Emotional numbing in PTSD is associated with lower amygdala reactivity to pain

Abbreviated title: Emotional Numbing link to Pain in PTSD

Nachshon Korem PhD[1,2]*, Or Duek PhD[1,2]*, Ziv Ben-Zion[1,2], Antonia N. Kaczkurkin PhD[3], Shmuel Lissek PhD[4], Temidayo Orederu BA[5], Daniela Schiller PhD[5], Ilan Harpaz-Rotem PhD ABPP[1,2,7,8,†] and Ifat Levy PhD[2,6,7,8,†]

* equal contribution first authors

[†] equal contribution senior authors

1. Yale University School of Medicine, Department of Psychiatry, New Haven, CT, 06511
2. U.S. Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, 06516
3. Department of Psychology, Vanderbilt University, Nashville, TN, 37203
4. Department of Psychology, University of Minnesota, Minneapolis, MN, 55455
5. The Nash Family Department of Neuroscience, Department of Psychiatry, and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, 10029
6. Yale University School of Medicine, Departments of Comparative Medicine and Neuroscience, New Haven, CT, 06511
7. Yale University Department of Psychology, New Haven CT, 06511
8. Wu Tsai Institute, Yale University New Haven, CT, 06510

Correspondence concerning this article should be addressed to Nachshon Korem, PhD., Department of Psychiatry, Yale School of Medicine, 300 George Street, Ste 837, New Haven, CT, 06511, 203.737.2779; Nachshon.Korem@yale.edu.

Number of pages: 27; Number of figures: 3; number of tables: 2;

Abstract

Posttraumatic stress disorder (PTSD) is associated with altered pain perception, namely increased pain threshold and higher pain response. While pain consists of physiological and affective components, affective components are often overlooked. Similar patterns of increased threshold-high response in PTSD were shown in response to emotional stimuli, i.e., emotional numbing. As both emotional numbing and pain processing are modulated by the amygdala, we aimed to examine whether individuals diagnosed with PTSD show lower amygdala activation to pain compared with combat controls, and whether the amygdala responses to pain correlates with emotional numbing. To do so, two independent samples of veterans (original study: 44 total (20 PTSD); conceptual replication study: 40 total (20 PTSD)) underwent threat conditioning, where a conditioned stimulus (CS+; visual stimulus) was paired with an unconditioned stimulus (US; electric-shock). We contrasted the amygdala activity to the CS+US pairing with the CS+ presented alone and correlated it with emotional numbing severity. In both samples, the PTSD group showed a robust reduction in amygdala reactivity to shock compared to the Combat Controls group. Furthermore, amygdala activation was negatively correlated with emotional numbing severity. These patterns were unique to the amygdala, and did not appear in comparison to a control region, the insula, a pivotal region for the processing of pain. To conclude, amygdala response to pain is lower in individuals with PTSD, and is associated with emotional numbing symptoms. Lower amygdala reactivity to mild

pain may contribute to the “all-or-none” reaction to stressful situations often observed in PTSD.

Introduction

Neuroimaging studies of posttraumatic stress disorder (PTSD) have consistently shown exaggerated amygdala activation [1], both in response to trauma-related stimuli and generic emotional stimuli [2]. This is in line with the hypothesis that PTSD results from dysregulation of fear [3], in which initial fear from the traumatic event persists for months and years, a long-time after the trauma has passed. Consequently, Pavlovian fear conditioning is one of the most common behavioral paradigms used to study PTSD in humans [4–6]. In this paradigm, one stimulus (conditioned stimulus, CS+) is occasionally followed by an aversive unconditioned stimulus (US; e.g., electric shocks), and a second stimulus (CS-) is never followed by the aversive US. Pavlovian fear conditioning studies have typically shown increased skin conductance response (SCR) to the CS- (i.e., overgeneralization of fear) and prolonged extinction of the CS+ (i.e., inhibition of extinction) in PTSD, compared to non-PTSD populations [7]. Neuroimaging studies comparing PTSD patients and trauma-exposed controls further report increased amygdala and anterior hippocampus responses to the CS+, both during fear acquisition and late extinction phases [8]. In contrast, the neural response to the US (e.g., receiving a mild electric shock) is often overlooked.

Pain and PTSD are often tied together. The traumatic event that leads to the development of this debilitating disorder usually consists of actual pain or threat of pain [9], and not surprisingly there is a high comorbidity between PTSD and chronic pain disorders [10,11]. Pain itself is often treated as a physiological phenomenon governed by the "pain matrix" [12], a subset of neural regions that are implicated in pain processing. While the exact composition of the matrix is still debated, the insula is the most consistently reported region [12]. However, pain has an additional (often overlooked) affective aspect [13–15], largely modulated by amygdala functionality [16]. Indeed, individuals diagnosed with PTSD often show abnormalities in both the physical and affective processing of pain. While PTSD patients rate suprathreshold aversive stimuli as more painful, they also demonstrate higher pain threshold [17,18], compared to healthy controls. This increased threshold for pain can be blocked with opioids antagonists, such as naloxone [19,20], and is most often observed under stress, and thus is referred to as "Stress-Induced Analgesia" (SIA) [19]. Individuals with PTSD show greater pain suppression (i.e., higher SIA response) to acute pain compared to both healthy individuals [17] and trauma-exposed controls [20,21], suggesting that SIA in PTSD is an exaggeration of a normal response (i.e., pain suppression under stress). The behavioral response characterizing SIA is commonly measured using self-reports [17,20,21]. However, there is scarce evidence of the amygdala response to pain during stressful or fear-inducing situations in PTSD.

The "high threshold-high response" to pain implicated in PTSD is similar to the response pattern to affective stimuli known as emotional numbing (EN). EN encompasses the restricted capacity to experience positive and/or negative emotions,

as well as hyper-responsivity to highly negative stimuli [22,23]. EN was previously associated with several pain symptoms in PTSD patients [24–26], including fear of pain, pain intensity, and pain disability [26]. In addition, higher pain tolerance and EN are two of the most prominent symptoms reported by veterans after deployment [25]. Therefore, it is possible that EN and SIA share a common mechanism.

To this end, we examined the affective response to pain in the amygdala and its modulation by EN symptoms, in trauma-exposed combat veterans with and without PTSD. We hypothesized that participants with PTSD would show lower amygdala activation to mild pain compared to trauma-exposed controls (i.e., higher pain threshold), and that decreased amygdala's activation would be associated with greater severity of EN symptoms. To assess the robustness of our findings, we further examine these hypotheses in an independent group of participants that performed an analogous paradigm (e.g., fear generalization) [27].

