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Hippocampal morphology mediates biased memories of chronic pain

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Abstract

Experiences and memories are often mismatched. While multiple studies have investigated psychological underpinnings of recall error with respect to emotional events, the neurobiological mechanisms underlying the divergence between experiences and memories remain relatively unexplored in the domain of chronic pain. Here we examined the discrepancy between experienced chronic low back pain (CBP) intensity (twice daily ratings) and remembered pain intensity (n = 48 subjects) relative to psychometric properties, hippocampus morphology, memory capabilities, and personality traits related to reward. 77% of CBP patients exaggerated remembered pain, which depended on their strongest experienced pain and their most recent mood rating. This bias persisted over nearly 1 year and was related to reward memory bias and loss aversion. Shape displacement of a specific region in the left posterior hippocampus mediated personality effects on pain memory bias, predicted pain memory bias in a validation CBP group (n = 21), and accounted for 55% of the variance of pain memory bias. In two independent groups (n

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Author contributions

AVA and TJS designed the study. SEB, EVP, TBA, and ATB collected the data. SEB and EVP coordinated the study; TBA recruited for the study. TJS overlooked all clinical data and safety monitoring. EVP, SEB, TBA, and ATB analyzed the data. SEB and EVP made the figures and tables. SEB, EVP, and AVA wrote the manuscript.

Conflicts of interest

Authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.10.030.

= 20/group), morphology of this region was stable over time and unperturbed by the development of chronic pain. These results imply that a localized hippocampal circuit, and personality traits associated with reward processing, largely determine exaggeration of daily pain experiences in chronic pain patients.

Keywords

Chronic pain; Memory; Hippocampus; Peak-end rule; Shape displacement

Introduction

Everyday existence is a mixture of experiences and memories, the confluence and interaction of which guide future behaviors, and likely reflect adaptations critical for enhancing survival of the organism. Unraveling biological mechanisms regarding the relationship between experiences and the memories of those experiences is a cornerstone from which neuroscience can inform and advance psychology. Yet, the neurobiological mechanisms that determine or control such interactions remain minimally known. The emotional context (including mood and motivation) during an experience or recall significantly influences subsequent declarative and non-declarative memories (Murty et al., 2010). Moreover, memories may be enhanced to various degrees with valence and levels of arousal (Miron-Shatz et al., 2009; Murty et al., 2010; Mirandola and Toffalini, 2016), and there is also evidence that emotional valence and salience can cause memories to become unreliable or inaccurate (Murty et al., 2010; Bookbinder and Brainerd, 2016; Turnbull and Salas, 2017). Numerous studies have shown that the hippocampus is a key region for emotional memory processing, including the production of false or incorrect memories (Ramirez et al., 2013; Liu et al., 2014b; Kim et al., 2017), memory interferences (Winocur, 1985), and both its anatomical structure and associated neurophysiology are implicated in memory distortions (Ramirez et al., 2013; Liu et al., 2014b; Kim et al., 2017; Leal et al., 2017).

Here we examine the topic from the viewpoint of the daily experience of patients suffering from chronic pain, a severe pathology that remains undertreated, poorly understood and a primary source of disability worldwide (Murray and Lopez, 2013). In addition to the intrinsic difficulty in describing and quantifying pain, it has been repeatedly shown that memories for painful events are inaccurate - when asked to recall a past painful event, people tend to overestimate their pain, with the intensity usually reported more severe than actually experienced (Salovey and Smith, 1997). The magnitude and direction of the discrepancy between remembered pain and actual pain seem to depend upon many factors, including emotional context (Eich et al., 1985; Norvell et al., 1987; Lowe and Roberts, 1988; Smith and Safer, 1993; Algom and Lubel, 1994; Salovey and Smith, 1997; Babel, 2015), an individual's personality traits and mood (Kent, 1985; Rocha et al., 2009), and the participants' previous experience with pain (Linton and Melin, 1982; Salovey and Smith, 1997; Feine et al., 1998). The psychometric properties of acute experimental pain also account for a large proportion of the error in remembering pain. An influential study by Redelmeier and Kahneman (1996) demonstrated that patients' memories of the amount of

discomfort reported after an acute minimally invasive procedure was determined primarily by the intensity of pain at both the procedure's worst and most recent episodes, a phenomenon now known as the “peak-end rule”. Memory biases have also been documented in chronic pain patients, with evidence that long-term pain is remembered less accurately than acute pain (Linton and Melin, 1982; Salovey and Smith, 1997) and that people with persistent pain report intensity of previous pain less accurately than healthy people (Liu et al., 2014a). These inaccuracies in the recall of spontaneous episodes of chronic pain can become worse over time and even impact memories of treatment efficacy (Feine et al., 1998). Chronic pain populations also have higher rates of psychological co-morbidities and mood disturbances, which can in turn influence pain memories: increased depression, elevated levels of emotional distress, and sustained presence of negative moods can all result in the overestimation of recalled pain in patients with various kinds of chronic pain conditions (Jamison et al., 1989; Bryant, 1993; Sohl and Friedberg, 2008; Lefebvre and Keefe, 2013).

Despite identifying heuristic strategies and mental “short-cuts” influencing pain memory bias, its neurobiology has not been explored, and more specifically, the neural substrate responsible for memory bias in pain patients has yet to be identified. In the present study, we combined daily measures of pain and mood collected using a smartphone app, questionnaire data, and morphometry of the hippocampus to explain pain memory bias in chronic low back pain (CBP). We hypothesized that CBP patients would show a discrepancy where their recalled pain at the end of the rating period would be significantly higher than the actual pain intensity they experienced while rating and that this bias would show evidence of the peak-end rule. Although autobiographical memory processes involve numerous brain regions, given the importance of the hippocampus in memory encoding and retrieval, its role in the development of chronic pain (Mutso et al., 2012, 2014; Apkarian et al., 2016; Vachon-Presseau et al., 2016), and previous findings showing that cells in the dentate gyrus can be optogenetically manipulated to induce context-specific false memory (Ramirez et al., 2013), we chose to investigate hippocampal anatomy specifically with regards to recalled pain intensity. We hypothesized that memory biases seen in CBP would be associated with differences in the morphology of the hippocampus as well as personality characteristics. We used a discovery and validation approach to ensure generalizability of obtained results, as well as an independent dataset to study the influence of presence of pain on our results, and a follow-up investigation to test robustness of pain memories in time and relative to other kinds of memories.

Methods and materials

Participants

The data presented here are from two separate studies investigating neural mechanisms of chronic pain and its relief. The memory-based (primary) dataset was taken from the initial baseline period of a clinical trial investigating brain mechanisms and biomarkers of placebo response in chronic pain. 72 participants with chronic low back pain (CBP) who completed at least the first two visits of the trial were initially included in this analysis. In order to meet inclusion criteria, individuals must have been 18 years or older with a history of lower back

pain for at least 6 months. No report or evidence of substance abuse or additional comorbid chronic pain, neurological, or psychiatric conditions was also required; as an additional filter for psychological and neurological problems, individuals who scored ≥19 on the Beck Depression Inventory (BDI-1a) at Visit 1 or whose neuroimaging scans at Visit 2 indicated a current or previous neurological injury or illness (determined by a radiologist) were dropped from the study and not included in any analyses. Additionally, participants must have had a pain intensity of at least 5/10 on a VAS scale at the initial screening interview, and they were asked to stop all current pain medications for the duration of the study, beginning the day of screening.

Morphometry of the hippocampus is sensitive to age and various pathologies, including chronic pain. To investigate whether hippocampal surface deformations were a consequence of either general aging processes or of having been in long-term pain, we wanted to compare our results to people without pain and to people whose pain had only recently developed, both within a time frame that would allow for anatomical changes (which are relatively slow). Therefore, we utilized a second dataset that was taken from a completed longitudinal study identifying neural substrates of pain persistence, portions of which have been used in previous publications (Baliki et al., 2013; Hashmi et al., 2013; Petre et al., 2015; Vachon-Presseau et al., 2016). Data from 22 healthy individuals who served as control (CON) participants and 21 individuals with subacute back pain that transitioned to become chronic persisting pain (SBPp) were used in the present analysis. Each group had multiple scans collected throughout the study; for our purposes, we used data from the first baseline scan (scan 1) and the fifth scan (scan 5) that occurred approximately 1 year later. To be recruited and eligible, all patients with SBPp had to report an initial duration of pain between 4 and 16 weeks. Additionally, SBPp participants were diagnosed with back pain by a clinician and reported pain intensity of >40/100 on a visual analogue scale. Their persistence in pain was defined by the observation that their pain levels taken at each visit did not decrease by at least 20% during the study. Healthy controls must have had no current pain or history of sustained pain in the last year. As with the CBP patients in the primary analysis, both SBPp and CON participants must have had no comorbid systemic, chronic pain, psychiatric, neurological, or substance abuse disorders (and must also have had a BDI score <19).

Participants from both datasets were recruited from general and clinical populations via community flyers and ads, as well as from physician referrals and hospital databases when applicable; demographics for all participants can be found in Table S1. The Northwestern University Institutional Review Board approved both studies, and all participants gave written informed consent prior to commencement of any research activities. A waiver of documentation of consent was provided for the follow-up analyses since they were not initially planned; those individuals who participated in the follow-up phone call (explained below) to assess memory of the study provided verbal consent prior to answering any questions.

