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Emotional memory bias in adolescents with chronic pain: examining the relationship with neural, stress, and psychological factors

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Abstract

Memory biases for pain-related information may contribute to the development and maintenance of chronic pain; however, evidence for when (and for whom) these biases occur is mixed. Therefore, we examined neural, stress, and psychological factors that could influence memory bias, focusing on memories that motivate disabling behaviors: pain perception, conditioned responses to threat-and-safety cues, and responses to aversive nonnoxious stimuli. Two studies were conducted with adolescents with and without chronic pain. Data from 58 participants were included in study 1 (chronic pain n = 34, pain free n = 24, mean age = 16 years), and 39 participants were included in study 2 (chronic pain n = 26, pain free n = 13, mean age = 16 years). Both studies used a threat–safety learning paradigm with memory recall (≈1 month later). Participants completed structural and functional (resting-state) magnetic resonance imaging, salivary cortisol measurements, and self-report measures. Adolescents with pain and pain-free peers consistently recalled being more afraid of safety cues (CS−) and, during heightened stress at encoding (higher cortisol levels), also reported being more afraid of threat cues (CS+). However, no memory bias was present for the emotional response to an aversive stimulus (US; loud scream) or for the recall of pain intensity. Functional connectivity of the amygdala and hippocampus with memory circuits related to the degree of memory bias, but the specific connections varied between the studies, and we observed no relationship between memory bias and brain morphology. Our findings highlight the value of considering the interaction between implicit and explicit memory systems, contributing to a more comprehensive understanding of emotional memory biases in the context of chronic pain.

Keywords: Chronic pain, Pediatric pain, Memory bias, Fear conditioning, Cortisol, Hippocampus, Amygdala

1. Introduction

Memory biases for pain-related information are posited as potential mechanisms contributing to pain chronicity.[11,39,40] However, experimental evidence for the presence of this bias is mixed, and when, and for whom, these biases are present remains unclear.[25,40,42] Based on theories of emotional memory enhancement, painful events should be recalled with high accuracy because of heightened arousal, facilitating adaptive behavior.[22,47,48] Increased levels of stress hormones indirectly increase amygdala activation and amygdala–hippocampal connectivity, promoting the consolidation of emotional memory and improving recall accuracy.[48] However, this is a U-shaped effect, with chronic stress resulting in decreased hippocampal volume and impaired episodic memory.[5,22,34] Concordantly, when pain is chronic, both adolescents[6] and adults[3] demonstrate a negative memory bias for pain, suggesting that prolonged stress has negatively affected recall accuracy.

However, previous studies on emotional memory bias in chronic pain have not consistently measured stress during encoding, limiting the assessment of its predictive role in observed biases. Furthermore, the connection between memory bias and the structure and functional connectivity of the amygdala and hippocampus remains unexplored in adolescents with chronic pain. Only one study, to date, has examined hippocampal shape in adults with chronic pain, finding a link between a more negative memory bias for pain and anterior hippocampal displacement.[3]

Research into implicit and explicit memory systems highlights the importance of considering individual differences in this heterogeneous sample. For example, youth who catastrophize more about their pain develop more negatively biased memories for pain (explicit memory system) several months after surgery[31,32] and demonstrate diminished extinction learning (implicit memory system).[19] These factors may also impact levels of stress at the time of encoding, serving as potential boundary conditions for the presence of a memory bias.

Therefore, in this study, we examine the relationship between amygdala and hippocampal structure and function, stress at the

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time of encoding through salivary cortisol, pain-related worry and distress (pain catastrophizing), and emotional memory bias. We aim to extend previous work by examining a range of emotional memories that may be relevant for maintaining pain chronicity,[12] eg, memory bias for learned (conditioned) responses to cues of threat or safety (**Fig. 1A**). Capturing the understudied interaction between implicit and explicit memory systems[13] related to these learned responses is a highly novel and therapeutically relevant avenue to understanding the maintenance of pain-related disability.

Given the lack of replicability in the field thus far, we will assess the robustness of our findings across 2 studies with small variations in conditioning paradigm and assess the specificity of any observed effects by comparing the responses of adolescents with chronic pain with those of a pain-free control group. We hypothesize that (H1) adolescents with chronic pain will show greater negative memory bias compared with pain-free peers; (H2) higher pain-related worry and distress will be related to greater negative memory bias in adolescents with chronic pain; (H3) higher stress (cortisol) at the time of encoding will be related to greater negative memory bias; and (H4) the degree of memory bias will be related to hippocampal and amygdala shape (4a) and functional connectivity (4b).

2. Methods

2.1. Participants

Adolescents with chronic pain were recruited from a pediatric pain management clinic (Chronic Pain Clinic at Boston Children's Hospital in study 1 and Pediatric Pain Management Clinic at Stanford Children's Health in study 2) when they presented for multidisciplinary evaluation. These data were collected as part of a larger study on threat–safety learning in chronic pain, and outcomes from study 1 have been published previously.[19] Participants between the ages of 10 and 24 years were included, in line with the definition of adolescence involving continued brain maturation during this period.[41] We excluded participants taking opioid or antipsychotic medications and/or who had significant cognitive impairment or psychiatric conditions (eg, active suicidality, eating disorder). Participants were not excluded for having anxiety or depressive symptoms and/or for taking selective serotonin reuptake inhibitors. Pain-free peers (ie, no current acute or history [>3 months] of chronic pain) were recruited through advertisements, with the same inclusion and exclusion criteria as for adolescents with chronic pain.

2.1.1. Study 1

A total of 97 participants were recruited (n = 61 chronic pain, n = 36 pain-free peers). A number of participants were excluded from the final data analysis due to incomplete magnetic resonance imaging (MRI) data collection (n = 5 chronic pain, n = 3 pain-free peers), technical errors during data collection (n = 2 chronic pain), excessive motion (>6 mm/degrees framewise displacement) during MRI data collection (n = 4 chronic pain), or lost to follow-up (n = 17 chronic pain, n = 9 pain-free peers). Participants who were excluded were significantly younger than those included in the final data analysis, $t(95) = -2.10$, $P = 0.038$, but did not differ on any other key demographics (as listed in Supplementary Materials A, Table S1, http://links.lww.com/PAIN/C116). The final sample for data analysis consisted of 34 adolescents with chronic pain and 24 pain-free peers.

