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# Altered development of hippocampus-dependent associative learning following early-life adversity

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ABSTRACT

Little is known about how childhood adversity influences the development of learning and memory and underlying neural circuits. We examined whether violence exposure in childhood influenced hippocampus-dependent associative learning and whether differences: a) were broad or specific to threat cues, and b) exhibited developmental variation. Children (n = 59; 8–19 years, 24 violence-exposed) completed an associative learning task with angry, happy, and neutral faces paired with objects during fMRI scanning. Outside the scanner, participants completed an associative memory test for face-object pairings. Violence-exposed children exhibited broad associative memory difficulties that became more pronounced with age, along with reduced recruitment of the hippocampus and atypical recruitment of fronto-parietal regions during encoding. Violence-exposed children also showed selective disruption of associative memory for threat cues regardless of age, along with reduced recruitment of the intraparietal sulcus (IPS) during encoding in the presence of threat. Broad associative learning difficulties may be a functional consequence of the toxic effects of early-life stress on hippocampal and fronto-parietal cortical development. Difficulties in the presence of threat cues may result from enhanced threat processing that disrupts encoding and short-term storage of associative information in the IPS. These associative learning difficulties may contribute to poor life outcomes following childhood violence exposure.

Childhood adversity is associated with psychopathology (Green et al., 2010; Kessler et al., 2010; McLaughlin et al., 2012), low academic achievement (De Bellis et al., 2013; Leiter and Johnsen, 1997), and poor socioeconomic outcomes in adulthood (Jaffee et al., 2018; Zielinski, 2009). Understanding how childhood adversity influences neurodevelopmental processes is critical for identifying mechanisms that contribute to these long-term outcomes. We examine how exposure to interpersonal violence in childhood—a form of adversity that has particularly strong associations with psychopathology and poor academic functioning (De Bellis et al., 2013; Green et al., 2010; McLaughlin et al., 2012)—influences hippocampus-dependent associative learning, a mechanism that could contribute to poor mental health, academic, and socioeconomic outcomes.

The ability to associate individual features of an event together—such as learning where an event occurred, who and what was present during an event, or the order of events—is critical to forming episodic memories. Structural and functional connectivity between the sensory cortex, hippocampus and surrounding medial temporal lobe (MTL) cortical regions, and prefrontal cortex (PFC) support learning and consolidation of episodic memories (Davachi, 2006; Euston et al., 2012; Lavenex and Amaral, 2000; Squire, 1992). Sensory cortical regions send separate streams of information (e.g., visual, auditory) to MTL cortical regions (perirhinal, parahippocampal, and entorhinal cortices), which project to the hippocampus. During early memory consolidation, the hippocampus and PFC are thought to reactivate regions of sensory cortex that sent the original information during encoding in order to bind a similar pattern of activity across those regions (Hoffman and McNaughton, 2002). Neuroimaging studies demonstrate that the hippocampus, MTL cortical regions, and PFC are involved in associative learning of visual (Henke et al., 1997; Kirwan and Stark, 2004; Sperling et al., 2003), verbal (Jackson and Schacter, 2004), temporal (DuBrow and Davachi, 2016), and contextual (Hayes et al., 2010, 2007) information in adults.

Childhood violence could impact associative learning and neural correlates through two mechanisms. First, violence could influence

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hippocampal and PFC development in ways that contribute to broad associative learning difficulties, regardless of the emotional nature of the stimuli being learned. Rodent research demonstrates the toxic and lasting effects of chronic stress and elevated glucocorticoids early in life on hippocampal neurons (Brunson et al., 2001; Ivy et al., 2010; Lupien et al., 2009). In humans, exposure to violence and other forms of adversity in childhood is associated with smaller volume of the hippocampus and parahippocampal gyrus (Busso et al., 2017; Gold et al., 2016; Hanson et al., 2015; Lambert et al., 2017b; McLaughlin et al., 2016; Teicher et al., 2012). Additionally, early-life stress results in lasting changes in PFC neuronal morphology in rodents (Muhammad et al., 2012), and violence-exposed children exhibit reduced PFC volume and thickness (De Brito et al., 2013; Edmiston et al., 2011; Gold et al., 2016; Hanson et al., 2010; Kelly et al., 2013). Alterations in hippocampal and PFC structure following childhood violence exposure could lead to global associative learning difficulties.

If violence exposure influences hippocampal and PFC development and these regions increasingly contribute to improvements in associative learning with age, then associative learning difficulties following childhood violence may become more pronounced with age. Episodic memory—such as memory of explicitly-encoded scenes and stimulus pairings—improves across childhood and adolescence (DeMaster and Ghetti, 2013; Ghetti et al., 2010; Ofen et al., 2012; Rosen et al., 2018b; Selmeczy et al., 2018). Some studies show developmental variation in the contribution of the hippocampus (Selmeczy et al., 2018) or of different hippocampal sub-regions (DeMaster and Ghetti, 2013; DeMaster et al., 2013) to episodic memory. However, other work shows that positive associations of MTL activation with episodic memory remain constant across development (Guler and Thomas, 2013; Ofen et al., 2012), while PFC involvement in episodic memory increases with development (DeMaster and Ghetti, 2013; DeMaster et al., 2013; Ofen et al., 2012; Selmeczy et al., 2018). We are unaware of research examining age-related variation in how childhood adversity—or violence exposure specifically—influences neural function underlying associative learning.

A second possibility is that childhood violence exposure leads to associative learning difficulties only when a threat cue is present. Violence-exposed children exhibit alterations in threat-related information processing (McLaughlin and Lambert, 2017). For example, violence-exposed children exhibit heightened attention to angry faces (Pollak and Tolley-Schell, 2003; Shackman et al., 2007), which could limit visual processing of surrounding episodic details and interfere with associative encoding. We recently showed that violence-exposed children had poor memory for contextual information presented behind angry faces, but not behind happy or neutral faces (Lambert et al., 2017b). Reductions in contextual memory were associated with lower hippocampal activation and greater hippocampus-ventrolateral PFC functional connectivity during encoding in the presence of angry faces (Lambert et al., 2017b). The ventrolateral PFC is involved in attention orienting (Bishop, 2008; Shiba et al., 2016), suggesting that attentional narrowing on threat cues may have occurred at the expense of hippocampus-dependent processing of broader contextual information. Because heightened attention to angry faces following violence can begin as early as infancy (Cicchetti and Curtis, 2005; Curtis and Cicchetti, 2011), associative learning deficits in the presence of threat would not be expected to change with age.

We examined whether childhood violence was related to associative memory performance and neural recruitment during learning, whether differences in performance and neural recruitment were broad or specific to threat-related cues, and whether associations of violence with performance and neural activation varied across development. Children with and without violence exposure completed an associative learning task with angry, happy, and neutral faces paired with objects during fMRI scanning. Outside the scanner, participants completed an associative memory test for face-object pairings. We expected that violence-exposed children would exhibit associative memory difficulties and reduced hippocampal recruitment during encoding. We also expected that differences would be most pronounced on trials involving angry faces and that threat-specific differences would not vary with age.

## 1. Methods

### 1.1. Sample

A sample of 66 participants aged 6–19 years (M = 13.68 years, SD = 3.23 years; 35 male) participated. The sample was recruited in Seattle, WA between February 2014 and February 2015. Youths were recruited at schools, after-school and prevention programs, medical clinics, and in the general community. To ensure variation in exposure to violence, recruitment targeted neighborhoods with high levels of violent crime, clinics that serve a predominantly low socioeconomic status (SES) area, and agencies that support families exposed to violence (e.g., domestic violence shelters and programs for parents mandated by Child Protective Services to receive intervention). The Institutional Review Board at the University of Washington approved all procedures. Written informed consent was obtained from legal guardians, and youths provided written assent.

One participant (female, 15 years) was excluded due to an incidental finding, one participant (male, 9 years) did not complete the memory task outside the scanner, and four participants (females, 8, 8, and 10 years; male, 9 years) did not complete the encoding task in the scanner. One participant was recruited as an age- and sex-matched control (male, 6 years) for a violence-exposed participant who did not complete the fMRI session, and was excluded to ensure an equal age distribution in both groups.

