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Child abuse interacts with hippocampal and corpus callosum volume on psychophysiological response to startling auditory stimuli in a sample of veterans

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Abstract

Child abuse (CA), which is linked to posttraumatic stress disorder (PTSD), has been associated with a reduction in both hippocampal and corpus callosum (CC) volume. However, few studies have explored these relationships on psychophysiological variables related to trauma exposure. Therefore, we assessed whether the interaction between CA and hippocampal and CC volume were associated with enhanced fear potentiated psychophysio-logical response patterns in a sample of Veterans. 147 Veteran participants who were part of a larger study of Gulf War Illness were exposed to startling sounds in no, ambiguous, and high threat conditions and also provided MRI data. The Clinician Administered PTSD Scale and Trauma History Questionnaire were used to measure PTSD and CA respectively. Psychophysiological response was measured by EMG, SCR, and heart rate. Repeated-measures mixed linear models were used to assess the significance of CA by neural structure interactions. CA interacted with both hippocampal and CC volume on psychophysiological response magnitudes, where participants with CA and smaller hippocampal volume had greater EMG ($p < 0.01$) and SCR ($p < 0.05$) magnitudes across trials and over threat conditions. Participants with CA and smaller CC volume had greater SCR magnitudes across trials and over threat conditions ($p < 0.01$). Hippocampal and genu volume mediated CA and psychophysiological response magnitude. CA may impact psychophysiological response via a reduction in hippocampal and CC volume. Volumetric reduction in these structures may indicate a neurofunctional, CA-related increase in threat sensitivity, which could portend increased PTSD susceptibility and adverse interpersonal and social consequences across the lifespan.

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Declarations of interest

None.

Keywords

CA; Hippocampus; Corpus callosum; Trauma exposure; Psychophysiology; Imaging

1. Introduction

Child abuse (CA) is associated with adverse events across the life span including increased risk of exposure to other traumas and greater burden of adverse physical and psychological health outcomes (Shrivastava et al., 2017). Though other childhood traumas can increase risk for posttraumatic stress disorder (PTSD), childhood physical and sexual abuse are particularly likely to be associated with PTSD susceptibility and other vulnerabilities, due to the nature of the abuse, the increased probability that the abuse is perpetrated by a family member, and the common co-occurrence of multiple forms of abuse (Dong et al., 2004). Converging evidence indicates CA may fundamentally alter information processing and prioritization across the lifespan by imparting toxic effects on the brain's flight or fight system (Hart and Rubia, 2012; Jovanovic and Ressler, 2010).

The hippocampus, a limbic structure key to memory and emotion regulation, have been implicated in PTSD symptom maintenance for some time (Sapolsky, 2000). The hippocampus' pyramidal cells, which are rich with glucocorticoid receptors, appear to be particularly susceptible to the neurotoxic effects of glucocorticoids (Wilson et al., 2011). While CA has been associated with smaller hippocampal volume in adults with PTSD (Driessen et al., 2000; Vythilingam et al., 2002), results for children have been varied. Previous findings did not evidence a relationship between CA and hippocampal reduction in children (Woon and Hedges, 2008), which suggests the effects of CA may be delayed (Wilson et al., 2011). Other findings have evidenced hippocampal volume reduction in traumatized inner-city children, which may indicate CA combined with chronic low to mid-level trauma exposure stemming from a toxic socioeconomic environment may adversely affect hippocampal development (Hanson et al., 2015). Conceptual models suggest CA-related hippocampal volume reduction may have broad neurobehavioral consequences over the lifespan (McLaughlin et al., 2014).

The corpus callosum (CC), which is the largest white matter tract in the brain, connects the left and right hemispheres and facilitates behavioral and emotional responses via interhemispheric communication (Aboitiz and Montiel, 2003). The CC is divided into anterior (genu), medial (truncus), and posterior (splenium) sections. The genu has tracts that radiate to the prefrontal cortex and the anterior cingulate cortex (Hofer and Frahm, 2006). The truncus, in addition to providing inter-hemispheric motor cortex communication (Hofer and Frahm, 2006), also has fibers that radiate through the cortical and limbic structures responsible for memory and emotional processing (e.g. the hippo-campus) (Jackowski et al., 2008). The splenium, which is also inter-hemispheric somatosensory communication (Hofer and Frahm, 2006), links these structures to prefrontal cortical areas via interhemispheric circuits that pass through it (Jackowski et al., 2011). Several studies have shown a relationship between CA and a broad reduction of CC volume (Teicher and Samson, 2016) and white matter integrity as measured by diffusion tensor imaging (Jackowski et al., 2008).

A reduction in CC size may promote hemispheric lateralization where one side of the brain may be functionally over-burdened resulting in ineffective interhemispheric communication and greater activation during emotional states (Weber and Reynolds, 2004). Furthermore, CA-related corpus callosum loss tends to be centralized in the truncus and splenium (Teicher and Samson, 2016). Given the CC's neuroanatomical proximity to the hippocampus, the neuropathogenesis of CA-related threat system dysregulation may be linked to both of these structures. The use of established biomarkers of threat such as the fear-potentiated startle response may aid us in uncovering how child hippocampal/CC volume reduction might modulate the relationship between CA and threat sensitivity.

