HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Neuroscience. 2023 July 01; 522: 81–97. doi:10.1016/j.neuroscience.2023.05.005.

Stress-induced changes in autonomic reactivity vary with adolescent violence exposure and resting-state functional connectivity

Heather E. Dark[1,a], **Nathaniel G. Harnett**[1,b,c], **Adam M. Goodman**[1,d], **Muriah D. Wheelock**[1,e], **Sylvie Mrug**[1], **Mark A. Schuster**[2], **Marc N. Elliott**[3], **Susan Tortolero Emery**[4], **David C. Knight, Ph.D.**[1]

[1]Department of Psychology, University of Alabama at Birmingham, Birmingham, AL

[2]Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA

[3]RAND Corporation, Santa Monica, CA

[4]School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX

Abstract

Exposure to violence during childhood can lead to functional changes in brain regions that are important for emotion expression and regulation, which may increase susceptibility to internalizing disorders in adulthood. Specifically, childhood violence exposure can disrupt the functional connectivity among brain regions that include the prefrontal cortex (PFC), hippocampus, and amygdala. Together, these regions are important for modulating autonomic responses to stress. However, it is unclear to what extent changes in brain connectivity relate to autonomic stress reactivity and how the relationship between brain connectivity and autonomic responses to stress varies with childhood violence exposure. Thus, the present study examined whether stress-induced changes in autonomic responses (e.g., heart rate, skin conductance level (SCL)) varied with amygdala-, hippocampus-, and ventromedial prefrontal cortex (vmPFC)-whole brain resting-state functional connectivity (rsFC) as a function of violence exposure. Two hundred and ninety-seven participants completed two resting-state functional magnetic resonance imaging scans prior to (pre-stress) and after (post-stress) a psychosocial stress task. Heart rate and SCL

To whom correspondence should be addressed: David C. Knight, Ph.D. Department of Psychology, The University of Alabama at Birmingham, CIRC 235H, 1720 2nd Ave S. Birmingham, AL 35294, 205-996-6344, knightdc@uab.edu.
[a]Laboratory of Behavioral Neuroscience, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA;
[b]Division of Depression and Anxiety, McLean Hospital, Belmont, MA, USA;
[c]Department of Psychiatry, Harvard Medical School, Boston, MA, USA;
[d]Department of Neurology, University of Alabama at Birmingham School of Medicine;
[e]Department of Radiology, Washington University in St. Louis, St Louis, MO, USA

Declarations of Interest: The authors declare that they have no actual or potential competing financial interests.

Data Statement: Participants in this study did not consent to the release of their data to a third party for reuse. Therefore, we are unable to publicly archive data due to the conditions of our ethics approval. Readers seeking access to the data should contact the corresponding author (David C. Knight). Data can and will only be released to named individuals who agree to collaborate with the principal investigators (i.e., through a formal collaboration agreement).

were recorded during each scan. Post-stress heart rate varied negatively with post-stress amygdala-inferior parietal lobule rsFC and positively with post-stress hippocampus-anterior cingulate cortex rsFC among those exposed to high, but not low, levels of violence. Results from the present study suggest that post-stress fronto-limbic and parieto-limbic rsFC modulates heart rate and may underlie differences in the stress response among those exposed to high levels of violence.

Keywords

functional connectivity; violence exposure; stress; heart rate; skin conductance

INTRODUCTION

Exposure to violence during childhood can have negative effects on emotional health that often persist into adulthood. Specifically, childhood violence exposure has been linked to internalizing symptomology (e.g., depression, anxiety) in both adolescence and adulthood (Hanson et al., 2008; Mrug & Windle, 2010). Further, childhood violence exposure can lead to stress-induced changes in brain regions that include the prefrontal cortex (PFC), hippocampus, and amygdala (Hart & Rubia, 2012; McEwen, 2006; Mead et al., 2010; Moffitt, 2013; Thomason & Marusak, 2017; Thomason et al., 2015). These brain regions form a network responsible for identifying, evaluating, and responding to acute stressors (Herringa et al., 2013; Orem et al., 2019; Thomason & Marusak, 2017). For example, these brain regions are important for modulating the peripheral emotional response to stress (Orem et al., 2019). The connectivity among the PFC, hippocampus, and amygdala appears to be altered by childhood violence exposure, which may disrupt the peripheral emotional response to stress during development and lead to changes in stress reactivity (e.g., a prolonged or blunted response) in adulthood (Arnsten, 2009; Dark et al., 2020; Hart & Rubia, 2012; Mead et al., 2010; Moffitt, 2013; Popoli et al., 2012; Thomason & Marusak, 2017; van Rooij et al., 2020). Further, prolonged stress responses are associated with greater susceptibility to internalizing disorders like depression and anxiety (Southwick et al., 2005). Therefore, examining how childhood violence exposure varies with adult brain function that supports the expression and regulation of the peripheral emotional response may elucidate the mechanisms through which violence exposure varies with stress reactivity.

Repeated childhood violence exposure is associated with alterations in stress-induced hypothalamic-pituitary-adrenal (HPA) axis function (Arnsten, 2009; Bevans et al., 2005; De Bellis, 2005; De Bellis, Baum, et al., 1999; De Bellis, Keshavan, et al., 1999; Hart & Rubia, 2012; Herman et al., 2003; Lupien et al., 2009; Mead et al., 2010). Further, prolonged HPA axis activity has a detrimental impact on brain regions (e.g., PFC, hippocampus, and amygdala) that underlie the emotional response to stress (Arnsten, 2009; Hart & Rubia, 2012; Lupien et al., 2009). For instance, when a stressor occurs, corticotrophin releasing hormone (CRH) stimulates the production of adrenocorticotropic hormone (ACTH), which triggers the production and release of glucocorticoids. Prolonged exposure to elevated glucocorticoid levels can result in neurotoxic effects on brain structure and function, especially during development (Lupien et al., 2009; Popoli et al., 2012). Additionally, prior work has linked childhood violence exposure to structural and functional changes within

these brain regions (Dark et al., 2020; De Bellis, 2005; Harnett et al., 2019; Hart & Rubia, 2012; Mead et al., 2010; Saxbe et al., 2018; Thomason & Marusak, 2017; Thomason et al., 2015). Further, the PFC and hippocampus provide context and direct attentional resources toward stressors, while the amygdala is responsible for important aspects of the peripheral emotional response (Cheng et al., 2006; Cheng et al., 2003; Knight et al., 2005; McEwen & Gianaros, 2010; Orem et al., 2019; van der Werff et al., 2013; Wood et al., 2014). Interactions among the PFC, hippocampus, and amygdala support adaptive responses to stressors, thus altered connectivity among these brain regions may underlie the prolonged autonomic response to stress that is exhibited by those exposed to childhood violence (Beissner et al., 2013; Eisenbarth et al., 2016; Saltzman et al., 2005; van der Werff et al., 2013). Taken together, these findings suggest that repeated childhood violence exposure alters brain regions that underlie the peripheral emotional response. While prior work shows that violence exposure is linked to changes in brain function and stress reactivity (Lambert et al., 2017; Saxbe et al., 2018; Weissman et al., 2020), few studies have examined how violence exposure modulates connectivity among these brain regions and the relationship between functional connectivity and peripheral stress responses.

Reciprocal connections among brain regions such as the PFC, hippocampus, and amygdala are important for healthy emotion regulation (Arnsten, 2009; Thomason & Marusak, 2017; Thomason et al., 2015; van der Werff et al., 2013). The functional connectivity among these regions appears to vary with childhood violence exposure (Arnsten, 2009; Dark et al., 2020; Mead et al., 2010; Miller et al., 2018; Teicher et al., 2016; Thomason & Marusak, 2017; Thomason et al., 2015; van Rooij et al., 2020). For example, adults exposed to childhood maltreatment, including violence, show changes in the resting-state functional connectivity (rsFC) of the PFC, hippocampus, and amygdala (Birn et al., 2014; Dark et al., 2020; Herringa et al., 2013; Jedd et al., 2015; van der Werff et al., 2013). Further, greater childhood maltreatment has been linked to decreased PFC rsFC with the amygdala and hippocampus during adolescence and adulthood (Birn et al., 2014; Burghy et al., 2012; Herringa et al., 2013; Thomason et al., 2015; van der Werff et al., 2013). Thus, changes in the rsFC among these regions may ultimately affect regulation of the emotional response to stress (Arnsten, 2009; Mead et al., 2010; Thomason & Marusak, 2017; Thomason et al., 2015). Taken together, this prior research suggests that the rsFC of brain regions important for emotion regulation (i.e., PFC, hippocampus, and amygdala) varies with childhood violence exposure. However, it is unclear whether stress-induced changes in brain connectivity vary with the peripheral emotional response to acute stress (e.g., acute psychosocial stress).