Materials and Method

Study 1 (original sample)

Participants and Clinical Assessment

Fifty veterans with combat experience were recruited from the VA hospital in West Haven, Connecticut, and provided informed consent (see Table 1). All participants underwent clinical screening using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) [28] and the Clinician-Administered PTSD Scale

for DSM-IV (CAPS-IV) [29]. Based on the latter, n=25 participants met PTSD diagnosis (i.e., "PTSD" group) and n=25 did not meet PTSD diagnosis (i.e., "Combat Controls" group). For exclusion criteria, please refer to the supplementary methods. In addition, participants completed two self-report questionnaires: PTSD Checklist for DSM-5 (PCL-5) [30] and Beck Depression Inventory-II (BDI-II) [31]. Six participants were excluded from the final analysis due to high movement ratio (3 from the PTSD group and 1 from the combat controls) or equipment failures (2 from the PTSD group). The remaining 44 participants (20 PTSD) were included in the final analyses.

Measures and Analyses

Emotional Numbing. Symptoms of EN were assessed using items 12-14 of the PCL-5, based on the 7 factor model of PTSD [32,33].

Fear Conditioning Task. Participants were asked to observe three colored squares (blue, yellow, and green) presented on a screen and assess the relationship between these squares and the probability of receiving an electric shock. The order of appearance of the different stimuli was counterbalanced between participants to control for the order effect. Two of the colored squares (CS+) were each partially paired with shock, with 7 presentations of CS+US and 9 presentations of CS+ alone (for a total of 14 CS+US and 18 CS+, 43.75% reinforcement rate; see Fig. 1a). In addition, there were 9 presentations of the third square which was never paired with shock (safety signal, CS-). Squares appeared for 4 seconds (with an ITI of 6-10

seconds). In CS+US trials, the shock was applied for 200 ms and overlapped with the offset of the square.

Electric Shock. The shock was administered by two electrodes placed on the inner wrist of the participant's dominant hand, connected to a Constant Voltage Stimulator – Unipolar Pulse *(Model STM200; Biopac Systems, Inc., Goleta, CA).* Shock levels were personally tailored for each participant. Starting at a minimal shock level (20 volts), the shock intensity was gradually increased by the experimenter. Participants were asked to report when the shock was "highly unpleasant but not painful", and this level was set for them throughout the entire duration of the experiment.

Skin Conductance Response (SCR). Individuals' physiological responses were assessed using two Ag–AgCl electrodes, connected to a BioPac Systems skin conductance module (EDA100C). The electrodes were attached to the first and second fingers of each participant's non-dominant hand, between the first and second phalanges. SCR waveforms were analyzed offline, using LedaLab version 3.4.9 (www.ledalab.de). Physiological data was downsampled to 100 HZ and smoothed using a Gaussian window (size of 8 samples). Next, SCRs were decomposed by continuous decomposition analysis (CDA) [34], extracting the phasic information underlying the skin conductance response. Maximum phasic driver-peaks (muS > 0.02) in a time window of 0.5 to 4.5 seconds after stimulus onset were extracted.

Magnetic Resonance Imaging (MRI). MRI data were collected using a 3T Siemens Prisma scanner at the Yale Magnetic Resonance Research Center (MRRC), using a 32-channel receiver array head coil. High-resolution structural images were acquired

by Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) imaging (TR = 2.5 s, TE = 2.83 ms, FOV = 256 x 256 mm^2, matrix = 256 x 256 mm^2, slice thickness = 1.0 mm without gap, 160 slices, voxel size 1.0 × 1.0 × 1.0 mm^3). Functional MRI scans were acquired during the fear conditioning task, using a multi-band Echo-planar Imaging (EPI) sequence (TR= 1000 ms, TE= 30ms, flip angle=60°, voxel size = 2 × 2× 2 mm^3, 60 2 mm-thick slices, in-plane resolution = 2 × 2 mm^2, FOV= 220mm).

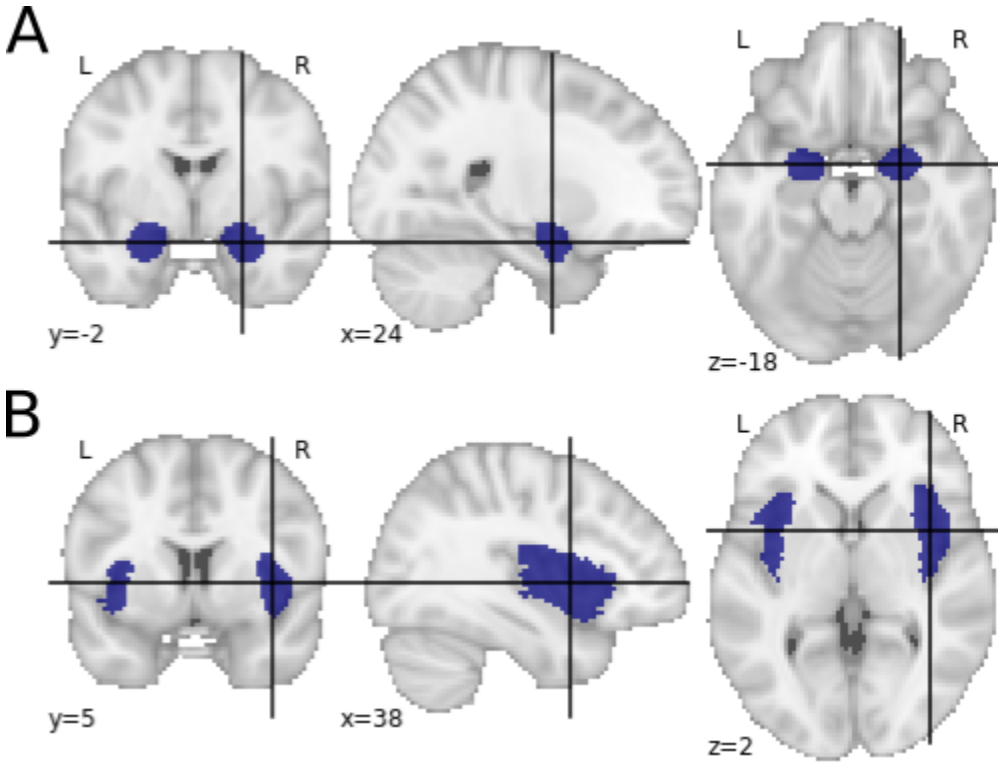
Neural Data Preprocessing. All preprocessing stages were performed using fMRIPrep 20.0.6 [35] and following standard procedures (For neuroimaging acquisition and preprocessing details, see the Supplementary Methods).