The final analytic sample included 59 participants aged 8–19 years (M = 14.07 years, SD = 2.93 years; 29 male). See Fig. 1 and Table 1 for demographic characteristics of the final sample according to violence exposure. Participants with violence exposure were matched to control participants on sex and age, *p's* = .43-.67. However, violence-exposed participants were less likely to be White ($p$ = .014), were more likely to be living in poverty ($p$ = .002), and were more likely to have parents with a high school degree or lower ($p$ < .0001) than participants without a history of experiencing violence. Violence-exposed participants also had more frequent exposure to violence ($p$ < .0001) and higher levels of internalizing ($p$ < .0001) and externalizing ($p$ = .001) symptoms than control participants.

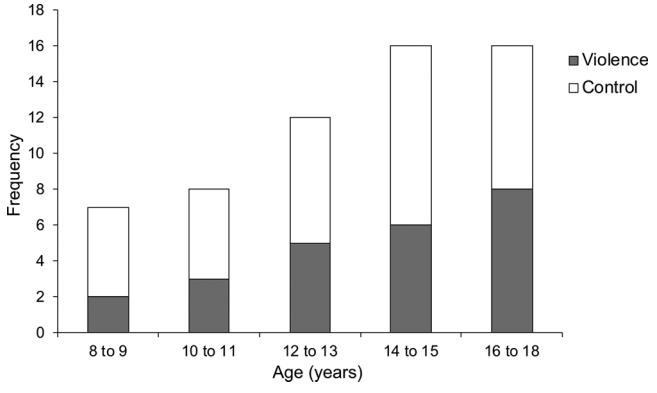


**Fig. 1.** Age distribution of violence-exposed and control participants.

**Table 1**
Distribution of Demographics by Violence Exposure (N = 59).

| | Violence-Exposed (n = 24) | | Controls (n = 35) | | | |
|---|---|---|---|---|---|---|
| | % | (n) | % | (n) | $\chi^2$ | p-value |
| Female | 54.2 | 13 | 48.6 | 17 | 0.18 | .673 |
| Race/Ethnicity | | | | | 12.58** | .014 |
| White | 37.5 | 9 | 68.6 | 24 | | |
| Black | 25.0 | 6 | 0.0 | 0 | | |
| Hispanic | 25.0 | 6 | 14.3 | 5 | | |
| Asian/Pacific Islander | 8.3 | 2 | 14.3 | 5 | | |
| Biracial/other | 4.2 | 1 | 2.9 | 1 | | |
| Poverty[a] | 61.9 | 13 | 19.4 | 6 | 9.78** | .002 |
| Parent(s) With High School Degree or Lower[b] | 59.1 | 13 | 12.1 | 4 | 13.64** | < .0001 |
| | M | (SD) | M | (SD) | t-value | p-value |
| Age | 14.44 | (3.01) | 13.81 | (2.89) | −0.80 | .425 |
| Frequency of Violence Exposure[c,e] | 1.18 | (1.90) | −0.76 | (0.31) | −5.95** | < .0001 |
| Internalizing Symptoms[d] | 57.04 | (9.50) | 46.38 | (10.77) | −3.89** | < .0001 |
| Externalizing Symptoms[d] | 55.58 | (11.21) | 45.56 | (11.21) | −3.36** | .001 |

Notes. Missing data from [a]3 violence-exposed and 4 control participants; [b]2 violence-exposed and 2 control participants; [c]1 violence-exposed participant; [d]1 control participant; [e]Standardized composite of CTQ and SAVE scores; *$p \leq 0.05$, **$p \leq 0.01$.

### 1.2. Associative learning task

#### 1.2.1. Encoding

Participants completed blocks of associative learning (face and object) and item learning (face or object alone) in the scanner (Fig. 2A). Facial stimuli were drawn from a standardized stimulus set (Tottenham et al., 2009) and included angry, happy, and neutral faces. Objects reflected a variety of activities (e.g., book, bike, soccer ball). During associative learning, participants were instructed that the emotional expression on the face reflected how the person felt about the activity (i.e., an angry face meant the person did not like the activity, a happy face meant the person liked the activity, and a neutral face meant the person did not like or dislike the activity) and to remember the pairings. Participants were presented with 30 pairs made up of 30 faces (10 unique people, each with three emotional expressions) and 30 objects. Face-object pairings were randomized and counterbalanced across participants. Each pair was presented 5–6 times, for a total of 176 pair trials. During item learning, participants viewed faces or objects that had not been presented as part of a pair and were instructed to remember the items. Items included 15 faces (5 unique people, each with three emotional expressions) and 15 objects. Each item was presented 5–6 times, for a total of 176 item trials.

Participants completed four runs total. Each run contained 5–6 pair and item blocks. The order of block presentation was pseudorandomized across participants. Pair and item blocks were interleaved with blocks of fixation. Each pair and item block contained 16 trials and lasted 24 s. Each trial involved a pair or item stimulus (1000 ms) and an inter-stimulus interval (500 ms).

#### 1.2.2. Memory

Outside the scanner at least 30 min after encoding, participants completed an associative memory test (Fig. 2B). Participants saw face-object pairs and were instructed to indicate whether a face with a particular emotion was presented with the object during encoding. Trials fell into several categories. Three categories tested associative memory specifically: 30 trials of the correct face-object pairings (10 trials of each emotion type); 15 trials of an incorrect facial identity paired with an object (5 trials of each emotion type); and 15 trials of a correct facial identity but with the incorrect emotion paired with an object (5 trials of each emotion type). All stimuli had previously been presented as part of a pair during encoding. To respond correctly, participants needed to remember the specific pairings between stimuli observed during encoding. We therefore based our calculation of associative memory on these three categories of trials.

Two additional sets of trials were included in the memory test, but did not directly assess associative memory: 15 trials of pairings of novel faces and objects not seen during encoding (5 trials of each emotion type) and 15 trials of pairings where the face and object were previously encoded as single items (5 trials of each emotion type). Because these trial types rely on recognition memory rather than associative memory, we did not include them in our analysis of associative memory.

Associative memory was assessed using discrimination sensitivity ($d'$), which was calculated using the following formula (Stanislaw and Todorov, 1999):

$$d' = \Phi^{-1}(\text{hits}) - \Phi^{-1}(\text{false alarms})$$

We first calculated the hit rate (responding “seen before” on correct trials / total number of correct trials) and the false alarm rate (1 – responding “not seen before” on incorrect trials / total number of incorrect trials). If either the hit rate or false alarm rate was 0 or 1, we converted the score to half of the distance between the next best or worse possible score (e.g., a hit rate or false alarm rate of 30/30 were converted to 29.5/30 and a hit rate or false alarm rate of 0/30 were converted to 0.5/30). Scores were then standardized using an inverse phi function, which converts accuracy scores to the portion of the normal distribution that lies to the left of the z-score. We then calculated $d'$ by subtracting the standardized false alarm rate from the standardized hit rate. A higher $d'$ score indicates a greater ability to distinguish signal (correct trials) from noise (incorrect trials), or a greater distance between the mean of the signal distribution and the mean of the noise distribution in standard deviation units (Stanislaw and Todorov, 1999). We calculated $d'$ overall (regardless of emotion) and separately for trials involving faces with different emotional expressions (angry, happy, and neutral).

