Stress-related hippocampus activation mediates the association between polyvictimization and trait anxiety in adolescents

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Abstract

Early life stress exposures are associated with adverse health outcomes and heightened anxiety symptoms in adolescents. Stress-sensitive brain regions like the hippocampus and amygdala are particularly impacted by early life adversities and are also implicated in the development of anxiety disorders. However, to date, no studies have specifically examined the neural correlates of polyvictimization (exposure to multiple categories of victimization) or the contribution of stress-sensitive neural nodes to polyvictimization's impact on mental health. To elucidate these relationships, the current study analyzed associations between polyvictimization, hippocampal and amygdalar activation during an acute stress task and trait anxiety in a sample of 80 children and adolescents aged 9–16 years (33 female participants). Results showed that polyvictimization was associated with higher trait anxiety as well as greater stress-related right hippocampus activation, and this greater hippocampal activity predicted heightened trait anxiety. Robust mediation analyses revealed that stress-related right hippocampus activation partially mediated the relationship between polyvictimization and trait anxiety. Our results expand upon the existing polyvictimization literature by suggesting a possible neurobiological pathway through which polyvictimization is connected to the etiology of mental illness.

Key words: polyvictimization; hippocampus; anxiety; adolescence; functional magnetic resonance imaging

Introduction

Exposure to victimization during childhood and adolescence impacts critical psychological and neurobiological developmental processes, often resulting in long-term deleterious effects on mental health (National Academies of Sciences, 2019b; Haahr-Pedersen et al., 2020). Disturbingly, 60% of children and adolescents in the USA experience or witness some form of victimization each year (Finkelhor et al., 2009). Recent neurobiological studies of victimization in adolescents typically focus on a single type, i.e. neighborhood violence (Miller et al., 2018) or victimization by peers (Quinlan et al., 2020). However, studying the isolated influences of specific types of victimization may overestimate any individual category's impact (Haahr-Pedersen et al., 2020), because children who experience one form of victimization in a given year are two to three times more likely to experience another kind (Finkelhor et al., 2009). This polyvictimization—defined here as exposure to multiple

categories of victimization—is associated with diverse psychological and behavioral problems in adolescents, including anxiety symptoms (Finkelhor et al., 2007; Haahr-Pedersen et al., 2020). Studying the relationship between polyvictimization and anxiety is crucial, because nearly one-third of adolescents meet the criteria for an anxiety disorder, increasing their likelihood of developing psychiatric conditions in adulthood (Merikangas et al., 2010; Doering et al., 2019).

Polyvictimization specifically is connected to increased risk for developing mental illness (Haahr-Pedersen et al., 2020), and exposure to more broadly defined forms of childhood adversity is associated with neurobiological changes and negative health outcomes (National Academies of Sciences, 2019b). Victimization exposure across different contexts—at home, at school or in the neighborhood—produces a significant emotional burden in adolescents, increasing feelings of powerlessness and reducing perceived emotional support (Turner et al., 2017).

Categorically defined polyvictimization, which measures the number of broader categories/contexts in which a child has experienced victimization, has been shown to uniquely predict negative outcomes, even when considering the total lifetime frequency of victimization exposures or influence of individual categories of victimization (Hickman *et al.*, 2013). However, current neuroimaging studies typically examine either total lifetime exposure to maltreatment (DelDonno *et al.*, 2019; Zhai *et al.*, 2019) or single types of victimization exposure (Telzer *et al.*, 2018; Čermaková *et al.*, 2020), and, to our knowledge, no studies have examined the specific relationship between polyvictimization and neural activity. Studying these associations in periadolescents (9- to 16-year-olds) is particularly important, because adolescence is a critical period for psychopathology onset, and adolescents face increased exposure to daily stressors while simultaneously undergoing neuromaturation in stress-sensitive brain regions (Seiffge-krenke, 2000; Romeo, 2013, 2017). Therefore, identifying neurobiological mechanisms connecting polyvictimization to anxiety in periadolescence is an important step for creating targeted preventative interventions to reduce the risk that polyvictimized youths will develop mental illnesses.

The acute stress response (ASR) to individual victimization events can activate the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, resulting in temporary biological changes including increased heart rate, stress hormone release and alterations in neural activity (Li *et al.*, 2013; Noack *et al.*, 2019). Polyvictimization represents the cumulative burden of these acutely stressful events across a variety of functional contexts and is thought to contribute to allostatic overload, which arises as the body adapts to repeated stress exposure. This can lead to altered neurobiological ASRs and increased risk for developing mood and anxiety disorders (Wolfe, 2018; Guidi *et al.*, 2021).

