Neurostructural associations with traumatic experiences during child- and adulthood

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Introduction

Posttraumatic stress disorder (PTSD) is a debilitating condition affecting about 3.9% of the global population during their lifetime [1]. It is characterized by intrusive re-experiencing of traumatic events, avoidance of trauma-related memories and external cues, and alterations in cognition, mood, arousal, and reactivity (DSM-5 [2]). Motivated by its severe consequences for well-being, health, and mortality [3, 4] and the extremely high prevalence of traumatic experiences worldwide (70% lifetime prevalence; [5]), there have been major ongoing efforts to identify vulnerability factors and refine pathophysiological models of PTSD with a strong focus on neuroimaging.

Among the most consistent neuroimaging findings are lower regional and global white- and gray-matter brain volumes in PTSD patients [6–8]. In terms of local regions, most research has been devoted to the amygdala and the hippocampus. Both regions are involved in cued and contextualized fear learning, show relatively consistent volume reductions in PTSD samples, and exhibit stress-dependent alterations in animal studies [9–12]. Moreover, smaller local volumes have been reported for the insula and the medial prefrontal cortex (PFC) [6], including alterations in interhemispheric white matter tracts in the PFC [13]. These regions play a key role in psychobiological models of PTSD [11, 14].

For the correct interpretation of these findings, it is crucial to distinguish which neural alterations are functionally related to PTSD symptoms and not a mere consequence of stress exposure in the absence of mental or physical sequelae [15]. A meta-analysis by Paquola and colleagues [16] demonstrated that hippocampal atrophies can be found even in healthy stress-exposed samples, while amygdala atrophies were only present in samples with PTSD. Using a more complete approach, the meta-analysis by Bromis and colleagues [6] found that PTSD samples had smaller hippocampal volumes than trauma-exposed controls, which in turn had smaller volumes than trauma-naïve controls, potentially reflecting a dose-response relationship of stress exposure. A similar pattern was descriptively found for the amygdala, but differences between groups were smaller and only statistically significant when the PTSD group was compared to the pooled control groups.

INTRODUCTION

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A major challenge for the field is the potential dependency of stress-brain associations on the timing of adverse experiences. This challenge has received substantial research attention during recent years in the literature on adverse childhood experiences, which is one of the strongest risk factors for PTSD [5]. Volume reductions following childhood maltreatment for both hippocampus and amygdala appear to be dependent on the developmental timing of events, supporting the existence of sensitive neurodevelopmental periods [17–22]. Moreover, the first evidence indicates timing effects generalize to amygdala function, revealing differential effects of trauma exposure and PTSD [23, 24]. These studies on trauma timing have added nuance to the interpretation of neural markers and contribute to theories of (mal-)adaptive neurodevelopment. Nevertheless, they have thus far focused on the period of childhood and adolescence, while studies on stress-exposed adults suggest volumetric alterations can still emerge later in life, although it is unclear whether these include the amygdala and hippocampus [25].

In the present study, we aimed to contrast the neurostructural associations with early and late trauma exposure, while also accounting for the role of psychopathology. We compared regional brain volumes of women who (a) either experienced traumatic events before or after entering adulthood (i.e., age 18) and (b) either developed PTSD or remained physically and mentally healthy. A trauma-naive healthy control group was included as well to assess the general effect of trauma exposure. All groups were matched for age to avoid confounding [26]. The main focus of our study was on the amygdala and the hippocampus, which have by far the strongest theoretical and empirical basis for associations between trauma timing and psychopathology. For exploratory analyses, we further included all structures for which differences between PTSD and (combined) controls were reported in a previous meta-analysis [6] to provide a first basis for the investigation of trauma timing effects on these regions. These exploratory regions included the inferior fronto-orbital gyrus (IFOG), anterior cingulate gyrus (ACG), anterior insula, posterior insula, middle temporal gyrus (MTG), and superior frontal gyrus (SFG).