Study design and procedure

A diagram of the study design is shown in Fig. 1a. At the initial screening visit (Visit 1), participants completed a battery of questionnaires measuring sensory and affective

components of their pain experience, current and general mood states, and personality traits. These self-report measures were collected online via REDCap (Research Electronic Data Capture version 6.5.16, ©Vanderbilt University) through a link sent to the participant's email addresses; if participants did not have an email address, a back-up email address created for the study was used. To avoid questionnaire fatigue, participants were encouraged to take breaks and walk around, although they were required to finish all questionnaires at the study visit. Once submitted by the participants, questionnaire answers were finalized and un-editable in the REDCap database. The remaining demographic and health history data was manually entered into REDCap at the visit by study staff.

At the end of this visit, participants were trained on how to use the electronic rating application (app) to rate their pain and mood on visual analogue scales (VAS, Fig. 1b), as well as document rescue medication usage. More details about the app design and participant instructions can be found in Supplementary Experimental Procedures. Participants were instructed to use the app two times per day, once in the morning and once at night. To encourage compliance, participants were compensated $0.25 for each rating they submitted up to $0.50 a day to be given to them when they completed the study. Rescue medication in the form of acetaminophen (500 mg each) was provided to all participants as a controlled replacement to their discontinued pain medication; they were instructed to only take the rescue medication if the pain became unbearable and to not exceed 4 pills in a day. In order to remain eligible for the study, participants must have had an average of 4/10 pain based on ratings in the phone app in between Visit 1 and Visit 2.

Approximately two weeks after Visit 1, participants returned for Visit 2 and completed a magnetic resonance imaging (MRI) scanning session that included acquiring a high-resolution anatomical T1 image. They filled out another battery of questionnaires, a selection of which was repeated from the first visit, and they were asked “What was your pain level on average, from 0 to 10, over the last week?” Any number reported – whole, decimal, or fraction-was recorded; for individuals who reported a range of numbers, we took the mean of that range (for example, if 6–8 was recorded, 7 was used as the final answer). We were then able to calculate a “discrepancy score” for each participant, which was the number obtained after subtracting their average pain rating over the last week from their recalled average pain over that same period. We did not attempt to model absent retrospective data; only one participant was missing this one-week retrospective pain rating and was subsequently removed from the analysis. Two additional participant's data were also removed from the study because their ratings did not vary (i.e., they consistently rated their pain or mood at the same number). After accounting for these 3 people, 69 participants had usable data for analyses. The first 48 were utilized as a discovery group, while the last 21 participants' data were saved for validation purposes and were used only to test the final model of memory bias.

After all neuroimaging analyses were completed, a post-hoc analysis was conducted. A follow-up phone call interview was created to assess participants’ episodic recall of study events during their time in the entire clinical trial, as well as test their general short-term memory (STM). Details about the phone call questions, recall tasks, and answers can be found in Supplementary Experimental Procedures. In addition to assessing episodic

memory, different questions had different purposes. We asked participants about their memories of pain and mood during the first 2 weeks of the study so that we could compare long-term memory biases with previous short-term memory biases, as well as compare memories of pain and mood (which we did not capture during the study). We also asked participants to recall the number of days they were in the study, the number of visits they came to the lab, and the number of visits that involved scan – this was done to provide us with a relatively neutrally-valenced set of numbers that would be similar across participants. In contrast, we also posed two questions about money – we asked participants to remember the total amount of compensation they received and the worth of one rating from the pain application. Because pain is negative and associated with punishment, these questions allowed us to compare negatively-valenced memories with positively-valenced memories of reward. Finally, an STM prompt was used to capture general ability to recall items; we used this to test whether biases seen in our participants, although most likely related to autobiographical memory processes, could also be dependent upon impairment or difficulty in short term memory.

Scanning protocol and data analysis

CBP participants' T1-weighted brain images were collected with a 64-channel head coil on a 3T scanner. Specific scanning parameters can be found in Supplementary Experimental Procedures. MRI data were analyzed using FMRIB's Software Library (FSL) version 5.0.8. Given its role in memory, we specifically investigated two morphological properties of the hippocampus – volume and shape. For each participants' T1 image, we removed the skull, linearly aligned the brains to a standard MNI152 template, and then segmented all 16 subcortical structures using FMRIB's integrate registration and segmentation tool (FIRST (Patenaude et al., 2011)); for details on the segmentation models and boundary correction used, please see Supplementary Experimental Procedures. All segmentations were checked for accuracy using visual inspection, and the gray matter volumes for right and left hippocampus were calculated for each participant; as an additional assessment of segmentation consistency, we excluded any participants whose hippocampus volume was outside of the group mean volume by ± 1.5 standard deviations. After verifying segmentation reliability, left and right hippocampal volumes were correlated to the participants' discrepancy scores. Although it is possible that other subcortical areas – such as the amygdala – may also be related to memory biases, we did not extract any other subcortical region's gray matter properties as we were only interested in testing the hypothesis that hippocampal morphology was involved in pain memory discrepancy.

Unlike volume measurements which provide a general whole-structure summary of a region, shape can reveal more subtle and nuanced changes in structure at subregional levels and is thought to indicate alterations or innate differences in the underlying neurocircuitry of a region. In order to capture locations of shape differences and the direction of these differences, points (vertices) are projected along the surface of a region according to predefined anatomical locations, and statistics are calculated on a vertex-by-vertex basis. Following structural segmentation and volume calculations, a mask of the surface shape for the right and left hippocampus was constructed based on the average surface of all participants and a 4D file was created that contained the associated displacement values at

each of the 732 vertices of the hippocampus for all participants (one image per person); this was an automated procedure that was also part of FIRST (first_utils). Positive values indicated outward displacements from the mean surface (expansion) whereas negative values indicated inward displacements from the mean surface (shrinkage). FSL's randomise option was then used for nonparametric statistics; data were permuted 5000 times and threshold-free cluster enhancement (TFCE) was used to correct for multiple comparisons. After identifying any areas that remained significant ($p < 0.05$) after this correction, we extracted the signed shape displacement values from all of the vertices in a significant area for every person, averaged these values within each area to obtain an average shape displacement for a given region, and correlated these surface displacements to the memory discrepancy scores. To account for possible individual differences in memory or gray matter shape due to age or gender, we regressed age and gender values from vertex displacements to verify that the results did not significantly change (all statistics and figures are calculated with these covariates regressed). For internal consistency, the same methods were applied to the scanning data from the 21 participants in the validation group that were left out for testing. More details regarding these shape displacement analyses can be found in the Supplementary Experimental Procedures.

For the secondary longitudinal analysis with CON and SBPp hippocampal data, we wanted to investigate whether areas identified in the CBP group changed as a property of time and/or pain. Therefore, we constructed a paired *t*-test design file for each group to compare the mean shape between the first scan (time 1) and the fifth scan (time 2). Vertex displacement values for both SBPp and CON were extracted only from coordinates within hippocampal areas that survived correction for multiple comparisons in the CBP discovery group. The average displacement values in these areas and the difference in displacement between scans were compared between groups. Additionally, to test time effects, the correlation between the number of days between scans and the difference in average displacement was calculated for both groups.

Analysis of behavioral and questionnaire data

Rating data and questionnaire data were preprocessed according to methods described in Supplementary Experimental Procedures. Data were analyzed using a combination of software. Metrics for pain and mood data were all computed in Matlab; these included average (mean pain rating over the previous 7 days), standard error (standard error of all pain ratings over the previous 7 days), peak (highest pain rating in the previous 7 days), minimum (lowest pain rating in the previous 7 days), end (last pain rating in the 7 day period), and total pain (area under the curve). These metrics were chosen based on previous literature (Redelmeier and Kahneman, 1996; Redelmeier et al., 2003; Kahneman, 2011). While the authors of these papers also used “initial pain” as a parameter, due to our participants having chronic pain for months to years, we did not include this metric as there was no way to capture the onset of their pain (although we did investigate the effects of pain duration on these measurements as part of our analysis). Examples of two participants’ pain data with a subset of these calculations can be seen in Fig. 1c. Final statistical analyses were done in STATA (Student Edition, version 11.0).

We first examined the relationships between the retrospective ratings (which we call "recalled pain"), the real-time pain and mood measurements taken, and same-day pain and mood questionnaire scores through Pearson correlations. To assess adequacy of these variables in explaining pain memory and best compare our results with others' cited in the literature, we tested four multivariate models: a pain only-model, a pain + mood model, a comprehensive behavioral model that combined previous pain and mood rating elements with the questionnaire scores, and a final neuroimaging + behavior model that combined the psychophysical and questionnaire variables with the neuroimaging results. Each multiple regression analysis was used to quantify the influence of the given set of independent variables on the dependent variable of memory (recalled pain). Each model was tested using backward stepwise regression; criteria for inclusion was $p < 0.05$ and criteria for exclusion was $p > 0.10$. Additionally, a hierarchical approach to the regressions was used to conserve degrees of freedom. Thus, only those variables that remained in a prior model based on inclusion/exclusion criteria were then entered into the next model; if they did not meet criteria, they were discarded from any future models. Importantly, no attempt was made to make the final comprehensive model better (i.e., we did not change which variables were input to increase the amount of variance explained, nor did we simultaneously assess fit of the model on the validation group while building it on the discovery group).

