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RESEARCH ARTICLE

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Neuroimmune mechanisms connecting violence with internalizing symptoms: A high-dimensional multimodal mediation analysis

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Abstract

Violence exposure is associated with worsening anxiety and depression symptoms among adolescents. Mechanistically, social defeat stress models in mice indicate that violence increases peripherally derived macrophages in threat appraisal regions of the brain, which have been causally linked to anxious behavior. In the present study, we investigate if there is a path connecting violence exposure with internalizing symptom severity through peripheral inflammation and amygdala connectivity. Two hundred and thirty-three adolescents, ages 12–15, from the Chicago area completed clinical assessments, immune assays and neuroimaging. A high-dimensional multimodal mediation model was fit, using violence exposure as the predictor, 12 immune variables as the first set of mediators and 288 amygdala connectivity variables as the second set, and internalizing symptoms as the primary outcome measure. 56.2% of the sample had been exposed to violence in their lifetime. Amygdala–hippocampus connectivity mediated the association between violence exposure and internalizing symptoms ($\widehat{\zeta}_{\text{Hipp}}\widehat{\pi}_{\text{Hipp}} = 0.059$, $95\%\text{CI}_{\text{boot}} = [0.009, 0.134]$). There was no evidence that inflammation or inflammation and amygdala connectivity in tandem mediated the association. Considering the amygdala and the hippocampus work together to encode, consolidate, and retrieve contextual fear memories, violence exposure may be associated with greater connectivity between the amygdala and the hippocampus because it could be adaptive for the amygdala and the hippocampus to be in greater communication following violence exposure to facilitate evaluation of contextual threat cues. Therefore, chronic elevations of amygdala–hippocampal connectivity may indicate persistent vigilance that leads to internalizing symptoms.

KEYWORDS
adolescence, amygdala, depression, hippocampus, immunology, violence

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1 | INTRODUCTION

Violence exposure is a major public health concern for adolescents in the United States. It has been estimated that childhood adversities such as physical abuse and family violence explain nearly 30% of all psychiatric disorders during adolescence (McLaughlin et al., 2012). This is especially worrisome because early adolescence may be a sensitive period for social brain development (Blakemore & Mills, 2014), and is a time where youth are more likely to engage in maladaptive emotion regulation strategies such as rumination, avoidance, and suppression (Cracco et al., 2017), which may be the source of the spike in depression seen during this phase of development (Avenevoli et al., 2015). Further, about 4.2% of adolescents in a representative sample of the United States have been physically abused, 4.4% have been sexually abused, and 8.4% have experienced family violence (McLaughlin et al., 2012). In Chicago, these rates are much worse. For instance, a high proportion of adolescents from Chicago have been exposed to violence in the past year: 15% experienced physical abuse at home, 10% were victims of violence at school, and 12% were victims of violence in their neighborhood (Lanfear et al., 2023; Slopen et al., 2012). Rates of witnessing interpersonal violence were also very high, ranging from 1% to 20% depending on the neighborhood. While little is known about the rates of different types of interpersonal violence exposures across the Chicago area, crime data show that homicide rates vary substantially across the metropolitan area (G. E. Miller et al., 2018). Therefore, the Chicago area is well suited for research to gain a better understanding of the mechanisms connecting violence exposure with psychopathology, which is critical for informing preventative interventions (Cicchetti & Gunnar, 2008).

Violence exposure is also important to study independent from other adversities, such as low socioeconomic status and lack of educational and nutritional resources, because it contributes unique variance in explaining severity of internalizing psychopathology (Lambert et al., 2017; A. B. Miller, Machlin, et al., 2021), and may have dissociable neurobiological underpinnings from other forms of adversity (McLaughlin et al., 2014). McLaughlin et al. (2014) suggested that deprivation and threat constitute two dimensions of adverse experiences that can be expected to have unique effects on the brain and psychopathology based on the animal literature on adversity. The authors postulated that threatening experiences in particular—such as violence exposure—will impact fear learning, disrupting threat circuitry in the brain (e.g., the amygdala, hippocampus, and prefrontal cortex), leading to internalizing symptoms. Herringa et al. (2013) supported this hypothesis, demonstrating that resting-state functional connectivity in threat circuitry mediates the association between maltreatment during childhood and internalizing symptoms during adolescence, an age at which youth are particularly sensitive to social cues (Foulkes & Blakemore, 2016; Haller et al., 2017). Considering both epidemiological and animal studies point toward the importance of violence exposure as a contributor to the onset of internalizing psychopathology during adolescence, it is critical that we gain a better understanding of how violence exposure impacts the brain to lead to more severe internalizing symptoms.

While the majority of research on the biological effects of adversity has focused on the brain, a growing body of literature suggests that the immune system is also mechanistically important for understanding the link between violence exposure and internalizing symptoms (Finegood et al., 2020; Mishra et al., 2023; Nusslock & Miller, 2016; Rasmussen et al., 2020). Recent research has investigated potential pathways by which the immune system can interact with the brain, giving us a better understanding of how these systems may interact after violence exposure (Nusslock & Miller, 2016). Cytokines—proteins secreted by immune cells to manage the response to infection and injury—can spread to the brain via the following systems: (1) active transport; (2) circumventricular organs; (3) leaky regions of the blood–brain barrier; and (4) afferent vagal signaling (Haroon et al., 2012; Irwin & Cole, 2011). Once immune cells accumulate in the amygdala, they modulate interactions between the amygdala and other parts of the brain. Inflammation in the amygdala increases excitatory, but not inhibitory, synaptic transmission from projection neurons, which connect the amygdala with the rest of the brain (Zheng et al., 2021). When these neurophysiological changes are blocked in mice, anxious and depressive behaviors do not develop following inflammation. Further, violence exposure increases amygdala neuronal firing, which can be prevented by blocking microglia—a type of immune cell—from releasing cytokines (Munshi et al., 2020). Human studies suggest that violence exposure alters functional connectivity—an approximation of interactions between brain regions—between the amygdala and a variety of other areas of the brain such as the subgenual cingulate cortex, the orbital frontal cortex, the insula, the medial prefrontal cortex, the posterior cingulate cortex, the dorsal precuneus, and the dorsal anterior cingulate cortex (Cheng et al., 2021; Herringa et al., 2013; Saxbe et al., 2018; Sheynin et al., 2020; Thomason et al., 2015), and that functional connectivity between the amygdala and other areas of the brain, such as the medial prefrontal cortex, the insula, and the orbital frontal cortex, may play a role in anxiety and depression (Burghy et al., 2012; Herringa et al., 2013; Kim et al., 2011; Mao et al., 2020; Roy et al., 2013). Together, these studies suggest that immune cells play an important role in disrupting the amygdala's interactions with other parts of the brain, which in turn can intensify anxiety and depression. Therefore, it is important that we consider neuroimmune pathways when investigating the biological mechanisms connecting violence exposure with psychopathology.

