Research Paper

PAIN®

The medial temporal lobe in nociception: a meta-analytic and functional connectivity study

Lizbeth J. Ayoub[a,b,c], Alexander Barnett[d], Aziliz Leboucher[a], Mitchell Golosky[a], Mary Pat McAndrews[b,e], David A. Seminowicz[f,g], Massieh Moayedi[a,c,h,*]

Abstract

Recent neuroimaging studies implicate the medial temporal lobe (MTL) in nociception and pain modulation. Here, we aim to identify which subregions of the MTL are involved in human pain and to test its connectivity in a cohort of chronic low-back pain patients (CBP). We conducted 2 coordinate-based meta-analyses to determine which regions within the MTL showed consistent spatial patterns of functional activation (1) in response to experimental pain in healthy participants and (2) in chronic pain compared with healthy participants. We followed PRISMA guidelines and performed activation likelihood estimate (ALE) meta-analyses. The first meta-analysis revealed consistent activation in the right anterior hippocampus (right antHC), parahippocampal gyrus, and amygdala. The second meta-analysis revealed consistently less activation in patients' right antHC, compared with healthy participants. We then conducted a seed-to-voxel resting state functional connectivity of the right antHC seed with the rest of the brain in 77 CBP and 79 age-matched healthy participants. We found that CBP had significantly weaker antHC functional connectivity to the medial prefrontal cortex compared with healthy participants. Taken together, these data indicate that the antHC has abnormally lower activity in chronic pain and reduced connectivity to the medial prefrontal cortex in CBP. Future studies should investigate the specific role of the antHC in the development and management of chronic pain.

Keywords: Pain, Medial temporal lobe, Hippocampus, MRI, FMRI, Functional connectivity, Meta-analysis, Activation likelihood estimation

1. Introduction

The medial temporal lobe (MTL) is a region canonically responsible for memory,[113] but several pain neuroimaging studies have reported activation within this region. An intriguing intersection of pain and memory comes from the case of patient H.M. who had a high tolerance for heat pain, in addition to global amnesia, after bilateral MTL resection for epilepsy.[49] The MTL region consists of the hippocampus (HC) and subiculum, parahippocampal gyrus (PHG), entorhinal and perirhinal cortices, and amygdala.[127] Activation of various MTL regions is observed in response to nociceptive stimuli of various modalities[64,78,82,110,121,143] and in different tissue types—cutaneous, muscular, and visceral.[22,59,134] In particular, several studies have associated MTL activation during experimental pain to emotionally driven modulatory processes.[11,111,116,118] However, there is little specificity or congruence across studies regarding which MTL subregions are involved in pain, and no specific role has been ascribed to MTL regions in nociceptive processing. Of importance, there has yet to be a formal investigation of the spatial consistency of MTL activations in healthy participants during experimental pain.

In addition to studies in healthy participants, extant evidence indicates aberrant MTL activity in various chronic pain conditions.[54,101,105] Recent evidence in patients with back pain suggests that the transition from subacute to chronic pain may be mediated by MTL structures.[131] Specifically, reduced MTL resting state functional connectivity (rsFC) to other cortical regions[104] and smaller MTL volume[132] predict this transition. However, as with experimental pain, it is not clear which regions within the MTL are implicated in chronic pain and what their role may be.

The overall aim of this study was to determine regions of the MTL consistently involved in nociceptive processing and pain modulation in health and disease. First, we sought to determine which regions of the MTL show consistent spatial activation in response to (1) experimental pain in healthy participants compared with baseline control conditions and (2) chronic pain patients compared with healthy participants. To that end, we performed 2 coordinate-based meta-analyses of functional magnetic resonance imaging (fMRI) studies of pain that indicated MTL engagement. We expected our first meta-analysis to show consistent MTL activation in the HC and PHG across studies

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Faculty of Dentistry, University of Toronto, Toronto, ON, Canada, [b] Systems Neuroscience Division, Krembil Research Institute, University Health Network, Toronto, ON, Canada, [c] University of Toronto Centre for the Study of Pain, University of Toronto, Toronto, ON, Canada, [d] Center for Neuroscience, University of California at Davis, Davis, CA, United States, [e] Department of Psychology, University of Toronto, Toronto, ON, Canada, [f] Department of Neural and Pain Sciences, School of Dentistry, University of Maryland Baltimore, Baltimore, MD, United States, [g] Center to Advance Chronic Pain Research, University of Maryland Baltimore, Baltimore, MD, United States, [h] Department of Dentistry, Mount Sinai Hospital, Toronto, ON, Canada

**Corresponding author. Address: Faculty of Dentistry, University of Toronto, Room 543, 124 Edward St, Toronto, ON M5G 1G6, Canada. Tel.: 416-864-8235. E-mail address: m.moayedi@dentistry.utoronto.ca (M. Moayedi).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 160 (2019) 1245–1260

http://dx.doi.org/10.1097/j.pain.0000000000001519

reporting MTL activity. We expected our second meta-analysis to show consistent MTL activation in the HC across chronic pain neuroimaging studies. These analyses are the first formalized investigation of MTL functioning in nociceptive processing.

To generate hypotheses about the mechanistic role of the HC in nociceptive processing from existing data, it is important to explore its network interactions. Thus, we aimed to determine the connectivity of those regions elucidated by our meta-analyses using data from 4 distinct cohorts of chronic low-back pain patients (CBP). Given previous observations of abnormal MTL engagement in CBP, we predicted that CBP would show abnormal rsFC to regions involved in processing the affective dimension of pain, ie, the anterior insula, midcingulate cortex, amygdala, and medial prefrontal cortex (mPFC).[24,30,32,108,131]

2. Methods

Our activation likelihood estimation (ALE) meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 guidelines and checklist.[100]

2.1. Article selection criteria

Our article selection followed the PRISMA flow diagrams[99] as shown in **Figure 1**. Studies were excluded based on any of the following 9 criteria: (1) animal studies; (2) did not use standardized stereotactic (Montreal Neurological Institute [MNI] or Talairach) brain coordinates; (3) case reports; (4) diagnostic or surgical MRI; (5) structural imaging; (6) studies of acute medical pain conditions; (7) fMRI studies without a baseline control (for experimental pain studies) or control group (for chronic pain studies); (8) studies not written in the English language; and (9) studies that are not peer-reviewed. As such, we selected human neuroimaging studies with whole-brain and region-of-interest analyses, reporting stereotactic brain coordinates. Three investigators (L.J.A., M.G., and M.M.) independently performed the database searches and followed PRISMA guidelines by screening and determining study eligibility. In addition, quality assessment for each article selected was conducted by using a modified version of Downs and Black's quality assessment score.[18,31] We accounted for statistical significance of the results by qualitatively assigning a maximum score of 2 for articles, which applied multiple comparison corrections to analyses (the Quality Assessment Scoresheet is available in the Supplementary content, available at http://links.lww.com/PAIN/A756).

2.2. Database searches

2.2.1. Traditional databases

We conducted a systematic search through the Pubmed, Web of Science, Embase, and Medline databases on November 9, 2017. A keyword search of the following terms was conducted on all databases (*medial temporal lobe OR hippocamp* OR parahippocamp**) *AND pain AND* ((*FMRI OR functional magnetic resonance imaging OR functional MRI*) *OR* (*BOLD OR blood oxygen level dependent*) *OR* (*PET OR positron emission tomography*) *OR* (*ASL OR arterial spin labelling*)).

2.2.2. Neurosynth

We also performed a search of the Neurosynth database (http://www.neurosynth.org)[141] on November 9, 2017, as this provides the ability to cross-search keywords ("pain," "painful," and "chronic pain") with brain coordinates. This increased the sensitivity of the meta-analysis as Neurosynth extracts coordinates from the tables in a catalogued study; therefore, even if the HC was not highlighted as a finding in the title, abstract, or keywords of a study, we would still be able to identify the study. The MNI coordinates used for the HC search were derived from our previous study of hippocampal parcellation[3] as follows: the right anterior hippocampus (antHC) is (24, 13, −21); the left antHC is (−22, −12, −20); the right posterior HC is (29, −26, −9); and left posterior HC is (−27, 25, −12). We used a liberal search sphere (radius = 15 mm) to maximize the number of studies identified and to include adjacent structures, such as the PHG and amygdala (see Supplementary Fig. 1, available at http://links.lww.com/PAIN/A756). The same article selection criteria set out for the traditional databases were applied, with the added constraint that the HC was listed as a significant finding in at least one contrast.

2.3. Coordinate-based meta-analysis

We performed a coordinate-based meta-analysis using the ALE algorithm to identify consistent regions of brain activity within the MTL in healthy participants and chronic pain patients. Brain coordinates (foci) were computed using GingerALE (v3.0) to generate probabilistic maps of activation[70] (http://brainmap.org/ale).

2.3.1. Activation likelihood estimation mask

We restricted the permutation space for the null distribution of our ALE meta-analysis to the MTL region. To do so, we constructed an MTL mask on the standard MNI152 brain in FSLeyes v.0.22.6. The mask comprised regions selected from the Jülich Histological Atlas, including the centromedial, laterobasal and superficial amygdalae, hippocampus cornu ammonis, entorhinal cortex, dentate gyrus, hippocampal amygdaloid transition, and subiculum. The final MTL mask includes the amygdala, hippocampus, and PHG (see Supplementary Fig. 2, available at http://links.lww.com/PAIN/A756).

2.3.2. Data organization

We conducted 4 separate meta-analyses as part of 2 investigations: (1) experimental pain in healthy participants and (2) chronic pain vs healthy participants. First, foci were manually extracted from selected articles and subsequently categorized into 4 separate datasheets according to the following contrasts: (1) greater MTL activation in healthy participants during experimental pain than in control conditions, such as warm, innocuous touch or baseline conditions (*experimental pain > control conditions*); (2) greater MTL activation during control conditions than painful conditions in healthy participants (*experimental pain < control conditions*); (3) greater MTL activation in chronic pain patients than in healthy participants (*chronic pain patients > healthy participants*); and (4) Greater MTL activation in healthy participants than in chronic pain patients (*chronic pain patients < healthy participants*). Foci derived from significant and nonsignificant statistical thresholds of contrasts reporting MTL activity were extracted from all studies. Three investigators (L.J.A., M.M., and M.G.) verified manual extraction of the foci, before running each meta-analysis.