In addition to childhood maltreatment, functional connectivity (i.e., both task-based and resting state) also varies with acute psychosocial stress in adults (Fan et al., 2015; Gilam et al., 2017; Maron-Katz et al., 2016; Quaedflieg et al., 2015; Veer et al., 2011; Wheelock et al., 2018). Specifically, psychosocial stress is associated with greater PFC-amygdala rsFC in response to acute stress (Fan et al., 2015; Veer et al., 2011). The PFC plays an important role in the regulation of the amygdala's response to stress (Carter & van Veen, 2007; Ochsner et al., 2012; Sylvester et al., 2012; Thomason & Marusak, 2017). Thus, changes in PFC-amygdala rsFC in response to acute stress may reflect top-down modulation of the amygdala by the PFC (Johnstone et al., 2007; Ochsner et al., 2012; Urry et al., 2006). Indeed, prior

work shows that the PFC (e.g., dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC)) regulates the amygdala response to stress (Hare et al., 2009; Johnstone et al., 2007; Morawetz et al., 2017; Ochsner et al., 2012; Urry et al., 2006). Thus, stress-elicited changes in PFC-amygdala connectivity may reflect this regulatory process. Additionally, prior work shows that stress increases the functional connectivity (i.e., both task-based and resting state) of the amygdala with the insula, inferior parietal lobule (IPL), anterior cingulate cortex (ACC), and posterior cingulate cortex (PCC) (Fan et al., 2015; van Marle et al., 2010; Veer et al., 2011). Connectivity among the amygdala, insula, and ACC is important for identifying the salience of emotion-related stimuli and integrating autonomic information (Fan et al., 2015; Menon, 2015). Hence, connectivity among these brain regions may play an important role in coordinating autonomic responses to stress (Thayer & Lane, 2000). Further, stress-elicited increases in the amygdala's rsFC with the insula, ACC, and IPL may also underlie changes in orientation to salient stimuli (Fan et al., 2015; Menon, 2011, 2015). However, to the authors' knowledge no studies have examined whether the relationship between autonomic responses and functional connectivity in response to stress vary as a function of adolescent violence exposure.

The amygdala, cingulate cortex, and insula constitute core regions of the central autonomic network (CAN), a brain network that plays a key role in autonomic function across a number of cognitive and emotional tasks (Beissner et al., 2013). Ultimately, connectivity among these and other regions (e.g., PFC, IPL, and hippocampus) modulates autonomic responses to stressful stimuli (Beissner et al., 2013; Benarroch, 1993; Eisenbarth et al., 2016; Thayer & Lane, 2000). Specifically, prior work shows greater amygdala connectivity with brain regions such as the ACC, PFC, and insula in response to stress (Fan et al., 2015). Additionally, greater amygdala connectivity with the ACC, PFC, and insula is associated with greater skin conductance level (SCL) (Baczkowski et al., 2017). These findings align with other work that has demonstrated that activity within the amygdala, ACC, insula, and PFC varies with autonomic responses to stress. Specifically, autonomic responses (e.g., heart rate and skin conductance) vary with activity in the vmPFC, ventrolateral PFC (vlPFC), dlPFC, ACC, insula, amygdala, parahippocampal gyrus, and hippocampus (Eisenbarth et al., 2016; Orem et al., 2019; Wheelock et al., 2016). Prior work also shows decreased hippocampal connectivity with the IPL and PFC post-stress (Dark et al., 2020; Sun et al., 2020). Further, hippocampus-PFC functional connectivity varies with heart rate (Norton et al., 2013). Thus, neural activity within these brain regions appears to underlie the autonomic response to stress. However, prior studies have not examined stress-induced changes in rsFC that vary with autonomic responses as a function of previous exposure to violence. Determining the relationships among violence exposure, brain connectivity, and autonomic reactivity may provide important new insights into individual differences in brain connectivity and stress reactivity among those exposed to violence.

The present study examined whether stress-induced changes in autonomic responses varied with stress-induced changes in rsFC among those exposed to violence. Acute stressors may elicit a different autonomic response in those who have experienced childhood violence compared to those without childhood violence exposure (Dark et al., 2020; Margolin & Gordis, 2004; Saltzman et al., 2005; Thomason & Marusak, 2017; Thomason et al., 2015). Further, connectivity among brain regions (e.g., amygdala, hippocampus, PFC, ACC,

insula) may underlie this variability in autonomic reactivity (Baczkowski et al., 2017). For example, stress increases amygdala connectivity with the PFC, ACC, and insula, but decreases hippocampal connectivity with IPL and PFC (Baczkowski et al., 2017; Dark et al., 2020; Fan et al., 2015; Sun et al., 2020). Increases in amygdala connectivity with the ACC, PFC, and insula and decreases in hippocampal connectivity with PFC vary with autonomic responses (e.g., heart rate and SCL) (Baczkowski et al., 2017; Norton et al., 2013). Thus, we hypothesized that 1) participants with high adolescent violence exposure would show amygdala rsFC with the PFC, ACC, and insula that varies positively with autonomic responses (e.g., heart rate and SCL) compared to participants who have experienced less violence during adolescence; 2) participants with high violence exposure would show hippocampal rsFC with the PFC and IPL that varies negatively with autonomic responses (e.g., heart rate and SCL) compared to participants who have experienced less violence during adolescence; and 3) participants with high adolescent violence exposure would show vmPFC rsFC with the PFC, ACC, insula, and amygdala that varies positively with autonomic responses compared to those who have experienced less violence during adolescence. Examining stress-induced changes in rsFC and autonomic responses may explain underlying variability in the stress response among those exposed to different levels of violence.

EXPERIMENTAL PROCEDURES

Participants

Three hundred and fifty participants volunteered for the present study. These volunteers were recruited from the Birmingham cohort of the Healthy Passages Study, a longitudinal, multi-site project designed to identify risk and protective factors for adolescent health (Schuster et al., 2012; Windle et al., 2004). The Healthy Passages study originally included 1,594 children at the Birmingham site. Participants in the Healthy Passages study were recruited from the 5th grade classrooms of local public schools, and were assessed at three separate time points (Mean Age±SD – Time 1: 11.20±0.49; Time 2: 13.03±0.50; Time 3: 16.19±0.51). An additional assessment (Mean Age±SD – Time 4: 19.19±0.1.19) followed by a Magnetic Resonance Imaging (MRI) session (Mean Age±SD = 20.13±1.56) were completed as a part of the current study. Analyses (e.g., chi-square and independent samples t-tests) were completed to determine whether there were differences between the MRI sample and the remaining participants from the Birmingham site. There was a significant difference in the proportions of black and white participants ($\chi^2_{(1)} = 12.20$, $p < .001$), with more black participants in the current sample compared to those that did not participate in the present study. There were no differences in the proportions of male and female participants ($\chi^2_{(1)} = 0.06$, p = ns) nor in the amount of violence exposure reported ($t_{(1483)} = 1.30$, p = ns). Fifty-three participants were excluded from the current analyses due to excessive motion, poor data quality, or incomplete data (e.g., not completing both resting state scans). Therefore, 297 young adults (Mean age±SD = 20.12±1.56) from the Birmingham site of the Healthy Passages Study were included in the present study. Exclusion criteria for the present study included standard MRI contraindications (e.g., metallic devices, pacemaker, metallic foreign body), left-handedness, previous head injury, loss of consciousness, spinal cord abnormalities, pregnancy, and history of claustrophobia,

seizures, psychotic symptoms, and blood or circulation disorders (e.g., sickle cell, anemia, diabetes). The present study is a secondary analysis of previously published work (Dark et al., 2020) that included a subset of the data presented in the current study (e.g., MRI, SCL, self-reported stress).