Allostatic overload can impact neural development and activation of the hippocampus and amygdala, which are instrumental in neurobiological ASRs (McEwen, 2002; Fan *et al.*, 2015; Kim *et al.*, 2015). The hippocampus and amygdala have substantial roles in cognitive and biological functions, including emotional processing and regulation of the HPA axis (Hanson *et al.*, 2015). Individually, the hippocampus is critical for episodic memory which provides context for threatening stimuli, while the amygdala is responsible for threat detection and prioritization of salient stimuli (Zheng *et al.*, 2017; Harnett *et al.*, 2020). Early life stress exposure has been connected to smaller hippocampal and amygdalar volumes (Gorka *et al.*, 2014; Hanson *et al.*, 2015; Weissman *et al.*, 2020), greater hippocampus and amygdala ASR (Seo *et al.*, 2014; Leicht-Deobald *et al.*, 2018), and increased stress-related amygdala-hippocampus functional connectivity (Elsey *et al.*, 2015). Critically, these differences in limbic structure and activation are linked to increased trait anxiety (Hyde *et al.*, 2011; Gorka *et al.*, 2014).

If the stress exposure associated with polyvictimization causes allostatic overload, polyvictimization would be connected to neurobiological adaptations in stress-regulatory systems, reflected by hippocampus and amygdala activation during acute stress (Beauchaine *et al.*, 2011; Widom *et al.*, 2015). Moreover, aberrant limbic ASR may mediate polyvictimization's contributions to anxiety. This proof-of-concept study provides justification for future longitudinal research needed to fully explicate these neurobiological relationships. Interventions that impact the limbic system could potentially mitigate polyvictimization's impact by alleviating anxiety symptoms in high-risk periadolescents.

Table 1. Sample characteristics

Characteristics	
Total (N)	80
Sex (% female)	41
Age (years)	12.9 (2.3)
Race (% White)	71
Race (% Black)	17
Race (% other)	12
On medication (%)	34
DSM-IV diagnosis (%)	50
STAIT	33.2 (6.7)

The goal of this paper is to elucidate the relationship between polyvictimization, stress-related hippocampus and amygdala activation, and trait anxiety in periadolescents. This study elicited ASRs using the Montreal Imaging Stress Task (MIST)—a well-validated functional magnetic resonance imaging (fMRI) task that produces stress-related changes in blood oxygen level–dependent (BOLD) signaling (Pruessner *et al.*, 2008; Noack *et al.*, 2019). We hypothesized that polyvictimization would be associated with higher trait anxiety and greater hippocampus and amygdala activation (less deactivation) during acute stress, and this stress-related limbic activity would mediate the relationship between polyvictimization and trait anxiety.

Methods
Participants
Eighty periadolescents aged 9–16 years (33 female participants, age M = 13.4, s.d. = 2.2) completed the MIST and victimization and trait anxiety questionnaires. In alignment with the Research Domain Criteria (RDoC) framework (Insel *et al.*, 2010), individuals were recruited using a stratified strategy to form a heterogenous sample exhibiting a range of cognitive disorganization and anxiety symptomatology. To allow for this variation, subjects were only excluded for neurological disorder, history of head injury, chronic medical condition that could impact stress systems or imaging, MRI contraindications, lifetime or current Diagnostic and Statistical Manual of Mental Disorders-fourth revision-text version (DSM-IV-TR) Axis I psychotic disorder, current major depressive disorder, post-traumatic stress disorder (PTSD), bipolar disorder and/or substance dependence. These participants were recruited from four primary sources (community schools, flyers, pediatric and psychiatric clinics and hospitals at UNC Chapel Hill and Duke University). The Institutional Review Boards of UNC Chapel Hill and Duke University approved the study and legal guardians provided consent and subjects gave assent. Further sample characteristics are mentioned in Table 1.

Psychological measures
Trained researchers determined the presence of DSM-IV Axis I disorders via an abbreviated form of the Structured Clinical Interview for DSM-IV (SCID) (First *et al.*, 1995), and diagnoses were confirmed via electronic health records when applicable. Half of the sample met criteria for DSM-IV disorders including attention-deficit/hyperactivity disorder (ADHD), generalized anxiety disorder, social anxiety disorder, panic disorder,

obsessive-compulsive disorder and adjustment disorder. Thirty-four percent of subjects were taking psychotropic medications known to impact neural activity, including stimulants, non-stimulant ADHD medication, antidepressants, antipsychotics and one case of an anticonvulsant.

The 20-item self-report State-Trait Anxiety Inventory for Children Trait (STAIT; Spielberger, 2010) scale, a well-validated measure for children and adolescents (Seligman et al., 2004), was administered to assess trait anxiety. Participants completed the State-Trait Anxiety Inventory (STAI) State scale (Spielberger, 2010) before and after each MRI scan to evaluate their current emotional state. Self-reported stress ratings were measured immediately before and after the stress task, with participants stating their current affect via verbal Likert scale rating, as explained in Corr et al. (2021).