2.3.3. Activation likelihood estimation meta-analysis

In preparation for the ALE meta-analysis, all foci were standardized into MNI space. Foci reported using Talairach coordinates were

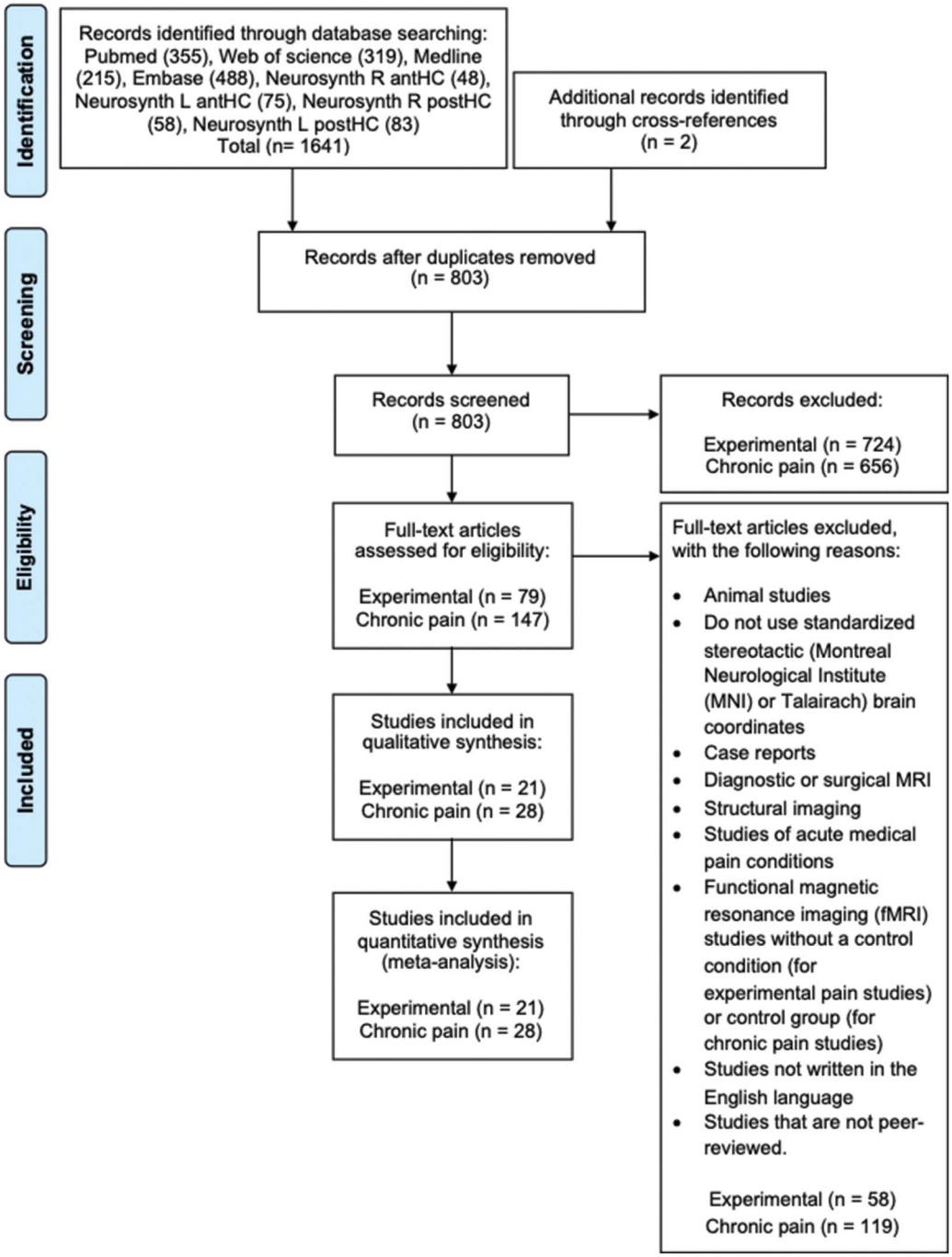

Figure 1. PRISMA flow diagram representing the process for article selection.

converted with "Talairach to MNI (FSL)".[17] For each set of foci per experiment, the number of participants was added for weighting purposes. Once finalized, each datasheet was entered and computed separately into the software using a single data set analysis.[35,36] We used the Turkeltaub algorithm to estimate the probability of activation at each voxel in the brain by reducing both within-experiment (interparticipants) and within-group (interlaboratory) variables.[130] The algorithm attributes an ALE score, a voxel-based value for each focus, to create a modeled activation map,[36] calculated using the maximum value with the "random effects" selection.[35] Furthermore, each focus is blurred with a Gaussian distribution, weighted by sample size, to minimize spatial uncertainty.[71] Finally, the cluster-level inference algorithm described by Eickhoff et al.[35] was used to compute the final thresholded ALE *P* value map with a permutation-based cluster correction $P < 0.05$ (cluster-forming height threshold of $P < 0.005$ with 1000 permutations), which uses a Monte Carlo simulation approach. The resulting maps were visualized and labelled in MNI space using FSLeyes v.0.22.6. Slice images were visualized and labelled in MNI space using "ch2bet" on MRIcron v2016.

2.4. Functional connectivity

Given that we found consistent pain-related activity in our meta-analyses in the right antHC region, and that rsFC of the antHC region has been previously shown to be a predictor for the

transition from subacute to chronic back pain,[104] we conducted a whole-brain seed-to-voxel rsFC study of the right antHC region to investigate whether there were connectional differences between healthy participants and CBP. Furthermore, since we have shown that the right antHC region is activated in response to experimental pain in healthy participants and has abnormal activity in chronic pain, we sought to determine whether abnormal right antHC connectivity in CBP was related to pain characteristics, including pain duration and pain intensity.

2.4.1. Participants

Four resting state fMRI data sets comprising a total of 156 participants (CBP [n = 77] and age-matched healthy participants [n = 79]) were included in the analysis. A summary of each data set characteristics is provided in **Table 1**.

2.4.1.1. Data set 1

The first data set initially consisted of 68 participants, 34 CBP and 34 healthy participants from the study by Mansour et al.[85] and was obtained from the "cbp_resting" provided by the OpenPain Project (OPP) database (Principal investigator: A. Vania Apkarian; http://www.openpain.org). We consented to and followed OpenPain Data Use Agreement, and procedures were approved by the University of Toronto's Human Research Ethics Board before data analysis. As described in the original manuscript, all participants were provided with written consent, and all experimental protocols were approved and conducted according to the Northwestern University's Institutional Review Board committee. Patients' clinical assessment included the Short-Form of the McGill Pain Questionnaire (SF-MPQ),[95] where the visual analog scale (VAS) (0 = no pain, 10 = worst pain imaginable) was used to evaluate pain intensity. Participants were given the questionnaire 1 hour before scanning.

2.4.1.2. Data set 2

The second data set initially consistent of 36 participants, 20 CBP and 16 healthy participants and was previously published in a study investigating rsFC in CBP and acquired from Stone et al.[19] The study was approved by McGill University Faculty of Medicine Institutional Review Board, the Montreal Neurological Institute (MNI) and Hospital Research Ethics Board, and the McGill University Health Centre Research Ethics Office. The participants gave written consent before starting the study. All participants completed the SF-MPQ for pain intensity before scanning; however, VAS data were not available.

2.4.1.3. Data set 3

The third data set initially included a total of 63 participants from Osaka, Japan (24 CBP, 39 healthy participants). This data set was obtained from "BrainNetworkChange_Mano" on OPP database. We consented to and followed OpenPain Data Use Agreement. The original study was approved by the Ethics Committee for Human and Animal Research of the National Institute of Information and Communications Technology, Japan (reference 20140611).[84] All participants gave written consent before participating in the study. Pain intensity was measured on a VAS scale as part of the SF-MPQ on the day of scanning.

2.4.1.4. Data set 4

The fourth data set initially included 34 participants, 17 CBP and 17 healthy participants from Cambridge, UK, in "BrainNetwork-Change_Mano" on OPP database. We consented to and followed OpenPain Data Use Agreement. The original study was approved by the East of England NRES Committee, Norfolk, UK (reference 13/EE/0098).[84] All participants gave written consent before participating in the study. The VAS scale as part of the SF-MPQ was to determine pain intensity on scan day.

2.4.2. Resting state functional magnetic resonance imaging data acquisition parameters

2.4.2.1. Data set 1

Functional T2*-weighting brain images were acquired using a 3T Siemens Trio whole-body scanner, with an 8-channel head coil, during rest, as follows: TR = 2.5 seconds; TE = 30 ms; flip angle = 90°; in-plane matrix resolution = 64 × 64; number of slices = 40;

Table 1

Data set characteristics.

Data set	N	Age (mean ± SD years)	Sex (W/M)	Healthy participants			CBP					Scanner	TR (s)	Head coil channels
				N	Sex (W/M)	Age (mean ± SD years)	N	Sex (W/M)	Age (mean ± SD years)	Pain duration (n = 69; mean ± SD years)	Pain intensity (n = 59; mean ± SD VAS [0-10])			
1	57	49.6 ± 8.4	26/31	31	13/18	49.9 ± 7.8	26	13/13	49.3 ± 9.1	15.0 ± 12.1	6.5 ± 1.7	3T Siemens Tim Trio	2.5	8
2	27	44.2 ± 11.4	14/13	12	6/6	42.2 ± 11.4	15	8/7	45.9 ± 11.6	5.2 ± 5.1	n/a	3T Siemens Tim Trio	2.26	8
3	48	42.9 ± 11.8	23/25	27	11/16	41.2 ± 11.9	21	12/9	45.0 ± 0.5	11.6 ± 9.5	2.6 ± 2.5	3T Siemens Tim Trio	2.5	12
4	24	44.7 ± 11.5	16/8	9	5/4	46.7 ± 0.5	15	11/4	43.5 ± 11.2	11.7 ± 7.3	4.7 ± 3.0	3T Siemens Tim Trio	2	12
Total	156	45.9 ± 10.8	79/77	79	35/44	45.4 ± 11	77	44/33	46.2 ± 10.7	11.5 ± 10.0	4.8 ± 2.8			

A summary of the 4 data sets included in the seed-to-voxel functional connectivity.

BDI, Beck Depression Inventory; CBP, chronic low-back pain patients; M, men; VAS, visual analogue scale; W, women.

slice thickness = 3 mm; field of view = 256 × 256 mm; and number of volumes = 244, 300, or 305.[85] In addition, for realignment purposes, T1-weighted brain images for each participant were acquired using the same scanner with the following parameters: isotropic resolution 1 mm; TR = 2.5 seconds; TE = 3.36 ms; flip angle = 9°; in-plane matrix resolution = 256 × 256; number of slices = 160; and field of view = 256 × 256 mm.[85]

2.4.2.2. Data set 2

Scans were acquired using a 3T Siemens Tim Trio scanner with an 8-channel head coil. Participants were instructed to "relax, keep your eyes open, and don't think about any one thing in particular."[19] The functional T2*-weighted imaging scans where acquired using echo planar imaging, TR = 2.26 seconds; TE = 30 ms; flip angle = 90°; in-plane matrix = 64 × 64; number of slices = 38; slice thickness = 4 mm; field of view = 256 × 256 mm; and number of volumes = 133.[19] The anatomical T1 scans were acquired using the following parameters: isotropic resolution 1 mm; TR = 2.3 seconds; TE = 2.98 ms; flip angle = 9°, in-plane matrix resolution = 256 × 256; number of slices = 176; and field of view = 256 × 256 mm.[19]

2.4.2.3. Data set 3

The MRI scans were performed using a 3T Siemens MRI Scanner Tim Trio scanner with a 12-channel head coil at CiNet (Osaka, Japan). During resting state scanning, participants were given the following instructions: "please relax during the scan; do not sleep and keep looking at the fixation point (a tiny cross-hair) presented at the center of the display; do not think of anything in particular." Functional T2* images were acquired with the following parameters: TR = 2.5 seconds; TE = 30 ms; flip angle = 80°; in-plane matrix resolution = 64 × 64; number of slices = 41; field of view = 212 × 212 mm; and number of volumes = 234.[84] The anatomical T1 scans were acquired using the following sequence: isotropic resolution 1 mm; TR = 2.25 seconds; TE = 3.06 ms; time of inversion = 900 ms; flip angle = 9°; in-plane matrix resolution = 256 × 256; number of slices = 208; and field of view = 256 × 256 mm.[84]