### 1.3. Violence exposure

Our main analyses were based on a dichotomous variable of violence exposure, consistent with prior work in this sample (Lambert et al., 2017b; Rosen et al., 2018a). An interview and a self-report questionnaire were used to assess exposure to violence. Specifically, we assessed exposure to physical abuse, sexual abuse, and domestic

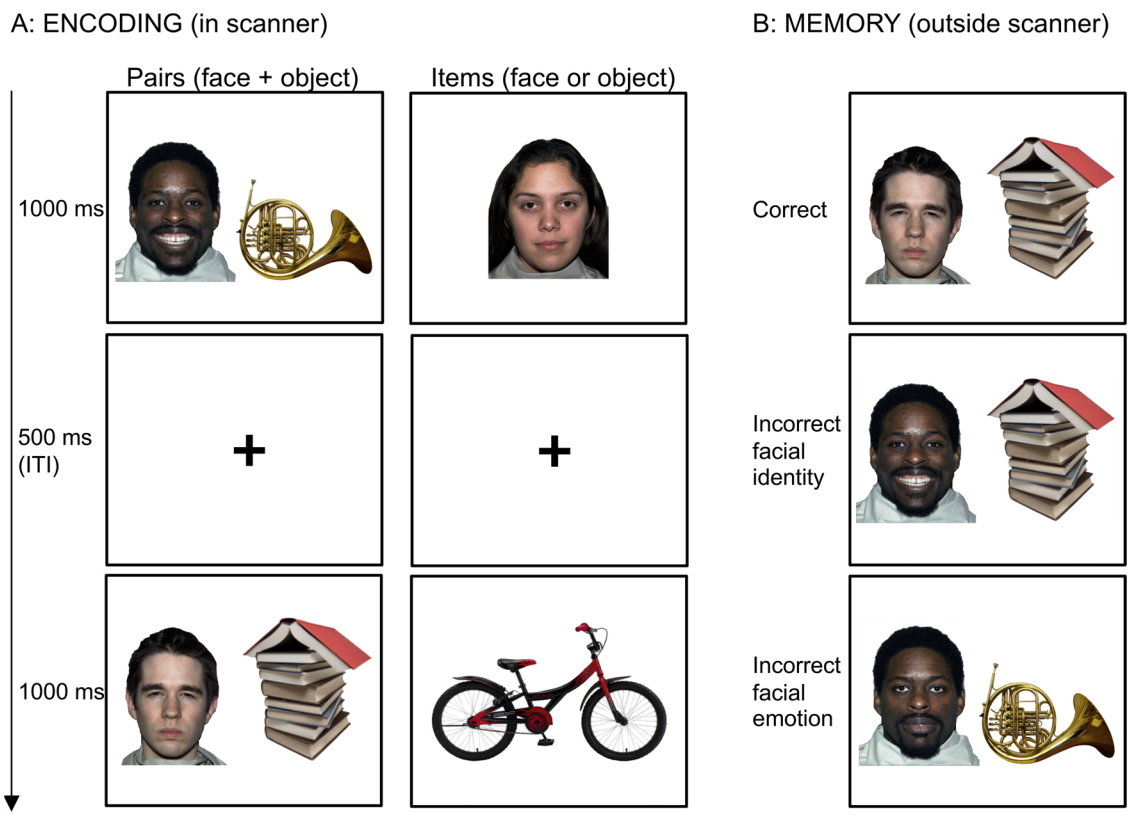


**Fig. 2.** Associative learning task. (A) Encoding. Participants were presented with pairs of stimuli (face and object) or single items (face or object alone). (B) Memory. Participants saw pairings of faces and objects. Face-object pairings fell into several categories that tested associative memory specifically: correct pairings (i.e., correct facial identity and emotion paired with object), incorrect facial identity (i.e., incorrect facial identity paired with object), and incorrect facial emotion (i.e., correct facial identity but incorrect emotion paired with object). Participants indicated whether or not the emotional faces were presented with the correct object.

violence—experiences that involve a high degree of threat. The Childhood Experiences of Care and Abuse (CECA) is an interview that assesses multiple aspects of caregiving experiences (Bifulco et al., 1997). We used the CECA to assess physical abuse, sexual abuse, and witnessing domestic violence (i.e. directly observing violence directed at a caregiver). Inter-rater reliability for CECA maltreatment reports is excellent, and multiple validation studies suggest high agreement between siblings on reports of maltreatment (Bifulco et al., 1997). We also administered the Childhood Trauma Questionnaire (CTQ), a self-report questionnaire that assesses the frequency of child maltreatment exposure, including physical and sexual abuse, and has sound psychometric properties (Bernstein et al., 1997). Participants were classified as violence-exposed if they reported physical or sexual abuse or witnessing more than two incidents of domestic violence on the CECA or if they received a score on the CTQ physical and sexual abuse subscales above a validated threshold (Walker et al., 1999). A total of 40.7% of the sample (n = 24) was violence-exposed based on this definition.

We also conducted analyses examining frequency of violence exposure. Frequency of violence exposure was based on the CTQ and the Screen for Adolescent Violence Exposure (SAVE) measure (Hastings and Kelley, 1997). The CECA was not used in our continuous measure of violence as all responses are coded as simply present or absent. The SAVE assesses the frequency of direct and indirect exposure to violence in school, home, and neighborhood settings and has high internal consistency, test-retest reliability, and discriminant and convergent validity with objective local crime data (Hastings and Kelley, 1997). Scores of 12 items assessing direct exposure to violence (e.g., being mugged, seeing someone get shot) were summed to produce a violence exposure score, with higher scores indicating greater exposure. Items used to produce the score were distinct from items on the CTQ (i.e., SAVE items assessing physical abuse were excluded). Following prior work (Lambert et al., 2017a), the total violence score was calculated by standardizing the CTQ physical and sexual abuse score and SAVE score for each participant and summing the standardized scores. The total violence score reflects frequency of exposure to multiple forms of violence, including abuse, domestic violence, and community violence.

### 1.4. Potential confounders

#### 1.4.1. Poverty

A parent or guardian completed a measure on socioeconomic status. The income-to-needs ratio was calculated by dividing total household income by the 2015 U.S. census-defined poverty line for a family of that size, with a value less than one indicating that a family was living below the poverty line.

#### 1.4.2. Parental education

A parent or guardian also provided information about highest educational attainment of each parent figure (i.e., less than high school, high school degree, some college, college degree, or graduate degree). We created a dichotomized variable reflecting whether or not all parent figures in the home had a high school degree or lower.

#### 1.4.3. Psychopathology

Participants completed the Youth Self Report (YSR), a measure of internalizing and externalizing symptoms (Achenbach, 1991). The YSR scales are among the most widely used measures of youth emotional and behavioral problems and use extensive normative data to generate age-standardized estimates of symptom severity. Higher scores indicate worse symptom severity. Symptom scores on the Child Behavior Checklist (Achenbach, 1991), the parent-report version of the YSR, were used for two participants with missing YSR data.

### 1.5. Image acquisition and processing

Before scanning, children 12 years and younger and any older children exhibiting anxiety about the scan were trained to minimize head movements in a mock scanner. They watched a movie with a head-mounted motion tracker that stopped playing if a movement of over 2 mm occurred. This method has been shown to significantly reduce head motion once children are in the scanner (Raschle et al., 2012). All participants wore a head-stabilizing device to further restrict movement in the scanner.

Scanning was performed on a 3 T Phillips Achieva scanner at the University of Washington Integrated Brain Imaging Center using a 32-channel head coil. T1-weighted multi-echo MPRAGE volumes were acquired (TR = 2530 ms, TE = 1640–7040 μs, flip angle = 7°, FOV = 256 $mm^2$, 176 slices, in-plane voxel size = 1$mm^3$). Blood oxygenation level dependent (BOLD) signal during functional runs was acquired using a gradient-echo T2*-weighted EPI sequence. Thirty-seven 3 mm thick slices were acquired parallel to the AC-PC line (TR = 2000 ms, TE = 25 ms, flip angle = 79°, FOV = 224 × 224, matrix size = 76 × 74, slice gap = .6 mm). Prior to each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

Pre-processing and statistical analysis of fMRI data were performed in a pipeline using Make, a software development tool that can be used to create neuroimaging work-flows that rely on multiple software packages (Askren et al., 2016). Pre-processing included realignment, slice-time correction, and spatial smoothing with a Gaussian kernel (6-mm full width at half maximum [FWHM]). Data were inspected for artifacts, and volumes with motion > 1.5 mm or change in signal intensity above 75% + 1.5 * IQR were excluded from analysis. Six rigid-body motion regressors were included in person-level models. Person- and group-level models were estimated in FSL. Regressors of the time series in white matter and the ventricles were included in person-level models to reduce noise associated with physiological fluctuations. Following estimation of person-level models, the resulting contrast images were normalized into standard space. Specifically, functional data were registered to each participant's T1 scan and were then normalized to an intermediary pediatric template of the same age as our sample (NIH Pediatric MRI Data Repository: https://pediatricmri.nih.gov/nihpd/info/index.html), then from the pediatric template to MNI space. Anatomical co-registration of the functional data with each participant's T1-weighted image was performed using surface-based registration in FreeSurfer verion 5.3 (Dale et al., 1999), which provides better alignment than other methods in children (Ghosh et al., 2010). Normalization was implemented in Advanced Normalization Tools (ANTs) software, version 2.1.0 (Avants et al., 2011).

