Title

Brain moderators supporting the relationship between depressive mood and pain.

Journal

Pain, 160(9)

ISSN

0304-3959

Authors

Adler-Neal, Adrienne L
Emerson, Nichole M
Farris, Suzan R
et al.

Publication Date

2019-09-01

DOI

10.1097/j.pain.0000000000001595

Peer reviewed

HHS Public Access

Author manuscript

Pain. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Pain. 2019 September ; 160(9): 2028–2035. doi:10.1097/j.pain.0000000000001595.

Brain moderators supporting the relationship between depressive mood and pain

Adrienne L. Adler-Neal[1], **Nichole M. Emerson**[1], **Suzan R. Farris**[1], **Youngkyoo Jung**[2], **Robert C. Coghill**[3,4], **Fadel Zeidan**[1,5]

[1]Department of Neurobiology and Anatomy, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem NC 27157

[2]Department of Radiology, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem NC 27157

[3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, United States

[4]Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

[5]Department of Anesthesiology, University of California San Diego, 9452 Gilman Drive, MC 0719, San Diego, CA, 92093

Keywords

fMRI; depression; negative mood; pain; arterial spin labeling; moderation

INTRODUCTION

The subjective experience of pain is driven, in part, by a host of factors predicated by affect, psychosocial context and the capacity to regulate behavioral responses to ascending nociceptive information [56; 61; 74]. It is not surprising then, that negative mood significantly exacerbates behavioral and neural pain responses [68; 72]. The contiguity between pain and dysphoria is also directly translatable to the development of pathological and clinical conditions [6]. That is, higher levels of depression predict greater chronic pain severity [54] and pain symptomology [15; 39].

In the presence of noxious stimulation in healthy individuals, negative affect is associated with **a)** higher experimentally-induced pain sensitivity [69; 78], **b)** attenuated pain thresholds [44] **c)** lower pain tolerance [66; 81] and **d)** greater activation in brain regions that process fear (amygdala) and the evaluation of sensory processes (anterior insula) [12]. Together, these findings suggest that distressed mood sensitizes an individual's attentional

Corresponding Author: Fadel Zeidan, PhD, Department of Anesthesiology, University of California San Diego, 9452 Gilman Drive, San Diego, CA, 92093, fzeidan@ucsd.edu, Telephone: 858-246-2391.

DISCLOSURES

The authors declare no competing financial interests or conflicts of interest.

propensity towards arising sensory events [13; 67]. Others have postulated that depressive mood increases pain-related ruminations [37] that may be more reflective of a generalized inability to self-regulate affective appraisals of noxious stimuli [10; 24]. Yet, the neural mechanisms supporting the facilitation of the *interplay* between depressive symptomology and pain remain poorly characterized.

The present study combined an optimized, arterial spin labeled fMRI technique [63] and psychophysical pain testing in healthy, non-depressed and pain-free individuals to determine **a)** if higher levels of depressive mood are associated with increased behavioral pain responses and **b)** the neural moderators supporting this postulated relationship. As employed and validated in previous studies examining healthy individuals [11; 30; 33; 34; 43; 70], the Beck Depression Inventory II (Beck et al., 1996a) was used in the present study as a measure of depressive mood. Alterations in the so called Default Mode Network, a neural network characterized by oscillating activation between the medial prefrontal (mPFC) and posterior cingulate cortex (PCC), are associated with heightened negative mood and pain through exacerbated self-referential ruminative appraisals of ascending nociceptive signaling [37; 38; 41; 62]. Further, negative mood during noxious heat is associated with higher pain reports and corresponding increases in pain-related lower level somatosensory activation [6; 13; 40; 68]. Novel, fMRI-based moderation analyses were employed to test the hypotheses that the positive relationship between pain and negative mood co-varies with greater activation in sensory discriminative brain regions (somatosensory/insular cortices and thalamus) [17] and brain regions supporting self-referential processes (mPFC; PCC) [19; 37].

METHODS AND MATERIALS

Participants

These data were collected as part of a previously published dataset examining brain mechanisms of meditation and placebo [180]. Eighty-five healthy, pain-free, right-handed volunteers completed the first two sessions of the experiment (see Study Design). MRI-related artifacts compromised data from nine subjects (defined below in the CBF Artifact Detection Procedures section). Data from 76 participants (mean age = 27 ± 5 years; 40 females; 36 males; 57 = White, 8 = Black, 5 = Asian, 5 = mixed race, 1 = Hispanic) are presented here (Table 1). Exclusion criteria included individuals regularly taking psychotropic (anti-depressants; anti-anxiety) or pain medications, and pregnant women. Wake Forest School of Medicine's Institutional Review Board approved all study procedures. All subjects provided written, informed consent recognizing that they would experience painful heat stimuli, that all methods were clearly explained, and that they were free to withdraw from the study.

Stimuli

As described previously [64; 79], a TSA-II device (Medoc) was used to deliver all thermal stimuli using a 16×16 mm thermal probe. The thermal probe was moved to a new stimulation site after each experimental series to reduce habituation. All stimulus temperatures were ≤ 49°C.

Psychophysical assessment of pain

Pain intensity and unpleasantness ratings were assessed separately using a 15 cm plastic sliding visual analog scale (VAS) [53]. The minimum rating ("0") was designated as "no pain sensation" or "not at all unpleasant," whereas the maximum rating ("10") was labeled as "most intense pain sensation imaginable" or "most unpleasant sensation imaginable," respectively. There was a high correlation between pain intensity and pain unpleasantness ratings ($r = .94$; $p < .001$). Thus, due to the high collinearity between pain intensity and unpleasantness ratings and to better avoid unreliable and poorly reproducible parameter estimates [50], functional neuroimaging analyses were conducted on pain intensity ratings only.