The fear-potentiated startle response is the largely unconscious defensive response to sudden stimuli (Ramirez-Moreno and Sejnowski, 2012). Elevated startle response is a key symptom of PTSD (American Psychiatric Association, 2013) and individuals diagosed with PTSD exhibit greater fear-potentiated psychophysiological responses to sudden or threatening stimuli compared to those who do not have a PTSD diagnosis (Niles et al., 2018; Orr et al., 1995; Pole et al., 2009). Startle response is moderated by limbic structures including the hippocampus, which shares functional connectivity with the CC (Aboitiz and Montiel, 2003), and is impacted by CA (McLaughlin et al., 2015). While findings indicate that CA is associated with greater startle response magnitudes (Jovanovic et al., 2009), the relationship between psychophysiological response and underlying neurobiological mechanisms with respect toto CA remains understudied. Evidence suggests that behavioral changes associated with CA may have neurobiological origins (Marusak et al., 2015; McLaughlin et al., 2016). Examining whether the CC and hippocampal morphometry modulates CA's impact on threat system dysfunction could be particularly illuminating.

Therefore, we investigated whether the interaction between CA and hippocampal and CC volume were associated with psychophysiological reactivity to startling sounds over successive trials across three different threat conditions in a sample of Gulf War Veterans. We hypothesized that: 1) the interaction between smaller hippocampal volume and CA would be associated with greater psychophysiological response magnitude across trials and greater SCR levels over threat conditions; and 2) the interaction between smaller CC volume and CA would be associated with greater psychophysiological response magnitude across trials and greater SCR levels over threat conditions. Based upon previous findings (Jackowski et al., 2008) and the results of hypothesis two, we also examined whether CA differentially interacted with sub-regions of the CC. Finally, we explored whether either hippocampal or CC volume mediated CA and psychophysiological reactivity to establish whether a pathway exists between CA and psychophysiological response via hippocampal and CC volume.

2. Method

2.1. Participants

We conducted a secondary analysis of data on Veterans from a cross-sectional study that was originally designed to assess the effects of Gulf War deployment on the brain. Gulf War Veterans were recruited between 2002 and 2007 using methods described elsewhere (Apfel et al., 2011). The Department of Defense Human Research Protection Office approved all

research protocols. Of the 369 Veterans from the original sample, 244 and 172 Veterans engaged in the psychophysiological response task and provided imaging data respectively. Data from 12 participants were not used due to their psychophysiological task data not meeting the requirements outlined in Section 2.2. Out of those, we had both psychophysiological task and imaging data from 147 Veterans. This investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was approved by both the Veterans Affairs and UCSF IRB committee, and informed consent was obtained after the nature of the procedures had been fully explained to all participants.

Participants' age, sex, education level, race (white versus minority), and PTSD diagnostic criteria were recorded for use as demographic variables in subsequent analyses based on prior literature linking them to traumatic stress response (Neylan et al., 2005). CA was defined as being exposed to either childhood physical or sexual abuse or both prior to the age of 16. The last six items of the Trauma History Questionnaire, which focus on childhood physical and sexual abuse were used to assess CA (Green, 1996). Current PTSD diagnostic criteria (i.e., within the past month) was evaluated by a Ph.D. level clinical interviewer using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Participants were diagnosed with PTSD based upon frequency and severity of their CAPS scores (i.e. the "1, 2" rule; for a review, see Blake et al., 2000).

2.2. Psychophysiological response procedure

Electromyogram (EMG), skin conductance response (SCR), and heart rate (HR) were collected by trained technicians blind to participants' clinical status. The participant's left eye blink EMG activity, SCR, and HR were assessed during a 2-min baseline. Participants were fitted with headphones and told that they would hear startling sounds. They were asked to focus their eyes on a monitor in front of them. A Coulbourn Instruments Lablinc V Modular System binaurally presented 106-dB(A), 40 ms white noise bursts with nominal 0-ms rise and fall times separated by inter-trial intervals of between 30 and 50 s in each threat condition. In the "no threat" condition, participants were instructed that they would not be shocked until later in the study. They were then exposed to ten startling sounds. Only their last five responses were included in analyses. In the "ambiguous threat" condition, participants were fitted with a Coulbourn Instruments Transcutaneous Aversive Finger Stimulator but were told that they would not be shocked. Five additional startling sounds were presented. In the "high threat" condition, Veterans wore the finger stimulator and were told that shocks were imminent. Then five additional startling sounds were presented followed by a 2.5 mA shock. Each condition lasted approximately 4 min and was separated by about 1 min. The ambiguous and high threat conditions were counterbalanced to minimize carry-over effects between these conditions. All physiologic signals were sampled at a 1000 Hz prior to and across acoustic startle stimulus presentations. After which, physiologic signals were digitized by a Coulbourn Instruments LabLinc V system and stored for off-line analysis. EMG, measured in microvolts was captured using three, 4-mm (sensor diameter) In Vivo Metrics Ag/AgCl surface electrodes filled with electrolyte paste according to specifications published elsewhere (Blumenthal et al., 2005). SCR was measured in microsiemens with InVivo Metrics Ag/AgCl electrodes placed on the hypothenar surface of

the medial phalanges of the middle and index fingers of the non-dominant hand as described in (Young et al., 2018). HR was measured in beats per minute and recorded via electrodes attached in a Type-I EKG configuration. Human Startle Software (Coulbourn Instruments, Allentown, PA) automatically calculated mean levels of EMG and SCR at baseline, during 1 s prior to each stimulus onset, the peak post-stimulus levels within 21–200 ms for eyeblink EMG and within 1–4 s for SCR. The last 2 inter-beat interval preceding startle stimulus onset was used to calculate HR baseline value. An accelerative HR response score was calculated for each trial by subtracting the HR baseline value from the highest HR level measured within 1–4 s after stimulus onset. No minimum response threshold was designated for any physiological measure. Each measurement of psychophysiological response was recorded prior to and following exposure to the startle stimulus on each of five trials under each threat condition. Participants needed at least four (of five) valid responses for all three psychophysiological measures within each threat condition to be included in the study. Responses were inspected for potential artifact and rejected accordingly.