Validation analyses

To test the validity of our model, the hippocampal surfaces from the validation group were correlated to discrepancy using the same design as before (with discrepancy being the covariate of interest). Shape displacement was extracted using the vertex coordinates for any significant (TFCE-corrected) areas from the discovery group and averaged within each area. In addition to these measurements, all parameters from the phone app were also calculated. Using the regression equation from the discovery analysis (final model), only those variables that remained within the model were entered from the validation group to predict their reported memory of pain (i.e., the intensity of pain that they recalled). This predicted memory score was then correlated to their actual memory reported to determine the accuracy of the predictive model.

Follow-up analyses

As part of the post-hoc phone call, we were interested in answering 3 main questions. First, we wanted to examine if any memory differences seen in CBP participants were representative of a general disturbance in short-term memory, since research suggests that chronic pain impacts attention and can cause both short-term and working memory deficits (Dick et al., 2002; Dick and Rashiq, 2007; Berryman et al., 2013; Mifflin et al., 2016). Therefore, participant's overall scores on the 5-word STM task were correlated with their initial memory discrepancy while in the study ("previous pain discrepancy") and with the memory discrepancy of their study pain reported during the phone call ("current pain discrepancy"). Second, we wanted to investigate the specificity of our results: were any discrepancies found in participants' memory during the study *pain*-specific or were they related to a person's baseline biases (i.e., their tendency to over- or under-exaggerate memories regardless of the valence, intensity, or context). We calculated the differences between participants' reported memories of different aspects of the study from their actual

values while in the study to obtain discrepancies for each item (recalled – actual). These discrepancy values were then correlated to current and previous pain discrepancies. We also investigated whether personality played a role in these biases by correlating the discrepancy scores with 4 questionnaire measures relating to pain sensitivity, pain avoidance/anxiety, pain catastrophizing, and loss-aversion, which were chosen based on previous studies indicating that these qualities may influence memory (Grisart and Van der Linden, 2001; Lefebvre and Keefe, 2002; Munoz and Esteve, 2005; Noel et al., 2015; Pallegama et al., 2016; Simon et al., 2016). Third, we wanted to know how generalizable our anatomical results were – did they also explain other behavioral or memory-related data in the study outside of pain memory. To investigate this, we correlated any surviving hippocampal areas from our final multivariate linear model with the phone call discrepancy values and the scores from the selected personality questionnaires. Finally, we ran a mediation analysis using Mplus (7.0) to further explore the relationships between discrepancy, loss aversion personality, and hippocampal shape; the indirect effects of this mediation were tested by bootstrapping the data over 1000 iterations.

Results

Chronic pain patients show memory bias in the setting of a clinical trial

72 CBP (divided into a discovery and a validation dataset, Table S1) were asked to rate their pain and mood for the duration of an 8-week clinical trial studying placebo response. In this report, we only analyzed data from one week of interest that preceded the administration of any treatment (Fig. 1a). During that week, patients rated their pain and mood 2 times per day using a smartphone app (Fig. 1b–c) and upon returning for a second visit, provided a verbal rating about their remembered average pain (0–10 VAS scale) experienced over the last week. Participants were generally compliant when entering their pain and mood ratings (average compliance = 77.7 ± 21.1% SEM for discovery group; 76.9 ± 20.9% SEM for validation group).

As expected (Tang et al., 2008), daily pain and mood ratings were anti-correlated for the majority of participants (75%) (Fig. 1d, mean coefficient correlation: −0.52 ± 0.05 SEM; $t_{(47)} = -4.76$, $p < 0.0001$; one sample *t*-test), and the recalled pain was significantly higher than the average daily experienced pain (Fig. 2a). The group-averaged memory discrepancy (defined as the recalled pain minus the average experienced pain rated over the previous week) was 1.05 ± 0.18 SEM units on a 0–10 VAS scale. The self-reported pain memory was on average 18% higher than the average daily app-based ratings, and 37 out of the 48 participants (77%) overestimated their pain intensity (Fig. 2b). Importantly, age and gender identity were not related to memory bias, nor was pain duration or medication usage (measured by the medication quantification scale, MQS); none of these measures correlated with pain memory or the direction or extent (absolute value) of the discrepancy.

We further examined which parameters of daily pain (Table S2) and mood (Table S3) app-based ratings contributed to this discrepancy. Given the peak-end rule (pain will be remembered depending on its worst intensity and ending intensity) (Redelmeier and Kahneman, 1996), we examined these characteristics in pain and mood ratings. As shown in (Redelmeier and Kahneman, 1996), the psychophysical properties of the pain ratings of our

CBP participants were highly correlated to one another and to their pain memory reports (Table S4, **top rows**). Unlike pain characteristics, none of the mood parameters correlated to recalled pain; however, both ending mood and ending pain were significantly anti-correlated to memory discrepancy (Table S4, **bottom rows**).

Shape displacement of the left posterior hippocampus reflects memory discrepancy

The volume of the left (average volume = 3755.5 ± 481.7 mm^3) and the right (average volume = 3855.1 ± 527.0 mm^3) hippocampus were invariant to memory discrepancy. However, a vertex-wise shape analysis in relation to pain memory bias uncovered left hippocampal areas correlated with memory discrepancy (Figs. S1a–b); Area 1 (A1) corresponded to the posterior hippocampus, Area 2 (A2) primarily to the intermediate hippocampus with some posterior overlap, and Area 3 (A3) to the anterior hippocampus. From these, only a portion of A1 survived threshold-free cluster enhancement (TFCE) correction for multiple comparisons (17 out of 732 total vertices), indicating that A1 posterior hippocampal shape distortion was significantly related to pain memory discrepancy (Fig. 2c–d). Importantly, neither hippocampal volume nor shape results were related to participant's previous medication usage reported at Visit 1, since MQS scores were not significantly correlated to any of these measures.

Regression models for pain memory

Multi-factor multiple regression analyses were used to examine whether the psychometric qualities (peak, end, total, and average) examined from the pain and mood daily ratings, current pain and mood parameters from the day of memory assessment (given (Eich et al., 1985; Norvell et al., 1987; Lowe and Roberts, 1988; Smith and Safer, 1993; Algom and Lubel, 1994; Salovey and Smith, 1997; Babel, 2015)), and A1 posterior hippocampal shape displacement could explain the pain memory values. We incrementally tested 4 separate multivariable models (Table 1); each regression built off the previous one to explain the memory of pain. To test the peak-end rule hypothesis (Redelmeier and Kahneman, 1996), the first model only used peak pain, end pain, average pain, and AUC, and showed that pain memory significantly depended on the peak pain and the average pain over the week. The second model entered these 2 variables with the 4 equivalent mood variables and indicated that the mood at the end of the rating period explained unique variance beyond peak pain and average pain; together, results from models 1 and 2 confirm the peak-end rule in our data and validate previous findings showing that mood at the end of a painful event can counteract or influence pain's effects in memory traces (Norvell et al., 1987; Lowe and Roberts, 1988; Algom and Lubel, 1994; Salovey and Smith, 1997). Given that concurrent mood and pain during the time of recall can also influence the way we reconstruct past events and in turn memories of those events (Eich et al., 1985; Turnbull and Salas, 2017), a third model combined these 3 surviving rating parameters with current pain (Numeric Rating Scale, NRS) and mood (Positive and Negative Affect Scale, PANAS) scores on the day of memory assessment; this model indicated that the current pain and emotional state failed to significantly contribute to pain memory. The fourth and final model was the most comprehensive, incorporating experienced pain, experienced mood, and hippocampal morphometry (average TFCE corrected A1 displacement); this model showed that A1

hippocampal shape in combination with average experienced pain accounted for 55% of the variance in pain memory (Table 1, last model).

Validation and predictive value of the model

To test the reliability and generalizability of obtained results, we attempted replication of our main findings in a subgroup of CBP patients (n = 21) reserved for validation. Over half of these patients (n = 12, ~57%) displayed a discrepancy biased toward an overestimation of their pain, although average memory and experienced pain outcomes were not significantly different from one another (Fig. 3a), a result likely driven by having a smaller sample size in the validation dataset. Importantly, for those individuals who displayed exaggerated pain memory, their pain memory report was on average 16% higher than their experienced pain during the study, replicating the overall magnitude of the effect seen in the discovery group. The vertex displacement values from the left posterior hippocampus were extracted and averaged for this validation CBP group within A1, using the 17 coordinates defined from the discovery group (Fig. 3b, **left,** and Fig. S1c). The final model from the discovery group (Model 4–A1 displacement + average rated pain) was used to predict these new participants' pain memory values. Fig. 3b **(right)** shows that the predicted values were strongly correlated to the actual memory values reported. These results validate our model.

