011; Sripada et al., 2012a), but also inconsistencies, such as hyperconnectivity between the dACC and left basolateral amygdala among combat veterans with PTSD in one study (Gallagher et al., 2014), but attenuated anti-correlation between the left amygdala and dACC among combat veterans with PTSD in another study (Sripada et al., 2012a). Though prior research has compared resting-state FC correlates of early life trauma to adult trauma among

adults (Birn et al., 2014), direct comparisons between adult and adolescent samples are lacking despite empirical reasons to expect differences in targeted neurocircuitry. For example, normative neurodevelopment involves significant shifts in local versus distal and intra- versus internetwork FC from childhood to adulthood, with adolescence characterized by the steepest shifts in neurodevelopment (Dosenbach et al., 2011; Gabard-Durnam et al., 2014). Prior studies among traumatized adolescents have demonstrated weakened amygdala-vmPFC FC (Burghy et al., 2012; Herringa et al., 2013), while one study found a trend for increased amygdala-vmPFC connectivity among adults with early life trauma who are psychiatrically healthy (Philip et al., 2013). Amygdala-vmPFC FC during threat processing also decreased with age among a pediatric PTSD sample but increased with age among a healthy control pediatric sample (Wolf and Herringa, 2016). Finally, a recent study found increased FC within a default mode network among a pediatric PTSD sample (Patriat et al., 2016), whereas prior studies among adult PTSD samples demonstrate decreased connectivity in a default mode network (Sripada et al., 2012b). Accordingly, a direct test of potential development differences in neurocircuitry related to trauma exposure and PTSD is warranted.

1.1 The current study

We conducted a preliminary examination of the effect of developmental stage on the intrinsic emotion regulation-related neurocircuitry correlates of early life assault and PTSD via secondary data analysis of fMRI scans from adolescent girls and adult women who either had or did not have histories of assaultive violence exposure. All participants selected for inclusion in one of the assaultive violence groups, regardless of age category, had experienced childhood assaultive violence. Contrastingly, the assaulted adolescent girls had a range of PTSD symptoms while the adult women all had current diagnoses of PTSD.¹ The focus on women and girls increases homogeneity of the sample, which is important in light of known sex-differences in childhood trauma and PTSD-related neurocircuitry (Burghy et al., 2012; Felmingham et al., 2010; Herringa et al., 2013). The focus on early life assaultive violence was motivated by the increased risk for psychopathology conferred through early life assault relative to other types of trauma (e.g., car accidents, natural disasters) (Cisler et al., 2012). As the samples analyzed here were recruited for separate and unrelated studies, the current study should be deemed an initial and exploratory investigation. However, consistent with a prior report (Patriat et al. 2016), we hypothesized that developmental stage would moderate the effects of early life trauma. We refrained from making more specific hypotheses given the exploratory nature of the investigation.

¹On one hand, this design was well-suited to a preliminary analysis of the trajectory of neurodevelopmental differences following early life trauma and associated with risk for PTSD; more specifically, given that early life trauma increases risk for adult PTSD following new traumas, women with PTSD represent the risk outcome for the adolescent girls with assault exposure. However, on the other hand our design was one in which age and PTSD status were confounded. This limitation is a significant one; however, we conducted several post-hoc analyses aimed at exploring age as a potential confound and found that our results were still maintained with very conceptually related statistical controls. Together, our investigation is an incremental addition to the literature which has the potential to inform novel research examining the relation between developmental stage, trauma, and resting state network connectivity, but should be taken as highly preliminary until our hypotheses and results can be re-examined using a more rigorous study design.

2. Methods and Materials

2.1 Participants

Participants were recruited as part of two separate studies comparing neural mechanisms among 1) assaulted adolescent girls and healthy control adolescent girls, aged 12–16 (Lenow et al., 2014), and 2) adult women with PTSD related to assaultive violence and healthy control adult women, aged 20–46 (Cisler et al., 2015). The resting-state data used here have not previously been published for either study. Data for both studies were acquired at the same site using the same scanner. The adult women with PTSD related to assaultive violence were selected from the larger study only if they experienced their first assault prior to the age of 16, so as to match the adolescent sample.