2.4.2.4. Data set 4

The MRI scans were performed with a 3T Siemens MRI Scanner Tim Trio scanner with a 12-channel head coil at Addenbrooke's Hospital in Cambridge, UK. During resting state scanning, participants were instructed to: "please relax during the scan; do not sleep and keep looking at the fixation point (a tiny cross-hair) presented at the center of the display; do not think of anything in particular." Functional T2* images were acquired with the following parameters: TR = 2 seconds; TE = 30 ms; flip angle = 80°; in-plane matrix resolution = 64 × 64; number of slices = 32; field of view = 212 × 212 mm; and number of volumes = 300.[84] The anatomical T1 scans were collected using the following sequence: isotropic resolution 1 mm, TR = 2.3 seconds; TE = 2.98 ms; time of inversion = 900 ms; flip angle = 9°; in-plane matrix resolution = 256 × 256; number of slices = 176; and field of view = 256 × 256 mm.[84]

2.4.3. Functional magnetic resonance imaging data preprocessing

Functional magnetic resonance imaging data were preprocessed for whole-brain rsFC using CONN toolbox v17f (http://www.conn-toolbox.org) implemented in Statistical Parametric Mapping software package (SPM v.12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and ran on MATLAB (R2016b v.9.1; Mathworks, Nantick, MA).[138] Each participant's anatomical T1-weighted and functional T2*-weighted scans were imported into CONN. Data were preprocessed as follows. Briefly, functional T2* scans underwent coregistration to the participant's structural T1 scans. Functional images were spatially realigned and unwarped. Realignment is defined by default by 6 dimensions, 3 translations and 3 rotations along the x, y, and z axes. Furthermore, each anatomical image was segmented for gray and white matter, and cerebrospinal fluid (CSF) and normalized to the T1-weighted MNI152 template. Functional magnetic resonance imaging data were also aligned to the MNI template. Data were resliced after normalization using the default Tissue Probability Maps (structural target resolution = 2 mm and functional target resolution = 2 mm) and subsequently smoothed with a Gaussian kernel of 8 mm at full-width half maximum. Once preprocessed, we checked the histogram plots of rsFC values (voxel-to-voxel correlation coefficient between BOLD times series and 512 subsets of voxels) for alignment centered at zero for quality assurance. If the data are completely without noise, then the correlation of a random subset of connections should center around zero, ie, no correlations. Skewness in the plots indicates noise related to physiological processes or subject motion; this skewness may artificially inflate connectivity strengths. Several steps were taken to mitigate these confounds. First, physiological noise was corrected by using aCompCor, an algorithm which performs a principal components analysis on fMRI signal from the white matter and CSF, areas of non-neuronal origin.[10] The white matter and CSF masks were generated by tissue segmentation performed using SPM and then eroded to minimize partial volume effects for each subject. These masks were visually inspected. In the denoising step, we regressed the following confounds: realignment of 6 dimensions with their first temporal derivatives (12 components), white matter (5 components), and CSF (5 components). A band-pass filter of 0.008 to 0.09 Hz was additionally applied to the data. To control for excessive motion, we used a criterion of framewise displacement (FD) greater than the absolute value of 0.5-mm threshold.[28,84] The mean FD (mFD) was computed using the weighted sum across 6 dimensions of the mean absolute scan to scan differences.[114] Participants were excluded if they met any of the following motion criteria: mFD > |0.5 mm| and at least 20% of the suprathreshold FD value > |0.5 mm|.[84,107] Both mFD and maximum FD (maxFD) were also computed for comparative purposes between healthy participants and CBP for each site (see Supplementary Table 1, available at http://links.lww.com/PAIN/A756). The maxFD was calculated using the weighted sum across 6 dimensions of the maximum absolute scan to scan differences.[114] The Mann–Whitney *U* test compared FD values between healthy participants and CBP for each site at $P < 0.05$. In addition, we excluded participants based on quality assurance, if they still presented a heavily skewed histogram plot of correlation coefficient after denoising. The residual fMRI signal of the included participants was used for whole-brain rsFC analysis.

Participants were removed from each data set, as follows. Furthermore, a summary is provided in Supplementary Table 2 (available at http://links.lww.com/PAIN/A756).

2.4.3.1. Data set 1

We excluded 11 participants (3 healthy participants and 8 CBP) from the initial data set after matching for age with the other 3 data sets (n = 1 control), after preprocessing (n = 3; 1 control and 2 CBP, scans could not be aligned), after denoising (n = 1 CBP, to meet quality assurance standards), and after motion correction (n = 6; 1 control, 3 CBP had an mFD value > |0.5 mm| and at least 20% of the suprathreshold FD value > |0.5 mm|), and 2 CBP had at least 20% of the suprathreshold FD value > |0.5 mm|. We included 57 participants in our analysis, which consisted of 26 CBP and 31 age-matched healthy participants.

2.4.3.2. Data set 2

We excluded 9 participants (4 healthy participants and 5 CBP): 2 healthy participants from the initial cohort to age match with the other 3 data sets and 2 that had at least 20% of the suprathreshold FD value > |0.5 mm|. Five CBP were excluded after motion correction (n = 5; one participant had an mFD value > |0.5 mm| and at least 20% of the suprathreshold FD value > |0.5 mm|), and 4 CBP had at least 20% of the suprathreshold FD value > |0.5 mm|. In sum, we included 27 participants in our analysis: 15 CBP and 12 age-matched healthy participants.

2.4.3.3. Data set 3

We excluded 15 participants (12 healthy participants and 3 CBP) to age-match with the other data sets (n = 7 healthy participants), to exclude healthy participants with pain (n = 4), to exclude one CBP after preprocessing because the skull was not properly removed (n = 1), and to exclude after motion correction (n = 3); one healthy participant had at least 20% of the suprathreshold FD value > |0.5 mm|, one CBP had an mFD value > |0.5 mm|, and one CBP had an mFD value > |0.5 mm| and at least 20% of the suprathreshold FD value > |0.5 mm|. We included 48 participants in our analysis, 21 CBP and 27 age-matched healthy participants.

2.4.3.4. Data set 4

We excluded 10 participants (8 healthy participants and 2 CBP) to age-match with the other data sets (n = 1 healthy participant), to exclude healthy participants with pain (n = 6), and to exclude after motion correction (n = 3); one healthy participant with at least 20% of the suprathreshold FD value > |0.5 mm|, one CBP with an mFD > |0.5 mm|, and one CBP with an mFD > |0.5 mm| and at least 20% of the suprathreshold FD value > |0.5 mm|. Finally, we included 24 participants in our analysis, 15 CBP and 9 age-matched healthy participants.

2.4.4. Whole-brain functional connectivity

We performed seed-to-voxel rsFC of the right antHC to the rest of the brain using the CONN toolbox. The antHC mask was derived from our previous parcellation study, which delineated the region of the right antHC using a hippocampal mask based on the Harvard-Oxford subcortical atlas on FSL v4.0.[3] This region overlaps with the result from our chronic pain meta-analysis. The center of gravity of the mask was (MNI = 24, 13, −21).[3] We conducted a first-level, fixed-effects analysis, which was a seed-to-voxel–based correlation between the right antHC ROI time series and every other voxel in the brain. We then performed a second-level random effects analysis to evaluate differences between healthy participants and CBP while regressing each data set (site) and sex as covariates of no interest. Site was included as a covariate of no interest to account for scanner-/site-specific noise. Sex was also included as a covariate because there are sex differences in resting state networks,[21,43,52,58,120,137] and our samples were not sex-matched. Voxelwise correlation coefficients were *z*-scored using the Fisher *r*-to-*z* transformation. To test whether the functional connectivity data were normally distributed, we performed the Shapiro–Wilk's test, with significance set at $P < 0.05$, in SPSS (v25, IBM corp, Armonk, NY). Group differences between CBP and healthy participants were assessed with parametric cluster-based statistics using family-wise error (FWE), and maps were thresholded using cluster size at $P_{FWE} < 0.05$ (cluster-forming height threshold of $P < 0.001$).

2.4.4.1. Post hoc correlations

We performed post hoc correlations to determine whether the aberrant antHC functional connectivity (CBP vs healthy participants) was associated with pain characteristics (ie, pain intensity and pain duration). Pain intensity was collected with the VAS scale on SF-MPQ on scan day in 3 data sets (1, 3, and 4). Data set 2 also collected part of the SF-MPQ, but VAS scores were not collected; as such, this data set was excluded for this analysis. In all data sets, pain duration was evaluated in number of years. We extracted the connection strength between the antHC seed and the resultant cluster (connection strength here is defined as the fisher-transformed correlation coefficient between BOLD activity in the antHC seed region and the resulting cluster) for each CBP subject, to assess whether they were correlated with clinical characteristics, including disease duration (n = 69 CBP) and pain intensity (n = 59 CBP) using Spearman's rank correlation. Significance was set at $P < 0.05$.

3. Results

3.1. Article selection

Our database and reference search identified a total of 49 articles that met our criteria of selection, as shown in **Figure 1**. **Table 2** provides a summary of the 21 studies included in the first meta-analysis, which reported MTL activity in response to experimental pain, compared with a control condition. **Table 3** provides a summary of the 28 studies of chronic pain patients reporting abnormal MTL activity compared with healthy participants that were included in our second meta-analysis.

3.2. Article quality assessment

Quality scores for each article included in each of the 2 meta-analyses are provided in **Tables 2 and 3**. Average scores for all articles included in the first meta-analysis were 17.52 ± 0.75 (mean ± SD score of 20) and 17.93 ± 1.05 for the articles in the second meta-analysis. The most notable limitation of these articles is that most did not report whether sample size calculations were conducted a priori. In addition, some articles did not account for variables of potential interest, such as sex/gender.

3.3. Contrast results

Our experimental pain and chronic pain meta-analyses resulted in the following number of experiments (contrasts within studies were accounted), foci, and participants as follows:

From the 21 studies investigating experimental pain, and reporting HC or PHG activation:

Table 2

Summary of experimental pain studies in healthy participants included in the meta-analysis.