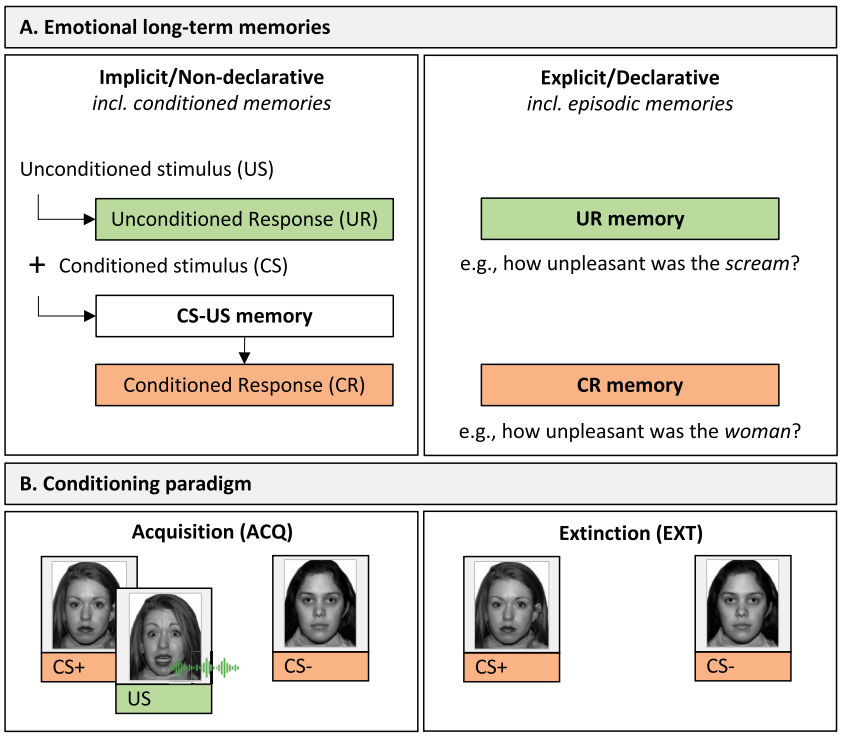

Figure 1. (A) Theoretical background depicting the mapping of explicit and implicit memory measures in this study. During the conditioning procedure, participants were asked to rate the unpleasantness of a loud scream (unconditioned stimulus [US]) as a measure of their unconditioned response (UR), and the unpleasantness of a neutral face (conditioned stimulus [CS]) as a measure of their conditioned response (CR). At the follow-up, participants were then asked to recall their UR and CR, as a measure of long-term *explicit* memory. (B) Summary of conditioning paradigm. During the acquisition (ACQ) phase, participants saw pictures of 2 female faces, one of the faces (CS+) repeatedly coterminated with the same face showing a scared expression, whereas a loud and unpleasant scream (unconditioned stimulus [US]) played over headphones. In the subsequent extinction (EXT) phase, participants were presented with the same 2 faces but neither coterminated with the scream.

2.1.2. Study 2

A total of 78 participants were recruited (n = 54 chronic pain, n = 24 pain-free peers). Participants were excluded from final data analysis because of incomplete MRI data collection (n = 7 chronic pain, n = 2 pain-free peers), technical errors during data collection (n = 5 chronic pain, n = 2 pain-free peers), excessive motion (>6 mm/degrees framewise displacement) during MRI data collection (n = 2 chronic pain, n = 1 pain-free peers), incidental MRI findings (n = 2 chronic pain), or lost to follow-up (n = 12 chronic pain, n = 6 pain-free peers). Participants who were excluded were significantly younger than those included in the final data analysis, $t(75) = -3.19$, $P = 0.002$, and had less pubertal development, $t(69) = -2.29$, $P = 0.025$, but did not differ on any other key demographics (as listed in Supplementary Materials A, Table S1, http://links.lww.com/PAIN/C116). The final sample for data analysis consisted of 26 adolescents with chronic pain and 13 pain-free peers.

2.2. "Screaming lady" conditioning paradigm

The screaming lady paradigm is an age-appropriate threat–safety learning paradigm[7,26] with neutral female faces serving as conditioned (threat–safety) stimuli (CSs) and a scared face paired with a loud (95 dB) aversive scream serving as the unconditioned (threat) stimulus (US) (**Fig. 1B**). Face and CS type were counterbalanced across participants. During the preacquisition phase, participants were presented with 2 CSs (4 times for 8 seconds each), neither of which were paired with the US. During acquisition, both CSs were presented again (10 times for 8 seconds each) with the CS+ coterminating with the US on 80% of the trials (delay conditioning) and the CS− never paired with the US. Extinction training consisted of 16 presentations for 8 seconds each of CS+ and CS−, with no US presentations across 2 blocks. Intertrial intervals were jittered ranging from 11 to 25 seconds. Note that for study 2 participants were presented with 2 CSs+ and 1 CS−, with one of these CS+ being presented twice (unreinforced) before extinction. The effect of this reactivation was then tested in session 2 with a return-of-fear test following reinstatement (4 US presentations). The design for study 2 was chosen to investigate memory consolidation interference, and the outcomes from this study will be published separately, and study 1 design is published.[19]

2.3. Procedure

2.3.1. Study 1

The protocol was approved by the Boston Children's Hospital Institutional Review Board (#P00013786). Participants and legal guardians provided written assent/consent and completed surveys; participants underwent the preacquisition and acquisition phases of the screaming lady paradigm. A 30 to 60 minutes of transition followed during which participants moved to the MRI scanner, to complete the extinction phase of the paradigm. The paradigm was administered using E-prime 2.0. Follow-up memory interviews (see "self-reported measures") were conducted by telephone at least 1 month after the initial study session (mean = 38 days, standard deviation = 10 days, range = 28-77 days).

2.3.2. Study 2

The study was approved by Stanford University Institutional Review Board (IRB-#38432). The study was divided into 2 visits. In session 1, participants and legal guardians provided written assent/consent and completed surveys, and participants underwent the acquisition, reactivation, and extinction phases of the screaming lady paradigm. Session 2 took place on average 7 days later in the MRI scanner, and consisted of the reinstatement, return-of-fear test, and re-extinction phases of the screaming lady paradigm. Here, we only focus on the acquisition and extinction phases of the conditioning paradigm. The paradigm was administered using E-prime 2.0 and 3.0. Follow-up memory interviews (see "self-reported measures") were conducted by telephone at least 1 month after the initial study session (mean = 45 days, standard deviation = 21 days, range = 27-122 days) to assess participants' explicit memory of the responses given during the conditioning paradigm.

2.4. Questionnaires

2.4.1. Demographics

Participants self-reported their age and sex, whereas pain duration (months) and pain type were derived from medical records.