Table 1 lists the demographic and clinical characteristics of our final study sample ($N = 61$) after exclusion of 6 subjects for excessive movement in the scanner. Polyvictimization was common in both trauma-exposed women and girls. All adult women had experienced the three types of assaultive violence assessed, while the trauma-exposed adolescents all endorsed experiencing physical assault in addition to most also endorsing experiencing sexual assault ($n = 11$ of 17; 64.7%) and witnessing assaultive violence ($n = 13$ of 17; 76.5%). Mean age at first trauma was not significantly different between girls ($M_{\text{age}} = 8.24$, $SD = 4.07$) and women ($M_{\text{age}} = 6.64$, $SD = 2.92$).

2.2 Assessment

Direct assaultive violence exposure was assessed via the trauma assessment sections of the National Survey of Adolescents and National Women's Survey (Cisler et al., 2012; Kilpatrick et al., 2003, 2000). These structured interviews use behaviorally-specific dichotomous questions to assess sexual assault, physical assault, severe abuse from a caregiver, and witnessed violence. When the presence of a form of assault is affirmed, more detailed follow-up questions are asked to further characterize the instance(s) of assault (e.g., frequency, perpetrator).

Participants' past and current mental health statuses were assessed by a trained master's level research coordinator using the K-SADS inventory for adolescents (Kaufman *et al.* 1997) and the SCID-I for adults (First et al., 2002). Adolescents completed the UCLA PTSD Index – Adolescent (Steinberg et al., 2004) and the Short Mood and Feelings Questionnaire (Angold et al., 1995) to assess PTSD and depression symptom severity respectively, while adults completed the PTSD Checklist (Blanchard et al., 1996) and the Beck Depression Inventory-II (Beck et al., 1996). Finally all participants completed the 36-item Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer 2004) to index emotion dysregulation. DERS items are presented on a 5-point Likert-type scale in which greater summed scores indicate more problems with emotion regulation. Consistent with prior research, we omitted the awareness subscale due to poor psychometric properties (Bardeen et al., 2012).

2.3 Image Acquisition and Preprocessing

All images were acquired on the same Philips 3T Achieva scanner and processed identically according to previously defined preprocessing steps (see Supplemental Material) (Power et

al., 2014, 2012). Although different headcoils were used to scan adolescents and adults, a test for a possible confounding effect of headcoil type on the moderating effect of age was nonsignificant as described in our supplemental material.

2.4 Selection of ROIs related to implicit emotion regulation

Previous resting-state analyses have used a number of strategies for selecting seed regions with which to examine FC, with some studies choosing canonical regions implicated in PTSD (e.g., amygdala, mPFC; Aghajani et al., 2016; Birn et al., 2014; Burghy et al., 2012; Herringa et al., 2013), others choosing nodes of alternative specific networks (e.g., posterior cingulate cortex [PCC] and ventromedial prefrontal cortex [vmPFC] as nodes of the default mode network; Sripada et al., 2012a, 2012b), and others differentiating between anatomically and functionally distinct subregions of canonical regions (e.g., basolateral vs centromedial amygdala; anterior vs posterior hippocampus; Chen and Etkin 2013; Brown et al., 2014). The diversity in seed region selection has created difficulty identifying patterns of intrinsic FC that may be characteristic of PTSD or trauma exposure.

One potentially helpful approach to more clearly delineating the core neural mechanisms in PTSD is to focus on neural mechanisms related to a particular psychological construct implicated in PTSD and trauma exposure. Here we chose to consider neural regions related to implicit emotion regulation, which has been strongly associated with PTSD (Badour and Feldner, 2013; Lilly et al., 2014; Tull et al., 2007). A recent neural model (Etkin et al., 2015, 2011) posited that the amygdala, insula, and dACC are the key neural structures involved in processing salient/emotional stimuli, and highlighted specific structures that are differentially associated with implicit versus explicit emotion regulation strategies. Specifically, the lateral prefrontal cortex and parietal cortices are the key neural structures involved in executive control/task-switching, which mediates explicit (i.e., model-based) emotion regulation, while the vmPFC (including the rostral anterior cingulate cortex [rACC]) is the key neural structure involved in inhibitory/regulatory processing mediating implicit (i.e., model-free) emotion regulation. The observation that regions within each of these individual neural systems are similarly implicated in PTSD provides strong evidence that altered neurocircuitry mediating emotion regulation is a core mechanism of the psychopathology identified as PTSD.