2.3. Image acquisition and processing

Subjects were scanned on a 1.5 Tesla Vision, Siemens MRI scanner (Siemens Medical Systems, Iselin, New Jersey). A T1-weighted 3D volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with the following parameters: repetition time/spin-echo time/inversion time = 10/4/300 ms, 1 mm × 1 mm in-plane resolution, and 1.5-mm slab thickness, angulated perpendicular to the long axis of the genu, splenium, and truncus of the CC and the hippo-campus. Freesufer version 4.5 (http://surfer.nmr.mgh.harvard.edu) was used to estimate each subject's left and right volumes of their rostral and CC along with their intracranial volume as previously described in (Chao et al., 2014).

2.4. Data analyses

Due to non-normal distribution, hippocampal and CC volumes were log transformed and entered in as continuous variables in all models. CA was entered as a dichotomous variable (presence vs. absence). Psychophysiological response outcome was assessed by using within trial square root post-minus pre-EMG, SCR, and HR responses. Repeated measures linear mixed models were used to assess all interactions between CA and hippocampal volume and CA and CC volume on psychophysiological response (McCulloch and Neuhaus, 2001). Each model included structure volume × CA × trial and structure volume × CA × threat condition interactions terms to assess whether any hippo-campus or CC volume on psychophysiological response relationship interacted with CA within each of the five trials and over the three threat (no threat, ambiguous threat, and high threat) conditions respectively. CC sub-regions were tested only if the overall CC region was significant. To adjust for multiple comparisons, a Bonferroni correction was used where $p \leq 0.05/3$; thus, the corrected alpha level for CC sub-regions was $p \leq 0.017$. Age, race (white vs. non-white), sex (female vs. male), education (in years), intracranial volume (log-transformed), and PTSD diagnostic status (as assessed by the CAPS) were included as covariates in all models. We also controlled for Gulf War Illness based on previous findings (Fukuda et al., 1998). Stata Statistical Software: Release 15.1 was used to conduct all statistical analyses (StataCorp LP, 2013 College Station, TX). Cohen's f^2 was used to assess proportion of

model variance explained. f^2 was generated using user written code based on previously published methods described elsewhere (Selya et al., 2012). We calculated the derivative of psychophysiological response magnitude with respect toto trial or threat condition (i.e. the interaction between neurostructural volume and CA with respect toto its between trial/threat condition changes in slope of psychophysiological response magnitude) to examine within model slope change, where EMG, SCR, or HR magnitude = m and trial or threat condition = t; thus, in standard notation, $m'(t) \approx 1/h\,[m(t + h) - m(t)]$. Mediation analyses were based on significant CA × hippocampal volume and CA × CC volume on EMG, SCR or HR across trials and over threat condition. Bootstrapping was used to assess whether either CC or hippocampal volume mediated CA and psychophysiological reactivity. Bootstrap estimates on 10,000 replications were obtained using a user written binary mediation program in conjunction with Stata's native bootstrap code and indirect effects were considered significant when confidence intervals did not overlap zero (Ender, 2017; Hayes, 2017).

3. Results

Demographics and their bivariate relationships to CA are described in Table 1. Our sample was predominantly White and male with a mean age of 50. Approximately 31% of participants reported CA. Women were more likely to report CA compared to men (χ^2 = 9.33; p = 0.002) and CA was associated with a greater rate of being diagnosed with PTSD (χ^2 = 6.43; p = 0.011).

3.1. Hippocampal volume

Model effects for EMG and SCR were significant (Wald χ^2 = 159.73; p < 0.001 and Wald χ^2 = 41.80; p < 0.001 respectively). Post-hoc analyses revealed a significant CA × hippocampus volume interaction on EMG where participants who reported CA and had smaller hippo-campal volumes exhibited greater mean EMG magnitudes across the five trials (χ^2 = 9.46; f^2 = 0.21; p = 0.008) and over the three threat conditions (χ^2 = 10.16; f^2 = 0.28; p = 0.006; see Fig. 1a. and 1b. respectively). Derivative analyses did not indicate significantly greater changes in mean EMG slope either for trial or threat condition (not shown). Significant CA × hippocampal volume interactions were also observed on SCR where participants who reported CA and had smaller hippocampal volumes exhibited greater mean SCR magnitudes across the five trials (χ^2 = 7.34; f^2 = 0.20; p = 0.035) and over the three threat conditions (χ^2 = 6.97; f^2 = 0.18; p = 0.012; see Fig. 1c. and 1d. respectively) compared to the other participants. Derivative analyses indicated that participants with both a history of child abuse and smaller hippocampal volumes had significantly greater changes in mean SCR slope across trials and over threat conditions ($m'(t)$ = 0.12; SE = 0.06; z = 2.07 p = 0.039 and $m'(t)$ = 0.13; SE = 0.06; z = 2.11 p = 0.035 respectively). CA did not significantly interact with hippo-campal volume on HR (see Table 2.).

3.2. Corpus callosum volume

A significant model effect was only found for the SCR repeated measures mixed model (Wald χ^2 = 73.14; p < 0.001). Post-hoc analyses revealed a significant two-way CA × CC interaction where participants who reported CA and had smaller CC volumes exhibited greater mean SCR magnitudes across the five trials (χ^2 = 8.39; f^2 = 0.36; p = 0.003). A

significant three-way CA × CC × threat condition interaction was also observed where CA exposed participants with smaller CC volumes exhibited greater mean SCR magnitudes over the three threat conditions compared to other participants ($\chi^2 = 8.44$; $p = 0.003$; $f^2 = 0.37$). Derivative analyses confirmed this where participants who reported CA and had smaller CC volumes exhibited greater changes in mean SCR slope across trials and over threat conditions compared to others in the sample ($m'(t) = 0.12$; $SE = 0.04$; $z = 2.90$ $p = 0.004$ and $m'(t) = 0.12$; $SE = 0.04$; $z = 2.72$ $p = 0.007$ respectively). Based upon these results, we proceeded to analyze the sub-regions of the CC.

