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Impaired mesocorticolimbic connectivity underlies increased mechanical pain sensitivity in chronic low back pain

Siyi Yu[1], **Wen Li**[2], **Wei Shen**[1], **Robert R. Edwards**[3], **Randy L. Gollub**[1], **Georgia Wilson**[1], **Joel Park**[1], **Ana Ortiz**[1], **Jin Cao**[1], **Jessica Gerber**[4], **Ishtiaq Mawla**[1], **Suk-Tak Chan**[4], **Jeungchan Lee**[4], **Ajay D. Wasan**[5], **Vitaly Napadow**[4], **Ted J. Kaptchuk**[6], **Bruce Rosen**[4], **Jian Kong**[1,4]

[1]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

[2]Department of Psychology, Florida State University, Tallahassee, FL, USA

[3]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[4]Department of Radiology, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

[5]Department of Anesthesiology, Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, USA

[6]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Abstract

Chronic low back pain (cLBP) is a prevalent disorder. A growing body of evidence linking the pathology of the reward network to chronic pain suggests that pain sensitization may contribute to cLBP chronification via disruptions of mesocortical and mesolimbic circuits in the reward system. Resting-state (RS) functional magnetic resonance imaging (fMRI) data was acquired from 90 patients with cLBP and 74 matched pain-free controls (HCs) at baseline and after a manipulation for back pain intensification. The ventral tegmental area (VTA) was chosen as a seed region to perform RS functional connectivity (FC) analysis. Baseline rsFC of both the mesocortical (between the VTA and bilateral rostral anterior cingulate cortex (rACC) / and medial prefrontal cortex (mPFC)) and mesolimbic (between the VTA and bilateral hippocampus/parahippocampus) pathways was reduced in patients with cLBP (vs. HCs). In addition, patients exhibiting higher back pain intensity (compared to the relatively lower back pain intensity condition) also showed increases in both mesocortical and mesolimbic connectivity, implicating these pathways in pain downregulation in cLBP. Mediation analysis further isolated the mesolimbic (VTA-hippocampus/

Correspondence to: Jian Kong, Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA 02129, jkong2@mgh.harvard.edu.

Ethics statement

This study was approved by the Institutional Review Board at Massachusetts General Hospital, and all subjects signed informed consent forms. J.K. has a disclosure to report (holding equity in a startup company, MNT, and pending patents to develop new neuromodulation tools) but declares no conflict of interest. All other authors declare no conflicts of interest.

Data and code availability statement

The data and code will be available per request.

parahippocampus) dysconnectivity as a neural mechanism mediating the association between mechanical pain sensitivity (indexed by P40 pressure) and cLBP severity. In sum, the current study demonstrates deficient mesocorticolimbic connectivity in cLBP, with the mesolimbic dysconnectivity potentially mediating the contribution of pain sensitization to pain chronification. These reward network dysfunctions and purportedly, dopaminergic dysregulations, may help us to identify key brain targets of neuromodulation in the treatment of cLBP.

Keywords

low back pain; central sensitization; pain sensitivity; quantitative sensory testing; mesocorticolimbic network; reward network; functional connectivity; ventral tegmental area

1. Introduction

Chronic low back pain (cLBP) poses a major health burden, with 50% to 85% of all people complaining of back pain at some time in their life (Andersson, 1999). The socioeconomic impact of cLBP is comparable to depression, heart disease, diabetes, and cancer (Dagenais et al., 2008; Maniadakis and Gray, 2000). In spite of such high prevalence and social burden, the pathophysiology of cLBP remains obscure, and treatment of cLBP is far from satisfactory.

Although still under investigation, literature suggests that central sensitization, which is defined as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input”, may be a key mechanism of chronic pain (Gold and Gebhart, 2010; Latremoliere and Woolf, 2009; Woolf, 2011). For instance, using quantitative sensory testing (QST) assessments, investigators have found widespread hyperalgesia at the back, and peripheral sites of chronic back pain patients have been reported using pressure (Clauw et al., 1999; Giesecke et al., 2004; Meints et al., 2019), electrical (Flor et al., 2004), and heat stimuli (Kleinbohl et al., 1999). Such intense and long-lasting nociceptive barrage can give rise to persistent central sensitization (Price, 1991), facilitating the onset of “chronic pain” (Coderre et al., 1993). However, it remains unclear what neural mechanisms underlie central sensitization in cLBP.

In parallel, the reward system and its anomalies have been increasingly linked to the pathophysiology of chronic pain (Baliki et al., 2010; Baliki et al., 2012; Borsook et al., 2016; Navratilova and Porreca, 2014; Porreca and Navratilova, 2017). Relief from pain can be viewed as a form of reward, whereas exacerbation of pain can be viewed as greater distance from reward (Benedetti et al., 2013). It has been postulated that the systems of pain and reward are deeply intertwined to the extent that pain and reward can be considered opposing processes (Becker et al., 2012) with shared neurobiological mechanisms (Leknes and Tracey, 2008). In support of this reward hypothesis of central pain sensitization, studies have found extensive similarities between the substrates of painful sensations and those of pleasant sensations in the reward network (Martikainen et al., 2015; Schweinhardt et al., 2009) and that analgesia can activate the same mesocorticolimbic reward network that is activated by typical rewards, such as food, money, and drugs (Kalivas et al., 1999; Kender et al., 2008).