No participants were excluded entirely for motion. We excluded runs if they had > 20% volumes with framewise displacement > 1.5 mm or > 3-SD change in signal intensity. One run from one participant (female, 8 years), two runs from one participant (male, 8 years), and three runs from one participant (female, 12 years) were removed from analyses due to excessive motion during those runs. For the included runs across all participants, the maximum percentage of volumes excluded from the analysis was less than 20% (mean = 5.66%, range = 0–19.23%, and median = 4.81% of volumes excluded).

### 1.6. Statistical analysis

#### 1.6.1. Potential confounders

To evaluate whether potential confounders should be controlled for in our analysis examining the associations of violence with memory performance and neural recruitment, we evaluated whether any of our potential confounders (i.e., poverty, parental educational attainment, internalizing symptoms, and externalizing symptoms) were associated with both violence exposure (Table 1) and behavioral and neural outcomes, including associative memory and BOLD signal in regions-of-interest (hippocampus, intraparietal sulcus [IPS], and middle frontal gyrus [MFG]) during associative learning (Supplemental Table 1). Factors that were associated with both violence and an outcome were controlled for in analyses examining that particular outcome. Additionally, age and sex were included as covariates in analyses if they were associated with the outcome of interest.

#### 1.6.2. Associative memory

A univariate analysis of variance (ANOVA) was used to examine associative memory based on violence exposure. To examine age-related variation in the association of violence exposure with behavioral performance, we examined whether age and violence interacted in predicting associative memory performance using linear regression. Variation in associative memory by emotion condition was examined with a repeated-measures ANOVA with emotion of the facial cue (angry, happy, and neutral) as a within-subjects factor and violence exposure as a between-subjects factor. We also examined whether the interaction between emotion and violence exposure on associative memory varied across age with a repeated-measures ANOVA with emotion as a within-subjects factor and violence exposure and age as between-subjects factors.

#### 1.6.3. Neural function

*1.6.3.1. Whole-brain analysis.* fMRI data processing was performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Regressors were created by convolving a boxcar function of phase, duration, and amplitude 1 with the standard double-gamma hemodynamic response function for each block type (pair blocks and item blocks) as well as for each trial type by emotion (angry, happy, and neutral pairs; angry, happy, and neutral face items). A general linear model was constructed for each participant. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Jenkinson et al., 2012). Individual-level estimates of BOLD activity for each contrast of interest were submitted to group-level random effects models.

Our first analysis identified clusters associated with associative learning overall (pair blocks > item blocks) in the entire sample. Our second analysis examined differences in neural recruitment during associative learning overall (pair blocks > item blocks) for participants exposed to violence versus control participants. Our third analysis examined whether the association of violence with neural recruitment during encoding overall (pair blocks > item blocks) varied by age. Our fourth analysis examined whether group differences varied across emotion conditions. To do so, we conducted a repeated-measures ANOVA to test an emotion (angry, happy, neutral) x group (violence, control) interaction on BOLD activation during encoding. Because FSL does not have the functionality to perform a within-subjects ANOVA, we conducted this analysis in AFNI using the 3dLME function. Pre-processed individual-level contrasts were converted for use in AFNI (Chen et al., 2013), and the results from 3dLME were cluster-corrected using the 3dClustSim tool in AFNI. A significant interaction was followed up with univariate ANOVAs examining violence-related group differences in BOLD activation during encoding separately for each emotion condition (angry pairs > angry face items; happy pairs > happy face items; neutral pairs > neutral face items) in FSL. There were a total of 57–60 pair trials and 29–30 face item trials per emotion, and object items were not included in this analysis.

We applied a cluster-level correction threshold to our models run in FSL FLAME (cluster-level threshold of $z > 2.3$, $p < .01$) that is not associated with elevated risk of either false positive or negative findings in simulations (Eklund et al., 2016). In AFNI, cluster thresholding was determined using the AFNI 3dFWHMx program to obtain the mixed-model spatial autocorrelation function parameters from the data residuals and the AFNI 3dClustSim program to generate Monte Carlo simulations that determine the appropriate cluster size for a given voxel-wise p-value ($p < 0.005$) and overall alpha level (alpha < 0.05). Based on these simulations, clusters larger than 30 voxels were considered significant.

*1.6.3.2. ROI analysis*. Because the hippocampus supports associative learning (Davachi, 2006), we additionally used a region-of-interest (ROI) analysis to examine hippocampal activation during encoding. An ROI was created by masking functional activation during associative learning overall (pair blocks > item blocks) from the whole-brain analysis in the entire sample with a structural mask of the hippocampus from the Harvard-Oxford Sub-cortical Atlas in FSL (20% threshold; separately for right and left hemispheres). This approach isolated the portion of the hippocampus that was active during associative learning in the whole sample. Parameter estimates for each block type (pair blocks and item blocks) as well as for each trial type by emotion (angry, happy, and neutral pairs; angry, happy, and neutral face items) were extracted for each participant. We used the same analysis approach for examining violence-related differences in hippocampal ROI activation during associative learning and whether differences varied by facial emotion or by age as we did for associative memory performance. Additionally, linear regression was used to examine associations of hippocampal BOLD signal during encoding overall (pair blocks > item blocks) with associative memory overall.

*1.6.3.3. Task-based functional connectivity analysis*. We conducted a whole-brain psychophysiological interaction (PPI) analysis (O'Reilly et al., 2012) to identify violence-related differences in functional connectivity of the hippocampus with other brain regions during associative learning overall (pair blocks > item blocks) and separately by emotion condition (angry pairs > angry face items; happy pairs > happy face items; neutral pairs > neutral face items). We did not find regions that exhibited functional connectivity with the hippocampus that survived cluster correction and did not conduct further functional connectivity analyses.

### *1.6.4. Violence exposure frequency*

We examined whether frequency of violence exposure was associated with associative memory and hippocampal ROI activation during encoding using the same analysis approach described above. Frequency of violence exposure was not related to associative memory or hippocampal activation, *p*'s = .08 - .84. We therefore only report results involving violence exposure as a dichotomous variable below.

## 2. Results

### *2.1. Associative learning and associated neural activation*

#### *2.1.1. Associative memory*

The mean *d'* score was positive (M = 1.04, SD = 0.81) indicating that associative memory performance overall was above chance in the entire sample. Associative memory varied by emotion condition, F (2,116) = 5.63, $p$ = .005. Post-hoc tests revealed better associative memory on angry trials (M = 1.20, SD = 0.94) than neutral trials (M = 0.89, SD = 0.80), $p$ = .015.

#### *2.1.2. Neural activation during associative learning*

Whole-brain analysis of activation during associative learning overall (pair blocks > item blocks) in the entire sample revealed 8 clusters of activation (Table 2, Fig. 3A). The first cluster spanned bilateral parietal (intraparietal sulcus [IPS], precuneus), occipital (cuneus, calcarine cortex, lingual gyrus, and occipital pole), and temporal (fusiform gyrus, parahippocampal gyrus, posterior cingulate, and middle and inferior temporal gyri) cortices, and also included the hippocampus, thalamus, brainstem, and cerebellum. There were six clusters in the PFC. Three clusters included right and left precentral gyrus and middle frontal gyrus (MFG), with one of the clusters extending into the left superior frontal gyrus and one extending into the right inferior frontal gyrus (IFG). One cluster included bilateral superior frontal gyrus, supplementary motor cortex, and paracingulate and cingulate gyri. Two clusters spanned right and left temporal pole into the orbitofrontal cortex. One cluster in the right temporal cortex included the superior and middle temporal gyri and extended into the supramarginal gyrus.