The 34-item Juvenile Victimization Questionnaire (JVQ) is used to assess a broad range of traumas and stressors experienced by children and adolescents throughout their life span (Finkelhor et al., 2005) with questions falling within five categories/subscales (nine questions about conventional crime, four about child maltreatment, seven about sexual victimization, six about peer/sibling victimization and eight about indirect/witnessing victimization). While the JVQ is well-validated for periadolescents and is commonly used to measure polyvictimization, there is a notable lack of consensus in the literature on polyvictims' classification using this scale (Haahr-Pedersen et al., 2020). We define polyvictimization categorically as the total number of categories/subscales within which a participant endorsed experiencing at least one type of victimization (with possible values ranging from 0 for subjects with no victimization experience to 5 for subjects who experienced some form of victimization in all categories/subscales; Hickman et al., 2013). An advantage of categorically defined polyvictimization, as opposed to other definitions of polyvictimization is that it independently predicts child behavioral problems, PTSD symptoms and parental stress, even when accounting for the total lifetime victimization exposure or frequency of most individual polyvictimization categories (Hickman et al., 2013).

Montreal Imaging Stress Task

The MIST was administered in accordance with existing literature (Pruessner et al., 2008; Khalili-Mahani et al., 2010; Kogler et al., 2015) using our previously reported paradigm (Corr et al., 2021). In brief, subjects completed three six-minute MIST runs, with each run containing three sets of rest, control and experimental conditions in a semi-randomized order. During the rest condition, participants focused on a stationary image of the task. The control condition required subjects to solve math problems by rotating a dial to indicate their answers. During the experimental condition, subjects were told their performance was being recorded, and math problems must be completed within a short time frame. A stressful tone with a rising pitch emphasized time pressure. Participants were told a bar at the top of the screen represented their performance vs average performance, but this was set to never indicate they were preforming above average. Between each run, researchers informed subjects that their performance was below average and instructed them to try harder during the experimental condition. Problem speed was dynamically adjusted so participants could only get ∼50% of questions correct. After the MRI session, participants were debriefed about the task.

Imaging procedures
fMRI acquisition
Subjects were scanned at the Duke-UNC Brain Imaging and Analysis Center on a 3T GE MR750 scanner. A three-dimensional fast spoiled-gradient-recalled sequence generated a high-resolution T1-weighted (T1w) anatomical image (repetition time (TR) = 8.2 ms; echo time (TE) = 3.22 ms; flip angle (FA) = 12°; field of view (FOV) = 240 × 240 × 166 mm^2; matrix size = 256 × 256 × 166; slice thickness = 1.0 mm). MIST functional imaging series were collected with an eight-channel head-coil using a spiral-in sensitivity encoding interleaved sequence (TR/TE = 2000/30 ms; FA = 60°; FOV = 24 cm; acquisition matrix = 64 × 64; slice thickness = 4 mm; 34 slices). To allow for steady-state equilibrium of the MR signal, each run began with four discarded acquisitions.

fMRI preprocessing and processing
Preprocessing was performed using fMRIPprep v1.2.4 (Esteban et al., 2019a,b), which is based on Nipype 1.1.6 (Gorgolewski et al., 2011, 2017). Each T1w volume was corrected for intensity non-uniformity using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.2.0 (OASIS template). Recon-all from FreeSurfer v6.0.1 (Dale et al., 1999) reconstructed brain surfaces, and the brain mask estimated was refined with a custom variation of the method to reconcile antsApplyTransforms (ANTs)-derived and FreeSurfer-derived segmentations of the cortical gray matter of Mindboggle (Klein et al., 2017). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template v2009c (Fonov et al., 2009) was performed through non-linear registration with the antsRegistration tool of ANTs v2.2.0 (Avants et al., 2008), using brain-extracted versions of T1w volume and template. Brain tissue segmentation of cerebrospinal fluid, white matter and gray matter was performed on the brain-extracted T1w using fast (Zhang et al., 2001).

Functional data was slice time-corrected using 3dTshift from AFNI v16.2.07 (Cox, 1996) and motion-corrected using mcflirt (FSL v5.0.9; Jenkinson et al., 2002). This was followed by co-registration to the corresponding T1w using boundary-based registration (Greve and Fischl, 2009) with nine degrees of freedom, using bbregister (FreeSurfer v6.0.1). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template Montreal Neurological Institute (MNI) warp were concatenated and applied using ANTs using Lanczos interpolation.

