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Peritraumatic Neural Processing and Intrusive Memories: The Role of Lifetime Adversity

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ABSTRACT

BACKGROUND: Pathological peritraumatic encoding is proposed as a proximal risk factor for the development of posttraumatic stress disorder (PTSD), with trauma-analog studies linking increased neural processing of trauma films to intrusive trauma recollections, a core symptom of PTSD. Cumulative lifetime adversity is proposed as a more distal risk factor, with research indicating a tipping point at about five events with regard to PTSD development following re-exposure to trauma. Thus, within a diathesis × stress framework, increased peritraumatic neural processing may constitute a specific risk factor for PTSD, particularly in individuals with several lifetime adversities.

METHODS: Fifty-three healthy women watched highly aversive films depicting severe interpersonal violence versus neutral films during functional magnetic resonance imaging, and they reported involuntary recollections during subsequent days. Moderation analyses tested the interactive relationship between peritraumatic neural processing and lifetime adversity in predicting intrusion load, i.e., the total number of intrusions weighted for their average distress.

RESULTS: Increased processing of aversive versus neutral films in the amygdala, anterior insula, dorsal and rostral anterior cingulate cortices, and hippocampus predicted increased intrusion load only in participants reporting above five lifetime adversities; for participants reporting few to none, no such relationship was found. This interactive relationship explained ≤59% of variance. Conditioned stimuli preceding film viewing mirrored this pattern.

CONCLUSIONS: Peritraumatic neural processing in multiple salience network regions and cumulative lifetime adversity interactively predicted PTSD-like symptomatology, representing a diathesis × stress framework that might guide identification of at-risk individuals and potential targets for symptom prevention after traumatic incidents.

Keywords: Adverse childhood experiences, Affective neuroscience, Diathesis-stress model, Pavlovian conditioning, Posttraumatic stress disorder, Trauma film

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While many individuals experience lifetime adversity such as a car accident, physical or sexual abuse, or a natural disaster, only a minority of persons with such experiences develop posttraumatic stress disorder (PTSD) (1,2). Clinical cognitive behavioral models of PTSD (3,4) and findings from trauma-exposed adults propose that neurocognitive processing during trauma (i.e., peritraumatic processing) contributes to the development and maintenance of PTSD symptoms (5). Evidence for the importance of peritraumatic processes mainly comes from clinical studies that rely on retrospective reports; thus, trauma processing and early memory formation itself escape the window of investigation in such studies. This shortcoming motivated laboratory trauma-analog studies (6,7) that allow for a prospective investigation of distressing recollections, i.e., daily-life intrusions resulting from laboratory exposure to highly aversive films (8,9). Such "intrusions" can be seen as an analog to involuntary re-experiencing of trauma (8), a hallmark symptom of PTSD.

Using this paradigm in a functional magnetic resonance imaging (fMRI) environment, Bourne *et al.* (9) compared brain activity in response to aversive film scenes that elicited intrusive memories with brain activity in response to film scenes that did not. Within-subject analyses revealed stronger activations in key nodes of the salience network (amygdala, insula) and the rostral anterior cingulate cortex (rACC) to intrusion-eliciting scenes than to non–intrusion-eliciting scenes. In line with these findings, researchers developing neuroscientific models of PTSD consistently discuss hyperactivity across key nodes of the salience network, including the amygdala, insula, and dorsal anterior cingulate cortex (dACC), as neural correlates of PTSD (7,10,11). These researchers further propose that in PTSD, a hypoactive medial prefrontal cortex, including ventromedial prefrontal cortex (vmPFC) and rACC, fails to downregulate the hyperresponsive salience network. This loss of top-down inhibition is thought to result in poor control over attention and response to trauma-related cues and may thus underlie the re-experiencing of trauma (10–13). Concerning hippocampal functioning, several research groups report hypoactivity in PTSD, implicating poor contextualization of

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trauma memories (14–16), whereas others report hyperactivity (10,17,18); thus, the picture regarding hippocampal function in PTSD remains unclear.

Besides increased peritraumatic neural processing (proximal risk factor), lifetime adversity constitutes a more distal, traitlike risk factor (diathesis) for developing PTSD on reexposure to trauma (19–21). Findings from neuroimaging studies suggest that lifetime adversity alters brain functioning involved in threat detection and emotion regulation, among others (22–24). Although it is commonly assumed that these adversity-related brain changes go along with psychopathology, evidence for this assumption is equivocal. While adversity-related brain changes are found in subjects with PTSD relative to the brains of those who are trauma exposed but resemble unexposed control subjects (25–27), a host of studies document the independence of adversity-related brain abnormalities from psychopathology (24). Therefore, adversity-related neural changes do not necessarily go along with psychopathology, which leads us to question the assumed path from lifetime adversity to PTSD through brain activity. Instead, lifetime adversity and increased neural processing in response to threatening stimuli may be two distinct, yet interacting, factors contributing to PTSD vulnerability within a diathesis × stress framework. In light of evidence pointing to a risk threshold of four previous traumatic events (28,29), increased peritraumatic neural processing may constitute a specific risk factor for PTSD, particularly in individuals with a higher number of lifetime adversities, while having little effect on those with low adversity. However, to the best of our knowledge, in no previous study have researchers investigated to what extent peritraumatic neural processing and lifetime adversity play together or may even interact in predicting PTSD-like symptoms.