Psychological Outcomes

The BDI-II is a 21 item assessment using a 4-point Likert scale (0–3) [9] with scores ranging from 0–63. Higher scores indicate greater levels of depressive symptomology/mood. In healthy participants, the Beck Depression Inventory II (BDI) measures depressive symptomology [11; 34; 43; 70], mood disturbance, negative affect and depressive mood [42; 60]. The BDI-II exhibits high internal consistency ($\alpha = .91$) [9]. As characterized previously and as used in general medical practice [9; 11], normal depressive symptomology is associated with scores lower than 10, mild/minor depressive symptomology corresponded to scores equal to and/or greater than 10 and moderate to severe depression is associated with scores equal to and/or greater than 19. Importantly, there was a good range of BDI scores (0–18; mean =2.92; SEM=0.52) and all participants in the present study exhibited BDI scores equal to or less than 18. Thus, all participants exhibited scores that were below the cutoff for clinically significant depression. The BDI-II was administered before session 1 to assess depressive mood (see Study Design).

Anatomical MRI Acquisition

Participants were scanned on a 3T Siemens Skyra scanner with a 32-channel head coil. High-resolution T1-weighted images were obtained using a MP-RAGE sequence: flip angle = 9°, T1 = 900 ms, TE = 2.95, TR = 2300 ms, pixel bandwidth = 240 Hz/pix, FOV = 25.6 × 24 cm, 192 slices, 1 mm isotropic spatial resolution, GRAPPA factor of 2, scan time = 5 min 12 s.

Functional MRI Acquisition

Four pseudo-continuous arterial spin labeling (PCASL) series [63] were performed to acquire whole-brain cerebral blood flow (CBF) images: 2D single shot EPI, tagging duration = 1.8 s, post-labeling delay = 1.2 s, TI = 3 s, TE = 12 ms, TR = 4s, flip angle = 90°, reps = 66, FOV = 22 × 22 cm, in-plane matrix size = 64 × 64, number of slices = 26, slice thickness = 5 mm with 1 mm slice gap, scan time = 4 min 24 s. Background suppression was not employed. The imaging slab covered the entire cerebellum and cerebrum, and the inferior edge of the imaging slab detected the bottom of the cerebellum. The tagging plane was set in a fixed position on the axial plane 2cm below the imaging slab. Our PCASL sequence largely followed the recommended guidelines [2] for the implementation of ASL for clinical applications, except for the employment of 3D GRASE acquisition and 2D EPI. Instead, we

employed a 2D EPI acquisition that is more suitable for functional measures due to lower sensitivity to motion artifacts [2]. A single-shot EPI acquisition with GRAPPA factor of 2 was used.

Study Design

Experimental Session 1: Psychophysical Training—After providing written consent, participants completed the BDI-II. As previously conducted [64; 79], participants underwent psychophysical training, where they were familiarized with 32, 5 second (s) duration stimuli (35 – 49°C) on ventral aspect of the left forearm and use of the VAS. The thermal probe was moved to a new location after each stimulus to reduce habituation/sensitization. Subjects were administered a 4 minute (min) 24 s thermal stimulation series delivered to the back of the left lower leg that was identical to the heat paradigm used in the subsequent MRI session. This heat series consisted of ten alternating 12s plateaus of 49°C and 35°C.

Experimental Session 2: MRI Session—On a separate day, participants reported to the Wake Forest MRI center and were positioned in the MRI scanner and placed their respective right calf on the thermal probe. During all MRI acquisition periods, participants were instructed to “stay still and keep eyes closed.” A structural MRI scan (~5 min) was acquired first. Next, four PCASL series were acquired (4 min 24 s each). The PCASL neutral series consisted of continual, innocuous (35°C) stimulation. The heat PCASL series included ten alternating, 12 s plateaus of 49°C and 35°C. Two heat and two neutral PCASL series were administered in an alternating fashion and the order of administration was counterbalanced across participants. After each PCASL series, participants were instructed to provide VAS pain intensity and pain unpleasantness ratings “corresponding to the overall experience” of the respective PCASL series. The thermal probe was moved to a new location on the right calf after each PCASL series.

Statistical Analysis of Behavioral Data

Behavioral data were analyzed using SPSS 19 software (IBM, Armonk, New York). As previously [79], pain intensity and unpleasantness ratings were analyzed separately. Bivariate correlational analyses examined the relationship between BDI and pain intensity and unpleasantness ratings, respectively.

Statistical Analysis of Neuroimaging Data

Calculation of Cerebral Blood Flow—Each 4D series of PCASL images was converted into a single CBF file. Alternating tag and control images were subtracted in order to generate perfusion-weighted series. Due to the motion-sensitive nature of PCASL, we filtered data with motion correction (DOF = 6) using FMRIB’s Linear Image Registration Tool (MCFLIRT) [32] and removed individual perfusion-weighted images exhibiting gross perfusion fluctuations (CBF values = 2.25 SD above/below corresponding series mean) that may corrupt the final CBF map [65]. To reduce the influence of subject motion on CBF quantification, the PCASL time series data were filtered to remove individual perfusion-weighted images with higher motion parameters and perfusion fluctuations that corrupt the final CBF map [65]. The PCASL sequence included 66 perfusion-weighted volumes

(images) per PCASL series per subject. Thus, across all four PCASL scans, there were a total of 264 images per subject. Of the 76 participants in the present study, images were filtered out of 27 subjects. In total there were 80 images removed across all 76 participants and their respective 20, 064 images. Thus, only .04% of the images were filtered out of the preprocessing stage. Long recovery time (3 TRs) after presaturation was used during the first volume of the PCASL data to allow for magnetization recovery. This volume was used to estimate the CSF M0 value and to scale raw perfusion weighted images into a quantitative CBF map according to the general kinetic model [14]. Global CBF was calculated by averaging the CBF of all voxels within the brain.

CBF Artifact Detection Procedures—Careful visual inspections were first performed on perfusion-weighted images to identify gross MRI-related artifacts. Next, regional masks were created to sample CBF in the territories of the carotid and vertebral arteries to identify potential tagging failures. Additionally, global CBF values were extracted to further characterize potential CBF artifacts. CBF images exhibiting low (≤ 20ml/100g tissue/min) global/regional CBF values were subsequently characterized as anomalous [80] and could lead to inaccurate statistical maps [21].