CompCor (Behzadi et al., 2007) extracted physiological noise regressors. Frame-wise displacement (Power et al., 2014) was calculated for each run using Nipype. Automatic removal of motion artifacts using independent component analysis was performed on the preprocessed BOLD on MNI space time series, after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6 mm full-width half-maximum (Pruim et al., 2015). White matter and cerebrospinal fluid were regressed out from the global signal using FSL (v5.0.10) fsl_regfilt (Jenkinson et al., 2012).

fMRI data processing used FEAT v6.00 (Jenkinson and Smith, 2001; Jenkinson et al., 2002), applying brain extraction tool (BET) (Smith, 2002) non-brain removal, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, sigma = 50.0 s) and prewhitening. Second-level analyses combined MIST runs within each subject and contrasted BOLD activation during the experimental vs control conditions. This 'stress - control' activation contrast was used for analyses, as is typical for MIST studies (Lederbogen et al., 2011; Chung et al., 2016b;
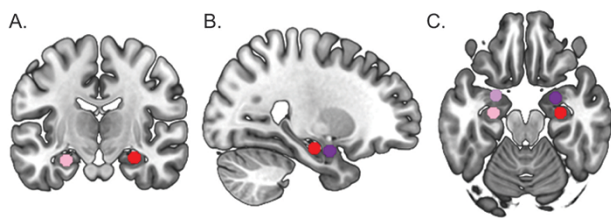
Fig. 1. Right (dark) and left (light) hippocampus (red) and amygdala (purple) ROIs depicted as (A) coronal slice ($y = -14$), (B) sagittal slice ($x = 28$) and (C) axial slice ($z = -20$).

Dong *et al.*, 2020); the contrast between conditions represents the unique neural impact of stress by controlling for the mathematical task's cognitive demands when administered under non-stressful conditions. Positive 'stress - control' contrast BOLD signal values were regarded as stress-related 'activation,' and negative values represented stress-related 'deactivation.'

Region of interest extraction

Left and right hippocampal and amygdalar regions of interest (ROIs; Figure 1) were defined in accordance with Leicht-Deobald *et al.* (2018) using 5 mm radius spheres centered on hippocampus ($-26, -14, -20$; $28, -14, -18$) and amygdala coordinates ($-24, 0, -20$; $24, -2, -20$) identified in a meta-analysis of 790 emotional processing and stress-reactivity fMRI studies (Yarkoni *et al.*, 2011). Contrasted mean BOLD signal between the MIST experimental and control conditions was extracted from these spheres for analysis. Five subjects were identified as outliers by our robust models (neural activation > 2.8 s.d. from the mean) and were removed, making our final sample 75 subjects.

Statistical analysis

Preliminary analyses aimed to identify variables that should be included in our primary robust linear models and mediation analysis. Correlations were run between polyvictimization, trait anxiety, age, and hippocampal and amygdalar activation (Table 2), and Welch's *t*-tests examined the relationship between these variables and sex (Supplementary Table S1A) and psychotropic medication use (coded binarily as 0 = not on medication, 1 = taking psychotropic meds, Supplementary Table S1B). An analysis of variance explored connections between polyvictimization and race (defined categorically as white, black or other), and a Spearman's rank correlation assessed associations between polyvictimization and parental socioeconomic status (defined by average parental education). To ensure results were unique to trait anxiety and not derived from state anxiety, supplementary analyses confirmed that state anxiety and subjective stress ratings were

not correlated with polyvictimization or brain region polyvictimization impacted (Supplementary Table S2). Pearson's chi-squared tests confirmed there were no significant sex differences in presence/absence of any of the five victimization categories (Supplementary Table S3). Based on these preliminary analyses and literature indicating their impact on neural circuitry (Lenroot and Giedd, 2010; Posner *et al.*, 2011; Wandschneider and Koepp, 2016; Telzer *et al.*, 2018), sex, age and medication use were included as covariates in all analyses.