Therefore, to select specific ROIs within these broad neuroanatomical regions implicated in the expression and implicit regulation of negative affect, we used a recent meta-analysis of functional activation differences in PTSD (Patel et al., 2012). This meta-analysis identified two clusters associated with PTSD (relative to trauma-exposed healthy controls) that fall into the larger region implicated in expression of negative affect: a hyperactive posterior region within the anterior mid-cingulate cortex (aMCC; $x y z$ Talairach coordinates = 2, 5, 37) and a more anterior hypoactive region within the aMCC ($x y z$ = 1, 25, 26). Without an empirical reason to select one of these aMCC regions over the other, we used both aMCC ROIs in analyses. For clarity, we will refer to the posterior aMCC region as the mid-cingulate and the anterior aMCC region as the dACC. The meta-analysis identified a single cluster in the rostral ACC ($x y z$ = -5, 42, 4) that falls within the broader region implicated in regulation of negative affect. Finally, we also selected the left amygdala cluster ($x y z$ = -21, -6, -14)

identified within this meta-analysis, given its broad implication in emotion reactivity in general and PTSD specifically. A graphical depiction of the four ROIs relevant to emotion regulation, comprising neuroanatomical regions implicated in both negative affect appraisal/ expression and negative affect regulation, used in the present analyses are available in Figure 1s (supplemental material).

2.4.1 First-level analyses.—For each participant and ROI, we extracted the first principal component timecourse from the voxels within the ROI using singular value decomposition (3dmaskSVD), then regressed this timecourse separately onto each voxel's timecourse (3dREMLfit) and performed an t -to- z transformation to improve the normality of distributions, creating a whole-brain seedmap representing the degree to which each voxel was functionally connected to the seed ROI.

2.4.2 Second-level analyses.—Separately for each ROI seedmap, we regressed each voxel's connectivity with the seed region simultaneously onto the main effects of developmental stage (adolescent = 0, adult = 1), trauma exposure (no trauma = 0, trauma = 1), and the development $\times$ trauma exposure interaction within a multiple regression framework using iteratively reweighted least squares regression (MATLAB's robustfit.m). Dummy variables were z-scored prior to regression. The group-level statistical maps were then masked with a group-level gray matter mask, created via segmentation with FSL on individual anatomical images. The cerebellum and brainstem were manually excluded from this group grey matter mask. Individual voxels within the group level mask were retained if they were within grey matter for $\geq 33\%$ of the sample. Cluster level thresholding was then applied to the resulting masked group-level statistical maps to correct for multiple comparisons in line with new thresholding standards (Eklund et al., 2016). We used AFNI's 3dFWHMx to estimate the effective amount of smoothing present in each dataset using a spatial autocorrelation function (-acf option in 3dFWHMx) and used the resultant mean smoothness parameter of all subjects in AFNI's 3dClustSim to identify the necessary cluster size to maintain a corrected $p < 0.05$, given a voxelwise $p = 0.001$. This resulted in a necessary cluster size of 18 contiguous voxels.

Significant clusters identified via the mass univariate analyses were then tested for their relationship with PTSD symptom severity² and difficulty with emotion regulation (DERS total score), separately in each group, as well as for all participants, controlling for age. Confounds of the primary finding were tested via post-hoc tests for interaction of behavioral variables on the effect of trauma on functional connectivity (FC). Finally, persistence of the identified interaction effect was tested in an omnibus interaction model including the identified potential confounding variables.

²The PCL and UCLA PTSD Index scores were separately normalized to their respective scale's max, to account for the different scales, and then z-scored together.