In line with this perspective, Wohleb et al. (2015) identified active monocyte trafficking to the brain as a key mechanism connecting violence with anxious and depressive behaviors. This is important because monocytes are pro-inflammatory. The authors found that if you block pro-inflammatory macrophages—the mature form of a monocyte once it has migrated from blood into tissue—from going to the brain after violence exposure, mice *do not* develop anxious and depressive behaviors. When macrophages are allowed to go to the brain, they selectively accumulate in regions important for threat appraisal, such as the amygdala, the prefrontal cortex, and the hippocampus. These results imply that immune to brain signaling is *necessary* for the development of anxious and depressive behaviors following violence exposure in mice.

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These results converge to suggest that violence exposure increases inflammation (Janusek et al., 2017; Kraynak et al., 2019; Kuhlman et al., 2020; Ferle et al., 2020; Finegood et al., 2020; Rasmussen et al., 2020; G. E. Miller et al., 2022), which in turn alters amygdala connectivity to lead to more severe internalizing symptoms. However, it is also possible that inflammation and amygdala connectivity act independently to explain the association between violence exposure and internalizing symptoms. Considering there are many markers of inflammation (Germolec et al., 2018), and the amygdala is deeply interconnected with most of the brain (Young et al., 1994), standard methods that test indirect effects independently are not optimal for the high-dimensional problem of testing if there are neuroimmune mechanisms that connect violence exposure with internalizing symptoms. Therefore, methods that capitalize on the covariance between potential mediators are superior because they increase our power to detect effects.

Here, we sought to test the hypothesis that violence exposure increases inflammation, which in turn alters amygdala connectivity to lead to more severe internalizing symptoms. Importantly, we used a high-dimensional multimodal mediation model (Zhao et al., 2021), with two sets of mediators: (1) peripheral inflammatory markers (cytokines and cell concentrations) and (2) amygdala connectivity throughout the brain. Using this model, we can determine if there are paths connecting violence exposure with internalizing symptoms through (a) peripheral inflammation (cytokines and cells), (b) amygdala connectivity, or (c) peripheral inflammation and amygdala connectivity in tandem.

2 | METHODS

2.1 | Participants

For our research question, we used the My World My Heart dataset (White et al., 2022; G. E. Miller et al., 2022; G. E. Miller et al., 2021; G. E. Miller, White, et al., 2021; Finegood et al., 2020; Jenkins, Chiang, Vause, Hoffer, Alpert, Parrish, & Wang, 2020; Jenkins, Chiang, Vause, Hoffer, Alpert, Parrish, & Miller, 2020; White et al., 2019). This dataset included violence and mental illness measures, in addition to a broad array of biological metrics. Between January 2015 and June 2019, 277 adolescents were recruited from the Chicago area to participate in the study. Adolescents were intentionally sampled to come from a diverse array of neighborhoods across the Chicago area so as to better represent the socioeconomic spectrum of the city. To be eligible, participants were required to be in eighth grade (typically 13–14 years old) at baseline, English-speaking, and in good health, defined as being (a) not pregnant, (b) without a history of chronic medical illness, (c) without a caregiver-reported history of formal psychiatric diagnosis, (d) free of prescription medications for the past month, (e) without acute infectious disease for 2 weeks, and (f) without functional magnetic resonance imaging (fMRI) scanning contraindications. Notably, few people receive formal diagnoses for psychiatric disorders (Leslie & Chike-Harris, 2018), and parents tend to not be aware of the extent of their child's internalizing symptoms (Cantwell et al., 1997). Each child gave written assent to participate, and a parent or guardian gave written consent. Northwestern University's Institutional Review Board approved the protocol.

Prior to exclusions ($N = 277$), the sample had the following characteristics: 63.90% female, mean age = 13.96 years, SD = 0.544 years. The following number of participants was missing each data type: one was missing violence data, four were missing immune data, 22 were missing imaging data, and no one was missing internalizing symptom data. Twenty-two participants were excluded due to insufficient coverage of the brain mask. After exclusions ($N = 233$), the sample had the following characteristics: 63.95% female, mean age = 14.03 years, SD = 0.549 years. On average, the assessment visit, which included questionnaires and the blood draw, was 26 days before the magnetic resonance imaging (MRI) visit (SD = 32 days). 219 of the assessment visits were done prior to the MRI visit and 14 were done on the same day. See Table 1 for additional sample characteristics after exclusions.

2.2 | Assessment

2.2.1 | Violence

Violence exposure was quantified as *whether or not participants had ever experienced interpersonal violence* using the exposure to violence (ETV) questionnaire (Thomson et al., 2002). The ETV questionnaire has been used in a variety of contexts, from Puerto Rico (Chen et al., 2013), to major metropolitan areas (Murali & Chen, 2005; Oransky et al., 2013; Suglia et al., 2008; Wright et al., 2004), the latter of which resemble the current sample. The types of violence exposure included in the ETV are as follows: (1) family member hurt or killed by a violent act; (2) friend hurt or killed by a violent act; (3) seen someone was attacked with a sharp object; (4) seen someone shot; (5) shoved/kicked/punched during angry argument; (6) attacked with a sharp object; and (7) shot at. Notably, adolescents reported on their own ETV, which is important because adolescents are considered to be the most reliable reporters of their own violence exposure (Mrug & Windle, 2010; Thomson et al., 2002), and previous studies have shown poor agreement between caretakers and adolescents on adolescents' ETV—with kappas ranging from −0.04 to 0.39—such that caretakers consistently underreport violence exposure (Thomson et al., 2002).