Posterior hippocampal shape is stable over 1 year and with development of chronic pain

The hippocampus is prone to dynamic changes in shape and volume as part of normal human development and aging (Gogtay et al., 2006), hippocampal volume is a risk factor for development of chronic pain (Vachon-Presseau et al., 2016), and that sub-regions of the hippocampus are differentially associated with stress and anxiety (Satpute et al., 2012). To test whether the left posterior hippocampal A1 shape displacement was either influenced by a general aging process or was a consequence of being in a constant state of stress (chronic pain (Vachon-Presseau et al., 2013)), we compared the displacement of vertices corresponding to A1 in two independent data sets (Fig. 4a). First, we tested the stability of A1 surface morphometry in healthy controls (CONs) between two scans, which were approximately 1 year apart (376.1 ± 13.3 days). The average change in displacement within this region was 0.06 mm ± 0.06 SEM; this change in shape did not survive TFCE correction, indicating that A1 was not an area that significantly changed in this timeframe. We next compared the A1 vertex displacement in 21 participants with subacute back pain between two scans that were also 1 year apart (379.1 ± 21.9 days). These individuals entered the study with a new onset of back pain (less than 3 months) and ended up having their subacute back pain persist (SBPp) over the year, thus developing chronic pain and essentially becoming similar to our CBP cohort. The average change in displacement within A1 for SBPp between scans was 0.09 mm ± 0.10 SEM; this result was also not significant and did not survive TFCE correction for multiple comparisons. Additionally, there were no differences between CON or SBPp (Fig. 4a) in either the average displacement of the region at scan 2 one year later (CON: 0.03 mm ± 0.13 SEM; SBPp: 0.05 mm ± 0.23 SEM; unpaired *t*-test: $t_{(41)} = -0.065$; $p = 0.95$) or the average change in displacement between scans (unpaired *t*-test: $t_{(41)} = -0.29$; $p = 0.77$). These results indicate that shape displacement in A1 of the posterior hippocampus is stable, as this region does not appear to change over the

course of 1 year, and it is not influenced by the stress of persistent pain over 1 year or the additional neural mechanisms underlying the transition from acute to chronic pain.

Pain memory bias is related to reward/punishment memories and personality traits

Although we uncovered that the memory of pain is systematically biased and related to the shape of a specific portion of the hippocampus, it remains unknown whether this bias and related hippocampal shape generalize to other memories or are a reflection to aberrances in memory or recall capabilities. As part of a follow-up phone call, we contacted and queried our participants regarding their memories of the study and also tested them for short-term memory deficits (Table S5). We attempted to call back all participants whose anatomical data were analyzed; of these, 25 people from the discovery group and 8 from the validation group were reached. Here, the two groups were combined to increase our sample size (total n = 33; Table 2). The average time between a participant's last visit date and subsequent phone contact was 216.7 ± 96.4 days, and importantly, none of the answers provided by participants significantly correlated to the length of this interim period, indicating that the amount of time between the study and the phone query did not impact obtained results. The participants' memory of their study baseline pain provided during the phone query was significantly correlated with the pain memory provided at their MRI visit ($r = 0.41$, $p = 0.019$, Fig. 4b); there was still a discrepancy in recalled pain ~216 days after the study, with over 75% of individuals remembering higher pain than the instantaneous pain they actually experienced in their daily app-based ratings (distribution also shown in Fig. 4b), indicating that once a memory trace of painful events is distorted, this bias persists over a long period of time.

To determine whether the pain memory discrepancy seen in our CBP participants was indicative of comorbid short-term memory (STM) impairments, we examined their scores on the Montreal Cognitive Assessment (MoCA) delayed recall task. On average, participants remembered 3 or 4 out of 5 words on this task (average = 3.70 ± 1.2 words, minimum: 0, maximum: 5), with only 15.2% (n = 5) remembering less than 3 words (Fig. 4c), implying that the majority of our participants had no problems with STM (Chandler et al., 2004). Additionally, the number of words remembered did not correlate with the original pain discrepancy (Spearman's $rho=-0.04$, $p = 0.83$), with pain memory from the follow-up phone call (Spearman's $rho = 0.05$, $p = 0.78$), or with the vertex displacement of the A1 posterior hippocampus (Spearman's $rho = -0.19$, $p = 0.29$). Therefore, we conclude that neither CBP patients' pain discrepancy nor their posterior hippocampal A1 displacement are related to insufficient STM capabilities and thus STM deficits are not driving our results.

Given that our patients' pain memory remained exaggerated ~216 days after the study ended, we presumed that this robust bias reflected long-term memory processes. To investigate the relationship between pain discrepancy findings and other memories related to the experience of participating in the trial, as well test whether participants displayed a general long-term memory impairment, a bias related to emotional quality of a memory, or a general tendency to exaggerate, we asked participants to recall different aspects of the study and computed a discrepancy score for all queries administered during the follow-up phone call. Questions were designed to elicit declarative memories, either episodic or factual in

nature, and that varied in valence (e.g., negative, neutral, or positive) (see Table 2 and Table S5). Responses regarding mood, number of visits, number of MRI scans, and monetary compensation received per app rating all showed discrepancy distributions centered around 0 (indicating either high response accuracy or no significant bias in either direction). Only memory of total compensation during the study (positively valenced) was skewed, with 59% of participants under-estimating the amount of money received (Fig. 4d and Table 2). We correlated the current pain memory bias (during the phone query) with these additional discrepancy scores. Again, only the recall of total monetary compensation showed a significant relationship with the current pain discrepancy (Fig. 4e). This relationship was negative – that is, the more pain someone remembered having, the less monetary compensation they also thought they received, suggesting a recall bias along a continuum between positively-valenced (reward) and negatively-valenced (punishment/pain) memories.

The relationship between pain and monetary memory biases suggest that our results may reflect personality properties. Therefore, we investigated their relationship to specific personality characteristics associated with reward processing and/or chronic pain. We examined correlations to four self-report outcome measures (Loss Aversion Questionnaire – LAQ (De Baets, 2012), Pain Catastrophizing Scale – PCS (Sullivan et al., 1995), Pain Sensitivity Questionnaire – PSQ (Ruscheweyh et al., 2012), and Pain Anxiety Symptoms Scale - PASS (McCracken and Dhingra, 2002); Table 2, **bottom**), collected at time of entry into the study (~216 days prior), chosen based on studies showing that the associated psychological traits are involved in reward/punishment processing (Berger et al., 2014) or influence pain memory recall (in healthy and patient populations) (Grisart and Van der Linden, 2001; Lefebvre and Keefe, 2002; Munoz and Esteve, 2005; Noel et al., 2015; Pallegama et al., 2016; Simon et al., 2016). Of these, only LAQ scores were negatively correlated with both pain and money discrepancies (Fig. 4f); moreover, both LAQ and money discrepancy positively correlated with hippocampal A1 shape displacement (Fig. 4g). To understand the co-dependencies between these 3 variables, we tested the hypothesis that A1 shape displacement mediated the effects of personality (LAQ) and pain memory discrepancy. Fig. 4h shows the paths and their standardized coefficients in this mediation model; there was a significant indirect effect from LAQ to pain discrepancy, indicating that posterior hippocampal A1 shape significantly mediated this relationship; there was no significant mediation effect of A1 between LAQ and monetary discrepancy.

Discussion

We identified psychometric, psychological, and neuroanatomical characteristics that underlie memory bias in self-reported intensity of chronic back pain. More than 70% of CBP patients exaggerated their pain memory by 18% from experienced pain ratings, a bias that persisted many months after study completion. In accordance with Redelmeier and Kahneman's (Redelmeier and Kahneman, 1996) peak-end rule, experienced peak and average pain ratings, in combination with ending mood ratings, explained more than 50% of the variance in pain memory. We also demonstrated that surface shape displacement in a area of the left posterior hippocampus, A1, was related to the discrepancy between pain memory and pain experience. This shape displacement, in combination with the average experienced pain, explained 55% of the variance in pain memory, a finding that was validated in a separate

group of CBP. Importantly, the shape of A1 was invariant over 1 year, unperturbed with development of chronic pain, and appeared to be independent from other likely confounds, including age, gender, duration of pain, short-term memory deficits, long-term memory dysfunctions, pain anxiety or catastrophizing, and generalized habits of exaggeration or increased pain sensitivity. A final mediation analysis showed that A1 shape linked loss-averse personality characteristics to back pain memory bias. Thus, we not only reproduce previous psychometric results found in pain and mood ratings but also identify a biological substrate responsible for enduring distortions in pain memories and related psychology, expanding on the role of the hippocampal mechanisms in chronic pain.

Our findings have important implications for understanding and treating chronic pain, showing a clear dissociation between experience and memory of suffering. Given the reliance on self-reported numerical ratings of pain to influence the type and duration of treatment in chronic pain patients, our results emphasize that such retrospective measures are inaccurate and on average are 16–18% higher than the patients' actual experience. Importantly, the magnitude of the discrepancy is close to corresponding thresholds often utilized in determining clinically meaningful interventions (~20–30% reduction in pain intensity (Farrar et al., 2001)). These results raise philosophical questions surrounding the relative influence of patient's experiences and memories of pain in clinical pain management decisions, not only with regards to the type and level of treatment provided, but also related to the long-term goals of the patient and provider. For example, could training patients to be more aware of their day-to-day pain and more focused on minimizing the discrepancy between their memory and experiences work to supplement treatment effects or potentially lower dependency on treatments? Our findings also put forth important practical considerations about how to determine appropriate effect sizes in clinical trials (i.e., which outcome – daily pain experience or reported memory of experience – should be given greater weight) and how to better measure pain outside of traditional numeric scales, recalled or otherwise.

