Reactivation of pain-related patterns in the hippocampus from single past episodes relates to successful memory-based decision making

G. Elliott Wimmer[1,2] and Christian Büchel[3]

[1] Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London, United Kingdom

[2] Wellcome Centre for Human Neuroimaging, University College London, London, United Kingdom

[3] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Corresponding author:

G. Elliott Wimmer
Max Planck UCL Centre for Computational
Psychiatry and Ageing
Wellcome Centre for Human NeuroImaging
10-12 Russell Square
University College London
e.wimmer@ucl.ac.uk

Abstract

Aversive and rewarding previous experiences can exert a strong influence on our subsequent behavior. During decision making, sampling from these previous episodes may support our choices, but relatively little is known about how the value of single experiences is represented. Further, while recent research has investigated reward-associated episodes, it is unclear if these results generalize to negative experiences such as pain. To investigate whether value-related regions or the hippocampus represent the value of previous aversive experiences, in our experiments participants experienced episodes of high or low pain in conjunction with incidental, trial-unique neutral pictures. In an incentive-compatible surprise test phase, we found that participants avoided pain-paired objects. In a separate fMRI experiment, participants exhibited significant source memory for value. Neurally, when participants were re-exposed to pain-paired objects, we found no evidence for reactivation of pain-related patterns in pain-responsive regions such as the anterior insula. Critically, however, we found that patterns of activity in the hippocampus significantly discriminated episodic pain associations. Further, stronger reactivation in the anterior hippocampus was related to improved value memory performance. Our results demonstrate that single incidental aversive experiences can build reliable memories that affect decision making and that this influence may be supported by the hippocampus.

Introduction

When choosing among fruits at the market, we could base our choice on a long-standing preference for a favorite fruit or perhaps instead on a single positive memory of tasting a novel tropical fruit that we see on offer. Research on learning and decision making has predominantly focused on the influence of well-learned values on choice (Daw and Doya, 2006; Schultz, 2006; Rangel et al., 2008). However, our behavior is often influenced by single past experiences, and we know surprisingly little about the cognitive and neural mechanisms that might support the use of such memories in value-based decision making (Wimmer and Buechel, 2016).

In the last few years, research in decision making has become increasingly integrated with research in memory, stimulated in part by proposals that value-based choice in some contexts can be supported by a mechanism that samples representations stored in memory (Hertwig et al., 2004; Weber and Johnson, 2006; Biele et al., 2009; Gluth et al., 2015; Shadlen and Shohamy, 2016). Importantly, for memories to guide value-based choices, those memories must be integrated with the positive or negative value we originally experienced.

Recent studies of decision making in the reward domain have shown an influence of single past episodes on decision making (Duncan and Shohamy, 2016; Murty et al., 2016; Wimmer and Buechel, 2016; Bornstein et al., 2017; Bornstein and Norman, 2017). Neuroimaging evidence has also shown that choices are biased by reactivation of distributed reward-related patterns of brain activity in regions outside of the hippocampus (Wimmer and Buechel, 2016).

The hippocampus is critical for episodic or relational memory (Eichenbaum and Cohen, 2001; Davachi, 2006), and it could also play a critical role in associating episodes with value. Importantly, thus far, no studies have demonstrated a role for the hippocampus in the implicit learning of values from episodes. Activation in the hippocampus has been shown to correlate with the value of stimuli and snack foods (Lebreton et al., 2009; Gluth et al., 2015). Studies have also reported that the hippocampus is associated with decision making processes for well-learned values such as snack foods, potentially implementing a memory sampling mechanism (Gluth et al., 2015; Bakkour et al., 2019). Particularly for negative experiences, understanding the role of the hippocampus in value memory is likely to be important for the understanding and treatment of mood disorders and post-traumatic stress disorder (Hamilton and Gotlib, 2008; Brewin et al., 2010; Shin and Liberzon, 2010).

The anterior hippocampus in particular may play an important role in encoding episodic memory together with value, given research demonstrating a central role for the anterior hippocampus in anxiety (Adhikari et al., 2010; Fanselow and Dong, 2010; Bach et al., 2014) as well as in memory integration and generalization (Poppenk et al., 2013; Schlichting et al., 2015; Brunec et al., 2018). In contrast, the gradual learning of stimulus-value associations over multiple experiences is known to involve systems including the dopaminergic midbrain, striatum, insula, and amygdala (Schultz et al., 1997; LeDoux, 2000; Seymour and al., 2004; Schiller et al., 2008). In the case of learning from aversive stimuli such as heat, a network of regions including the insula and secondary somatosensory cortex respond to pain (Seymour et al., 2004; Apkarian

et al., 2005; Tracey and Mantyh, 2007; Roy et al., 2014; Horing et al., 2019), suggesting a potential substrate for memory for the value of pain.

In the following experiments, we investigated whether single aversive episodes influence memory-based decision making and whether such an influence is supported by reactivation of distributed patterns of activity. During an incidental learning phase, neutral objects were presented once, incidentally paired with high or low pain (**Fig. 1a**). A surprise behavioral choice phase or a scanned memory test phase followed (**Fig. 1b-c**). In the memory test phase of the fMRI experiment, participants were re-exposed to objects from the preceding phase while being asked to remember whether objects had been paired with high versus low heat pain, thus allowing us to measure value memory performance and test for reactivation of pain-related patterns.

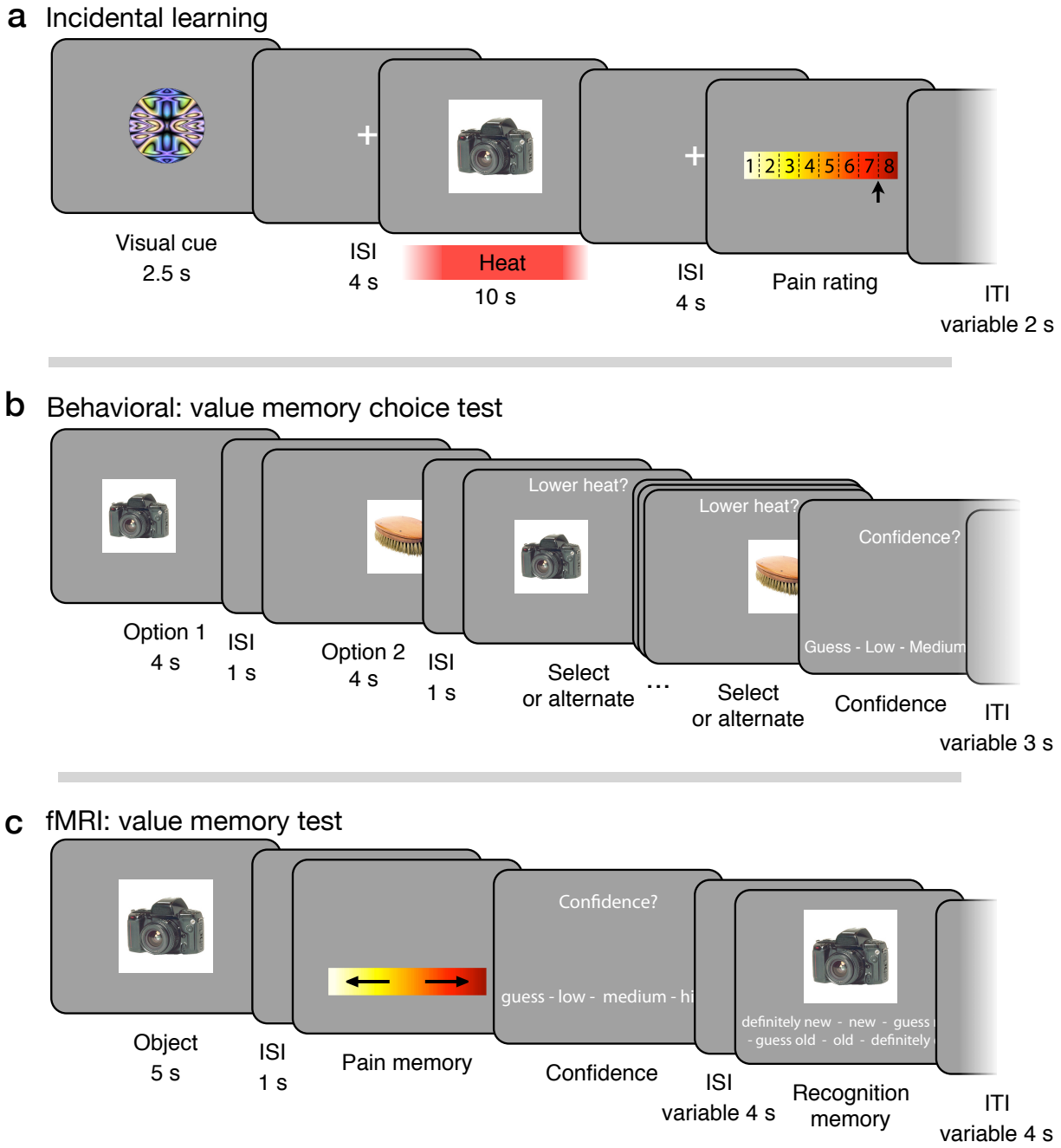

Figure 1. Pain value memory experimental design. ***a***, In the incidental learning phase, participants experienced high or low heat pain while being exposed to incidental trial-unique object pictures. Participants then rated their experienced level of pain. ***b***, Value choice phase in the behavioral experiment. Each trial presented two objects from the incidental learning phase in sequence. Participants then alternated between objects to select the object that they thought had been associated with lower heat pain. ***c***, Value

memory test phase in the fMRI experiment. Each trial presented a single object and participants responded with whether the object was paired with high or low heat pain and then rated their confidence in this response. Finally, participants then rated their recognition strength on a 6-point new-to-old scale.

Materials and Methods

Participants. A total of 26 subjects participated in the behavioral choice experiment. Participants were right-handed fluent German speakers with no self-reported neurological or psychiatric disorders. Data from two participants were excluded due to technical problems with the thermode and data from two additional participants were excluded due to errors in response recording, leaving 21 participants (13 female; mean age 25.1 years; range 18-42). A total of 31 subjects participated in the fMRI experiment. Participants were right-handed fluent German speakers with no self-reported neurological or psychiatric disorders and normal or corrected-to-normal vision. Data from two participants were excluded due to technical problems with the thermode, leaving 29 participants (15 female; mean age 26.0 years; range 20-33 years). In one participant, pain memory confidence ratings and memory recognition strength in the immediate test session were not recorded due to a technical error. The Ethics committee of the Medical Chamber Hamburg approved the study and all participants gave written consent.