In this study, we investigated to what extent a history of individual differences in lifetime adversity modulates the relationship between the neural processing of analog trauma and the development of intrusive memories, a core symptom of PTSD. We implemented the trauma film paradigm in the fMRI scanner and subsequently assessed intrusions ambulatorily on 3 consecutive days. As clinical research shows that intrusions perceived as very distressing are those that are primarily linked to persistent PTSD (30), we were primarily interested in the frequency of intrusions weighted for their distress (intrusion load). We expected peritraumatic neural processing (increased amygdala, anterior insula, and dACC activity, as well as decreased vmPFC activity, with no clear prediction for the hippocampus) and lifetime adversity to combine their risk potential in an interactive way, i.e., particularly individuals with high levels on both risk factors should be susceptible to intrusion development after analog trauma (diathesis × stress model). We only tentatively expected peritraumatic processing alone (stress) or lifetime adversity alone (diathesis) to predict intrusion load. Exploratory analyses examined to what degree neutral visual stimuli preceding repeated film presentations would reflect this pattern [compare with differential fear acquisition during Pavlovian conditioning as a model of PTSD (11)]. Since lifetime adversity may be related to common psychopathology traits represented by elevated anxiety or depressive symptoms, we additionally included them as covariates.

METHODS AND MATERIALS

Participants

Fifty-three healthy female participants (mean age = 22.90 years, SD = 4.18 years) were included in the analyses. Exclusion criteria were blood-injury-injection phobia, self-report of psychosis, use of psychotropic medication, substance abuse/dependency, bipolar disorder, serious medical conditions, and history of traumatic head injury. Further exclusion criteria were extensive media consumption of violent or medical content (more than three times a week) and poor sleep quality [≤7 on the Pittsburgh Sleep Quality Index (31)]. For fMRI, exclusion criteria were pregnancy, ferromagnetic implants, other nonremovable metal objects, and claustrophobia. Two participants were excluded because of technical problems and five because of missing questionnaire data. The study was approved by the local ethics committee, and participants provided informed consent before participation.

Apparatus and Physiological Recordings

Stimulus presentation and behavioral data acquisition were controlled by E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA).

fMRI Recording. MRI data of the experimental task were acquired on a 3T system (Siemens MAGNETOM Trio Tim Syngo) with a 12-channel head coil. For each session, 758 volumes aligned to the anterior and posterior commissure plane were acquired, and the first six volumes were discarded to allow for stabilization of the blood oxygen level–dependent signal. Functional images were acquired with a T2-weighted gradient echo-planar imaging sequence (repetition time = 2250 ms, echo time = 30 ms, matrix 64 × 64, field of view = 192 mm, flip angle = 70°). Thirty-six slices with a slice thickness of 3 mm and a slice gap of 0.3 mm were acquired within the repetition time. An additional magnetization-prepared rapid-acquisition T1-weighted gradient echo structural image (voxel size of 1 × 1 × 1.2 mm) was acquired for coregistration. Participants viewed the visual stimuli through a head-coil–mounted mirror, and sounds were presented via noise-shielding headphones.

Materials and Procedure

One week before fMRI scanning, participants completed the State-Trait Anxiety Inventory (32) [German version (33)] and the Center for Epidemiologic Studies Depression Scale (34) [German version (35)]. At the end of the study, participants completed a questionnaire assessing traumatic life experiences, the Traumatic Life Events Questionnaire (36) [German version (37)]. For further detail, see the Supplement.

Film Viewing. This study used an adaption of the conditioned intrusion paradigm that was previously developed in our laboratory (38–40) for fMRI. Six different 16-second-duration aversive film scenes depicting severe interpersonal violence and six 16-second-duration neutral film scenes depicting nonviolent interpersonal interactions were presented twice in pseudorandom order (restriction: not more than two consecutive aversive or neutral films), with interfilm intervals varying

between 14 and 18 seconds. Aversive and neutral clips were extracted from commercial movies (see the Supplement). They were preceded by two different 4-second-duration static neutral face stimuli (for investigating classical conditioning, 75% reinforcement rate).