Since the dopaminergic system plays a critical role in reward (Haber and Knutson, 2010), key regions of this system have been the focus of research into reward functioning in pain (Baliki et al., 2010; Lammel et al., 2011; Vachon-Presseau et al., 2016). The VTA is the primary origin of the dopamine system, innervating widespread limbic and cortical targets via dopaminergic projections known as the mesolimbic and mesocortical pathways (Morales and Margolis, 2017; Subramaniam and Roeper, 2017). Manipulation of these dopaminergic pathways has been shown to reliably modulate the affective component of pain and motivated behavioral responses to pain relief (Navratilova et al., 2012). In addition, in chronic pain including cLBP, aberrant activity and functional connectivity involving cortical and limbic targets of the VTA (e.g., anterior cingulate cortex, medial prefrontal cortex, and hippocampus) have been repeatedly identified (Egorova et al., 2015; Gondo et al., 2012; Li et al., 2017; Mutso et al., 2014; Ploghaus et al., 2001; Tu et al., 2019; Zhang et al., 2019). Therefore, it is likely that these mesolimbic and mesocortical pathways are intimately associated with the pathophysiology of cLBP and central sensitization.

This study thus aims to test the hypothesis that 1) alterations in mesocortical and mesolimbic functional connectivity are involved in the pathophysiology and neural underpinnings of cLBP, and 2) mesocortical and mesolimbic functional connectivity may mediate the association between central sensitization (as indicated by increased pain sensitivity) and LBP severity. Specifically, we first compared VTA functional connectivity between healthy controls (HCs) and a relatively large cohort of cLBP patients to isolate VTA circuitry pathology related to chronic pain. Then, by applying pain-exacerbating maneuvers to induce pain intensification, we established the involvement of these pathways in cLBP pathology by demonstrating alterations (or lack thereof) in VTA resting-state functional connectivity. Finally, we applied a mediation model to directly test the hypothesis that aberrant mesocorticolimbic connectivity mediates increased mechanical pain sensitivity in cLBP patients. In a previous behavioral study (Meints et al., 2019), we applied quantitative sensory testing methods to investigate pain sensitization in patients with cLBP (N = 167) and pain-free controls (N = 33) (most cLBP patients and pain-free controls in this study were included in the published study). We found that cLBP patients had increased sensitivity to mechanical (deep-tissue) pressure stimuli and more lingering pain afterwards compared to pain-free controls. In addition, we found that P40 score (the pressure at which moderate pain, rated 40/100, is induced) is associated with pain bothersomeness in cLBP patients. We thus decided to perform a mediation analysis to test the hypothesis that aberrant mesocorticolimbic connectivity mediates the contribution of P40 score to cLBP severity.

2. Materials and Methods

2.1 Participants

This study was approved by the Institutional Review Board at Massachusetts General Hospital, and all subjects signed informed consent forms. Nonspecific cLBP patients (Balague et al., 2012) and age- and gender-matched pain-free HCs were recruited in this study.

Inclusion criteria: 1) 20–50 years old, 2) Presence of nonspecific cLBP for a duration of at least 6 months with the condition established by a clinical evaluation, including the use of

X-ray/MRI reports, when available, 3) Pain intensity averaging at least 4 on a 0–10 visual analog scale (VAS). Exclusion criteria: 1) Specific causes of back pain (e.g., cancer-related back pain, post-surgical and traumatic back pain, neuropathic back pain, rheumatoid arthritis, widespread pain such as fibromyalgia), 2) Complicated back problems (e.g., prior back surgery, medicolegal issues), 3) Major systemic and/or psychiatric diseases or history of head injury or coma, 4) Presence of any contraindications to MRI scanning, 5) History of substance abuse or dependence.

The dataset has been used to explore the alteration in amplitude of low-frequency fluctuation (Zhang et al., 2019) and functional connectivity of the occipital cortex in patients with chronic low back pain (Shen et al., 2019). This study aims to explore alterations in mesocorticolimbic connectivity using seed-based functional connectivity methods in patients with cLBP, which has not been previously published.

2.2 Clinical assessment

Pain Bothersomeness Scale (Cherkin et al., 2009; Deyo et al., 1998; Yuan et al., 2008): This is a self-reported measure of cLBP pain severity that is commonly used to assess clinical chronic pain. Participants rated how bothersome their LBP was in the previous week with a VAS scale (0–10) from “not at all bothersome” (0) to “extremely bothersome” (10).

Current low back pain rating: Participants also rated the intensity of their current pain intensity using a 1–100 VAS (from “no pain” to “worst pain imaginable”). This rating was used to measure acute changes in low back pain intensity following our pain-exacerbating maneuver described below. Specifically, ratings were acquired right before and after each resting state fMRI scan and were averaged to index current pain intensity for each resting scan.