Robust linear regressions, using the R *robustbase* library (Maechler *et al.*, 2020), explored the relationships between (i) polyvictimization and trait anxiety, (ii) polyvictimization and hippocampus/amygdala activation and (iii) hippocampus/amygdala activation and trait anxiety. Multicollinearity diagnostics were assessed for each model via the R *car* package (Fox *et al.*, 2019) and were within an acceptable range (variance inflation factors < 1.25). Robust mediation analyses run using the R *robmed* package (Alfons *et al.*, 2018) examined the direct and indirect effects of polyvictimization (X) on trait anxiety (Y) through mediation by stress-related limbic activity (M). Preliminary multiple linear regressions investigated if there was a significant moderation of X × M → Y and determined that the relationship between polyvictimization and trait anxiety was not moderated by left or right hippocampal or amygdalar activation ($P > 0.05$). All robust analyses used bias-corrected and accelerated bootstrap 95% confidence intervals (CIs) with 10 000 iterations. Bootstrapping is used to compensate for lower power and asymmetrical distributions. The 'SMDM' method—which was developed for use with smaller samples (Koller and Stahel, 2011)—and the 'optimal' psi were used for robust regression analyses.
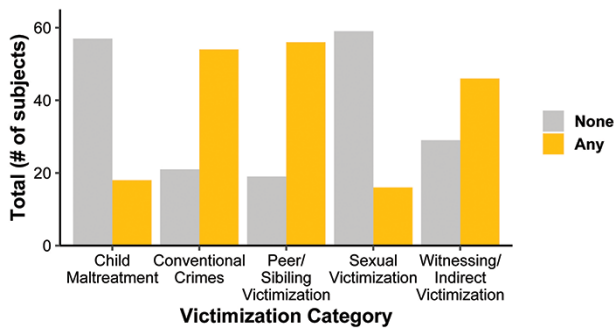
Results

Polyvictimization and relationships between measures—preliminary analyses

Of the 75 periadolescents included in the neural analysis, 89.3% ($N = 67$) had experienced victimization in at least one category, 74.7% ($N = 56$) endorsed exposure to two or more categories and 29.3% ($N = 22$) experienced victimization across four or more of the five categories. Figure 2 depicts prevalence of the five victimization categories. Correlations between measures are reported in Table 2. While females exhibited greater trait anxiety than males (Welsh's $t(63.5) = 2.57$, $P = 0.012$), there was not a sex difference in polyvictimization (Welsh's $t(66.6) = 1.28$, $P = 0.203$, see Supplementary Table S1A for all sex results). Polyvictimization was not associated with race ($F(2,72) = 0.25$, $P = 0.779$) or parental socioeconomic status ($r_s(70) = -0.13$, $P = 0.285$). Polyvictimization and trait anxiety were not correlated with stress-related activation in the left hippocampus, left amygdala or right amygdala, but both were correlated with right stress-related hippocampal activation

Table 2. Averages, standard deviations (s.d.) and correlations between measures ($N = 75$)

Variable	Mean	s.d.	Range	1	2	3	4	5	6
Polyvictimization	2.53	1.4	[0, 5]						
Trait anxiety	33.05	6.6	[20, 49]	0.41***					
Age	12.99	2.2	[9, 16]	0.10	0.25*				
Hippocampus (L)	−3.84	10.2	[−34.4, 26.3]	0.03	0.13	0.13			
Hippocampus (R)	−3.56	8.3	[−24.6, 13.8]	0.24*	0.37**	0.09	0.27*		
Amygdala (L)	−1.41	12.1	[−36.1, 29.6]	0.10	0.03	0.03	0.36**	0.27*	
Amygdala (R)	−2.03	11.0	[−28.5, 20.1]	0.13	0.19	0.11	0.39**	0.25*	0.58***

***$P \leq 0.001$, **$P \leq 0.01$, *$P \leq 0.05$.

Fig. 2. Relative frequency of different victimization types.

(Table 2). Accordingly, only the right hippocampus was included in the main results, but supplementary analyses confirmed that left hippocampal and bilateral amygdala activation did not mediate the relationship between polyvictimization and trait anxiety (see Supplementary Results).

Greater polyvictimization is associated with increased trait anxiety and stress-related right hippocampal activation

Robust linear regressions controlling for sex, age and medication use revealed that polyvictimization was strongly associated with trait anxiety ($B = 1.75$, $t(71) = 3.24$, $P = 0.002$, Figure 3A), with greater polyvictimization predicting increased trait anxiety. Polyvictimization was also linked to greater right hippocampal activation—indicating reduced deactivation—during stress ($B = 1.40$, $t(71) = 1.99$, $P = 0.050$, Figure 3B). Finally, greater right hippocampal activation (reduced deactivation) was associated with increased trait anxiety ($B = 0.25$, $t(71) = 2.80$, $P = 0.007$, Figure 3C).

Right hippocampus activation partially mediates the relationship between polyvictimization and trait anxiety

A robust regression mediation analysis, controlling for sex, age and medication use, indicated that right hippocampal ASR partially mediated the relationship between polyvictimization and trait anxiety (Figure 4). The total effect of polyvictimization on trait anxiety was significant ($c = 1.66$, $SE = 0.57$, $P = 0.004$), and polyvictimization served as a predictor of right hippocampus activation during acute stress ($a = 1.37$, $SE = 0.68$, $P = 0.044$).