**METHODS AND MATERIALS**

**Participants**
The total sample of 156 adult women (mean age = 35.3; SD = 10.6; range: 20–60 years) was pooled from two cross-sectional MRI studies on adverse experiences and psychopathology, conducted at the same scanner and facilities between 2010 and 2018 at the Central Institute of Mental Health (CIMH) in Mannheim, Germany. One participant had to be excluded from the analyses due to motion artifacts, resulting in an effective sample size of 155 participants. Sample 1 assessed adult women with traumatic experiences before the age of 18; sample 2 assessed adult women with traumatic experiences during adulthood. Both studies comprised three groups: patients with trauma exposure and PTSD (PTSD), trauma-exposed healthy controls (TC), and trauma-naive healthy controls (HC). Hence, the pooled sample consists of six groups, with 26 female participants in each group (see Procedures and MRI data acquisition for detailed description). Groups from the childhood sample are denoted with a subscripted “child” (e.g., PTSDchild; groups from the adulthood sample are denoted with a subscripted “adult” (e.g., PTSDadult). Demographic and clinical data can be found in Table 1 and Suppl. Table 1. For further notable differences between the two samples, see the Methods section on procedures and the Discussion section on limitations.

All participants received reimbursement for participation (10€/h) and travel expenses. Patients were offered treatment in the outpatient clinics of the CIMH in Mannheim and the outpatient treatment center of Goethe University in Frankfurt. The study was carried out following the Code of Ethics of the World Medical Association (World Medical Association, Declaration of Helsinki, seventh revision, 2013). The study was approved by the Ethical Review Board of the Medical Faculty of Mannheim (Heidelberg University) and the ethics committee of Goethe University. All participants gave written informed consent, including consent for data re-analysis.

**Procedures**

**Sample 1: Trauma experience in childhood.** Participants with PTSD after traumatic experiences in childhood (PTSDchild) were recruited from a larger randomized controlled psychotherapy study [27, 28]. Inclusion criteria were the experience of physical or sexual abuse before the age of 18 as well as female sex and gender identity. Moreover, participants had to fulfill the diagnostic criteria for Borderline Personality Disorder (BPD), including the criterion for affective instability. They underwent MRI measurements between randomization and the first therapy session. PTSD was assessed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) [29]. Trauma exposure was measured by the Life Events Checklist (LEC-5; [30]), which was also used to determine the index traumatic event. Additionally, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; [31]) and the BPD section of the International Personality Disorder Examination were administered (IPDE; [32]). The CAPS-5 assesses the severity of 20 symptoms in relation to the index trauma. Symptoms are assessed on a 5-point scale ranging from 0 (no impairment) to 4 (extreme impairment). In addition to establishing PTSD diagnoses, the total CAPS-5 score with a maximum of 80, gives an indication of clinical severity.

Further self-report measures included retrospective questionnaires on childhood trauma (Childhood Trauma Questionnaire [CTQ]; [33]), PTSD symptoms (PTSD checklist for DSM-5 [PCL-5] [34] Davidson Trauma Scale [DTS] [35]), and severity of depression (Beck Depression Inventory 2 [BDI-II] [36]). Healthy trauma-exposed controls (TCchild) who reported physical or sexual abuse before the age of 18 and healthy trauma-naive controls (HCchild) were recruited with advertisements in local newspapers, flyers, and over the internet.

Exclusion criteria for all participants were age under 18 or over 65, metal implants, pregnancy, left-handedness, and claustrophobia. Exclusion criteria for PTSD participants specifically covered current and lifetime schizophrenia or bipolar-I disorder, mental retardation, or severe psychopathology requiring immediate treatment in a different setting (e.g., BMI < 16.5), medical conditions contradicting exposure-based treatment (e.g., pregnancy), a highly unstable life situation (e.g., homelessness), a life-threatening suicide attempt within the last two months, and substance dependence with no abstinence within two months prior to the study. Exclusion criteria for the trauma controls were any current or previous mental disorder, any prior psychotherapy, or any intake of psychotropic medication.

Structural MRI analyses on a partially overlapping sample have been previously published [18].