Pain sensitization: We applied a quantitative sensory testing (QST) method to assess pain sensitization. We focused on P40 pressure, a reliable (inverted) index of deep-tissue hyperalgesia (Meints et al., 2019). P40 pressure refers to the pressure at which moderate pain, rated 40/100, is induced. Therefore, lower P40 pressure indicates higher pain sensitization. This index was obtained with cuff pressure algometry (CPA), which determines an individual’s responses to deep pressure pain using a Hokanson rapid cuff inflator (Wey et al., 2014). Cuff stimulation was applied to the left gastrocnemius muscle and a limits procedure was used to determine the P40 pressure. This pressure was maintained for a duration of 2 minutes, during which participants provided verbal ratings of pain and unpleasantness every 30 seconds as well as fifteen seconds after cuff deflation (Meints et al., 2019).

2.3 Experimental procedures

Patients with cLBP underwent two MRI scan sessions. The first MRI session included a dimensional structural T1-weighted MRI and a resting state fMRI (RS-fMRI) scan. After this session, subjects exited the scanner and performed maneuvers to increase their LBP by about 30%. The maneuvers included lumbar flexion, extension, or rotation, which were

tailored to each subject based on what they reported would exacerbate LBP. Maneuvers were not performed if subjects were reluctant to increase their pain or if their pain was already very strong (greater than 70 on a 0–100 VAS)(Kong et al., 2013; Lee et al., 2018). After the maneuvers, which took around 15 minutes, subjects re-entered the scanner for the second (identical) RS-fMRI scan.

2.4 MRI data acquisition

The fMRI brain-imaging data was acquired with a 3T Siemens whole-body scanner using a 32-channel radio-frequency head coil at the Martinos Center for Biomedical Imaging. T2*-weighted functional images encompassing the whole brain were acquired with the gradient-echo EPI sequence (echo time: 30 ms, repetition time: 3,000 ms, flip angle: 90°, slice thickness: 2.6 mm, 44 slices, voxel size: 2.62×2.62×3.12 mm^3, field of view: 220×220 mm^2, matrix: 84×84 mm^2, slice orientation: axial, order of slice accession: interleaved). During the 6-minute resting state fMRI scan, subjects were asked to keep their eyes open and blink normally. High-resolution brain structural images were also acquired with a T1-weighted three-dimensional multi-echo magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time: 2,530 ms, echo time: 1.69 ms, slice thickness 1 mm, flip angle: 7°, 176 sagittal slices covering the whole brain, voxel size: 1×1×1 mm^3, field of view: 256×256 mm^2, matrix: 256×256 mm^2, inversion time: 1100 ms).

2.5 fMRI data processing and analysis

The fMRI data was preprocessed and analyzed using CONN toolbox version 18a (http://www.nitrc.org/projects/conn) in MATLAB (Math Works, Inc., Natick, MA, USA). We used the default preprocessing pipeline for volume-based analysis (direct normalization to MNI-space). The specific steps were as follows: slice timing correction; head motion correction; skull-stripping using BET; co-registration of the anatomical image to the mean functional image; segmentation of the anatomical gray matter, white matter, and CSF; normalization to MNI152 standard template; and smoothing with a 6-mm Gaussian kernel. Band-pass filtering was performed with a frequency band of 0.008–0.09 Hz.

To eliminate head motion and artifacts, we identified outlier time points in the motion parameters and global signal intensity using ART (http://www.nitrc.org/projects/artifactdetect). For each subject, we treated images (time points) as outliers if composite movement from a preceding image exceeded 0.5 mm, or if the global mean intensity was greater than 3 standard deviations from the mean image intensity for the entire resting scan. Outliers were included as regressors in the first-level general linear model along with motion parameters. In addition, to investigate the effect of head motion during the resting state scans, mean framewise displacement (FD)(Power et al., 2012) was calculated for each participant.

No significant difference in head movement was found between the cLBP patients and HCs ($p = 0.58$; cLBP: 0.039 ± 0.025; HC: 0.037 ± 0.025; two sample t-test). We also did not observe a significant difference between low pain and high pain conditions ($p = 0.08$; LP: 0.038 ± 0.025; HP: 0.044 ± 0.028; paired t-test).

2.6 Functional connectivity (FC) analysis

The VTA was our *a priori* seed for the seed-based connectivity analysis. We derived the bilateral VTA ROI from a probabilistic atlas of the dopaminergic system (Murty et al., 2014). This seed has also been used in a previous FC study on chronic pain (Liu et al., 2019). First-level correlation maps were produced by extracting the residual BOLD timeseries from the VTA seed and correlating that with the timeseries of all other voxels in the brain. The obtained (Pearson's) correlation coefficients (i.e., FC values) were further normalized into Z scores using Fisher transformation.

A whole-brain paired t-test was conducted to compare VTA FC at "low pain" and "high pain" conditions as indicated by low back pain intensity ratings during the fMRI scan and before and after the pain-exacerbating maneuvers. In addition, whole-brain Analyses of Covariance (ANCOVAs) of Group were conducted to compare VTA FC between the LBP and HC groups, with age and gender entered as covariates. Thresholds of voxel-wise $p < 0.005$ (uncorrected) and cluster-level $p < 0.05$ false discovery rate (FDR) correction were applied for whole brain analysis. Furthermore, conjunction analysis was used to identify any common VTA FC alterations in cLBP and different conditions.