2.2.2 | Psychopathology

Symptoms of depression and anxiety were assessed using a 25-item version of the Revised Child Anxiety and Depression Scale (Chorpita et al., 2005). Adolescents were asked to rate how often each item applies to them on a scale from 0 to 3 corresponding to "never," "sometimes," "often" and "always." Items tapped into symptoms of depression (11 items), social phobia (3), panic (3), generalized anxiety (3), obsessions and compulsions (3), and separation anxiety (2). For

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TABLE 1 Sample characteristics by violence exposure.

	Not violence exposed ($N = 102$)	Violence exposed ($N = 131$)	Overall ($N = 233$)
Age			
Mean (SD)	14.0 (0.566)	14.0 (0.537)	14.0 (0.549)
Median [Min, Max]	14.0 [12.3, 15.4]	14.0 [11.9, 15.2]	14.0 [11.9, 15.4]
Sex			
Female	72 (70.6%)	77 (58.8%)	149 (63.9%)
Male	30 (29.4%)	54 (41.2%)	84 (36.1%)
Black			
No	79 (77.5%)	68 (51.9%)	147 (63.1%)
Yes	23 (22.5%)	63 (48.1%)	86 (36.9%)
White			
No	50 (49.0%)	84 (64.1%)	134 (57.5%)
Yes	52 (51.0%)	47 (35.9%)	99 (42.5%)
Hispanic			
No	68 (66.7%)	91 (69.5%)	159 (68.2%)
Yes	34 (33.3%)	40 (30.5%)	74 (31.8%)
BMI percentile			
Mean (SD)	69.7 (25.8)	71.3 (25.6)	70.6 (25.7)
Median [Min, Max]	76.4 [5.30, 99.5]	79.2 [2.80, 99.7]	76.7 [2.80, 99.7]
Puberty category			
Mean (SD)	3.63 (0.757)	3.73 (0.702)	3.68 (0.727)
Median [Min, Max]	4.00 [1.00, 5.00]	4.00 [2.00, 5.00]	4.00 [1.00, 5.00]
IPR			
Mean (SD)	4.38 (3.37)	3.23 (3.92)	3.73 (3.73)
Median [Min, Max]	3.34 [0.202, 15.9]	2.07 [0, 34.5]	2.83 [0, 34.5]

Note: Puberty category levels are 1 = prepubertal, 2 = early pubertal, 3 = midpubertal, 4 = late pubertal, 5 = postpubertal; IPR = income-to-poverty ratio.

instance, symptoms of depression were assessed in part with the following items: "I feel sad or empty," "Nothing is much fun anymore," and "I feel worthless." Other items included "I worry when I think I have done poorly at something," "I worry what other people think of me," and "I have to do some things in just the right way to stop bad things from happening." Exploratory factor analyses on the current sample demonstrate a largely unidimensional structure ($\lambda_1 = 7.00$, $\lambda_2 = 1.67$, $\alpha = 0.89$, $\omega_H = 0.71$), which implies good internal consistency and justifies using a sum score of the 25 items (Widaman & Revelle, 2023).

2.2.3 | Potential confounders

Potential pretreatment confounders included in the sensitivity analysis included age, sex, race, and income-to-poverty ratio. Puberty category—as measured by the Peterson Puberty Scale (Petersen et al., 1988)—was also included, given established associations between the onset of puberty and worsening internalizing symptoms, especially in girls (Crockett et al., 2013; Hayward et al., 1997; Marceau et al., 2012), as a way to reduce variance in the estimator for the association between violence exposure and internalizing symptoms. Note that violence exposure has been shown to predict puberty onset (Colich & McLaughlin, 2022), which could render puberty category an inappropriate control variable as it is a posttreatment covariate that may have been affected by violence exposure (Mendle et al., 2014). Future studies should examine puberty onset as a potential mediator connecting violence exposure with internalizing symptoms. Other variables, such as peer social support and parental warmth, were considered, but were determined to be too likely to be affected by violence exposure, and as such, were deemed inappropriate to include (D. E. Ho et al., 2007). Race was quantified as self-reported racial categories, with indicators for identifying as black, white, or another race included as covariates on which the full matching procedure aimed to achieve balance.

2.3 | Immunology

Antecubital blood was collected between 8:00 a.m. and 10:00 a.m., after an overnight fast, to minimize the influence of dietary intake and circadian variation. Serum levels of inflammatory biomarkers—CRP,

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IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNFα), and urokinase plasminogen activator receptor—were quantified. CRP was measured by high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c 502 analyzer (Roche Diagnostics, Basel, Switzerland) (lower limit of detection, 0.2 mg/L). The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A (Meso Scale Discovery, Rockville, MD) with a Human Proinflammatory Ultra-Sensitive assay kit (Meso Scale Discovery), following the manufacturer's instructions. The kit's lower limits of detection range from 0.19 pg/ml (IL-6) to 0.57 pg/ml (IL-10).