Neural Data Analysis. All analyses were carried out using FSL imaging suite (version 6.00) (www.fmrib.ox.ac.uk/fsl). Each subject's BOLD signal was smoothed using a 6-mm^3 full width at half maximum (FWHM) Gaussian kernel, and then corrected for the effects of motion estimated during the realignment step (total of 6 confounds -rotation and translation). Next, data was corrected for framewise displacement (FD), spatial distortion (std DVARS), and noise (the first 6 anatomical components from CompCor) [36]. A general linear model (GLM) was calculated for each participant using FSL via the nipype interface [37,38]. The GLM included predictors for each condition, and amygdala/insula activation was examined in the contrasts: (1) CS+US>CS+ and (2) CS+>baseline between the two study groups (PTSD vs. Combat Controls).

Region-of-Interest (ROI) analysis. To examine the amygdala's response to pain, we conducted an ROI analysis. To assess the specific role of the amygdala in affective processing of pain, the insula, an area associated with the physical properties of pain,

was used for comparison [12]. Bilateral amygdala and insula ROI masks were taken from the "Neurosynth" database [39] using the terms "amygdala" and "insula", respectively (see figure 2a, 2b). Amygdala activation, across all voxels included in the mask, was averaged to a single amygdala activation score per subject. Amygdala's activation analysis between groups (PTSD vs. Combat Controls) was conducted using Stan statistical language, via cmdStanpy interface. The same steps were repeated for the insula.

Figure 2: Amygdala and insula masks



A. Bilateral amygdala from the "Neurosynth" database (932 voxels) B. Bilateral insula from the "Neurosynth" database (3256 voxels).

Statistical Analyses. All analyses were conducted in Stan, a probabilistic programming language, using its interface with Python (cmdStanPy). All results are reported based on the posterior distribution using mean and 89% Highest Posterior Density Interval (HPDi) [40,41]. Comparison of amygdala activation between groups was done using a simple linear model, with amygdala's average activation as the dependent variable and group (PTSD/Combat Controls) as the independent variable. Partially informed priors were used in these analyses, with both slope and intercept assumed to be normally distributed (Mean=0,SD=1). EN served as the dependent variable and amygdala activity to shock was the independent variable with the intercept and coefficient prior normally distributed (Mean=0, SD=10, as the PCL scores have higher variance) [42].

Robust Baysian Regression Analysis. To examine the association between amygdala and insula response to mild pain (i.e., electric shock) and EN symptoms, and to reduce the influence of outliers on the model, a robust Bayesian regression analysis was conducted [43]. Participants' EN score was set as the dependent variable with amygdala or insula average activation as the independent variable. Partially informed priors were used in these analyses, with the intercept and slope prior normally distributed (Mean=0, SD=10, as PCL scores have higher variance) [42]. For the independent variable (i.e., amygdala or insula), the model used a Student's t distribution (to account for outliers) with the ν prior distributed as a Gamma distribution (k=2, θ=0.1) as prior [41,44,45]. All Stan models can be found in the study GitHub repository (https://github.com/LevyDecisionNeuroLab/SIA_PTSD).

Study 2 (Conceptual replication sample)

Participants and Clinical Assessment

Seventy-one veterans were recruited for the previously reported study by Kaczkurkin et al. [27]. All participants (N=71) were screened using CAPS-IV [29], and based on that categorized into three groups: “PTSD” (N=26), “Subthreshold PTSD” (CAPS score: 20-39 ;N=23), and “Combat Controls" (CAPS score: 0 to 19; N=22). As this sample was used for conceptual replication of the original study, the subthreshold group was excluded from the current analysis (see Table 2). In addition to the CAPS-IV, participants completed the self-report Posttraumatic Stress Disorder Checklist - Military Version (PCL-M) [46]. Those who did not show fear response (4 PTSD; 1 combat control) and those with excessive head motion (2 PTSD; 1 combat control) were excluded from the final analysis, resulting in a final sample of 40 participants in the final analysis (20 PTSD). For more details, see Kaczkurkin et al. [27].

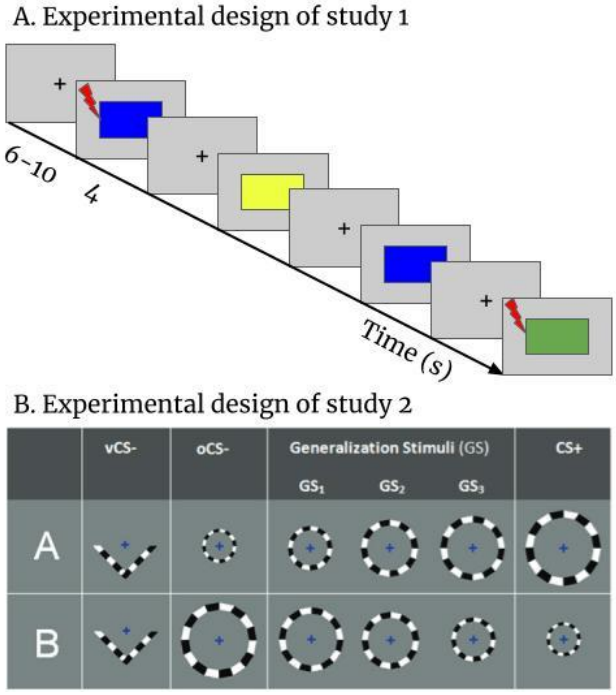
Emotional Numbing. Kaczkurkin et al. [27] collected PCL-M, unlike PCL-5 in the original sample, hence, EN was assessed using items 8-12, based on the 5-factor model of PTSD [47].

Fear conditioning (generalization) task [27]. Participants were asked to view stimuli and were instructed that they “might learn to predict the shock if they attend to the presented stimuli”. The original CS+ was a checkerboard textured ring (see figure 1b). For the generalizability task, there were 5 sizes for the ring, with only one size (biggest/smallest; counterbalanced) associated with a shock. Two different safety

cues were used for the CS- (ring-shaped biggest/smallest or 'V'-shaped stimuli). The CS+ was presented 35 times, with 22 co-terminated with a shock (CS+US; 63% reinforcement rate). The US was a 100ms electric shock (3-5mA individually adjusted to a "highly uncomfortable or mildly painful" level) delivered to the right ankle.

Preprocessing conceptual replication. All preprocessing was performed using Analysis of Functional Neural Images (AFNI) [48] (for complete details, see Kaczkurkin et al. [27] and the Supplementary materials). Both datasets were analyzed using the same ROI analysis and robust regression analysis (see study 1 methods).

Figure 1: Experimental Designs of the Original and Conceptual Replication Studies.



A. In study 1, participants watched a pseudo-random series of three colored squares. Two of these colored squares co-terminated with a US (i.e., electric shock) in 14 out of the 32 (43.75%) presentations (each colored-squared was paired with shock 7 out of 16 times). A third-colored square appeared 9 times and was never paired to the US (shock). B. In Study

2, adapted from Kaczkurkin et al [27], participants saw a pseudo random order of the shown stimuli. Each stimulus was presented for 4 seconds with an ITI of 2.4-4.8 seconds. Only the CS+ co-terminated with a US (i.e., electric shock) in 22 out of the 35 (63%) presentations.