MTL finding		N	Sex (W/M)	Age (mean ± SD/range/ SEM in years)	Foci	Stimuli			Ref.	QS (/20)
Pain > control	Pain < control					Contrast	Modality	Body part		
(1) L HC	(2) L PHG	12	6/6	28.8 (21-41)	(1) 17 (2) 9	(1) Heat pain > warm (2) Warm > heat pain	Thermal laser	R dorsum of the hand	27*	17
B HC		8	0/8	22-40	9	Heat pain > baseline	Thermal	L dorsum of the hand	111	17
B HC		14	1/13	25.8 (21-41)	12	Thermal laser > baseline	Thermal laser	B dorsum of the hand	13	17
B HC		12	6/6	25.42 ± 5.43 (20-35)	16	Heat pain > baseline	Thermal	L dorsum of the hand	37	19
(1) B HC (2) L HC		22	(1) 9/10 (2) 9/8	(1) 26 ± 1/34 ± 4 (2) 26 ± 1/31 ± 4	(1) 8 (2) 6	(1) Muscle pain (saline injections) > baseline (2) Cutaneous pain (saline injections) > baseline	Chemical	(1) R muscle lower leg (2) R cutaneous lower leg	50	17
B HC		11	0/11	28 ± 4	24	Pressure pain after saline injections > baseline	Mechanical and chemical	R lower leg	78	18
L HC, B PHG		9	5/5†	29.7 ± 8.7	8	Pricking pain > burning pain	Thermal laser	L dorsum of the foot	134	17
	B PHG/HC	61	33/28	26.6 ± 4.7	18	Low thermal pain < baseline	Thermal	R volar forearm	68	17
R HC		7	3/4	18-36	9	Heat pain > warm	Thermal	L dorsum of the hand	88	17
B PHG		11	11/3‡	26.9 ± 4.7	5	Transcutaneous stimulation > baseline	Electrical	R ankle	110	17
B HC		12	7/5	20-31	10	Heat pain expectancy > baseline	Thermal	L or R wrist	143	17
R PHG		31	16/15	30 (22-38)	25	Painful esophageal stimulation > baseline	Mechanical	Esophagus	22	17
R PHG		34	18/16	23.4 ± 2.5	36	Heat pain > warmth baseline	Thermal	L lower leg	69	19
R PHG		14	8/6	26.1 (21-37)	13	Heat pain > baseline	Thermal	L volar forearm	62	19
(1) L PHG	(1) L PHG (2) B PHG	32	(1) 16 (2) 16	(1) 30.9 ± 7.8 (2) 27.8 ± 7.1	(1) 57 (2) 70	Painful esophageal stimulation > baseline	Mechanical	Esophagus	64	18
R HC		12	6/6	29.9 ± 2.5	22	Heat pain > baseline cerebral blood flow	Thermal	L dorsum of the hand	82§	18
B HC		20	5/15	35 (26-56)	38	Painful electrical shock > baseline	Electrical	R volar forearm	129	17
B PHG		15	7/8	25.7 (22-30)	12	Pain > baseline	Chemical	R lower back muscle (fourth lumbar vertebra)	142	17
(1) L HC (2) R HC		24	24/0	31.3 (24-45)	44	(1) Laser heat > baseline (2) Noxious cold > baseline	Thermal	(1) L dorsum of hand (2) R foot	15	18
R HC		24	10/14	25 ± 5	13	Heat pain nocebo‖ < high heat pain	Thermal	L volar forearm	59	17
B HC/ PHG		23	12/11	27.8 ± 4.2	15	Electrical pain > baseline	Electrical	L dorsum of the hand/ forehead	121	18

A detailed description of all 21 experimental pain fMRI studies (with the exception of one ASL and the other PET) of healthy participants included in the ALE meta-analysis.

* PET study.

† One participant (gender unspecified) was excluded from the study.

‡ Three participants (gender unspecified) were excluded from the study.

§ ASL study.

‖ Low heat pain nocebo was control to high heat pain.

ALE, activation likelihood estimation; ASL, arterial spin-labeled magnetic resonance imaging; B, bilateral; HC, hippocampus; L, left; M, men; PET, positron emission tomography; PHG, parahippocampal gyrus; QS, quality score; R, right; W, women; MTL, medial temporal lobe.

(1) Healthy participants during experimental pain > control conditions (baseline):
22 experiments, 398 foci, and 385 participants;
(2) Healthy participants during experimental pain < control conditions (baseline):
3 experiments, 100 foci, and 105 participants.
From the 28 studies investigating chronic pain, and reporting HC or PHG activation:
(3) Chronic pain patients > healthy participants: 17 experiments, 173 foci, and 629 participants;

Table 3

Summary of chronic pain studies included in the meta-analysis.

Pain condition	Sex (W/M)		Age (mean ± SD/range/SEM in years)		Foci	Stimuli			MTL finding		Ref.	QS (/20)
	P	C	P	C		Contrast	Modality	Body part	P > C	P < C		
CD	9/16	6/19	31.72 ± 8.05	29.24 ± 6.85	2	Resting state conditions			L HC/PHG		8	19
FD	31/18	25/14	22.55 ± 1.78	22.18 ± 0.85	4	Resting state conditions				L PHG	77	19
	20/10	19/11	22.50 ± 1.46	22.23 ± 0.94	13	Resting state conditions			L HC/PHG		76	18
FM	6/0	8/0	53.0 ± 4.8	51.4 ± 3.9	14	FDOPA uptake < control	Chemical			B HC	140	18
	29/0	31/0	49.8 (25-64)	46.3 (20-63)	7	Incongruent > congruent stimuli	Stroop color	Word test		L HC	87	18
	37/6	10/5	46.3 ± 11.4	44.1 ± 14.8	34	(1) Cuff stimulation > baseline (2) Stimulus offset (still in pain)	Mechanical	L lower leg	(1) R HC/PHG (2) B HC, R PHG		123	17
	15/0	15/0	52.07 ± 7.14 (42-64)	52.67 ± 6.23 (46-69)	1	Controllability during expectation of pain > control condition	Controllability in reaction time task		R HC		46	19
IBS	5/3	5/3	41.3 (27-64)	39.4 (24-54)	3	Rectal distention > baseline	Mechanical/auditory	Rectum	R HC		5	18
	15/15	15/15	21.7 ± 3.0	21.4 ± 1.5	4	Cognitive task < baseline	Stroop task			R HC	4	17
	33/0	18/0	32.5 (20-60)/40.3 (21-60)	32.5 (21-54)	3	Expectation of high distention > control	Mechanical	Rectum	R HC		72	18
	11/6	11/6	36.0 ± 10.8	37.4 ± 10.2	13	Analgesia > control	Suggestion-/conditioning-enhanced placebo		R PHG		73	19
	76/42	31/29	29.39 ± 9.93/35.95 ± 12.97	30.65 ± 10.71/37.28 ± 10.75	3	Resting state conditions			R HC		53	17
	15/2	10/11	47.96 ± 3.7	34.76 ± 2.8	2	Visual cue > control cue	Visual task with rectal distention	Rectum	B HC		56	19
	7/14	10/11	41.82 ± 11.92	35.91 ± 14.76	8	Resting state conditions				R HC	80	18
ITN	10/7	10/9	63.41 ± 7.25	62.53 ± 7.41	3	Resting state conditions				R PHG	136	19
LBP	5/6	6/5	20.4	21.5	27	Task picture > no task picture	Visual task picture		B PHG		125	19
	16/15	18/13	51.8 ± 9.9	49.3 ± 8.2	2	Task picture > no task picture	Visual task picture			R HC	9	17
Migraine	9/1	9/1	37.9 ± 4.7	37.8 ± 4.8	2	Pain-related words > baseline (negative words)	Verbal stimuli		R HC/PHG		34	19
	55/0	44/0	34.5 ± 11.0	34.3 ± 14.3	15	Resting state conditions			B HC		44	19
	8/3	8/3	42.5 ± 11.9	42.3 ± 11.9	2	Heat pain > baseline	Thermal	Painful facial side (patients)/matched (healthy participants)	R HC		103	18
	19/5	22/5	36.2 ± 11.3	33.7 ± 12.5	9	Heat pain > baseline	Thermal	L volar forearm	L HC		124	18
MOH	30/7	20/12	41.27 ± 9.27	41.34 ± 10.89	1	Resting state conditions				R PHG	20	18
MPS	10/6	8/6	32.6 ± 7.2	30.6 ± 9.0	15	Electrical pain > baseline	Electrical	L shoulder		B HC, L PHG	105	16
OA	16/0	17/0	60.87	64.17	51	Resting state conditions			L HC/PHG		55*	17
PD	34/0	34/0	21.5 ± 1.2	22.2 ± 1.7	5	Resting state conditions			L HC		61	19

(*continued on next page*)

Table 3 (*continued*)

Pain condition	Sex (W/M)		Age (mean ± SD/range/SEM in years)		Foci	Stimuli			MTL finding		Ref.	QS (/20)
	P	C	P	C		Contrast	Modality	Body part	P > C	P < C		
SPD	5/7	4/6	45.83 ± 14.95	35.2 ± 10.78	10	Electrical pain > baseline	Electrical	†lower leg		R PHG	79	17
	11/6	11/6	44.7 ± 9.1	45.4 ± 9.2	22	Pricking > baseline	Mechanical	L lower leg	B HC, L PHG		128	15
WAD	17/4	9/9	37.0 ± 11.0	35.0 ± 9.0	15	Resting state conditions			B PHG		75	17

A detailed description of 28 chronic pain studies selected for the ALE meta-analysis.
* ASL study, the rest of the studies used fMRI.
† Laterality not specified.
ALE, activation likelihood estimation; ASL, arterial spin-labeled magnetic resonance imaging; B, bilateral; C, healthy controls; CD, Crohn's disease; FD, functional dyspepsia; FDOPA, 6-[$_{18}$F]fluoro-L-DOPA; FM, fibromyalgia; fMRI, functional magnetic resonance imaging; HC, hippocampus; IBS, irritable bowel syndrome; ITN, idiopathic trigeminal neuralgia; L, left; LBP, lower back pain; M, men; MOH, medication overuse headache; MPS, myofascial pain syndrome; MTL, medial temporal lobe; OA, osteoarthritis; P, patients; PD, primary dysmenorrhea; PHG, parahippocampal gyrus; SPD, somatoform pain disorder; R, right; QS, quality score; W, women; WAD, whiplash-associated disorder.

(4) Chronic pain patients < healthy participants: 11 experiments, 81 foci, and 583 participants.

3.4. Activation likelihood estimation meta-analyses

3.4.1. Experimental pain studies

Our ALE meta-analysis of experimental pain studies in healthy participants is reported in **Table 4**, **Figure 2**, and Supplementary Fig. 3 (available at http://links.lww.com/PAIN/A756). The contrast *experimental pain > control conditions* identified consistently greater activations in the right antHC, amygdala, and PHG at a cluster-corrected $P < 0.05$ at cluster-forming height threshold of $P < 0.005$ with 1000 permutations. The *experimental pain < control conditions* contrast did not have a sufficient number of experiments to perform the analysis.

3.4.2. Chronic pain studies

Our ALE meta-analysis of chronic pain studies vs healthy participants is shown in **Table 4** and **Figure 3** and Supplementary Fig. 4 (available at http://links.lww.com/PAIN/A756). The contrast *chronic pain patients < healthy participants* found consistently less activation in the right antHC at a cluster-corrected $P < 0.05$ at cluster-forming height threshold of $P < 0.005$ with 1000 permutations. There were no significant clusters for the *chronic pain patients > healthy participants* contrast.

3.5. Group differences in anterior hippocampus functional connectivity

Our whole-brain seed-to-voxel functional connectivity analysis of the right antHC seed yielded reduced connectivity in CBP compared with healthy participants in the (mPFC; peak MNI coordinates: −10, 56, −02; cluster size = 328 mm^3, cluster-corrected $P_{FWE} < 0.05$) including bilateral pregenual anterior cingulate cortex and the left medial frontal pole (**Fig. 4**). We found that the functional connectivity result was normally distributed ($P > 0.05$). Data are shown in Supplementary Fig. 5 (available at http://links.lww.com/PAIN/A756). Post hoc analyses were performed to determine whether the aberrant connectivity was related to pain characteristics (pain intensity and pain duration). Reduced antHC–mPFC connectivity values in CBP were not significantly correlated with pain intensity (n = 59 CBP, $r = -0.129$, $P = 0.329$) nor pain duration (n = 69 CBP, $r = -0.088$, $P = 0.471$). Post hoc analyses investigating sex differences are reported in the Supplementary Materials (available at http://links.lww.com/PAIN/A756).