3. Results

3.1 Primary analyses

Given that the purpose of this study was specifically to examine development as a potential moderator of the effect of early life assaultive violence exposure on resting-state FC amongst regions associated with implicit emotion regulation, we focus our results here on the interaction between development and early life assault exposure.³ Cluster size and peak t values for all interaction analyses are available in Table 2 (see also Table 2s for all follow-up comparisons). For the left amygdala, one significant cluster was identified in the left ventral anterior cingulate gyrus (BA 12) / ventral anterior superior frontal gyrus (BA 11); (Figure 1). Follow-up analyses, in which the mean FC z-scores across voxels within the cluster were extracted for each participant, demonstrated that left amygdala FC with the left ventral anterior cingulate gyrus was reduced among assaulted adolescents relative to control adolescents ($t = 2.35$, $p = 0.025$), but increased among assaulted adults relative to control adults ($t = 3.56$, $p = 0.002$). Consistent with the overall interaction, there was a significant difference between assaulted adolescents and adults in left amygdala–left ventral anterior cingulate gyrus FC, with adults exhibiting increased connectivity ($t = 4.28$, $p < 0.001$).

For the rACC (Figure 2), significant clusters were identified in the ventral anterior superior frontal gyrus (BA 11) and right precuneus (BA 31). Follow-up analyses demonstrated that rACC–ventral anterior superior frontal gyrus (BA 11) connectivity was reduced among assaulted adolescents compared to control adolescents ($t = -3.96$, $p < 0.001$) but increased for assaulted adults compared to control adults ($t = 2.54$, $p = 0.018$). For rACC–right precuneus FC, we again found that connectivity was reduced among assaulted adolescents compared to control adolescents ($t = -3.91$, $p < 0.001$); however, FC for assaulted compared to control adults did not differ ($t = 1.73$, $p = 0.097$). Consistent with the overall interaction, the difference between assaulted adolescents and adults was significant, with adults exhibiting increased connectivity ($t = 5.35$, $p < 0.001$ [rACC–ventral anterior superior frontal gyrus (BA 11)] and $t = 2.26$, $p = 0.031$ [rACC–right precuneus]).

For the dACC, significant clusters were identified in the left precuneus, left lingual gyrus, and left angular gyrus (Figure 3). Follow-up analyses demonstrated that in each of these regions, connectivity was reduced among assaulted adolescents compared to control adolescents ($t = 4.91$, $p < 0.001$ [dACC–left precuneus], $t = -3.64$, $p < 0.001$ [dACC–left lingual gyrus], and $t = 3.85$, $p < 0.001$ [dACC–left angular gyrus]). There were not significant FC differences between assaulted adults and control adults for any of these regions (all $ps > 0.18$). The specific difference between exposed adolescents and adults was again significant, with adults exhibiting increased connectivity ($t = 3.48$, $p = 0.002$ [dACC–left precuneus], $t = 2.96$, $p = 0.006$ [dACC–left lingual gyrus], and $t = 3.25$, $p = 0.003$ [dACC–left angular gyrus]).

There were no significant interactions of age $\times$ trauma on mid-cingulate FC.

³Results for the main effects of development and early life assault exposure on FC with these seed regions are available upon request from the last author.

3.2 Post-hoc analyses

3.2.1 Connections between FC and emotion dysregulation.—Follow-up analyses tested the relationship between mean FC of the significant clusters representing the development $\times$ assault exposure interactions and difficulty with emotion regulation. Controlling for current age, these analyses demonstrated that among adult women with PTSD, connectivity between the ventral anterior superior frontal gyrus (BA 11) and the rACC ($t = 3.57$, $p = 0.004$) and between the left ventral anterior cingulate gyrus and the left amygdala ($t = 2.37$, $p = 0.040$) was associated with worse emotion regulation (i.e., scaled positively with DERS scores). These relations were absent in the adult control women ($ps > 0.36$).⁴ A standard GLM moderation analysis (Baron and Kenny, 1986) among all adult women demonstrated that the magnitude of the relationship between DERS score and FC between the left ventral anterior cingulate gyrus and left amygdala ($t = 2.18$, $p = 0.03$) and rACC ($t = 3.61$, $p = 0.001$) was greater among adult women with PTSD compared to healthy control women. In contrast, the comparable relationships and interactions were absent in both adolescent groups (main effect $ps > 0.30$, interaction $ps > 0.19$).