Procedure

The original Healthy Passages study, from which the participants in the present study were recruited, was approved by the Centers for Disease Control and Prevention and the institutional review boards of the original study site institutions. Upon arrival to the laboratory for the present study, participants provided written informed consent as approved by the University of Alabama at Birmingham Institutional Review Board. Participants completed two 6-minute resting-state functional MRI (fMRI) scans during which they were instructed to remain still with their eyes open and not think about anything in particular. Resting-state scans were completed prior to (pre-stress) and after (post-stress) a modified version of the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2005). The MIST is a psychosocial stress protocol designed for functional brain imaging settings and consists of computerized mental arithmetic challenges and social evaluative threat. Participants completed two MIST scans (e.g., a Control scan followed by a Stress scan). The version of the MIST and resting-state fMRI procedures used for the present study have been described in prior work (Dark et al., 2020; Goodman et al., 2016; Wheelock et al., 2016).

Measures

Violence Exposure.—Violence exposure was assessed using the Healthy Passages Violence Exposure measure (Eaton et al., 2006; Mrug et al., 2008; Windle et al., 2004) at each of the four time points described above. Participants reported whether they *witnessed* 1) a threat of physical violence, 2) actual physical violence, and 3) a threat or actual violence involving a weapon; and whether they were a *victim* of 1) a threat of physical violence, 2) actual physical violence, 3) a threat or actual violence involving a weapon, and 4) physical violence inflicting an injury that required medical care in the past 12 months. Participants responded to each item using a 4-point scale ranging from 0 (*never*) to 3 (*many times*). Responses to each item on the scale were averaged across all time points to index violence exposure (Mrug et al., 2008).

Heart Rate.—Cardiac data were collected using an MRI compatible pulse oximeter (Siemens, Munich, Germany). Data were sampled at 50 Hz from the distal phalanx of the index finger of the nondominant hand. The average heart rate (bpm) was computed for both the pre-stress and post-stress resting state scans using QRSTool software. Data from 151 participants were excluded from the analyses due to equipment malfunction or unmeasurable heart rate (e.g., due to low signal-to-noise), in addition to the 53 participants that were excluded for excessive motion or poor quality fMRI data. Thus, all heart rate analyses included 146 participants.

Skin Conductance Level (SCL).—SCL data were collected using MRI compatible physiological monitoring equipment (Biopac Systems; Goleta, CA). Data were sampled at 10 kHz using two disposable radio translucent electrodes attached to the thenar and

hypothenar eminence of the non-dominant hand. Data were filtered using a 1 Hz Infinite Impulse Response (IIR) low pass filter, resampled to 250 Hz, and transformed based on the resistance level set for each participant using Acqknowledge 4.1.0 software. Separate averages of SCL amplitude were acquired for the pre-stress and post-stress resting-state scans. Data acquisition methods were similar to prior work (Knight & Wood, 2011; Wheelock et al., 2016). Data from 26 participants were excluded from analyses due to equipment malfunction or unmeasurable SCL, in addition to the 53 participants that were excluded for excessive motion or poor quality fMRI data. Thus, all SCL analyses included 271 participants.

Self-Reported Stress.—Participants completed a measure of self-reported stress composed of eight statements for both the Control and Stress conditions of the MIST. Participants rated each item on a 5-point scale ranging from 1 (not at all) to 5 (extremely). The scale included four items that were positively worded (e.g., I felt I had control) and four that were negatively worded (e.g., I felt overwhelmed). The total possible score for self-reported stress could range from 8 to 40 for each condition (e.g., Control and Stress) (Wheelock et al., 2016; Wheelock et al., 2018). Cronbach's alphas for the self-reported stress measures were .85 (Control MIST) and .85 (Stress MIST). Self-reported stress data for 13 participants were not collected (n=284).

FMRI

Image Acquisition.—Structural and functional MRI data were collected using 3T Siemens Allegra (n = 241) and Prisma (n = 56) scanners. High resolution T1 weighted structural magnetization-prepared rapid gradient-echo (MPRAGE) images were collected as an anatomical reference for fMRI data: Allegra scanner (TR = 2300 ms, TE = 3.90 ms, flip angle = 12°, FOV = 25.6 cm, matrix = 256 × 256, slice thickness = 1 mm, gap = 0.5 mm); Prisma scanner (TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, FOV = 25.6 cm, matrix = 256 × 256, slice thickness = 1 mm, gap = 0.5 mm). Resting state blood oxygen level dependent (BOLD) fMRI was measured with a gradient-echo echoplanar pulse sequence in an oblique axial orientation (Allegra and Prisma scanners: TR = 2000 ms, TE = 30 ms, flip angle = 70°, FOV = 24 cm, matrix = 64×64, voxel size = 3.75 × 3.75 × 4.0 mm, slice thickness = 4 mm, no gap).

Preprocessing.—Images were preprocessed using the Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software package, FMRIB Software Library (FSL) (Smith et al., 2004), and MRIcron (Rorden & Brett, 2000). Imaging data for pre-stress and post-stress scans were reconstructed (using the Dicom to Nifti option in MRIcron) and reregistered to minimize movement artifact and generate motion parameters for use as covariates in subsequent analyses (using 3dvolreg in AFNI). Images were then corrected for slice timing offset (using 3dTshift in AFNI) and spatially smoothed using a 4 mm full-width-at-half-maximum Gaussian filter (using 3dmerge in AFNI). Timecourse data for tissue-based regressors, including cerebrospinal fluid (CSF) and white matter (WM), were extracted from the functional dataset prior to spatial smoothing (using 3dSeg in AFNI).

Data Analyses

Behavioral.—Three paired-samples t-tests were conducted to assess the stress response. One t-test was conducted to assess differences in heart rate from pre- to post-stress. A second t-test was conducted to assess differences in SCL from pre- to post-stress. The third t-test was conducted to assess differences in self-reported stress between Control and Stress conditions of the MIST.

FMRI. First-level analyses.—Individual subject-level analyses were completed using a multiple linear regression (3dDeconvolve in AFNI) to account for variables of no interest, including 1) mean CSF timecourse, 2) mean WM timecourse, 3) six motion parameters, 4) six motion derivatives, and 5) 111 bandpass timecourses (Bandpass filter: $0.01< f >0.1$ Hz). These variables were regressed out of the gray matter (GM) timecourse for each participant. Time points where >3% of voxels were greater than five times the median absolute deviation (i.e., outliers) of the timeseries were excluded from the individual subject analysis as outliers. Excluded volumes were ignored in subsequent statistical analyses. Participants with less than 80% useable TRs were excluded from further analyses (n = 1). The functional dataset was then normalized to the Talairach and Tournoux stereotaxic coordinate system (Talairach & Tournoux, 1988). For each participant, a sphere (6 mm) was placed in six seed regions – the amygdala (right: x=23 y=−5 z=−15; left: x=−23 y=−5 z=−15); hippocampus (right: x=30 y=−24 z=−9; left: x=−30 y=−24 z=−9); and vmPFC (right: x=12 y=49 z=4; left: x=−12 y=49 z=4), resulting in an average timecourse for each of the six seeds. Twelve (pre-stress and post-stress seed to whole brain correlation analyses for each of the 6 seeds) voxel-wise Pearson correlation analyses were conducted to determine whether the average timeseries of each seed region varied with the timeseries of all other voxels throughout the brain. The correlation analyses resulted in one pre-stress and one post-stress region of interest (ROI)-whole brain correlation map for each ROI (i.e., bilateral amygdala, hippocampus, and vmPFC). Each Pearson correlation value was then converted to a Fisher's Z value to normalize the distribution for each participant, and each map was resampled to 1 mm isotropic voxels.

Group-level analyses.—Linear mixed effects (LME) model analyses (described below) were conducted using 3dLME (Chen et al., 2013) in AFNI to determine whether stress-induced changes in resting-state functional connectivity (rsFC) varied with violence exposure and the psychophysiological response to stress (i.e., heart rate and SCL). A Monte Carlo simulation was conducted (3dClustSim in AFNI), using an uncorrected significance threshold of $p<0.005$ to determine the cluster corrected significance threshold, in an effort to reduce familywise error (FWE). Smoothness was estimated based on the spherical autocorrelation function parameter (3dFWHMx in AFNI) (Cox et al., 2017) by averaging participants' residual timeseries from the first level analysis, resulting in a voxel-wise cluster threshold of 540 mm^3 ($p_{corrected}<0.05$). An additional simulation was performed for small volume correction using masks of the hippocampus and amygdala. These simulations used a voxel-wise threshold of $p<0.005$ and a cluster threshold of 169 mm^3 to achieve a corrected significance threshold of $p<0.05$. Sensitivity analyses were completed to determine whether calculating a cluster extent threshold based on estimates of smoothness generated solely from the hippocampus and amygdala (i.e., instead of smoothness estimates generated

from the whole brain) result in a different small volume cluster extent threshold (see Supplemental Material) that would alter the current findings. Sensitivity analyses revealed that alternative approaches to calculating the small volume cluster extent threshold would not alter the results presented.