Results

Demographic and clinical characteristics group comparisons

Demographics and clinical characteristics of the original and conceptual replication samples are presented in Table 1. No significant differences were found between PTSD and Combat Controls in age, SCR response to the US, or the personally selected shock levels between the group ($p>0.05$; SCR data available only for study 1).

Table 1. Demographic and clinical characteristics of the original sample and conceptual replication sample

Original sample (N=44)				
	Combat Controls (N = 24)	PTSD (N = 20)	t(42), p	BF10
Age (years)	42.33 (12.29)	43.4 (12.22)	0.7, NS	0.31s
Sex	21 (87.5%) males	19 (95%) males	(X^2) 0.74, NS	
PCL-5 Total Scores	12.5 (15.8)	38.35.6 (16.)	5.37, p<0.05	4572.7
Emotional Numbing Scores	1.87 (2.5)	5.75 (3.61)	4.15, p<0.05	148.8
CAPS-4 Total Score (past month)	6.5 (9.9)	60.25 (21.56)	9.51, p<0.05	7.64e+07
CAPS-4 Total Score	18.83 (13.86)	90.18 (19.49)	12.48,	5.15e+10

(lifetime)			p<0.05	
SCR to US (μs)	0.97 (.55)	0.74 (.59)	0.93, NS	2.24
Shock levels (mA) *	16.88 (13.23)	14.54 (12.53)	0.48, NS	2.61
Conceptual Replication sample (N=40)				
	Combat Controls (N = 20)	PTSD (N = 20)	t(38), p	BF10
Age	33.45 (9.7)	33.50 (9.63)	0.01, NS	*0.31*
Sex	20 males	20 males		
PCL-M Total Scores	*32.13 (9.58)*	*53.7 (12.66)*	*6.01, <0.05*	*19850*
Emotional Numbing Scores	*8.35 (3.85)*	*15.05 (3.74)*	*5.57, <0.05*	*6173*
CAPS-4 Total Score	*13.95 (6.4)*	*59.6 (15.7)*	*12.4, < 0.05*	*5.9e+11*

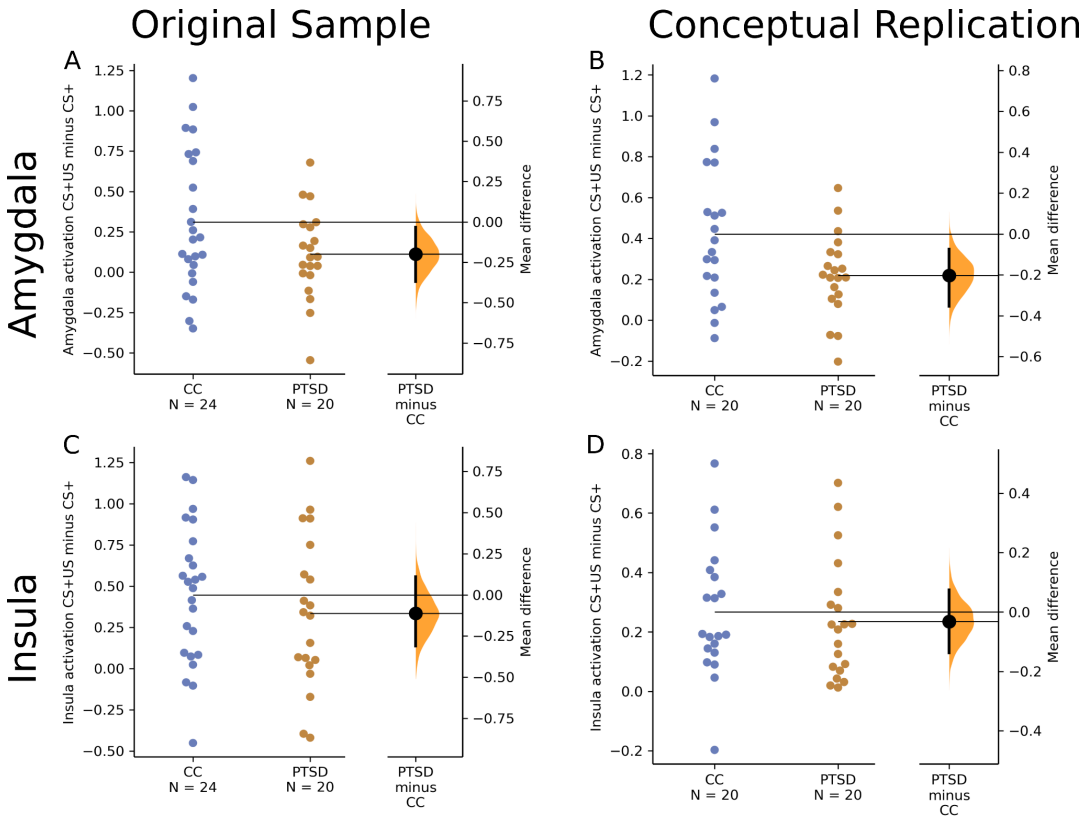
**Shock levels were only recorded for several subjects (13 PTSD and 16 Combat Controls) PCL-5 = PTSD Checklist for DSM-5; CAPS-5 = Clinical-Administered PTSD Scale for DSM-IV; SCR = Skin conductance response; US = Unconditioned Stimuli, BF10 = Bayes Factor for H1.*

Decreased amygdala responsivity to shock in PTSD patients

Consistent with our hypothesis, the PTSD group showed decreased bilateral amygdala activation to the shock compared to the Combat Controls group (Study 1: β = -.20; SD = .11; 89% HPDi = [-.40, -.02]; Figure 3a; Study 2: β = -.16; SD = .08; 89% HPDi = [-.29, -.02]; Figure 3b). There was no group difference in the amygdala response to the non-reinforced CS+ stimuli (i.e., vs. fixation; Study 1: β = .073; SD = .20, 89% HPDi = [-.29, .40]; Study 2: β = -.031; SD = .05, 89% HPD = [-.12, .05]), suggesting that the difference is specific to the shock administration, and does not result from overall heightened arousal in the PTSD group.