3.3. Sub-regions of the corpus callosum

There were significant model effects for the CA × genu (Wald $\chi^2 = 169.82$; p < 0.001) and CA × truncus (Wald $\chi^2 = 177.36$; $p < 0.001$) on SCR repeated measures mixed models but not the CA × splenium model (not shown). Bonferroni corrected post-hoc analyses revealed the CA × genu volume interaction was associated with greater mean SCR magnitudes across the five trials ($\chi^2 = 8.33$; $f^2 = 0.34$; $p = 0.004$) and over the three threat conditions ($\chi^2 = 7.64$; $f^2 = 0.38$; $p = 0.006$; see Fig. 2a. and 2b. respectively). Derivative analyses con-firmed participants exposed to CA who had smaller genu volume exhibited greater changes in mean SCR slope across trials and over threat conditions compared to others in the sample ($m'(t) = 0.10$; $SE = 0.04$; $z = 2.75$ p = 0.006 and $m'(t) = 0.10$; $SE = 0.04$; $z = 2.77$ $p = 0.006$ respectively). Significant three-way CA × truncus × trial ($\chi^2 = 4.82$; $f^2 = 0.16$; $p = 0.014$) and CA × truncus × threat condition interactions ($\chi^2 = 8.36$; $f^2 = 0.24$; $p = 0.004$) were also associated with greater mean trial SCR magnitudes and mean threat condition SCR magnitudes (Bonferroni corrected; see Fig. 2c. and 2d. respectively). Derivative analyses confirmed CA exposed participants with smaller truncus volumes exhibited greater changes in mean SCR slope across trials and over threat conditions compared to others in the sample ($m'(t) = 0.09$; $SE = 0.03$; $z = 2.89$ $p = 0.004$ and $m'(t) = 0.09$; $SE = 0.03$; $z = 2.89$ $p = 0.004$ respectively). No CA × splenium interaction was observed on SCR.

3.4. Mediation analyses

3.4.1. Hippocampal volume mediation analyses—

We assessed whether hippocampal volume accounted for the effect of CA on EMG magnitude and whether hippocampal volume mediated CA and SCR magnitude across trials and over threat conditions. Bootstrapped estimates indicated significant indirect effects of reduced hippocampal volume on CA and EMG and SCR magnitudes over threat condition (95% CI [0.004; 0.010] and 95% CI [0.002; 0.003] respectively; see Fig. 3a. and 3b.) but not across trials.

3.4.2. Corpus callosum mediation analyses—

We assessed whether CC volume mediated CA and SCR magnitude across trials and over threat conditions. Bootstrapped estimates were nonsignificant for CC volume on CA and SCR response magnitude across trials or over threat conditions. We then assessed whether sub-regions of the CC mediated CA and SCR magnitude. Bootstrapped estimates indicated significant indirect effects of reduced genu volume on CA and SCR response magnitude across trials and SCR magnitudes over threat condition (95% CI [0.005; 0.03] and [0.003; 0.009] respectively; see Fig. 3c. and 3d.). Bootstrapping estimates for the truncus and splenium were nonsignificant.

4. Discussion

Although prior findings have suggested that CA is associated with lasting neurobiological changes, research linking these changes to psychophysiological outcomes associated with PTSD has been limited. We found that individuals with histories of CA who had smaller hippocampal and CC volumes exhibited greater within trial psycho-physiological response magnitudes (both EMG and SCR) over the three threat conditions even after controlling for factors such as age, sex, and PTSD diagnostic status. Moreover, while CA interacted with whole CC volume, only the genu and truncus were associated with greater SCR magnitudes. Similarly, while we also found that both hippocampal and genu volume mediated CA and psychophysiological response magnitudes over threat conditions, only genu volume did the same in terms of psychophysiological response magnitudes across trials. Our findings intimate two important clinical implications. First, participants with CA histories and smaller hippocampal/CC volumes were especially sensitive to the startle probe, which may indicate that these participants have a greater sensitivity to threat. This interpretation is particularly compelling based upon examination of Fig. 1d. 2b. and 2d., where SCR response magnitudes appear significantly elevated in the no threat condition. A simple effects post hoc analysis with the CA × hippo-campal/CC volume interaction terms on SCR levels at the no threat condition confirmed this (CA × hippocampus ($\chi^2 = 6.02$; $p = 0.014$); CA × CC ($\chi^2 = 6.60$; $p = 0.010$)). Therefore, individuals with CA and smaller hippocampal/CC volumes may not only be prone to react excessively during threatening situations, they may also have an impaired capacity to attune to environmental safety cues, which may be associated with inappropriate threat reactivity in innocuous situations. Secondly, if we presume that hippocampal and genu volume reduction occurred after CA exposure (per the requisites of a statistical mediation model, Hayes, 2017) and given that a significant number of participants in this sample who were exposed to CA also had PTSD ($\chi^2 = 6.43$; $p = 0.011$), our results indicate that CA may increase PTSD susceptibility subsequent to adult trauma exposure at least in part via hippo-campal and genu mediated alterations in threat sensitivity, which could increase PTSD susceptibility. More broadly, while our results extend previous findings that have shown a relationship between CA and greater startle magnitude in adults (Jovanovic et al., 2009), they add further evidence that psychopathology stemming from early trauma exposure may manifest through volumetric changes in neural circuitry related to an individual's threat response system, which could be linked to adverse consequences across their lifespan.