Heart Rate.: LME analyses were conducted to determine whether violence exposure and pre- to post-stress differences in rsFC varied with pre- to post-stress differences in heart rate. Violence exposure and heart rate (pre-stress and post-stress) were centered prior to analyses. Condition (pre-stress, post-stress) was entered as a dichotomous within-subjects factor, while heart rate was entered as a continuous within subjects factor, and violence exposure was entered as a continuous between subjects factor. Race, sex, and scanner were entered as covariates of no interest.

SCL.: LME analyses were also conducted to determine whether violence exposure and pre- to post-stress rsFC varied with pre- to post-stress SCL. Violence exposure and SCL data (pre-stress and post-stress) were centered prior to analyses. Condition (pre-stress, post-stress) was entered as a dichotomous within subjects factor, while SCL was entered as a continuous within subjects factor, and violence exposure was entered as a continuous between subjects factor. Race, sex, and scanner were entered as covariates of no interest.

Self-reported Stress.: Given that self-reported stress ratings were acquired with reference to the MIST scans, and not the resting-state scans, LME model analyses examining the association between rsFC and self-reported stress were not completed.

Follow-up analyses.—After completing the LME analyses, follow-up analyses were conducted to further examine significant interactions. For each significant interaction term, the average Fisher's Z values were extracted from each significant volume of activity for both pre-stress and post-stress scans. When the significant interaction included Condition (i.e., a pre- to post-stress difference), two separate follow-up analyses were completed. One analysis used pre-stress rsFC and the other used post-stress rsFC. Analyses for main effects and interactions that did not contain the Condition term averaged pre-stress rsFC and post-stress rsFC to reflect an overall rsFC value, which was then used as the predictor variable for follow-up analyses. The PROCESS macro (Hayes, 2012; Hayes & Preacher, 2013) using SPSS Statistical software was used to compute simple slopes for each significant interaction. Each simple slopes analysis examined the conditional effects of rsFC on heart rate or SCL at two levels of violence exposure: 1 SD below the mean (low) and 1 SD above the mean (high) (Hayes, 2012). In addition, partial correlation analyses were used as a follow-up analysis for significant Condition × Heart rate or Condition × SCL interactions. The partial correlation analyses compared heart rate or SCL to rsFC pre-stress and post-stress while controlling for race, sex, and scanner type. The main effects of condition and violence exposure, and the interaction of condition and violence exposure are not included in the present manuscript as they have been reported previously (Dark et al., 2020).

RESULTS

Behavioral results

Paired samples t-tests were conducted to assess changes in heart rate and SCL from pre- to post-stress. Heart rate (n=146) was greater post-stress (Mean = 67.72, SEM = 0.97) than pre-stress (Mean = 66.50, SEM = 0.88; $t_{(145)} = 1.96$, $p_{\text{one-tailed}} = .026$). Similarly, SCL (n=271) was greater post-stress (Mean = 7.69, SEM = 0.40) than pre-stress (Mean = 6.75, SEM = 0.37; $t_{(270)} = 6.49$, $p_{\text{one-tailed}} < .001$). An additional paired-samples t-test was conducted to compare self-reported stress between the Control and Stress conditions of the MIST. Participants (n=284) reported greater stress for the Stress (M = 25.95, SEM = 0.40) than Control (M = 14.96, SEM = 0.34) condition of the MIST ($t_{(283)} = 22.51$, $p_{\text{one-tailed}} < .001$). A subset of the SCL and stress rating data have been reported previously (Dark et al., 2020). Taken together, these behavioral results suggest that the procedures used in the present study successfully manipulated stress across conditions. Self-reported stress data were collected and described here as a manipulation check to demonstrate that participants subjectively experienced greater stress in the stress than control condition of the MIST.

Heart Rate and rsFC results (n=146)

Amygdala-whole brain rsFC (Table 1)—LME model analyses were completed to determine whether heart rate varied with violence exposure and the rsFC of the amygdala. The following section reports findings from brain regions outlined in our hypotheses about the rsFC of the amygdala and the rest of the brain. Full results from the amygdala LME analyses are reported in Table 1, and follow-up analyses are reported in Table S1 and Figures S1–S4.

Heart rate main effects.: Heart rate varied with the rsFC of the left amygdala with the left dlPFC, left parahippocampal gyrus (PHG), and right hippocampus (Table 1). Specifically, heart rate varied negatively with the left amygdala's rsFC with the PHG and hippocampus, while heart rate varied positively with the left amygdala's rsFC with the dlPFC. Heart rate also varied with the right amygdala's rsFC with the left dlPFC. Specifically, heart rate varied positively with right amygdala rsFC with two separate areas within the left dlPFC (Table S1; Figure S1).

Condition × Heart rate.: Heart rate varied with the change in the left amygdala's rsFC to the right dlPFC from pre- to post-stress (Table 1). Although heart rate did not vary with the rsFC of these regions pre-stress, heart rate varied negatively with left amygdala-right dlPFC rsFC post-stress (Table S1; Figure S2).

Violence exposure × Heart rate.: No significant relationships with rsFC were observed (Table 1; Figure S3).

Condition × Violence exposure × Heart rate.: A Condition × Violence exposure × Heart rate interaction was observed in the left amygdala's rsFC with the right inferior parietal lobule (IPL) (Table 1). Heart rate did not vary with left amygdala-right IPL rsFC pre-stress for those with high or low violence exposure. However, heart rate varied negatively with

left amygdala-right IPL rsFC post-stress for those exposed to high, but not low levels of violence (Table S1; Figure S4). A similar interaction was observed in the rsFC of the right amygdala to the bilateral IPL (Table 1). Specifically, heart rate did not vary with right amygdala-IPL rsFC pre-stress for those with high or low violence exposure. In contrast, right amygdala-bilateral IPL rsFC varied negatively with heart rate post-stress for those exposed to high, but not low levels of violence (Figure 1; Table S1; Figure S4).

Hippocampus-whole brain rsFC (Table 2)—LME model analyses were completed to determine whether violence exposure and hippocampus-whole brain rsFC varied with heart rate. The following section reports findings from brain regions outlined in our hypotheses about the rsFC of the hippocampus and rest of the brain. Full results from the hippocampus LME analyses are reported in Table 2, and follow-up analyses are reported in Table S2 and Figures S1–S4.

Heart rate main effects.: Heart rate varied with the rsFC of the left hippocampus with the left amygdala, right PHG, and bilateral insula (Table 2). Specifically, heart rate varied negatively with the rsFC of the left hippocampus with the left amygdala, right PHG, and bilateral insula (Table S2; Figure S1). Heart rate also varied with right hippocampus rsFC with the bilateral dmPFC, right dlPFC, bilateral posterior cingulate cortex (PCC), left amygdala/inferior putamen, and bilateral insula (Table 2). Specifically, heart rate varied negatively with right hippocampus rsFC with the left amygdala/inferior putamen and bilateral insula, while heart rate varied positively with right hippocampus rsFC with the bilateral dmPFC, right dlPFC, and bilateral PCC (Table S2; Figure S1).

Condition × Heart rate.: Heart rate varied with the change in left hippocampus rsFC to the left dlPFC from pre- to post-stress (Table 2). Specifically, heart rate varied positively with left hippocampus-left dlPFC rsFC pre-stress, but not post-stress (Table S2; Figure S2).

Violence exposure × Heart rate.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. However, relationships with other regions that were not detailed in our hypotheses are outlined in Table 2, Table S2, and Figure S3.

Condition × Violence exposure × Heart rate.: A Condition × Violence exposure × Heart rate interaction was observed in the rsFC of the right hippocampus with the left dmPFC and right anterior cingulate cortex (ACC) (Table 2). Heart rate did not vary with right hippocampus-left dmPFC rsFC pre-stress for those with high violence exposure, but varied positively with right hippocampus-left dmPFC rsFC pre-stress for those with low violence exposure. Heart rate did not vary with right hippocampus-left dmPFC rsFC post-stress for those with high or low violence exposure. Heart rate did not vary with right hippocampus-right ACC rsFC pre-stress for those with high or low violence exposure. In contrast, heart rate varied positively with right hippocampus-right ACC rsFC post-stress for those with high, but not low violence exposure (Figure 2; Table S2; Figure S4).