Experimental design. The experiments were designed to allow an investigation of two areas: first, the cognitive and neural mechanisms that support memory for aversive experiences, which is the focus of the current report, and separately the behavioral and

neural correlates of pain modulation of short term and very long-term recognition memory. For the latter question, a subset of participants returned one year later to assess whether the maintenance of recognition memory was modulated by pain and neural activity during the fMRI session; these results will be published separately (Wimmer and Buechel, 2015).

The behavioral and fMRI experiments started with a heat calibration phase. This was followed in both experiments by the incidental learning phase, where abstract cues probabilistically associated with high or low heat were followed by the presentation of trial-unique objects in conjunction with high or low heat pain. A test phase followed that explored the role of negative episodes on value-based decision making (in the behavioral experiment) and memory for pain (in the fMRI experiment). The test phase in the fMRI experiment allowed for the investigation of the critical question of whether pain-related patterns of activity were re-activated upon re-exposure to objects and whether this related to behavior.

Heat calibration. Before the incidental learning phase, heat levels were calibrated for each participant to achieve the same subjective high and low aversive pain experience across participants. Thermal stimulation was delivered via an MRI compatible 3 × 3 cm Peltier thermode (MSA; Somedic, Sweden) applied to the inner left forearm. During the visual presentation of a white square, heat was applied for 10 s. For pain ratings, we used a 1-8 rating scale with 0.5-point increments, superimposed on a yellow-to-red gradient (as depicted in **Fig. 1a**). An arrow cursor was moved from the initial mid-point starting location using left and right key-presses and ratings were confirmed with the

space bar. A rating of ‘8’ corresponded to the highest level of heat pain a participant could endure multiple times. If the level of pain was intolerable, participants moved the rating past the ‘8’ end of the scale, at which point a ‘9’ appeared on the screen. Participants rated the pain associated with a pseudo-random list of 10 different temperatures ranging from 39.5 to 49.5ºC. A linear interpolation algorithm then selected a low temperature estimated to yield a ‘2’ rating and a high temperature estimated to yield a ‘7.5’ rating.

Procedure: incidental learning phase. In the incidental learning phase, participants experienced high or low heat pain while being exposed to trial-unique object pictures (**Fig. 1a**; common to both the behavioral and fMRI experiments). Importantly, the encoding of the object pictures was incidental (not instructed) in order to more closely resemble the incidental nature of encoding in many real-world situations. Color pictures of objects were drawn from a database of images compiled via internet search (as used previously; Wimmer and Buechel, 2016); objects were largely composed of familiar non-food household items set on white backgrounds. To maintain attention on the screen during object presentation, participants were instructed to respond to occasional flickers in image brightness. Heat pain was probabilistically cued (70% predictive) to allow for some prediction of pain but also for surprise at pain onset, with a design adapted from Atlas et al. (2010) (see also Geuter et al., 2017; Fazeli and Buchel, 2018). Across 4 blocks, 33 high heat trials and 33 low heat trials were presented (**Fig. 1a**), including 10 low-to-high and 10 high-to-low mismatch trials. Given the low number of mismatch trials and the relatively low effect of cues on ratings (see Results), all analyses focused on

administered heat irrespective of cued heat to ensure reliability of imaging estimates. Two additional low heat trials were presented at the beginning of the task, with the incidental objects from these trials also shown during the beginning of the memory test phase. To allow for initial adjustment to the task, data from these initial trials in all phases were excluded from analysis.

In each incidental learning phase trial a visual cue signaling likely high or low heat was presented for 2.5 s. After a 4 s ISI, the incidental object appeared. To allow for a better match between the appearance of the object and the onset of noticeable heat, heat onset started 0.75 s prior to object appearance (for a similar method, see Forkmann et al., 2013). The incidental object was presented for a total duration of 10 s. The thermode temperature increased from baseline (33°C) to the desired temperature at a rate of 5 degrees per second, which translates to approximately 3.5 s to reach the range of the high heat temperature. After the 10 s object presentation period, the thermode temperature decreased at a similar rate. Following the heat stimulation and after a 4 s ISI, a pain rating scale appeared. Participants used left and right buttons to move a selection arrow from the initial cursor position (randomized between 4.5-5.5) to their experienced pain level and pressed the down button twice to make their selection; responses were self-paced. After the participant entered their response, trials were followed by a variable 2 s mean (range: 0.5-6 s) inter-trial-interval (ITI).

To maintain attention on the screen during visual cue presentation, the visual cue illumination flickered (decreased in illumination) once for 0.35 s in a random 50% of trials. Flicker timing was randomly distributed throughout the first 1.5 s of visual cue presentation. Similarly, in a separately determined random 50% of trials the object

picture flickered in illumination during heat stimulation. When either a visual cue or object flicker was detected, participants were instructed to press the down button.

Two pseudo-random orderings of incidental object pictures were used for counterbalancing object and heat associations. The assignment of abstract circles to high and low heat was also counterbalanced across participants. Further, after the first two blocks of the experiment, two new abstract circles were used as cues, with visual and verbal instruction about the new cues preceding the block. Visual cues were probabilistically associated with the level of heat, correctly predicting high or low heat in 70% of trials (Atlas et al., 2010). On invalid trials, the alternative heat level was administered. Additionally, 6 trials included a probe of cue-related pain expectancy: after 2.5 s of cue presentation, a question appeared below the cue asking participants whether they expected low or high heat to follow. These probes were used to test memory for cue-pain associations. After the probe, trials continued as normal. After each incidental learning phase block, the thermode was moved to a new location on the inner arm to avoid sensitization.

To maintain similar differences in subjective experience between the high and low heat conditions, temperatures were automatically adjusted throughout the task to maintain the targeted pain rating values. If the median of the previous 6 validly cued low heat trials fell below a rating of 1.5, the low temperature was increased by 0.2 ºC; if the median rating was above 3, the low temperature was decreased by 0.2 ºC. For the high temperature, if the median rating fell below 7.5, the high temperature was increased by 0.2 ºC (if the temperature was below 50.5 ºC). If a rating of “9” was given, indicating an intolerably high level of pain, the high temperature was decreased by 0.8 ºC. Such on-

line adjustments of administered temperature are not commonly employed in pain research that focuses on effects of expectation or placebo (e.g. Atlas et al., 2010), as in these cases administered temperature needs to be constant across the task. However, our focus here was on the subjective response to pain, and thus on-line adjustment allowed us to maintain very similar subjective responses to the majority of high and low heat stimuli.

Procedure: behavioral choice test phase. In the behavioral study, a surprise choice test phase followed the incidental learning phase. Participants made choices between two objects: an object that had been associated with the administration of high heat (independent of the cue) and an object that had been associated with low heat (independent of the cue). Participants were instructed that they could win €0.50 euro for each correct choice on top of their payment for participation.

The choices sampled each object without repetition, resulting in 33 choices. The objects from the first two trials in the incidental learning phase were not included in any choice. Choices were presented in a pseudo-random order. A given choice included either 2 objects that had been correctly cued to be of low and high heat or a choice between one validly cued object and one invalidly cued object. We found no influence of the invalid cue or whether pain was higher or lower than expected on choice accuracy (p-values > 0.31) so we collapse across this factor in all analyses. Following these choices, an additional 4 trials presented choices between the abstract circle cues that had been predictive of high versus low heat pain.

On a choice trial, the choice options were presented serially in a random order (**Fig. 1b**). The first option was presented either on the left side or on the right side of the screen (determined at random) for 4 s, followed by a 1 s ISI. The second option was then presented in the alternate spatial location for 4 s, followed by a 1 s ISI. Then the first option returned to the screen, below the prompt "Lower heat? (€0.50 reward)". Participants could select the on-screen option by pressing the 'space' key, or press the 'left' or 'right' key to alternate between the options. Alternation was allowed for an unlimited amount of time. After choice entry, a confidence rating followed, presenting the options: "Guess", "Low", "Medium", and "High". Participants responded using the 1-4 keys. A variable 3 s ITI followed.

Procedure: fMRI memory test phase. In the fMRI study, a surprise memory test followed the incidental learning session. While collecting fMRI data, we assessed memory for the level of pain experienced with the object and recognition memory strength (**Fig. 1c**). Participants saw each of the "old" objects from the incidental learning phase. The first two trials allowed for habituation and presented the first two objects from the incidental learning phase; these trials were not analyzed. The old objects were intermixed with 20 "new" objects. On each trial a single object was presented alone for 5 s. Next, after a 1 s ISI, an unmarked yellow-to-red heat scale with superimposed left- and right-pointing arrows was shown. Participants pressed the left or right buttons to indicate whether they thought that the object had been associated with low heat pain or high heat pain in the incidental learning phase. For objects that participants definitely considered to be "new", participants were told that they could pick either the high or low

heat response at random. If they were not sure if an object was new, participants were instructed to try to recall the level of heat it may have be paired with. All test phase responses were self-paced. Next, a confidence rating screen appeared with 4 levels of response: “guess”, “somewhat certain”, “certain”, and “very certain”. For stimuli participants believed were definitely new and thus had no associated heat experience, participants were instructed to respond with a low confidence answer. After a variable ISI (mean: 4 s; range: 3-6.5 s), a 6-point memory recognition strength scale was presented (e.g. Schwarze et al., 2012). Participants indicated whether they thought the object was “new” (not previously seen) or “old” (seen during the learning task) with 6 levels of response: “certain new”, “somewhat certain new”, “guess new”, “guess old”, “somewhat certain old”, “certain old”. Participants used the left and right buttons to move from the randomly initially highlighted “guess new” or “guess old” response option to their selected response and then pressed the down button twice to make their selection. A variable ITI with a mean of 4 s (range: 2-8 s) followed. The order of the old pictures was pseudo-randomized from the incidental learning phase order, and the old and new pictures were pseudo-randomly intermixed. The duration and distribution of ITIs (or “null events”) was optimized for estimation of rapid event-related fMRI responses as calculated using Optseq software (http://surfer.nmr.mgh.harvard.edu/optseq/).