**Sample 2: Trauma experience in adulthood.** All participants were assessed by a trained psychologist for trauma exposure using a list of possible traumatic events, taken from the Posttraumatic Diagnostic Scale [37] followed by the SCID-I and II for DSM-IV-TR [29, 38, 39]. Participants were assigned to the PTSD group when the diagnostic criteria were fulfilled in the SCID-I interview. The index events reported by participants in sample 2 were not exclusively limited to interpersonal violence. Participants, reporting other traumatic events fulfilling DSM-V criteria A of the PTSD diagnostics, were also included. In addition, participants were assessed with the German version of the Clinician-Administered Posttraumatic Stress Scale for DSM-IV (CAPS [40, 41]) and had to fulfill criteria B through F. The CAPS score for symptom severity ranges from 0 to 100, assessed on a 5-point scale ranging from zero (“never”/“none”) to four most or all of the (“time”/“extreme”).

For the sample of patients with trauma experience in adulthood (PTSDadult), the following exclusion criteria were applied in the original studies: younger than 18 years, any traumatic experience (interpersonal or any other) before the age of 18 years, comorbid current or lifetime psychotic symptoms, current alcohol/ drug dependence or abuse, borderline personality disorder, cardiovascular or neurological disorders, brain injury, acute pain, continuous pain or medication for attention deficit hyperactivity disorder, pregnancy, and metal implants. Importantly, patients and trauma-exposed individuals in sample two had no traumatic experience before the age of 18 years (telephone screening with PDS and SCID). The healthy trauma-exposed individuals in this sample were trauma-exposed in adulthood (TCadult) but did not fulfill any criteria for a current or past mental disorder as assessed with the SCID-interview as well as the CAPS. Healthy trauma-naive individuals (HCadult) did not fulfill any criteria for a mental disorder.

**MRI data acquisition**

For both samples, we acquired T1-weighted, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) images using the same 3 T Magnetom TRIO whole-body magnetic resonance scanner (Siemens).
Medical Solutions, Erlangen, Germany) equipped with a standard 12-channel volume head coil. Slightly different acquisition parameters were used in each sample, for which we accounted in the preprocessing steps. In the sample of trauma experienced in childhood (sample 1), the following parameters were applied: TR = 1570 ms, TE = 2.75 ms, flip angle 15°, FOV: 256 × 256 mm², matrix size: 256 × 256, voxel size: 1.0 × 1.0 × 1.0 mm³, 176 sagittal slices. In the sample of trauma experience in adulthood (sample 2), the following parameters were applied: TR = 2300 ms, TE = 2.98 ms, flip angle 9°, FOV: 256 × 256 mm², matrix size: 256 × 256, voxel size: 1.0 × 1.0 × 1.1 mm³, 160 sagittal slices.

Clinical assessments for both samples
Traumatic childhood experience was assessed with the German version of the childhood trauma questionnaire (CTQ [42, 43]). The self-report instrument assesses the severity of trauma exposure, such as emotional abuse and neglect, physical abuse and neglect as well as sexual abuse. The 25 items ask how often each event occurred during the participant’s upbringing, and each item is rated on a 5-point Likert scale ranging from 1 (“never at all”) to 5 (“very often”). The overall sum score was calculated, which is calculated by the sum of the five subscales, ranging from 25 to 125. In sample two, the 40-item version of the CTQ was used, with additional two subscales and six items, in which participants could rate the age at which the childhood experiences occurred. However, for the purpose of this study, we only calculated the sum score of the same 25 items as for sample one.

T1-weighted MR imaging of the brain Neuroimaging and the morphometric software tool for the definition of region of interest (ROIs). We then extracted gray matter volumes from CAT12, which is given in Milliliters (mL or ml). We chose to use the unit instead of ml (1 cm³ = 1 ml), which is equivalent. This was done for eight predefined ROIs, following the results by a recent meta-analysis.[6] amygdala, hippocampus, IFG, anterior cingulate ACG, anterior insula, posterior insula, MTG, SFG. Data were assessed for head motion, excluding one participant from the PTSDchil group moving more than the maximum translation of 1 mm in x-, y-, or z-direction and the maximum angular motion of 1° throughout the course of the scan.