Ambulatory Assessment of Intrusive Memories. After scanning, participants were instructed to report intrusive memories of the film clips experienced on the day of film viewing and on the following 3 days in an event-based manner (40). Intrusive memories were defined as recurring images or thoughts about the film but also as recurring thoughts or feelings that had been present during viewing [Intrusive Memory Questionnaire (41,42)]. Participants were instructed to report involuntary memories only, without deliberate recall; intrusions during the night (e.g., in dreams, during awakenings) were also counted. In addition, participants had to briefly describe the content of each intrusion and to report the distress associated with it (visual analog scale from 0 [not at all distressing] to 100 [extremely distressing]). If participants did not report any intrusion for a respective day, intrusion frequency and distress were set to 0. Intrusions were assessed via a customized e-diary application (PsyDiary) (43) installed on participants' smartphones.

Data Reduction

Self-report Data. To assess the occurrence of lifetime adversity, we computed a sum score that included all traumatic events reported in the Traumatic Life Events Questionnaire (results were similar if traumatic events were weighted for their distress). To assess intrusion load following the film viewing, we weighted the frequency of intrusions for their distress across the 3 days of assessment (total frequency × average distress = intrusion load). For detailed analyses of intrusion frequency and distress, see the Supplement.

fMRI Data. Preprocessing and analysis was performed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Details can be found in the Supplement.

Parameter estimates were extracted with MarsBaR using WFU PickAtlas masks implemented in SPM (44) for the amygdala, hippocampus, and vmPFC. dACC and rACC masks were built with WFU PickAtlas toolbox using the procedures described by Cascio *et al.* (45) and Bryant *et al.* (46). Anterior insula region of interest was downloaded from an online atlas of functional regions of interest (47). Parameter estimates of bilateral amygdala, anterior insula, hippocampus, rACC, dACC, and vmPFC activations to neutral film clips were subtracted from activations to aversive clips. As left and right activations yielded similar results, we report only mean activations (*p* values for the statistical moderation analysis including either left or right activations did not substantially change, and all interaction effects showed $p < .001$).

Statistical Analyses

Regression analyses checked for a simple effect of peritraumatic neural processing (amygdala, anterior insula, rACC, dACC, hippocampus, and vmPFC; stress model) on intrusion load and a simple effect of cumulative lifetime adversity (diathesis) on intrusion load. Moderation analyses (diathesis × stress model) were computed to examine the role of neural threat processing (amygdala, anterior insula, rACC, dACC, hippocampus, and vmPFC) on intrusion load as a function of lifetime adversity (see the Supplement for intrusion frequency and distress as independent variables). Additional analyses included trait anxiety and depression in the moderation models as covariates, to exclude the possibility that findings for lifetime adversity were mainly due to current psychopathological traits. Regression and moderation analyses were computed using MPlus (48); Bayesian statistics were used (using noninformative priors), as this type of analysis does not rely on data distribution assumptions (49). All predictors were mean centered, and R^2 is reported as effect size. Bonferroni-adjusted α level was used, correcting for analyses testing for six brain regions separately: $\alpha = .05/6 = .008$.

The interaction effect was evaluated using the Johnson-Neyman technique to examine significant interactions between continuous predictors (50,51). This technique plots regions of significance, the value range of lifetime adversity in which neural processing had significant effects on intrusion load [95% confidence interval; range of the moderator within which the simple slope of y on x is significantly different from 0 (52,53)]. The y-axis displays the slope of neural processing on intrusion load, and the x-axis shows continuous levels of the moderating variable, lifetime adversity. This technique does not require the selection of two arbitrary values of the moderator at which to assess the significance of neural processing (e.g., ±1 SD from the mean), and it provides a more complete picture than do traditional methods.

In the Supplement, we report our additional analysis of the role of three dysfunctional circuits implicated in PTSD symptomatology (54) on intrusion load as a function of lifetime adversity. We further report psychophysiological interaction analyses that checked for the role of amygdala-hippocampus coupling on intrusion load as a function of lifetime adversity. Additionally, we also investigated the link between differential (conditioned stimulus positive [CS+] vs. conditioned stimulus negative [CS−]) neural acquisition learning on intrusion load and the role of lifetime adversity on this.

RESULTS

Distinct Neural Activation Patterns to Trauma Films: Aversive > Neutral

Viewing of aversive versus neutral films resulted in higher brain activity in a widespread network including the amygdala, anterior insula, dACC, rACC, and hippocampus (see Figure 1 and Supplemental Table S1). The reverse contrast (neutral > aversive) activated the precuneus, posterior insula, and middle frontal gyrus, among other regions (see Supplemental Table S2 and Supplemental Figure S1).