From the same blood draw, major leukocyte subsets (granulocytes, monocytes, lymphocytes) were enumerated with an automated hematology analyzer (AcT 5Diff; Beckman Coulter, Brea, CA). A standardized flow cytometry protocol was used to enumerate populations of classical and nonclassical monocytes (Heimbeck et al., 2010). Antecubital blood was drawn into sodium-heparin Vacutainers (Becton, Dickinson and Company; Franklin Lakes, NJ). After red blood cells had been removed (Pharm Lyse; Becton, Dickinson and Company), the pelleted cells were washed, blocked with normal human serum, and stained with mouse, anti-human monoclonal antibodies against CD14 (fluorescein isothiocyanate), CD16 (phycoerythrin), human leukocyte antigen DR isotype (peridinin chlorophyll protein complex [PerCPCy5.5]), and CD45 (allophycocyanine) (all purchased from Becton, Dickinson and Company). Following a 20-min incubation, the cells were washed and fixed (CytoFix/CytoPerm; Becton, Dickinson and Company) and then incubated for another 20 min. Data were acquired on a Guava 6HT-2L benchtop flow cytometer (Millipore Sigma, Burlington, MA), with 30,000 events collected per specimen, and analyzed using FlowJo software (FlowJo, Ashland, OR). Following previous work (Heimbeck et al., 2010), populations of classical ($CD14^{++}/CD16^{-}$) and nonclassical ($CD14^{++}/CD16^{**}$) monocytes were defined by a sequential gating procedure. In sum, classical monocytes, nonclassical monocytes, neutrophils, lympocytes, eosinophils, and basophils were enumerated and made up the first set of mediators in the analysis, along with serum levels of inflammatory biomarkers. We primarily expected the monocytes to emerge as mechanistically important, however, given that they are proinflammatory (Kapellos et al., 2019; Ong et al., 2018).

2.4 | Neuroimaging

2.4.1 | Acquisition

Imaging data were collected at Northwestern's Center for Translational Imaging on a Siemens Prisma 3T scanner with a 64-channel phased-array head coil. Structural imaging consisted of a high-resolution navigated multiecho magnetization prepared rapid acquisition gradient echo sequence (TR = 2300 ms, TEs = 1.86 ms, 3.78 ms; flip angle = 7°, voxel size = 0.8 mm^3). Three functional acquisitions were used from the current study: a resting-state scan, a task showing angry and happy faces, and a task asking participants to choose to approach or avoid risking money based on a shape that predicted the outcome (G. E. Miller, White, et al., 2021). All functional scans used T2* echoplanar imaging. The resting-state scan utilized a fast repetition time sequence (TR = 555 ms; TE = 22 ms; flip angle = 47°; voxel size = 2.0 mm^3; multiband factor = 8; partial Fourier factor = 6/8; 1110 volumes; 10.2675 min), while the faces (TR = 2000 ms; TE = 20 ms; flip angle = 80°; voxel size = 1.7 mm^{33}; 200 volumes; 6.66 min) and avoidance (TR = 2000 ms; TE = 20 ms; flip angle = 80°; voxel size = 1.7 mm^3; 300 volumes; 10 min) tasks did not.

2.4.2 | Processing

MRI data were processed using fMRIPrep version 21.0.2 (Esteban et al., 2019) and NiLearn version 0.8.1 (Huntenburg et al., 2017) in Python version 3.8.4 (Van Rossum & Drake Jr, 1995). T1-weighted images were corrected for intensity nonuniformity, skull-stripped, segmented, and normalized to the group template (MNI152NLin6Asym) through a subject-specific template. Functional images were slice-time corrected, resampled into their native space, co-registered to the T1-weighted reference image, and then resampled into the standard space by using a composite transformation matrix. After preprocessing was completed, first-level general linear models were fit for the avoidance and faces tasks, including regressors for sources of task-related variance, for the purpose of obtaining near-resting-state data.

The faces task consisted of participants looking at faces that are making expressions at varying degrees of intensity that are either happy or sad. For modeling this task, regressors were every unique combination of the following parameters, derivatives and dispersions of these parameters, and seven drift terms: (1) sex of the face (male and female); (2) emotion of the face (angry and happy); and (3) intensity of the emotion of the face (10, 20, 30, 40, and 50). The passive avoidance task progressed as follows: (1) a shape is presented during the cue phase, which predicts whether a participant would gain or lose money if they chose to risk the money (during this time they also chose whether or not they want to risk money); (2) a blank screen in anticipation of feedback; (3) feedback as to whether or not they lost money, if they chose to risk it; and (4) a blank screen before the next trial. For modeling this task, regressors were the following parameters, derivatives and dispersions of these parameters, and seven drift terms: (1) whether the participant chose to risk points during the cue phase; (2) whether it was during a waiting period after the cue phase; and (3) whether the subject gained or lost money, and how much ($10 or $50), during the feedback phase. For both tasks, the noise model was auto-regressive (1), and the hemodynamic response function was a double gamma. After the general linear model was fit, residuals were obtained from the model to be utilized as near-resting-state data (Al-Aidroos et al., 2012; Fair et al., 2007). This approach helps to identify stable individual differences in brain network organization which are present across task states, and are unreliable with 10 min of data (Kraus et al., 2021).

The preprocessed resting-state data and the residuals from the task models were then detrended, and nuisance regression was

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performed. Nuisance regressors included translation (*x*, *y*, *z*), and rotation (yaw, pitch, roll) parameters, and global signal, and the derivatives, second powers, and second powers of the derivatives (i.e., the Friston expansion terms) (Büchel et al., 1998). Signal from white matter and cerebral spinal fluid were excluded because they were highly correlated with global signal. Volumes were censored if their filtered framewise displacement (fFD) was greater than 0.1, or if there were five or fewer contiguous volumes left after identifying the volumes with fFD > 0.1 to reduce contamination of motion parameters by respiratory artifacts (Fair et al., 2020; Gratton et al., 2020). Censored volumes were then interpolated over using a cubic spline method implemented in SciPy (Virtanen et al., 2020). After interpolation, the fMRI data were band-pass filtered (low pass = 0.08, high pass = 0.009), simultaneously with nuisance regression, as specified in Lindquist et al. (2019). Then, volumes that were identified as needing to be censored previously were removed, and functional connectivity was estimated as the correlation between the time series of the amygdala and 288 of the 300 regions in the Seitzman et al. (2020) atlas. Connectivity matrices from resting-state and task scans were averaged to obtain more reliable estimates of functional connectivity (Kraus et al., 2021). This approach is beneficial because estimates of cortical functional connectivity are not very reliable with only 10 min of resting-state data (the spatial correlation with the group map is approximately 0.7 for 10 min of data, while with 30 min of data, the correlation is 0.8), and the benefits of adding task-regressed functional data outweighs the cost of any remaining task effects (Kraus et al., 2021). Future studies will need to evaluate if the same gains are present for subcortical functional connectivity. Notably, having lots of data is even more important for studying subcortical effects, as the subcortex has a low signal-to-noise ratio (Maugeri et al., 2018). Considering past studies primarily use 5–10 min of resting-state data to estimate functional connectivity metrics (Elliott et al., 2019; Laumann et al., 2015; Noble et al., 2017), the current study represents a major step forward with respect to utilizing more reliable estimates of functional connectivity, considering combining the task and rest data results in 27 min of fMRI data.