2.4.2. Pain catastrophizing scale for children

The pain catastrophizing scale for children (PCS-C) is a 13-item questionnaire that assesses pain-related worry and distress, including rumination, magnification, and helplessness.[10] Higher scores indicate greater pain-related worry and distress. The measure has been shown to be valid and reliable in children older than 9 years.[35] Internal consistency within both samples was high (study 1 $\alpha = 0.93$, study 2 $\alpha = 0.92$).

2.4.3. Fear of pain questionnaire for children

The fear of pain questionnaire for children (FOPQ-C) is a 24-item questionnaire validated in children older than 8 years that assesses pain-related fear and activity avoidance, with higher scores indicating greater pain-related fear.[44] Internal consistency within both samples was high (study 1 $\alpha = 0.95$, study 2 $\alpha = 0.94$).

2.4.4. State-trait anxiety inventory for children

The state-trait anxiety inventory for children (STAI-C) is a 20-item questionnaire that assesses children's state and trait anxiety symptoms through 2 separate subscales, with higher scores indicating greater anxiety.[45] Internal consistency within both samples was high (study 1 State $\alpha = 0.89$, study 1 trait $\alpha = 0.91$, study 2 State $\alpha = 0.84$, study 2 trait $\alpha = 0.90$).

2.4.5. Functional disability inventory

The functional disability inventory (FDI) is a 15-item questionnaire that assesses children's perceived difficulty in performing common activities because of pain, with higher scores indicating greater disability.[50] Internal consistency within both samples was high (study 1 $\alpha = 0.94$, study 2 $\alpha = 0.93$).

2.4.6. Pubertal development scale

The pubertal development scale (PDS) is a 5-item questionnaire that approximates the stage of pubertal development through a series of questions focused on physical changes to the body (growth in height, growth in body hair, skin changes, male: voice change, facial hair, female: breast development, menstruation).[38] Items are coded on a 4-level ordinal response scale (*has not*

begun to *seems complete*). Items are summed and divided by 5 to preserve a 1 to 4 pubertal development metric.

2.5. Ratings

2.5.1. Threat-safety learning task (implicit memory)

The *conditioned response* (*CR*) was assessed by responding to the question, "How unpleasant is this woman?", through an 11-point numerical rating scale (NRS) with scale anchors of "not unpleasant" to "extremely unpleasant." The *unconditioned response* (*UR*) was assessed (only after acquisition) by responding to the question, "How unpleasant was the scream?", through an 11-point NRS with scale anchors of "not unpleasant" to "extremely unpleasant." Current *pain intensity* was assessed (for the chronic pain group only) by responding to the question, "How much pain are you in right now?" through an 11-point NRS with scale anchors of "no pain" to "worst possible pain."

2.5.2. Test of explicit emotional memory recall

The follow-up memory interviews were composed of a *free recall* portion with prompts (eg, "what else happened?" "tell me more") to encourage elaboration in describing their experience during the study visit, which was then followed by *probed recall* with the visual presentation of face stimuli from the study visit. Specifically, during the follow-up, telephone interview participants were asked to recall how they felt during the testing session (threat safety learning task) in an open-ended manner. They were then shown the CSs from the threat learning task and received the instruction to "… think back to the [first/second] part, [when you were sitting at the computer/were in the MRI scanner] looking at the faces. Take a few seconds and try to remember being there in the testing room and what that felt like" followed by "How unpleasant was this face?" (*memory for the conditioned response*), "How unpleasant was the scream" (*memory for the unconditioned response*), and "How much pain did you feel?" (*memory for pain intensity*). Similar approaches have previously been used to assess memory in youth undergoing surgery and needle procedures.[31,32,37]

2.6. Cortisol

Saliva samples were collected at several time points during the study visit, including 15 minutes after the acquisition and extinction phases and to limit confounding, participants were instructed to not eat and drink in the hour before the study visit. Saliva was collected using passive drooling into a tube using disposable funnels. All tubes were labeled and after collection, the samples were immediately stored at −20°C. Cortisol was determined by enzyme linked immunosorbent assay (ELISA) and enzymatic kits, respectively, performed by Salimetrics (salimetrics.com).

2.7. Magnetic resonance imaging

2.7.1. Study 1

Data were acquired on a 3T MRI scanner (Siemens Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) using a 12-channel head coil. For the resting-state functional images, a T2*-weighted standard echo-planar imaging sequence was used to acquire 51 axial slices (3-mm isotropic) covering the entire cortical volume, using the following parameters: repetition time (TR) = 1110 milliseconds, echo time (TE) = 30 milliseconds, flip angle = 70°, field of view = 228 × 228 mm, matrix size = 76 × 90, and slice acceleration factor = 3. In total, 425 functional volumes were collected with eyes open looking at a black screen. In addition, 8 functional volumes using the same parameters, but reverse phase encoding direction (posterior to anterior) were acquired. Structural T1-weighted anatomical images were acquired using a 3D multiecho, magnetization-prepared, rapid gradient-echo (ME-MPRAGE) sequence with the following parameters: 176 slices, 1-mm isotropic, TR = 2520 milliseconds, TE1 = 1.74 milliseconds, TE2 = 3.6 milliseconds, TE3 = 5.46 milliseconds, TE4 = 7.32 milliseconds, flip angle = 7°, field of view = 240 × 240, and GRAPPA acceleration factor = 2.

2.7.2. Study 2

Data were acquired on a 3T GE Premier MR 750 system (GE Healthcare, Richard M. Lucas Center for Imaging) using a 32-channel Nova head coil. For the resting-state functional images, a T2* simultaneous multislice (SMS) EPI sequence was used to acquire 45 axial slices (3-mm isotropic) covering the entire cortical volume, using the following parameters: repetition time (TR) = 1.11 seconds, echo time (TE) = 30 milliseconds, flip angle (FA) = 70°, SMS factor = 3, field of view = 228 × 228 mm. In total, 435 functional volumes were collected with eyes open looking at a black screen. Before functional images, an ASSET calibration scan and a higher-order shimming protocol were used to measure coil sensitivity profiles and field inhomogeneities, and correct gradients accordingly. Structural T1-weighted anatomical images were acquired using a standard GE 3D BRAVO sequence, an IR-prep, fast 3D spoiled gradient-recalled (SPGR) sequence, using the following parameters: TR = 8.6 milliseconds, TE = 3.4 milliseconds, FA = 15°, FOV = 256 × 256 mm, 176 sagittal slices, voxel size 1-mm isotropic.