Sample Characteristics

Participants reported on average 1.55 intrusions (SD = 2.02 intrusions) that induced an average distress level of 11.58 (SD = 14.69, scale 0–100) across the 3 days of assessment (with an exponential decay pattern across days typical for trauma film studies). On average, participants reported 4.98

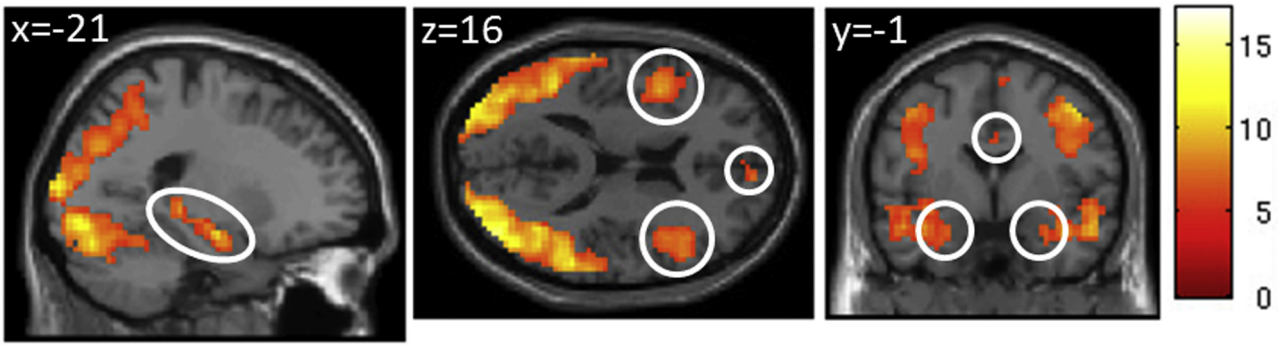

Figure 1. The aversive > neutral contrast, whole-brain $p < .05$ familywise error corrected, $k = 10$, resulted in higher brain activity in widespread bilateral areas including (left panel) the hippocampus, (middle panel) the anterior insula and rostral anterior cingulate cortex, and (right panel) amygdala and dorsal anterior cingulate cortex (Supplemental Table S1).

lifetime adversities (median = 2 adversities, SD = 5.98 adversities, range = 0–21 adversities); depressive symptoms and trait anxiety were within normal range (number of depressive symptoms: mean = 9.94, SD = 6.08; State-Trait Anxiety Inventory score, mean = 35.43, SD = 7.13).

Stress Model: Link Between Neural Responses and Intrusion Load

Using the Bonferroni-adjusted α level, we found that increased dACC activity was significantly related to increased intrusion load, which explained 21.4% of the variance (mean brain activity in response to the negative compared to the neutral films in arbitrary units = .08, SD = .33; $b = 141.44$ [95% confidence interval (CI), 66.97 to 216.08], $p < .001$); activity in none of the other brain regions was significant (amygdala: mean = .27, SD = .29; $b = 63.46$ [95% CI, −30.29 to 157.44], $p = .180$; insula: mean = .18, SD = .32; $b = 80.68$ [95% CI, −1.66 to 163.21], $p = .054$; $R^2 = .07$; hippocampus: mean = .19, SD = .18; $b = 62.18$ [95% CI, −87.85 to 212.57], $p = .410$; rACC: mean = .02, SD = .22; $b = 64.28$ [95% CI, −61.13 to 188.60], $p = .312$; vmPFC: mean = −.09, SD = .27; $b = -14.68$ [95% CI, −117.38 to 87.15], $p = .774$).

Diathesis Model: Link Between Lifetime Adversity and Intrusion Load

Cumulative lifetime adversity was related to increased intrusion load, which explained 19.5% of the variance ($b = 7.35$ [95% CI, 3.25 to 11.45], $p < .001$).

Diathesis × Stress Model: Lifetime Adversity Moderates Link Between Neural Responses and Intrusion Load

Using the Bonferroni-adjusted α level, we found a significant interaction effect between peritraumatic processing and lifetime adversity on intrusion load for the amygdala ($b = 26.65$ [95% CI, 17.07 to 36.33], $p < .001$; total $R^2 = .54$), insula ($b = 19.57$ [95% CI, 11.19 to 27.98], $p < .001$; total $R^2 = .50$), dACC ($b = 16.26$ [95% CI, 9.78 to 22.88], $p < .001$; total $R^2 = .59$), hippocampus ($b = 48.46$ [95% CI, 28.62 to 68.24], $p < .001$; total $R^2 = .48$), and rACC activity ($b = 40.62$ [95% CI, 25.11 to 56.20], $p < .001$; total $R^2 = .50$). As evident in Figures 2 and 3, peritraumatic neural processing was linked to increased intrusion load only in individuals reporting above five lifetime adversities ($N = 16$). No interaction effect was found between peritraumatic neural processing and lifetime adversity for the vmPFC ($b = 10.68$ [95% CI, −9.01 to 30.42], $p = .282$; total $R^2 = .23$). For intrusion frequency and distress analyzed separately (see the Supplement), the overall pattern of results was similar for distress. For frequency, several regions did not reach significance after Bonferroni correction.