To assess the specificity of the effect to the amygdala, we tested the same hypothesis in a different neural region (bilateral Insula, see methods). As expected, in both the original and replication cohorts, there was no group difference in bilateral Insula activation to the shock (Study 1: β = -.01; SD =1.4 ; 89% HPDi = [-.35, .12]; Study 2: β = -.018; SD =0.06 ; 89% HPDi = [-.12, .08])

Figure 3: Reduced amygdala (but not insula) response to shock in PTSD



Average neural activation to shock (i.e., the contrast of paired CS+US vs. unpaired CS+ trials) in the Combat Control (blue) and PTSD (orange) groups. The right side of each figure depicts the curve of the resampled distribution of differences between the two groups (PTSD - CC). The mean of the PTSD group relative to controls is indicated by the black dot,

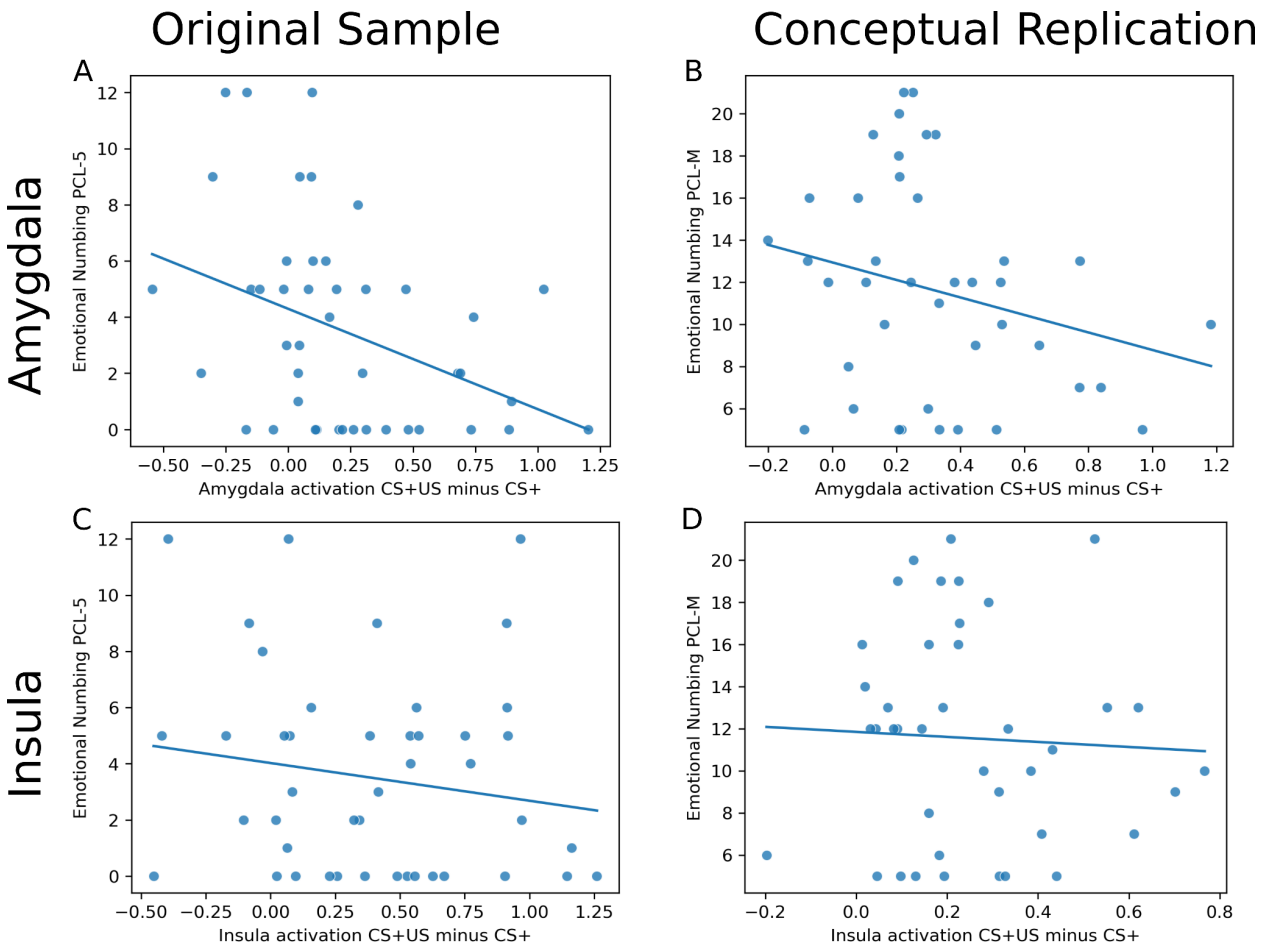
and the 89% confidence interval is indicated by the thick black line. Results from the original sample (Study 1) are presented in panels A and C, while results from the conceptual replication sample (Study 2) are presented in panels B and D. Results of the bilateral amygdala are presented in panels A and B, whereas results of the bilateral insula are presented in panels C and D.

Amygdala's responsivity to shock is associated with emotional numbing symptoms

Consistent with our hypothesis, Robust regression analysis revealed a negative correlation between amygdala activation and the EN score (Study 1: ϱ = -3.6, SD = 1.4, 89% HPDi = [-6.1, -1.2]; Figure 4a; Study 2: ϱ = -4.2, SD =2.6, 89% HPD = [-8.7, -.00]; Figure 4b), such that lower amygdala reactivity to the shock corresponded to higher EN scores.

In the specificity analysis, as expected, no significant association was found between the insula activation and EN (study 1: ϱ =-1.3, SD =1.3, 89% HPD = [-3.6, 0.9]; study 2: ϱ = -1.2, SD =3.7, 89% HPD = [-7.8, 4.9]).

Figure 4: Robust regression between amygdala and insula activation and emotional numbing score.



Robust Bayesian regression between average neural activation to shock (i.e., the contrast of paired CS+US vs. unpaired CS+ trials) and emotional numbing based on the PCL questionnaire (Study 1: PCL-5 items 12-14; Study 2: PCL-M items 8-12). Results from the original sample (Study 1) are presented in panels A and C, while results from the replication sample (Study 2) are presented in panels B and D. Results of the bilateral amygdala are presented in panels A and B, whereas results of the bilateral insula are presented in panels C and D.

Several control analyses were conducted on data from the original sample to assess the specificity of the suggested EN-amygdala link (see supplementary results for complete statistics). First, amygdala response was not correlated with depression

symptoms score (BDI; ϱ = -3.9,SD = 5.3, 89% HPDi = [-13.0, 4.9]). Second, multiple robust regressions, each including EN and one other PTSD cluster from the 7 factor model of PTSD [32,49], showed no robust additive predictive value for any other cluster (Avoidance: ϱ=0.01, 89% HPDi = [-0.05, 0.07]; Intrusion: ϱ=0.01, 89% HPDi = [-0.02, 0.04]; Negative affect: ϱ=-0.01, 89% HPDi = [-0.05, 0.02]; Externalized behavior: ϱ=0.04, 89% HPDi = [-0.03, 0.11]; Dysphoric arousal: ϱ=0.01, 89% HPDi = [-0.05, 0.07]; Anxious arousal: ϱ=0.01, 89% HPDi = [-0.03, 0.06]). Finally, the results were not affected by movement artifacts: a group by condition analysis on framewise displacement (FD) showed no group (β = 0.01, SD = 0.02, 89% CI [-0.03, 0.04]), condition (β = -0, SD = 0.01, 89% CI[-0.02, 0.00]) or interaction effects (β = 0.01, SD = 0.01, 89% CI[-0.01, 0.03]).