Statistical analyses
Statistical analyses were performed in R-Statistics [45] using the packages dplyr [46] for data processing, and rstatix and emmeans for the analyses, and ggplot2 [47] for plotting. We assessed all data for the appropriate assumptions, including normal distribution and outliers. Data was in line with these assumptions, if not stated otherwise below. For the sociodemographic data, two-sample t-tests, as well as Chi-square tests of frequency distributions were applied. We then performed a mixed 3 (group: PTSDchild, PTSDadult) x 2 (sample: childhood, adulthood) x 2 (hemisphere: left, right) Analysis of Covariances (ANCOVAs) for each of the eight ROIs with total intracranial volume (TIV) as a covariate. To counter inflation of Type I errors, Bonferroni corrections were applied (α/8 = 0.05/8 = 0.00625). Post hoc single-step multiple comparison t-tests were applied with Bonferroni corrections.

RESULTS

Sample descriptions
The two patient groups (PTSDchild, PTSDadult) had similar education levels (Table 1, Suppl. Table 1). The age at index trauma was significantly lower in PTSDchild than PTSDadult. Similarly, CTQ scores differed strongly between the two groups (Table 1). There were significant differences in the types of traumatic events experienced in each patient group, with PTSDchild experiencing significantly more interpersonal trauma (e.g., physical or sexual abuse) than PTSDadult. Significantly more patients in the PTSDchild group had comorbid mental disorders on axis-I as well as a borderline personality disorder (Suppl. Table 1). In addition, patients in the PTSDchild group reported significantly higher anxiety scores on the STAI-T. Finally, there was no difference in an overall number of participants taking medication (dichotomous: yes/no) and the kind of medication taken between the PTSDchild and PTSDadult groups (Table 1, Suppl. Table 1). Medication dosage was not assessed.

Amygdala
Comprehensive inferential statistics for all regions of interest are reported in Table 2. Region-wise means and standard deviations can be found in Suppl. Table 2.

We found a significant interaction between the group and sample (Fig. 1; Table 2; Suppl. Fig. 4; Suppl. Table 2). Post hoc t-tests revealed an effect of trauma timing: Amygdala volume was significantly higher for participants with adult trauma compared to those with childhood trauma. This was also apparent in a time series of index traumas in the PTSD groups with a finer time resolution (Fig. 2, Suppl. Table 4). In comparison to the trauma-naive healthy control groups, we found opposite effects dependent on timing: For childhood trauma, the PTSDchild group exhibited significantly smaller amygdala volumes than the HCchild group. For adulthood trauma, both PTSDadult and TCadult had significantly larger amygdala volumes compared to the HCadult group.

We found a significant main effect of the hemisphere, with the right amygdala showing significantly lower volume than the left amygdala. There were no further interactions between the hemisphere and the other independent variables.

Hippocampus
We found a significant main effect of the hemisphere, with a larger volume in the right hippocampus (Fig. 1; Table 2; Suppl. Fig. 4; Suppl. Table 2). All remaining effects were not significant. Descriptively, similar to the pattern for the amygdala, only the PTSDchild group had smaller hippocampal volumes than their reference groups, while both groups with adulthood trauma actually had slightly higher hippocampal volumes, opposite to the expected effect direction.

Exploratory regions of interest
Quantitative results and graphical representations for all exploratory ROIs can be found in Table 2 and Figs. 3 and 4 (as well as Suppl. Figs. 5 and 6; Suppl. Table 2).

IFG. A significant main effect of the group was found. Post-hoc tests revealed that within the childhood sample, both control groups had larger left IFG volumes than the PTSD group.

Anterior insula. A significant main effect of the group was found. Post hoc tests showed that within the adulthood sample, TCs had larger volumes than HCs.
Table 1. Socio-demographic and clinical characteristics of sample.