2.7 Regions of Interest (ROIs)

Guided by our previous findings concerning cLBP (Li et al., 2017; Yu et al., 2014; Zhang et al., 2019), we focused on a set of pain-related ROIs, including cortical structures of the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) and subcortical limbic structures of the amygdala, hippocampus, and nucleus accumbens. The ROIs were defined using the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). To correct for multiple comparisons, Monte Carlo simulations using 3dFWHMx and 3dClustSim ([https://afni.nimh.nih.gov] released in July 2017) were applied to the ROIs.

2.8 Mediation analysis

In this study, we detected a significant association between P40 measurements, a pain sensitivity measurement, and LBP severity (pain bothersomeness) in cLBP patients (see Results section for details). We then performed mediation analysis to examine VTA FC as a potential mediator of this relationship, provided that a direct association between them was confirmed.

We used a simple mediation model from PROCESS Macro in SPSS for the mediation analysis (model 4) (Hayes, 2013). It is based on 10,000 bootstrap samples for a bias-corrected bootstrap confidence interval (CI). The indirect effect is considered significant when the 95% CI does not include zero (with a null hypothesis that there is no indirect effect). Three-step regression models were constructed as follows:

$$Y = cX + c_1U_1 + c_2U_2 + c_3U_3 + e1$$

$$M = aX + a_1U_1 + a_2U_2 + a_3U_3 + e2$$

$$Y=c'X+bM+b_1U_1 + B_2U_2 + b_3U_3 + e3$$

In these models, X is the independent variable (P40 score), Y is the dependent variable (bothersomeness), and M is the mediator (VTA FC with each brain region showing group differences between cLBP patients and HCs). Each variable was entered separately. U_1 and U_2 are gender and age, respectively. The *direct effect* is the effect of X on Y, independent of the effect of M on Y (path *c*'). The *direct effect* between X and Y is not a necessary prerequisite for mediation (Hayes, 2009). The *indirect effect,* or the effect of X on Y via M, is estimated as the product of the effect of X on M and the effect of M on Y, controlling for X (*ab* with 95% bootstrap CI). The total effect of X on Y is the sum of the direct and indirect effects (path c) (Figure 2).

3. Results

3.1 Demographic data

Ninety nonspecific cLBP patients and 74 age/gender-matched HCs were recruited for this study. The demographic data and pain-related parameters for cLBP and HC subjects are presented in Table 1. Patients' bothersomeness scores in the past week and duration of cLBP were 5.06 ± 1.88 (mean ± SD) and 6.94 ± 6.20 years, respectively.

Of all patients and controls, the P40 assessments were available on 80 cLBP patients and 33 pain-free controls. A comparison of P40 scores between the two groups showed that the P40 pressure score was significantly lower in the cLBP group than in the HC group ($P = 0.04$).

3.2 Pain rating changes following pain-exacerbating maneuvers

Of the 90 patients who completed the study, the average pain rating at baseline (before maneuver) was 31.65 ± 20.07 (mean ± SD). 76 patients showed increased LBP following the pain-exacerbating maneuver (55.23 ± 19.56, mean ± SD). For these patients, the first RS scan was defined as the "low pain" (LP) condition and the second RS scan the "high pain" (HP) condition. Eight patients reported a reduction in low back pain during the second versus the first RS-fMRI scan due to 1) a starting pain rating over 70 (on the 0–100 VAS) that precluded the maneuver, 2) their reluctance to perform the maneuver, or 3) a reduction of pain during the second scan after the maneuver. Since the aim of this study was to explore VTA changes when back pain increased (as compared to a low pain intensity condition), we chose to include these eight patients by assigning their second scan as the LP and first scan as the HP condition to be consistent with their actual pain levels. Excluding these patients did not change the results of the analyses. Finally, six patients who reported the same pain level during the first and second RS-fMRI scans were excluded from comparisons between the HP and LP conditions. Overall, self-reported pain intensity for the LP condition (31.33 ± 20.02, mean ± SD) was significantly lower than that of the HP condition (51.83 ± 22.21, mean ± SD,) ($p < 0.001$).

3.3 VTA-based FC amplification due to pain intensity increase

We first established the involvement of VTA pathways in cLBP pathophysiology by examining perturbations in these pathways in response to increased pain intensity. Comparing the LP and HP conditions in patients with cLBP, we observed increased VTA FC at the bilateral mPFC, bilateral rACC, and left hippocampus in the HP condition (Table 2 and Figure 1A). These results suggest that in cLBP, the mesocortical and mesolimbic pathways remain somewhat responsive to phasic increases in back pain.