VmPFC-whole brain rsFC (Table 3)—LME model analyses were completed to determine whether violence exposure and vmPFC-whole brain rsFC varied with heart rate. The following section reports findings from brain regions outlined in our hypotheses about

the rsFC of the vmPFC and rest of the brain. Full results from the vmPFC LME analyses are reported in Table 3, and follow-up analyses are reported in Table S3 and Figures S1–S4.

Heart rate main effects.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. However, relationships with other regions that were not detailed in our hypotheses are outlined in Table 3, Table S3, and Figure S1.

Condition × Heart rate.: Heart rate varied with the change in left vmPFC rsFC with the left IPL from pre- to post-stress (Table 3). Heart rate varied negatively with left vmPFC-left IPL rsFC pre-stress and varied positively with left vmPFC-left IPL rsFC post-stress (Table S3; Figure S2).

Violence exposure × Heart rate.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. However, relationships with other regions that were not detailed in our hypotheses are outlined in Table 3, Table S3, and Figure S3.

Condition × Violence exposure × Heart rate.: No significant relationships with rsFC were observed (Table 3; Figure S4).

SCL and rsFC results (n=271)

Amygdala-whole brain rsFC (Table 4)—LME model analyses were completed to determine whether violence exposure and amygdala-whole brain rsFC varied with SCL. The following section reports findings from brain regions outlined in our hypotheses about the rsFC of the amygdala and rest of the brain. Full results from the amygdala LME analyses are reported in Table 4, and follow-up analyses are reported in Table S4 and Figures S5–S8.

SCL main effects.: SCL varied with left amygdala rsFC with the right amygdala/inferior putamen (Table 4). Specifically, SCL varied negatively with left amygdala rsFC with the right amygdala/inferior putamen (Table S4). SCL also varied with right amygdala rsFC with the bilateral PHG/amygdala, right mid cingulate, and bilateral IPL (Table 4). Specifically, SCL varied negatively with right amygdala rsFC with the bilateral PHG/amygdala and SCL varied positively with right amygdala rsFC with the right mid cingulate and bilateral IPL (Table S4; Figure S5).

Condition × SCL.: SCL varied with the change in left amygdala rsFC with the right PHG/amygdala from pre- to post-stress (Table 4). SCL did not vary with left amygdala-right PHG/amygdala rsFC pre-stress, however SCL varied negatively with left amygdala-right PHG/amygdala rsFC post-stress (Table S4; Figure S6).

Violence exposure × SCL.: A Violence exposure × SCL interaction was observed in the rsFC of the right amygdala with the right IPL (Table 4). SCL varied negatively with right amygdala-right IPL rsFC for those with high violence exposure. In contrast, SCL did not vary with right amygdala-right IPL rsFC for those with low violence exposure (Table S4; Figure S7).

Condition × Violence exposure × SCL.: No significant relationships with rsFC were observed (Table 4; Figure S8).

Hippocampus-whole brain rsFC (Table 5)—LME model analyses were completed to determine whether violence exposure and hippocampus-whole brain rsFC varied with SCL. The following section reports findings from brain regions outlined in our hypotheses about the rsFC of the hippocampus and rest of the brain. Full results from the hippocampus LME analyses are reported in Table 5, and follow-up analyses are reported in Table S5 and Figures S5–S8.

SCL main effects.: SCL varied with left hippocampus rsFC with the bilateral vlPFC, right PHG/amygdala, and left IPL (Table 5). Specifically, SCL varied negatively with left hippocampus rsFC with the vlPFC, PHG/amygdala, and IPL (Table S5; Figure S5). SCL also varied with right hippocampus rsFC with the right amygdala/inferior putamen and bilateral insula (Table 5). Specifically, SCL varied negatively with right hippocampus rsFC with the amygdala/inferior putamen and insula (Table S5; Figure S5).

Condition × SCL.: No significant relationships with rsFC were observed (Table 5; Figure S6).

Violence exposure × SCL.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. Significant connections with regions not detailed in our hypotheses are outlined in Table 5, Table S5, and Figure S7.

Condition × Violence exposure × SCL.: A Condition × Violence exposure × SCL interaction was observed in the rsFC of the right hippocampus with the right IPL (Table 5). More specifically, SCL did not vary with right hippocampus-right IPL rsFC pre-stress for those with high violence exposure, but varied negatively pre-stress for those with low violence exposure. SCL did not vary with right hippocampus-right IPL rsFC post-stress for those with high or low violence exposure (Table S5; Figure S8). A Condition × Violence exposure × SCL interaction was also observed in the rsFC of the left hippocampus with the left amygdala (Table 5). No significant simple slopes were observed for SCL and left hippocampus-left amygdala rsFC (Table S5; Figure S8).

VmPFC-whole brain rsFC (Table 6)—LME model analyses were completed to determine whether violence exposure and vmPFC-whole brain rsFC varied with SCL. The following section reports findings from brain regions outlined in our hypotheses about the rsFC of the vmPFC and rest of the brain. Full results from the vmPFC LME analyses are reported in Table 6, and follow-up analyses are reported in Table S6 and Figures S5–S8.

SCL main effects.: SCL varied with left vmPFC rsFC with the right IPL and left insula. (Table 6). Specifically, SCL varied negatively with left vmPFC rsFC with the IPL and insula (Table S6; Figure S5).

Condition × SCL.: SCL varied with the change in left vmPFC rsFC to the right dmPFC and left dlPFC from pre- to post-stress (Table 6). SCL varied positively with left vmPFC-right

dmPFC rsFC pre-stress, but not post-stress. Further, SCL varied positively with left vmPFC-left dlPFC rsFC pre-stress, but not post-stress (Table S6; Figure S6).

Violence exposure × SCL.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. Significant relationships with the rsFC of other regions that were not detailed in our hypotheses are outlined in Table 6, Table S6, and Figure S7.

Condition × Violence exposure × SCL.: No significant relationships with rsFC were observed within regions outlined in our hypotheses. Significant relationships with other regions that were not detailed in our hypotheses are outlined in Table 6, Table S6, and Figure S8.

RsFC and motion (Tables S7 and S8)—Secondary analyses were completed to determine whether 1) there were differences in motion pre- to post-stress and 2) observed differences in pre- to post-stress rsFC varied with motion (See Supplemental Methods, Results, and Tables S7 and S8).

DISCUSSION

Repeated exposure to violence during adolescence is associated with the development of internalizing disorders in both adolescence and adulthood (Hanson et al., 2008; Hooven et al., 2012; Mrug et al., 2010; Cooley-Quille et al., 2001). The relationship between violence exposure and internalizing symptoms appears to be modulated by functional brain changes that underlie stress reactivity. For example, violence exposure in adolescence alters the connectivity among fronto-limbic and parieto-limbic brain regions that modulate the peripheral emotional response (Dark et al., 2020; Lambert et al., 2017; Saxbe et al., 2018; Fan et al., 2015; Menon, 2015; Saltzman et al., 2005). However, few studies have examined changes in fronto-limbic and parieto-limbic brain regions that vary with autonomic responses among those exposed to violence during adolescence. Changes in the connectivity among these brain regions may underlie differences in the stress response among those exposed to childhood violence (Busso et al., 2017; Harnett et al., 2019; Murali & Chen, 2005; Saltzman et al., 2005). Therefore, the present study examined the relationship between stress-induced changes in rsFC and autonomic responses among young adults exposed to violence during adolescence. Connectivity among the amygdala, hippocampus, PFC, cingulate, IPL and insula varied with heart rate and SCL suggesting that connectivity among these brain regions underlie autonomic activity. We also demonstrated that hippocampal and amygdala rsFC with the dlPFC varied with autonomic activity both before and after an acute psychosocial stress task, suggesting that these regions may underlie stress reactivity. Finally, we demonstrated that differences in fronto- and parieto-limbic rsFC modulate autonomic activity post-stress among those with high violence exposure. These findings suggest that pre- to post-stress changes in rsFC may explain differences in the stress response among those exposed to high levels of violence.