In the field of pain, the peak-end rule has identified that humans in acute pain do not simply sum their pain over time to report a totality of experience but instead average their worst painful moment with their most recent level of pain. Replication of this memory shortcut in our participants’ chronic pain ratings highlights its robustness as a heuristic strategy utilized across individuals and in situation of acute or chronic pain. Furthermore, several studies have demonstrated how mood during a painful event can influence recalled discomfort (Eich et al., 1985). Kent (1985) showed that individuals who were highly anxious regarding dental examinations later rated their remembered pain as higher than experienced compared to individuals with lower anxiety; similar findings have also been reported in children (Rocha et al., 2009). Likewise, labor pain is retrospectively rated as less severe than was previously rated (Norvell et al., 1987; Lowe and Roberts, 1988; Algom and Lubel, 1994; Salovey and Smith, 1997), as is the pain of running a marathon (Babel, 2015), both of which are likely due to the impact of positive emotions at the end of each event. Our results also match these previous findings, as pain was shown to be anti-correlated with mood, and the mood at the end of the rating period also accounted for a significant portion of the variance in the reported pain memory. Thus the peak-end rule for both pain and mood are present to various extents in the data presented here.

Our results also have novel implications regarding memory organization/ representation in the hippocampus, especially for recall of emotionally salient events. The volume of the human hippocampus has been used to predict or explain a variety of inter-individual differences, including cognitive ability, psychiatric illnesses, and risk for chronic pain (Johnson et al., 2013; Saletin et al., 2016; Vachon-Presseau et al., 2016), and the shape of the left hippocampus along the anterior-posterior axes has been linked to memory across the adult lifespan (Voineskos et al., 2015). However, this is the first evidence for the shape of the hippocampus within a specific area, A1, in the posterior hippocampus being associated with pain memory discrepancy. The general surface area of the hippocampus is thought to reflect the migration, proliferation, differentiation, and targeting of various cells as part of the neurodevelopment process; outward displacements of the surface may then reflect enhanced intra- or extracellular connectivity of this region (Voineskos et al., 2015), whereas inward displacement may represent decreased connectivity due to abnormal development or perturbations to the area. Here we show that the more someone over-estimates their previous pain (i.e., the larger memory discrepancy), the more outwardly displaced was a small area of the posterior hippocampus (A1). The result mirrors previous findings comparing healthy and Alzheimer's patients, showing that disrupted episodic memory was not initially driven by global atrophy but rather associated with regionally-specific changes in the shape of the left hippocampus (Thomann et al., 2012). Additionally, the finding that the validation group did not have a significant difference between experienced and recalled pain but still replicated the regional hippocampal displacements seen in the discovery group suggests that pain memory bias is a continuum, and that A1's shape distortions may be indicative of this continuum as opposed to a simple exaggeration or a positively skewed bias.

The hippocampus can be subdivided functionally and structurally along the anterior-posterior (longitudinal) axis (Bannerman et al., 2004; Strange et al., 2014), with distinctions made according to genetic expression, cell type patterns, and connectivity to other brain regions (Fanselow and Dong, 2010). According to this division, the posterior hippocampus is primarily associated with conceptual or spatial memories, including recall of rules, contexts, language, and spatial navigation, although it is also more generally involved in learning, information processing, timing of repeated events, and memory retrieval and consolidation (Fanselow and Dong, 2010; Poppenk et al., 2013). To identify potential functions of our posterior area, we used a reverse-inference term-based meta-analytic approach (Neurosynth (Yarkoni et al., 2011)) and found that the words most associated with A1 included “encoding”, “retrieval”, “details”, and “episodic memory”; these associations substantiate previous findings about the posterior hippocampus's function in declarative memory processes and in encoding and retrieval biases. Remarkably, the surface distortion of A1 in relation to memory discrepancy was replicated in a separate CBP group, suggesting that the deformation pattern within A1 is generalizable. For example, while we know that the posterior hippocampus is generally responsible for retrieval of memories, properties of A1 suggest that specific kinds of memory traces are recalled in distinct regions that might reflect yet another level of organization within the hippocampus, where a topography of encoding “type” is superimposed on existing cellular networks mapping space and place. Liu and colleagues (Liu et al., 2012) have previously demonstrated that re-activation of a specific set of hippocampal neurons that contribute to the encoding of a memory trace is

sufficient to induce recall of that memory. While storage of pain memories are likely distributed across multiple neural networks, the specific neuronal ensembles within A1 could be involved in the encoding and/or retrieval of pain-specific memory engrams in a spatially specialized organization. Preliminary evidence of this can be seen in our own data; we selected a coordinate from A1 (−16, −36, −4) and utilized it as a seed in Neurosynth to investigate what areas it is co-activated with in resting state fMRI (Fig. S2). In addition to the strong functional connections within the left hippocampus and some bilateral co-activations in the right hippocampus, A1 also displayed weak functional connections with the precuneus and amygdala, corticolimbic regions that have been shown to be involved in both acute and chronic pain processing (Koyama et al., 2005; Goffaux et al., 2009; Neugebauer, 2015; Vachon-Presseau et al., 2016).

The asymmetry of this shape displacement is noteworthy, as only the left hippocampus showed any relationship with pain memory discrepancy. An accumulating body of evidence supports the notion that the hippocampus has hemispheric functional specialization, relatively preserved across species (Robinson et al., 2016), indicating that this functional asymmetry interacts with its antero-posterior structural segregations to give rise to combined functional-structural specifications. For example, the left hippocampus is associated with verbal memory processes whereas the right is associated with more spatially-dependent memories (Robinson et al., 2016); moreover, a longer and wider longitudinal axis in the left hippocampus significantly predicts working memory performance, with no corresponding finding for the right hippocampus (Voineskos et al., 2015). Additionally, distribution of functional networks from the right and left hippocampus differ depending on location, with the right anterior and left posterior hippocampus exhibiting large, distributed functional networks, whereas the left anterior and right posterior segments are primarily confined to fronto-limbic networks (Robinson et al., 2016). Regarding pain memories specifically, researchers investigating acute painful stimuli and associated memory of pain found that left hippocampal activity corresponded to remembering higher levels of pain, with no corresponding activity from the right side (Fairhurst et al., 2012). However, more studies will be necessary to understand the role of hippocampal shape and laterality in chronic pain and memory bias.

Critically, deformations within A1 remained relatively unchanged across 1 year for two separate participant groups, did not change with the continued presence of pain, and did not significantly differ between controls or SBPp. This suggests that the regional shape displacement seen in A1 is stable in time, despite the hippocampus being a structure with a high level of neural plasticity, and implies that the memory bias seen in our CBP patients is unlikely related to having developed chronic pain, and instead may be present even before the development of chronic pain. Additionally, given that memory biases like the peak-end rule for pain are seen in individuals without chronic pain, it's unlikely that the relationship between pain memory discrepancy and hippocampal shape is specific to CBP. Instead, it possible that the observed pain memory bias reflects pre-determined biases for negative affect memories, especially because the personality characteristics commonly associated with chronic pain were not related to the observed exaggerated memories and were instead related to monetary reward and loss aversion characteristics. However, it is still unclear exactly how structure (in this case, differences in surface morphometry) dictates function,

and further research is needed to better clarify underlying cellular properties in the A1 region contributing to pain memory and related behaviors, as well as when these circuitries are formed and how durable they are. Moreover, given that the data utilized here are a subset of a larger clinical trial aimed at studying changes in chronic pain in response to placebo, we did not directly capture memory discrepancy in non-CBP participants and thus lack proper healthy or subacute control groups who have completed a similar pain memory task. Therefore, we cannot conclude whether the related A1 hippocampus shape displacements are specific to memories of chronic pain or to memories of pain in general (regardless of etiology or duration); more research is needed to answer this question.

Our results suggest that the bias in retrospective assessments seen here are not failures of memory or representative of a general tendency to over-exaggerate, since participants were neither impaired in STM functioning or LTM recall related to the study, nor did they display systematic exaggerations across kinds of declarative memories, and instead reflect memory encoding invoked for highly salient or strongly valenced memories along a reward-punishment continuum. We showed that memories of pain (negative/punishment) were anti-correlated with memories of monetary compensation received (positive/reward) and that both biases were related to self-reported loss-aversion traits; furthermore, shape displacement of posterior hippocampus A1 mediated the effect of loss aversion personality traits on the extent of pain memory bias. While the relationship between loss aversion and memory of pain or reward is complex and not yet well understood, research has shown that people often underestimate not only the amount of money they earned in reward tasks, but also the number of times they receive money, indicating that people downplay monetary gains in general (Yu et al., 2008). Additionally, we have previously reported that CBP patients show aberrant behavioral loss aversion, displaying increased gain sensitivity in a gambling paradigm compared to healthy controls (Berger et al., 2014); these previous findings, in combination with our current results, suggest that loss aversion and the experience and memory of pain are intimately linked through durable neurophysiological and psychological mechanisms, for example the strength of functional/anatomical connectivity to cortical and limbic structures (nucleus accumbens and/or medial prefrontal cortex, structures commonly associated with loss aversion characteristics (Carter et al., 2009)). The extent to which experiences and memories in other domains are also embedded in similar neurobiology or personality traits remains a topic for future exploration. Our results suggest the existence of specific hippocampal domains sub-serving types/classes of memories, which would underlie specific cortical and limbic interactions, a concept that proposes novel rules regarding the organization of the hippocampus and of memory processing by the brain in general.