3.4 VTA-based FC alterations in patients with cLBP

We then examined the difference in VTA pathways between cLBP patients and HCs to test the hypothesis of mesocortocolimbic circuitry pathology in cLBP. A comparison between the two groups (at the baseline RS scan) showed that VTA-based FC was significantly lower in cLBP patients at the bilateral mPFC, bilateral rACC, and bilateral HIP/parahippocampus (PHG) (Figure 1B, Table 2). By contrast, there was no significant VTA FC increase in patients with cLBP. Notably, these clusters in the mPFC and rACC highly overlapped with those identified in the cLBP HP-LP comparison (Figure 1C), emphasizing a paradoxical and potentially maladaptive tonic dysconnectivity of the VTA mesocortical and mesolimbic pathways that could underlie the pathophysiology of low back pain.

Findings from our previous studies suggest that the rACC plays a prominent role in the pathophysiology of chronic pain. Resting state rACC oscillations are positively correlated with pain severity in patients with cLBP (Zhang et al., 2019), and decreased rACC volume is associated with protracted duration of chronic pain (Jensen et al., 2013). We therefore explored the association between VTA-rACC FC and cLBP duration and severity. We found that VTA-rACC FC strength was negatively correlated with cLBP pain severity (pain bothersomeness; $r = -0.22$, $p = 0.039$ FDR corrected) in the previous week (Figure 1D) but not back pain intensity during the MRI scan. Furthermore, this VTA-rACC FC was also negatively correlated with cLBP duration ($r = -0.24$, $p = 0.039$ FDR corrected) (Figure 1E), highlighting its involvement in cLBP chronification.

3.5 Reduced VTA-HIP/PHG FC mediated the association between pain sensitization and cLBP severity

Correlation analysis between pain sensitization and cLBP severity confirmed their association as reported previously by our group (Meints et al., 2019) using a larger sample size (167 cLBP patients and 33 controls). Specifically, we found that LBP severity (bothersomeness in the past week) was negatively associated with pain sensitization (P40 pressure; $r = -0.329$, $p = 0.003$).

We then tested the hypothesized mediation effect of VTA-based FC on the association between pain sensitization and cLBP severity. Mediation analysis revealed a significant indirect effect of VTA-HIP/PHG FC ($\beta = 0.0009$, 95% CI = 0.0001, 0.0035) on the relationship between sensitization and pain severity in patients with cLBP (Figure 2), indicating that VTA-HIP/PHG connectivity mediated the effects of sensitization on pain bothersomeness. No mediation effects were found for VTA FC with other ROIs (rACC and mPFC).

4. Discussion

In a large sample of patients with cLBP and matched healthy controls, we observed that patients with cLBP had reduced intrinsic functional connectivity between the VTA and its cortical and limbic targets, including the bilateral mPFC, rACC, and medial temporal lobe (HIP/PHG). We further confirmed a strong association between pain sensitization (P40 pressure) and clinical pain severity (pain bothersomeness in the past week) among patients, and importantly, demonstrated that this association was mediated by reduced VTA-right-hippocampus connectivity. Critically, mesocortical and mesolimbic pathways were strengthened when low back pain intensity was higher (compared to the relatively lower back pain intensity condition). These findings thus implicate mesocorticolimbic dysconnectivity in the pathophysiology of cLBP and highlight deficient VTA-HIP/PHG connectivity as a neural underpinning for the contribution of pain sensitization in patients with chronic low back pain.

The mesocorticolimbic pathways are known to mediate reward processing. Here, we found that increased back pain intensity induced a phasic increase in mesocortical connectivity, lending further credence to the notion that the pain and reward systems share these dopaminergic VTA pathways. The rACC, a structure repeatedly identified in cLBP (Baliki et al., 2012; Jensen et al., 2013; Yu et al., 2014; Zhang et al., 2019), is densely populated with opioid receptors (Vogt et al., 2001) and is known to play a key role in the descending pain modulatory system (DPMS) (Fields, 2004; Kong et al., 2009; Kong et al., 2018; Kong et al., 2019; Li et al., 2016), which initiates the release of endogenous opioids and inhibits nociceptive signaling from the periphery (Cheriyan and Sheets, 2018; Fields, 2004).

Although verification in human trials is still needed, investigators on a rodent study (Chen et al., 2018) found that selective activation of ACC-spinal cord projecting neurons caused behavioral pain sensitization, while inhibition induced analgesic effects. As such, the VTA-rACC pathway can efficiently execute phasic analgesic modulation and motivate pursuit of pain relief (Elston and Bilkey, 2017; Vogt et al., 2001). Therefore, we speculate that when back pain intensity increases (compared to the relatively lower intensity back pain condition), the increased VTA connectivity with the rACC /mPFC may upregulate activity in these prefrontal cortices to blunt pain responses via descending analgesic signal transmission.

Interestingly, at baseline (i.e., a tonic state), patients with cLBP exhibited reduced connectivity in VTA-rACC and VTA-mPFC pathways compared to HCs. These prefrontal cortical regions were identified in both analyses, attesting to their functional relevance to low back pain processing. It is also worth noting that similar pattern changes have also been detected in primary somatosensory cortex (S1) functional connectivity in cLBP patients (i.e., S1 functional connectivity decreased when cLBP patients experienced low intensity LBP as compared with healthy controls, and S1 functional connectivity increased when cLBP patients experienced high intensity LBP as compared with the low intensity condition)(Kong et al., 2013).