Amygdala, hippocampus, and vmPFC rsFC and autonomic activity.

Connectivity among several brain regions appears to play an important role in the peripheral expression of emotion. For example, we found that the functional connectivity among

regions that include the amygdala, hippocampus, vmPFC, dlPFC, dmPFC, IPL, PHG, insula, and cingulate varied with measures of the peripheral emotional response (i.e., heart rate and SCL). These findings generally suggest that fronto-limbic, fronto-parietal, and parieto-limbic rsFC modulate the peripheral expression of emotion.

The present study also demonstrated changes in pre- to post-stress rsFC among the amygdala, hippocampus, and dlPFC. The dlPFC modulates amygdala and hippocampal activity (Benoit & Anderson, 2012; Benoit et al., 2015; Comte et al., 2016; Delgado et al., 2008; Johnstone et al., 2007; Ochsner et al., 2009; Ochsner et al., 2012), which are important for the peripheral expression of emotion (Cheng et al., 2003; Cheng et al., 2006; Klumpers et al., 2017; Knight et al., 2005; Orem et al., 2019; Wood et al., 2014). Further, the dlPFC appears to modulate the amygdala response to threatening stimuli (Wheelock et al., 2014), and amygdala-dlPFC connectivity is frequently observed during emotion regulation tasks (Banks et al., 2007; Comte et al., 2016; Ochsner et al., 2012). Further, these brain regions have been linked to psychophysiological stress reactivity (Orem et al., 2019; Wheelock et al., 2016). Thus, connectivity between the amygdala and dlPFC may underlie important psychophysiological aspects of the stress response. In the present study, amygdala-dlPFC rsFC varied negatively with heart rate post-stress, but not pre-stress. Decreased heart rate may reflect greater emotion regulation post-stress. Therefore, increased amygdala-dlPFC connectivity may underlie a decreased heart rate response to stress, which may reflect greater post-stress regulation of autonomic activity. In contrast, hippocampal-dlPFC rsFC varied positively with heart rate pre-stress, but not post-stress. Prior work has demonstrated decreased hippocampal-PFC rsFC post-stress and suggests that the hippocampus is important for modulating HPA axis and autonomic activity (Kalisch et al., 2006; Kim and Diamond 2002; Sun et al., 2020; Ulrich-Lai and Herman, 2009). Taken together with prior work, the findings from the present study suggest that hippocampal and amygdala rsFC with the dlPFC may underlie autonomic activity prior to and after acute stress exposure.

Amygdala rsFC, heart rate, and violence exposure.

In the present study, we found that among those with high violence exposure, amygdala-IPL rsFC varied negatively with heart rate. The amygdala is important for responding to salient emotional information including threats (McEwen & Gianaros, 2010; Phelps, 2004; Wood et al., 2014), while the IPL is important for emotion processing and top-down attentional control over the amygdala (Sylvester et al., 2012; Wheelock et al., 2014). Therefore, greater connectivity between the amygdala and IPL in those exposed to high levels of violence may reflect greater attention to salient information. In the present study, post-stress amygdala-IPL rsFC varied negatively with heart rate in those with high levels of violence exposure, suggesting that greater amygdala-IPL rsFC may underlie the modulation of heart rate (e.g., decreased heart rate) post stress in these individuals. In contrast, lower post-stress amygdala-IPL rsFC may reflect poorer modulation of heart rate (e.g., increased heart rate) post stress among those with high violence exposure. Additionally, heart rate did not vary with rsFC pre- or post-stress among those with low violence exposure. The lack of a relationship between amygdala-IPL rsFC and heart rate in those with low violence exposure may suggest that those with low violence exposure recover faster from acute stress exposure. Overall,

differences in amygdala-IPL rsFC may reflect differences in how those exposed to high levels of violence respond to stressors. Further, prior work suggests that those exposed to high levels of violence demonstrate greater stress reactivity, while other studies demonstrate no differences in stress reactivity among those exposed to high levels of violence (Busso et al., 2017; Harnett et al., 2019; Murali & Chen, 2005; Saltzman et al., 2005). Taken together with this prior work, the present findings suggest that differences in amygdala-IPL rsFC may explain why some individuals exposed to high levels of violence show greater reactivity, while others show less reactivity to acute stress (Busso et al., 2017; Harnett et al., 2019; Murali & Chen, 2005; Saltzman et al., 2005).

Hippocampus rsFC, heart rate, and violence exposure.

In the present study, we found that among those with high violence exposure, hippocampus-ACC rsFC varied positively with heart rate post stress. In contrast, there was no relationship among participants with low violence exposure. The ACC is important for modulating autonomic activity (Beissner et al., 2013; Critchley, 2005; Critchley et al., 2003; Kalisch et al., 2006; Thayer & Lane, 2000), while the hippocampus is important for the consolidation of salient emotion-related memories and modulating HPA axis and autonomic reactivity (Goodman et al., 2018; Kalisch et al., 2006; Kim & Diamond, 2002; Sun et al., 2020; Ulrich-Lai & Herman, 2009). Therefore, functional connectivity between the hippocampus and ACC may underlie the modulation of autonomic responses to acute stress. In the present study, increased connectivity between these brain regions was associated with greater heart rate, which suggests a greater autonomic response to acute stress. In contrast, decreased connectivity of the hippocampus and ACC may suggest a decreased stress response (e.g., lower heart rate), and thus greater modulation of autonomic function in response to acute stress. Together, these findings suggest that variability in hippocampus-ACC rsFC may underlie autonomic function among those exposed to high levels of violence.

Strengths and limitations.

The present study has several strengths. First, it included a large community sample of black and white male and female participants, which increases statistical power and generalizability. Additionally, violence exposure data were collected at four time points between ages of 11–19 years, providing a longitudinal assessment of violence exposure throughout adolescence. Another strength of the present study is that it focuses on a single type of violence exposure. Much of the previous research has combined measures of abuse, neglect, and violence exposure into a single index of childhood maltreatment. The combination of different types of violence makes it difficult to isolate the specific effect of each type of violence on the brain. However, the present study is not without limitation, and findings should be interpreted with the following considerations. First, a small volume correction was used to determine whether there were significant stress-induced changes within the amygdala and hippocampus. While small volume correction is important to detect significant activity in smaller brain regions, it is not without limitation. Specifically, cluster thresholding may be inappropriate for smaller brain regions as significant clusters may extend beyond the boundaries of the ROI (Woo et al., 2014). Further, cluster thresholding relies on random field theory which assumes uniform spatial smoothness over the whole brain, therefore, by independently investigating specific ROIs, this assumption

is violated (Brett et al., 2003). Second, although the present study found relationships between adolescent violence exposure and young adult brain connectivity, participants only completed one neuroimaging scan. Therefore, we cannot determine whether relationships between violence exposure and functional brain connectivity represent a change from previous functioning or a preexisting relationship. Future studies should employ longitudinal designs to determine whether violence exposure affects functional connectivity over time.

Conclusion.

Adolescent exposure to violence varies both positively and negatively with the rsFC among regions that are important for emotion regulation. Changes in the connectivity among these brain regions may vary with the emotional response to stress and increase susceptibility to internalizing symptomology. In the present study, violence exposure moderated the relationship between rsFC and autonomic activity post-stress. Specifically, among those with high violence exposure fronto- and parieto-limbic rsFC varied with post-stress heart rate. These findings suggest that fronto- and parieto-limbic rsFC may underlie differences in the stress response among those with high violence exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This research was supported by the National Institutes of Health (Grant number: 1R01 MH098348). Data from the Healthy Passages study was supported by cooperative agreements (CCU409679, CCU609653, CCU915773, U48DP000046, U48DP000057, U48DP000056, U19DP002663, U19DP002664, and U19DP002665) with the Centers for Disease Control and Prevention. The funding sources had no role in the analysis or interpretation of the data, writing of the manuscript, or the decision to submit the paper for publication. S.M., M.A.S, M.N.E, S.T.E, and D.C.K conceptualized and designed the project. H.E.D, N.G.H, A.M.G, and M.D.W. collected data for the project. H.E.D and N.G.H analyzed the data. H.E.D, D.C.K, and S.M. interpreted the data.