Discussion

This study aimed to investigate affective neural processing of mild subthreshold pain and its relation to EN in individuals diagnosed with PTSD. To this end, we isolated the response of the amygdala and insula to electric shocks, an unconditioned stimuli during the acquisition stage of a fear conditioning task, in trauma-exposed combat veterans with and without PTSD diagnosis (PTSD and Combat Control group, respectively). To examine the replicability and generalizability of the results, we re-run the analysis using an independent sample. In both samples, we found an overall reduction in amygdala (but not insula) responsivity to mild pain in the PTSD group,compared with Combat Controls. Furthermore, amygdala (but not insula) responsivity was negatively correlated with the degree of EN symptoms,

consistent with the suggested link between numbing of both emotions and emotional pain processing within the amygdala.

Results of this work support a common mechanism for EN and stress-induced analgesia (SIA). Foa and colleagues [48] were the first to suggest this "common-mechanism", based on animal research of inescapable shock. Further evidence for this link between SIA and EN comes from studies showing associations between EN and: (1) pain symptoms in PTSD patients [26], (2) reduced functioning in chronic pain patients [51], and (3) pain disability in healthy individuals after surgery [52]. Moreover, EN may actually be context-dependent [22], expressed mostly in stressful situations (i.e., stress-induced numbing). Our findings further suggest that the potential shared mechanism for SIA and EN is mediated specifically by the amygdala's activity (and not by the insula, a physical pain perception area). Indeed, several neurofeedback studies have shown that reducing amygdala response to threatening stimuli can reduce pain perception [53] and increase emotion regulation [54,55].

Previous studies investigating the association between the amygdala response to mild pain in PTSD populations report inconsistent results, with some showing reduced activation to pain and others demonstrating the opposite. For example, Geuze and colleagues [56], using a block-design study, have shown reduced activation of the amygdala to heat pain in veterans with PTSD (compared to veterans without PTSD). However, their design used the interval between blocks as baseline, and thus does not account for the effects of anticipation on the amygdala [57]. In contrast, Linnman and colleagues [58], showed an increase in amygdala activity in PTSD compared with

trauma control, to pain induction by electric shocks during a fear conditioning paradigm. In an attempt to control for anticipatory effects, they focused on the shock onset, as it coincided with the cue offset, thus, comparing the interval between trials. Nevertheless, in such a design, the brief shocks (0.5 s) account for a very small percentage of the recording time (TR = 3 s). Thus, the analyses focused mostly on blank screens, which can include unrelated noise as during resting-state scans [59].

These contradictory results could be due to three main factors: pain type (heat vs. shock), paradigm (block-design vs. event-related fear conditioning paradigm), and recording window (few long continuous trials vs. many short windows). In our study, we focused on the entire period of the cue and the pain (CS+US). This window enabled us to distinguish between amygdala response to stress (anticipatory adverse event) [60] and the additive value of pain [61] without introducing the noise associated with blank screens. We also used a recording sequence of TR = 1 s, which allowed better temporal resolution compared to previous studies. As recent work showing the difficulty to replicate results in fMRI studies, even when using the same exact dataset [62], our ability to replicate the results using an independent data set from a different group using an analogous paradigm [27] further strengthens the finding that PTSD patients have a diminished response in the amygdala to mild pain [18].

The most probable mechanism at the core of the relation between SIA and EN is μ-opioid receptor inhibition of the amygdala. During stress, the body secretes endorphins (endo-opioids) that reduce the sensation of pain, so the organism can better cope with a potential threat [63]. Both pain and affect trigger the release of

endorphins in the amygdala [64,65], which in turn, mediates the antinociceptive response [64]. Thus, higher endorphin-mediated inhibition of the amygdala response to mild stimuli propagates a lower amygdala response. In turn, a lower amygdala response fails to trigger an "appropriate" emotional response. This inhibition of pain and affect is supposed to help the organism cope with an immediate threat. However, in PTSD, where trauma reminders are constant, such lower emotional tone might cause EN. Alterations in the opioid system in individuals diagnosed with PTSD provide further support for this suggested theory. Indeed, PTSD was previously associated with both at-rest lower plasma-endorphin tone [66] and a steep incline in endorphins following stress [67]. Moreover, compared with trauma controls, individuals with PTSD show a higher binding potential of μ-opioid receptors in the amygdala [68]. These results explain how Naloxone, a μ-opioid antagonist, can block the effect of SIA [20,69]. This pathophysiological mechanism might be at the core of many symptoms and deficiencies related to PTSD, such as impaired emotion regulation [70]. For example, by not initiating an appropriate emotional response to a stimulus in time, the individual might be less able to engage in effective emotion regulation strategies [71].

While our results are robust, several limitations should be noted. First, both samples included only veterans and were mainly males (Study 1: 90.1%; Study 2: 100%), which suggests a relatively heterogeneous trauma type. Thus, we are limited in our ability to generalize our findings to other trauma types or females. Hence, future research should try and look at different trauma type and sex differences. Second, our cross-sectional design cannot assess stability over time or directionality

of the pain-EN relation. Future longitudinal studies may shed light on the causality of this relation. Finally, as our aim was only to look at the amygdala response to mild (sub-threshold) pain, we did not directly test pain thresholds or tolerance.

In conclusion, decreased amygdala activation to pain is linked to difficulty experiencing emotions (i.e., EN) in two independent samples of combat-exposed veterans. These findings further advance our understanding of the neural mechanisms underlying pain perception in PTSD and their relationship to an extensive literature investigating EN in PTSD. Future work is needed to test the hypothesis that opioid receptor inhibition of the amygdala contributes to the relationship between pain suppression and EN in PTSD.

Clinical implications stem from this research suggest that psychological treatment should aim at assisting PTSD patients to be more mindful of their feeling, especially in stressful situations, and then be able to react to painful/emotional stimuli earlier and thus be more effective.

Funding and Disclosure

The authors declare no competing financial interests.

This work was supported by NIH R01MH105535 to DS and IHR, CSRD CX001538 grant to IHR, NIH R01MH118215 to IL, and NSF BCS-1829439 to IL. DS is supported by the NIMH (R01MH122611, R01MH123069) and the Misophonia Research Fund. Replication study was originally supported by NIMH grant MH-080130 to SL.