2.7.3. Preprocessing

Results included in this manuscript come from preprocessing performed using fMRIPrep 20.2.0[14] (RRID:SCR_016216), which is based on Nipype 1.5.1[16,17] (RRID:SCR_002502). The full preprocessing pipeline can be found in Supplementary Materials B, http://links.lww.com/PAIN/C116. In brief, the structural T1-weighted (T1w) image was corrected for intensity inhomogeneities, skull-stripped, and standardized using nonlinear transformation to MNI152 space. Functional T2*-weighted data were coregistered to the T1w (following susceptibility distortion correction for study 1 data), motion-corrected, slice-time corrected, and standardized to MNI152 space.

2.8. Statistical analyses

2.8.1. Questionnaire measures

Group differences in demographics were analyzed using χ^2 contingency tests, for the categorical variables gender and pain type, and 2 (group: chronic pain/pain free) × 2 (study: 1/2) ANOVAs for the continuous variables age, STAI-state, STAI-trait, FDI, PCS, FOPQ, and pubertal development. An independent samples *t* test was used to compare pain duration between the 2 studies, with Welch correction for unequal variances. Alpha criterion for all tests was $\alpha = 0.05$.

2.8.2. Memory bias

To test for the presence of memory biases and potential differences between the groups (H1), data were analyzed using linear mixed-effects models as implemented in Matlab (R2021b). The follow-up scores were modeled as dependent variables, and baseline scores

(grand mean centered) were entered as fixed-effects predictor variables. A significant relationship between baseline and follow-up was indicative of no memory bias (ie, baseline and follow-up scores were significantly similar). The linear mixed-effects model assumes that the dependent variable is normally distributed, and although Shapiro-Wilk tests indicated that the data were not normally distributed ($P < 0.05$), inflation of this P value because of the large number of values was likely. Inspection of the test statistic indicated that $W > 0.9$ for all measures, confirming the visual inspection of normally distributed data.[20] CS type (CS+/CS−), phase (acquisition/extinction), group (chronic pain/pain-free peers), and their interaction terms were included as fixed-effects predictors as appropriate. Participant was included as a random-effects predictor (random intercept).

To investigate the effect of individual differences on memory bias (H2), an additional model was tested in adolescents with chronic pain, which included PCS (fixed effect). To test the effect of stress at encoding on memory bias (H3), an additional model was tested, which included cortisol and controlled for sex and puberty (fixed effects), which are known to influence cortisol levels.[21] The alpha criterion for all tests was Bonferroni corrected to $\alpha = 0.016$ to correct for the 3 tests (memory bias for the CR, UR, and pain) of each hypothesis. Correlations between the length of follow-up was examined in relation to memory bias across stimuli. No associations were significant.

For all linear mixed-effects models, we calculated variance inflation factors (VIFs) (calculated as the diagonal elements of the inverse of the correlation matrix[2]) to assess that P values were not inflated by problematic multicollinearity between the fixed-effects predictors. All predictors were below the commonly used threshold of VIF < 5.[9,46]

2.8.3. Magnetic resonance imaging: morphology

Amygdala and hippocampal shape was calculated using FSL's FIRST pipeline.[36] Briefly, segmentation of these regions was performed on the T1w images and visually inspected for accuracy. Each region was then represented as a mesh, and a group-average was calculated. Vertexwise deviation from the group mean was then calculated for each participant. FSL's randomise[52] was then used to calculate nonparametric statistics for the GLM analysis. Follow-up scores (grand mean centered) and group were entered as predictors in a GLM analysis of the shape displacement meshes created for each region of interest. The baseline values and age (both grand mean centered) were entered as covariates of no interest. The resulting statistical maps were thresholded using TFCE-correction for multiple comparisons.

2.8.4. Magnetic resonance imaging: connectivity

Resting-state functional connectivity analyses were performed in CONN toolbox [CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550)[51]]. Before analysis, the first 6 volumes of the resting-state data were removed for stabilization effects, and data were spatially smoothed with a 6-mm FWHM Gaussian kernel. Data were denoised using a 0.008—0.3 Hz band-pass filter simultaneously applied as regression of confounds (6 realignment parameters and their first-order derivatives and quadratics, average cerebrospinal fluid [CSF] time course and its first-order derivative, and scrubbing predictors calculated by fMRIprep). ROI-to-whole brain connectivity matrices were computed. Follow-up ratings and group were entered as predictors with baseline ratings and age included as covariates of no interest. Within this multivariate model, 2 subdivisions of each region of interest (eg, posterior/anterior hippocampus[15] or basolateral/centromedial amygdala[49]) were included for each hemisphere separately. ROIs were resampled to the resolution of the functional images and masked to avoid overlap between the subdivisions and regions. Resulting statistical maps were thresholded using FDR correction.

2.8.5. Cortisol

Values more than 3 standard deviations from the mean (for that time point) were removed as outliers (2.11% of all values). To ensure that the obtained samples reflect the expected peak in cortisol response following the learning phase of interest, samples were removed if they were not collected approximately 15 minutes after this phase (10-20 minutes). For study 1, 10% of acquisition samples and 14% of extinction samples were removed. For study 2, 8% of acquisition samples and 31% of extinction samples were removed.

3. Results

3.1. Participant demographics

A 2 [study 1/study 2] × 2 [chronic pain/pain free] ANOVA showed that participants recruited for study 2 did not significantly differ from study 1 in age ($F(1,93) = 0.24$, $P = 0.623$), FDI ($F(1,93) = 0.89$, $P = 0.348$), PCS ($F(1,93) = 1.85$, $P = 0.178$), sex ($X^2 = 3.34$, $P = 0.068$), pubertal stage ($F(1,92) = 0.04$, $P = 0.835$), or pain type ($X^2 = 2.58$, $P = 0.276$). However, there was a significant difference in STAI-state ($F(1,93) = 364.25$, $P < 0.001$), STAI-trait ($F(1,93) = 10.69$, $P = 0.002$), FOPQ ($F(1,93) = 6.63$, $P = 0.012$), and pain duration ($t_{Welch}(36.02) = -2.24$, $P = 0.031$). Specifically, participants in study 2 were higher in trait anxiety and FOPQ, had longer pain duration, but were lower in state anxiety.

There were no interactions between group and study, indicating that the differences between the chronic pain and pain-free groups did not vary between the 2 studies. However, the groups (chronic pain vs pain-free) did differ in STAI-state ($F(1,93) = 4.15$, $P = 0.044$), STAI-trait ($F(1,93) = 22.75$, $P < 0.001$), FDI ($F(1,93) = 63.67$, $P = <0.001$), PCS ($F(1,93) = 28.54$, $P < 0.001$), and FOPQ ($F(1,93) = 51.35$, $P < 0.001$). Full demographics are available in Supplementary Materials A (Table S1, http://links.lww.com/PAIN/C116).