While CA has previously been linked to hippocampal structure alterations (Bremner et al., 1997; Tupler and De Bellis, 2006) and PTSD in adults (Logue et al., 2018), ours is the first to show hippocampal volume mediates CA and psychophysiological response levels, which may be associated with enhanced sensitivity to threat. These findings are in line with work that has shown reduced hippocampal volume partially mediates CA and behavioral problems in low income children (Hanson et al., 2015). Other related research has shown a positive correlation between hippocampal signaling and the magnitude of CA when viewing unfamiliar faces in an adult sample (Edmiston and Blackford, 2013). On the other hand, a recent study showed child and adolescent participants with reduced hippocampal volume and CA-related PTSD were associated with blunted psychophysiological response patterns

(McLaughlin et al., 2016). It is possible that differences in age of the subjects in the McLaughlin study relative to ours accounts for the divergent findings and reflects how CA impacts hippocampal function at different neurodevelopmental stages. Thus, our findings may demonstrate the long-term effects of CA on hippocampal volume in adulthood resulting in a greater sensitivity to threat whereas McLaughlin et al.'s findings may represent the more immediate adverse effects of CA on the hippocampus resulting in a blunted stress response. While further research is needed, this interpretation is plausible given studies using animal models have shown the hippocampus appears to gate fear expression (for a review, see Hartley and Phelps, 2010) and traumatized children have reduced hippocampal volume 12–18 months after trauma exposure (Carrion et al., 2007).

We also found that CA exposed participants who had smaller CC volumes exhibited greater physiological response magnitudes. However, genu and truncus but not splenium volume interacted with CA on greater SCR magnitude and only genu volume mediated CA and psychophysiological response magnitude. Others have suggested that the truncus and splenium deficits may be associated with PTSD symptomatology (Jackowski et al., 2008). While our results do not directly contradict this line of thinking, they do suggest genu volume reduction, with its connectivity to the hippocampus via the septum pellucidum and hippocampal commissure and the projections that pass through it into the prefrontal cortex (Sisti et al., 2012), may affect the regulation of emotional response patterns. Reduced genu volume as a result of CA not only could impair interhemispheric communication but also inhibit prefrontal cortex and hippocampal engagement when a survivor of CA is exposed to novel or ambiguously threatening stimuli leading to threat response-related circuitry over-activation and prefrontal under-engagement.

Although it is unclear why the CA-related hippocampal and CC volume reduction is associated with psychophysiological response, it is tempting to implicate glucocorticoids in the neuropathogenesis of hippocampal and CC volume reduction and subsequent threat response over-activation. Animal research suggests how glucocorticoid over-exposure may be involved in CA-related hippocampal and CC volume reduction on threat reactivity. For example, rodents have been shown to both misidentify threat cues and exhibit exaggerated fear responses to non-threatening cues after receiving an infusion of glucocorticoids in their hippocampi (Kaouane et al., 2012). Similarly, non-human primates with significantly elevated cortisol levels stemming from maternal abuse had reduced CC white matter integrity in adolescence (Howell et al., 2013). Thus, while more research using both humans and animals is needed to explore this further, our results could suggest that elevated glucocorticoids stemming from CA may have detrimental effects on both hippocampal circuitry and white matter integrity leading to a loss of hippocampal and CC volume and subsequent threat response overactivity later in life.

There are several limitations of note. First, this was a cross-sectional study and mediation does not afford us the ability to make causal inferences. Second, while we did control for sex in our models, our sample was comprised of mostly male white veterans, which limits the generalizability of our findings to the broader non-white civilian population. Nonetheless, similar results have been observed in other populations (Jovanovic et al., 2009). We were also statistically underpowered to use repeated measures linear mixed models to investigate

CA × hippocampal volume and CA × CC volume relationships on psycho-physiological response magnitude in a PTSD only subsample in this study. Future investigations examining the relationship between CA and neural structures on psychophysiological response magnitude should attempt to engage a larger participant pool so that analyses using a PTSD subgroup might be statistically feasible. Findings from such a study would provide a more definitive explanation of the impact that these neural structures have, particularly in terms of how they might modulate the effects CA on threat sensitivity with respect toto PTSD. We also used a retrospective measure of CA, which may be subject to recall issues. Finally, we did not have the means to explore what impact these relationships have on therapeutic outcomes and no study that we are aware of has investigated the relationship between CA and either hippocampal or CC volume on PTSD treatment outcome. Although, recent studies suggest that reduced hippocampal volume is associated with both the persistence of PTSD symptoms and worse treatment outcomes (Rubin et al., 2016; Van Rooij et al., 2015), these studies did not take into consideration the impact of CA. More broadly, while research investigating how trauma impacts neural structural/functional integrity within a clinical context is important, “the bottom line is that studies assessing the pathophysiology of psychiatric disorders need to take into account the confounding role of childhood maltreatment” (Teicher and Samson, 2016, p. 245).