4. Discussion

Neuroimaging evidence suggests that MTL structures are involved in acute pain and exhibit abnormal activity in chronic pain. To determine which regions of the MTL are involved, we performed 2 meta-analyses. The first meta-analysis investigated MTL activation in experimental pain studies of healthy participants and found consistent activation in the right antHC. The second meta-analysis investigated MTL activation in chronic pain patients compared with controls and found that patients have consistently less activation in the right antHC. Because functional connectivity of the antHC region has been previously shown to be a predictor for the transition from subacute to chronic back pain,[104] we further conducted a seed-to-voxel rsFC analysis of the right antHC region in a large sample of CBP patients pooled from 4 different cohorts. Our analysis showed reduced

Table 4

Activation likelihood estimation results of experimental pain and chronic pain studies.

Brain region	MNI			ALE value	Cluster size (mm^3)
	X	Y	Z		
Healthy participants: Experimental pain > control conditions					
R antHC/PHG/amygdala	30	−10	−24	0.025	808
Chronic pain patients < healthy participants					
R antHC	26	−16	−16	0.021	840

ALE results of all significant contrasts. One significant activation cluster resulted from the ALE meta-analysis of healthy participants during experimental pain compared with control conditions (n = 22 experiments, cluster-corrected $P < 0.05$, threshold $P < 0.005$ with 1000 permutations). One significant activation cluster in chronic pain patients compared with healthy participants resulted from the ALE meta-analysis of chronic pain studies (n = 11 experiments, cluster-corrected $P < 0.05$, threshold $P < 0.005$ with 1000 permutations).
ALE, activation likelihood estimation; antHC, anterior hippocampus; BA, Brodmann area; MNI, Montreal Neurological Institute; PHG, parahippocampal gyrus; R, right.

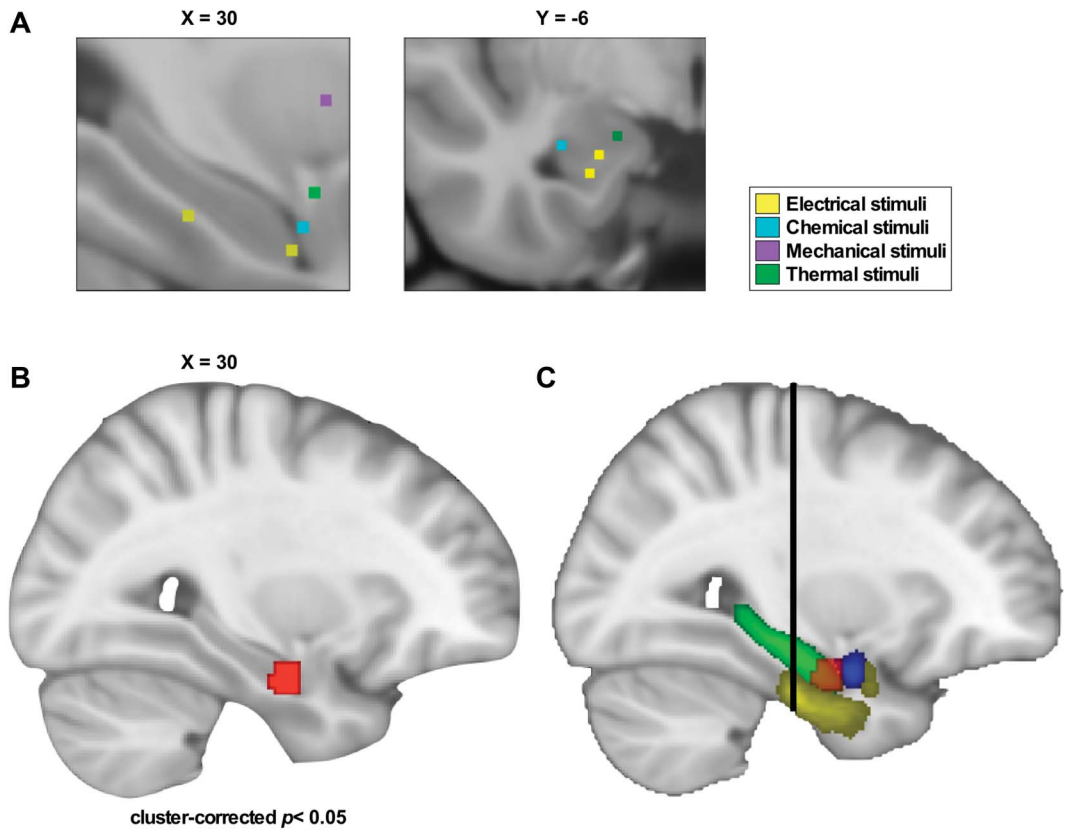

Figure 2. Peak activation in the anterior hippocampus in healthy participants during experimental pain conditions, compared with control conditions. The ALE meta-analysis of noxious experimental conditions and baseline conditions in healthy participants with MTL activation (n = 22 experiments). (A) Close-up of foci activation in the MTL, color-labelled according to stimuli. (B) The map shows one significant cluster (red) in the right anterior hippocampus (antHC), parahippocampal gyrus, and amygdala (cluster-corrected $P < 0.05$, cluster-forming height threshold of $P < 0.005$ with 1000 permutations). (C) The map shows the delineation of the significant cluster in red and the different regions of the MTL: parahippocampal gyrus (yellow), amygdala (blue), and hippocampus (green). The black line represents MNI, Y = −21, which represents the border between the anterior and posterior hippocampus.[113] ALE, activation likelihood estimation; MTL, medial temporal lobe.

antHC–mPFC functional connectivity compared with controls. These data suggest the right antHC is involved in healthy nociception but is dysfunctional in chronic pain.

4.1. Medial temporal lobe activity during experimental pain

The first key ALE finding is that experimental pain leads to right antHC activation. The HC, PHG, and amygdala are key structures of the Papèz circuit, which is involved in memory and emotional processing. The HC/PHG is canonically responsible for learning and retention; the HC being a key structure for consolidation of contextual and spatial memory.[113] Notably, these MTL structures show pain-related activity in animal studies.[26,33,66,81,94] By contrast, several human studies have linked HC/PHG activity to a negative affect modulation of pain.[11,116,118] For example, one study found greater activity in the entorhinal cortex (the major interface between the HC and neocortex) during painful heat stimuli under elevated anxiety, compared with a low-anxiety condition.[111] Activity in entorhinal cortex was correlated with the midinsula in anxiety-induced hyperalgesia.[111] This finding is in line with the Gray-McNaughton theory of anxiety: the hippocampal formation amplifies anxiety-related signals in threatening situations.[47]

Furthermore, the amygdala plays an integral role in the affective component of pain and is an opiate-rich brain region.[13,39,80,83,96,116,126] The amygdala engages autonomic and emotional responses such as unpleasantness and fear,[106] suggesting an intrinsic role in pain-related negative affect processing. In the context of stress or fear, the amygdala may induce hypoalgesia to minimize pain sensation during noxious stimuli.[133] There are well-known antHC–amygdala interactions in both encoding and retrieval of affective information,[30,108] which can certainly extend to situations involving experimental pain.

To our knowledge, we present the first meta-analysis of experimental pain studies with MTL activity and report that MTL structures are consistently coactivated. Thus, our findings lend some new insights into potential memory and affective processing in this context.

4.2. Medial temporal lobe activity in chronic pain

Our second aim was to identify which MTL region show consistent activation in chronic pain since recent studies have highlighted the MTL as a potential site for understanding the onset and development of chronic pain.[6,131] Our main finding yielded consistently less activation in the right antHC in chronic pain patients, compared with controls. This antHC region overlaps with the area activated in experimental pain in healthy participants.

The HC is longitudinally divided into the antHC and posterior HC with distinct functional properties.[3,113] The antHC is implicated in mood-related functions,[67,112] and stress modulation,[38] likely through interactions with the amygdala. Thus, abnormal antHC activity in chronic pain may be related to

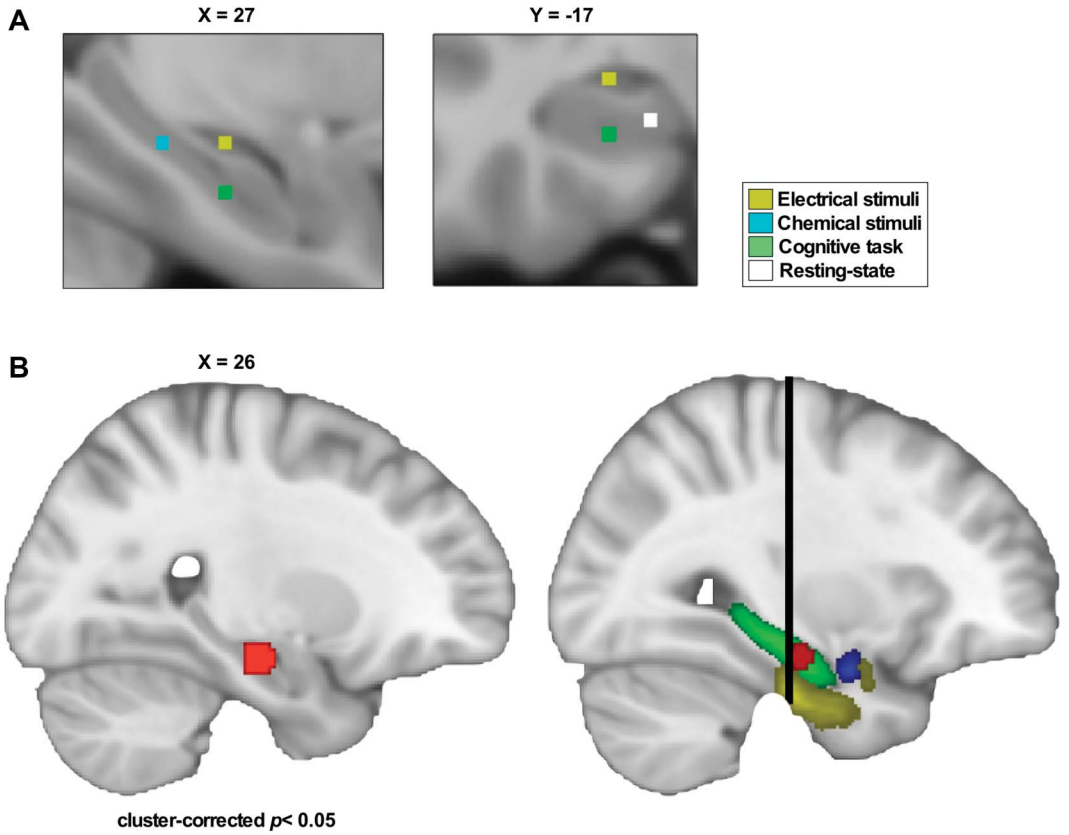

Figure 3. The anterior hippocampus shows significantly less activity in chronic pain, compared with healthy participants. The ALE meta-analysis compared chronic pain studies vs healthy participants with MTL activation (n = 11 experiments). (A) Close-up of foci activation in the MTL, color-labelled according to stimuli. (B) The map represents one significant cluster in the right anterior hippocampus (antHC). Patients with chronic pain had consistently lower activity in this region compared with healthy participants (cluster-corrected $P < 0.05$ at cluster-forming height threshold of $P < 0.005$ with 1000 permutations). (C) The map shows the cluster in relation to other MTL structures: the hippocampus (green), the amygdala (blue), and the parahippocampal (yellow). The black line represents MNI, Y = −21, which represents the border between the anterior and posterior hippocampus.[113] ALE, activation likelihood estimation; MTL, medial temporal lobe.

dysregulation in stress modulation. Chronic pain can be considered as a stressor, eliciting a prolonged stress response[25]—ie, chronic pain poses an allostatic load on the brain.[16,93,132] The HC is particularly sensitive to the neurotoxic effects of prolonged exposure to stress hormones,[23,89] thus affecting its structure[93] and function.[51] Although working memory deficits have been reported in chronic pain,[12,90] there has not been a systematic investigation of types of memory processes most sensitive to hippocampal dysfunction such as associative recollection. A few neuroimaging studies addressed the interruptive function of pain in relation to memory function,[14,42] where reduced right antHC activity and poor visual encoding were observed in response to pain stimuli.[42] Interestingly, HC activity is related to psychologically induced analgesia.[48] As such, our finding could reflect HC dysregulation related to prolonged stress exposure, with chronic pain as the stressor. The HC subregions could certainly be further investigated in the context of memory and pain in future mechanistic studies.