To assess whether the chronic pain samples tested in study 1 and study 2 were representative of the population that presents for pain care in a tertiary pain setting, demographics for these study samples were compared with data obtained from the initial evaluations conducted at the Pediatric Pain Management Clinic (PPMC) at Lucile Packard Children's Hospital Stanford between September 2019 and June 2022 (population pool for study 2). Compared with this population, both study samples differed in race and ethnicity, with fewer Hispanic/Latino individuals, and fewer Black/African American and Asian individuals represented in the study. In addition, the sample in study 1 had significantly fewer male subjects and were significantly older than the population sample (full statistics reported in Supplementary Materials A, http://links.lww.com/PAIN/C116).

4. Results: study 1

4.1. Are there group-related differences in memory bias (H1)?

For the CR memory bias, we observed a significant interaction between baseline and CS type ($F(1,220) = 8.74$, $P = 0.003$),

which was driven by memory bias for the CS− at ACQ (β = 0.17, F(1,220) = 1.80, P = 0.181), but no memory bias for the CS− at EXT or for the CS+ at ACQ or EXT. Although the majority of participants rated the CS− as mildly unpleasant (<5) at baseline, at follow-up, these ratings increased to highly unpleasant (>5), indicative of a negative memory bias (**Fig. 2A**). Contrary to our hypotheses, we did not observe a significant difference between adolescents with and without chronic pain, nor did we identify any evidence of memory bias for the UR or pain (for full statistical tables see Supplementary Materials C, http://links.lww.com/PAIN/C116).

4.2. Are differences in memory bias related to pain-related worry and distress (H2)?

When focused on the chronic pain group and introducing PCS as a covariate, we still observed a significant memory bias for the CS− at ACQ, and a memory bias for the CS− at EXT emerged (β = 0.36, F(1,126) = 2.35, P = 0.020). However, there was no significant effect of PCS, nor was PCS related to memory bias for the UR or pain.

4.3. Does stress during encoding relate to the degree of memory bias (H3)?

When cortisol levels were included in the model for the full sample, the memory bias for CS− at ACQ remained, and there was also a significant interaction between cortisol and memory bias for CS+ (β = −0.15, F(1,204) = 12.47, P = 0.001), with individuals with higher cortisol showing a stronger memory bias.

4.4. Is the degree of memory bias related to amygdala and hippocampal shape (H4a)?

To assess whether the degree of memory bias is related to amygdala and hippocampal structure, the follow-up scores (grand mean centered) were entered as predictors in a GLM analysis of the shape displacement meshes created for each region of interest. Given the high correlation between the ACQ and EXT phases for both CS+ (r = 0.70, P < 0.001) and CS− (r = 0.71, P < 0.001), these values were averaged, as were the pain values for ACQ and EXT (r = 0.83, P < 0.001). This resulted in 4 tests in the full sample: CR memory bias for the CS+, pain memory bias for the CS− (for adolescents with chronic pain only), and UR memory bias, with a Bonferroni-adjusted α-criterion of 0.013. However, we did not observe that any shape displacements significantly correlated with memory bias for any of the 4 measures.

4.5. Is the degree of memory bias related to amygdala and hippocampal connectivity (H4b)?

As with the investigation of amygdala and hippocampal structure, we assessed whether resting-state functional connectivity in the full sample was related to either the CR memory bias for CS+ and CS− (averaged over phase), UR memory bias, or pain memory bias (for adolescents with chronic pain only), with a Bonferroni-adjusted α-criterion of 0.013.

Both the right and left hippocampus showed increased connectivity with the right middle frontal gyrus that was related to increased memory bias for pain; however, only the connectivity with the right hippocampus survived Bonferroni correction. Furthermore, the strength of connectivity between the right hippocampus and the precentral gyrus and angular gyrus was differentially related to memory bias for the CR (CS+) for individuals with chronic pain and their pain-free peers. A positive relationship was present for adolescents with chronic pain: stronger connectivity was related to more negative memory bias, whereas a negative relationship was present for pain-free peers: weaker connectivity was related to more negative memory bias. A similar pattern was also present for connectivity between the right hippocampus and the supramarginal gyrus and superior frontal gyrus, related to memory bias for the UR (**Table 1**).

5. Results: study 2

5.1. Are there group-related differences in memory bias (H1)?

We observed a significant memory bias for both CS+ and CS− at ACQ and at EXT (main effect of baseline: F(1,128) = 5.18, P = 0.025; for full statistics see Supplementary Materials C, http://links.lww.com/PAIN/C116), with a visual inspection of the data distribution suggesting that this effect was largely driven by individuals rating low/mild CS unpleasantness at baseline but providing higher ratings at follow-up, consistent with a negative memory bias. Similar to study 1, there were no effects of group and no evidence of memory bias for the UR or pain (**Fig. 2B**).

5.2. Are individual differences in memory bias related to pain-related worry and distress (H2)?

Within the chronic pain group, all effects remained when controlling for PCS, and there were no interactions between PCS and memory bias for the CR, UR, or pain.

5.3. Does the emotional state during encoding relate to the degree of memory bias (H3)?

When cortisol levels were included as a covariate in the model for the full sample, the CR memory bias remained, and the absence of memory bias for the UR and for pain remained unchanged from the H1 model.

5.4. Is the degree of memory bias related to amygdala and hippocampal shape (H4a)?

We assessed whether the degree of memory bias is related to amygdala and hippocampal structure by using the follow-up scores (grand-mean centered) as predictors in a GLM analysis of the shape displacement meshes created for each region of interest, controlling for baseline values and age. Ratings for CS+, CS−, and pain were averaged across phases, resulting in 4 tests: CR memory bias for the CS+, pain memory bias for the CS−, and UR memory bias, with a Bonferroni-adjusted α-criterion of 0.013. However, we did not observe any shape displacements that significantly correlated with memory bias for any of the 4 measures (**Fig. 3**).

5.5. Is the degree of memory bias related to amygdala and hippocampal connectivity (H4b)?

As with the investigation of amygdala and hippocampal structure, we assessed whether resting-state functional connectivity was related to either the CR memory bias for CS+ and CS− (averaged over phase), UR memory bias, or pain memory bias (for adolescents with chronic pain only), with a Bonferroni-adjusted α-criterion of 0.013.