At the end of the experiment, participants completed a written questionnaire querying their knowledge of the task instructions and their expectations (if any) regarding the incidental object pictures. Task instructions and on-screen text were

presented in German for all parts of the experiment; for the figures and methods, on-screen text has been translated into English.

Data Acquisition. The experiment was presented using Matlab (Mathworks, Natick, MA) and the Psychophysics Toolbox (Brainard, 1997). For the behavioral study and the pain calibration phase of the fMRI study, data were collected using a 15” Apple Macbook Pro laptop. Responses were made using left and right arrow keys and the space key. In the scanner for the fMRI study, the task was projected onto a mirror above the participant’s eyes. Responses were made using a 4-button interface with a “diamond” arrangement of buttons. Skin conductance was recorded from the hypothenar of the left hand. The signal was amplified using a CED 2502 amplifier and digitized at 200 Hz using a CED micro1401 (both by Cambridge Electronic Design, Cambridge, UK) and downsampled offline to 100 Hz.

Whole-brain imaging was conducted on a Siemens Trio 3 Tesla system equipped with a 32-channel head coil (Siemens, Erlangen, Germany). Functional images were collected using a gradient echo T2*-weighted echoplanar (EPI) sequence with blood oxygenation level-dependent (BOLD) contrast (TR = 2460 ms, TE = 26 ms, flip angle = 80; GRAPPA factor of 2; 2 x 2 x 2 mm voxel size; 40 axial slices with a 1 mm gap). Slices were tilted approximately 30° relative to the AC–PC line to improve signal-to-noise ratio in the orbitofrontal cortex (Deichmann et al., 2003). Head padding was used to minimize head motion; no participant’s motion exceeded 3 mm in any direction from one volume acquisition to the next. For each functional scanning run, five discarded volumes were collected prior to the first trial to allow for magnetic field equilibration.

During the incidental learning phase, four functional runs of an average of 190 TRs (7 min and 48 s) were collected, each including 17 trials. During the memory test phase, four functional runs of an average of 196 TRs (8 min and 2 s) were collected, each including 22 trials. If a structural scan had been collected for the participant at the center within the past 6 months, the previous structural scan was used. If not, structural images were collected using a high-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (1 x 1 x 1 mm voxel size) between the incidental learning phase and the immediate memory test phase.

All voxel locations are reported in MNI coordinates, and results are displayed overlaid on the average of all participants' normalized high-resolution structural images using the xjView toolbox (http://www.alivelearn.net/xjview) or AFNI (Cox, 1996).

Behavioral Analysis. Our primary behavioral question was whether memory-based decisions were influenced by the pain associated with objects in the incidental learning phase. In the behavioral experiment, choice trials were excluded if the administered heat for the high heat stimulus did not exceed that for the low heat stimulus (in rare cases when the thermode failed to increase temperature; on average less than 1 trial per participant).

In both experiments, we conducted simple a priori comparisons of behavioral performance to chance (50%) using t-tests, with a significance threshold of $p < 0.05$ (two-tailed). We also examined the influence of cue expectation on pain ratings using a paired t-test. In the fMRI experiment, we further verified in initial comparisons that "old"

objects (whether paired with high or low pain) were recognized at a higher rate than "new" objects.

To further investigate value memory, multilevel regression models were implemented in R using the lmer4 package following previous procedures (Braun et al., 2018). In all regressions, participant was entered as a random effect along with all other variables of interest. To ensure convergence, all models were run using the bobyqa optimizer set to 10^6 iterations. We estimated confidence intervals using the confint.merMod function and p-values using the bootMer function (both from the lmer4 package) using 2500 iterations. All reported p-values are two-tailed. In a control model, we verified that the presence vs. absence of a visual "flicker" during object presentation was not related to value memory or recognition memory strength.

We additionally tested whether nonsignificant results were weaker than a moderate effect size using the two-one-sided t-test (TOST) procedure (Schuirmann, 1987; Lakens, 2017) and the TOSTER library in R (Lakens, 2017). In the behavioral experiment (n = 21), we used bounds of Cohen's d = 0.64, where power to detect such a medium-size is estimated to be 80%. In the larger fMRI sample (n = 29), we used bounds of Cohen's d = 0.55 to achieve the same estimated power.

fMRI preprocessing. Preprocessing and data analysis were performed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). Before preprocessing, slices with artifacts were identified as having mean image intensity greater than or equal to 5% above the across-run slice mean. Individual slices with artifacts were replaced with the mean of the two

surrounding timepoints using a script adapted from the ArtRepair toolbox (Mazaika et al., 2009). Images were then slice-timing corrected, realigned to correct for participant motion, and then spatially normalized to the Montreal Neurological Institute (MNI) coordinate space by estimating a warping to template space from each participant's anatomical image and applying the resulting transformation to the EPIs. Images were filtered with a 128 s high-pass filter and resampled to 2 mm cubic voxels. Images were then smoothed with a 6 mm FWHM Gaussian kernel for univariate and connectivity analyses.

fMRI univariate analyses. fMRI model regressors were convolved with the canonical hemodynamic response function and entered into a general linear model (GLM) of each participant's fMRI data. The six scan-to-scan motion parameters produced during realignment were included as additional regressors in the GLM to account for residual effects of participant movement. All regressions were conducted with automatic orthogonalization in SPM turned off.

We first conducted "localizer" univariate analyses to identify main effects of pain during the incidental learning phase. The GLM included regressors for the cue period (2.5 s duration), the initial pain onset period (2 s), the full pain and object presentation period (10 s), and the pain rating period (with a variable duration based on response time). The cue period regressor was accompanied by a parametric modulator contrasting high versus low expected pain. The pain onset period regressor was accompanied by two parametric modulators: the mismatch between cue and pain as well as the unsigned (absolute value) mismatch between cue and pain (these

regressors were not correlated; r = 0.007). The full pain period regressor was accompanied by a parametric modulator representing the pain rating given on that trial. Note that the regions identified as correlating with pain during the 10 s pain period were the same with or without the inclusion of the 2 s pain onset regressor.

We conducted a secondary univariate analysis of the test phase related to our multivariate approach below. This analysis identified any effects of the original pain rating during the re-presentation of objects in the test phase. A 5 s regressor modeled activity during the re-presentation of the object. This regressor was accompanied by a parametric regressor representing the level of heat pain experienced in the preceding phase. Additional regressors modeled the pain memory response period, the pain memory confidence response period, and the memory response period (durations for all these periods matched the participant's response time).

Two additional univariate analyses examined correlates of successful encoding of pain associations during the incidental learning phase as well as successful retrieval of pain associations during the test phase. These models augmented the two GLMs described above. Thus, in addition to the pain rating parametric regressor, these models also included a parametric regressor representing value memory success (at encoding or retrieval) separately for the high and low pain-associated objects.

Multivariate fMRI analyses. To test whether patterns of BOLD activity associated with negative emotional experience were reactivated at retrieval, we utilized multivariate classification analyses. These analyses used the non-smoothed fMRI data. In the incidental learning phase and the memory test phase we estimated mass-univariate

GLMs where each trial was modeled with a separate regressor. For the incidental learning phase, each regressor modeled the onset of an object and continued through the 10 s duration of the heat stimulus. For the memory test phase, each regressor began at the onset of the object and continued for the 5 s duration of object presentation (prior to any responses). Models included the six nuisance motion regressors (translations and rotations).

Multivariate analyses were conducted using The Decoding Toolbox (Hebart et al., 2014). Classification utilized a L2-norm learning support vector machine (LIBSVM; Chang and Lin, 2011) with a fixed cost of $c = 1$. The classifier was trained on the full incidental learning phase balanced via bootstrapping. The trained classifier was then tested on the full memory test phase data. Note that for the primary across-phase classification analysis, no cross-validation is necessary for training because no inferences are drawn and no results are reported from the incidental learning phase data. Memory test phase classification is reported as area under the curve (AUC), which uses graded decision values and better accounts for biases in classification that may arise due to the different processes engaged by the incidental learning and memory test phases. Supplemental ROI analyses examined training and testing within the learning phase or memory test phase used cross-validation. Using cross-validation, we computed the strength of discriminability in the localizer phase in our regions of interest.

Additionally, we conducted a searchlight analysis for further localization using The Decoding Toolbox (Hebart et al., 2014). We used a 4-voxel radius spherical searchlight (approx. 208 voxels). Training of the classifier on the incidental learning phase and testing on the memory test phase were conducted as described above for

the ROI MVPA analyses. Individual subject classification accuracy maps were smoothed with a 6 mm FWHM kernel before group-level analysis. We also performed covariate analyses to determine whether behavioral performance was correlated with classification accuracy.

It has been shown that it is not valid to conduct statistical inference specifically on cross-validated classification accuracy measures of information using *t*-tests (Allefeld et al., 2016). In part, as informational measures cannot be below zero, assumptions underlying the *t*-test are violated for cross-validation within the same dataset. Our classifier training and testing were conducted on separate datasets ("cross-classification" between the incidental learning and the memory test phase) which does allow for potential "true" below-zero values, a case not addressed by Allefeld et al. (2016). Further, we found that cross-classification AUC values in all our regions of interest followed a normal distribution (Anderson-Darling goodness-of-fit hypothesis test). While the above concern may still apply to inferences made about the main effects of pain during the incidental learning phase, our primary hypothesis rests on the cross-classification of pain-related patterns from the memory test phase.

Connectivity analyses. We additionally conducted psychophysiological interaction (PPI) analyses to examine differences in functional connectivity for successful versus unsuccessful value memory retrieval. These analyses used a hippocampal ROI as the seed region (defined in Results). In the incidental learning phase, we estimated a PPI contrasting correct versus incorrect later retrieval, modeling the 10 s duration of the object and pain period. In the memory test phase, we estimated a similar PPI analysis,

modeling the 5 s duration of the object presentation period. At the second level, we performed correlation analyses to determine whether behavioral performance was related to differences in connectivity for correct versus incorrect encoding / retrieval.