4.3. Anterior hippocampus functional connectivity in chronic low-back pain patients

Our third aim was to identify whether abnormal right antHC activity was accompanied by abnormal rsFC in CBP. We found reduced right antHC–mPFC connectivity in CBP compared with controls, in line with a previous study that showed disrupted antHC–mPFC connectivity predicts the transition from subacute to chronic back pain.[104] These results suggest this aberrant connectivity is also involved in sustaining maladaptive pain, but how it is implicated in chronic pain is not well understood.

The literature indicates antHC–mPFC interaction in memory encoding and retrieval, future decision-making, and autobiographical memory.[92,102] Specifically, the mPFC integrates spatial and contextual information,[29,60,139] attributing behavioral, cognitive, and emotional relevance to a particular stimulus.[139] As such, the antHC–mPFC connectivity facilitates the encoding and retrieval of global schemas, contextual event information, and emotional cues and enables future memory-guided behaviors.[102,117] Reduced connectivity between these regions is seen in conjunction with poor autobiographical memory in patients with MTL damage[91] and is associated with deficits in emotional decision-making as observed previously in CBP.[7] Of interest, the right antHC is consistently activated to a greater extent when simulating future events compared with recalling past memories.[2,119] The antHC–mPFC functional connectivity also mediates extinction learning.[63,97] Extinction learning is the process of forming new memories that decouple conditioned responses (eg, fear) to a stimulus (eg, tone). This results when the stimulus is repeatedly presented without the unconditioned stimulus (eg, electric shock) which caused the conditioned response.[109,115] Chronic stressors, including chronic pain, impair extinction learning.[1,40,57,98] In particular, chronic stress blocks long-term potentiation between the HC and mPFC[45,86] and contributes to

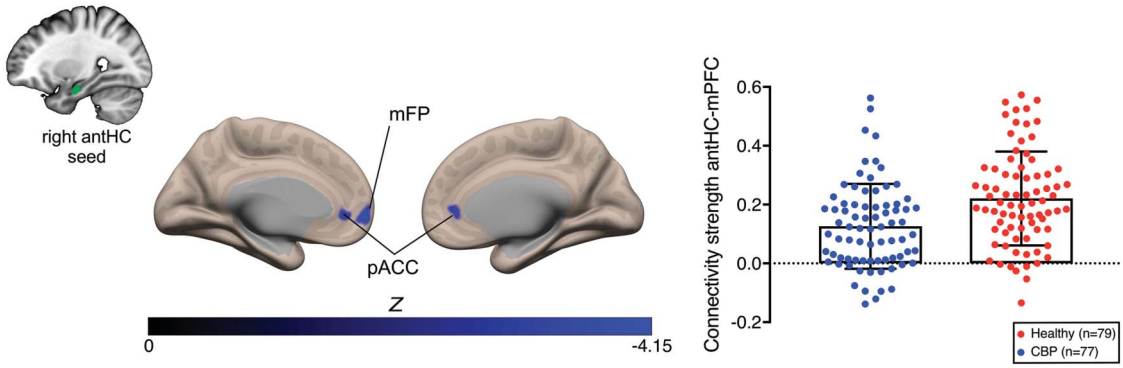

Figure 4. Chronic low-back pain patients have weaker functional connectivity to the medial prefrontal cortex. Whole-brain seed-to-voxel resting state functional connectivity in 4 data sets (n = 156) of the right anterior hippocampus (antHC) seed in CBP compared with healthy participants. Patients had weaker functional connectivity between the right antHC, the medial prefrontal cortex, including the bilateral pregenual anterior cingulate cortex and the left medial frontal pole, compared with healthy participants (cluster size $P_{FWE} < 0.05$, with a cluster-forming height threshold of $P < 0.001$). Functional connectivity strength (mean ± SD) is represented for both CBP and healthy participants. Significant clusters are shown on a semi-inflated MNI brain in CONN. antHC, anterior hippocampus; CBP, chronic low-back pain patients; mFP, medial frontal pole; pACC pregenual anterior cingulate cortex.

dendritic regression in mPFC and HC.[74] In CBP, there is impaired extinction learning and slower extinction to pain and verbal responses,[41] and muscular reactivity[41,122] compared with controls. Perhaps, reduced antHC–mPFC connectivity in CBP reflects a memory network deficit which fails to inhibit the memory of pain or to enable non-pain memory schemas that would allow retrieval of alternate memories.

4.4. Study limitations

Chronic pain conditions are heterogeneous and, accordingly, may have different patterns of brain activity. This is compounded by individual variability in chronic pain. Hence, the antHC network found in CBP is only relevant for the specific cohorts and not representative of chronic pain as a whole. For example, in burning mouth syndrome, patients had stronger antHC–mPFC connectivity than controls, but only in the presence of spontaneous pain.[65] The finding that successful recovery in patients with subacute back pain is accompanied by increased antHC–mPFC connectivity[104] suggests it is at least robust in back pain.

Furthermore, advances in MRI technology have led to variability in data quality and coordinates collected between laboratories through years of publications. To minimize this variability, we used the Turkeltaub algorithm, which accounts for such heterogeneity. In addition, foci derived from heterogeneous statistical thresholds were included in the meta-analyses—not accounting for these studies could lead to false negative findings, and thus bias the outcome of the result. Importantly, given our article selection and use of an MTL mask, our results do not speak to the consistency of MTL activation in pain in general, nor to coactivated regions outside the MTL.

To achieve sufficient statistical power, it has been reported that an ALE meta-analysis requires 8 to 15 experiments per contrast.[126,135] Based on this heuristic, our contrast of *healthy participants during experimental pain < control conditions* was underpowered, and this negative result should be interpreted with caution.

We hope the current findings stimulate future studies that could provide a mechanistic account of antHC in pain. The seeming contradiction of greater antHC activation in acute pain and reduced activity associated with chronic pain portrays a complex role and raises questions as to whether activation magnitude is a cause or consequence of pain experience. Experimental fMRI studies of pain and analgesia would be useful here. Furthermore, investigating functional connectivity during acute pain would be helpful to clarify how correlated activity in the target regions varies with the stimulus and task. Finally, investigating the relationship of these pain-related effects to other known functions of the antHC such as autobiographical memory retrieval or context modulation of anxiety is clearly warranted. Such studies are necessary to provide "meat on the bones" for the relationship of antHC and pain that we have identified.

5. Conclusion

In conclusion, we performed the first meta-analyses of the MTL in pain and determined that in studies reporting MTL abnormalities in chronic pain, the most common subregion was the antHC. The antHC has abnormal rsFC to the mPFC in CBP, reflecting cognitive and affective abnormalities. These data shed novel and important mechanistic information on the role of the HC in chronic pain.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

L.J. Ayoub was supported by the Harron G. Wilson Trust Bursary, the Harron Scholarship and the UTCSP Pain Scientist Award. M. Moayedi was supported by Connaught Fund from the University of Toronto and acknowledges support from the Bertha Rosenstadt Endowment Fund. He also holds a National Science and Engineering Research Council Discovery Grant RGPIN-2018-04908. The OPP project (Principal Investigator: A. Vania Apkarian, Ph.D. at Northwestern University) is funded by the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Drug Abuse (NIDA). D.A. Seminowicz was funded by National Institute of Dental and Craniofacial Research R21DE023964.
Author contributions: L.J. Ayoub, M. Golosky, and M. Moayedi: article search and data aggregation; L.J. Ayoub, A. Leboucher, and M. Moayedi: analysis of data; L.J. Ayoub, A. Barnett, and M. Moayedi: drafting of manuscript; M.P. McAndrews and M. Moayedi: conception and design of study; D.A. Seminowicz,

M. Moayedi, and M.P. McAndrews: revising the manuscript. All authors have approved the final version and agree to be accountable for all aspects of the work.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A756.

Article history:
Received 22 January 2018
Received in revised form 23 January 2019
Accepted 1 February 2019
Available online 8 February 2019