Statistical Analysis of Regional Signal Changes Within the Brain—FSL's [Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (Center for FMRIB Version 5.0, University of Oxford, Oxford, UK)] FMRIB Local Analysis of Mixed Effects (FLAME 1+2) was used for image processing and analysis [80]. Individual CBF volumes from each PCASL series were concatenated into one 4D volume for first-level analyses (4-volume series). Functional data were spatially smoothed with a 9mm full-width at half-maximum 3D isotropic Gaussian kernel prior to standard processing within the FEAT module of FSL. Each CBF volume was scaled by its mean global intensity (intensity normalization) within the FEAT module of FSL to minimize confounds arising from global CBF fluctuations. Temporal filtering was not performed since each CBF volume in the series is temporally independent from adjacent CBF volumes. Functional images were registered to their respective structural space using a six-parameter linear 3D transformation. Brain-extracted structural data were transformed into standard stereotaxic space (as defined by Montreal Neurologic Institute) using a 12-parameter affine transformation followed by a nonlinear transformation (FNIRT; 10×10×10mm resolution) [3; 4; 32]. This nonlinear transformation was then applied to CBF data.

Statistical analysis of regional signal changes were performed on 4D concatenated CBF data (first-level analyses) using fixed-effects general linear modeling (GLM) [75]. Activation across individuals was assessed using random-effects analyses. T/F statistic images were Gaussianized and thresholded using clusters determined by a $z > 2.3$. Corrected cluster significance threshold was set at $p < 0.05$ [77]. This procedure ensures that the probability of false-positive findings was corrected for multiple comparisons [76].

Brain Moderation Analyses: A first-level ANOVA was first performed for each participant to identify the main effect of pain (heat vs. neutral stimulation). A second-level analysis was then performed across individuals to a) identify significant mean effects corresponding to the main effect of pain and b) brain moderators supporting the relationship between VAS

pain intensity ratings and BDI-II scores. The interaction between mean-centered pain intensity ratings and BDI was characterized as the moderation term [31]. Mean centered BDI and pain intensity ratings were entered as the first and second regressors, respectively. The moderation term between demeaned BDI and pain intensity ratings (BDI × INT) was modeled as the third regressor. Binary masks corresponding to significant brain activation maps from the first two regressors' contrast images were created to extract mean intensity values (FSL's Featquery tool) to verify that significant neural activation was significantly correlated with BDI or pain intensity ratings.

The SPSS PROCESS moderation/mediation macro [31] was employed to confirm the *directionality* of significant BDI × INT moderation effects. Binary masks corresponding to the significant brain moderation effects were created to extract mean intensity values for each participant (FSL's Featquery tool). These mean intensity values were designated and entered as moderator (M) values in the confirmatory moderation analyses (SPSS PROCESS). We assessed the influence of mean intensity values (M) on the relationship between BDI (X) and pain intensity ratings (Y). Finally, we employed the pick-a-point approach [8; 31] to identify the directionality of significant X*M moderation effects.

Specifically, the "pick-a-point" approach can also be referred to as an analysis of simple slopes or a spotlight analysis. It entails the most common approach to probing interaction effects and is used to delineate and explain the results of multiple regression with interactions (i.e. moderation effects) [18; 31]. The procedure involves selecting a value of the moderator (M), and then calculating the conditional effect of X on Y at the chosen value of M.

For our study, "M" is a quantitative variable that corresponds to brain activation levels (i.e. mean intensity value) for each participant. When "M" is a quantitative variable, a common strategy when probing the moderation effect is to estimate the conditional effect of X (BDI) on Y (pain) when M (mean intensity value) is equal to the mean, 1 standard deviation below the mean, and 1 standard deviation above the mean [1]. As such, the "points" chosen within the "pick-a-point" approach were delineated, by convention, at three values of the moderator (i.e. 1 SD below the mean, the mean, and 1 SD above the mean). In this way, it can be ascertained whether BDI is related to pain ratings among those participants with "relatively low" (i.e. 1 SD below the mean), "moderate" (i.e. the mean), and "relatively high" (i.e. 1 SD above the mean) brain activation.

In summary, the pick-a-point approach determines the conditional effect of X (BDI) on Y (pain intensity) at low [1 standard deviation (SD) below the mean], average (mean), and high levels (1 SD above mean) of brain activation (M) [8; 31].

RESULTS

Behavioral Results

Dispositional negative mood is positively associated with pain ratings—Higher BDI-II scores were associated with greater pain intensity ($p = .01$, r = .30; Figure S1) and pain unpleasantness ratings ($p = .006$, r = .31; Figure S2). Pain intensity and unpleasantness

ratings were significantly correlated with each other ($p < .001$; r = .94). Demographic variables (i.e., age and sex) did not significantly co-vary with pain intensity ratings or pain unpleasantness ratings ($ps > .05$) (Table 1).

Brain Moderation Findings

Noxious heat-induced brain activation—When compared to 35°C stimulation, noxious (49°C) heat produced significant activation in the primary somatosensory cortex (SI) corresponding to the stimulation site, bilateral thalamus, cerebellum, secondary somatosensory cortex (SII), inferior frontal gyrus, anterior/posterior insula, and the supplementary motor area (SMA) ($p < .001$) and significant deactivation in the bilateral prefrontal cortex (PFC), and PCC/precuneus ($p < .001$; Figure 1a; Table S1).

Pain intensity-related brain activation—Between subjects differences in pain intensity ratings were negatively associated with supramarginal gyrus and angular gyrus activation (r = −.42; $p < .001$; Figure 1b; Table S1). There were no significant positive correlations between neural activation and pain intensity ratings.