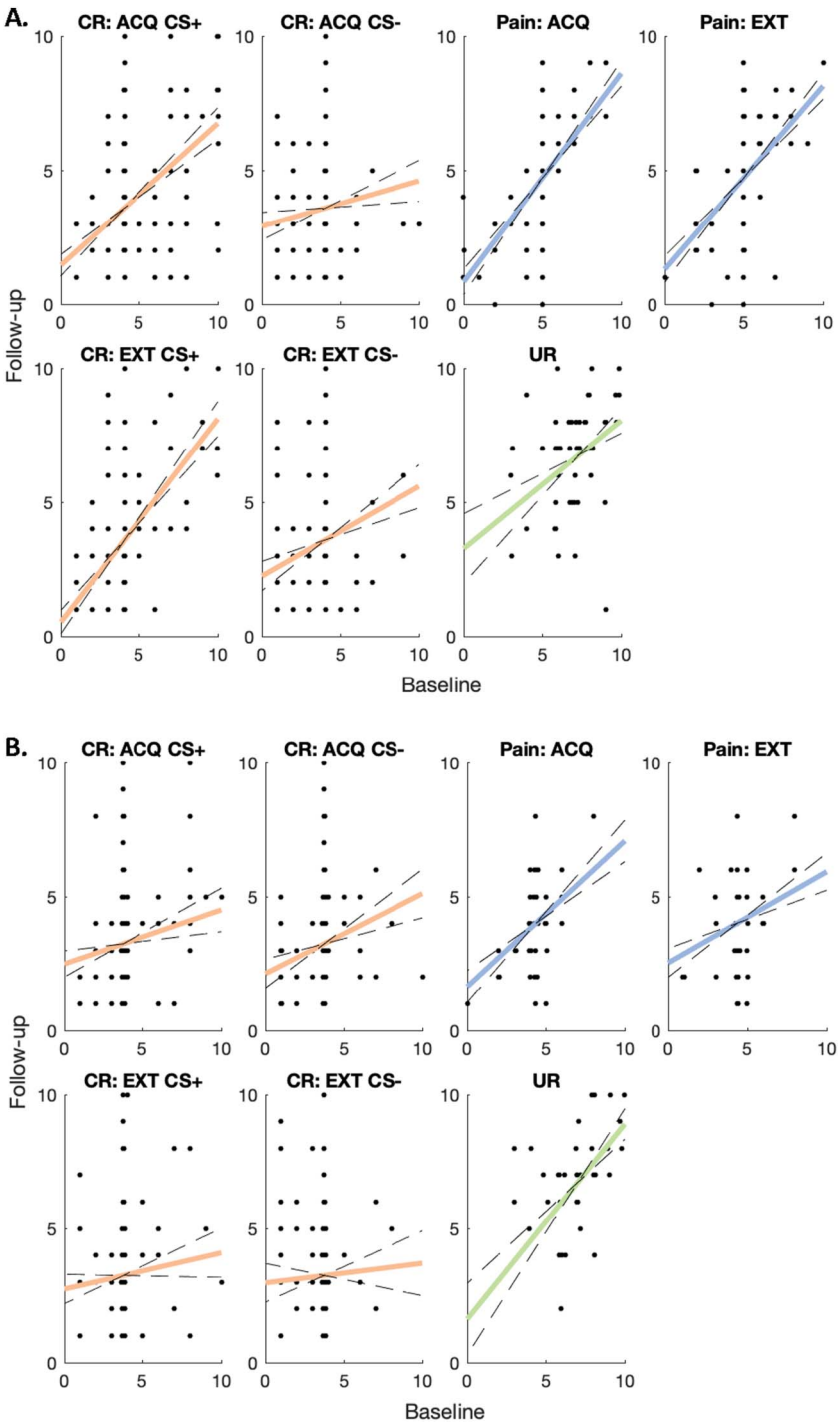

Figure 2. Relationship between follow-up and baseline ratings for study 1 (panel A) and study 2 (panel B). Memory bias is indicated by a lack of a significant relationship between follow-up and baseline. Memory for the conditioned responses (CR) at acquisition (ACQ) and extinction (EXT) are indicated in orange, memory for the unconditioned response (UR) is indicated in green, and memory for pain intensity is indicated in blue. For visual purposes, overlapping points are jittered.

Resting-state connectivity between the left amygdala and a diffuse cluster in the brain stem/cerebellum was related to memory bias for the CR (CS−), as was connectivity between the right hippocampus and an overlapping cerebellar region. Memory bias for the UR was related to the connectivity between the right amygdala and bilateral precuneus and intracalcarine cortex. Furthermore, connectivity between the left hippocampus and intracalcarine cortex, and left hippocampus and lingual gyrus, was related to memory bias for the UR in pain-free individuals but not in individuals with chronic pain (**Table 2**).

6. Discussion

We aimed to explore the conditions for the presence of an emotional memory bias in adolescents with and without chronic pain. Using a developmentally appropriate threat–safety learning paradigm, we tested cortisol at the time of emotional stimulus

Table 1

Clusters showing connectivity related to the degree of memory bias in study 1.

Seed region	Cluster	Size (# voxels)	Peak (x y z)	p-FDR
Memory bias for pain				
L. Hipp.	Middle frontal gyrus	124	−26 +42 +32	0.026
R. Hipp.	Middle frontal gyrus	271	−26 +38 +32	<0.001*
Memory bias for CR (CS+): chronic pain ≠ pain free				
R. Hipp.	Precentral gyrus	225	−26 −24 +68	0.004*
	Angular gyrus	205	+54 −52 +14	0.004*
	Inferior temporal gyrus	104	+62 −60 −12	0.049
	Superior temporal gyrus	101	−62 −40 +08	0.049
	Fusiform gyrus	101	+40 −72 −18	0.049
Memory bias for UR: chronic pain ≠ pain free				
R. Hipp.	Supramarginal gyrus	182	−60 −48 +42	0.005*
	Superior frontal gyrus	168	+22 +12 +66	0.005*
	Supramarginal gyrus	94	+58 −40 +12	0.044

* Significance at the Bonferroni-corrected α-criterion of 0.013.

encoding, and individual differences in pain-related worry and distress (pain catastrophizing), amygdala and hippocampal structure and functional connectivity, and how these relate to the strength of memory bias. Given the lack of replicability in the field thus far, we assessed the robustness of our findings across 2 studies.