Pairwise correlations of activations (aversive > neutral) between the six brain regions ranged from .11 (insula and vmPFC) to .87 (insula and dACC) (mean = .53, SD = .20), thus explaining between 1% and 76% shared variance (mean = .35, SD = .23). On average, activations were statistically sufficiently independent and are theoretically implicated in different neurocognitive processes to justify separate analyses. Previous lifetime adversity did not correlate with any neural responses ($|r| \leq .19$).

Including either depressive symptoms or trait anxiety in the moderation analyses did not change interaction effects (p values $< .001$). R^2 values increased by less than 3% (see the Supplement).

DISCUSSION

The current study investigated the moderating role of cumulative lifetime adversity on the relationship between peritraumatic neural processing during analog trauma and intrusion load, thereby testing a diathesis × stress interaction model of PTSD-like intrusion formation. Cumulative lifetime adversity appeared to "gate" the influence of peritraumatic neural processing on intrusion load, with increased processing in the amygdala, dACC, anterior insula, hippocampus, and rACC during analog trauma, predicting intrusion load during subsequent days only in individuals reporting above five lifetime adversities ($R^2 \approx 50\%$); in individuals with low lifetime adversity, equivalent neural responding to the films did not translate into higher intrusion load. When intrusion load was split into distress and frequency, it was largely intrusion distress that accounted for these results. Relatively weak evidence was found for a simple stress model, since only dACC activity ($R^2 \approx 21\%$) and none of the other brain regions predicted intrusion load. Cumulative lifetime adversity (diathesis) alone was a significant predictor of intrusion load. However, the variance explained was substantially higher (approximately 30% increase) for the interactive diathesis × stress frame.