Brain moderators supporting the relationship between depressive mood and pain intensity—The relationship between BDI-II and pain intensity ratings (BDI × INT) was significantly moderated by activation in the contralateral SII, parietal and central operculum, posterior insula, and activation extending from the orbitofrontal cortex (OFC) to the ventrolateral PFC (vlPFC), and anterior insula ($p < .001$; Figure 2; Table S1; Table S2). The pick-a-point approach [8; 31] confirmed that high activation (i.e., 1SD above mean neural activation) in these brain regions, $t(72) = 3.64$, $p < .001$, but not mean $t(72) = 1.79$, $p = .08$ or low $t(72) = -.17$, $p = .87$ (i.e., 1SD below mean brain activation) activation, moderated the positive relationship between BDI scores and pain intensity ratings (Figure 2).

DISCUSSION

The present findings demonstrate that the relationship between depressive mood and pain intensity ratings was driven by high activation (mean intensity values = 1 SD above mean activation) in brain mechanisms supporting somatosensory processing (contralateral SII, parietal-central operculum, posterior insula) [17] and cognitive-affective appraisals of nociceptive information (OFC; vlPFC; anterior insula) [5; 59; 64] (Figure 2). Our hypotheses were partially confirmed. That is, heightened somatosensory but not default mode network-based processing moderated the positive relationship between depressive mood and pain.

High vlPFC, insular, and somatosensory activation moderated the positive relationship between BDI-II and pain intensity ratings

Prefrontal, insular, and somatosensory regions are anatomically connected and well positioned [27; 48; 49] to assimilate ascending nociceptive information into corresponding cognitive appraisals [64]. High contralateral vlPFC, insular, SII, and anterior insula, parietal-central operculum activation moderated the positive relationship between BDI scores and

pain intensity ratings (↑ pain + ↑depressive symptoms; ↓pain + ↓depressive symptoms) (Figure 2). This is fitting for a number of reasons. For one, the vlPFC and anterior insula play a multimodal role in modulating pain and affect [20; 35; 36; 59; 71]. Activation in the vlPFC is associated with a) exacerbating pain in response to heightened fear and anxiety [35; 51] and b) reappraisal-based pain relief [59; 73]. Further, the anterior insula incorporates ascending nociceptive information and real-time appraisals to formulate a contextually relevant evaluation of pain [52]. Here we propose that the vlPFC and anterior insula are involved in modulating pain in a context-dependent manner that is dependent on an individual's affect [26; 27; 64].

High contralateral SII, parietal operculum, and posterior insula activation also moderated the relationship between BDI-II and pain intensity ratings (Figure 2). Activation in these neural regions is associated with facilitating pain-related attentional biases in depressed individuals [28; 29]. Surprisingly, higher somatosensory and insular activation also moderated low depression ratings and low pain scores. However, recent evidence demonstrates that this process potentially signifies the attention capturing nature of a noxious/intrusive stimulus [45; 46; 58] as opposed to pain intensity reports [45]. Although we did not explicitly test this, we propose that individuals with higher depressive mood characterized noxious stimuli as more painful, whereas participants with lower negative mood deemed the said stimuli as more salient. The vlPFC/OFC is well positioned to integrate the behavioral significance of an external stimulus [57], an individual's dispositional temperament to construct the subjective experience of pain [7] and the contextualization of one's sensory environment [55]. Thus, we propose that the vlPFC/OFC is a primary neural substrate that facilitates the bidirectional relationship between depressive mood and pain by regulating whether a noxious sensory event is perceived as salient or painful.

It is important to note that this work is also explicitly generalizable to healthy rather than clinically depressed individuals. Although numerous studies [11; 30; 33; 34; 43; 60; 70] have validated the utility of measuring depressive symptomology/negative mood with the BDI-II in healthy participants, the BDI-II was originally employed to measure depressive symptomology in clinically depressed individuals. It is notable that a more conservative multiple comparison threshold would lower family wise error rates (FWE) [22]. However, the results from the present study may be less susceptible to inflated FWE rates because we employed perfusion-based fMRI, FSL's conservative FMRIB's Local Analysis of Mixed Effects (FLAME 1+2) Bayesian estimation method and larger voxel sizes than conventional slice parameters. Together, these approaches are associated with significantly lower FWE rates [25; 47]. Of note, we did not observe any significant relationship between brain activation and BDI ratings. We postulate that variability related the interaction term might have predicted the majority of the variance associated with BDI-related brain activation. In light of previous work delineating the relationship between individual differences in subjective reports of pain and pain-related brain activation [16], we were a bit perplexed by the inverse relationship between pain intensity ratings and activation of the right inferior parietal lobe (i.e., supramarignal gyrus; angular gyrus). This pattern of activity does resemble the regions of the parietal lobe where grey matter density was inversely related to

pain sensitivity [23]. Nevertheless, better delineating the relationship between individual differences in pain sensitivity and brain activation remains a topic of ongoing research.

CONCLUSIONS

The current findings are consistent with previous work demonstrating that executive-level and sensory-discriminative brain regions can increase and attenuate pain responses [20; 35; 36; 51; 59; 68; 80]. We provide novel evidence that said neural regions process pain-related appraisals in a multimodal manner that is dependent on an individual's mood.

ACKNOWLEDGEMENTS

This work was supported by the National Center for Complementary and Integrative Health (R21-AT007247, F32-AT006949, K99-AT008238, R00-AT008238, F30-AT009165; R01-AT009693), the National Institute of Neurological Disorders and Stroke (R01-NS239426), the Mind and Life Institute Francisco J. Varela Award, and the Wake Forest Center for Integrative Medicine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

[1]. Aiken LS, West SG Multiple regression: Testing and interpreting interactions. Thousand Oaks, CA: Sage Publications, 1991.

[2]. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, Lu H, MacIntosh BJ, Parkes LM, Smits M, van Osch MJ, Wang DJ, Wong EC, Zaharchuk G. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magnetic resonance in medicine 2015;73(1):102–116. [PubMed: 24715426]

[3]. Andersson J, Jenkinson M, Smith SM. FMRIB Technical Report TR07JA1, Non-linear optimisation., 2007.

[4]. Andersson J, Jenkinson M, Smith SM. FMRIB Technical Report TR07JA2, Non-linear registration, aka spatial normalisation., 2007.