This paradoxical deficit in baseline connectivity in cLBP suggests that cortical pain modulatory processes can break down due to overcompensation in response to persistent pain throughout the course of the development of chronic pain. In keeping with this notion, cLBP patients with phasic low back pain increase exhibited greater reduction in baseline VTA-rACC connectivity, and longer duration of cLBP was coupled with greater reduction in connectivity. This idea of maladaptive pain modulation via the rACC and mPFC in cLBP aligns with a previous report that the rACC and mPFC are recruited into the pain network as low back pain becomes chronic (Hashmi et al., 2013). The VTA-rACC pathway has also been found to be deficient in other chronic conditions (such as anhedonia; (Wacker et al., 2009). Future study is needed to provide a better interpretation of the finding.

Patients with cLBP also showed decreased functional connectivity of the mesolimbic (VTA-HIP/PHG) pathway. The hippocampus is a key region in learning and memory, and it has been previously identified in fMRI studies on pain and anxiety. Studies have also shown that it plays an important role in anxiety of pain (Ploghaus et al., 2001) and the nocebo effect (Kong et al., 2008). Chronic pain has been conceptualized as a type of long-term learning (Apkarian et al., 2009). A previous study found that processing reorganization within the hippocampus and between the hippocampus and cortex may contribute to the transition from subacute to chronic pain and may also underlie learning and emotional abnormalities associated with chronic pain (Mutso et al., 2014).

Mesolimbic circuits involving the hippocampus have been associated with pain relief and pain-induced analgesia (Gear et al., 1999; Gondo et al., 2012; Navratilova et al., 2012), and the reduced VTA-hippocampus connectivity in cLBP corroborates the notion that altered hippocampal functional connectivity contributes to the development of chronic back pain (Egorova et al., 2015; Gondo et al., 2012; Mutso et al., 2014; Ploghaus et al., 2001). Importantly, we found that this VTA-HIP/PHG connectivity reduction mediated the association between P40 and cLBP symptom severity, suggesting that individuals with weak VTA-HIP/PHG FC showed strong contribution of pain sensitization to cLBP severity.

This mediation effect of VTA-HIP/PHG dysconnectivity may support the stress model of chronic pain, which implicates stress-related alterations of hippocampal functioning in pain sensitization (Gondo et al., 2012; Kong et al., 2008; Ploghaus et al., 2001) and chronification (Vachon-Presseau et al., 2013). According to this model, anxiety and stress can affect hippocampus connectivity, including VTA-hippocampus connectivity (Marusak et al., 2017), thereby heightening pain sensitization by priming aversive responses to pain stimulation and impairing inhibitory modulation of midbrain activity to suppress fear responses. As a result, pain outcomes worsen, increasing clinical symptoms and precipitating the onset of chronic pain (Gondo et al., 2012; Kong et al., 2008; Ploghaus et al., 2001).

While both mesocortical (involving the rACC and mPFC) and mesolimbic (involving the hippocampus) pathways are disrupted in cLBP, current results suggest that dysfunctions in the mesolimbic pathway could be even more severe and consequential (i.e., connectivity enhancement following pain intensification). Second, the mediation effect between pain sensitization and cLBP severity was observed for VTA-HIP/PHG (but not mesocortical) dysconnectivity, suggesting a critical role of this mesolimbic pathology in pain sensitization

in cLBP. These two consequences of VTA-HIP/PHG dysconnectivity, whether additive (parallel) or supra-additive (interactive), accentuate mesolimbic dysconnectivity in the chronification of cLBP. However, it is worth noting that this difference between mesocortical and mesolimbic pathways is likely quantitative as opposed to qualitative. In fact, a *post hoc* analysis indicated that reductions in VTA-HIP/PHG and VTA-rACC connectivity were somewhat correlated ($r = .15$, $p = .046$, one-tailed), suggesting a considerable degree of shared pathology in these circuits.

There are several limitations to this study. First, it is a cross-sectional (vs. longitudinal) design and thus cannot reveal causal relationships in the etiology and maintenance of cLBP. Second, the connectivity analysis concerns inter-regional functional coupling as opposed to directional, causal effects between regions. Thirdly, we did not collect data such as depression scores in healthy subjects, which could confound our correlation analysis. Nonetheless, as the average BDI score in our study is quite low (with an average score of 6.12 ± 6.0), less than mild depression (score > 14) as defined by the BDI manual, we believe that this confound is rather minimal. Finally, we cannot completely exclude the potential influence of medication in patients with chronic low back pain. Nevertheless, to avoid the potential influence of opiates, only low-dose opioid use was allowed in this study (less than 10 mg/per day), and only a small portion of participants were taking this medication (see Supplementary Table 1 for details of medication use). We thus do not believe medication is a major confounding factor in this study.