Statistical correction and regions of interest. For both univariate and searchlight results, linear contrasts of univariate SPMs were taken to a group-level (random-effects) analysis. We report results corrected for family-wise error (FWE) due to multiple comparisons (Friston et al., 1993). We conduct this correction at the peak level within small volume ROIs for which we had an a priori hypothesis or at the whole-brain cluster level (in each case using a cluster-forming threshold of $p < 0.005$ uncorrected, except for the pain rating correlation, where we used $p < 0.0001$ to yield more interpretable clusters).

We focused on two a priori ROIs motivated by two separate hypotheses. Given the anterior insula's role in processing the affective qualities of pain (Kurth et al., 2010; Wiech et al., 2014), we predicted that the insula may relate to the modulation of memory by pain. For this pain hypothesis-motivated anterior insula ROI, we first created a bilateral anterior insula mask (Brooks et al., 2002; Wiech et al., 2014), covering the insular cortex anterior to $y = 9$, as well as up to 4 millimeters lateral or superior to the insular cortex to account for signal blurring and anatomical variability. This mask was further restricted by the main effect of pain rating taken from the incidental learning phase localizer GLM defined above, thresholded at $p < 0.0001$ uncorrected (https://neurovault.org/collections/6126/). We also defined a broader pain-related mask based on the localizer GLM thresholded at $p < 0.0001$ uncorrected, excluding the

cerebellum. Separately, we focused on the hippocampus because of its role in episodic and relational memory (Eichenbaum and Cohen, 2001; Davachi, 2006). We also conducted follow-up analyses in the anterior hippocampus, given its role in negative emotion-related memory and generalization (Fanselow and Dong, 2010; Poppenk et al., 2013). The bilateral hippocampus ROI was derived from the Harvard-Oxford atlas at a threshold of 50%. We focused on a restricted mask of the hippocampus in order to limit the size of the ROI for multivariate analyses. We confirmed that there was no overlap between the hippocampus and pain-related masks. We defined the anterior hippocampus as the mask region anterior to Y = -21, approximating the position of the uncal apex (Poppenk et al., 2013). While somatic processing of thermal pain does not primarily involve the amygdala, as a control we also examined the amygdala, defined from the Harvard-Oxford atlas at a threshold of 50%.

Correlations between classification accuracy and behavioral performance were conducted using Pearson' correlation. Statistical comparison of the difference between correlations was computed using Steiger's test for differences in dependent correlations.

Data availability. Behavioral data are available on the Open Science Framework (https://osf.io/gr9xd/). Whole-brain fMRI results are available on NeuroVault (https://neurovault.org/collections/6126/).

Results

Choice study behavior.

Our primary behavioral question was whether single aversive episodes can support later value-based decision making. In the behavioral study, participants experienced episodes of low or high heat pain incidentally associated with trial-unique object pictures. Subsequently, in a surprise choice test phase, participants made choices between two objects that had been incidentally associated with different levels of heat, with the goal of choosing the object that had been paired with low heat.

During the incidental learning phase, participants could clearly discriminate the heat pain levels: on the 1-8 rating scale, where '8' corresponds to high pain, the mean pain rating for high pain stimuli was 7.00 (95% CI [6.68 7.31]), while the mean pain rating for low pain stimuli was 2.26 [1.94 2.57]. Participants' pain ratings were also highly correlated with the administered heat temperature on a trial-to-trial basis (mixed-effects model coefficient β = 0.9399 [0.7682 1.036]; z = 10.899 $p < 0.001$). The cue preceding the high or low pain was inaccurate on 30% of trials. We found no significant interaction between high versus low pain and cue validity (β = 0.0292 [-0.0295 0.0867]; t = 1.010, p = 0.326). There was no significant effect of invalid cues on low pain ratings (valid 2.23 [1.94 2.52]; invalid 2.32 [1.93 2.72]; β = 0.0472 [-0.0349 0.1304]; t = 1.106, p = 0.282) and a no significant effect of invalid cues on high pain ratings (valid 7.00 [6.69 7.32]; invalid 6.98 [6.64 7.33]; β = -0.0111 [-0.0893 0.0655]; t = -0.287, p = 0.821). The minimal influence of the cue on ratings is likely due to the use of two very different and

easily discriminable temperatures, which differs from previous work (Atlas et al., 2010; Fazeli and Buchel, 2018).

In the incentivized choice test phase, participants were successfully able to choose the low pain object over the high pain object (mean 58.7% correct choices [53.2 64.2]; versus chance (50%), $t_{(20)} = 3.28$, $p = 0.0037$). We found that choice performance significantly increased with the difference in pain ratings between the two choice objects ($\beta = 0.1278$ [0.0237 0.2297]; $z = 2.387$, $p = 0.0144$; **Fig. 2a**). Choice performance also increased with higher levels of choice confidence ($\beta = 0.4409$ [0.2554 0.6322]; $z = 4.546$, $p < 0.001$). These results demonstrate that value-based choices can be guided by single negative experiences.

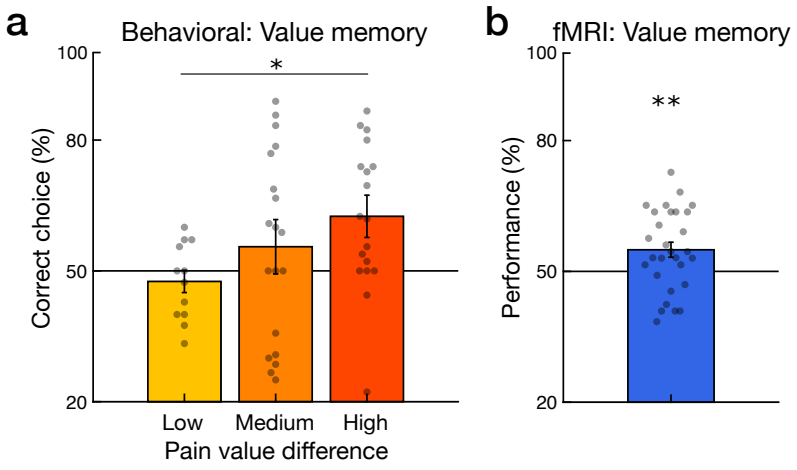

Figure 2. Decision making and value memory performance. ***a***, In the behavioral experiment, accuracy in selecting the object that had been incidentally associated with low versus high pain was significantly related to the difference in pain reported for the objects during the incidental learning phase (regression on continuous measure). For visualization only, the pain rating difference between choice options was binned based on whether the options differed by <= 3 rating points (Low), > 3 and <= 5 points (Medium), and 5 or more points (High). ***b***, Test phase performance in the fMRI study.

Participants exhibited significant source memory for the value of single episodes. (Individual points represent individual participants; error bars represent standard error of the mean (SEM); * $p < 0.05$; **$p < 0.01$.)

fMRI study behavior.

In the fMRI study, as in the behavioral study, participants experienced episodes of low or high heat pain incidentally associated with trial-unique object pictures. Subsequently, in a surprise memory test, participants were cued with an object and instructed to remember whether the object was associated with high or low pain in the preceding incidental learning phase. We refer to this as value memory (Wimmer and Buechel, 2016), but this judgment could equally be considered a source memory judgment, i.e. a judgment of whether an episode had certain information or not. Following this rating, in each trial participants then rated their familiarity with the object.

In the incidental learning phase, pain ratings given after each trial reliably differentiated high and low heat (high, 7.34 95% CI [7.203 7.475]; low, 2.34 [2.134 2.553]; scale range: 1-8). Participants' pain ratings were highly correlated with the administered heat temperature on a trial-to-trial basis ($\beta = 0.7093$ [0.6406 0.7799]; $z = 20.12$, $p < 0.001$). The cue preceding the high or low pain was inaccurate in 30% of trials. We found a significant interaction between high versus low pain and cue validity ($\beta = 0.0870$ [0.0428 0.1310]; $t = 3.967$, $p < 0.001$). This interaction was driven by a positive effect of invalid cues on low pain ratings (valid 2.27 [2.09 2.44]; invalid 2.52 [2.19 2.85]; $\beta = 0.1260$ [0.0287 0.2264]; $t = 2.461$, $p = 0.008$) and a numerically negative effect of invalid cues on high pain ratings (valid 7.37 [7.24 7.50]; invalid 7.27 [7.10 7.45]; $\beta = -0.0480$ [-0.1047 0.007]; $t = -1.686$, $p = 0.094$).

In the surprise memory test, we found that value memory accuracy was significantly above chance (54.99% correct [51.43 58.49]; $t_{(28)} = 2.879$, $p = 0.0076$; **Fig. 2b**). Value memory accuracy significantly increased with increasing confidence (β = 0.2910 [0.179780 0.4053]; $z = 4.99$, $p < 0.001$; n = 28 participants with confidence and memory ratings), with mean performance rising to 72.42% correct at the highest confidence level. While mean performance was significant, the level of performance was lower than that we observed previously in a study where monetary reward was used to associate value with objects (61 %; Wimmer and Buechel, 2016).

In the memory test, participants exhibited a non-significant bias toward selecting the 'low pain' response option (46.69% high pain responses [43.08 50.31]; $t_{(28)} = -1.87$, $p = 0.073$). This bias was related to confidence, such that higher confidence was positively associated with a response of high versus low pain (β = 0.416 [0.283 0.548]; $z = 6.15$, $p < 0.001$). We did not find a relationship between original pain ratings and accuracy for high or low pain objects (high pain rating difference between correct versus incorrect episodes, $p = 0.341$; low pain rating difference, $p = 0.753$), unlike the behavioral experiment. It is possible that the binary choice measure in the behavioral study was more sensitive to this effect.

Recognition memory strength was not modulated by heat pain (where a rating of '6' represents sure old: high pain 4.86 [4.65 5.07]; low pain 4.87 [4.65 5.09]; TOST equivalence test $t_{(27)} = 2.693$, $p = 0.006$; n = 28 participants with confidence and memory ratings). Further, participants reliably discriminated old from new objects (old object mean 4.87 [4.65 5.09]; new object mean 2.11 [1.85 2.37], p-value < 0.001)(Wimmer and Buechel, 2015). We also found that pain value memory

performance was highly correlated with recognition memory strength (corrected hit rate) across participants ($r = 0.702$, $p < 0.001$).