[5]. Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. The Journal of neuroscience : the official journal of the Society for Neuroscience 2010;30(39):12964–12977. [PubMed: 20881115]

[6]. Baliki MN, Apkarian AV. Nociception, Pain, Negative Moods, and Behavior Selection. Neuron 2015;87(3):474–491. [PubMed: 26247858]

[7]. Bar KJ, Wagner G, Koschke M, Boettger S, Boettger MK, Schlosser R, Sauer H. Increased prefrontal activation during pain perception in major depression. Biol Psychiat 2007;62(11): 1281–1287. [PubMed: 17570347]

[8]. Bauer DJ, Curran PJ. Probing Interactions in Fixed and Multilevel Regression: Inferential and Graphical Techniques. Multivariate behavioral research 2005;40(3):373–400. [PubMed: 26794689]

[9]. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. Journal of personality assessment 1996;67(3):588–597. [PubMed: 8991972]

[10]. Beevers CG, Clasen P, Stice E, Schnyer D. Depression symptoms and cognitive control of emotion cues: a functional magnetic resonance imaging study. Neuroscience 2010;167(1):97–103. [PubMed: 20116416]

[11]. Ben Dor R, Harsh VL, Fortinsky P, Koziol DE, Rubinow DR, Schmidt PJ. Effects of pharmacologically induced hypogonadism on mood and behavior in healthy young women. The American journal of psychiatry 2013;170(4):426–433. [PubMed: 23545794]

[12]. 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(11):1083–1090. [PubMed: 20303069]

[13]. Boettger MK, Schwier C, Bar KJ. Sad mood increases pain sensitivity upon thermal grill illusion stimulation: implications for central pain processing. Pain 2011;152(1):123–130. [PubMed: 20980103]

[14]. Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magnetic resonance in medicine 1998;39(6):855–864. [PubMed: 9621908]

[15]. Carroll LJ, Cassidy JD, Cote P. Depression as a risk factor for onset of an episode of troublesome neck and low back pain. Pain 2004;107(1–2):134–139. [PubMed: 14715399]

[16]. Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain. Proceedings of the National Academy of Sciences of the United States of America 2003;100(14):8538–8542. [PubMed: 12824463]

[17]. Coghill RC, Sang CN, Maisog JH, Iadarola MJ. Pain intensity processing within the human brain: A bilateral, distributed mechanism. J Neurophysiol 1999;82(4):1934–1943. [PubMed: 10515983]

[18]. Cohen J, Cohen P, West SG, Aiken LS Applied multiple regression and correlation for the behavioral sciences. Mahwah, NJ: Lawrence Erlbaum Associates, 2003.

[19]. Cooney RE, Joormann J, Eugene F, Dennis EL, Gotlib IH. Neural correlates of rumination in depression. Cognitive, affective & behavioral neuroscience 2010;10(4):470–478.

[20]. de la Vega A, Yarkoni T, Wager TD, Banich MT. Large-scale Meta-analysis Suggests Low Regional Modularity in Lateral Frontal Cortex. Cerebral cortex 2017:1–15. [PubMed: 28365777]

[21]. Deibler AR, Pollock JM, Kraft RA, Tan H, Burdette JH, Maldjian JA. Arterial spin-labeling in routine clinical practice, part 1: technique and artifacts. AJNR American journal of neuroradiology 2008;29(7):1228–1234. [PubMed: 18372417]

[22]. Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Proceedings of the National Academy of Sciences of the United States of America 2016;113(28):7900–7905. [PubMed: 27357684]

[23]. Emerson NM, Zeidan F, Lobanov OV, Hadsel MS, Martucci KT, Quevedo AS, Starr CJ, Nahman-Averbuch H, Weissman-Fogel I, Granovsky Y, Yarnitsky D, Coghill RC. Pain sensitivity is inversely related to regional grey matter density in the brain. Pain 2014;155(3):566–573. [PubMed: 24333778]

[24]. Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, Mathews J, Sheline YI. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry 2008;63(4):377–384. [PubMed: 17719567]

[25]. Flandin G, Friston KJ. Analysis of family-wise error rates in statistical parametric mapping using random field theory. Human brain mapping 2017.

[26]. Friedman DP, Murray EA. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. The Journal of comparative neurology 1986;252(3):348–373. [PubMed: 3793981]

[27]. Friedman DP, Murray EA, O'Neill JB, Mishkin M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. The Journal of comparative neurology 1986;252(3):323–347. [PubMed: 3793980]

[28]. Gotlib IH, Krasnoperova E, Yue DN, Joormann J. Attentional biases for negative interpersonal stimuli in clinical depression. Journal of abnormal psychology 2004;113(1):121–135. [PubMed: 14992665]

[29]. Hauck M, Lorenz J, Engel AK. Attention to painful stimulation enhances gamma-band activity and synchronization in human sensorimotor cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience 2007;27(35):9270–9277.

[30]. Havranek MM, Bolliger B, Roos S, Pryce CR, Quednow BB, Seifritz E. Uncontrollable and unpredictable stress interacts with subclinical depression and anxiety scores in determining anxiety response. Stress 2016;19(1):53–62. [PubMed: 26669536]

[31]. Hayes A Introduction to meditation, moderation, and conditioned process analysis: a regression-based approach. New York, NY: The Guilford Press, 2013.