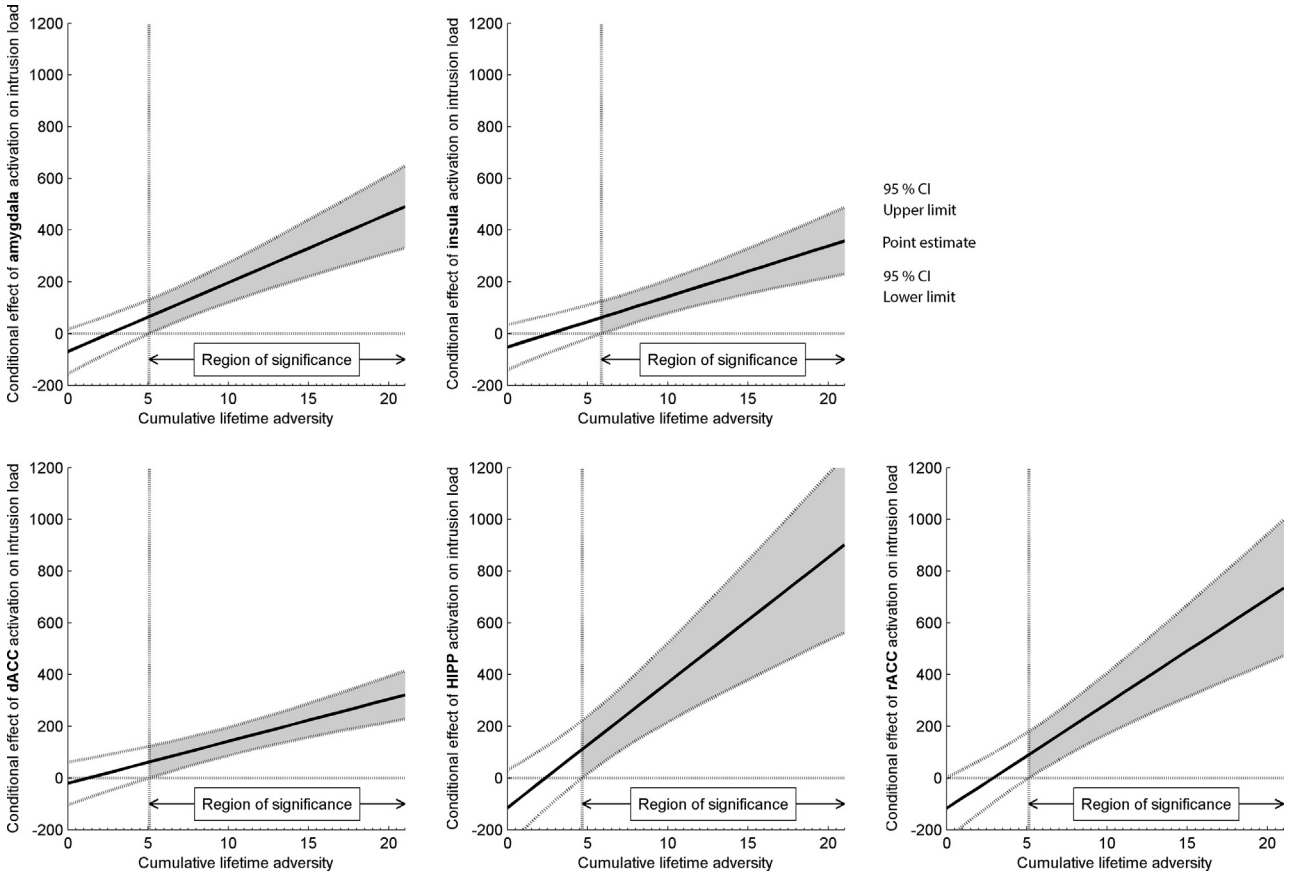

Figure 2. A Johnson-Neyman plot displaying the regions of significance for the interaction effect between lifetime adversity and neural responses (diathesis × stress) on intrusion load. Point estimates are marked by a solid line, and the upper and lower limits of the 95% confidence intervals (CIs) are marked by dotted lines. Slopes of linear regression estimates for neural activity on intrusion load (conditional effect; y-axis) are plotted against the number of lifetime adversities (x-axis). When cumulative lifetime adversity exceeded a certain threshold (>5 events; >4 events for the hippocampus (HIPP); none of the participants reported exactly five lifetime adversities; for all brain regions, 16 participants exceeded this threshold), the slopes of neural activity on intrusion load reached significance, as the CIs did not enclose the value of 0. Regions of significance are marked in gray. dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex.

As expected, for individuals reporting several adversities, a differentiated brain response emerged in predicting ambulatory intrusion load. The positive association between heightened activity in the amygdala, dACC, anterior insula, and hippocampus with subsequent intrusion load in participants with high lifetime adversity, which is well in line with the findings of Bourne *et al.* (9), among others (55,56), and with current neural models of PTSD (7,10,11), might point to a generalized fear network hyperactivity, in terms of both saliency [amygdala, anterior insula, dACC (10,57)] and memory consolidation [hippocampus (58)]. Amygdala activity has been consistently linked to increased processing and encoding of emotional events (11,16,59), and this may have facilitated subsequent vivid recollections of trauma films (60). Similarly, dACC hyperactivity has been linked to exaggerated fear learning and expression, thereby increasing PTSD vulnerability and, later, symptom severity (59,61). In addition, anterior insula hyperactivity has been linked to increased salience detection and interoceptive and emotional awareness, and it is often found in anxiety disorders (12,62–64). According to the triple-network model, the salience network supports the filtering of relevant autonomic, interoceptive, and emotional information and thereby identifies homeostatically relevant stimuli (65,66). Therefore, in individuals reporting several lifetime adversities, salience network responsivity could have resulted in heightened encoding of aversive film clips and more enduring stimulus-based memory representations (7). This may have further potentiated attention to perceptual input resembling the analog trauma (7,67) and thereby reactivated these stimulus-based representations in daily life when a similar perceptual input was perceived.

Additionally, in individuals with high lifetime adversity, increased activity of the hippocampus during analog trauma predicted subsequent intrusion load. This finding is in line with research linking hippocampal hyperactivity with PTSD-related symptomatology (10,18,68), as opposed to accounts based on hypoactivity or volume reductions (7,13). Hippocampal hyperactivity plays a critical role in perceptual processing/encoding of arousing autobiographical memories (69), as well as their consolidation (58). As increased arousal and unpleasantness of aversive films have recently been linked to higher hippocampal activity (70), hippocampal hyperactivity may have induced increased memory formation or