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Highlights:

- Emotion expression varies with frontal, parietal, and limbic brain connectivity
- Amygdala-parietal connectivity is associated with autonomic reactivity to stress
- Stress reactivity is linked to amygdala and parietal functional brain connectivity
- The link between connectivity and stress reactivity varies with violence exposure

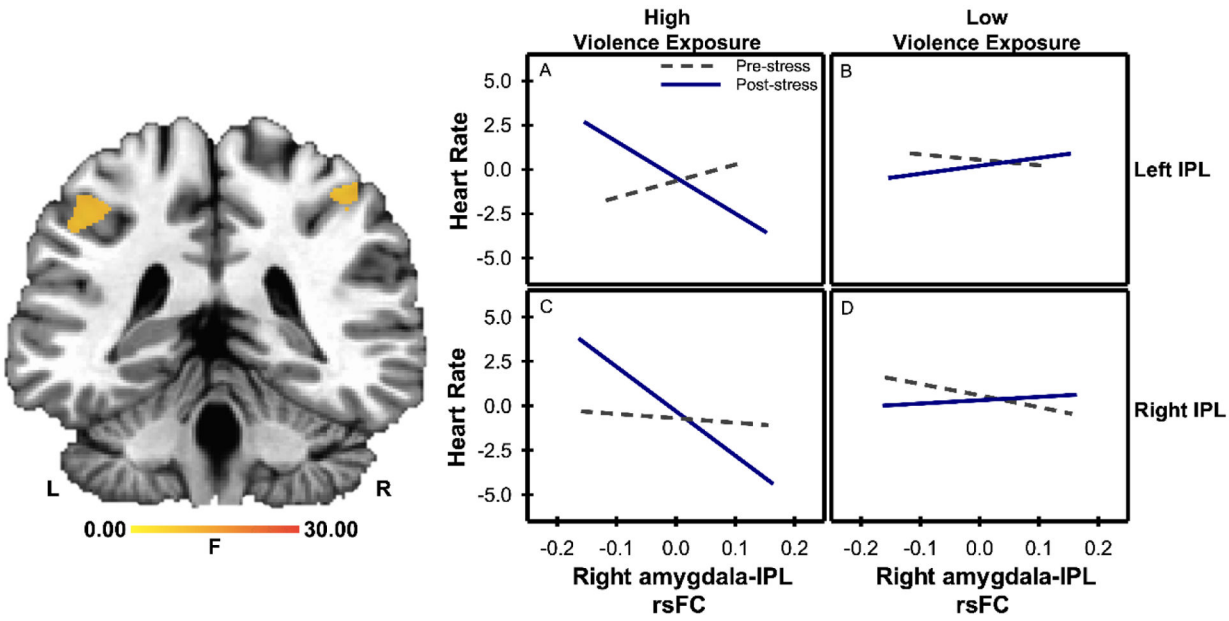

Figure 1. Right amygdala-IPL resting state functional connectivity (rsFC).

The figure depicts the Condition × Violence Exposure × Heart Rate results from the right amygdala linear mixed effects (LME) analysis. The graphs show the simple slopes analysis elucidating the relationship between pre-stress and post-stress right amygdala-IPL rsFC, pre-stress and post-stress heart rate, and violence exposure. (A) Right amygdala-left IPL rsFC did not vary with heart rate pre-stress, but varied negatively with heart rate post-stress for those with high violence exposure. (B) Right amygdala-left IPL rsFC did not vary with heart rate pre- or post-stress for those with low violence exposure. (C) Right amygdala-right IPL rsFC did not vary with heart rate pre-stress, but varied negatively with heart rate post-stress for those with high violence exposure. (D) Right amygdala-right IPL rsFC did not vary with heart rate pre- or post-stress for those with low violence exposure.

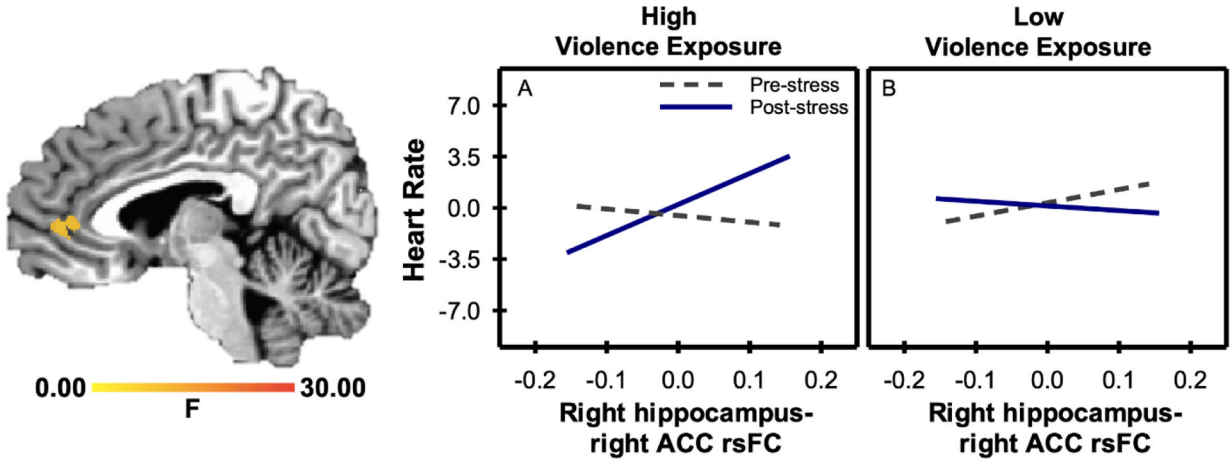

Figure 2. Right hippocampus-right anterior cingulate cortex (ACC) resting state functional connectivity (rsFC).

The figure depicts the Condition × Violence Exposure × Heart Rate interaction from the right hippocampus linear mixed effects (LME) analysis. The graphs show the simple slopes analysis elucidating the relationship between pre-stress and post-stress right hippocampus-right ACC rsFC, pre-stress and post-stress heart rate, and violence exposure. (A) Right hippocampus-right ACC rsFC showed no relationship with heart rate pre-stress, but varied positively with heart rate post-stress for those with high violence exposure. (B) In contrast, right hippocampus-right ACC rsFC did not vary with heart rate pre- or post-stress for those with low violence exposure.

Table 1.

The association among violence exposure, amygdala rsFC, and heart rate

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left Amygdala					mm^3	x, y, z
	Heart rate	dlPFC	Left	18.23	906	−17, 19, 58
		STG	Left	14.32	768	−51, −31, 12
		STG	Right	12.96	679	53, 2, −3
		PHG	Left	17.26	693	−21, 2, −11
		Hippocampus	Right	15.55	259	30, −28, −4
		Cerebellar tonsil	Right	14.54	624	2, −52, −47
	Condition × Heart rate	dlPFC	Right	13.51	582	32, 47, 24
		Precentral gyrus	Left	15.38	608	−41, −11, 43
	Violence exposure × Heart rate[a]	-	-	-	-	-
	Condition × Violence exposure × Heart rate	IPL	Right	15.64	1297	52, −36, 45
Right Amygdala						
	Heart rate	dlPFC	Left	14.21	1102	−18, 21, 57
		dlPFC(2)	Left	22.34	946	−18, 37, 38
		STG	Left	16.32	1786	−46, −21, 6
	Condition × Heart rate	Precuneus	Left	13.99	729	−33, −71, 39
	Violence exposure × Heart rate[a]	-	-	-	-	-
	Condition × Violence exposure × Heart rate	Precentral gyrus	Right	18.03	747	38, −13, 52
		IPL	Right	14.19	759	40, −36, 49
		IPL	Left	18.58	748	−43, −32, 38

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: dlPFC: dorsolateral prefrontal cortex; IPL: inferior parietal lobule; PHG: parahippocampal gyrus; STG: superior temporal gyrus. $p_{FWE}<.05$; df =140.

[a]No significant activity present.

Table 2.