[32]. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 2002;17(2):825–841. [PubMed: 12377157]

[33]. Kamata M, Suzuki A, Yoshida K, Takahashi H, Higuchi H, Otani K. Genetic polymorphisms in the serotonergic system and symptom clusters of major depressive disorder. Journal of affective disorders 2011;135(1–3):374–376. [PubMed: 21917318]

[34]. Klumpers UM, Veltman DJ, van Tol MJ, Kloet RW, Boellaard R, Lammertsma AA, Hoogendijk WJ. Neurophysiological effects of sleep deprivation in healthy adults, a pilot study. PloS one 2015;10(1):e0116906. [PubMed: 25608023]

[35]. Koric L, Volle E, Seassau M, Bernard FA, Mancini J, Dubois B, Pelissolo A, Levy R. How cognitive performance-induced stress can influence right VLPFC activation: an fMRI study in healthy subjects and in patients with social phobia. Human brain mapping 2012;33(8):1973–1986. [PubMed: 21769993]

[36]. Koyama T, McHaffie JG, Laurienti PJ, Coghill RC. The subjective experience of pain: where expectations become reality. Proceedings of the National Academy of Sciences of the United States of America 2005;102(36):12950–12955. [PubMed: 16150703]

[37]. Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. The Journal of neuroscience : the official journal of the Society for Neuroscience 2014;34(11):3969–3975. [PubMed: 24623774]

[38]. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. The Journal of neuroscience : the official journal of the Society for Neuroscience 2011;31(9):3217–3224. [PubMed: 21368033]

[39]. Leino P, Magni G. Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: a 10-year follow-up of metal industry employees. Pain 1993;53(1):89–94. [PubMed: 8316395]

[40]. Letzen JE, Robinson ME. Negative mood influences default mode network functional connectivity in patients with chronic low back pain: implications for functional neuroimaging biomarkers. Pain 2017;158(1):48–57. [PubMed: 27583568]

[41]. Loggia ML, Kim J, Gollub RL, Vangel MG, Kirsch I, Kong J, Wasan AD, Napadow V. Default mode network connectivity encodes clinical pain: An arterial spin labeling study. Pain 2013;154(1):24–33. [PubMed: 23111164]

[42]. Martin CK, Bhapkar M, Pittas AG, Pieper CF, Das SK, Williamson DA, Scott T, Redman LM, Stein R, Gilhooly CH, Stewart T, Robinson L, Roberts SB, Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy Phase 2 Study G. Effect of Calorie Restriction on Mood, Quality of Life, Sleep, and Sexual Function in Healthy Nonobese Adults: The CALERIE 2 Randomized Clinical Trial. JAMA internal medicine 2016;176(6):743–752. [PubMed: 27136347]

[43]. Matsushima J, Kawashima T, Nabeta H, Imamura Y, Watanabe I, Mizoguchi Y, Kojima N, Yamada S, Monji A. Association of inflammatory biomarkers with depressive symptoms and cognitive decline in a community-dwelling healthy older sample: a 3-year follow-up study. Journal of affective disorders 2015;173:9–14. [PubMed: 25462389]

[44]. Meagher MW, Arnau RC, Rhudy JL. Pain and emotion: effects of affective picture modulation. Psychosomatic medicine 2001;63(1):79–90. [PubMed: 11211069]

[45]. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the “pain matrix”. NeuroImage 2011;54(3):2237–2249. [PubMed: 20932917]

[46]. Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol 2009;101(6):3258–3269. [PubMed: 19339457]

[47]. Mueller K, Lepsien J, Moller HE, Lohmann G. Commentary: Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Frontiers in human neuroscience 2017;11:345. [PubMed: 28701944]

[48]. Mufson EJ, Mesulam MM. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. The Journal of comparative neurology 1982;212(1):23–37. [PubMed: 7174906]

[49]. Mufson EJ, Mesulam MM, Pandya DN. Insular interconnections with the amygdala in the rhesus monkey. Neuroscience 1981;6(7):1231–1248. [PubMed: 6167896]

[50]. Mumford JA, Poline JB, Poldrack RA. Orthogonalization of regressors in FMRI models. PloS one 2015;10(4):e0126255. [PubMed: 25919488]

[51]. Ochsner KN, Ludlow DH, Knierim K, Hanelin J, Ramachandran T, Glover GC, Mackey SC. Neural correlates of individual differences in pain-related fear and anxiety. Pain 2006;120(1–2): 69–77. [PubMed: 16364548]

[52]. Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting discrimination of sensory features of pain: a new model. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29(47):14924–14931. [PubMed: 19940188]

[53]. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56(2):217–226. [PubMed: 8008411]

[54]. Rayner L, Hotopf M, Petkova H, Matcham F, Simpson A, McCracken LM. Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and impact on health care costs. Pain 2016;157(7):1472–1479. [PubMed: 26963849]

[55]. Rolls ET, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. Progress in neurobiology 2008;86(3):216–244. [PubMed: 18824074]

[56]. Roy M, Piche M, Chen JI, Peretz I, Rainville P. Cerebral and spinal modulation of pain by emotions. Proceedings of the National Academy of Sciences of the United States of America 2009;106(49):20900–20905. [PubMed: 19926861]

[57]. Sakagami M, Tsutsui K. The hierarchical organization of decision making in the primate prefrontal cortex. Neuroscience research 1999;34(2):79–89. [PubMed: 10498334]

[58]. Salomons TV, Iannetti GD, Liang M, Wood JN. The “Pain Matrix” in Pain-Free Individuals. JAMA neurology 2016;73(6):755–756. [PubMed: 27111250]

[59]. Salomons TV, Johnstone T, Backonja MM, Shackman AJ, Davidson RJ. Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex. Journal of cognitive neuroscience 2007;19(6):993–1003. [PubMed: 17536969]

[60]. Schaller G, Lenz B, Friedrich K, Dygon D, Richter-Schmidinger T, Jacobi A, Mueller SE, Maihofner C, Sperling W, Kornhuber J. Repetitive transcranial magnetic stimulation influences mood in healthy male volunteers. Journal of psychiatric research 2011;45(9):1178–1183. [PubMed: 21397253]

[61]. Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cerebral cortex 2007;17(6):1412–1422. [PubMed: 16908493]

[62]. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS, Raichle ME. The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences of the United States of America 2009;106(6): 1942–1947. [PubMed: 19171889]

[63]. Shin DD, Liu TT, Wong EC, Shankaranarayanan A, Jung Y. Pseudocontinuous arterial spin labeling with optimized tagging efficiency. Magnetic resonance in medicine 2012;68(4):1135–1144. [PubMed: 22234782]