**Table 2**
Regions of the Brain with Significant Blood Oxygen Level-Dependent (BOLD) Activation During Encoding (Pair Blocks > Item Blocks) in the Entire Sample (N = 59).

| Anatomical Region | x | y | z | voxels | z-max | p-value |
|---|---|---|---|---|---|---|
| Lingual Gyrus (R, L)<br>Calcarine Cortex (R, L)<br>Middle Temporal Gyrus (R, L)<br>Inferior Temporal Gyrus (R, L)<br>Intraparietal Sulcus (R, L)<br>Lateral Occipital Cortex (R, L)<br>Posterior Cingulate (R, L)<br>Precuneus (R, L)<br>Cuneus (R, L)<br>Parahippocampal Gyrus (R, L)<br>Fusiform Gyrus (R, L)<br>Occipital Pole (R, L)<br>Thalamus (R, L)<br>Brain-Stem (R, L)<br>Hippocampus (R, L)<br>Cerebellum (R, L) | −6 | −82 | 0 | 34,388 | 10.1 | < .0001 |
| Precentral Gyrus (L)<br>Middle Frontal Gyrus (L) | −38 | −2 | 44 | 1,371 | 5.85 | < .0001 |
| Paracingulate Gyrus (R, L)<br>Superior Frontal Gyrus (R, L)<br>Supplementary Motor Cortex (R, L)<br>Cingulate Gyrus (R, L) | −8 | 12 | 50 | 898 | 4.86 | < .0001 |
| Precentral Gyrus (R)<br>Middle Frontal Gyrus (R)<br>Superior Frontal Gyrus (R) | 40 | −2 | 44 | 513 | 4.81 | < .0001 |
| Inferior Frontal Gyrus (R)<br>Precentral Gyrus (R)<br>Middle Frontal Gyrus (R) | 36 | 8 | 24 | 259 | 4.13 | < .0001 |
| Temporal Pole (L)<br>Orbitofrontal Cortex (L) | −52 | 16 | −20 | 196 | 4.26 | < .001 |
| Temporal Pole (R)<br>Orbitofrontal Cortex (R) | 40 | 22 | −34 | 195 | 4.12 | < .001 |
| Superior Temporal Gyrus (R)<br>Supramarginal Gyrus (R)<br>Middle Temporal Gyrus (R) | 46 | −34 | 6 | 176 | 4.44 | .002 |

Notes. L = left; R = right.

### *2.2. Violence-related differences in associative learning*

#### *2.2.1. Associative memory*

Violence exposure was unrelated to associative memory overall, F (1,56) = 1.59, $p$ = .21 (Fig. 4A).

#### *2.2.2. Neural activation during associative learning*

We first evaluated differences in neural activation during associative learning for participants exposed to violence versus control participants in a whole-brain analysis. Violence-exposed participants exhibited greater activation during encoding overall (pair blocks > item blocks) in one cluster in the right PFC, which included the precentral gyrus, MFG, and superior frontal gyrus (Table 3).

Second, we completed ROI analysis to examine the influence of

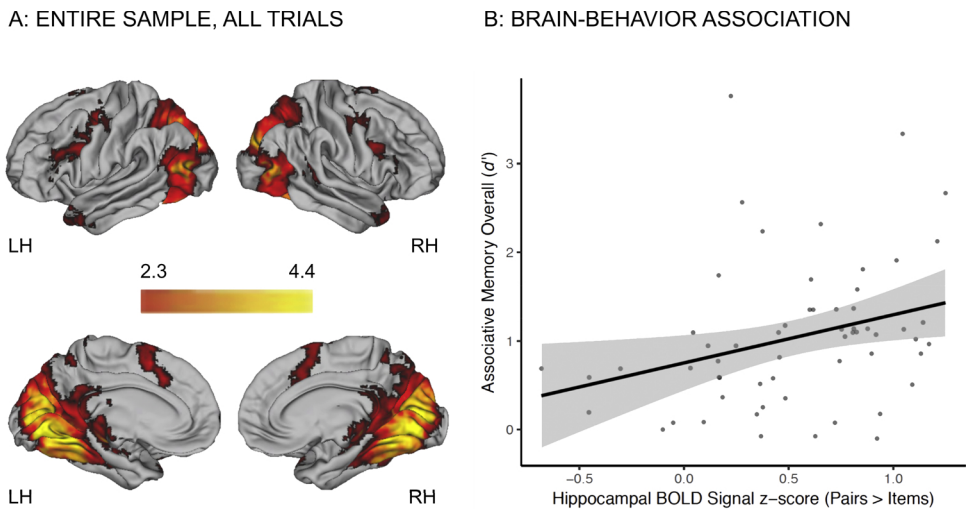


**Fig. 3.** (A) Regions of the brain with significant blood oxygen level-dependent (BOLD) activation during encoding (pair blocks > item blocks) in the entire sample (N = 59). (B) Hippocampal BOLD signal during encoding (pair blocks > item blocks) and associative memory performance overall; β = 0.30, $p$ = .021.

violence exposure on activation in bilateral hippocampus (BOLD units presented as z-scores). Violence exposure was associated with hippocampal activation during associative learning overall (pair blocks > item blocks), $F(1,57) = 4.90$, $p$ = .031. Participants exposed to violence had less hippocampal activation (M = 0.38, SD = 0.47) than control participants (M = 0.64, SD = 0.41). Greater hippocampal

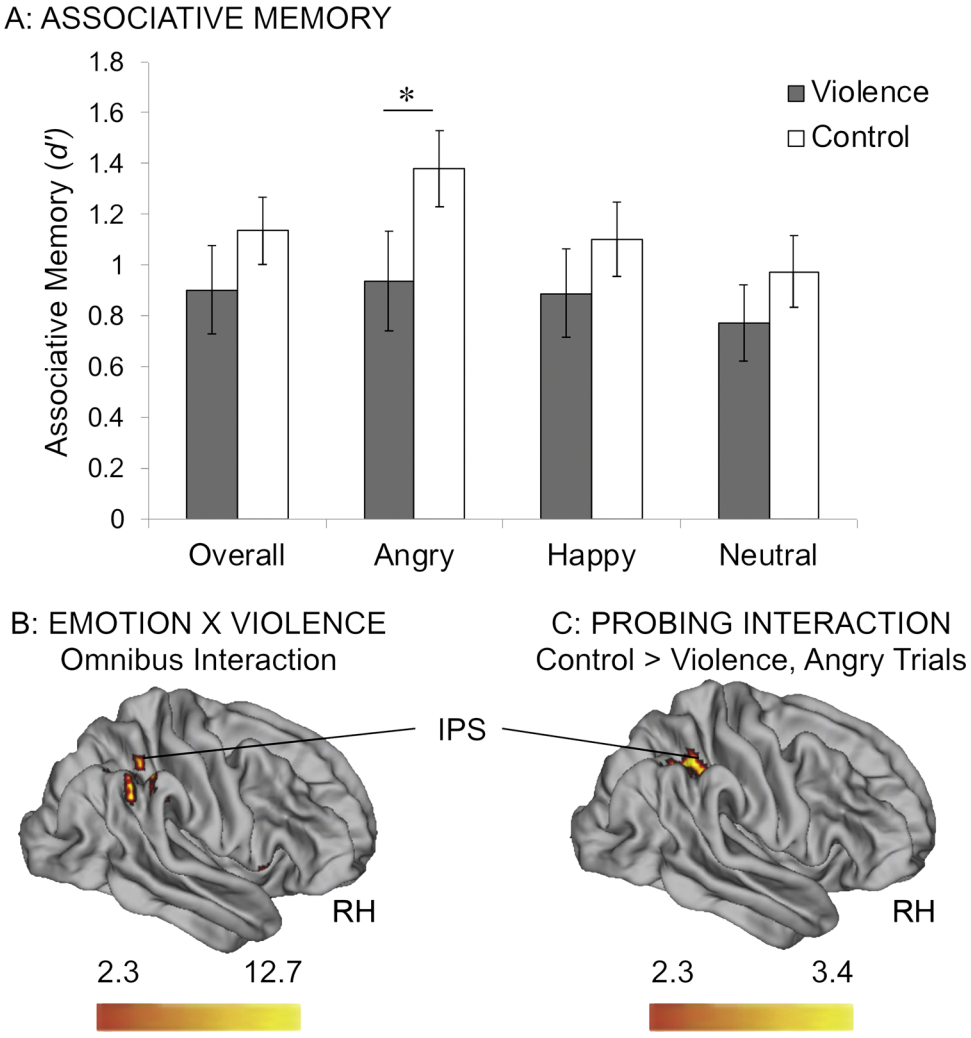


**Fig. 4.** (A) Violence exposure and associative memory performance overall and separately by emotion condition. (B) Emotion x violence exposure omnibus interaction on BOLD signal during encoding. (C) Follow-up univariate ANOVA examining differences in BOLD signal during encoding on angry trials (angry pairs > angry face items) for participants exposed to violence versus control participants. IPS = Intraparietal sulcus.