| Demographics | Childhood \(N = 77\) | Adulthood \(N = 78\) | Analyses |
|---------------|----------------------|----------------------|-----------|
|               | PTSD_{child} \(n = 25\) | TC_{child} \(n = 26\) | HC_{child} \(n = 26\) | PTSD_{adult} \(n = 26\) | TC_{adult} \(n = 26\) | HC_{adult} \(n = 26\) |
| Sex (female)  | M | SD | n | % | M | SD | n | % | M | SD | n | % | M | SD | n | % | F_{group}(1,151) = 0.08, \(p = 0.78\) | F_{sample}(1,151) = 0.28, \(p = 0.60\) | F_{group×sample}(1,151) = 0.18, \(p = 0.67\) |
| Age (in years) | 38.5 | 9.9 | 26 | 100 | 33.8 | 7.6 | 26 | 100 | 34.0 | 11.2 | 26 | 100 | 33.7 | 11.3 | 0.08 | 0.28 | 0.18 |
|              | 0.08 | 0.28 | 0.18 | 0.78 | 0.60 | 0.67 |
| Education    | M | SD | n | % | M | SD | n | % | M | SD | n | % | M | SD | n | % | X^2 | T | df | p |
| No graduation/still at school | 2 | 1 | 1.47 | 3 | 0.69 |
| Junior high school [Hauptschule] | 5 | 4 | 12 |
| Junior high school [Realschule] | 10 | 8 | 12 |
| A-level/American SAT [Abitur] | 8 | 12 |
| Trauma time since trauma (in years) | 29.7 | 11.4 | 25 | 8.3 | 6.79 | 25 | 8.04 | 39.04 | <0.001 |
| Trauma age at index trauma (in years) | 8.8 | 4.4 | 25 | 30.0 | 11.1 | 25 | 10.13 | 32.90 | <0.001 |
| Type of traumatic event (index trauma) | Total (caused voluntarily) | 25 | 100.0 | 16 | 64.0 | 8.67 | 1 | 0.003 |
| (1) Imprisonment | - | - | - |
| (2) Physical violence | 4 | 5 | 12 |
| (3) Sexual abuse | 21 | - | - |
| (4) Rape | - | - | - |
| (5) Wartime experience | - | - | - |
| (6) Witness of sudden death/serious injury of so. | - | - | - |
| (7) Other experience | - | - | - |
| Total (caused involuntarily) | 0 | 0 | 9 | 36.0 | 1 |
| (1) Natural disaster | - | - | - |
| (2) Fire or explosion | - | - | - |
| (3) Accident | - | - | - |
| (4) Sudden death of so. | - | - | - |
| (5) Other experiences | - | - | - |
| Trauma diagnostics | CAPS-4 | - | - | - | 57.0 | 18.9 | 26 |
| CAPS-5 | 42.6 | 9.15 | 25 | - | - | - |
| CTQ | 85.1 | 21.9 | 16 | 44.4 | 19.0 | 25 |
| BSL | 2.1 | 0.7 | 25 | - | - | - |
| Comorbidities | Axis I disorder | Yes/no | 23/2 | 15/11 | 6.20 | 1 | 0.013 |
| Type Axis I | Major depressive disorder | 20 | 80.0 | 11 | 44.0 |
| Anxiety | 10 | 64.0 | 16 | 40.0 |
| Substance abuse/addiction | 3 | 8.0 | 2 | 12.0 |
**Table 1.**

|                         | PTSDchild [n = 25] | PTSDadult [n = 26] | Analysis |
|-------------------------|-------------------|--------------------|----------|
| **Axis II disorder**    |                   |                    |          |
| Yes/no                  | 16/9              | 5/21               |          |
| **Borderline**          |                   |                    |          |
| Total (yes)             | 16                | 9                  |          |
| **STAI-T**              |                   |                    |          |
| Total (yes)             | 62.4              | 48.6               |          |
| BC                       |                   |                    |          |
| Total (yes)             | 10                | 3.6                |          |
| **Psychopharmacological** |               |                    |          |
| Total (yes)             | 20                | 76.9               |          |
| **Other**               |                   |                    |          |
| Total (yes)             | 5                 | 12                 |          |

Significant group differences are marked with bold values. ACG = Group of healthy control subjects (a– adulthood, c– childhood), who have at least experienced one traumatic event but do not fulfill the criteria for PTSD.

Posterior insula. There were significant main effects for the group, sample, and hemisphere, as well as a significant interaction between the sample and hemisphere. Only the post-hoc tests for hemisphere survived multiple comparison corrections, confirming larger volumes of the right insula in all groups.

ACG. As for the posterior insula, we found a significant main effect of group, sample, and hemisphere, as well as a significant interaction between sample and hemisphere. Post-hoc effect indicated larger brain volumes in HCchild than PTSDchild within the left ACG. There was also a significant difference between the two healthy control groups within the right ACG.