[64]. Starr CJ, Sawaki L, Wittenberg GF, Burdette JH, Oshiro Y, Quevedo AS, Coghill RC. Roles of the insular cortex in the modulation of pain: insights from brain lesions. The Journal of

neuroscience : the official journal of the Society for Neuroscience 2009;29(9):2684–2694. [PubMed: 19261863]

[65]. Tan H, Maldjian JA, Pollock JM, Burdette JH, Yang LY, Deibler AR, Kraft RA. A fast, effective filtering method for improving clinical pulsed arterial spin labeling MRI. Journal of magnetic resonance imaging : JMRI 2009;29(5):1134–1139. [PubMed: 19388118]

[66]. Tang NK, Salkovskis PM, Hodges A, Wright KJ, Hanna M, Hester J. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. Pain 2008;138(2):392–401. [PubMed: 18325674]

[67]. Terhaar J, Boettger MK, Schwier C, Wagner G, Israel AK, Bar KJ. Increased sensitivity to heat pain after sad mood induction in female patients with major depression. European journal of pain 2010;14(5):559–563. [PubMed: 19837623]

[68]. Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29(3):705–715. [PubMed: 19158297]

[69]. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. Pain 2003;106(1–2):101–108. [PubMed: 14581116]

[70]. Vynorius KC, Paquin AM, Seichepine DR. Lifetime Multiple Mild Traumatic Brain Injuries Are Associated with Cognitive and Mood Symptoms in Young Healthy College Students. Frontiers in neurology 2016;7:188. [PubMed: 27843436]

[71]. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron 2008;59(6):1037–1050. [PubMed: 18817740]

[72]. Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. Pain 2005;117(3):450–461. [PubMed: 16154274]

[73]. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. The Journal of neuroscience : the official journal of the Society for Neuroscience 2006;26(44):11501–11509. [PubMed: 17079679]

[74]. Woo CW, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. PLoS biology 2015;13(1):e1002036. [PubMed: 25562688]

[75]. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage 2001;14(6):1370–1386. [PubMed: 11707093]

[76]. Worsley K. Functional MRI: An Introduction to Methods In: Jezzard P, Matthews PM., Smith SM, editor. Statistical analysis of activation images. New York: OUP, 2001.

[77]. Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 1992;12(6):900–918.

[78]. Wunsch A, Philippot P, Plaghki L. Affective associative learning modifies the sensory perception of nociceptive stimuli without participant's awareness. Pain 2003;102(1–2):27–38. [PubMed: 12620594]

[79]. Zeidan F, Adler-Neal AL, Wells RE, Stagnaro E, May LM, Eisenach JC, McHaffie JG, Coghill RC. Mindfulness-Meditation-Based Pain Relief Is Not Mediated by Endogenous Opioids. The Journal of neuroscience : the official journal of the Society for Neuroscience 2016;36(11):3391–3397. [PubMed: 26985045]

[80]. Zeidan F, Emerson NM, Farris SR, Ray JN, Jung Y, McHaffie JG, Coghill RC. Mindfulness Meditation-Based Pain Relief Employs Different Neural Mechanisms Than Placebo and Sham Mindfulness Meditation-Induced Analgesia. Journal of Neuroscience 2015;35(46):15307–15325. [PubMed: 26586819]

[81]. Zelman DC, Howland EW, Nichols SN, Cleeland CS. The effects of induced mood on laboratory pain. Pain 1991;46(1):105–111. [PubMed: 1896201]

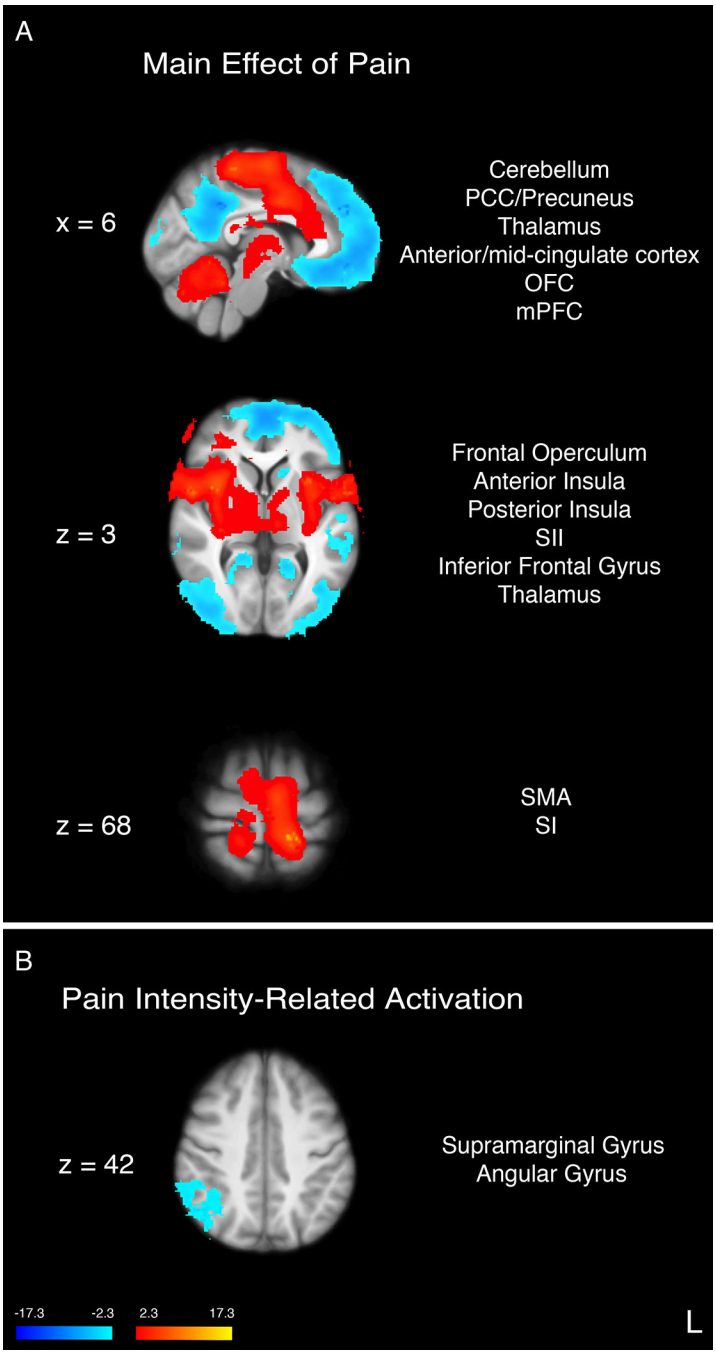

Figure 1.