In summary, CA appears to negatively impact threat sensitivity to novel or ambiguous stimuli via the reduction of both hippocampal and genu volume. Based upon the interpretation of our findings, CA may increase PTSD susceptibility through a reduction of hippocampal and genu volume, which may be linked to an increase in threat sensitivity. Our findings add evidence that CA may have cascading effects on interconnected neuronal systems leading to a dysregulated threat response system, which may lead to detrimental outcomes across the lifespan. Specifically, CA associated threat sensitivity stemming from smaller hippocampal/genu volume could be linked to inappropriate interpersonal and social engagement where individuals with a history of CA and have hippocampal/genu volumetric deficits react threateningly out of context and/or have disproportionate threat responses during situations of perceived threat (Hanson et al., 2015). In addition to replicating the current findings, examining these CA × hippocampal and CA × CC interactions on psychophysiological response and indices of threat sensitivity in a sizable PTSD sample would be a logical next step in terms of expanding our knowledge of how these factors interact to increase PTSD susceptibility. Although costly and logistically complex, future studies should also apply longitudinal designs to establish whether a pathway exists between CA and threat sensitivity that lies through hippocampal and CC morphometric irregularities along with investigating how our results map onto neurofunctional differences as they relate to CA and indices of arousal.

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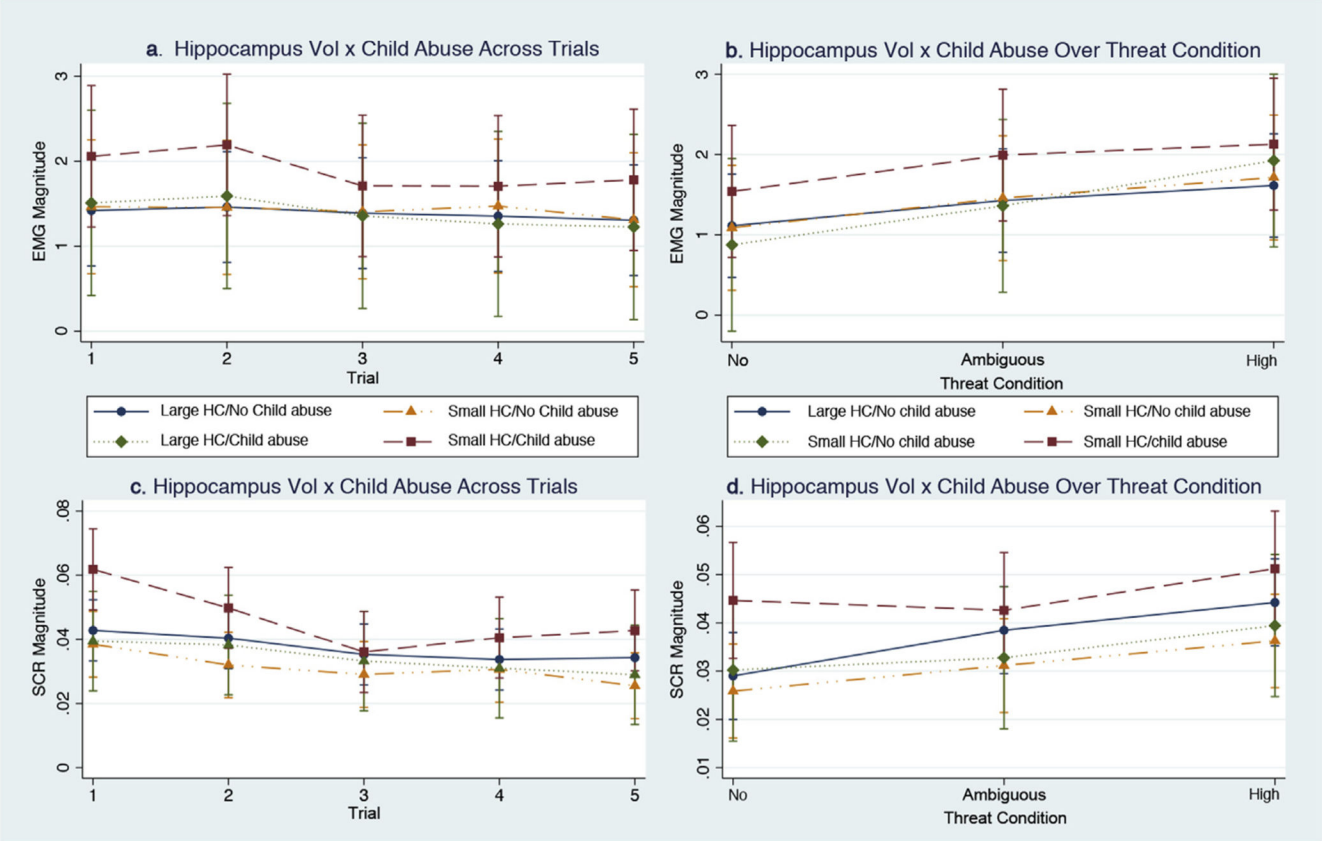

Fig. 1.

Note: HC = hippocampus; for the purposes of visual clarity, HC volume have been dichotomized; EMG = electromyogram; SCR = skin conductance response; EMG and SCR were measured in √μV and √μS respectively; model covariates included: age, race, years of education, PTSD diagnostic status, intercranial volume, adult trauma exposure, GW illness, and high threat condition exposure order.