**Table 3**
Differences in BOLD Signal During Encoding (Pair Blocks > Item Blocks) for Participants Exposed to Violence Versus Control Participants.

| Controls > Violence | | | | | | |
|---|---|---|---|---|---|---|
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| – | – | – | – | – | – | – |
| **Violence > Controls** | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Precentral Gyrus (R)<br>Middle Frontal Gyrus (R)<br>Superior Frontal Gyrus (R) | 38 | −4 | 58 | 187 | 4 | .001 |

Notes. L = left; R = right.

**Table 4**
Age x Violence Exposure Omnibus Interaction in BOLD Signal During Encoding (Pair Blocks > Item Blocks).

| Controls > Violence[a] | | | | | | |
|---|---|---|---|---|---|---|
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Intraparietal Sulcus (L)<br>Postcentral Gyrus (L) | −18 | −48 | 60 | 178 | 4.38 | .002 |
| **Violence > Controls[b]** | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Middle Frontal Gyrus (R)<br>Frontal Pole (R) | 46 | 30 | 38 | 143 | 3.42 | .010 |

Notes. L = left; R = right; aClusters where the association of age with activation is greater for control participants than violence-exposed participants; bClusters where the association of age with activation is greater for violence-exposed participants than control participants.

BOLD signal during encoding overall (pair blocks > item blocks) was associated with better associative memory performance overall, $\beta = 0.30$, $p = .021$ (Fig. 3B).

### 2.3. Violence-related differences in associative learning vary across development

We next evaluated whether the effect of violence on behavioral and neural outcomes varied across age (i.e., violence x age interactions).

#### 2.3.1. Associative memory

The association between violence exposure and associative memory overall varied significantly as a function of age, $\beta = -0.35$, $p = .041$ (Fig. 5). To probe this interaction, we estimated the simple slopes of the association between age and associative memory overall for participants with and without violence exposure. For children and adolescents without violence exposure, associative memory performance increased significantly with increasing age, b = 0.12, 95% CI = [0.03, 0.21]. For participants with violence exposure, however, we observed no age-related improvement in associative memory overall, b = -0.03, 95% CI = [-0.13, 0.08].

#### 2.3.2. Neural activation during associative learning

Because there was a significant interaction between age and violence exposure on associative memory performance overall, we next examined whether there was a similar interaction on neural recruitment during encoding (pair blocks > item blocks) in a whole-brain analysis. Whole-brain analyses revealed a significant violence x age interaction on BOLD signal in the left IPS and right MFG during encoding overall (pair blocks > item blocks). We performed additional ROI analyses to examine: a) the simple slopes of age with left IPS and right MFG activation (pair blocks > item blocks) separately for violence-exposed and control participants, and b) the associations of BOLD signal in these two ROIs during encoding overall (pair blocks > item blocks) with associative memory performance overall. ROIs were constructed using structural masks of the left IPS and right MFG from the Harvard-Oxford Cortical Structural Atlas in FSL (20% threshold). Because group-level activation in these regions during encoding overall (pair blocks > item blocks) did not intersect with the areas of activation in these regions that differed between groups as a function of age in the whole-brain analyses, we did not mask group-level activation onto structural masks.

Age was more strongly associated with neural activity during encoding (pair blocks > item blocks) in one cluster (left IPS and postcentral gyrus) for control participants than for violence-exposed participants (Table 4; Fig. 6A). Follow-up ROI analysis demonstrated that left IPS activation increased with age for participants without violence

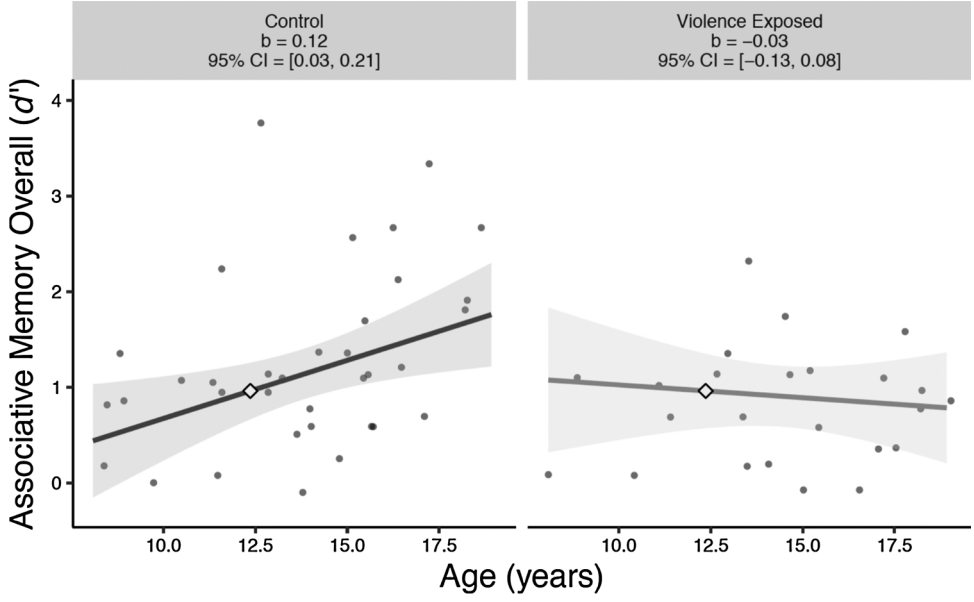


**Fig. 5.** Simple slopes of the association between age and associative memory overall for participants with and without violence exposure.

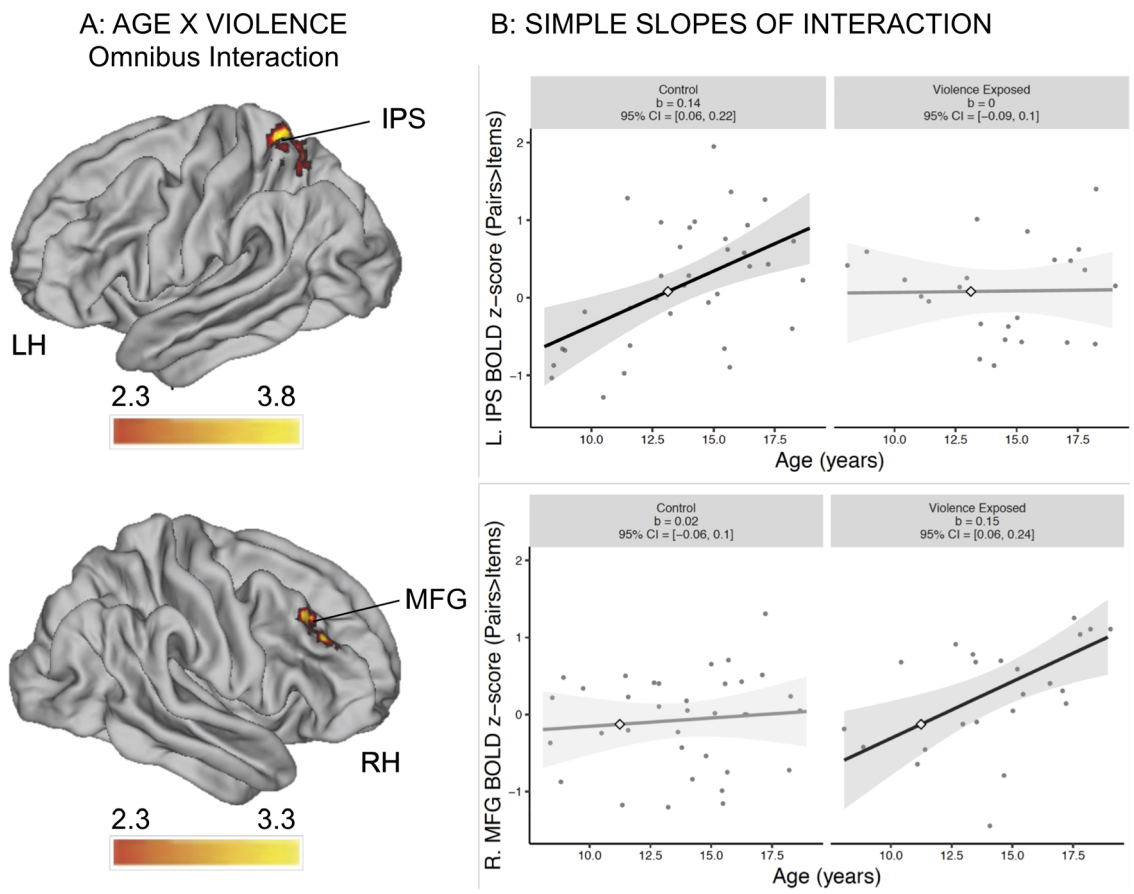


**Fig. 6.** A) Age x violence exposure omnibus interaction in BOLD signal during encoding (pair blocks > item blocks). Association of age with activation is greater for control participants than violence-exposed participants in the left IPS. Association of age with activation is greater for violence-exposed participants than control participants in the right MFG. B) Simple slopes of the association between age and left IPS BOLD signal, and age and right MFG BOLD signal during encoding (pair blocks > item blocks) for participants with and without violence exposure. IPS = Intraparietal sulcus; MFG = Middle frontal gyrus.