The association among violence exposure, hippocampus rsFC, and heart rate

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left Hippocampus					mm^3	x, y, z
	Heart rate	Insula	Left	18.87	900	−30, 24, 9
		Insula	Right	15.61	2123	44, 9, −4
		STG	Right	18.73	934	44, −20, 7
		Amygdala	Left	14.31	243	−24, −1, −9
		PHG	Right	19.18	730	34, −17, −21
		Precuneus	Left	18.17	726	−8, −45, 64
		Lingual gyrus	Left	20.94	3627	−5, −81, −8
		Culmen	Left	16.63	1828	−30, −47, −20
		Culmen(2)	Left	22.21	869	−3, −36, −19
	Condition × Heart rate	dlPFC	Left	16.70	1272	−24, 45, 9
		Lingual gyrus	Left	15.38	958	−8, −76, 3
	Violence exposure × Heart rate	Precentral gyrus	Right	18.34	567	44, −16, 47
		Lingual gyrus	Left	16.61	613	−20, −55, 1
	Condition × Violence exposure × Heart rate[a]	-	-	-	-	-
Right Hippocampus						
	Heart rate	dmPFC	Left	18.66	2103	−4, 31, 52
		dmPFC	Right	21.81	1261	11, 34, 47
		dlPFC	Right	13.52	653	21, 53, 18
		Insula	Left	21.55	7917	−41, −19, 12
		Insula	Right	28.44	7742	43, −4, 8
		PCC	Left	19.49	557	−2, −53, 14
		PCC	Right	18.84	1556	3, −52, 16
		Amygdala/Inferior putamen	Left	19.36	1609	−23, 1, −8
		Hippocampus	Right	13.76	381	29, −26, −6
		Cuneus	Left	23.93	817	−16, −85, 10
		Culmen	Left	28.29	1940	−9, −34, −26
		Cerebellar tonsil	Right	28.15	1965	3, −47, −43
	Condition × Heart rate[a]	-	-	-	-	-
	Violence exposure × Heart rate[a]	-	-	-	-	-
	Condition × Violence	ACC	Right	14.74	665	4, 42, 5

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
	exposure × Heart rate					
		dmPFC	Left	25.78	1060	−12, 42, 18

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; PCC: posterior cingulate cortex; PHG: parahippocampal gyrus; STG: superior temporal gyrus. $p_{FWE}<.05$; df =140.

[a]No significant activity present.

Table 3.

The association among violence exposure, vmPFC rsFC, and heart rate

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left vmPFC					mm^3	x, y, z
	Heart rate[a]	-	-	-	-	-
	Condition × Heart rate	IPL	Left	13.51	575	−44, −52, 24
	Violence exposure × Heart rate	Cuneus	Right	13.05	758	3, −74, 22
	Condition × Violence exposure × Heart rate[a]	-	-	-	-	-
Right vmPFC						
	Heart rate	ITG	Right	15.12	895	51, −69, 1
	Condition × Heart rate[a]	-	-	-	-	-
	Violence exposure × Heart rate[a]	-	-	-	-	-
	Condition × Violence exposure × Heart rate[a]	-	-	-	-	-

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: ITG: inferior temporal gyrus; IPL: inferior parietal lobule; vmPFC: ventromedial prefrontal cortex. p_{FWE} <.05; df =140.

[a]No significant activity present.

Table 4.

The association among violence exposure, amygdala rsFC, and SCL

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left Amygdala					mm^3	x, y, z
	SCL	STG	Left	22.68	2877	−63, −35, 8
		STG(2)	Left	15.98	1736	−47, 2, 0
		STG	Right	19.39	2197	50, −19, 1
		STG(2)	Right	14.83	981	55, −47, 12
		Amygdala/inferior putamen	Right	20.65	1231	23, 1, −6
		Inferior Putamen	Left	15.95	690	−26, −0, −4
	Condition × SCL	PHG/Amygdala	Right	16.92	547	23, −2, −25
	Violence exposure × SCL[a]	-	-	-	-	-
	Condition × Violence exposure × SCL[a]	-	-	-	-	-
Right Amygdala						
	SCL	STG	Left	23.99	11056	−60, −46, 20
		STG	Right	22.31	4611	55, −25, 5
		Mid Cingulate	Right	24.75	2402	6, −28, 32
		IPL	Left	14.20	893	−39, −54, 39
		IPL	Right	15.35	1405	38, −53, 41
		PHG/Amygdala	Left	15.74	1865	−19, −1, −12
		PHG/Amygdala	Right	16.39	1360	27, 1, −6
		MTG	Right	14.74	1327	53, −46, 9
		MOG	Right	14.24	806	39, −67, −9
		IOG	Left	18.35	678	−34, −89, −5
		Culmen	Right	12.88	620	34, −54, −21
	Condition × SCL[a]	-	-	-	-	-
	Violence exposure × SCL	STG	Left	15.19	562	−49, 6, −7
		IPL	Right	14.58	692	61, −25, 31
		Tuber	Right	13.96	542	41, −66, −27
	Condition × Violence exposure × SCL[a]	-	-	-	-	-

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: IOG: inferior occipital gyrus; IPL: inferior parietal lobule; MOG: middle occipital gyrus; MTG: middle temporal gyrus; PHG: parahippocampal gyrus; SCL: skin conductance level; STG: superior temporal gyrus. $p_{FWE}<.05$; df=265.

[a]No significant activity present.

Table 5.

The association among violence exposure, hippocampus rsFC, and SCL

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left Hippocampus					$_{mm}^3$	x, y, z
	SCL	vlPFC	Left	18.88	1332	−42, 26, 5
		vlPFC	Right	18.52	941	45, 26, 2
		IPL	Left	15.78	794	−59, −48, 23
		Putamen	Left	11.88	970	−24, −2, −1
		PHG/Amygdala	Right	15.04	1213	23, 2, −12
		Cuneus	Left	28.82	6995	−6, −82, 30
		Uvula	Right	14.70	696	17, −68, −23
	Condition × SCL[a]	-	-	-	-	-
	Violence exposure × SCL[a]	-	-	-	-	-
	Condition × Violence exposure × SCL	STG	Right	18.55	758	56, 0, −3
		Amygdala	Left	11.72	202	−23, 0, −21
Right Hippocampus						
	SCL	vlPFC/precentral gyrus/Insula	Left	28.14	13779	−48, −2, 7
		Insula	Right	16.39	2279	34, 24, 10
		Amygdala/inferior putamen	Right	18.54	575	29, 5, −10
		SPL	Right	14.96	1502	31, −69, 50
		Precuneus	Left	27.72	971	−6, −77, 47
		Cuneus	Right	13.75	1039	9, −82, 37
		Postcentral gyrus	Right	19.47	652	64, −19, 24
	Condition × SCL[a]	-	-	-	-	-
	Violence exposure × SCL	STG	Right	18.75	563	57, −1, −4
		Cuneus	Left	17.00	1128	0, −84, 27
		Declive	Left	15.79	1003	−8, −81, −15
	Condition × Violence exposure × SCL	IPL	Right	16.52	815	46, −51, 26

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: IPL: inferior parietal lobule; PHG: parahippocampal gyrus; SCL: skin conductance level; SPL: superior parietal lobule; STG: superior temporal gyrus; vlPFC: ventrolateral prefrontal cortex. p_{FWE} <.05; df=265.

[a]No significant activity present.

Table 6.

The association among violence exposure, vmPFC rsFC, and SCL

Seed Region	Term	Significant connection	Hemisphere	F value (Peak voxel)	Volume	Peak voxel (Talairach Coordinates)
Left vmPFC					mm^3	x, y, z
	SCL	MTG	Right	19.46	2244	41, −57, 8
		Insula	Left	18.11	1004	−47, −3, 5
		IPL	Right	16.26	1220	61, −24, 24
	Condition × SCL	dlPFC	Left	13.69	540	−22, 47, 29
		dmPFC	Right	13.64	735	10, 22, 39
		Culmen	Left	14.84	944	−33, −49, −27
	Violence exposure × SCL	Precentral gyrus	Left	14.76	661	−40, −11, 46
	Condition × Violence exposure × SCL[a]	-	-	-	-	-
Right vmPFC						
	SCL[a]	-	-	-	-	-
	Condition × SCL[a]	-	-	-	-	-
	Violence exposure × SCL	Cerebellum	Right	22.19	944	7, −73, −43
	Condition × Violence exposure × SCL	Cuneus	Right	13.91	545	7, −76, 15

Note. Condition: pre-stress versus post-stress. Interactions that include the Condition variable indicate a difference in Fisher's Z values pre- to post-stress. The main effect for Condition, Violence exposure and the interaction of Condition × Violence exposure have been presented elsewhere (Dark et al., 2020). Abbreviations: dlPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; IPL: inferior parietal lobule; MTG: middle temporal gyrus; SCL: skin conductance level; vmPFC: ventromedial prefrontal cortex. $p_{FWE}<.05$; df=265.

[a]No significant activity present.