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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.

## 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-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; Cougle 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., 2018; 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

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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 inter-network 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.

## 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 ($M_{age} = 8.24$, $SD = 4.07$) and women ($M_{age} = 6.64$, $SD = 2.92$).

### 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 and Roemer, 2004) to index emotion dysregulation. DERS items are presented on a 5-point

[1] On 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.