Right hippocampus activation during acute stress still predicted trait anxiety when additionally controlling for polyvictimization, ($b = 0.19$, $SE = 0.08$, $P = 0.021$). The indirect effect of polyvictimization on trait anxiety via right hippocampus activation was significant ($ab = 0.27$, 95% CI = [0.03, 0.76]), as was the direct effect ($c' = 1.40$, $SE = 0.59$, $P = 0.019$). Sex, age and medication covariates were non-significant ($P > 0.05$) in all mediation model steps. A supplementary mediation analysis additionally controlling for presence/absence of SCID diagnosis found the SCID covariate was non-significant ($P > 0.05$) in every step of the model, and the overall model results were the same as those presented above (see Supplementary Results).

Discussion

To our knowledge, this is the first study examining the association between polyvictimization and neural activation in periadolescents. Polyvictimization was associated with heightened trait anxiety and stress-related right hippocampal activation, and greater right hippocampal activation was associated with higher trait anxiety. Further analysis revealed that stress-related right hippocampal activation partially mediated the relationship between polyvictimization and trait anxiety. These findings provide insight into the neurobiological mechanisms connecting polyvictimization to negative psychological outcomes.

Polyvictimization, trait anxiety and stress-related hippocampal activation

Polyvictimization was associated with elevated trait anxiety, in alignment with the positive correlation between anxiety and polyvictimization typical of extant literature (Haahr-Pedersen *et al.*, 2020). Polyvictimization and trait anxiety were positively associated with greater right hippocampal activation (reduced deactivation) during acute stress, which is supported by previous research; emotional abuse exposure predicts reduced hippocampal deactivation (Leicht-Deobald *et al.*, 2018), greater right hippocampus activation is correlated with higher cumulative adversity exposure (Seo *et al.*, 2014) and trait anxiety is associated with greater bilateral hippocampal activation in response to threat (Satpute *et al.*, 2012) and during psychosocial stress induced by the MIST (Wheelock *et al.*, 2016). Together, this literature and our findings support the theory that the cumulative burden of categorically defined polyvictimization exposure may result in allostatic overload, as participants with polyvictimization exhibited altered neurobiological ASR and increased anxiety symptoms.
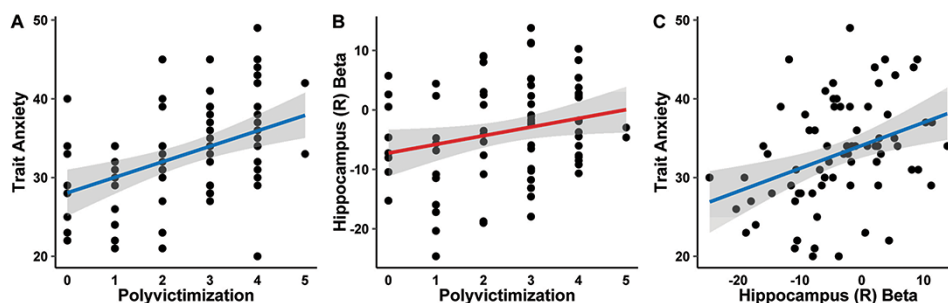
Fig. 3. (A) Polyvictimization is associated with higher trait anxiety. (B) Polyvictimization is associated with greater right hippocampal activation (reduced deactivation); individuals with high polyvictimization exposure exhibited less negative right hippocampal activity than those with low exposure to polyvictimization. (C) Greater right hippocampal activation is associated with higher trait anxiety. For illustration purposes, graphs depict linear models unadjusted for covariates.
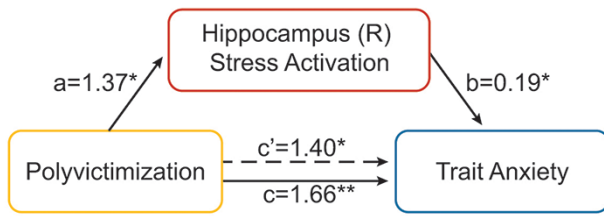
Fig. 4. Mediation model depicting the effect of polyvictimization on trait anxiety via stress-related right hippocampus activation. Standardized coefficients are in parentheses. **$P \leq 0.01$, *$P \leq 0.05$.

However, left hippocampus activation was not correlated with polyvictimization or trait anxiety. An analysis of 16 fMRI PTSD studies found consistent right hippocampus hyperactivation in subjects with PTSD across tasks, with bilateral hippocampal activation present only in studies focused on combat-related trauma (Boccia *et al.*, 2016). These findings suggest the left hippocampus may only be impacted by specific types of trauma, while exposure to multiple forms of victimization influences the right hippocampus. Furthermore, because PTSD was associated with right hippocampal hyperactivation across several neuroimaging tasks, it is possible that lateralized hippocampal activity is a more state-like consequence of polyvictimization, i.e. that differences between left and right hippocampal activation are present during varied cognitive conditions rather than unique to acute stress. However, there is limited research on the laterality of hippocampal activation related to childhood trauma exposure, acute stress or trait anxiety. Our results suggest that lateralization could be a biologic consequence of polyvictimization, representing a gap in the literature that should be addressed in future work.