The results from both the behavioral and fMRI experiments demonstrate that single aversive episodes associated with high or low heat pain can support later memory-based decisions. Note that these effects cannot be easily attributed to participants using only memory for associated arousal to guide choices. In a previous behavioral study in which choices directly compared reward and pain associated objects, we found that performance was actually numerically higher than the condition where choices were only between different reward levels (Wimmer and Buechel, 2016).

fMRI univariate results.

In the imaging analyses, we first examined whether heat pain activated the network of regions implicated in pain processing (Apkarian et al., 2005; Tracey and Mantyh, 2007). We found that trial-by-trial pain ratings positively correlated with activation in regions previously associated with pain processing including the anterior and posterior insula, cingulate, thalamus, and secondary somatosensory cortex (all $p < 0.05$ whole-brain FWE corrected; **Fig. 3** and **Supplementary Table 1**). A region of the right hippocampus also showed a correlation with pain ratings (20, -18, -14; $z = 3.55$, $p = 0.025$ SVC), although this univariate effect was likely driven by spread from activity in the adjacent ventral thalamus. We also examined the response to pain-predictive cues. We found activation for high versus low cues in a cluster extending from the left anterior orbitofrontal cortex (OFC) to more posterior medial OFC (-32, 50, -14; $z = 4.12$; $p < 0.001$ whole-brain FWE; https://neurovault.org/collections/6126/), but no significant

activation in pain-related regions or the hippocampus. No regions exhibited significantly greater activity for low versus high pain cues.

Next, we examined the results of several exploratory univariate analyses related to pain and memory. First, we looked for overall activation differences at test due to the incidental association of objects with high versus low heat pain, parallel to the multivariate results reported below. We found no evidence of pain value memory reactivation in the test phase in pain-related ROIs, the hippocampus, or across the whole brain (https://neurovault.org/collections/6126/). We also examined univariate correlates of subsequent successful pain association memory. During the incidental learning phase, we found no significant positive correlations with accuracy. However, we did find a region of the right ventral anterior insula that exhibited greater activity for incorrect versus correct later value memory (40, 24, -12; $z = 3.75$, $p = 0.045$ SVC; this effect was numerically stronger in the low pain condition ($p = 0.072$) versus high pain condition ($p = 0.553$)). In the test phase, we found no activity significantly correlated with value memory accuracy across high and low pain or separately within the memory contrasts for high and low pain-paired objects. However, for high pain objects, several clusters at the whole-brain level showed a negative effect for value memory accuracy including the left visual cortex (-10, -88, -2; $z = -5.21$, $p < 0.001$ whole-brain FWE) and bilateral lateral pre- and post-central gyrus (left -62, -2, 38; $z = -3.73$, $p = 0.026$; right 56, -6, 30; $z = -3.71$, $p = 0.028$ whole-brain FWE).

fMRI multivariate results.

Next, we addressed our primary question of whether distributed patterns of activity during object re-presentation were related to incidental value associations. We trained a multivoxel pattern analysis classifier on the activation evoked by actual pain in the incidental learning phase. To check whether the classifier trained on actual pain experience during the incidental learning phase was able to classify pain, we examined cross-validated results in regions of interest defined by the univarate correlation with pain ratings. We defined two masks, one including voxels in the anatomical anterior insula that exhibited a correlation with pain ratings (using an uncorrected $p < 0.0001$ threshold) and one including any brain voxels correlated with pain ratings ($p < 0.0001$ unc.). MVPA analyses revealed high rates of classification of high versus low pain in the anterior insula (84.5% AUC classification performance) and from the whole-brain pain region mask (89.1%); note that these results are provided for illustration only given that the definition of the ROI was itself based on pain responses. We also found that distributed activity patterns in the hippocampus discriminated high versus low pain (68.4%, $p < 0.0001$).

Building on the behavioral finding that single aversive experiences can support memory-based decisions, we then turned to our primary question, asking whether patterns of neural activity during high versus low heat pain exposure were reactivated when participants were re-presented with heat-paired object pictures during the memory retrieval phase. During the memory retrieval phase, participants were presented with an object for 5 s and then a heat rating prompt, where they responded with whether they remembered that the object picture had been paired with high versus low heat (**Fig. 1c**). Using the multivoxel pattern analysis classifier trained on the activation evoked by

actual pain in the incidental learning phase, we then tested the performance of this classifier on activation during the test phase when objects were presented in the absence of heat stimulation.

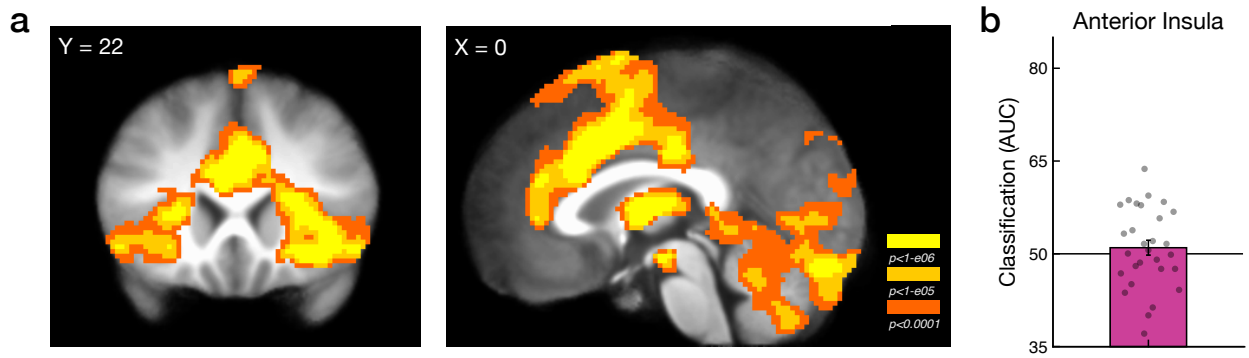

Figure 3. Heat pain response during the incidental learning phase and insula classification of reactivation. ***a***, Pain rating correlation during heat pain administration in the anterior insula and other regions (images thresholded at $p < 0.0001$, activation significant at $p < 0.05$ FWE; unthresholded map available at https://neurovault.org/images/306227/). ***b***, Classification of later re-presentation of high- versus low-pain objects in the memory test phase based on patterns of activation to pain in the anterior insula pain-responsive region of interest. Individual points represent individual participants; error bars represent SEM.

Upon re-exposure to objects incidentally paired with heat pain, we found no significant evidence for reactivation of pain-related patterns in traditional pain-processing regions, including the anterior insula (**Fig. 3a**). Classification performance in the anterior insula was not greater than chance (51.43 AUC [48.84 53.51]; $t_{(28)} = 1.07$, $p = 0.312$; TOST $p = 0.032$; **Fig. 3b**). Further, in a network of regions across the whole brain that exhibited a correlation with pain experience, classification performance at test was also not greater than chance (51.43 [48.70 54.17]; $t_{(28)} = 1.07$, $p = 0.293$; TOST p =

0.035). We predicted that somatic sensation (heat) would primarily be reflected in the insula, but we also examined activity in the amygdala as a control region. Amygdala patterns of activity did not show evidence of reactivation of pain associations (50.61 [47.52 53.71]; $t_{(28)} = 0.41$, $p = 0.688$; TOST $p = 0.008$).

In the hippocampus, however, we found evidence for significant reactivation of pain-related patterns (53.31 [50.30 56.32]; $t_{(28)} = 2.25$, $p = 0.032$; **Fig. 4a**). As value memory behavioral performance in the current experiment was relatively low, we also examined a subgroup of participants that approximated the stronger behavioral performance in our previous study using reward (Wimmer and Buechel, 2016). Within a subgroup of 21 participants who exhibited value memory performance above 50% (mean 59.5% performance), we found numerically stronger classification of pain-associated episodes in the hippocampus (55.07 [51.38 58.77]; $t_{(20)} = 2.87$, $p = 0.0096$).

We tested for but did not find a difference in classification accuracy in the hippocampus based on whether participants were correct in their pain memory response (correct high pain vs low: 54.56 [49.93 59.20]; $t_{(28)} = 2.018$, $p = 0.053$; incorrect high pain vs low: 52.31 [48.32 56.31]; $t_{(28)} = 1.186$, $p = 0.26$; comparison, $t_{(28)} = 0.75$, $p = 0.46$). If such a difference in classification due to correct behavioral responses had been found, it would have been difficult to distinguish actual value memory reactivation from an effect of behavioral response (high versus low pain) in the test phase that itself triggered an affective reaction. We also verified that the reactivation effect was not driven by a simple effect of pain memory response in the test phase: a classifier trained on pain and tested on test phase behavioral response (high vs low) did not show an effect (50.20 [46.95 53.44]; $t_{(28)} = 0.13$, $p = 0.90$; TOST $p = 0.004$).

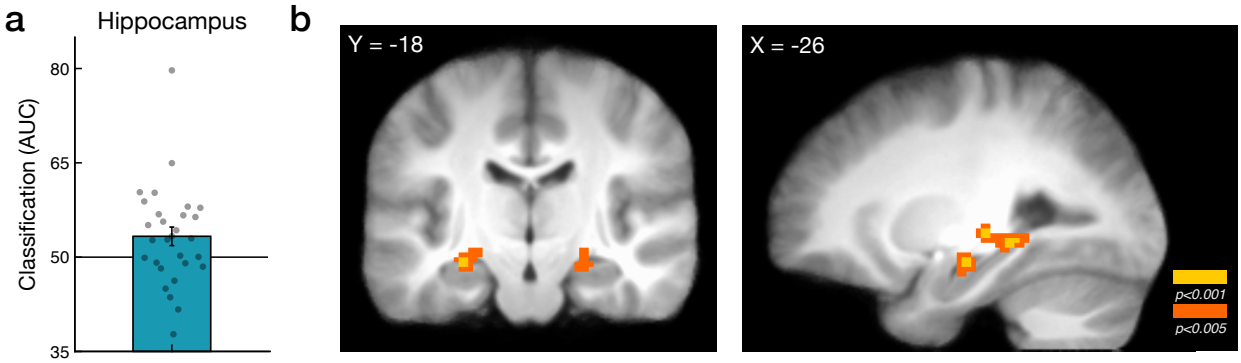

Figure 4. Heat pain reactivation in the hippocampus during re-presentation of objects. ***a***, Significant classification of later re-presentation of high versus low pain objects in the test phase based on incidental learning phase patterns of activation to pain in the hippocampus ($p = 0.032$). Individual points represent individual participants; error bars represent SEM. ***b***, Searchlight pattern classification of high pain versus low pain associated objects (images thresholded at $p < 0.005$ uncorrected for display, $p < 0.10$ SVC; unthresholded map available at https://neurovault.org/collections/6126/).