In conclusion, the present study demonstrated VTA-based mesocorticolimbic pathway deficits in patients with cLBP, though both mesocortical and mesolimbic pathways were still somewhat functional as indicated by increased FC (in pain-induced analgesia). This disruption in the mesolimbic (VTA-HIP/PHG) circuit facilitates pain sensitization, thereby perpetuating pain symptoms and promoting the development of chronic back pain. Overall, our findings highlight the importance of the mesocorticolimbic network in the neuropathology of cLBP. Critically, the isolation of mesolimbic dysconnectivity in the central sensitization and chronification of cLBP may help to identify key targets of neuromodulation methods (such as transcranial magnetic stimulation) that could significantly improve the treatment of this highly prevalent and debilitating disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlight

Mesocortical and mesolimbic connectivity decreased in cLBP patients compared to controls. Mesocortical and mesolimbic connectivity increased when back pain intensity increased. Mesolimbic connectivity mediated the association between pain sensitivity and cLBP severity.

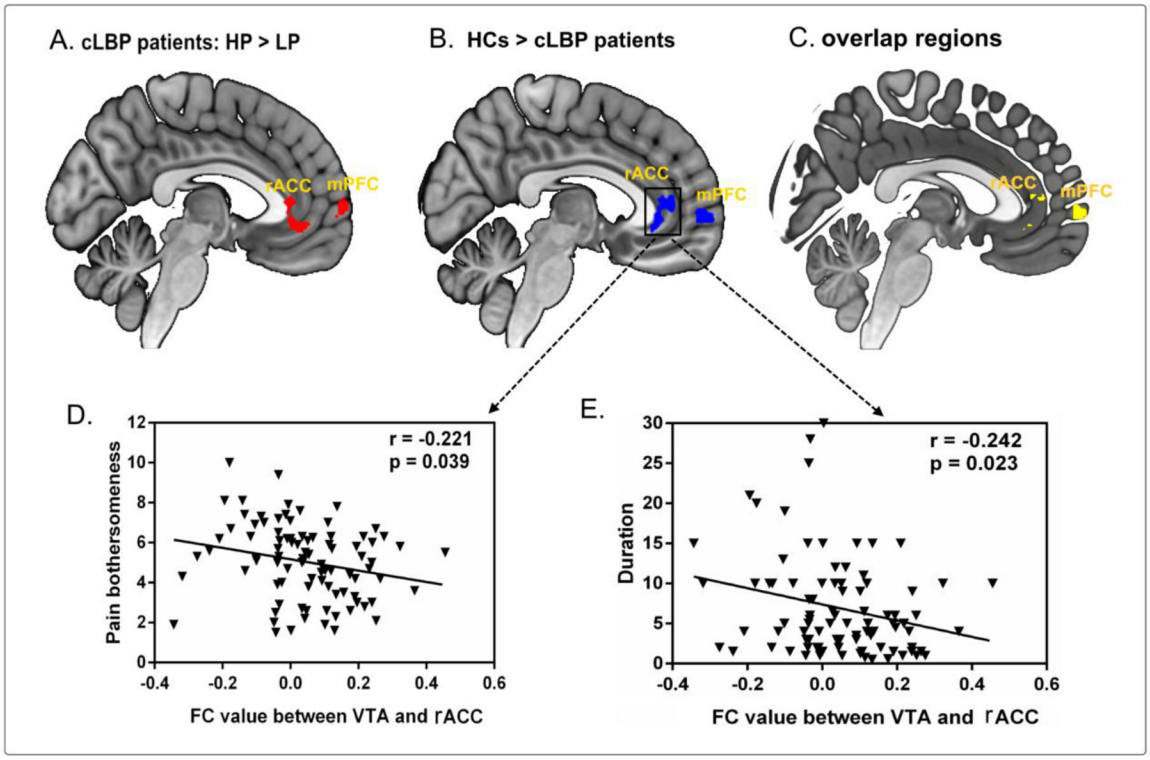

Figure 1.

A. Group comparison between cLBP patients with high and low pain. cLBP patients in the HP condition had increased FC in the bilateral mPFC and rACC compared to cLBP patients in the LP condition. B. Group comparison between cLBP patients and HCs. Compared to healthy controls, cLBP patients had significantly lower FC in the bilateral rACC and mPFC. C. Overlap between the two analyses at the bilateral rACC and mPFC. D. Reduced FC value between the VTA and rACC was negatively associated with increased bothersomeness score (left column) and duration (right column) in cLBP patients, controlled for age and gender. Abbreviations: cLBP, chronic low back pain; FC, functional connectivity; HC, healthy control; HP, high pain; LP, low pain; mPFC, medial prefrontal cortex; rACC, rostral anterior cingulate cortex; VTA, ventral tegmental area.