3.2.2 Exploring potential confounds.—Variables that correlated with age or that significantly differed between age groups presented potential confounding effects on the interpreted developmental stage $\times$ trauma interaction effects. For example, the length of time elapsed since the occurrence of initial assault was highly correlated with current age ($r = 0.93$), as was the time since most recent trauma ($r = 0.53$). To address this, we performed post-hoc cluster analyses to determine if these variables could explain the differential effect of trauma on mean cluster functional connectivity with the emotion regulation regions of interest. Controlling for age, several variables individually moderated the effect of trauma on mean functional connectivity (Table 1s). The original age $\times$ trauma interaction term remained significant in predicting mean FC in all clusters in this larger model.

4. Discussion

Although our study design necessitates that the results of our investigation must be viewed as preliminary (i.e. participants were not observed longitudinally), we provide data that incrementally advances knowledge on the potentially critical role of developmental stage in interpreting neurological changes present in PTSD. Additionally, though the samples of assaulted adolescent girls and adult women differed in more ways than just age (e.g., PTSD symptom severity, time since first trauma exposure, etc.), we were able to statistically examine these potentially confounding variables and consistently observed that age was the most powerful factor moderating the neurocircuitry tested here.

Our results found that current developmental stage significantly moderated the effect of early life assault on FC between regions implicated in implicit emotion regulation (i.e., amygdala, dACC and rACC) and regions involved in self-directed mentation and stimulus-independent thought (i.e., vmPFC, precuneus, and lateral parietal cortex). Specifically, left ventral anterior cingulate gyrus connectivity with the left amygdala and ventral anterior

⁴A graphical depiction of these results are available in Figure 2s (supplemental material).

superior frontal gyrus connectivity with the rACC was reduced among assaulted adolescent girls relative to adolescent controls, replicating past research examining maltreated youth (Aghajani et al., 2016; Burghy et al., 2012; Herring et al., 2013), while left ventral anterior cingulate gyrus connectivity with the amygdala and right ventral anterior superior frontal gyrus with the rACC was contrastingly increased among assaulted adult women with PTSD relative to control women. FC of the rACC and dACC with the precuneus was also reduced among assaulted adolescent girls. The overall pattern of results suggests that, whereas normative neurodevelopment appears to be characterized by decreasing FC between these identified neural regions, early life assault appears to invert this developmental trajectory. While this pattern was generally true of each of the clusters of FC identified for the age $\times$ trauma interaction, it was most prominent for FC between the vmPFC (i.e., ventral anterior superior frontal gyrus and left ventral anterior cingulate gyrus) and the left amygdala and rACC.

Importantly, our follow-up analyses provided evidence that the aforementioned alterations predict clinically relevant outcomes (i.e., emotion dysregulation) related to a host of psychological disorders (Mennin et al., 2007), including PTSD (Badour and Feldner, 2013; Lilly et al., 2014; Tull et al., 2007). Among assaulted adult women, greater connectivity between the ventral anterior superior frontal gyrus and rACC and left ventral anterior cingulate gyrus and left amygdala was associated with worse self-reported emotion regulation. Future longitudinal studies should explore whether this increased connectivity and corresponding poor emotion regulation is predicted by the inversely decreased connectivity observed in assaulted adolescents.

It is relevant to note that there is conflicting evidence about whether normative development is characterized by increased or decreased FC between neural networks (Dosenbach et al., 2011; Gu et al., 2015). Similarly, while some studies have found that amygdala-vmPFC resting-state FC *increases* with age (Gabard-Durnam et al., 2014; Qin et al., 2012), another recent study did not find an association between age and amygdala-vmPFC FC (Alarcón et al., 2015). Future longitudinal research is needed to corroborate this exploratory cross-sectional study and demonstrate that early life assault is associated with altered neurodevelopment of these brain networks on a within-subject level.

4.1 Limitations

The results of this study should be considered in context of its limitations. First, we used a small sample of female participants. Replication of our findings in a larger sample would be merited in future studies, and examination of our study hypotheses in a male sample would speak to potential generalizability. Second, while our study methods allowed for a novel investigation into whether developmental stage moderates the neurocircuitry potentially underlying PTSD and emotion regulation, our data were cross-sectional and preclude direct causal inferences. Resting-state analyses have limited ability to inform functional inferences, though the associations with self-reported emotion regulation support our assertion that the regions we examined are involved in emotion regulation processes. Further, not all participants included in the trauma-exposed adolescent sample met criteria for a PTSD diagnoses, potentially introducing an additional source of error into our models given that