A. Brain activations and deactivations associated with the main effect of pain. Significant activations during painful stimulation were seen in the primary somatosensory cortex (SI) corresponding to the stimulation site, bilateral thalamus, cerebellum, anterior and mid-cingulate cortices, anterior/posterior insula, frontal operculum, secondary somatosensory cortex (SII), supplementary motor area (SMA), and inferior frontal gyrus. Significant deactivations were detected in the bilateral medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and posterior cingulate cortex (PCC)/precuneus. **B. Lower pain**

intensity ratings associated with higher activation in the inferior parietal lobe. Lower pain intensity reports during noxious heat stimulation were associated with greater activation in the supramarginal gyrus and angular gyrus ($p < .001$). Slice locations correspond to standard stereotaxic space.

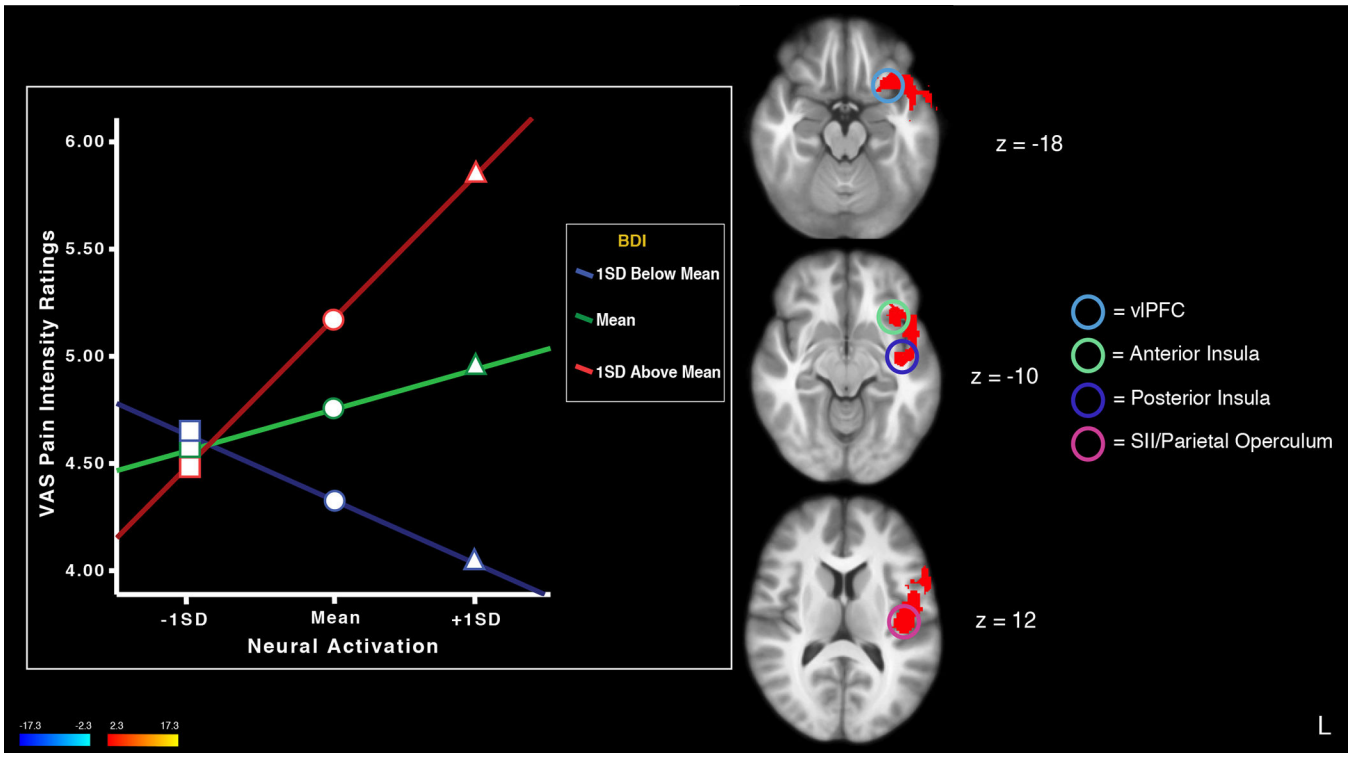

Figure 2. Brain regions moderating the relationship between depressive mood and pain intensity.

The positive relationship between BDI-II and pain intensity ratings was moderated by high activation [1SD greater than average (+1SD); $p < .001$] in the contralateral ventrolateral prefrontal cortex (vlPFC), anterior insula, secondary somatosensory cortex (SII), parietal/central operculum, posterior insula during noxious stimulation. Squares (□) are indicative of brain activation 1 SD below the mean (-1SD). Circles (○) are indicative of mean brain activation, and triangles (△) indicate brain activation that is 1 SD greater than the mean. Slice locations correspond to standard stereotaxic space.

Table 1.

Participant age and mean (SEM) Beck Depression Inventory (BDI-II) and pain intensity ratings.

Variable	Males (n=36)	Females (n=40)	Combined (n=76)
Age	26.97 (.71)	27.10 (.90)	27.04 (.58)
BDI-II	5.44 (.75)	4.45 (.72)	4.92 (.52)
Pain Intensity	4.49 (.37)	5.00 (.32)	4.76 (.24)
Pain Unpleasantness	4.60 (.41)	5.41 (.35)	5.02 (.27)