MTG. There was a significant interaction between the sample and hemisphere, but post-hoc tests did not survive correction for multiple comparisons. Descriptively, the significant interaction is most likely driven by the larger right volumes in the two trauma groups exposed during adulthood, with visual similarity to the disordinal pattern found for the amygdala.

SFG. Significant main effects for the group, sample, and hemisphere were found, with no post-hoc contrasts surviving correction for multiple comparisons.

**DISCUSSION**

In the research literature on early adversity, trauma-induced differences in brain volume are increasingly viewed as largely dependent on the neurodevelopmental timing of events. Still, most studies on sensitive periods limited their scope to events occurring during childhood and adolescence. Extending research on sensitive periods to adverse events during adulthood may further help differentiate early neurodevelopmental processes from life-long plasticity.

The amygdala and the hippocampus play a key role in psychobiological models of PTSD and have been highlighted in research on sensitive periods during early childhood and early adolescence [11, 18, 48]. Building on this research, we found evidence that amygdala volumes strongly depended on the timing of events, revealing qualitative differences between individuals who were traumatized in childhood or adulthood (see the limitation section for a discussion of potential confounders). While participants with PTSD following childhood trauma had lower amygdala volumes compared to trauma-naive healthy controls, participants with adult trauma had higher amygdala volumes. These higher volumes were apparent in both trauma-exposed groups with- and without psychopathology, potentially indicating general neuroplastic events in response to exposure, rather than clinically meaningful differences. Similar qualitative differences have been reported for amygdala responses to facial expressions as a function of trauma timing for early childhood versus adolescence, but the study did not test for adulthood trauma [24].

While these qualitative differences in amygdala volumes might be explained by neurodevelopmental timing, repeated exposure represents a plausible alternative explanation. Kuo et al. [49] found that amygdala volumes decreased with combat exposure in veterans who experienced early trauma, indicated by fulfilling PTSD criterion A of the DSM-5. In contrast, amygdala volumes increased with combat exposure in veterans without criterion A childhood trauma. Hence, while adult trauma by itself might lead to increased amygdala volumes, severe childhood adversity might function as a moderator which reverses the effect direction. This finding could also plausibly explain why childhood trauma led to smaller amygdala volumes only for the PTSD sample and not the trauma-exposed controls, as participants with severe psychopathology likely experience more severe and frequent stress in adulthood than trauma-exposed healthy controls. Still, this
Table 2. Results of ANCOVAs on volumetric data.