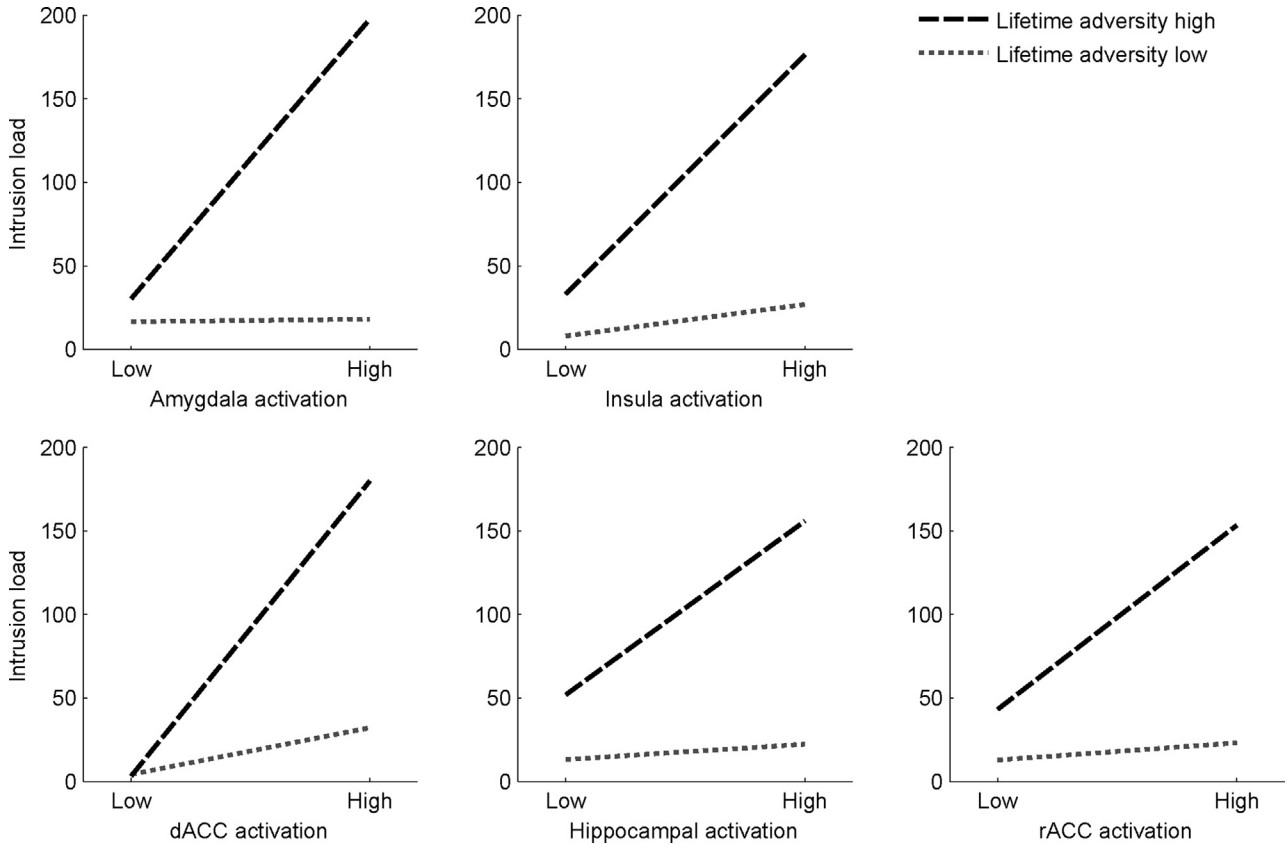

Figure 3. A depiction of the interaction effect between lifetime adversity and peritraumatic neural processing (low = −1 SD below the mean; high = +1 SD above the mean) in predicting intrusion load. The Johnson-Neyman technique (see Figure 2) was used to split the sample into participants reporting "high lifetime adversity" (>5 events; >4 events for the hippocampus) and those reporting "low lifetime adversity" (≤5 events; ≤4 events for hippocampus). Participants below and above this cutoff score were similar in age (p = .279), trait anxiety (p = .563), and depressive symptoms (p = .463). dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex.

consolidation of trauma films, increasing subsequent recollections especially in participants with high lifetime adversity. In addition, increased hippocampal activity has also been linked to increased mental integration as well as autobiographical memory retrieval (69), with both processes playing a role in intrusive memory formation.

Furthermore, in this study, rACC hyperactivity was related to intrusion load in participants with high lifetime adversity. Those findings are well in line with findings by Bourne *et al.* (9) that show stronger rACC activity to intrusion-eliciting versus non–intrusion-eliciting aversive film scenes, though a history of lifetime adversity was not taken into account. Although some clinical PTSD studies reported rACC hypoactivity in association with amygdala inhibition (13), others reported hyperactivity (71–73). Moreover, as rACC hyperactivity has been linked to increased attention to salient information (66,74,75), those findings could further be in line with increased salience mapping as a mechanism explaining increased intrusion load; however, rACC hyperactivity could also implicate unsuccessful emotional regulation (76), particularly in participants reporting several lifetime adversities. Although vmPFC hyporesponsiveness in PTSD (15) has been linked to deficient emotion regulation, this study could not show a link between vmPFC activity and subsequent intrusion load. Of note, this could have also resulted from noncoherent vmPFC activation or deactivation across individuals watching aversive versus neutral films (see Figure 1, Supplemental Figure S2, and Supplemental Table S1 and S2).

In this study, individuals at greatest risk for experiencing elevated intrusion load were those who displayed high peritraumatic neural processing and concurrently reported above five lifetime adversities. This concurs well with previous studies that linked lifetime adversity of four events or more to worse functioning in PTSD (28) and generally worse health outcomes (29). In this study, in individuals with lifetime adversity beyond this tipping point, high salience network activity during analog trauma might have reactivated preexisting neural threat structures or schemas, thereby initiating negative cognitive and affective reactions (77). This, in turn, might have reduced efficient emotional processing and memory consolidation during sleep (78) and reinforced peritraumatic memory reconsolidation, increasing subsequent re-experiencing of trauma.