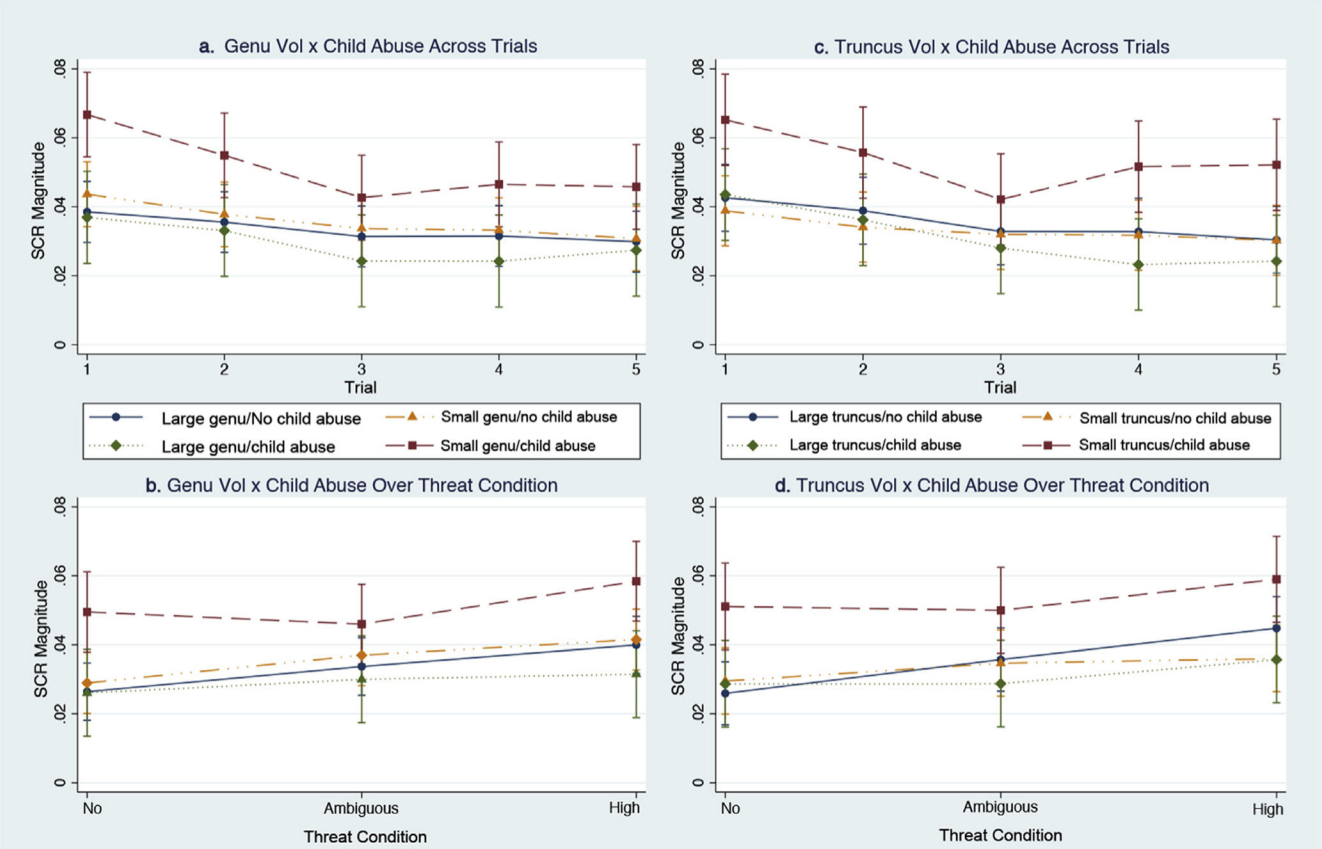

Fig. 2.

Note: For the purposes of visual clarity, genu and truncus volume have been dichotomized; SCR = skin conductance response; SCR was measured in √μS; model covariates included: age, race, years of education, PTSD diagnostic status, intercranial volume, adult trauma exposure, GW illness, and high threat condition exposure order.

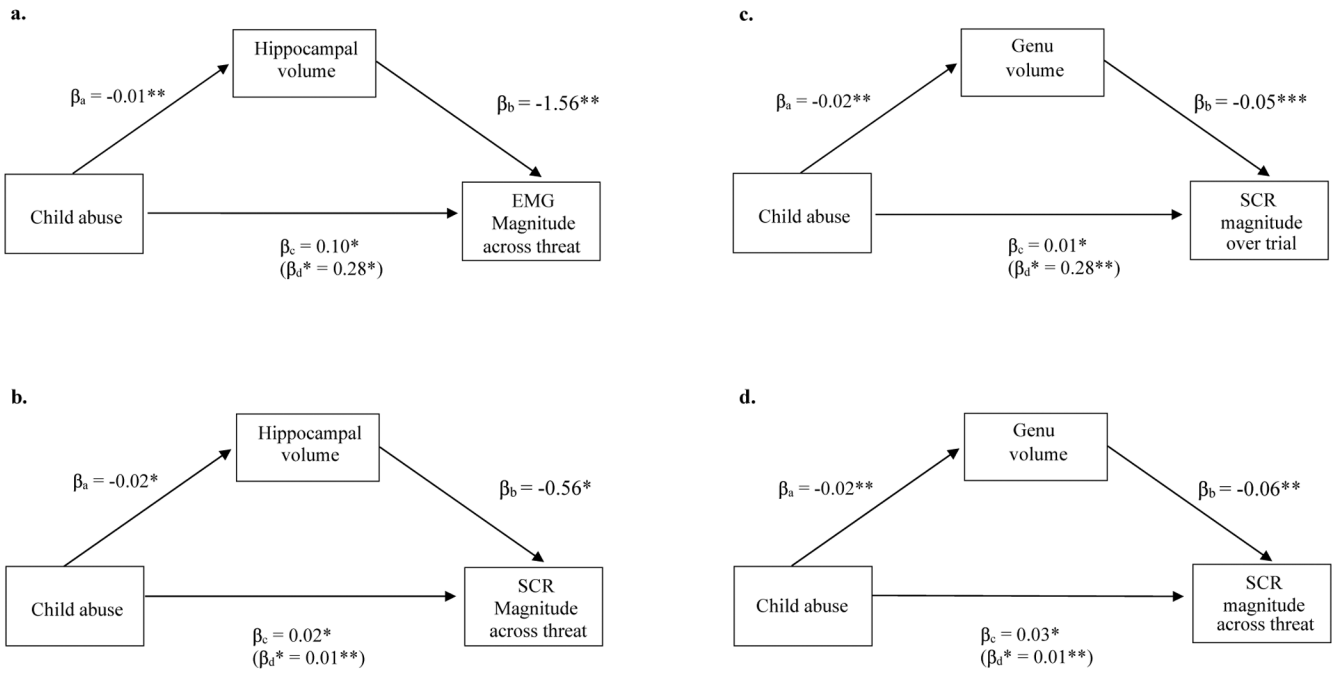

Fig. 3.