Author contributions

N.K. conceptualization and design, data analysis, interpretation of the data, writing initial draft, editing manuscript, gave final approval for the version to be published and is accountable for all aspects of the work including accuracy and integrity. O.D. conceptualization and design, acquisition of data, data analysis, interpretation of the data, writing initial draft, editing manuscript, gave final approval for the version to be published. Z.B.Z. interpretation of the data, editing manuscript, gave final approval for the version to be published. A.N.K. acquisition of data, data analysis, editing manuscript, gave final approval for the version to be published. S.L. acquisition of data, editing manuscript, gave final approval for the version to be published. T.O. acquisition of data, data analysis, gave final approval for the version to be published. D.S. interpretation of the data, editing manuscript, gave final approval for the version to be published. I.H.R. interpretation of the data, editing manuscript, gave final approval for the version to be published. I.L. interpretation of the data, editing manuscript, gave final approval for the version to be published.

References

1. Koenigs M, Grafman J. Posttraumatic Stress Disorder: The Role of Medial Prefrontal Cortex and Amygdala. The Neuroscientist. 2009;15:540–548.
2. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012;13:769–787.
3. Kredlow AM, Fenster RJ, Laurent ES, Ressler KJ, Phelps EA. Prefrontal cortex, amygdala, and threat processing: implications for PTSD. Neuropsychopharmacology. 2021:1–13.
4. Lissek S, van Meurs B. Learning Models of PTSD: Theoretical Accounts and Psychobiological Evidence. Int J Psychophysiol Off J Int Organ Psychophysiol. 2015;98:594–605.
5. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012;35:24–35.
6. Dunsmoor JE, Cisler JM, Fonzo GA, Creech SK, Nemeroff CB. Laboratory models of post-traumatic stress disorder: The elusive bridge to translation. Neuron. 2022. 23 March 2022. https://doi.org/10.1016/j.neuron.2022.03.001.
7. Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, et al. Updated Meta-Analysis of Classical Fear Conditioning in the Anxiety Disorders. Depress Anxiety. 2015;32:239–253.
8. Suarez-Jimenez B, Albajes-Eizagirre A, Lazarov A, Zhu X, Harrison BJ, Radua J, et al. Neural signatures of conditioning, extinction learning, and extinction recall in posttraumatic stress disorder: a meta-analysis of functional magnetic resonance imaging studies. Psychol Med. 2020;50:1442–1451.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013.
10. Shipherd JC, Keyes M, Jovanovic T, Ready DJ, Baltzell D, Worley V, et al. Veterans seeking treatment for posttraumatic stress disorder: what about comorbid chronic pain? J Rehabil Res Dev. 2007;44:153–166.
11. Scioli-Salter ER, Forman DE, Otis JD, Gregor K, Valovski I, Rasmusson AM. The Shared Neuroanatomy and Neurobiology of Comorbid Chronic Pain and PTSD: Therapeutic Implications. Clin J Pain. 2015;31:363–374.
12. Tanasescu R, Cottam WJ, Condon L, Tench CR, Auer DP. Functional reorganisation in chronic pain and neural correlates of pain sensitisation: A coordinate based meta-analysis of 266 cutaneous pain fMRI studies. Neurosci Biobehav Rev. 2016;68:120–133.
13. Pace M c., Mazzariello L, Passavanti M b., Sansone P, Barbarisi M, Aurilio C. Neurobiology of pain. J Cell Physiol. 2006;209:8–12.
14. Neugebauer V. Amygdala Pain Mechanisms. In: Schaible H-G, editor. Pain Control, Berlin, Heidelberg: Springer; 2015. p. 261–284.
15. Peirs C, Seal RP. Neural circuits for pain: Recent advances and current views. Science. 2016;354:578–584.
16. Neugebauer V, Mazzitelli M, Cragg B, Ji G, Navratilova E, Porreca F. Amygdala,

neuropeptides, and chronic pain-related affective behaviors. Neuropharmacology. 2020;170:108052.
17. Defrin R, Schreiber S, Ginzburg K. Paradoxical Pain Perception in Posttraumatic Stress Disorder: The Unique Role of Anxiety and Dissociation. J Pain. 2015;16:961–970.
18. Defrin R, Ginzburg K, Solomon Z, Polad E, Bloch M, Govezensky M, et al. Quantitative testing of pain perception in subjects with PTSD – Implications for the mechanism of the coexistence between PTSD and chronic pain. PAIN. 2008;138:450–459.
19. Butler RK, Finn DP. Stress-induced analgesia. Prog Neurobiol. 2009;88:184–202.
20. van der Kolk BA, Greenberg MS, Orr SP, Pitman RK. Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder. Psychopharmacol Bull. 1989;25:417–421.
21. Diener SJ, Wessa M, Ridder S, Lang S, Diers M, Steil R, et al. Enhanced stress analgesia to a cognitively demanding task in patients with posttraumatic stress disorder. J Affect Disord. 2012;136:1247–1251.
22. Litz BT, Gray MJ, Gray MJ. Emotional Numbing in Posttraumatic Stress Disorder: Current and Future Research Directions. Aust N Z J Psychiatry. 2002;36:198–204.
23. Sippel LM, Watkins LE, Pietrzak RH, Hoff R, Harpaz-Rotem I. The Unique Roles of Emotional Numbing and Arousal Symptoms in Relation to Social Connectedness Among Military Veterans in Residential Treatment for PTSD. Psychiatry. 2018;81:271–282.
24. Langford DJ, Theodore BR, Balsiger D, Tran C, Doorenbos AZ, Tauben DJ, et al. Number and Type of Post-Traumatic Stress Disorder Symptom Domains Are Associated With Patient-Reported Outcomes in Patients With Chronic Pain. J Pain. 2018;19:506–514.
25. Lusk J, Brenner LA, Betthauser LM, Terrio H, Scher AI, Schwab K, et al. A Qualitative Study of Potential Suicide Risk Factors Among Operation Iraqi Freedom/Operation Enduring Freedom Soldiers Returning to the Continental United States (CONUS). J Clin Psychol. 2015;71:843–855.
26. López-Martínez A e., Ramírez-Maestre C, Esteve R. An examination of the structural link between post-traumatic stress symptoms and chronic pain in the framework of fear-avoidance models. Eur J Pain. 2014;18:1129–1138.
27. Kaczkurkin AN, Burton PC, Chazin SM, Manbeck AB, Espensen-Sturges T, Cooper SE, et al. Neural Substrates of Overgeneralized Conditioned Fear in PTSD. Am J Psychiatry. 2016;174:125–134.
28. First MB, Gibbon M. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). 2004. 2004.
29. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a clinician-administered PTSD scale. J Trauma Stress. 1995;8:75–90.
30. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30:383.
31. Beck AT, Steer RA, Brown GK. Manual for the BDI-II. San Antonio, TX:

Psychological Corporation; 1996.
32. Duek O, Spiller TR, Pietrzak RH, Fried EI, Harpaz-Rotem I. Network analysis of PTSD and depressive symptoms in 158,139 treatment-seeking veterans with PTSD. Depress Anxiety. 2021;38:554–562.
33. Pietrzak RH, Tsai J, Armour C, Mota N, Harpaz-Rotem I, Southwick SM. Functional significance of a novel 7-factor model of DSM-5 PTSD symptoms: results from the National Health and Resilience in Veterans study. J Affect Disord. 2015;174:522–526.
34. Benedek M, Kaernbach C. A continuous measure of phasic electrodermal activity. J Neurosci Methods. 2010;190:80–91.
35. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. FMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019;16:111–116.
36. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage. 2007;37:90–101.
37. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208–S219.
38. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, et al. Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. Front Neuroinformatics. 2011;5:13.
39. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods. 2011;8:665–670.
40. McElreath R. rethinking: Statistical Rethinking book package. R package version 1.391. 2014.
41. McElreath R. Statistical rethinking: A Bayesian course with examples in R and Stan. Chapman and Hall/CRC; 2018.
42. Juárez MA, Steel MFJ. Model-Based Clustering of Non-Gaussian Panel Data Based on Skew-t Distributions. J Bus Econ Stat. 2010;28:52–66.
43. Berger JO, Moreno E, Pericchi LR, Bayarri MJ, Bernardo JM, Cano JA, et al. An overview of robust Bayesian analysis. Test. 1994;3:5–124.
44. Geweke J. Bayesian treatment of the independent Student-t linear model. J Appl Econom. 1993;8:S19–S40.
45. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. 2013. 2013.
46. Weathers FW, Huska JA, Keane TM. PCL-M for DSM-IV. Boston Natl Cent PTSD-Behav Sci Div. 1991. 1991.
47. Elhai JD, Biehn TL, Armour C, Klopper JJ, Frueh BC, Palmieri PA. Evidence for a unique PTSD construct represented by PTSD's D1–D3 symptoms. J Anxiety Disord. 2011;25:340–345.
48. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996;29:162–173.
49. Claycomb Erwin M, Charak R, Durham TA, Armour C, Lv X, Southwick SM, et al. The 7-factor hybrid model of DSM-5 PTSD symptoms and alcohol consumption and consequences in a national sample of trauma-exposed veterans. J Anxiety

Disord. 2017;51:14–21.
50. Foa EB, Zinbarg R, Rothbaum BO. Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model. Psychol Bull. 1992;112:218.
51. Clapp JD, Beck JG, Palyo SA, Grant DM. An examination of the synergy of pain and PTSD on quality of life: Additive or multiplicative effects? PAIN. 2008;138:301–309.
52. Katz J, Asmundson GJG, McRae K, Halket E. Emotional numbing and pain intensity predict the development of pain disability up to one year after lateral thoracotomy. Eur J Pain. 2009;13:870–878.
53. Goldway N, Ablin J, Lubin O, Zamir Y, Keynan JN, Or-Borichev A, et al. Volitional limbic neuromodulation exerts a beneficial clinical effect on Fibromyalgia. NeuroImage. 2019;186:758–770.
54. Herwig U, Lutz J, Scherpiet S, Scheerer H, Kohlberg J, Opialla S, et al. Training emotion regulation through real-time fMRI neurofeedback of amygdala activity. NeuroImage. 2019;184:687–696.
55. Zotev V, Phillips R, Young KD, Drevets WC, Bodurka J. Prefrontal Control of the Amygdala during Real-Time fMRI Neurofeedback Training of Emotion Regulation. PLOS ONE. 2013;8:e79184.
56. Geuze E, Westenberg HGM, Jochims A, Kloet CS de, Bohus M, Vermetten E, et al. Altered Pain Processing in Veterans With Posttraumatic Stress Disorder. Arch Gen Psychiatry. 2007;64:76–85.
57. Nitschke JB, Sarinopoulos I, Oathes DJ, Johnstone T, Whalen PJ, Davidson RJ, et al. Anticipatory Activation in the Amygdala and Anterior Cingulate in Generalized Anxiety Disorder and Prediction of Treatment Response. Am J Psychiatry. 2009;166:302–310.
58. Linnman C, Zeffiro TA, Pitman RK, Milad MR. An fMRI study of unconditioned responses in post-traumatic stress disorder. Biol Mood Anxiety Disord. 2011;1:1–12.
59. Finn ES. Is it time to put rest to rest? Trends Cogn Sci. 2021;25:1021–1032.
60. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10:423–433.
61. Veinante P, Yalcin I, Barrot M. The amygdala between sensation and affect: a role in pain. J Mol Psychiatry. 2013;1:9.
62. Botvinik-Nezer R, Holzmeister F, Camerer CF, Dreber A, Huber J, Johannesson M, et al. Variability in the analysis of a single neuroimaging dataset by many teams. Nature. 2020;582:84–88.
63. Volpicelli J, Balaraman G, Hahn J, Wallace H, Bux D. The Role of Uncontrollable Trauma in the Development of PTSD and Alcohol Addiction. Alcohol Res Health. 1999;23:256–262.
64. Zubieta J-K, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, et al. Regional Mu Opioid Receptor Regulation of Sensory and Affective Dimensions of Pain. Science. 2001. 13 July 2001. https://doi.org/10.1126/science.1060952.
65. Zubieta J-K, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, et al. Regulation of Human Affective Responses by Anterior Cingulate and Limbic μ-Opioid Neurotransmission. Arch Gen Psychiatry. 2003;60:1145–1153.
66. Hoffman L, Watson PB, Wilson G, Montgomery J. Low Plasma β-Endorphin in

Post-Traumatic Stress Disorder. Aust N Z J Psychiatry. 1989;23:269–273.
67. Hamner MB, Hitri A. Plasma beta-endorphin levels in post-traumatic stress disorder: A preliminary report on response to exercise-induced stress. J Neuropsychiatry Clin Neurosci. 1992;4:59–63.
68. Liberzon I, Taylor SF, Phan KL, Britton JC, Fig LM, Bueller JA, et al. Altered Central μ-Opioid Receptor Binding After Psychological Trauma. Biol Psychiatry. 2007;61:1030–1038.
69. al'Absi M, Nakajima M, Bruehl S. Stress and pain: modality-specific opioid mediation of stress-induced analgesia. J Neural Transm. 2021;128:1397–1407.
70. Frewen PA, Lanius RA. Toward a Psychobiology of Posttraumatic Self-Dysregulation. Ann N Y Acad Sci. 2006;1071:110–124.
71. Gross JJ. The emerging field of emotion regulation: an integrative review. Rev Gen Psychol. 1998;2:271.