The Seitzman et al. (2020) atlas consists of regions from the atlas defined in Power et al. (2011) with additional subcortical and cerebellar regions. This atlas was used because it includes widespread areas of the cortex, subcortex, and cerebellum, and creates nodes such that they are internally coherent and independent, separable units. This is an achievable goal for the Seitzman et al. (2020) atlas in large part because it does not include every voxel of gray matter in at least one parcel, which may result in the atlas excluding voxels where there is substantial interindividual variability. Regions were excluded if 10 or more subjects' brain masks did not include the region.

2.5 | Statistics

We hypothesized that violence exposure increases inflammation, which in turn alters amygdala connectivity to lead to more severe internalizing symptoms. In addition, we explored whether there are paths connecting violence exposure with internalizing symptoms just through inflammation, or just through amygdala connectivity. Note that, while not all of the immune measures are pro-inflammatory, we took an inclusive approach given the high-dimensional nature of the model. However, causal claims are limited by (1) the timing and time frame of some of the measurements (e.g., internalizing symptoms were asked about without a specific time frame); (2) our lack of knowledge about the optimal timing of when to take the various measurements with respect to each other; and (3) the lack of pretreatment confounders (e.g., we do not have measurements of inflammation prior to violence exposure).

The hypotheses were tested using a high-dimensional multimodal mediation model proposed by Zhao et al. (2021) (see Figure 1). This model allows us to identify pathways through a variety of immune markers and amygdala connectivity throughout the brain that explain the association between violence exposure and internalizing symptoms, while minimizing the possibility of false positives by applying a penalization scheme to the regression coefficients and selecting the final model by using the set of hyperparameters that minimize the modified Bayesian Information Criterion, effectively controlling for multiple comparisons (Zhao et al., 2021). Zhao et al. (2021) demonstrated that using the Bayesian Information Criterion resulted both in high sensitivity and high specificity with respect to identifying pathway effects in a series of simulation studies varying the sample size and the dimension of the mediators. In a simulation study using 100 potential mediators in $\mathbf{M}_1$ and $\mathbf{M}_2$, they found that when they used 50 observations, sensitivity equaled 0.668 and specificity equaled 0.998, and that when they used 500 observations, sensitivity equaled 1 and specificity equaled 0.999. For *n* independent and identically distributed observations, the model is as follows:

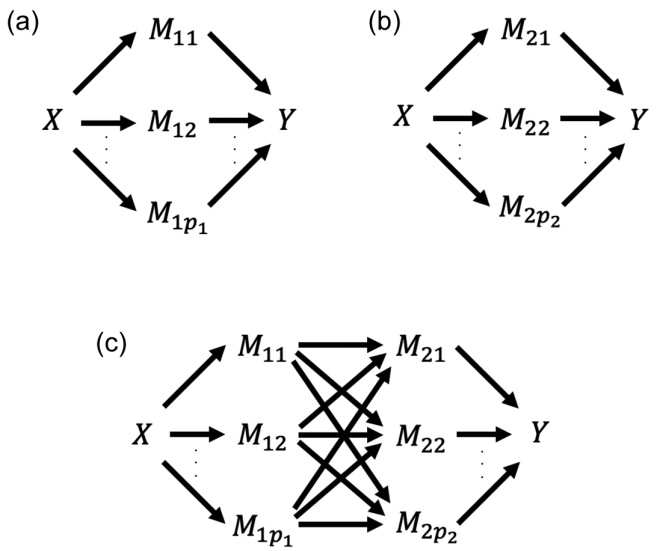

FIGURE 1 Schematic of the indirect paths tested in the high-dimensional multimodal mediation model. Panels show the (a) indirect paths through M_1 (immune variables), (b) indirect paths through M_2 (amygdala connectivity variables), and (c) indirect paths through M_1 and M_2 in tandem.

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$$\mathbf{M}_{1j} = \mathbf{X}\beta_j + \boldsymbol{\varepsilon}_j, j = 1,\ldots,p_1,$$
$$\mathbf{M}_{2k} = \mathbf{X}\zeta_k + \sum_{j=1}^{p_1} \mathbf{M}_{1j}\lambda_{jk} + \vartheta_k, k = 1,\ldots,p_2,$$
$$\mathbf{Y} = \mathbf{X}\delta + \sum_{j=1}^{p_1} \mathbf{M}_{1j}\theta_k + \sum_{j=1}^{p_2} \mathbf{M}_{2k}\pi_k + \boldsymbol{\xi},$$

where $\mathbf{X} \in \mathbb{R}^n$ is a vector of violence exposures, $\mathbf{Y} \in \mathbb{R}^n$ is a vector of internalizing symptom severity scores, $\mathbf{M}_{1j} \in \mathbb{R}^n$ is a vector of immune values for the jth immune variable, and $\mathbf{M}_{2k} \in \mathbb{R}^n$ is a vector of amygdala connectivity values for the kth region. Moreover, the parameters β_j, ζ_k, λ_{jk}, δ, θ_j, and π_k are scalar coefficients, and $\boldsymbol{\varepsilon}_j \in \mathbb{R}^n$, $\vartheta_k \in \mathbb{R}^n$, and $\boldsymbol{\xi} \in \mathbb{R}^n$ are normal random errors with zero means, $j = 1,\ldots,p_1$, $k = 1,\ldots,p_2$. $n =$ the number of subjects, $p_1 =$ the number of immune variables, and $p_2 =$ the number of amygdala connectivity variables. The error terms in $\boldsymbol{\varepsilon}$ and $\boldsymbol{\theta}$ are dependent, due to the associations among the mediators within a modality. Additional analyses were run adjusting for age, sex, race, income-to-poverty ratio, and puberty category. To adjust for these covariates, full matching was performed (Stuart & Green, 2008) using the MatchIt package (Stuart et al., 2011).