| ROI          | Analysis                                                                 | Post-Hoc t-tests                                                                 |
|--------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|              |                                                                           | Post-hoc comp. | Group/ sample | Hemisphere | Contrast      | MoE 95% CI | t    | df | P_m.s.e. | Hedge’s g |
|              |                                                                           | Adult > child | 0.05          | 0.02:08     | 3.13          | 147 | .002 | 0.50 |
|              |                                                                           | Adult > child | 0.06          | 0.03:09     | 3.81          | 151 | <.001 | 0.61 |
|              |                                                                           | Adult > child | 0.02          | 0.01:05     | 2.10          | 475 | <.001 | 0.60 |
|              |                                                                           | Adult > child | 0.10          | 0.07:16     | 4.72          | 423 | <.001 | 1.32 |
|              |                                                                           | Adult > child | 0.13          | 0.08:18     | 5.07          | 439 | <.001 | 1.41 |
|              |                                                                           | Adult > child | 0.08          | 0.03:13     | 2.99          | 468 | <.01  | 0.83 |
|              |                                                                           | Adult > child | 0.09          | 0.04:14     | 3.62          | 460 | <.002 | 1.01 |
|              |                                                                           | Adult > child | 0.07          | 0.02:11     | 2.61          | 479 | <.002 | 0.73 |
|              |                                                                           | Adult > child | 0.07          | 0.02:11     | 2.91          | 437 | <.016 | 0.81 |
|              |                                                                           | Adult > child | 0.07          | 0.02:11     | 2.68          | 443 | <.031 | 0.75 |
|              |                                                                           | Adult > child | 0.28          | 0.12:44     | 3.23          | 488 | <.002 | 0.95 |
|              |                                                                           | Adult > child | 0.29          | 0.15:43     | 3.08          | 495 | <.001 | 1.15 |
|              |                                                                           | Adult > child | 0.30          | 0.14:47     | 3.06          | 475 | <.001 | 1.04 |
|              |                                                                           | Adult > child | 0.30          | 0.15:46     | 3.24          | 499 | <.001 | 1.09 |
|              |                                                                           | Adult > child | 0.32          | 0.15:49     | 3.14          | 495 | <.002 | 1.06 |
|              |                                                                           | Adult > child | 0.30          | 0.11:48     | 3.24          | 492 | <.001 | 0.89 |
|              |                                                                           | Adult > child | 0.19          | 0.06:31     | 2.92          | 486 | <.016 | 0.82 |
|              |                                                                           | Adult > child | 0.20          | 0.06:34     | 2.96          | 489 | <.014 | 0.83 |
|              |                                                                           | Adult > child | 0.28          | 0.12:44     | 3.23          | 488 | <.002 | 0.95 |
|              |                                                                           | Adult > child | 0.29          | 0.15:43     | 3.08          | 495 | <.001 | 1.15 |
|              |                                                                           | Adult > child | 0.30          | 0.14:47     | 3.06          | 475 | <.001 | 1.04 |
|              |                                                                           | Adult > child | 0.30          | 0.15:46     | 3.24          | 499 | <.001 | 1.09 |
|              |                                                                           | Adult > child | 0.32          | 0.15:49     | 3.14          | 495 | <.002 | 1.06 |
|              |                                                                           | Adult > child | 0.30          | 0.11:48     | 3.24          | 492 | <.001 | 0.89 |
|              |                                                                           | Adult > child | 0.19          | 0.06:31     | 2.92          | 486 | <.016 | 0.82 |
|              |                                                                           | Adult > child | 0.20          | 0.06:34     | 2.96          | 489 | <.014 | 0.83 |
|              |                                                                           | Adult > child | 0.44          | 0.13:76     | 2.81          | 434 | <.022 | 0.78 |
|              |                                                                           | Adult > child | 0.27          | 0.11:44     | 3.34          | 496 | <.002 | 0.93 |
|              |                                                                           | Adult > child | 0.26          | 0.21:05     | 4.79          | 485 | <.001 | 1.33 |
|              |                                                                           | Adult > child | 0.26          | 0.14:38     | 4.33          | 462 | <.001 | 1.23 |
|              |                                                                           | Adult > child | 0.34          | 0.20:51     | 4.70          | 480 | <.001 | 1.31 |
|              |                                                                           | Adult > child | 0.26          | 0.10:41     | 3.34          | 456 | <.002 | 0.93 |
|              |                                                                           | Adult > child | 0.38          | 0.18:58     | 3.77          | 490 | <.001 | 1.05 |
|              |                                                                           | Adult > child | 0.45          | 0.09:82     | 2.52          | 441 | <.046 | 0.71 |
|              |                                                                           | Adult > child | 0.40          | 0.06:74     | 4.24          | 470 | <.021 | 0.66 |

Note: All results are significant at p < 0.05.
Table 2. continued

| ROI         | Analysis                                                                 | Post-hoc t tests                                                                 |
|-------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|             |                                                                           | Post-hoc comp. | Group/ sample | Hemisphere | Contrast | M_{off} | 95% CI | t     | df | p_{bonferroni, cor} | Hedge's g |
| MTG         | \( F_{\text{MTG}}(1, 148) = 115.36, \ p < .001, \ \eta^2 = .41 \)       |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{MTG}}(2, 148) = 1.56, \ p = .21, \ \eta^2 = .02 \)           |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{MTG}}(1, 148) = 1.48, \ p = .23, \ \eta^2 = .01 \)           |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{MTG}}(1, 148) = 1.17, \ p = .26, \ \eta^2 = .01 \)           |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{group x sample}}(2, 148) = 0.60, \ p = .68, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{group x hemisphere}}(2, 148) = 0.38, \ p = .68, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{sample x hemisphere}}(1, 148) = 4.66, \ p = .01, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{hemisphere}}(1, 148) = 102.79, \ p < .001, \ \eta^2 = .38 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{hemisphere}}(1, 148) = 4.65, \ p = .03, \ \eta^2 = .03 \)   |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{hemisphere}}(1, 148) = 5.46, \ p = .02, \ \eta^2 < .01 \)   |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{group x sample}}(2, 148) = 0.16, \ p = .85, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{group x hemisphere}}(2, 148) = 0.35, \ p = .71, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{sample x hemisphere}}(1, 148) = 0.11, \ p = .74, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |
|             | \( F_{\text{sample x hemisphere}}(2, 148) = 2.25, \ p = .11, \ \eta^2 < .01 \) |                                                        |                                                                    |           |          |         |       |       |     |                |           |