The above classification analyses demonstrated that distributed patterns of activity in the hippocampus but not pain-related regions showed significant classification of pain reactivation. To examine classification performance based on local information, we performed a searchlight analysis (Kriegeskorte et al., 2006). This analysis revealed no significant clusters across the whole brain, no effects in the insula or wider pain-related ROI mask, and no significant effects in the hippocampus. However, three clusters in the hippocampus showed non-significant positive effects (left posterior: -26, -36, -4; $z = 3.35$, $p = 0.088$ SVC; right middle: 24, -24, -12; $z = 3.34$, $p = 0.091$ SVC; left anterior: -26, -16, -14; $z = 3.71$, $p = 0.097$; **Fig. 4b**).

We then examined the critical question of whether pain-related reactivation was related to participants' pain value memory performance. We correlated the whole-brain

searchlight analysis results with individual performance in value memory retrieval. A region in the right anterior hippocampus showed a significant relationship between searchlight classification ability and behavioral performance (-28, -12, -26; z = 3.64, p = 0.038; **Fig. 5a**). This correlation was also evident in an ROI analysis in the anterior hippocampus (**Fig. 5b**). Post-hoc comparisons showed a numerically stronger correlation with behavior in the anterior versus posterior hippocampus (r = 0.470 versus r = -0.108; difference z = 2.36, p = 0.018).

These results demonstrate that for single aversive episodes, wide-spread multivariate patterns in the hippocampus during object re-presentation significantly resemble those evoked by actual pain during the original experience. More generally, this demonstrates that affect-related neural patterns are re-expressed at later recollection.

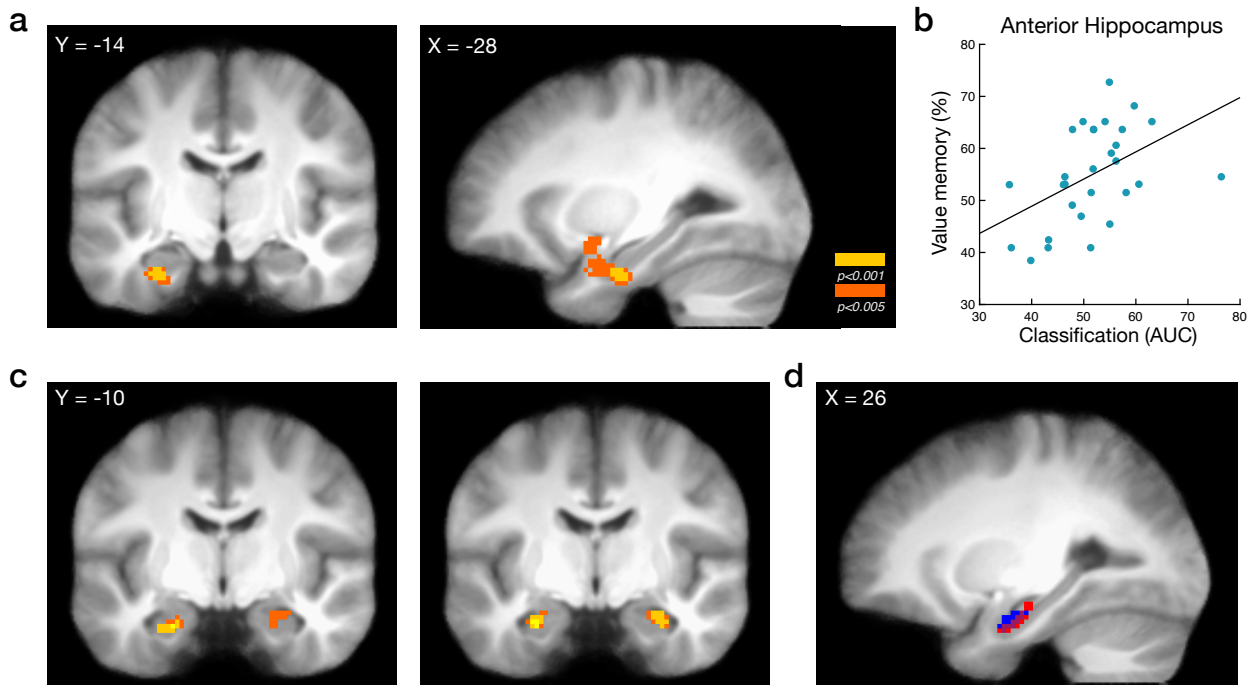

Figure 5. Hippocampal classification and the relationship between hippocampal connectivity and behavior. ***a***, In a searchlight analysis, the reactivation of pain patterns

in the left anterior hippocampus was positively associated with value memory behavioral performance across participants (full anterior MTL cluster selected for display; images thresholded at $p < 0.005$ for display, $p = 0.038$ SVC; https://neurovault.org/collections/6126/) ***b***, Illustration of the anterior hippocampus reactivation-performance relationship in an anatomical anterior hippocampal mask. Individual points represent individual participants. ***c***, Connectivity between the anterior hippocampus for correct versus incorrect value memory retrieval trials correlated with value memory performance during the incidental learning phase (left panel; left hippocampus $p = 0.022$ SVC; right hippocampus $p = 0.084$ SVC) and during the memory test phase (right panel; left hippocampus $p = 0.003$ SVC; right hippocampus $p = 0.035$ SVC). ***d***, Conjunction of connectivity relationship with individual differences in value memory performance in the incidental learning phase (red), memory test phase (blue) and overlap (purple). (Unthresholded maps available at https://neurovault.org/collections/6126/)

Connectivity and value memory performance.

Finally, we examined brain activity during the incidental learning phase and the memory test phase based on trial-by-trial successful value memory. We examined relationships between connectivity and performance, focusing on the hippocampus. In a PPI analysis of the incidental learning phase, we used the region of the left anterior hippocampus that correlated with behavioral performance as a seed (masking the effect by the hippocampus anatomical mask). The behavioral contrast was trial-by-trial correct versus incorrect later value memory performance. We found no overall differences in connectivity between the anterior hippocampus and any other hippocampal region or brain region. However, individual differences in behavioral performance were significantly correlated with the PPI results in a region of the left anterior hippocampus (-

22, -10, -24; z = 3.78, p = 0.022 SVC; **Fig. 5c**, left) and at a positive but non-significant level in the right anterior hippocampus (22, -12, -22; z = 3.34, p = 0.084 SVC).

We then conducted a similar connectivity analysis in the memory test phase, again using the left anterior hippocampus as a seed and correct versus incorrect value memory performance as the contrast. We found no overall connectivity differences. Again, however, we found an association between anterior hippocampal connectivity with the bilateral hippocampus and individual differences in value memory performance (-22, -10, -22; z = 4.34, p = 0.003 SVC; 30 -10 -20; z = 3.69, p = 0.035 SVC; **Fig. 5c**, right). The bilateral hippocampal clusters identified in the learning phase PPI overlapped with the clusters identified in the memory test phase (**Fig. 5d**). These results indicate that in individuals with better behavioral discrimination of high versus low heat pain episodes, intra-hippocampal connectivity is stronger during both successful encoding and successful retrieval.

Discussion

We found that memory for the values of single aversive experiences can guide later decision making and that memory was related to reactivation of neural patterns from the original experience. In our experiments, we first presented incidental, trial-unique object pictures during high or low pain episodes. Then we administered a surprise test assessing source memory for incidental value associations for these objects. Pain-related patterns of activity in the hippocampus – but not in traditional pain-associated regions such as the secondary somatosensory cortex and the insula – were reinstated upon re-exposure to objects. Importantly, individual differences in the strength of reactivation positively related to value memory behavioral performance.

As the majority of research on value-based learning has studied learning with many repetitions of stimulus-outcome associations, it has remained largely unknown whether and how single episodes of negative or positive experience contribute to behavior. Our results suggest that after an aversive experience, a reminder of the event can reactivate neural patterns in the hippocampus to promote avoidance.

The hippocampus is critical for forming memory for episodes, and more generally for forming relational associations between elements of experience (Eichenbaum and Cohen, 2001; Davachi, 2006). Our results demonstrate that the hippocampus is also important for integrating memory for items with representations of value. The potential role of the hippocampus in value learning aligns with research demonstrating that the hippocampus is important for using relational associations to automatically infer reward value (Wimmer and Shohamy, 2012) and to imagine the value of novel experiences

(Barron et al., 2013). While these and other studies in humans have primarily shown a role for the hippocampus in reward domains (Lebreton et al., 2009; Peters and Buchel, 2010; Foerde and Shohamy, 2011; Foerde et al., 2013; Gluth et al., 2015; Wimmer et al., 2018), our results suggest that the hippocampus may also play a role in associating episodic experiences with negative value. Our findings also accord with the role of the hippocampus in fast learning during contextual fear conditioning in rodents (Phillips and LeDoux, 1994).

We found that the degree of reactivation in the anterior hippocampus was related to better performance. The anterior hippocampus has been associated with anxiety (Adhikari et al., 2010; Fanselow and Dong, 2010; Bach et al., 2014) as well as memory integration and generalization (Poppenk et al., 2013; Schlichting et al., 2015; Brunec et al., 2018). Given that episodes of experience never repeat exactly, successful use of previous experiences to guide future decisions is likely to involve significant generalization, which may be facilitated by the anterior hippocampus.

Instead of choices being driven by gradually-acquired values, recent research has proposed that choices may be guided by sampling representations of previous experiences stored in memory (Hertwig et al., 2004; Lengyel and Dayan, 2005; Weber and Johnson, 2006; Biele et al., 2009; Gluth et al., 2015; Shadlen and Shohamy, 2016). Whether and how agents form successful memory for the value of episodes is a critical component of memory-based models of decision making. Several previous studies provided initial evidence that agents are capable of learning and using the value or “remembered utility” of previous experiences such as freezing cold water or pleasant vacations (Kahneman et al., 1993; Redelmeier and Kahneman, 1996; Fredrickson,

2000; Wirtz et al., 2003). Similarly, animal research has shown robust behavioral changes from single-trial contextual fear conditioning (e.g. Blanchard et al., 1968), and taste aversion learning also only requires a single experience (Welzl et al., 2001).