Conclusions

The connection between a person's real-time experience and their memory of this experience represents a fundamental relationship that influences our perceived reality on a moment-to-moment basis. This study uses a combination of advanced neuroimaging techniques with daily pain and mood measurements to probe the cognitive and neural contributors of pain memory in individuals with chronic low back pain (CBP). Building on existing knowledge about common heuristic strategies and shortcuts used by humans when remembering acute

pain, we find that CBP patients show discrepancy in their recall of previous spontaneous pain, with memories biased towards greater pain than they had originally rated. This memory discrepancy was driven by a combination of key elements in a person's experience (including worst pain, recent mood, and average rated pain), as well mediated by the surface morphometry of a specific region of the left posterior hippocampus. From these findings, we begin to unravel the psychological and neurological underpinnings of pain memory and report, identifying novel biomarkers of pain memory bias and associated personality traits. These results provide new insights about hippocampal functionality and the neural organization of pain perception and memory in general, as well elicit important considerations for future clinical practice and pain management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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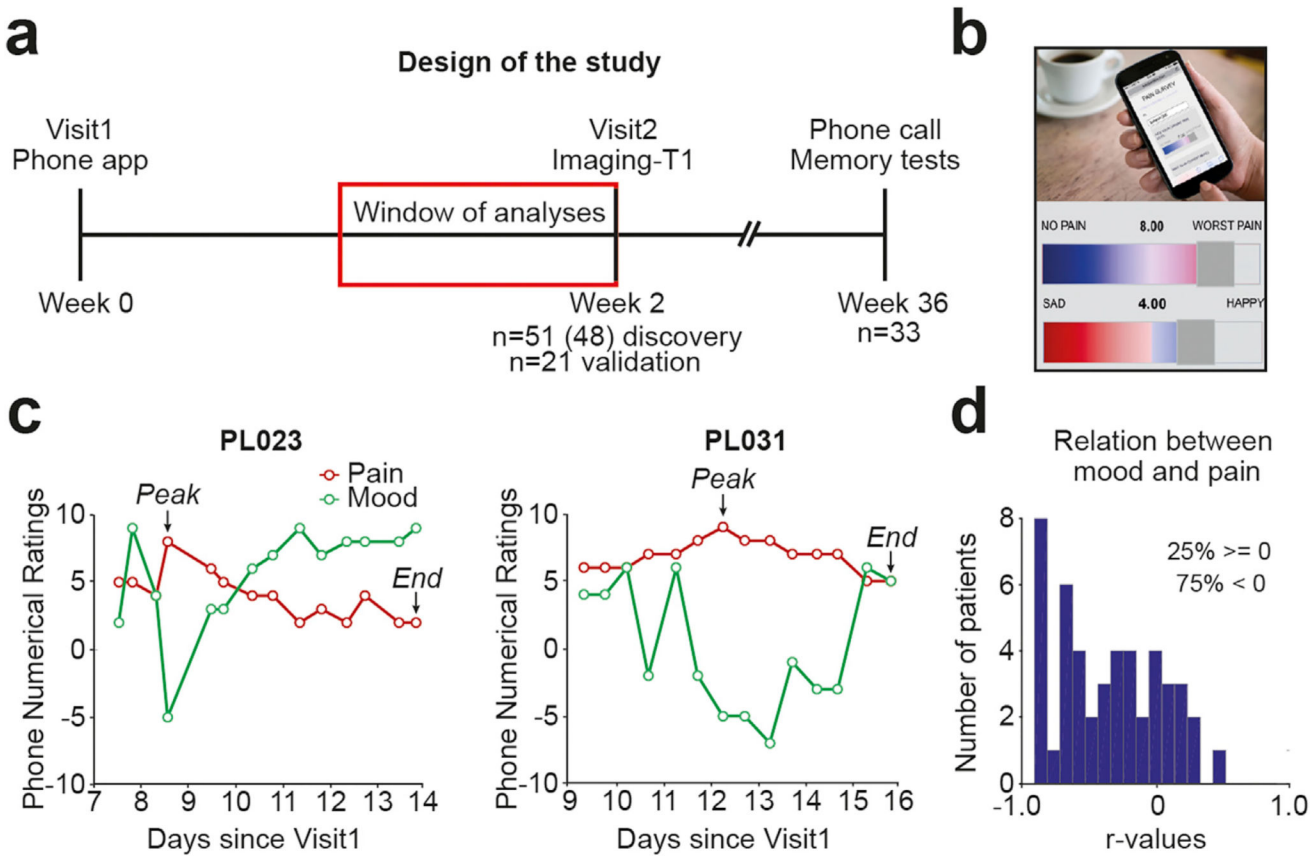

Fig. 1. Study design and psychometric parameters derived from ratings of experienced CBP pain

a. Illustration of study design. Participants completed a battery of questionnaires at visit 1 (week 0) and were provided with a smart phone application (app) to track their back pain and mood twice a day for 2 weeks, after which they returned to complete an MRI scan and another set of questionnaires. Red box indicates that only the last 7 days of this rating period were used in analyses. A total of 72 people were enrolled; 48 were used as a discovery group, 21 set aside for validation, and 3 excluded from analysis. After completion of the study, a subset of individuals (n = 33) were contacted and asked follow-up questions to probe their memory of the study (on average 217 days after Visit 1). **b.** Example of the rating app. After entering in their participant IDs, patients rated how much pain they currently felt from 0 to 10 and the valence and magnitude of their current mood from −10 to +10. **c.** Examples of two participants' pain and mood ratings over one-week of the rating period are shown, with the peak and end indicated. **d**. Distribution of correlations between pain and mood ratings; the majority of participant's moods were negatively correlated to their pain intensity as expected.

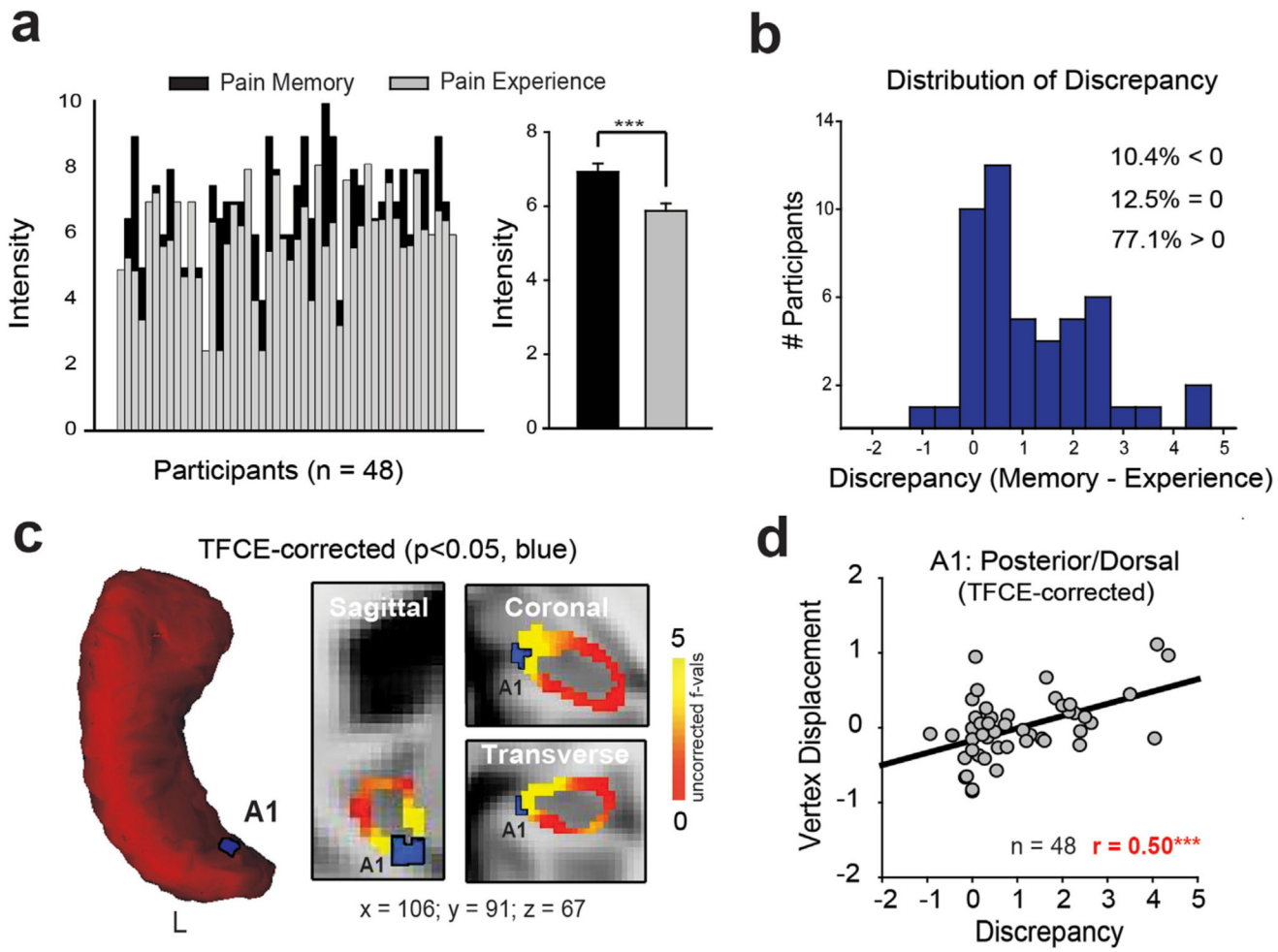

Fig. 2. Chronic back pain patients show exaggerated pain memory and this discrepancy correlated with left hippocampal shape displacement