*\( p_{\text{bonferroni, cor}} = 0.05/8 = .006 \).

ACG: Anterior cingulate gyrus, Ant. Insula: Anterior insula, IFOG: Inferior fronto-orbital gyrus, MTG: Middle temporal gyrus, Pos. Insula: Posterior insula, SFG: Superior frontal gyrus.
was facilitated by the study procedure. Therefore, it is possible that differences might be attributable to these confounders instead of trauma timing. Still, such differences in confounders might be inherent to realistic occurrences of traumatic events in feasible designs using human neuroimaging. For example, the whole childhood sample experienced maltreatment, a distinct trauma type without a direct counterpart in adulthood which usually coincides with higher multiplicity and duration. Even for singular and highly random adverse events that might seem comparable at first glance (e.g., certain cases of natural disasters and sexual assault), the meaning and impact are vastly different for affected children and adults. Hence, while our design cannot rule out many important confounders, suggesting a careful interpretation of results, these confounders might be inherent differences between typical trauma during childhood and adulthood. Importantly, the opposite effects for amygdala volume in childhood and adulthood are not compatible with a monotonic dose-response effect of variables like duration and multiplicity.

CONCLUSION

Our findings suggest that amygdala aberrations following adverse experiences might be dependent on timing and could occur in response to traumatic events in both childhood and adulthood. Adversity effects during childhood and adulthood had opposing directions, highlighting the importance to differentiate between neurodevelopmental mechanisms and life-long plasticity. These findings add nuance to the interpretation of brain volumetric associations with adverse experiences. We did not observe such effects of timing for other predefined brain regions implicated in

Fig. 1  Gray matter volume in amygdala and hippocampus. Volumetric differences in the amygdala and hippocampus between samples (childhood, adulthood), groups (PTSD, TC, HC), and hemispheres (left, right) in cm³.

Fig. 2  Gray matter volume by age in amygdala and hippocampus. Volumetric differences in the amygdala and hippocampus for both patient groups (PTSD_{adult}, PTSD_{child}) in time bins defined by the age of the index trauma separately for each hemisphere (left, right) in cm³.
Fig. 3 Gray matter volume in IFOG, ACG, ant. insula and post. insula. Volumetric differences in the inferior fronto-orbital gyrus (IFOG), anterior cingulate gyrus (ACG), anterior (ant.), and posterior (pos.) insulae between samples (childhood, adulthood), groups (PTSD, TC, HC) and hemispheres (left, right) in cm$^3$.

Fig. 4 Gray matter volume in the MTG and SFG. Volumetric differences in the middle temporal gyrus (MTG) and superior frontal gyrus (SFG) between samples (childhood, adulthood), groups (PTSD, TC, HC), and hemispheres (left, right) in cm$^3$. 
volumetric brain differences related to PTSD. Through our three-group design, our study might inform not only future studies on timing but also help differentiate the effects of psychopathology and trauma exposure.

DATA AVAILABILITY

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Ethical restrictions to protect participant confidentiality prevent us from making study data publicly available. This also refers to the analysis/experimental code, and any other digital materials, where participant-related information (like sex or psychopathological status) is also included. Readers seeking access to the study data and materials should contact the corresponding author based on a formal collaboration agreement. This formal collaboration agreement indicates that data will be shared with other researchers who agree to work with the authors, and for the sole purpose of verifying the claims in the paper. The data and materials will be released to requestors after approval of this formal collaboration agreement by the local Ethics Committee of the Medical Faculty Mannheim.

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