exposure, b = 0.14, 95% CI = [0.06, 0.22] (Fig. 6B). However, there were no age-related increases in left IPS activation for participants with violence exposure, b = 0.00, 95% CI = [-0.09, 0.1] (Fig. 6B). In contrast, the association of age with activation during encoding (pair blocks > item blocks) was greater in one cluster (right MFG) for violence-exposed participants than for control participants (Table 4; Fig. 6A). For participants without violence exposure, right MFG activation did not change with age, b = 0.02, 95% CI = [-0.06, 0.1], but increased with age for participants with violence exposure, b = 0.15, 95% CI = [0.06, 0.24] (Fig. 6B). Activation in the left IPS and right MFG ROIs (pair blocks > item blocks) were not associated with associative memory performance overall, *p's* = .36 -.88.

The association between violence exposure and activation in the hippocampus (pair blocks > item blocks) did not vary by age, $p = .71$.

### 2.4. Violence and threat-specific differences in associative learning

Next, we tested whether the effect of violence on behavioral and neural outcomes varied across the three emotion conditions of the task (i.e., violence x emotion interactions).

#### 2.4.1. Associative memory

There was no interaction between violence exposure and emotion in predicting associative memory, $F(2,112) = 1.35$, $p = .26$. Because we hypothesized that violence-related differences would be most pronounced on trials involving threatening stimuli, we also examined performance separately by emotion type. Violence exposure was associated with performance on trials involving angry faces, $F(1,56) = 4.57$, $p = .037$, but not on trials involving happy or neutral faces, *p's* = .28-.29 (Fig. 4A). Specifically, participants exposed to violence exhibited lower associative memory for objects paired with angry faces (M = 0.94, SD = 0.96) than control participants (M = 1.38, SD = 0.89).

#### 2.4.2. Neural activation during associative learning

We next examined whether violence-related differences varied across emotion condition (angry, happy, neutral) in a whole-brain analysis. The omnibus test for an emotion x group interaction revealed five significant clusters (Table 5). One cluster included the right intraparietal sulcus (IPS), supramarginal gyrus, angular gyrus, and postcentral gyrus (Fig. 4B), and another cluster included the right inferior frontal gyrus (IFG) and orbitofrontal cortex. Two additional clusters included the right cerebellum, and one included the right brainstem. To follow up this interaction, we examined differences in BOLD activation during encoding as a function of violence exposure for each emotion condition separately. We observed differences in the right IPS for the angry condition, but not for happy or neutral conditions. Specifically, control participants exhibited greater activation during encoding than youth with violence exposure in one cluster that included the right IPS, supramarginal gyrus, angular gyrus, and postcentral gyrus on trials involving angry stimuli (angry pairs > angry face items) (Table 5; Fig. 4C). We observed differences in the right IFG for the neutral condition only. Specifically, violence-exposed participants exhibited greater activation during encoding than control participants in one cluster that included the right IFG, precentral gyrus, and insula on trials involving neutral stimuli (neutral pairs > neutral face items) (Table 5).

The association between violence exposure and activation in the hippocampus did not vary by emotion type, $F(2,114) = 0.37$, $p = .69$.

**Table 5**
Differences in BOLD Signal During Encoding for Participants Exposed to Violence Versus Control Participants Across Emotion Conditions.

| **Emotion x Group[a]** | | | | | | |
|---|---|---|---|---|---|---|
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Supramarginal Gyrus (R)<br>Intraparietal Sulcus (R)<br>Angular Gyrus (R)<br>Postcentral Gyrus (R) | 46 | −42 | 56 | 294 | 12.72 | < .005 |
| Brainstem (R) | 6 | −34 | −28 | 173 | 17.91 | < .005 |
| Cerebellum (R) | 34 | −50 | −30 | 54 | 9.49 | < .005 |
| Inferior Frontal Gyrus (R)<br>Orbitofrontal Cortex (R) | 56 | 20 | 0 | 35 | 9.14 | < .005 |
| Cerebellum (R) | 20 | −68 | −52 | 34 | 10.76 | < .005 |
| **Angry[b]** | | | | | | |
| Controls > Violence | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Supramarginal Gyrus (R)<br>Intraparietal Sulcus (R)<br>Angular Gyrus (R)<br>Postcentral Gyrus (R) | 42 | −44 | 48 | 281 | 3.47 | < .0001 |
| Violence > Controls | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| – | – | – | – | – | – | – |
| **Neutral[b]** | | | | | | |
| Controls > Violence | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| – | – | – | – | – | – | – |
| Violence > Controls | | | | | | |
| Anatomical Region | x | y | z | voxels | z-max | p-value |
| Inferior Frontal Gyrus (R)<br>Precentral Gyrus (R)<br>Insula (R) | 56 | 14 | 2 | 307 | 3.89 | < .0001 |

Notes. L = left; R = right; aEmotion x violence exposure omnibus interaction on BOLD signal during encoding; bFollow-up univariate ANOVA examining differences in BOLD signal during encoding on angry trials (angry pairs > angry face items) and neutral trials (neutral pairs > neutral face items) for participants exposed to violence versus control participants.

### 2.5. Violence-related differences in threat-specific associative learning are age invariant

Finally, we evaluated whether the violence x emotion interactions on behavioral and neural outcomes varied across age (i.e., violence x emotion x age interaction). The violence x emotion interaction on associative memory did not vary by age overall, $p = .72$, and the association of violence with associative memory on angry trials specifically also did not vary by age, $p = .09$. The violence x emotion interaction in predicting activation in a right IPS ROI (defined structurally) also did not vary by age, $p = .29$.

## 3. Discussion

Remarkably little is known about how childhood adversity influences the development of basic forms of learning and memory and underlying neural function. This study examined whether violence exposure early in life influences hippocampus-dependent associative learning, whether associative learning differences are broad or occur only when a threatening cue is present, and whether associative learning differences remain stable across middle childhood or worsen with age. Children exposed to violence exhibited broad associative memory difficulties that became more pronounced with age as well as associative memory difficulties specifically in the presence of threat that did not change with age. We identified two potential neural mechanisms underlying broad associative memory difficulties following childhood violence exposure. First, children exposed to violence exhibited reduced hippocampal recruitment during encoding (regardless of the emotion of the facial cue) that did not change with age and that was associated with broad associative memory difficulties. Second, children exposed to violence exhibited differences in recruitment of fronto-parietal regions during encoding (regardless of the emotion of the facial cue) that became more pronounced with age, including greater MFG and reduced IPS recruitment. These fronto-parietal regions become increasingly recruited during working memory (Klingberg et al., 2002; Kwon et al., 2002; Thomason et al., 2009) and episodic memory (DeMaster and Ghetti, 2013; DeMaster et al., 2013; Ofen et al., 2012; Selmeczy et al., 2018) across development. We identified one potential neural mechanism underlying threat-specific associative memory difficulties following childhood violence exposure. Children exposed to violence exhibited reduced IPS activation during encoding specifically in the presence of threat cues.