In both study 1 and study 2, we observed a memory bias for responses to the safety cue (CS−), with a tendency to recall the CS− as being more unpleasant than reported at the time. This bias was present for adolescents with and without chronic pain and was not related to pain-related worry and distress, or cortisol levels at the time of encoding. In study 2, the strength of memory bias for safety cues was related to connectivity between the left amygdala and the cerebellum, and the right hippocampus and the cerebellum, with cerebellar clusters aligning with right Crus I-V, regions previously implicated in safety learning.[23,24]

Although in study 1, there was no overall memory bias for the threatening cue (CS+), we observed a significant positive relationship between stress (cortisol) and memory bias for the CS+. Furthermore, in study 2, we observed an overall negative memory bias for the CS+. Together, these findings suggest that there is consistently poor recall for the CS−, potentially due to a lack of emotional memory enhancement by a cue that is relatively low in valence. Conversely, the CS+ has higher valence and benefits from emotional memory enhancement, unless stress is too high, when encoding may be impaired and lead to later recall deficits. Notably, cortisol levels were overall higher and showed less variance in study 2 vs study 1 (Supplementary Material A, Table S1, http://links.lww.com/PAIN/C116), which could explain why a memory bias for CS+ was present in study 2 but not study 1, and why the relationship between cortisol and memory bias for CS+ was present only in study 1 and not study 2. These results are consistent with previous literature focusing on acute (surgical) pain memories among adolescents.[8,30,31] Although the short and controlled nature of the response evoked by the CS+ would not typically be expected to lead to memory-encoding impairments, recent evidence has shown that adolescents show altered emotional memory enhancement compared with adults, potentially because of limited attentional resources in this population,[53] which could explain why we observed poor recall at relatively mild levels of stress.

Despite the similarity in valence and response intensity to the CS+ and the US, we did not observe any evidence of a memory bias for the UR (ie, how unpleasant they found the scream). This discrepancy suggests that the mechanism generating the emotional response being recalled affects the degree of disruption that can occur in the pathway from encoding to retrieval: ie, the fear response evoked by an innately aversive (unconditioned) stimulus, compared with the (conditioned) fear response evoked by a threat cue. Potentially, the distinct neural pathways in the underlying fear system[18] interact with the episodic memory system, with the encoding of memories for conditioned responses showing greater modulation by the stress response. Furthermore, the added complexity of competing acquisition and extinction memory traces for a CS may result in less accurate retrieval. However, memories of the most recent learning episode (extinction) were not more accurate than those of the earlier episode (acquisition), suggesting a bidirectional influence rather than a recency effect.[1] The connectivity between the right amygdala and the precuneus, as well as the intracalcarine cortex, was related to the degree of memory bias for the UR in study 2. Furthermore, in both studies, the 2 groups differed in the correlation between memory bias for UR and functional connectivity. In study 1, this was observed between the right hippocampus and superior frontal and supramarginal gyrus. Although in study 2, this was present between the left hippocampus and intracalcarine and lingual gyri. Although these results did not fully replicate, they do indicate a functional reorganization of episodic memory neurocircuitry, particularly involving the hippocampus, between those with and without chronic pain. Potentially, different regions are being recruited into these circuits as a compensatory mechanism to maintain emotional memory enhancement, resulting in similar self-reports between the 2 groups, generated by different neural mechanisms.

In addition to a lack of memory bias for the UR, we did not observe a memory bias for pain intensity. Although both pain and the scream are innately aversive, only the memory of pain intensity was a perceptual recall of an unevoked experience. However, the observed lack of memory bias suggests that both perceptual and emotional memories of responses evoked by aversive stimuli are processed similarly. Furthermore, as with memory bias for the