FC may differ for individuals who have experienced assaultive violence versus those who meet criteria for PTSD (cf. Jin et al., 2014). Because healthy control participants were selected in part on the basis of not having directly experienced assaultive violence, we are also limited in our ability to disentangle whether it is the effect of assaultive violence exposure, PTSD symptoms, or both that is moderated by developmental stage. Relatedly, there are inherent potentially confounding factors when comparing adult samples exposed to early life trauma to adolescent trauma samples, such as the fact that more time has necessarily passed since the early life trauma occurred in the adult sample compared to the adolescent sample. Limitations of cross-sectional comparisons could be addressed with future longitudinal studies. Future work could build on our study by identifying the contributions of discrete types of trauma exposure (e.g., general childhood maltreatment vs. assaultive violence exposure specifically) and its sequela (e.g., PTSD symptoms) to changes in functional connectivity over development. The head coil used during scanning also differed between adult and adolescent groups; however, we did not observe any significant development $\times$ trauma exposure interactions on temporal signal to noise ratios (supplementary material), and all participants were imaged using the same scanner. Furthermore, our reliance on preselected seed regions limits our ability to speak to how trauma and/or development may impact other networks.

4.2 Conclusion

This study has potentially significant implications for neurocircuitry models of trauma and PTSD. Specifically, while current models posit that PTSD is characterized by hyperactivity in the amygdala and hypoactivity in the vmPFC, the current results suggest that neither hyperconnectivity nor hypoconnectivity between these regions is necessarily adaptive or maladaptive. Rather, the developmental context needs to be considered when interpreting the adaptive value of the identified brain circuits. Our findings are also consistent with past research that has found structural differences across developmentally distinct groups in pediatric PTSD (Keding and Herringa, 2015; Woon and Hedges, 2008). Given the significant neurodevelopment that takes place across childhood to adulthood, and in line with the current results, it is plausible that the neurocircuitry conferring risk for PTSD differs depending on developmental stage and that early trauma alters the normative trajectory of the development of neurocircuitry mediating important constructs in PTSD (e.g., emotion regulation). It is also possible that connectivity changes are compensatory; for example, given prior findings of age-related increases in amygdala reactivity in pediatric PTSD (Keding and Herringa, 2016), the reduced connectivity between the left amygdala-left ventral anterior cingulate gyrus found among assaulted adolescents in this study may function to reduce amygdala reactivity. As noted above, additional future research is needed to corroborate these hypotheses with larger mixed-sex studies utilizing longitudinal designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Current neurocircuitry models of PTSD do not account for developmental effects.
- Found significant interactions between development and trauma exposure on RSN FC.
- Women and girls had opposite FC patterns in regions related to emotion regulation.
- Development must be considered when interpreting trauma-related FC differences.

Figure 1.

Significant development $\times$ trauma exposure interaction on functional connectivity between left amygdala and left ventral anterior cingulate gyrus. Bar graphs indicate mean functional connectivity within each group. Error bars denote standard error.

Figure 2.

Significant development × trauma exposure interaction on functional connectivity between rostral ACC and the ventral anterior superior frontal gyrus and right precuneus. Bar graphs indicate mean functional connectivity within each group for the separate clusters. Error bars denote standard error.

Figure 3.

Significant development $\times$ trauma exposure interaction on functional connectivity between dorsal ACC and the left parietal cortex and precuneus. Bar graphs indicate mean functional connectivity within each group for the separate clusters. Error bars denote standard error.

Table 1.

Demographic and clinical characteristics of study participants.