To the best of our knowledge, our study is the first to use a prospective trauma film design to attempt to experimentally disentangle the influence of peritraumatic neural processing and lifetime adversity on vulnerability for PTSD-symptom development. Notably, although previous research places both neural processing and lifetime adversity as risk factors for PTSD, so far, the unique and synergistic effect of these factors

remains poorly understood. Such disentanglement has been difficult to achieve, since investigating predisposing factors is bound to the time frame before PTSD onset. As real-life trauma is a random, rare, and heterogeneous occurrence, peritraumatic (neural) responses can be investigated only by analog trauma. Thus, using analog trauma, this study was designed to capture the influence of peritraumatic processing on intrusion load (a core symptom of PTSD) while concurrently examining the role of lifetime adversity on this relationship. With this approach, our study provided experimental evidence for a recent account suggesting hyperresponsivity in salience network nodes as predisposing factor for PTSD development. In addition, results suggest that lifetime adversity constitutes a risk factor for intrusive memory development regardless of peritraumatic neural processing, whereas others proposed an indirect effect of lifetime adversity through neural processing only (59). Most importantly, our results suggest that lifetime adversity might set the stage for elevated peritraumatic neural processing generating subsequent intrusion load.

The current study points to lifetime adversity gating the influence of peritraumatic neural processing on subsequent PTSD-like symptoms. As suggested in a recent meta-analysis (79), individuals with high lifetime adversity may benefit from emotion regulation training following stressor exposure to build resilience against PTSD development. Our results indicate that this training may work by promoting downregulation of salience network activity during psychological stressors. Of course, the trauma-analog design permits only a tentative interpretation of our findings with respect to clinical implications. Whether higher intrusion load after trauma film viewing is indeed a vulnerability factor for PTSD needs further testing in prospective longitudinal designs. We further want to note that different cognitive processes and/or brain activations may be related to pathological encoding during (analog) trauma rather than to the retrieval of past traumatic events (typically assessed by clinical studies), restricting comparability and generalizability of implicated brain regions and networks [see the Supplement for analyses on three dysfunctional circuits implicated in PTSD symptomatology (54)]. Moreover, further research investigating how connectivity between brain regions is related to intrusion load is needed. Exploratory analyses (see the Supplement) pointed to peritraumatic amygdala-hippocampus coupling predicting intrusion load, suggesting functional coupling between threat processing (amygdala) and encoding (hippocampus) in individuals reporting several lifetime adversities. Analyses further showed that lifetime adversity also moderated the link between differential neural acquisition learning (positive conditioned stimulus vs. negative conditioned stimulus; see the Supplement) and intrusion load. Specifically, stronger conditioned responding in the amygdala, insula, dACC, and hippocampus predicted higher intrusion load only in individuals with high lifetime adversity. This finding is in line with the theoretical assumption of exaggerated acquisition of fear associations as an explanation for PTSD development (11), and it points to a sensitizing role of previous traumatization. Furthermore, this corresponds with previous work by Rattel *et al.* (80) that showed a close link between unconditioned trauma film responding and acquisition learning in predicting intrusion load.

Lifetime adversities are common among young healthy samples (81), and although their effects are mostly subclinical, they do influence how individuals respond to future adversity. In this study, the average age at which the most severe lifetime adversity indicated was experienced was 15 years (median = 16 years; range = 5–21 years)—thus, well within adolescence. In line with our findings, past epidemiological studies linked lifetime adversity during adolescence to increased PTSD symptoms following subsequent trauma (81,82). Since adolescence is a critical period in neural development, lifetime adversity endured during this time frame may place individuals at a particular risk for future PTSD development by altering the neurocognitive processing of adverse events during adulthood (59). Future studies should investigate how nonexposure compared with exposure to traumatic lifetime adversities differentially influences intrusion load following analog trauma, using more detailed assessment methods of traumatic events. Furthermore, this study's healthy sample was too small to compute subanalyses for specific trauma types. Given that some epidemiological studies document an increased risk for PTSD following certain trauma types [such as sexual abuse (83,84)], future studies should follow up on this. Future studies should further investigate whether lifetime adversity also moderates the relationship between neural responses and involuntary as well as voluntary recall assessed during scanning (85) and how these findings are similar among or differ between PTSD patients and control subjects (86). Given that previous studies showed that men respond differently to aversive film clips than do women (87), it will be important to investigate the current research question in a mixed sample. Lastly, compared with results from past analog intrusion studies, both intrusion frequency and distress were rather low in the current sample. We believe that differences between studies may have emerged because of differences in film stimuli and sampling modes (event-based vs. time-based), though we cannot ascribe this to one particular cause (40).

Conclusions

Peritraumatic neural processing and cumulative lifetime adversity combined their risk potential in an interactive way when predicting PTSD-like symptoms. Specifically, increased peritraumatic processing in neural networks implicated in saliency processing (amygdala, anterior insula, dACC, rACC) and memory encoding and/or consolidation (hippocampus) during analog trauma predicted intrusion load primarily in individuals reporting above five lifetime adversities.

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ARTICLE INFORMATION

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