### 3.1. Neural mechanisms underlying broad associative memory difficulties

#### 3.1.1. Reduced hippocampal recruitment

Animal research documents the toxic and persistent effects of chronic stress and glucocorticoids early in life on hippocampal neurons (Lupien et al., 2009). Reduced hippocampal volume has been observed in children exposed to violence in numerous studies (Hanson et al., 2015; Teicher et al., 2012), including in this sample (Lambert et al., 2017b). However, the precise hippocampal functions that are disrupted as a result of these changes in hippocampal structure following early-life adversity are largely unknown. Given the central role of the hippocampus in associative learning (Davachi, 2006), broad difficulties with associative learning could be one functional consequence of altered hippocampal development following childhood violence exposure. Here, children exposed to violence exhibited less hippocampal activation during associative learning compared to children who never experienced violence. This activation pattern did not vary depending on the emotion of the facial cue being encoded (e.g., angry, happy, or neutral), suggesting that these alterations in hippocampal recruitment are not specific to situations that involve threat. Reductions in hippocampal activation during encoding were associated with broad associative memory difficulties.

The association of violence exposure with hippocampal recruitment did not change across the wide age range of our sample. Although differences in hippocampal activation during encoding following violence exposure emerged before middle childhood, broad associative memory difficulties did not emerge until adolescence. Explicit forms of associative learning that improve with age may depend upon emerging connectivity between the hippocampus and fronto-parietal regions rather than just upon the hippocampus, as discussed below in Section 3.1.2. In contrast, implicit forms of associative learning depend primarily on the hippocampus, and differences in both hippocampal activation and performance emerge early in development following violence exposure (Lambert et al., 2017b).

#### 3.1.2. Atypical recruitment of fronto-parietal regions

Associative memory performance—regardless of the emotional nature of the stimuli—improved with age for children and adolescents without violence exposure, but not for youths exposed to violence. We also found that atypical patterns of recruitment in fronto-parietal regions during associative learning (regardless of the emotion of the facial cue) emerged later in development and became more pronounced with

age in children exposed to violence. Specifically, activation in the left IPS increased more with age for children without violence exposure than for children exposed to violence. In contrast, right MFG activation increased more with age for children with violence exposure than for children unexposed to violence.

The IPS and MFG support working memory. The posterior parietal cortex, including the IPS, stores and maintains internal representations of visual and spatial information in working memory prior to long-term storage (Nelson et al., 2000; Peverill et al., 2016; Todd and Marois, 2004). The MFG sustains attention on the internal representations stored in the posterior parietal cortex (Curtis and D'Esposito, 2003; Feredoes et al., 2011; Sakai et al., 2002). Across development, children exhibit increases in IPS and MFG recruitment during working memory along with improvements in working memory performance (Klingberg et al., 2002; Kwon et al., 2002; Thomason et al., 2009). An absence of developmental increases in IPS recruitment during associative learning in children exposed to violence could reflect difficulties with the initial storage of the paired associates in short-term memory, contributing to their lack of improvement in associative memory performance across development. Increased MFG recruitment across development in children exposed to violence without associated gains in memory performance may reflect greater effort required to sustain attention on the representation of the paired-associates.

Both of these patterns—greater MFG-mediated attentional effort and reduced IPS-mediated short-term storage—could be driven by weaker associative binding during initial encoding, as reflected in reduced hippocampal recruitment. Although we might expect that to be reflected in atypical patterns of functional connectivity of the hippocampus with the MFG and IPS, our PPI analysis revealed no task-related connectivity with the hippocampus that survived cluster correction. Examination of these functional connectivity patterns in larger samples is an important goal for future research.

### 3.2. Neural mechanisms underlying threat-specific associative memory difficulties

We also identified a possible neural mechanism underlying associative learning difficulties that emerge specifically in the presence of threat cues in children exposed to violence. Children exposed to violence exhibited worse associative memory performance when the face they were asked to encode as part of the pair was exhibiting an angry expression compared to children without violence exposure, and this pattern did not vary with age. This pattern extends findings from a recent study showing that children exposed to violence had poor memory of contexts paired with angry faces, but not happy or neutral faces—a pattern that also did not change with age during middle childhood and adolescence (Lambert et al., 2017b). Violence-related differences in neural activation during associative learning also varied as a function of the facial emotion being expressed. Children without violence exposure had greater activation in the right IPS during encoding specifically on angry trials than children with violence exposure.

Children exposed to violence exhibit greater perceptual sensitivity, faster attention orienting, and longer sustained attention to threatening faces (Pollak et al., 2000; Pollak and Kistler, 2002; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003; Shackman et al., 2007). These patterns of information processing that facilitate the rapid identification of environmental threats following violence exposure have been observed as early as infancy (Cicchetti and Curtis, 2005; Curtis and Cicchetti, 2011). Children exposed to violence may have therefore focused their attention preferentially on the angry face at the expense of processing the object paired with the face, preventing the storage of the face-object pair in working memory in the IPS. An alternative explanation is that violence-exposed children directed attention away from the angry facial cues, reducing encoding of object-face pairings. However, violence-exposed children in this sample exhibited better working memory for angry faces than for happy or neutral faces in a different task (Jenness et al., 2018), indicating that attentional bias to threat cues may be a more likely explanation for poor associative encoding in the presence of threat.

### 3.3. Limitations

Several limitations are worth noting. First, we examined neural activation during associative learning, but not during retrieval. Activation in the hippocampus, PFC, and parietal cortex occurs during retrieval of episodic information across development (DeMaster and Ghetti, 2013; DeMaster et al., 2013; Guler and Thomas, 2013; Ofen et al., 2012; Selmeczy et al., 2018), suggesting that childhood violence exposure may also impact the consolidation and retrieval of associative information. Examining how childhood violence exposure influences neural function underlying associative retrieval is an important direction for future research. Second, faces are emotionally salient regardless of emotional expression (Thomas et al., 2001). Future research should clarify whether associative learning difficulties following childhood violence exposure are specific to emotionally salient cues (e.g., faces) or extend to stimuli lacking in emotional content (e.g., objects or shapes). There is some reason to believe that difficulties with higher order cognition and memory following childhood violence exposure are specific to emotionally salient cues. For example, in previous work we have shown that childhood violence exposure was associated with worse inhibition of a dominant response in a task using emotional faces, but not in an identical task using neutral arrows as stimuli (Lambert et al., 2017a). Third, two features of the task design may have affected encoding-related neural activation. Participants learned multiple associations for each individual person (10 unique people, each with three emotional expressions), which may have resulted in interference. Additionally, each unique pair was presented multiple times, which may have resulted in habituation and made it more difficult to detect neural activation during encoding, which is important to consider when interpreting any null effects. Replication of our results using a different associative learning task that addresses these issues is an important next step. Fourth, because children with violence exposure are difficult to recruit, our sample was relatively small, which limited power to detect group differences. Future studies with larger samples are needed to replicate our findings and examine whether childhood violence exposure influences functional connectivity in the fronto-parietal network or between the hippocampus and specific nodes of the fronto-parietal network during encoding and retrieval. Finally, it remains unclear whether these effects on hippocampal function and associative learning are specific to violence or would be observed following other types of adversity in childhood, like low socio-economic status, which is associated with reduced hippocampal volume in childhood in some studies (Yu et al., 2018). However, we did not observe associations of poverty or parental education with behavioral or neural outcomes in this sample.

## 4. Conclusion

We identify several potential neurodevelopmental mechanisms underlying associative learning difficulties following childhood violence exposure. First, altered hippocampal function following violence exposure does not change with age after early childhood and contributes to broad associative learning deficits. Second, increased MFG and reduced IPS activation during encoding emerge with increasing age in children exposed to violence and may reflect greater effort required to maintain attention on the representation of the pairs and less efficient short-term storage. These neural patterns likely explain the absence of broad associative memory improvements across development in children exposed to violence. Third, increased attention to threat cues in children exposed to violence may come at the expense of processing features paired with those cues, which may additionally interfere with storing the paired-associate representation in working memory in the

IPS and ultimately with retrieving associative memories of objects paired with angry faces. Future research should examine whether associative learning difficulties contribute to poor episodic memory and adverse long-term mental health, academic, and socio-economic outcomes among children who have been raised in dangerous environments.

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## Declarations of interest

None.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2019.100666.

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