	<u>Controls</u>			<u>Experienced Assault</u>			<u>Group comparison (Teens vs. Adults)</u>
	Teens (<i>n</i> = 19)	Adults (<i>n</i> = 11)	<u>Control comparison</u>	Teens (<i>n</i> = 17)	Adults (<i>n</i> = 14)	<u>Assault comparison</u>	
	<i>M (SD) or %</i>	<i>M (SD) or %</i>	<i>p-value</i>	<i>M (SD) or %</i>	<i>M (SD) or %</i>	<i>p-value</i>	<i>p-value</i>
Age	13.95 (1.43)	32.00 (7.68)	<0.001	15.12 (1.05)	30.14 (5.56)	<0.001	<0.001
Ethnicity ^a	84.2% White	81.8% White	0.870	58.8% White	60% White	0.760	0.980
	15.8% Black	18.2% Black		29.4% Black	26.7% Black		
				5.9% Biracial	13.3% Biracial		
				5.9% Hispanic			
Emotion Dysregulation ^b	52.74 (19.98)	43.19 (7.6)	0.141	75.88 (25.01)	81.29 (29.34)	0.584	0.900
PTSD Symptoms ^c	1.47 (5.34)	19.36 (2.87)	0.614	22.53 (19.51)	58.43 (18.20)	0.010	0.019 *
Depressive Symptoms ^d	2.84 (3.25)	2.00 (2.45)	0.057	8.94 (7.33)	25.43 (13.96)	0.524	0.756
CTQ severity	40.32 (3.53)	39.55 (3.56)	0.570	58.94 (14.73)	86.79 (21.21)	<0.001	0.003 *
Current PTSD	0%	0%	>0.99	41.2%	100.0%	<0.001	0.003 *
Current Anxiety Disorder ^e	0%	0%	>0.99	29.4%	85.7%	0.002	0.004 *
Current Depressive Disorder	0%	0%	>0.99	23.5%	57.1%	0.056	0.044 *
Current Drug or Alcohol Abuse	0%	0%	>0.99	11.8%	21.4%	0.470	0.370
Psychotropic medication ^f	5%	18.2%	0.256	35.3%	57.1%	0.224	0.078

Notes: *p*-values refer to chi-square goodness of fit tests on categorical variables and independent-samples *t*-tests on continuous variables where scores were normalized by dividing by assessment scale maximum and *z*-scoring.

^a Ethnicity was dummy coded for minority (Black, Hispanic, and Biracial = 0) vs. non-minority (White = 1) status.

^b Difficulties in Emotion Regulation Scale (DERS; range: 30–150)

^c UCLA PTSD Index for adolescents (range: 0–68) and PTSD Checklist-IV for adults (range: 17–85)

^d Short Mood and Feelings Questionnaire for adolescents (range: 0–26) and Beck Depression Inventory-II for adults (range: 0–63). Raw scores for depression and PTSD symptoms are provided for the purpose of interpretability.

^e Anxiety disorder diagnoses do not include current PTSD. Medication use was dummy coded wherein individuals taking psychotropic medications = 1 and individuals not using psychotropic medications = 0.

* Variables identified for further testing in univariate confound models (Table 1s).

Table 2.

Intrinsic connectivity significantly moderated by development $\times$ assault status.

Seed Region (5 mm radius ROI)	Center-of-Mass Talairach Coordinates			Functionally connected cluster	Center-of-Mass Talairach Coordinates			Cluster size(voxels)	Peak <i>t</i> value
	x	y	z		x	y	z		
Dorsal anterior cingulate cortex, BA 24	1	25	26	left precuneus, BA 31	-9	-65	21	20	4.12
				left angular gyrus, BA 39	-41	-75	31	22	4.85
				left lingual gyrus, BA 18	-7	-56	0	22	5.02
Rostral anterior cingulate cortex, BA 32	-5	42	4	right precuneus, BA 31	2	-64	18	27	4.43
				right ventral anterior superior frontal gyrus, BA 11	1	53	-5	21	5.21
Left amygdala	-21	-6	-14	Left ventral anterior cingulate gyrus, BA 12	-5	48	-6	22	4.67

Table 3.Post-hoc test of all interaction terms to predict mean FC in clusters moderated by age $\times$ assault status

Seed Region (5 mm radius ROI)	Functionally connected cluster	Omnibus interaction model (potential confounder $\times$ assault status) Robust-fit (p-value)	
		CTQ severity	Age group
Dorsal anterior cingulate cortex, BA 24	left precuneus, BA 31	0.48	0.004
	left angular gyrus, BA 39	0.02	0.02
	left lingual gyrus, BA 18	0.92	0.001
Rostral anterior cingulate cortex, BA 32	right precuneus, BA 31	0.56	0.0002
	right ventral anterior superior frontal gyrus, BA 11	0.05	0.003
Left amygdala	left ventral anterior cingulate gyrus, BA 12	0.03	0.004