This analysis also did not reveal significant relationships between stress-related amygdala activation and polyvictimization or trait anxiety. While amygdala activation during threat has previously been tied to childhood trauma exposure (Dannlowski *et al.*, 2012) and trait anxiety (Hyde *et al.*, 2011), there are several potential explanations for our lack of findings. The stress associated with the MIST paradigm may not elicit the same neural response as threat and indeed amygdalar MIST responses have not been consistent; in response to the MIST, early work identified decreased amygdala activation (Pruessner *et al.*, 2008), but recent studies have found activation (Lederbogen *et al.*, 2011; Chung *et al.*, 2016a) or no changes (Inagaki *et al.*, 2016). Variations in findings may arise from additional factors; perceived social support has been shown to moderate the relationship between threat-related amygdala activation and trait anxiety (Hyde *et al.*, 2011). Further MIST research found that, while early life emotional abuse was not directly related to stress-related amygdala activation, coworker social support moderated the relationship between emotional abuse and amygdala activity (Leicht-Deobald *et al.*, 2018). Participants in this study may be experiencing a differential range of social support, which may be confounding our neural findings. Future polyvictimization models should incorporate social support to elucidate the complex relationships between amygdala activation, victimization and trait anxiety.

Neural mechanism of the effect of polyvictimization on trait anxiety

Our robust mediation analysis revealed that right hippocampus activation during acute stress partially mediated the relationship between polyvictimization and trait anxiety, with polyvictimization predicting greater stress-related right hippocampal activation, which was associated with higher trait anxiety. While no studies have specifically examined whether stress-related hippocampal activation mediates the relationship between victimization exposure and psychiatric outcomes, research does suggest the hippocampus influences the relationship between trauma and health (Herringa *et al.*, 2013; Gorka *et al.*, 2014; Seo *et al.*, 2014). Identifying the impact of polyvictimization on the hippocampus and how it relates to anxiety is critical for targeted treatment opportunities, and there are intervention options shown to affect the hippocampus. Altered hippocampal activation after several forms of psychotherapy is associated with improvement in PTSD symptoms (Malejko *et al.*, 2017), suggesting that learning emotion regulation techniques can influence hippocampal function. A supportive parenting program provided to parents of 11-year-olds ameliorated the impact of childhood poverty on their hippocampal volume in adulthood (Brody *et al.*, 2017). Neurofeedback training focused on emotion regulation and positive autobiographical memories indicates that individuals with depression can learn to regulate their hippocampal activity, and neurofeedback training centered on the corticolimbic system can reduce rumination and depressive symptoms (Quevedo *et al.*, 2019, 2020; Zhu *et al.*, 2019). Therefore, individuals with anxiety who have been exposed to polyvictimization may benefit from therapeutic interventions and/or hippocampal neurofeedback training—a promising direction for future research.

It is important to note that the direct effect of polyvictimization on trait anxiety ($c' = 1.40$) was larger than the indirect effect mediated by the hippocampus ($ab = 0.27$). Therefore, while treatments known to impact the hippocampus could reduce anxiety symptoms in polyvictimized individuals, reducing victimization exposure remains primary in mitigating the adverse impacts of polyvictimization. Poor self-control and self-regulation skills predict increased risk for future polyvictimization (Tanksley *et al.*, 2020); thus, interventions that reduce sources of victimization as well as enhance self-regulation and executive function of periadolescents in high-risk environments may represent important areas for mental health policy engagement.

Limitations and future directions

While our model was statistically supported, the cross-sectional nature of our study merits caution when interpreting results; this analysis represents one possible model explaining correlations between polyvictimization, stress-related hippocampal activation and trait anxiety, not a causal relationship. Polyvictimization was reported retrospectively, and it logically follows that polyvictimization leads to increased hippocampal activation/trait anxiety rather than the converse. However, anxious periadolescents may be more likely to perceive themselves as having been victimized and therefore report greater polyvictimization or be more likely to experience further victimization. Additionally, polyvictimization may increase trait anxiety, and this greater trait anxiety may then drive increased hippocampal activation. Longitudinal analyses or animal models are needed to disentangle these complicated relationships.