Memory sampling models of decision making have been supported by recent experimental evidence in humans in the reward domain (Gluth et al., 2015; Murty et al., 2016; Wimmer and Buechel, 2016; Bornstein et al., 2017; Bornstein and Norman, 2017; Enkavi et al., 2017; Bakkour et al., 2019), which our results extend to aversive valuations. Notably, only the current study and our recent study in the reward domain (Wimmer and Buechel, 2016) examined the influence of episodes in the absence of explicit – and often extensive – instructions to participants to remember the unique episodes. We prioritized the use of incidental encoding to increase ecological validity, with the goal of understanding neural mechanisms that are generalizable to non-laboratory environments.

From a learning perspective, episodic or single-shot learning of value is not easily accounted for by reinforcement learning models (Sutton and Barto, 1998). Rapid learning can be accomplished in reinforcement learning models with a very high learning rate for positive and negative events, but with repetition, this would lead to the complete forgetting of all but the most recent experiences. More realistic episodic-like learning can be accomplished in these models by dynamically decreasing the learning rate based on the number of exposures to a similar situation (e.g. Schiller et al., 2008). A potential convergence between the predictions of reinforcement learning models with a decreasing learning rate and memory sampling accounts is that memory models can

naturally implement an exponentially decreasing learning rate: as related episodes accumulate, each new experience will have a weaker effect on choice.

In a previous study using monetary reward instead of pain, we did not find evidence for reactivation of value-related patterns from single episodes in the hippocampus (Wimmer and Buechel, 2016). In addition to the higher salience for pain compared to monetary reward, one difference between these experiments is that the current study utilized a relatively slow trial duration and longer separation of emotional events, potentially leading to better separation of individual episodes and greater hippocampal involvement in memory encoding (Ezzyat and Davachi, 2011). Also in contrast to our previous study, here we did not find evidence of reactivation of affect-related patterns outside of the hippocampus. Specifically, we found no evidence for the reactivation of pain-related patterns or even univariate activation at test in traditional pain-related regions such as the insula. These results contrast with our previous findings, where regions responsive to the positive value of monetary reward including the striatum exhibited reactivation (Wimmer and Buechel, 2016).

Previous studies on memory for negative events (where otherwise neutral stimuli were initially paired with negative content) have reported univariate activation of the same regions during encoding and retrieval or attributed activation at retrieval to emotion using reverse inference (Maratos et al., 2001; Smith et al., 2004; Erk et al., 2005; Smith et al., 2006; Albanese et al., 2007; Tsukiura and Cabeza, 2008; Kuhl et al., 2010; Fairhurst et al., 2012; Forkmann et al., 2015; Bowen and Kensinger, 2017). However, no studies have shown that negative emotion-related neural patterns

expressed within the same participants during encoding are re-activated at retrieval, or whether reactivation is related to memory for the aversive associations.

We did not identify any regional overlap between pain experience and object re-exposure. One potential reason for this null finding could be that in the current design, pain was largely predicted by a preceding cue, resulting in minimal surprise (or prediction error) when heat was administered in conjunction with the incidental object stimuli. This decoupling of the prediction error learning signal from heat onset may have contributed to the numerically weaker behavioral memory for value in the current study as compared to our previous study using monetary reward (Wimmer and Buechel, 2016). It is possible that in a design in which aversive stimuli are more unexpected, pain-responsive regions may also show reactivation at test. The question of whether extra-hippocampal regions show pattern reactivation for negative experiences will be important to explore in future studies.

Conclusion

Our results demonstrate a mechanism by which memory can support adaptive behavior: patterns of value-related neural activity in the hippocampus from original experiences can be reactivated to guide later decision making. While much is known about how repeated experiences can build simple associations between stimuli and rewards, the encoding of single episodes has remained relatively unexplored. From everyday experience, it is clear that decisions can be based on single episodes. Given the considerable capacity of episodic memory in humans, it represents a rich cache of information that can support future decision making. Remembering the value of single

episodes may be particularly important given that the circumstances associated with strongly reinforcing events – such as potentially life threatening experiences – are unlikely to be repeated, thus making gradual learning via traditional reinforcement learning mechanisms difficult. Translationally, understanding overactive or underactive reactivation of negative experiences may inform the treatment of post-traumatic stress disorder, depression, and other mood disorders (Hamilton and Gotlib, 2008; Brewin et al., 2010; Shin and Liberzon, 2010).

Author Contributions: G.E. Wimmer and C. Büchel designed the experiment; GEW collected and analyzed data; GEW and CB wrote and revised the manuscript.

Acknowledgments: This work was supported by ERC-2010-AdG_20100407 and DFG SFB TRR 58 and SFB 936. We thank Lea Kampermann and Lidia Meißner for assistance with data collection and translation.

References

Adhikari, A., Topiwala, M.A., and Gordon, J.A. (2010). Synchronized activity between the ventral hippocampus and the medial prefrontal cortex during anxiety. *Neuron 65*, 257-269.

Albanese, M.C., Duerden, E.G., Rainville, P., and Duncan, G.H. (2007). Memory traces of pain in human cortex. *J Neurosci 27*, 4612-4620.

Allefeld, C., Gorgen, K., and Haynes, J.D. (2016). Valid population inference for information-based imaging: From the second-level t-test to prevalence inference. *Neuroimage 141*, 378-392.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., and Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain 9*, 463-484.

Atlas, L.Y., Bolger, N., Lindquist, M.A., and Wager, T.D. (2010). Brain mediators of predictive cue effects on perceived pain. *J Neurosci 30*, 12964-12977.

Bach, D.R., Guitart-Masip, M., Packard, P.A., Miro, J., Falip, M., Fuentemilla, L., and Dolan, R.J. (2014). Human hippocampus arbitrates approach-avoidance conflict. *Current biology : CB 24*, 541-547.

Bakkour, A., Palombo, D.J., Zylberberg, A., Kang, Y.H., Reid, A., Verfaellie, M., Shadlen, M.N., and Shohamy, D. (2019). The hippocampus supports deliberation during value based decisions. *Elife 8*.

Barron, H.C., Dolan, R.J., and Behrens, T.E. (2013). Online evaluation of novel choices by simultaneous representation of multiple memories. *Nat Neurosci 16*, 1492-1498.

Biele, G., Erev, I., and Ert, E. (2009). Learning, risk attitudes and hot stoves in restless bandit problems. *Journal of mathematical psychology 53*, 155-167.

Blanchard, R.J., Dielman, T.E., and Blanchard, D.C. (1968). Prolonged aftereffects of a single foot shock. *Psychon Sci 10*, 327-328.

Bornstein, A.M., Khaw, M.W., Shohamy, D., and Daw, N.D. (2017). Reminders of past choices bias decisions for reward in humans. *Nat Commun 8*, 15958.

Bornstein, A.M., and Norman, K.A. (2017). Reinstated episodic context guides sampling-based decisions for reward. *Nat Neurosci 20*, 997-1003.

Bowen, H.J., and Kensinger, E.A. (2017). Recapitulation of emotional source context during memory retrieval. *Cortex 91*, 142-156.

Brainard, D.H. (1997). The psychophysics toolbox. *Spat Vis 10*, 433-436.

Braun, E.K., Wimmer, G.E., and Shohamy, D. (2018). Retroactive and graded prioritization of memory by reward. *Nat Commun 9*, 4886.

Brewin, C.R., Gregory, J.D., Lipton, M., and Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychol Rev 117*, 210-232.

Brooks, J.C., Nurmikko, T.J., Bimson, W.E., Singh, K.D., and Roberts, N. (2002). Fmri of thermal pain: Effects of stimulus laterality and attention. *Neuroimage 15*, 293-301.

Brunec, I.K., Bellana, B., Ozubko, J.D., Man, V., Robin, J., Liu, Z.X., Grady, C., Rosenbaum, R.S., Winocur, G., Barense, M.D., and Moscovitch, M. (2018). Multiple scales of representation along the hippocampal anteroposterior axis in humans. *Current biology : CB 28*, 2129-2135 e2126.

Chang, C.C., and Lin, C. (2011). Libsvm: A library for support vector machines. *ACM Trans. Intell. Syst. Technol. 2*, 1-27.

Cox, R.W. (1996). Afni: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res 29*, 162-173.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr Opin Neurobiol 16*, 693-700.

Daw, N.D., and Doya, K. (2006). The computational neurobiology of learning and reward. *Curr Opin Neurobiol 16*, 199-204.

Duncan, K.D., and Shohamy, D. (2016). Memory states influence value-based decisions. *J Exp Psychol Gen 145*, 1420-1426.

Eichenbaum, H., and Cohen, N.J. (2001). From conditioning to conscious recollection: Memory systems of the brain (New York: Oxford University Press).

Enkavi, A.Z., Weber, B., Zweyer, I., Wagner, J., Elger, C.E., Weber, E.U., and Johnson, E.J. (2017). Evidence for hippocampal dependence of value-based decisions. *Sci Rep 7*, 17738.

Erk, S., Martin, S., and Walter, H. (2005). Emotional context during encoding of neutral items modulates brain activation not only during encoding but also during recognition. *Neuroimage 26*, 829-838.

Ezzyat, Y., and Davachi, L. (2011). What constitutes an episode in episodic memory? *Psychol Sci 22*, 243-252.

Fairhurst, M., Fairhurst, K., Berna, C., and Tracey, I. (2012). An fmri study exploring the overlap and differences between neural representations of physical and recalled pain. *PLoS One 7*, e48711.

Fanselow, M.S., and Dong, H.W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron 65*, 7-19.

Fazeli, S., and Buchel, C. (2018). Pain-related expectation and prediction error signals in the anterior insula are not related to aversiveness. *J Neurosci 38*, 6461-6474.

Foerde, K., Race, E., Verfaellie, M., and Shohamy, D. (2013). A role for the medial temporal lobe in feedback-driven learning: Evidence from amnesia. *J Neurosci 33*, 5698-5704.