a. All participants' (discovery group) experienced (rated) pain from the app (averaged over one week, gray) plotted over their pain memory (black) during the same 7-day period. Visible black bars indicate a bias toward remembering higher pain than was actually experienced. Bar graph is group averaged result (average pain memory: 6.93 ± 0.22 SEM; average rated pain: 5.87 ± 0.21 SEM; $t_{(47)} = 5.75$, paired *t*-test). **b.** Distribution of all participant's memory discrepancies (pain memory– rated pain). The majority of participants displayed a bias favoring greater memory. **c.** Left hippocampal shape displacement was correlated to the memory discrepancy values displayed in **b**. Statistics (shown in Supplementary fig. S1) were corrected for multiple comparisons using threshold free cluster enhancement (TFCE). Only one small area in the posterior hippocampus, A1, remained significant; a blue mask indicating the area (17 vertices total) with p-values <0.05 after TFCE is displayed on the surface of the left hippocampus and overlaid on the original f-stat map in the brain. **d**. Correlations between left hippocampal vertex displacements and memory discrepancies for A1 are shown. To display the direction of the relationship between morphometry and discrepancy, the change in shape from each vertex (vertex displacement) in A1 was extracted, averaged within the area, and correlated to discrepancy.

Positive displacement values indicate an outward direction (expansion of shape) on average, whereas negative values indicate inward direction (shrinking of shape). More outward displacement of A1 correlated to higher memory discrepancy. For all imaging analyses, age and sex have been regressed as covariates of no interest. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; ns = not significant.

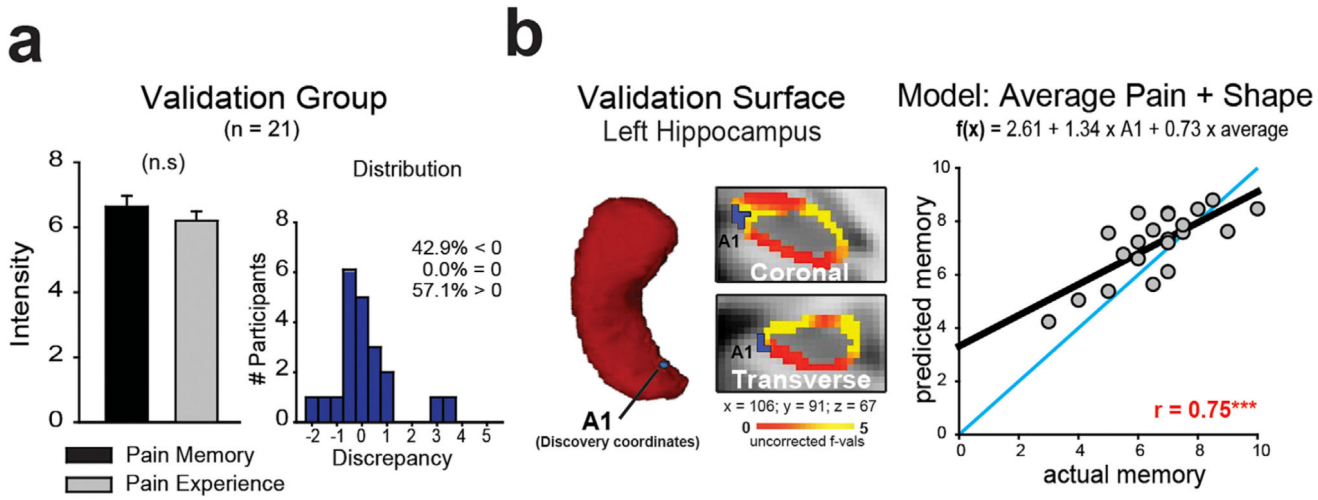

Fig. 3. Validation and replication of left posterior hippocampus shape displacement for pain memory discrepancy

a. Unlike the discovery group, the validation group (n = 21) did not result in a statistically significant difference between pain memory and pain experience (left panel, memory = 6.52 ± 0.33 SEM; experience = 6.26 ± 0.29 SEM; $t_{(20)} = 1.08$, p = 0.29, paired *t*-test), although the majority of individuals still reported higher pain memory than experienced, indicating a memory bias (right panel). **b**. Left panel shows 3D rendering of the left hippocampus in the validation group and its corresponding surface outline with original statistics (as shown in Fig. 2c). To validate the model from the discovery group, the vertex displacement from the 17 significant vertices in discovery area 1 (A1, blue mask displayed on both surfaces) were extracted from the left posterior hippocampus of the validation group. Participant's average pain from the daily ratings and A1 vertex displacement values were entered into the model equation (provided at the top of the graph, right panel) to predict their memory of pain. The correlation between the predicted memory from the equation parameters and the actual memory reported is shown – these values were significantly and strongly correlated, validating the model. An identity line, indicating a perfect correlation, is shown in blue. *** = p < 0.001; ns = not significant.

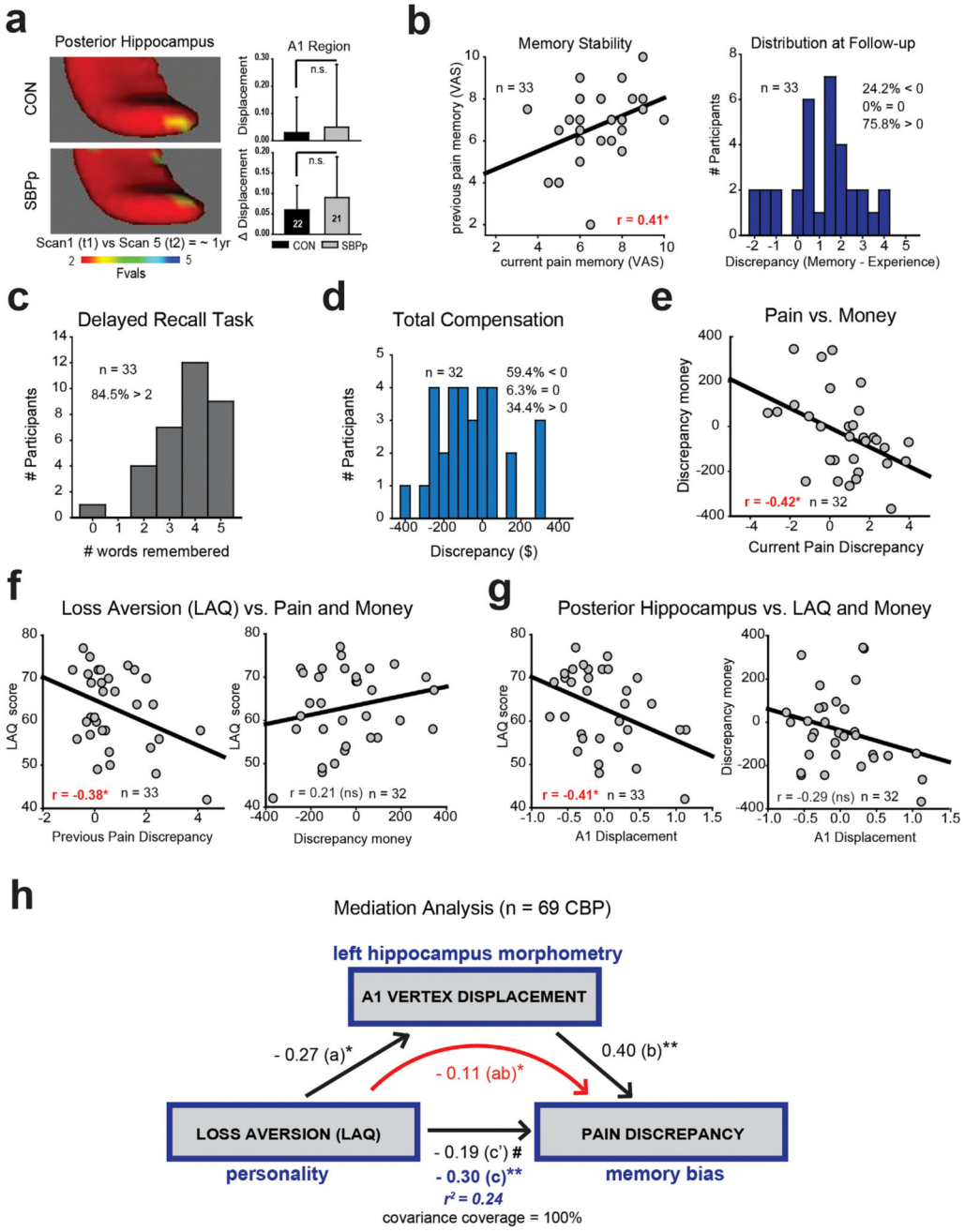

Fig. 4. Longitudinal and follow-up analyses relate pain memory bias to loss aversion