References

[1] Abdallah CG, Geha P. Chronic pain and chronic stress: two sides of the same coin? Chronic Stress (Thousand Oaks) 2017;1. doi: 10.1177/2470547017704763 [E-pub ahead of print].
[2] Addis DR, Cheng T, Roberts RP, Schacter DL. Hippocampal contributions to the episodic simulation of specific and general future events. Hippocampus 2011;21:1045–52.
[3] Adnan A, Barnett A, Moayedi M, McCormick C, Cohn M, McAndrews MP. Distinct hippocampal functional networks revealed by tractography-based parcellation. Brain Struct Funct 2016;221:2999–3012.
[4] Aizawa E, Sato Y, Kochiyama T, Saito N, Izumiyama M, Morishita J, Kanazawa M, Shima K, Mushiake H, Hongo M, Fukudo S. Altered cognitive function of prefrontal cortex during error feedback in patients with irritable bowel syndrome, based on FMRI and dynamic causal modeling. Gastroenterology 2012;143:1188–98.
[5] Andresen V, Bach DR, Poellinger A, Tsrouya C, Stroh A, Foerschler A, Georgiewa P, Zimmer C, Mönnikes H. Brain activation responses to subliminal or supraliminal rectal stimuli and to auditory stimuli in irritable bowel syndrome. Neurogastroenterol Motil 2005;17:827–37.
[6] Apkarian AV, Mutso AA, Centeno MV, Kan L, Wu M, Levinstein M, Banisadr G, Gobeske KT, Miller RJ, Radulovic J, Hen R, Kessler JA. Role of adult hippocampal neurogenesis in persistent pain. PAIN 2016;157:418–28.
[7] Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy RE, Harden RN, Chialvo DR. Chronic pain patients are impaired on an emotional decision-making task. PAIN 2004;108:129–36.
[8] Bao CH, Liu P, Liu HR, Wu LY, Jin XM, Wang SY, Shi Y, Zhang JY, Zeng XQ, Ma LL, Qin W, Zhao JM, Calhoun VD, Tian J, Wu HG. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. PAIN 2016;157:1037–44.
[9] Barke A, Preis MA, Schmidt-Samoa C, Baudewig J, Kröner-Herwig B, Dechent P. Neural correlates differ in high and low fear-avoidant chronic low back pain patients when imagining back-straining movements. J Pain 2016;17:930–43.
[10] Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 2007;37:90–101.
[11] Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biol Psychiatry 2010;67:1083–90.
[12] Berryman C, Stanton TR, Jane Bowering K, Tabor A, McFarlane A, Lorimer Moseley G. Evidence for working memory deficits in chronic pain: a systematic review and meta-analysis. PAIN 2013;154:1181–96.
[13] Bingel U, Quante M, Knab R, Bromm B, Weiller C, Büchel C. Subcortical structures involved in pain processing: evidence from single-trial fMRI. PAIN 2002;99:313–21.
[14] Bingel U, Rose M, Gläscher J, Büchel C. fMRI reveals how pain modulates visual object processing in the ventral visual stream. Neuron 2007;55:157–67.
[15] Bogdanov VB, Viganò A, Noirhomme Q, Bogdanova OV, Guy N, Laureys S, Renshaw PF, Dallel R, Phillips C, Schoenen J. Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. Behav Brain Res 2015;281:187–98.
[16] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;2012:7.
[17] Brett M, Johnsrude IS, Owen AM. The problem of functional localization in the human brain. Nat Rev Neurosci 2002;3:243–9.
[18] Burns E, Chipchase LS, Schabrun SM. Primary sensory and motor cortex function in response to acute muscle pain: a systematic review and meta-analysis. Eur J Pain 2016;20:1203–13.
[19] Ceko M, Shir Y, Ouellet JA, Ware MA, Stone LS, Seminowicz DA. Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. Hum Brain Mapp 2015;36:2075–92.
[20] Chen Z, Chen X, Liu M, Dong Z, Ma L, Yu S. Altered functional connectivity architecture of the brain in medication overuse headache using resting state fMRI. J Headache Pain 2017;18:25.
[21] Clemens B, Junger J, Pauly K, Neulen J, Neuschaefer-Rube C, Frölich D, Mingoia G, Derntl B, Habel U. Male-to-female gender dysphoria: gender-specific differences in resting-state networks. Brain Behav 2017;7:e00691.
[22] Coen SJ, Kano M, Farmer AD, Kumari V, Giampietro V, Brammer M, Williams SC, Aziz Q. Neuroticism influences brain activity during the experience of visceral pain. Gastroenterology 2011;141:909–17 e901.
[23] Conrad CD. Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. Rev Neurosci 2008;19:395–411.
[24] Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharmacol 2013;8:518–34.
[25] Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. Neuroimage 2009;47:864–71.
[26] Delgado JM. Cerebral structures involved in transmission and elaboration of noxious stimulation. J Neurophysiol 1955;18:261–75.
[27] Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. PAIN 1997;73:431–45.
[28] Dixon ML, De La Vega A, Mills C, Andrews-Hanna J, Spreng RN, Cole MW, Christoff K. Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. Proc Natl Acad Sci U S A 2018;115:E1598–607.
[29] Dolan RJ, Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 1997;388:582–5.
[30] Dolcos F, LaBar KS, Cabeza R. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc Natl Acad Sci U S A 2005;102:2626–31.
[31] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–84.
[32] Duerden EG, Albanese MC. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Hum Brain Mapp 2013;34:109–49.
[33] Dutar P, Lamour Y, Jobert A. Activation of identified septo-hippocampal neurons by noxious peripheral stimulation. Brain Res 1985;328:15–21.
[34] Eck J, Richter M, Straube T, Miltner WH, Weiss T. Affective brain regions are activated during the processing of pain-related words in migraine patients. PAIN 2011;152:1104–13.
[35] Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. Neuroimage 2012;59:2349–61.
[36] Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 2009;30:2907–26.
[37] Fairhurst M, Wiech K, Dunckley P, Tracey I. Anticipatory brainstem activity predicts neural processing of pain in humans. PAIN 2007;128:101–10.
[38] Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 2010;65:7–19.
[39] Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. Prog Brain Res 2000;122:245–53.
[40] Flor H. The functional organization of the brain in chronic pain. Prog Brain Res 2000;129:313–22.
[41] Flor H, Knost B, Birbaumer N. The role of operant conditioning in chronic pain: an experimental investigation. PAIN 2002;95:111–8.
[42] Forkmann K, Wiech K, Ritter C, Sommer T, Rose M, Bingel U. Pain-specific modulation of hippocampal activity and functional connectivity during visual encoding. J Neurosci 2013;33:2571–81.
[43] Galli G, Santarnecchi E, Feurra M, Bonifazi M, Rossi S, Paulus MP, Rossi A. Individual and sex-related differences in pain and relief

responsiveness are associated with differences in resting-state functional networks in healthy volunteers. Eur J Neurosci 2016;43: 486–93.
[44] Gao Q, Xu F, Jiang C, Chen Z, Chen H, Liao H, Zhao L. Decreased functional connectivity density in pain-related brain regions of female migraine patients without aura. Brain Res 2016;1632:73–81.
[45] Garcia R, Spennato G, Nilsson-Todd L, Moreau JL, Deschaux O. Hippocampal low-frequency stimulation and chronic mild stress similarly disrupt fear extinction memory in rats. Neurobiol Learn Mem 2008;89: 560–6.
[46] Gonzalez-Roldan AM, Bomba IC, Diesch E, Montoya P, Flor H, Kamping S. Controllability and hippocampal activation during pain expectation in fibromyalgia syndrome. Biol Psychol 2016;121:39–48.
[47] Gray JA, McNaughton N. The Neuropsychology of Anxiety. Oxford: Oxford Univ Press, 2000.
[48] Hashmi JA, Kong J, Spaeth R, Khan S, Kaptchuk TJ, Gollub RL. Functional network architecture predicts psychologically mediated analgesia related to treatment in chronic knee pain patients. J Neurosci 2014;34:3924–36.
[49] Hebben N, Corkin S, Eichenbaum H, Shedlack K. Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M. Behav Neurosci 1985;99:1031–9.
[50] Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: a retrospective study of single-trial fMRI data. Neuroimage 2008;39:1867–76.
[51] Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1201–13.
[52] Hjelmervik H, Hausmann M, Osnes B, Westerhausen R, Specht K. Resting states are resting traits—an FMRI study of sex differences and menstrual cycle effects in resting state cognitive control networks. PLoS One 2014;9:e103492.
[53] Hong JY, Kilpatrick LA, Labus J, Gupta A, Jiang Z, Ashe-McNalley C, Stains J, Heendeniya N, Ebrat B, Smith S, Tillisch K, Naliboff B, Mayer EA. Patients with chronic visceral pain show sex-related alterations in intrinsic oscillations of the resting brain. J Neurosci 2013;33: 11994–2002.
[54] Howard MA, Krause K, Khawaja N, Massat N, Zelaya F, Schumann G, Huggins JP, Vennart W, Williams SC, Renton TF. Beyond patient reported pain: perfusion magnetic resonance imaging demonstrates reproducible cerebral representation of ongoing post-surgical pain. PLoS One 2011;6:e17096.
[55] Howard MA, Sanders D, Krause K, O'Muircheartaigh J, Fotopoulou A, Zelaya F, Thacker M, Massat N, Huggins JP, Vennart W, Choy E, Daniels M, Williams SC. Alterations in resting-state regional cerebral blood flow demonstrate ongoing pain in osteoarthritis: an arterial spin-labeled magnetic resonance imaging study. Arthritis Rheum 2012;64:3936–46.
[56] Icenhour A, Langhorst J, Benson S, Schlamann M, Hampel S, Engler H, Forsting M, Elsenbruch S. Neural circuitry of abdominal pain-related fear learning and reinstatement in irritable bowel syndrome. Neurogastroenterol Motil 2015;27:114–27.
[57] Izquierdo A, Wellman CL, Holmes A. Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J Neurosci 2006;26:5733–8.
[58] Jamadar SD, Sforazzini F, Raniga P, Ferris NJ, Paton B, Bailey MJ, Brodtmann A, Yates PA, Donnan GA, Ward SA, Woods RL, Storey E, McNeil JJ, Egan GF, Group AI. Sexual dimorphism of resting-state network connectivity in healthy ageing. J Gerontol B Psychol Sci Soc Sci 2018. doi: 10.1093/geronb/gby004 [E-pub ahead of print].
[59] Jensen KB, Kaptchuk TJ, Chen X, Kirsch I, Ingvar M, Gollub RL, Kong J. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cereb Cortex 2015;25:3903–10.
[60] Jin J, Maren S. Prefrontal-hippocampal interactions in memory and emotion. Front Syst Neurosci 2015;9:170.
[61] Jin L, Yang X, Liu P, Sun J, Chen F, Xu Z, Qin W, Tian J. Dynamic abnormalities of spontaneous brain activity in women with primary dysmenorrhea. J Pain Res 2017;10:699–707.
[62] Johnstone T, Salomons TV, Backonja MM, Davidson RJ. Turning on the alarm: the neural mechanisms of the transition from innocuous to painful sensation. Neuroimage 2012;59:1594–601.
[63] Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J Neurosci 2006; 26:9503–11.
[64] Kano M, Farmer AD, Aziz Q, Giampietro VP, Brammer MJ, Williams SC, Fukudo S, Coen SJ. Sex differences in brain response to anticipated and experienced visceral pain in healthy subjects. Am J Physiol Gastrointest Liver Physiol 2013;304:G687–99.
[65] Khan SA, Keaser ML, Meiller TF, Seminowicz DA. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. PAIN 2014;155:1472–80.
[66] Khanna S, Sinclair JG. Noxious stimuli produce prolonged changes in the CA1 region of the rat hippocampus. PAIN 1989;39:337–43.
[67] Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB. Reduced fear expression after lesions of the ventral hippocampus. Proc Natl Acad Sci U S A 2002;99:10825–30.
[68] Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. PAIN 2010; 148:257–67.
[69] Kunz M, Chen JI, Lautenbacher S, Vachon-Presseau E, Rainville P. Cerebral regulation of facial expressions of pain. J Neurosci 2011;31: 8730–8.
[70] Laird AR, Eickhoff SB, Kurth F, Fox PM, Uecker AM, Turner JA, Robinson JL, Lancaster JL, Fox PT. ALE meta-analysis workflows via the brainmap database: progress towards a probabilistic functional brain atlas. Front Neuroinform 2009;3:23.
[71] Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 2005;25:155–64.
[72] Larsson MB, Tillisch K, Craig AD, Engstrom M, Labus J, Naliboff B, Lundberg P, Strom M, Mayer EA, Walter SA. Brain responses to visceral stimuli reflect visceral sensitivity thresholds in patients with irritable bowel syndrome. Gastroenterology 2012;142:463–72.e463.
[73] Lee HF, Hsieh JC, Lu CL, Yeh TC, Tu CH, Cheng CM, Niddam DM, Lin HC, Lee FY, Chang FY. Enhanced affect/cognition-related brain responses during visceral placebo analgesia in irritable bowel syndrome patients. PAIN 2012;153:1301–10.
[74] Leuner B, Gould E. Structural plasticity and hippocampal function. Annu Rev Psychol 2010;61:111–3, C111–113.
[75] Linnman C, Appel L, Söderlund A, Frans O, Engler H, Furmark T, Gordh T, Långström B, Fredrikson M. Chronic whiplash symptoms are related to altered regional cerebral blood flow in the resting state. Eur J Pain 2009;13:65–70.
[76] Liu P, Qin W, Wang J, Zeng F, Zhou G, Wen H, von Deneen KM, Liang F, Gong Q, Tian J. Identifying neural patterns of functional dyspepsia using multivariate pattern analysis: a resting-state FMRI study. PLoS One 2013;8:e68205.
[77] Liu P, Zeng F, Zhou G, Wang J, Wen H, von Deneen KM, Qin W, Liang F, Tian J. Alterations of the default mode network in functional dyspepsia patients: a resting-state fmri study. Neurogastroenterol Motil 2013;25: e382–8.
[78] Lorenz IH, Egger K, Schubert H, Schnürer C, Tiefenthaler W, Hohlrieder M, Schocke MF, Kremser C, Esterhammer R, Ischebeck A, Moser PL, Kolbitsch C. Lornoxicam characteristically modulates cerebral pain-processing in human volunteers: a functional magnetic resonance imaging study. Br J Anaesth 2008;100:827–33.
[79] Luo Y, Yan C, Huang T, Fan M, Liu L, Zhao Z, Ni K, Jiang H, Huang X, Lu Z, Wu W, Zhang M, Fan X. Altered neural correlates of emotion associated pain processing in persistent somatoform pain disorder: an fMRI study. Pain Pract 2016;16:969–79.
[80] Ma X, Li S, Tian J, Jiang G, Wen H, Wang T, Fang J, Zhan W, Xu Y. Altered brain spontaneous activity and connectivity network in irritable bowel syndrome patients: a resting-state fMRI study. Clin Neurophysiol 2015;126:1190–7.
[81] Maclean PD, Delgado JM. Electrical and chemical stimulation of frontotemporal portion of limbic system in the waking animal. Electroencephalogr Clin Neurophysiol 1953;5:91–100.
[82] Maleki N, Brawn J, Barmettler G, Borsook D, Becerra L. Pain response measured with arterial spin labeling. NMR Biomed 2013;26:664–73.
[83] Manning BH, Merin NM, Meng ID, Amaral DG. Reduction in opioid- and cannabinoid-induced antinociception in rhesus monkeys after bilateral lesions of the amygdaloid complex. J Neurosci 2001;21:8238–46.
[84] Mano H, Kotecha G, Leibnitz K, Matsubara T, Sprenger C, Nakae A, Shenker N, Shibata M, Voon V, Yoshida W, Lee M, Yanagida T, Kawato M, Rosa MJ, Seymour B. Classification and characterisation of brain network changes in chronic back pain: a multicenter study. Wellcome Open Res 2018;3:19.
[85] Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang PC, Huang L, Apkarian AV, Baliki MN. Global disruption of degree rank order: a hallmark of chronic pain. Sci Rep 2016;6:34853.
[86] Maren S, Holmes A. Stress and fear extinction. Neuropsychopharmacology 2016;41:58–79.
[87] Martinsen S, Flodin P, Berrebi J, Löfgren M, Bileviciute-Ljungar I, Ingvar M, Fransson P, Kosek E. Fibromyalgia patients had normal distraction related pain inhibition but cognitive impairment reflected in caudate