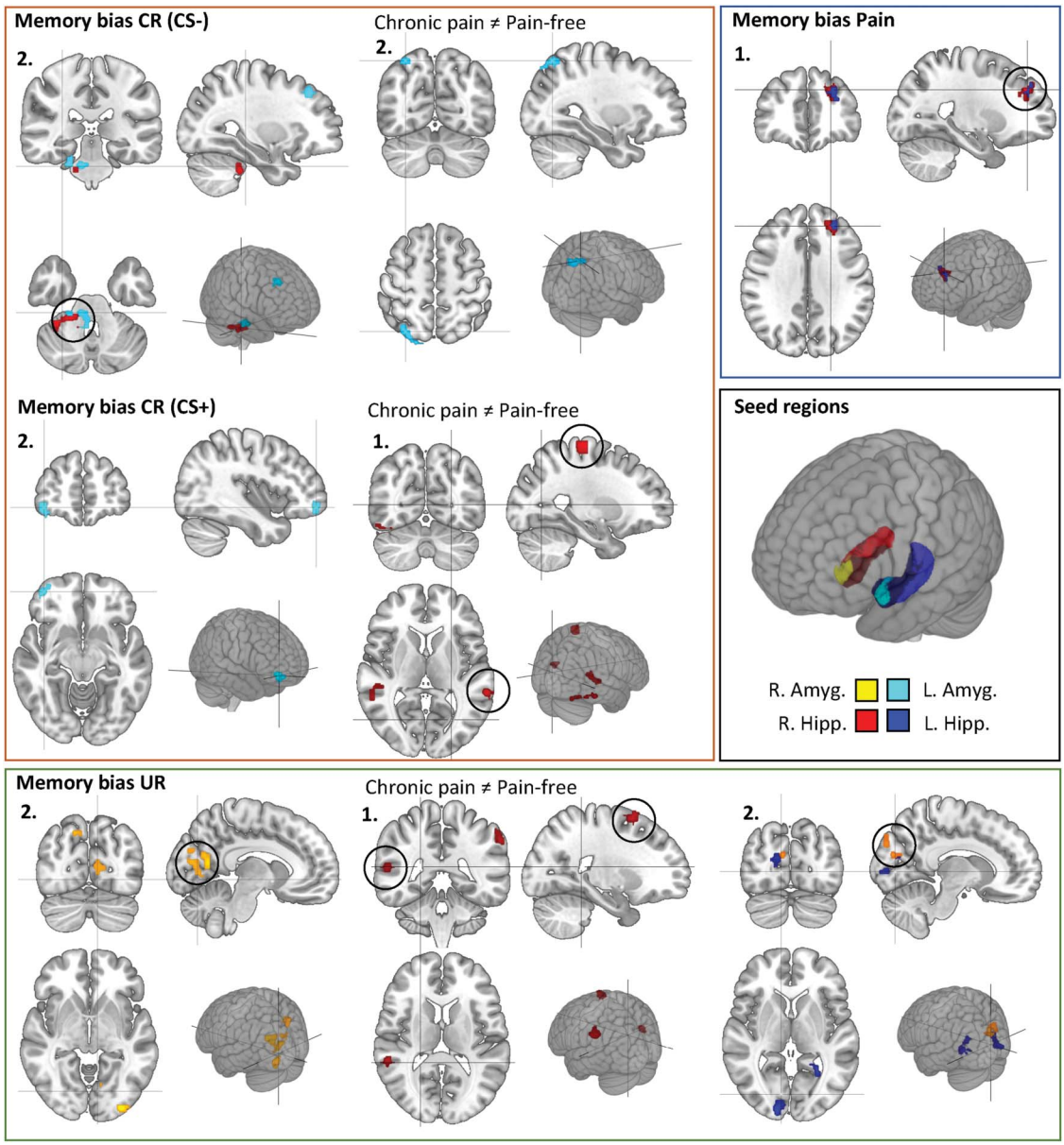

Figure 3. Functional connectivity of amygdala and hippocampus seed regions in study 1 (1.) and study 2 (2.) maps show FDR-corrected results. Cluster colors indicate seed region and clusters, which survived Bonferroni correction are circled. Box colors indicate the memory bias being tested: memory bias for conditioned responses in orange, memory bias for pain in blue, memory bias for unconditioned responses in green.

UR, we did observe that the hippocampus resting-state connectivity correlated with the degree of memory bias; specifically, in study 1, the connectivity between the right (and left, uncorrected) hippocampus and the middle frontal gyrus. This cluster is consistent with the dorsolateral prefrontal cortex (dlPFC) region, commonly implicated in both chronic pain[43] and the encoding of episodic memories.[33] However, this pattern was not replicated in study 2.

Contrary to our findings, previous research has observed a negative memory bias for unevoked pain among both adults and adolescents with chronic pain.[3,6] However, both previous studies collected pain reports in a naturalistic setting, which may have differed in stress from the experimental context in this study. This distinction may be particularly important when considering the memories that are being formed during stressful learning events. As demonstrated by Noel et al.,[31] the pain intensity that children reported 2 weeks after surgery highly correlated (baseline and follow-up correlation: $r = 0.68$) with the pain intensity they recalled 2 to 4 months postsurgery, showing an even greater memory enhancement than in the current study (baseline and follow-up correlation: study 1 $r = 0.40$ and study 2 $r = 0.52$).

6.1. Strengths and limitations

The 2-study approach allowed us to assess the robustness of observed effects across small variations in study design and sample characteristics. Study 1 used a simple differential fear conditioning paradigm, whereas study 2 incorporated a more complex paradigm with an additional CS+ and multiple learning phases. In addition, the extinction phase in study 2 occurred in a laboratory setting, whereas in study 1, it took place in the scanner, which could be considered a more stressful environment. Participants in study 1 displayed lower levels of trait anxiety had reduced fear of pain and experienced shorter pain durations compared with those in study 2. However, participants in study 1

Table 2

Clusters showing connectivity related to the degree of memory bias in study 2.

Seed region	Cluster	Size (# voxels)	Peak (x y z)	p-FDR
Memory bias for CR (CS−)				
L. Amyg.	Brain stem/cerebellum	151	+08 −34 −32	0.016*
	Middle frontal gyrus	116	+30 +36 +42	0.025
R. Hipp.	Cerebellum	266	+18 −34 −34	0.003*
Memory bias for CR (CS+)				
L. Amyg.	Frontal pole	127	+42 +50 −10	0.028
Memory bias for UR				
R. Amyg.	Precuneus	250	−18 −64 +20	0.002*
	Intracalcarine cortex	194	−08 −78 +12	0.005*
	Precuneus	157	+12 −72 +44	0.011*
	Occipital pole	121	−32 −94 −04	0.025
Memory bias for CR (CS−): chronic pain ≠ pain free				
L. Amyg.	Lateral occipital cortex	169	+20 −80 +56	0.017
Memory bias for UR: chronic pain ≠ pain free				
L. Hipp.	Intracalcarine cortex	296	+16 −96 +02	0.003*
	Lingual gyrus	242	−30 −58 +00	0.006*
R. Amyg.	Occipital cortex	205	−02 −88 +32	0.014

* Significance at the Bonferroni-corrected α-criterion of 0.013.

exhibited higher levels of state anxiety compared with those in study 2 (potentially because of the anticipated MRI). Although these differences may explain the lack of replicability between the 2 studies, they are arguably not substantial differences. Instead, they allow us to explore the generalizability of our findings across a broader population of interest, encompassing the general population of adolescents with chronic pain, which is crucial in the translation from basic to clinical research. Finally, this study was not preregistered because it was devised before the implementation of this new standard of practice for rigor and transparency in science.

7. Conclusions

We observed a reliable negative memory bias for emotional responses to cues of safety, and a negative memory bias for responses to cues of threat—but only when stress was high. Memories of emotional responses to an aversive stimulus, and memories of pain intensity, were largely accurate. Although we did not observe any morphological changes in the hippocampus or the amygdala that related to the degree of memory bias, we did observe associations with resting-state connections from the amygdala and hippocampus. However, the replicability of these findings was limited, with results suggesting that further investigating overlap in implicit and explicit memory networks (ie, cerebellum, dlPFC, amygdala, and hippocampus) is needed to understand the neural mechanisms underlying emotional memory biases.

By studying both implicit and explicit memory systems, we demonstrated that the processes influencing memory recall vary depending on the specific mechanisms that elicit emotional states, e.g., conditioned and unconditioned responses. These differences may be associated with distinct neural networks that trigger these emotional states, as suggested by previous research in nonhuman animals,[18] raising the question of whether similar variations exist for different conditioned responses, such as fear of pain vs the fear of nonpainful aversive events that were present in this study.[4] Existing research has focused on how a negative memory bias for unpleasant events predicts future experiences.[8,29] However, our results suggest that the memory for responses to safety cues consistently exhibits a more negative recall bias. Given the important role of threat-and-safety cues in guiding adaptive behavior, inferior memory consolidation of these cues during periods of high stress, and thus negatively biased recall, could be an important factor in maintaining pain chronicity. This finding, combined with evidence indicating impaired safety learning,[27,28] highlights the potential value of interventions targeting improved threat/safety discrimination and reducing negative memory bias for safety. Such interventions could help individuals reengage with activities they value, offering promising avenues for therapeutic interventions.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Data availability: The analysis scripts and results files are openly available on OSF at [https://osf.io/shj3w/?view_only=4a4e387bc327445382373793fbbcc106]. The raw data that support the findings of this study are available on request from the authors (L.E.S.).

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