a. Paired t-tests of hippocampal shape displacement between two scans separated by approximately 1 year. Surface map F-statistics for the left hippocampus for healthy controls (CON, n = 22) and individuals with persisting sub-acute back pain (SBPp, n = 21); images focus on the posterior portion and the lack of significance in this region can be visually appreciated. Statistics performed on both groups showed no within subject differences due to time in A1. Bar graphs indicate between subject statistics; there were no differences in the average displacement of this A1 region (top) or average change in A1 displacement (delta, bottom) between CON and SBPp. **b.** Recalled pain memory assessed 36 weeks after study

completion (current pain memory) was significantly correlated to the memory of the pain assessed at the end of the week during the study (previous pain memory), with the majority of participants still maintaining a discrepancy biased towards exaggerated pain memory (distribution plot). **c.** Participants performed at or above average in the delayed recall task, with the majority remembering at least 3 words **d.** Discrepancies were calculated for all questions asked during the follow-up phone call (Table S5). Only total compensation (the amount of money earned during the entire trial) showed a memory bias (Table 2). **e.** Discrepancy of money and pain memories were anti-correlated, such that participants biased toward overestimated pain levels tended to underestimate the amount of money they received during the study. **f.** Loss aversion (LAQ) scores were significantly anti-correlated with pain discrepancy; the opposite relationship with money discrepancy was found but not significant. **g.** LAQ scores were also significantly negatively correlated to posterior shape distortion of the left hippocampus; discrepancy of money was not. **h.** After combining all participants from discovery and validation groups, a mediation analysis was used to measure the contribution of shape displacement of the hippocampus on the relationship between reward-related personality (loss aversion) and memory bias based on pain discrepancy scores. This effect was significantly mediated by left posterior hippocampal A1 shape (indirect pathway 95% CI: [−0.196,−0.022]; $R^2 = 0.074$ of unique variance). Path a = effect of LAQ on mediator variable (hippocampal shape); path b = effect of mediator on pain memory discrepancy; path c = effect of LAQ on pain memory discrepancy (*total effect*); path c' = effect of LAQ on pain memory after controlling for hippocampal shape (*direct effect*); path ab = amount of mediation produced by the hippocampal vertex displacement (*indirect effect*). * = $p < 0.05$; ** = $p < 0.01$; # = $0.05 < p < 0.10$ (trending).

Table 1

Summary of model results

Multivariate linear regression models.

Model	Surviving Parameter(s)	Coef ficient (SEM)	p-value	95% C.I.	Eliminated Variables (p > 0.10)
1	**Basic Pain Model (App Data)**				
	peak pain	0.396 (0.16)	0.02	[0.07,0.73]	End pain, total (auc) pain
	average pain	0.369 (0.17)	0.04	[0.02,0.71]	
	$N = 48$; $R^2 = 0.48$; Adj $R^2 = 0.46$; $F(2,45) = 21.03$; $p < 0.0000$				
2	**Basic Pain + Mood Model (App Data)**				
	peak pain	0.438 (0.16)	0.01	[0.12,0.76]	auc mood, average mood, peak mood
	average pain	0.362 (0.16)	0.03	[0.03,0.69]	
	end mood	−0.09 (0.04)	0.03	[−0.17, −0.01]	
	$N = 48$; $R^2 = 0.54$; Adj $R^2 = 0.51$; $F(3,44) = 17.17$; $p < 0.0000$				
3	**App Data + Current Variables (Pain + Mood)**				
	peak pain	0.322 (0.17)	0.06	[−0.02,0.66]	PANAS negative, PANAS positive, NRS
	average pain	0.453 (0.17)	0.01	[0.11,0.79]	
	end mood	−0.717(0.04)	0.08	[−0.15,0.01]	
	$N = 47$; $R^2 = 0.53$; Adj $R^2 = 0.50$; $F(3,43) = 16.06$; $p < 0.0000$				
4	**Comprehensive Model (Pain + Mood + Neuroimaging)**				
	average pain	0.734 (0.10)	$p < 0.0000$	[0.53,0.94]	peak pain, end mood
	posterior hippocampal (A1)	1.336 (0.33)	$p < 0.0000$	[0.66,2.01]	
	$N = 48$; $R^2 = 0.57$; Adj $R^2 = 0.55$; $F(2,45) = 29.69$; $p < 0.0000$				
	Final equation: recalled pain = f(x) = 2.61 + 1.34 × A1 + 0.73*average pain				

Multiple regression analyses were performed to uncover independent variables significantly influencing participants' pain memory (recalled pain = dependent variable). Regressions were run in a hierarchical manner such that each model built off of the previous one; only those variables that survived the previous model(s) were entered into the subsequent one. Groupings of variables were chosen a-priori based on previous literature; the first model tested the peak-end rule based on daily app ratings, the second added mood ratings, the third incorporated current pain and mood, and the fourth and final regression entered all surviving pain and mood parameters with the significant hippocampal area 1 (A1, corrected for multiple comparisons using TFCE) shape displacement to create a comprehensive model accounting for behavior and neuroanatomy.

Adj R^2 = adjusted R^2, which represents the coefficient of determination after accounting for the number of predictors in the model; SEM = standard error; C.I. = confidence interval; auc = area under the curve.

Table 2

Summary of responses from follow-up queries

Follow-up phone call responses.

Recalled Values (compared to those expected for most participants)						
Question Topic	mean	sem	*N*	expected[&]		
Average **Pain** during first 2 weeks of study	7.0	1.22	33	-		
Average **Mood** during first 2 weeks of study	3.5	0.60	32	-		
# **Visits** (total) during the study	7.7	1.34	30	~6 visits		
# Visits with **Scans** (total) during the study	4.5	0.78	33	~4 scans		
Total **Compensation** ($) from all visits	372.0	64.76	32	~ $448.00		
One phone **Rating's** worth ($)	1.5	0.25	29	$0.25 each		
Discrepancy Values (Recalled during phone call - Actual during study)						
Question Topic	mean	sem	*N*	%<0	%=0	%>0
Average Pain during first 2 weeks of study	0.8	0.30	33	24.2	0.0	75.8
Average Mood during first 2 weeks of study	−0.7	0.96	32	50.0	0.0	50.0
# Visits (total) during the study	0.1	0.70	30	30.0	20.0	50.0
# Visits with Scans (total) during the study	0.3	0.38	33	33.3	30.3	36.4
Total Compensation ($) from all visits	−37.9	31.22	32	59.4	6.3	34.4
One phone Rating's worth ($)	1.2 [&&]	0.71	29	11.5	80.8	7.7
Current Measurements During Phone Call						
Question Topic	mean	sem	*N*			
Pain (VAS, 0 to 10)	5.4	0.94	33			
Mood (VAS, −10 to +10)	5.3	0.94	33			
Behavioral Data						
Questionnaire Scores from Visit 1	mean	sem	*N*[&&&]	Pain (r-val)	$(r-val)	A1(r-val)

LAQ	62.9	1.55	33	−0.38 *	0.21	−0.41 *
PCS rumination	7.3	0.70	33	0.15	0.16	0.05
PCS magnification	4.0	0.46	33	0.25	−0.20	−0.002
PCS helplessness	8.6	0.79	33	−0.06	0.09	−0.12
PSQ no-pain subscale	4.6	0.75	33	−0.14	−0.10	−0.11
PSQ pain subscale	75.2	4.13	33	0.08	0.03	0.16
PASS avoidance behavior	13.0	1.25	33	−0.16	−0.004	−0.12
PASS cognitive anxiety	11.8	1.26	33	0.09	−0.12	−0.12
PASS fear	7.4	1.11	33	0.14	−0.08	−0.09
PASS physiological anxiety	6.0	0.95	33	0.02	−0.05	−0.20

Data corresponds to answers from questions given in Table S5. Discrepancy scores for every question were calculated, with positive scores indicating greater (exaggerated) recalled answers than what actually happened and negative scores indicating lower (under-estimated) recalled answers. Percentages indicate accuracy measurements: 0 = perfectly accurate memories, <0 = underestimation, and >0 = overestimation. Other than pain memory, memory of total compensation was the only other measure that was not centered around 0 (showing a systematic bias). Average scores and sub-scores for 4 self-report measures were also provided (LAQ: Loss Aversion Questionnaire; PCS: Pain Catastrophizing Scale; PSQ: Pain Sensitivity Questionnaire; PASS = Pain Anxiety Symptoms Scale). R-values indicate the correlation with each of the scales and the 3 main parameters of interest: pain memory discrepancy (pain), total compensation discrepancy ($), and hippocampal shape displacement (posterior area A1).

- = data not applicable for this measure;

& = values are estimated based on what the majority of participants would have experienced but there are exceptions, as some patients did not complete the study and therefore would have had less visits and less scans, for example. Actual values differed from expected values and were calculated based on each participant's data.

&& = this particular measurement had outlying values in it that drove the mean up (3 participants responded with values between $7 and $18); if those 3 values are removed (n = 26), the discrepancy becomes −0.0008 ± 0.017 SEM, indicating high accuracy.

&&& = there were no missing values for any questionnaire measures, resulting in a sample size of n = 33 for all scores; however, one person was missing from the monetary ($) calculation, so this correlation had a sample size of n = 32 for all scores;

* = $p < 0.05$.