After variable selection was performed using the high-dimensional multimodal mediation model, coefficients were estimated with the selected variables, and 95% bootstrapped confidence intervals were generated using lavaan (Rosseel, 2012). Reported effects are those that were both selected by the high-dimensional multimodal mediation model, and were deemed significant via the bootstrap confidence intervals, in line with the conservative approach taken in Zhao et al. (2021). All analyses were run using R version 4.1.0 (R Core Team, 2021).

3 | RESULTS

In the current study, we tested whether markers of peripheral inflammation and amygdala connectivity mediate, in tandem or individually, the association between violence exposure and internalizing symptoms. To do so, we used a high-dimensional multimodal mediation model proposed by Zhao et al. (2021), and tested if the results were robust to potential confounding using a full-matching procedure (Stuart & Green, 2008). Correlations between variables of interest and potential confounders can be found in Figure 2. 56.2% of the sample had been exposed to violence in their lifetime. Of those who had ever been exposed to violence, 100% had been exposed in the past year. The average score on the internalizing symptom measure was 16.29, with values ranging from 0 to 51. Note that, the maximum possible value is 75, which would indicate that the participant constantly experiences all of the enumerated symptoms.

The high-dimensional multimodal mediation model selected one immune variable and five amygdala connectivity variables as important indirect effects connecting violence exposure with internalizing symptoms, but only one of the amygdala connectivity variables remained significant after estimating 95% bootstrap confidence intervals: amygdala–hippocampus connectivity (center of the hippocampus region is $x = 25$, $y = -11$, $z = -23$, which is in the right hemisphere; $\hat{\zeta}_{\text{Hipp}} = 0.293$, 95%$\text{CI}_{\text{boot}} = [0.031, 0.554]$; $\hat{\pi}_{\text{Hipp}} = 0.201$, 95%$\text{CI} = [0.080, 0.311]$; $\hat{\zeta}_{\text{Hipp}}\hat{\pi}_{\text{Hipp}} = 0.059$, 95%$\text{CI}_{\text{boot}} = [0.009, 0.134]$) (see Figure 3). This effect was also robust to potential confounders ($\hat{\zeta}_{\text{Hipp}} = 0.326$, 95%$\text{CI}_{\text{boot}} = [0.079, 0.577]$; $\hat{\pi}_{\text{Hipp}} = 0.208$, 95%$\text{CI} = [0.016, 0.378]$; $\hat{\zeta}_{\text{Hipp}}\hat{\pi}_{\text{Hipp}} = 0.068$, 95%$\text{CI}_{\text{boot}} = [0.008, 0.170]$).

Suitable balance on the covariates was achieved during the full matching process, indicating that the group of adolescents exposed to violence is similar to those who were not after weighting the observations (see Figure 4). Note that better balance occurs when the observations are weighted such that the two groups are more similar on pretreatment covariates. All other paths were either not selected by the high-dimensional multimodal mediation model, or were not

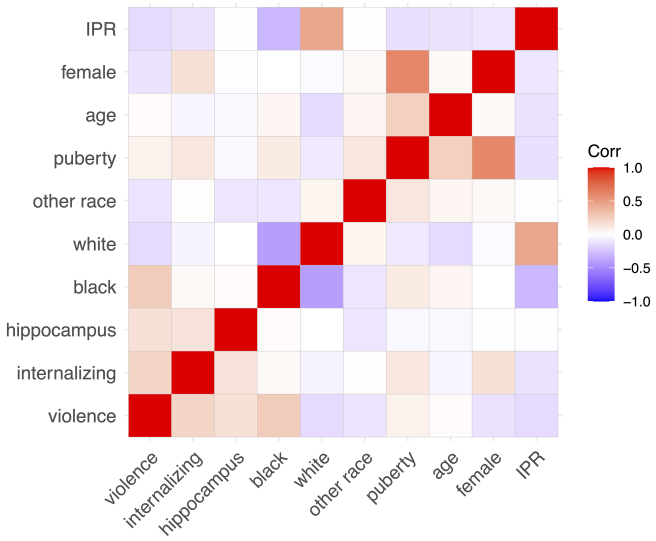

FIGURE 2 Correlations between violence, internalizing symptoms, the selected mediator (amygdala–hippocampus connectivity), and potential confounders. IPR = income-to-poverty ratio. Note that none of the potential confounders are highly correlated with the predictor—violence (maximum in magnitude $r_{\text{violence,black}} = .263$)—or the outcome—internalizing symptoms (maximum in magnitude $r_{\text{internalizing,female}} = .150$)—implying that none of the selected potential confounders had a large confounding effect.

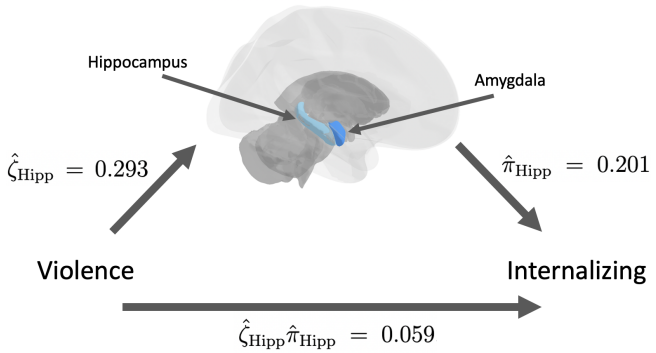

FIGURE 3 Amygdala–hippocampus connectivity mediates the association between violence exposure and internalizing symptoms.