Mediation analyses representing the relationship between child abuse and psychophysiological response magnitude being partially mediated by hippocampal and genu volume. *Note*: EMG and SCR magnitudes have been log transformed; this figure is for illustrative purposes only and is consistent with the outcomes obtained from bootstrapping methods described in our Results section; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 1

Descriptive statistics and pairwise comparisons by reported history of child abuse (CA) N = 147.

Characteristics	CA	No CA	Total
N (%)	45 (30.61)	102 (69.39)	147 (100)
Sex			
Male	30 (66.67)	85 (83.33)	115 (78.23) **
Female	15 (33.33)	17 (16.67)	32 (21.77)
Race			
Asian/PI	2 (4.44)	6 (5.88)	8 (5.44)
Black	8 (17.78)	13 (12.75)	21 (14.29)
Latino	4 (8.89)	7 (6.86)	11 (7.48)
White	32 (71.11)	69 (67.64)	101 (68.71)
Other	1 (2.22)	5 (4.90)	6 (4.08)
Exposure to trauma			
Adult trauma	28 (62.22)	48 (47.06)	76 (51.70) **
PTSD diagnosis	24 (53.33)	23 (22.55)	47 (31.97) *
Gulf War Illness	9 (20.00)	13 (12.75)	22 (14.97)
Alcohol Use Disorder	10 (22.22)	26 (25.49)	36 (24.49)
Mean (SD)			
Age	50.10 (8.58)	50.25 (9.76)	50.21 (9.38)
Education[a]	15.53 (1.97)	14.60 (1.92)	14.90 (1.98)
Intracranial volume[b]	1,534,573 (25,171.47)	1,594,005 (15,449.04)	1,573,850 (13,503.32) *
Hippocampus volume[b]	8810.15 (834.23)	8897.83 (815.94)	8868.10 (819.58)
Corpus callosum volume[b]	3330.44 (506.23)	3328.08 (403.20)	33,02.44 (439.07)
EMG[c]	1.21 (1.27)	1.37 (1.28)	1.25 (1.26)
SCR[c]	0.13 (0.10)	0.13 (0.08)	0.11 (0.09)
HR[c]	0.15 (0.12)	0.16 (0.14)	0.16 (0.15)

Note: SD = standard deviation; PI = Pacific Islander.

N (%) and mean (SD) pairwise statistics were given by the χ^2 and t statistic respectfully;

* $p < 0.05$;

** $p < 0.005$;

*** $p < 0.001$.

[a] Education is given in years.

[b] Volume is given in mm^3.

[c] EMG, SCR, and HR are averaged across trials and threat conditions.

Table 2

Mixed models on psychophysiological response magnitudes.

Measure	Predictors by Trial	χ^2	f^2	Predictors by Threat	χ^2	f^2
EMG	Trial	23.23***	0.24	Threat	50.93**	0.50
	CA × Trial	0.00	0.00	CA × Threat	10.04**	0.00
	HC × Trial	0.94	0.00	HC × Threat	4.09	0.00
	CA × HC	9.46**	0.21	CA × HC	10.16**	0.28
	CA × HC × Trial	1.70	0.00	CA × HC × Threat	0.43	0.00
	CC × Trial	1.21	0.00	CC × Threat	2.48	0.00
	CA × CC	0.64	0.00	CA × CC	1.30	0.00
	CA × CC × Trial	0.01	0.00	CA × CC × Threat	3.50	0.00
SCR	Trial	54.63***	0.45	Threat	84.43***	0.46
	CA × Trial	5.53+	0.05	CA × Threat	6.97*	0.00
	HC × Trial	6.33+	0.00	HC × Threat	2.86	0.00
	CA × HC	5.26*	0.16	CA × HC	0.26	0.00
	CA × HC × Trial	7.34*	0.20	CA × HC × Threat	6.97*	0.18
	CC × Trial	4.06	0.16	CC × Threat	0.55	0.00
	CA × CC	8.39**	0.36	CA × CC	6.97*	0.16
	CA × CC × Trial	5.43	0.32	CA × CC × Threat	8.44**	0.37
HR	Trial	3.71	0.00	Threat	11.56***	0.20
	CA × Trial	0.00	0.00	CA × Threat	0.07	0.00
	HC × Trial	6.93+	0.00	HC × Threat	3.93	0.00
	CA × HC	0.95	0.00	CA × HC	0.92	0.00
	CA × HC × Trial	0.40	0.00	CA × HC × Threat	1.73	0.00
	CC × Trial	0.57	0.00	CC × Threat	4.77+	0.05
	CA × CC	0.16	0.00	CA × CC	0.06	0.00
	CA × CC × Trial	0.00	0.00	CA × CC × Threat	0.66	0.00

Note: CA = child abuse; CC = corpus callosum; HC = hippocampus; all models included the following covariates: age, sex, race, years of education, PTSD diagnostic status, intracranial volume, adult trauma exposure, and the order that participants were exposed to the high threat condition;

+ $p < 0.10$;

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$.