Foerde, K., and Shohamy, D. (2011). Feedback timing modulates brain systems for learning in humans. *J Neurosci 31*, 13157-13167.

Forkmann, K., Wiech, K., Ritter, C., Sommer, T., Rose, M., and Bingel, U. (2013). Pain-specific modulation of hippocampal activity and functional connectivity during visual encoding. *J Neurosci 33*, 2571-2581.

Forkmann, K., Wiech, K., Sommer, T., and Bingel, U. (2015). Reinstatement of pain-related brain activation during the recognition of neutral images previously paired with nociceptive stimuli. *Pain*.

Fredrickson, B.L. (2000). Extracting meaning from past affective experiences: The importance of peaks, ends, and specific emotions. *Cognition Emotion 14*, 577-606.

Friston, K.J., Worsley, K.J., Frackowiak, S.J., Mazziotta, J.C., and Evans, A.C. (1993). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping 1*, 210-220.

Geuter, S., Boll, S., Eippert, F., and Buchel, C. (2017). Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. *Elife 6*.

Gluth, S., Sommer, T., Rieskamp, J., and Buchel, C. (2015). Effective connectivity between hippocampus and ventromedial prefrontal cortex controls preferential choices from memory. *Neuron 86*, 1078-1090.

Hamilton, J.P., and Gotlib, I.H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biol Psychiatry 63*, 1155-1162.

Hebart, M.N., Gorgen, K., and Haynes, J.D. (2014). The decoding toolbox (tdt): A versatile software package for multivariate analyses of functional imaging data. *Frontiers in neuroinformatics 8*, 88.

Hertwig, R., Barron, G., Weber, E.U., and Erev, I. (2004). Decisions from experience and the effect of rare events in risky choice. *Psychol Sci 15*, 534-539.

Horing, B., Sprenger, C., and Buchel, C. (2019). The parietal operculum preferentially encodes heat pain and not salience. *PLoS Biol 17*, e3000205.

Kahneman, D., Fredrickson, B.L., Schreiber, C.A., and Redelmeier, D.A. (1993). When more pain is preferred to less: Adding a better end. *Psychol Sci 4*, 401-405.

Kriegeskorte, N., Goebel, R., and Bandettini, P. (2006). Information-based functional brain mapping. *Proc Natl Acad Sci U S A 103*, 3863-3868.

Kuhl, B.A., Shah, A.T., DuBrow, S., and Wagner, A.D. (2010). Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. *Nat Neurosci 13*, 501-506.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., and Eickhoff, S.B. (2010). A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. *Brain structure & function 214*, 519-534.

Lakens, D. (2017). Equivalence tests: A practical primer for t tests, correlations, and meta-analyses. *Soc Psychol Personal Sci 8*, 355-362.

Lebreton, M., Jorge, S., Michel, V., Thirion, B., and Pessiglione, M. (2009). An automatic valuation system in the human brain: Evidence from functional neuroimaging. *Neuron 64*, 431-439.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci 23*, 155-184.

Lengyel, M., and Dayan, P. (2005). Hippocampal contributions to control: The third way. In Advances in neural information processing systems 20, J. Platt, D. Koller, Y. Singer, and S. Roweis, eds. (Cambridge: MIT Press), pp. 889-896.

Maratos, E.J., Dolan, R.J., Morris, J.S., Henson, R.N., and Rugg, M.D. (2001). Neural activity associated with episodic memory for emotional context. *Neuropsychologia 39*, 910-920.

Mazaika, P., Hoeft, F., Glover, G.H., and Reiss, A. (2009). Methods and software for fmri analysis for clinical subjects. In Hum Brain Mapp.

Murty, V.P., FeldmanHall, O., Hunter, L.E., Phelps, E.A., and Davachi, L. (2016). Episodic memories predict adaptive value-based decision-making. *J Exp Psychol Gen 145*, 548-558.

Peters, J., and Buchel, C. (2010). Episodic future thinking reduces reward delay discounting through an enhancement of prefrontal-mediotemporal interactions. *Neuron 66*, 138-148.

Phillips, R.G., and LeDoux, J.E. (1994). Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. *Learn Mem 1*, 34-44.

Poppenk, J., Evensmoen, H.R., Moscovitch, M., and Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends Cogn Sci 17*, 230-240.

Rangel, A., Camerer, C., and Montague, P.R. (2008). A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci 9*, 545-556.

Redelmeier, D.A., and Kahneman, D. (1996). Patients' memories of painful medical treatments: Real-time and retrospective evaluations of two minimally invasive procedures. *Pain 66*, 3-8.

Roy, M., Shohamy, D., Daw, N., Jepma, M., Wimmer, G.E., and Wager, T.D. (2014). Representation of aversive prediction errors in the human periaqueductal gray. *Nat Neurosci 17*, 1607-1612.

Schiller, D., Levy, I., Niv, Y., LeDoux, J.E., and Phelps, E.A. (2008). From fear to safety and back: Reversal of fear in the human brain. *J Neurosci 28*, 11517-11525.

Schlichting, M.L., Mumford, J.A., and Preston, A.R. (2015). Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. *Nat Commun 6*, 8151.

Schuirmann, D.J. (1987). A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm 15*, 657-680.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annu Rev Psychol 57*, 87-115.

Schultz, W., Dayan, P., and Montague, P.R. (1997). A neural substrate of prediction and reward. *Science 275*, 1593-1599.

Schwarze, U., Bingel, U., and Sommer, T. (2012). Event-related nociceptive arousal enhances memory consolidation for neutral scenes. *J Neurosci 32*, 1481-1487.

Seymour, B., and al., e. (2004). Temporal difference models describe higher-order learning in humans. *Nature 429*, 664-667.

Seymour, B., O'Doherty, J.P., Dayan, P., Koltzenburg, M., Jones, A.K., Dolan, R.J., Friston, K.J., and Frackowiak, R.S. (2004). Temporal difference models describe higher-order learning in humans. *Nature 429*, 664-667.

Shadlen, M.N., and Shohamy, D. (2016). Decision making and sequential sampling from memory. *Neuron 90*, 927-939.

Shin, L.M., and Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology 35*, 169-191.

Smith, A.P., Henson, R.N., Dolan, R.J., and Rugg, M.D. (2004). Fmri correlates of the episodic retrieval of emotional contexts. *Neuroimage 22*, 868-878.

Smith, A.P., Stephan, K.E., Rugg, M.D., and Dolan, R.J. (2006). Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron 49*, 631-638.

Sutton, R.S., and Barto, A.G. (1998). Reinforcement learning: An introduction (Cambridge: MIT Press).

Tracey, I., and Mantyh, P.W. (2007). The cerebral signature for pain perception and its modulation. *Neuron 55*, 377-391.

Tsukiura, T., and Cabeza, R. (2008). Orbitofrontal and hippocampal contributions to memory for face-name associations: The rewarding power of a smile. *Neuropsychologia 46*, 2310-2319.

Weber, E.U., and Johnson, E.J. (2006). Constructing preferences from memory. In The construction of preference, P. Slovic, and S. Lichtenstein, eds. (New York: Cambridge University Press).

Welzl, H., D'Adamo, P., and Lipp, H.P. (2001). Conditioned taste aversion as a learning and memory paradigm. *Behav Brain Res 125*, 205-213.

Wiech, K., Jbabdi, S., Lin, C.S., Andersson, J., and Tracey, I. (2014). Differential structural and resting state connectivity between insular subdivisions and other pain-related brain regions. *Pain 155*, 2047-2055.

Wimmer, G.E., and Buechel, C. (2015). Pain to remember: A single incidental association with pain leads to greater memory for neutral items one year later. *bioRxiv*.

Wimmer, G.E., and Buechel, C. (2016). Reactivation of reward-related patterns from single past episodes supports memory-based decision making. *J Neurosci 36*, 2868-2880.

Wimmer, G.E., Li, J.K., Gorgolewski, K.J., and Poldrack, R.A. (2018). Reward learning over weeks versus minutes increases the neural representation of value in the human brain. *J Neurosci 38*, 7649-7666.

Wimmer, G.E., and Shohamy, D. (2012). Preference by association: How memory mechanisms in the hippocampus bias decisions. *Science 338*, 270-273.

Wirtz, D., Kruger, J., Napa Scollon, C., and Diener, E. (2003). What to do on spring break? The role of predicted, on-line, and remembered experience in future choice. *Psychol Sci 14*, 520-524.

Supplementary Table 1. Neural correlates of pain ratings during pain administration in the incidental learning phase, relating to Fig. 3a. All p-values are whole-brain FWE-corrected.

Region	Right	Anterior	Superior	Z-score	Voxels	p-value
Right anterior insula	32	14	8	6.36	1222	< .001
Right inferior frontal gyrus / precentral gyrus	48	4	8	5.99		
	52	10	2	5.86		
Cingulate	0	12	34	6.03	537	< .001
	2	22	30	5.85		
	-4	22	22	5.22		
Left anterior insula	-36	10	10	5.9	757	< .001
Left inferior frontal gyrus	-50	18	-8	5.44		
	-56	6	0	5.43		
Left postcentral gyrus / secondary somatosensory cortex	-60	-24	26	5.58	120	< .001
Left cerebellum	-44	-50	-42	5.42	106	< .001
	-44	-60	-32	4.97		
Thalamus	-2	-6	4	5.38	156	< .001
	0	-14	8	5.19		
Left thalamus	-14	-6	10	4.76		
Right subthalamic nucleus	12	-18	-6	5.33	100	< .001
Right midbrain	12	-10	-10	5.33		
Left cerebellum	-24	-50	-46	5.27	72	< .001
Right postcentral gyrus / secondary somatosensory cortex	52	-28	24	5.2	78	< .001
	60	-26	18	4.88		
Cingulate	0	-22	34	5.15	25	.004
Right middle frontal gyrus	40	44	24	5.03	47	< .001
	36	38	20	4.97		
	38	52	18	4.74		
Left middle frontal gyrus	-30	48	20	5.03	54	< .001
	-32	40	24	4.86		
Left cerebellum	-26	-64	-22	5	52	< .001
	-24	-74	-20	4.84		
Right thalamus	14	-14	6	4.91	48	< .001
	12	-2	10	4.9		