nucleus and hippocampus during the Stroop Color Word Test. PLoS One 2014;9:e108637.
[88] Matre DA, Hernandez-Garcia L, Tran TD, Casey KL. "First pain" in humans: convergent and specific forebrain responses. Mol Pain 2010;6: 81.
[89] May A. Chronic pain may change the structure of the brain. PAIN 2008; 137:7–15.
[90] Mazza S, Frot M, Rey AE. A comprehensive literature review of chronic pain and memory. Prog Neuropsychopharmacol Biol Psychiatry 2018; 87:183–92.
[91] McCormick C, Moscovitch M, Valiante TA, Cohn M, McAndrews MP. Different neural routes to autobiographical memory recall in healthy people and individuals with left medial temporal lobe epilepsy. Neuropsychologia 2018;110:26–36.
[92] McCormick C, St-Laurent M, Ty A, Valiante TA, McAndrews MP. Functional and effective hippocampal-neocortical connectivity during construction and elaboration of autobiographical memory retrieval. Cereb Cortex 2015;25:1297–305.
[93] McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. Ann N Y Acad Sci 2001;933:265–77.
[94] McKenna JE, Melzack R. Analgesia produced by lidocaine microinjection into the dentate gyrus. PAIN 1992;49:105–12.
[95] Melzack R. The short-form McGill pain questionnaire. PAIN 1987;30: 191–7.
[96] Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998;395:381–3.
[97] Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007;62: 446–54.
[98] Miracle AD, Brace MF, Huyck KD, Singler SA, Wellman CL. Chronic stress impairs recall of extinction of conditioned fear. Neurobiol Learn Mem 2006;85:213–8.
[99] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2006;6:7.
[100] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[101] Moisset X, Villain N, Ducreux D, Serrie A, Cunin G, Valade D, Calvino B, Bouhassira D. Functional brain imaging of trigeminal neuralgia. Eur J Pain 2011;15:124–31.
[102] Moscovitch M, Cabeza R, Winocur G, Nadel L. Episodic memory and beyond: the Hippocampus and neocortex in transformation. Annu Rev Psychol 2016;67:105–34.
[103] Moulton EA, Becerra L, Maleki N, Pendse G, Tully S, Hargreaves R, Burstein R, Borsook D. Painful heat reveals hyperexcitability of the temporal pole in interictal and ictal migraine States. Cereb Cortex 2011; 21:435–48.
[104] Mutso AA, Petre B, Huang L, Baliki MN, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol 2014; 111:1065–76.
[105] Niddam DM, Chan RC, Lee SH, Yeh TC, Hsieh JC. Central representation of hyperalgesia from myofascial trigger point. Neuroimage 2008;39:1299–306.
[106] Paré D, Quirk GJ, Ledoux JE. New vistas on amygdala networks in conditioned fear. J Neurophysiol 2004;92:1–9.
[107] Parkes L, Fulcher B, Yücel M, Fornito A. An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. Neuroimage 2018;171:415–36.
[108] Phelps EA. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol 2004; 14:198–202.
[109] Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 2005;48: 175–87.
[110] Piché M, Arsenault M, Rainville P. Dissection of perceptual, motor and autonomic components of brain activity evoked by noxious stimulation. PAIN 2010;149:453–62.
[111] Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci 2001;21: 9896–903.
[112] Pohlack ST, Nees F, Ruttorf M, Schad LR, Flor H. Activation of the ventral striatum during aversive contextual conditioning in humans. Biol Psychol 2012;91:74–80.
[113] Poppenk J, Evensmoen HR, Moscovitch M, Nadel L. Long-axis specialization of the human hippocampus. Trends Cogn Sci 2013;17: 230–40.
[114] Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 2012;59:2142–54.
[115] Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 2008;33:56–72.
[116] Rainville P, Bao QV, Chrétien P. Pain-related emotions modulate experimental pain perception and autonomic responses. PAIN 2005; 118:306–18.
[117] Ranganath C, Ritchey M. Two cortical systems for memory-guided behaviour. Nat Rev Neurosci 2012;13:713–26.
[118] Roy M, Piché M, Chen JI, Peretz I, Rainville P. Cerebral and spinal modulation of pain by emotions. Proc Natl Acad Sci U S A 2009;106: 20900–5.
[119] Schacter DL, Addis DR, Buckner RL. Remembering the past to imagine the future: the prospective brain. Nat Rev Neurosci 2007;8:657–61.
[120] Scheinost D, Finn ES, Tokoglu F, Shen X, Papademetris X, Hampson M, Constable RT. Sex differences in normal age trajectories of functional brain networks. Hum Brain Mapp 2015;36:1524–35.
[121] Schmidt K, Forkmann K, Sinke C, Gratz M, Bitz A, Bingel U. The differential effect of trigeminal vs. peripheral pain stimulation on visual processing and memory encoding is influenced by pain-related fear. Neuroimage 2016;134:386–95.
[122] Schneider C, Palomba D, Flor H. Pavlovian conditioning of muscular responses in chronic pain patients: central and peripheral correlates. PAIN 2004;112:239–47.
[123] Schreiber KL, Loggia ML, Kim J, Cahalan CM, Napadow V, Edwards RR. Painful after-sensations in fibromyalgia are linked to catastrophizing and differences in brain response in the medial temporal lobe. J Pain 2017;18:855–67.
[124] Schwedt TJ, Chong CD, Chiang CC, Baxter L, Schlaggar BL, Dodick DW. Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. Cephalalgia 2014;34: 947–58.
[125] Shimo K, Ueno T, Younger J, Nishihara M, Inoue S, Ikemoto T, Taniguchi S, Ushida T. Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain. PLoS One 2011;6:e26681.
[126] Simons LE, Moulton EA, Linnman C, Carpino E, Becerra L, Borsook D. The human amygdala and pain: evidence from neuroimaging. Hum Brain Mapp 2014;35:527–38.
[127] Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991;253:1380–6.
[128] Stoeter P, Bauermann T, Nickel R, Corluka L, Gawehn J, Vucurevic G, Vossel G, Egle UT. Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: an fMRI study. Neuroimage 2007; 36:418–30.
[129] Ter Minassian A, Ricalens E, Humbert S, Duc F, Aubé C, Beydon L. Dissociating anticipation from perception: acute pain activates default mode network. Hum Brain Mapp 2013;34:2228–43.
[130] Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. Hum Brain Mapp 2012;33:1–13.
[131] Vachon-Presseau E, Centeno MV, Ren W, Berger SE, Tetreault P, Ghantous M, Baria A, Farmer M, Baliki MN, Schnitzer TJ, Apkarian AV. The emotional brain as a predictor and amplifier of chronic pain. J Dent Res 2016;95:605–12.
[132] Vachon-Presseau E, Roy M, Martel MO, Caron E, Marin MF, Chen J, Albouy G, Plante I, Sullivan MJ, Lupien SJ, Rainville P. The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans. Brain 2013;136:815–27.
[133] Veinante P, Yalcin I, Barrot M. The amygdala between sensation and affect: a role in pain. J Mol Psychiatry 2013;1:9.
[134] Veldhuijzen DS, Nemenov MI, Keaser M, Zhuo J, Gullapalli RP, Greenspan JD. Differential brain activation associated with laser-evoked burning and pricking pain: an event-related fMRI study. PAIN 2009;141:104–13.
[135] Wagner S, Sebastian A, Lieb K, Tüscher O, Tadić A. A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci 2014;15:19.
[136] Wang Y, Zhang X, Guan Q, Wan L, Yi Y, Liu CF. Altered reginal homogeneity of spontaneous brain activity in idiopathic trigeminal neuralgia. Neuropsychiatr Dis Treat 2015;11:2659–66.
[137] Weissman-Fogel I, Moayedi M, Taylor KS, Pope G, Davis KD. Cognitive and default-mode resting state networks: do male and female brains "rest" differently? Hum Brain Mapp 2010;31:1713–26.

[138] Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2:125–41.
[139] Wirt RA, Hyman JM. Integrating spatial working memory and remote memory: interactions between the medial prefrontal cortex and hippocampus. Brain Sci 2017;7. doi: 10.3390/brainsci7040043 [E-pub ahead of print].
[140] Wood PB, Patterson JC II, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL. Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study. J Pain 2007;8:51–8.
[141] Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 2011;8:665–70.
[142] Zhang SS, Wu W, Liu ZP, Huang GZ, Guo SG, Yang JM. Altered regional homogeneity in experimentally induced low back pain: a resting-state fMRI study. J Neuroeng Rehabil 2014; 11:115.
[143] Ziv M, Tomer R, Defrin R, Hendler T. Individual sensitivity to pain expectancy is related to differential activation of the hippocampus and amygdala. Hum Brain Mapp 2010;31: 326–38.