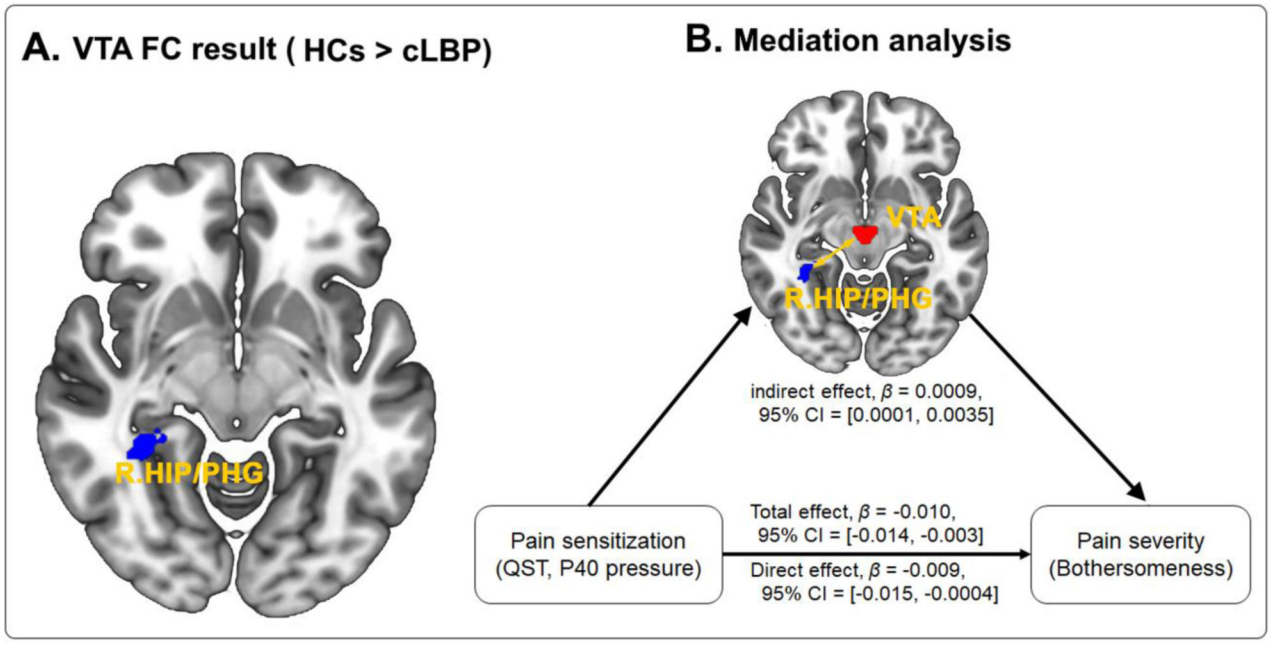

Figure 2.

A. Group comparison between cLBP patients and HCs. Compared to healthy controls, cLBP patients had significantly lower FC in the right HIP/PHG. B. Mediation effects of VTA-HIP/PHG functional connectivity on the association between pain sensitization (P40 pressure) and pain severity (bothersomness) in cLBP patients. Abbreviations: cLBP, chronic low back pain; FC, functional connectivity; HC, healthy control; HIP, hippocampus; PHG, parahippocampus; QST, quantitative sensory testing; VTA, ventral tegmental area.

Table 1.

Demographic and clinical traits for all participants (mean ± SD)

Characteristic	cLBP (n=90)	HCs (n=74)	*T* or x^2	p value
Age	34.46±8.97	32.44±8.38	1.47	0.14
Gender (n, male/female)	38/52	31/43	0.97	0.55 †
BDI	6.12±6.00	-	-	-
QST P40 pressure (mmHg) [a]	171.09±68.09	201.94±79.81	−2.02	0.04
Pain bothersomeness [b]	5.06±1.88	-	-	-
Pain intensity (low pain condition) [c]	31.33±20.02	-	-	-
Pain intensity (high pain condition) [c]	51.83±22.21	-	-	-

†, the *p* value was obtained by a chi-square test; other *p* values were obtained by a two-sample t-test.

[a], the number of cLBP subjects was 80, and the number of HCs subjects was 33.

[b], pain bothersomeness: low back pain bothersomeness during the last week.

[c], pain intensity of 84 cLBP subjects whose pain intensity increased in the post-maneuver scan; the pain intensity of the patients in the high pain condition was significantly higher than that of patients in the low pain condition ($p<0.001$).

Abbreviations: BDI, Beck Depression Inventory; QST, Quantitative Sensory Testing; cLBP, chronic low back pain; HC, healthy control.

Table 2.

Results derived from whole brain and ROI VTA FC analysis

Contrast	Brain regions	Cluster size (voxels)	MNI coordinates (x, y, z)	Peak Z- value
HCs > cLBP	Bilateral rACC	189	−4,34,−2	4.25
	Bilateral mPFC	125	4,62,0	3.75
	Left HIP *	41	−26,−38,−2	3.78
	Right HIP/PHG	132	34,−42,−4	4.73
HCs < cLBP	No region above threshold			
HP > LP	Bilateral mPFC *	80	−2,62,2	3.42
	Bilateral rACC *	119	2,40,−4	3.44
	Left HIP *	11	−34,−26,−14	3.15
HP < LP	No region above threshold			

*, results were significant at cluster $P < 0.05$ after 3dFWHMx and 3dClustSim correction. Other results were significant at cluster $P_{FDR} < 0.05$ corrected at the whole brain level.

Abbreviations: cLBP, chronic low back pain; FC, functional connectivity; HC, healthy control; HP, high pain; LP, low pain; mPFC, medial prefrontal cortex; HIP, hippocampus; PHG, parahippocampus; rACC, rostral anterior cingulate cortex; VTA, ventral tegmental area.