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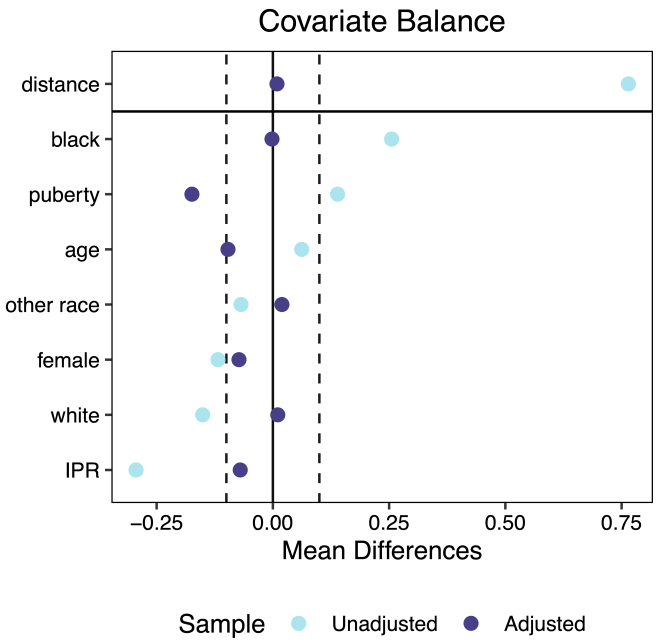

FIGURE 4 Balance was improved by the full matching procedure. After full matching, the absolute standardized mean differences between the group exposed to violence and the group not exposed to violence generally decreased. For instance, before adjustment, absolute standardized mean differences were high on an indicator for being black and income-to-poverty ratio, but after matching, the differences were close to zero.

significant according to the 95% bootstrap confidence intervals. No peripheral inflammatory markers, and no other amygdala connectivity variables, were found to mediate the association independently, nor were any pairs of inflammatory markers and amygdala connectivity variables found to mediate the effect in tandem.

4 | DISCUSSION

In the current study, we proposed and began to investigate a model that suggests that violence exposure increases inflammation, which in turn alters amygdala connectivity to lead to more severe internalizing symptoms. In addition, we tested if there were paths connecting violence exposure with internalizing symptoms just through peripheral inflammation or just through amygdala connectivity. We found evidence that functional connectivity between the amygdala and hippocampus mediated the association between violence exposure and internalizing symptoms, and that this effect was robust to a select group of potential confounders (i.e., age, sex, race, income-to-poverty ratio, and puberty category). However, we did not find evidence that peripheral inflammation mediated the association between violence exposure and internalizing symptoms, nor that peripheral inflammation and amygdala connectivity mediated the association in tandem.

The fact that we found evidence that connectivity between the amygdala and the hippocampus mediates the association between violence exposure and internalizing symptom severity is thought provoking because the amygdala and the hippocampus work together to encode, consolidate, and retrieve contextual fear memories (Chaaya et al., 2018). Violence exposure may be associated with greater connectivity between the amygdala and the hippocampus because it could be adaptive for the amygdala and the hippocampus to be in greater communication following violence exposure to facilitate evaluation of contextual threat cues. While adaptive in acute situations, chronic elevations of amygdala–hippocampus connectivity may indicate persistent vigilance that leads to internalizing symptoms. Being on the lookout for contextual fear cues is protective from danger, but it also puts individuals on edge, leading to more severe internalizing symptoms. The extant literature generally confirms the pattern of increased amygdala–hippocampus connectivity under stress in animal and human studies, highlighting the replicability of these results (de Voogd et al., 2017; Fan et al., 2015; Ghosh et al., 2013; Jedd et al., 2015; Vaisvaser et al., 2013). Ghosh et al. (2013) demonstrated that beta and gamma synchrony was enhanced between the lateral amygdala and the hippocampus following chronic stress in rats. This effect was elaborated upon in human studies showing that maltreatment and stress are associated with greater functional connectivity between the amygdala and the hippocampus (Fan et al., 2015; Jedd et al., 2015; Vaisvaser et al., 2013). Not all studies confirm this effect, however (Cheng et al., 2021). This discrepancy may be explained in part by the fact that many studies using resting-state functional connectivity have short acquisitions (typically 5–10 min), which do not result in reliable estimates of functional connectivity (Elliott et al., 2019; Gordon et al., 2017; Laumann et al., 2015; Noble et al., 2017), especially with regions in the subcortex because these regions have low signal to noise ratios (Robinson et al., 2008). Considering both the amygdala and hippocampus are in the subcortex, longer acquisitions are particularly important for obtaining sufficiently reliable estimates of functional connectivity between these two regions. The current study addresses the issue of short acquisitions by combining task and rest data, giving us more reliable estimates of amygdala connectivity than are typically found in the literature.

The current study is limited by a few key interrelated factors: measurement, timing, and missing potential confounders. The violence measure is limited in that it is simply an indicator of whether or not someone has ever been exposed to a violent event. There are many important nuances to violence exposure, however, such as developmental timing, perpetrator, frequency, severity, controllability, and predictability that may further explain variance in internalizing symptoms. The dimensional model of adversity and psychopathology postulates that the frequency and severity of threatening experiences may play particularly important roles in fear learning, putting youth at risk for more severe externalizing and internalizing symptoms (DeCross et al., 2022; Lurie et al., 2023; Machlin et al., 2019; McLaughlin & Sheridan, 2016). However, no matter the context, dichotomizing a continuous variable will, in most cases, result in a reduction in the observed effect size, and as such, is generally not advisable (Royston et al., 2006). Therefore, we are likely underestimating the magnitude of the effect that violence has on peripheral inflammation, amygdala connectivity, and internalizing symptoms. Future research should (1) develop high-dimensional multimodal mediation models that allow for continuous exposure variables; and

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(2) collect more detailed measures of violence exposure so that the impact of developmental timing, perpetrator, frequency, severity, controllability, and predictability can be evaluated systematically.