Furthermore, even though all models statistically controlled for sex, age and medication use, these variables could have impacted our findings. Considering that sex was not associated with polyvictimization, but was related to hippocampal activation and trait anxiety, sex or pubertal status may additionally moderate these relationships. Longitudinal analyses examining connections between neural development and pubertal status or

sex hormones could improve this model. Indeed, a recent moderated mediation analysis showed right hippocampus connectivity mediates the relationship between early life socioeconomic deprivation and trait anxiety only in women (Čermaková et al., 2020). Other research indicates the specific age and developmental stage during which an individual experiences polyvictimization affects their risk for psychiatric symptoms (Dierkhising et al., 2019), which was outside the scope of this analysis. Medication use was coded binarily, but medications may have heterogeneously impacted the brain. We did not exclude subjects on medication in order to recruit a sample exhibiting varied stress regulation profiles and anxiety symptoms, but replication in a medication-naïve sample would further support our results. Relatedly, while this analysis focused on anxiety symptoms, the parent study excluded individuals with PTSD or current depression. Because polyvictimized adolescents are likely to exhibit post-traumatic or depressive symptoms (Haahr-Pedersen et al., 2020), excluding participants with depression or PTSD reduces generalizability of our findings to these populations. Examining negative psychiatric outcomes beyond anxiety, like depressive or PTSD symptoms, is another important next direction. Future research should also consider factors like social support or emotional coping strategies that promote resilience to the neurobiological and psychological impacts of adversity exposure (Holz et al., 2020).

Stress-related activation of brain regions, including the insula and medial prefrontal cortex, involved in stress regulation, emotional processing and executive control (National Academies of Sciences, 2019a); hippocampal volumes (Rao et al., 2010; Hanson et al., 2015; McLaughlin et al., 2016); and activation of/connectivity between the anterior and posterior hippocampus subregions (Xu et al., 2020), may also serve as biological mediators between polyvictimization and trait anxiety. These neurobiological variations are linked to both childhood trauma exposure and later behavioral problems, depression and anxiety (Gorka et al., 2014; Hanson et al., 2015). Furthermore, evidence suggests that both chronic early life stress and acute stress can impact functional connectivity in the default mode, salience and central executive networks (Zhang et al., 2015; Lu et al., 2017; van Oort et al., 2017; Miller et al., 2018). Future research should examine polyvictimization's impact on these networks, as aberrant functional connectivity within and between them is found across psychiatric and neurological disorders and is implicated in neurobiological models of PTSD (Liu et al., 2017; Menon, 2019). While the limbic system is a logical focus for research connecting polyvictimization to the ASR, analyzing other neurobiological factors is necessary to comprehensively understand these relationships.

Prior analysis of this sample demonstrated that the MIST significantly stressed participants, as indicated by greater self-reported stress ratings, increased heart rate and cortisol release (Corr et al., 2021). The MIST is a well-validated fMRI psychosocial stress task which elicits several types of stress arising from pressure to preform, experiencing failure and receiving negative social feedback (Haahr-Pedersen et al., 2020). However, polyvictimized periadolescents may exhibit greater neural responses to stressors more directly related to victimization exposure—e.g. reading personalized scripts describing previous stressful/traumatic events a participant experienced (Elsey et al., 2015)—which should be evaluated by future studies.

Although polyvictimization is consistently associated with psychiatric symptomatology in periadolescents, differences in polyvictimization prevalence estimates and statistical results between studies may arise from inconsistent methods used to define polyvictimization and varied number of questionnaire items included (Haahr-Pedersen et al., 2020). Research has defined polyvictimization by categorizing polyvictims as those with the highest 10% of JVQ scores in their study (Turner et al., 2010; Jackson-Hollis et al., 2017) or highest 10% in each age group within their sample (Finkelhor et al., 2011; Babchishin and Romano, 2014), using cluster analysis or latent variable modeling techniques (Alvarez-Lister et al., 2016; Turner et al., 2016), or totaling the number of JVQ categories/subscales a participant endorsed at least one item on (Hickman et al., 2013; Fisher et al., 2015). This paper used the categorical method, which has the benefit of producing a continuous polyvictimization variable that is able to convey an individual's relative degree of polyvictimization without selecting arbitrary cutoff points to fit the specific distribution of the study population.

Conclusion

This study demonstrates that right hippocampal activation during acute stress partially mediates the relationship between polyvictimization and trait anxiety in periadolescents; polyvictimization exposure was associated with greater stress-related right hippocampal activation, which in turn was associated with heightened trait anxiety. Polyvictimization is known to correlate with wide-ranging psychiatric symptoms (Haahr-Pedersen et al., 2020), but, to our knowledge, this paper represents the first analysis connecting polyvictimization to neural activation. Future longitudinal designs are necessary to determine the causal relationship between these variables and identify other factors impacting these pathways.

Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary data

Supplementary data is available at SCAN online.

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