The timing of the violent events with respect to inflammation, connectivity and internalizing symptoms is also largely unknown, limiting our ability to discern mechanisms. For instance, it is possible that peripheral inflammation is only elevated for a few weeks or months following violence exposure. If this is the case, we are likely missing the window during which inflammation was elevated among these adolescents, resulting in the current study giving us the false impression that peripheral inflammation is not mechanistically important in connecting violence exposure with internalizing symptoms, a result which others have found (Iob et al., 2022). While the time course of inflammation following violence exposure has not been well characterized, human studies have confirmed increases in peripheral inflammation following acute stressors (Kautz et al., 2020). Further, stimulation and inhibition measures of inflammation may prove to be more mechanistically important, considering cytokines take time to accumulate, while stimulation and inhibition measures are inherently functional, and as such might show the greatest plasticity in response to experience during sensitive periods of development (Lam et al., 2022). Multi-wave longitudinal studies should be conducted to determine the time frames that these variables are elevated with respect to one another so as to inform data collection for future mechanistic studies.

Finally, future studies of neurobiological mechanisms connecting violence exposure with psychopathology should prioritize capitalizing on existing samples following children from gestation so as to capture important potential confounders prior to the onset of violence. For example, it is possible that amygdala–hippocampus connectivity is elevated among individuals who go on to experience violence compared to those who do not. If this is the case, amygdala–hippocampus connectivity represents a risk factor for, opposed to a consequence of, violence exposure. This highlights the importance of identifying pretreatment confounders (Imai et al., 2010), of which the most important are pretreatment levels of the outcome variables of interest.

Despite these limitations, the current study moves the area of neuroimmune mechanisms connecting violence exposure with internalizing psychopathology forward by taking a high-dimensional multimodal mediation approach (Zhao et al., 2021). The high-dimensional multimodal mediation model allowed us to test many potential mechanistic paths connecting violence exposure with internalizing psychopathology, including paths through (1) peripheral inflammation (cytokines and cells), (2) amygdala connectivity, and (3) peripheral inflammation and amygdala connectivity in tandem. Traditional methods of testing mediation would not allow for examining as many possible mechanistic pathways because they do not leverage the covariance between the potential mediators within a modality (e.g., covariance between the amygdala connectivity variables). Considering there are many markers of peripheral inflammation, and the amygdala is deeply interconnected with most of the brain, it is essential to use methods tailored to high-dimensional data when studying neuroimmune mechanisms.

Another strength of the current study is that it rigorously handles potential confounders to achieve balance on pretreatment covariates across the violence-exposed and the nonviolence-exposed groups. Common practice is to include potential confounders as covariates in a multiple regression model, but this method has drawbacks. In order to be able to make causal claims, one must satisfy the strong ignorability assumption, which, in part, states that potential outcomes must be independent of treatment assignment given pretreatment covariates (D. E. Ho et al., 2007). In a multiple regression framework, the assumption becomes that potential outcomes must be independent of treatment assignment given a *linear combination* of pretreatment covariates. Considering it is extremely difficult to verify that you have the correct functional form for treatment assignment, methods that flexibly account for more complicated functional forms are desirable (D. E. Ho et al., 2007; Stuart & Green, 2008). Therefore, utilizing a full matching procedure to obtain balance on pretreatment covariates—as was done in the current study—is a superior method. However, there are many other possible confounders for the relationship between violence exposure and amygdala–hippocampus connectivity, and between amygdala–hippocampus connectivity and internalizing symptoms. This highlights the importance of the sequential ignorability assumption in a mediation model, which states that after controlling for the mediator and the independent variable, the outcome variable is independent of unmeasured confounders that may affect both the mediator and the outcome variable. Unfortunately, we were unable to select potential confounders for the association between amygdala–hippocampus connectivity and internalizing symptoms, due to difficulties with determining temporal ordering. Therefore, whether or not violence causes an increase in amygdala–hippocampus connectivity, which in turn increases internalizing symptoms, remains a largely open question as we have only taken preliminary steps toward addressing potential confounders.

Finally, the current study benefits from the fact that it utilizes a sample of early adolescents because this is the time of life when youth experience a spike in assaults that lead to injury, and assaults committed by peers (Finkelhor et al., 2013), which is important because this is the age when youth are particularly sensitive to social cues (Foulkes & Blakemore, 2016; Haller et al., 2017). Of note, sensitivity to social cues during early adolescence might be a mechanism leading to a spike in the onset of Major Depressive Disorder between the ages of 12 and 14 (Avenevoli et al., 2015; Nyquist & Luebbe, 2020). However, adolescents were excluded if their caregivers reported that they had previously been diagnosed with a psychiatric disorder, limiting the generalizability of the findings. Nonetheless, by evaluating adolescents at a time where they are likely to be early on in the course of developing severe internalizing symptoms, we are well-positioned to better understand how violence exposure impacts neurobiology to put adolescents at risk for internalizing disorders, opposed to observing correlates of chronic mental illness.

To conclude, violence exposure has consistently been linked with worse internalizing symptoms, but extant studies have not rigorously examined many neuroimmune paths by which violence could lead to

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internalizing psychopathology. The current study improved upon prior research by using a high-dimensional multimodal mediation model to test possible paths, thus allowing us to investigate many possible mechanistic pathways simultaneously. Using this model, we found evidence that amygdala–hippocampus functional connectivity is a plausible mechanistic path by which violence exposure confers its risk for internalizing symptoms. Of note, this effect was robust to potential confounders, including income-to-poverty ratio, suggesting that there are unique effects of interpersonal violence exposure on amygdala–hippocampus connectivity and internalizing symptoms independent of socioeconomic status.

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CONFLICT OF INTEREST

The authors declare no relevant conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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