Research Paper

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Negative mood influences default mode network functional connectivity in patients with chronic low back pain: implications for functional neuroimaging biomarkers

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Abstract

The default mode network (DMN) has been proposed as a biomarker for several chronic pain conditions. Default mode network functional connectivity (FC) is typically examined during resting-state functional neuroimaging, in which participants are instructed to let thoughts wander. However, factors at the time of data collection (eg, negative mood) that might systematically impact pain perception and its brain activity, influencing the application of the DMN as a pain biomarker, are rarely reported. This study measured whether positive and negative moods altered DMN FC patterns in patients with chronic low back pain (CLBP), specifically focusing on negative mood because of its clinical relevance. Thirty-three participants (CLBP = 17) underwent resting-state functional magnetic resonance imaging scanning before and after sad and happy mood inductions, and rated levels of mood and pain intensity at the time of scanning. Two-way repeated-measures analysis of variances were conducted on resting-state functional connectivity data. Significant group (CLBP > healthy controls) × condition (sadness > baseline) interaction effects were identified in clusters spanning parietal operculum/postcentral gyrus, insular cortices, anterior cingulate cortex, frontal pole, and a portion of the cerebellum ($P_{FDR} < 0.05$). However, only 1 significant cluster covering a portion of the cerebellum was identified examining a two-way repeated-measures analysis of variance for happiness > baseline ($P_{FDR} < 0.05$). Overall, these findings suggest that DMN FC is affected by negative mood in individuals with and without CLBP. It is possible that DMN FC seen in patients with chronic pain is related to an affective dimension of pain, which is important to consider in future neuroimaging biomarker development and implementation.

Keywords: Default mode network, Biomarker, Chronic low back pain

1. Introduction

Neuroimaging biomarker development for chronic pain has become increasingly popular in recent years.[2,13,29,46,48,56,73,74,76,80,91] These studies have provided useful mechanistic information about pain perception, and their specific application to measure neurobiological processes underlying pain[89] is certainly warranted. However, potential issues arise in the clinical application of such biomarkers to classify (ie, diagnose) individuals, which should be addressed before proposed biomarkers are clinically translated.

The initial rationale for pain biomarker development was largely based on the notion that pain self-report is "unreliable",[49] and "an imperfect measure of subjective experience".[80] Although biomarker proponents have moved away from this rationale, the inherent assumption of this argument persists; namely, neuroimaging is presumed to be a more stable and informative measure of pain perception than self-report. Neuroimaging is undoubtedly valuable for understanding the complexity of pain ratings and mechanisms underlying chronic pain conditions; however, the stability of findings over time, an essential characteristic for biomarker implementation,[52] remains questionable.

Aside from concerns about error impacting reproducibility of functional magnetic resonance imaging (fMRI) data,[5,43,77] variables that systematically alter pain perception have received little attention in context of neuroimaging biomarkers for chronic pain. Factors that affect pain ratings and concomitant brain activity include mood,[6,72,78,82] recall of autobiographical painful experiences,[22,36,40] social support/distraction,[11,21,23,87] and expectations of pain intensity/relief.[19,39,47,67,86] Given that such factors have been widely demonstrated to influence pain perception and its neural correlates, it is likely that these variables will similarly impact functional neuroimaging pain biomarkers.

Among ostensible biomarkers of chronic pain, the default mode network (DMN) has been named as a candidate marker for at least 5 conditions.[8,13,48,55,73,91] The DMN is a correlated set of brain regions showing increased activity during wakeful rest (ie, resting-state) and self-referential tasks.[62] Although the exact function of the DMN is still debated, it is postulated to be involved in spontaneous cognition related to self-referential thought (eg, mind wandering, autobiographical memory) and/or intrinsic

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

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PAIN 158 (2017) 48–57

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http://dx.doi.org/10.1097/j.pain.0000000000000708

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neural dynamics.[18,60,65,90] Default mode network functional connectivity (FC) is commonly captured using resting-state fMRI in which participants are typically asked to let their minds wander.

Critical reviews of the resting-state paradigm have cited modest reproducibility of results as the largest barrier to clinical translation.[25] One potential reason for replication issues is the lack of information regarding individuals' mental state at the time of scanning.[10,18] In the case of previous studies naming the DMN as a potential pain biomarker, factors that influence mental state and/or pain perception itself during scanning are rarely considered. This information is vital to (1) understand exactly which aspects of a clinical pain condition are captured by the proposed neural signature (eg, pain intensity/unpleasantness, clinical mood disturbance), and (2) inform the use of functional neuroimaging biomarkers for clinical decision–making by determining how a neural signature might change based on behavioral factors. The goal of this study was to measure whether negative mood, a variable known to increase pain ratings and alter brain activity in individuals with and without chronic low back pain (CLBP),[72,82] impacted DMN FC during resting-state scanning.

2. Methods

2.1. Participants

Participants for this study were recruited through flyers posted around the Gainesville community, as well as through HealthStreet, a University of Florida–based organization designed to reduce health and research disparities in underrepresented populations. Specific inclusion criteria for the CLBP group included (1) experiencing CLBP for greater than the past 3 months that meets at least one of the following Quebec Task Force on Spinal Disorders diagnostic criteria[71]: 1c (CLBP without radiation below the gluteal fold), 2c (CLBP with proximal radiation to the knee), or 3c (CLBP with distal radiation below the knee), and (2) no history of psychological or neuropsychological disorder. In addition, participants were included if they endorsed having vivid memories of (1) a past event in which they experienced extreme happiness, and (2) a past, isolated event in which CLBP caused sadness. Presence of such memories was necessary for the study's mood induction procedures. Because the self-report of reduced quality of life is high in patients with chronic pain, we included patients with CLBP who endorsed a subclinical level of depressive symptoms on a questionnaire related to mood [defined as Beck Depression Inventory–II, (BDI-II) score < 21, based on a previous study[27]].

Specific inclusion criteria for the healthy controls (HC) group included (1) no history of chronic pain, psychological, or neuropsychological disorder, (2) a vivid memory of a past event in which they experienced extreme happiness, and (3) a vivid memory of a past, isolated event in which acute pain caused sadness. Participants were excluded if they endorsed (1) use of analgesics that could not be stopped the day before the study, (2) use of serotonin reuptake inhibitors, serotonin antagonists, or tricyclic antidepressants at the time of the study, (3) positive result on a pre-MRI metal screening or pregnancy test, and (4) pain symptoms inconsistent with Quebec Task Force on Spinal Disorders diagnostic criteria mentioned above.

Data from 33 participants were used in this study (n: CLBP = 17, HC = 16). To ensure that participants did not have a significant level of mood disturbance or neurocognitive deficits that could confound results, participants were screened using the BDI-II and Mini Mental Status Examination. Groups did not specifically differ on age ($t(31) = 1.52$, $P = 0.14$), sex (CLBP females = 10; HC females = 9), global neurocognitive functioning, or level of endorsed depressive symptoms (**Table 1**). Ethnically, 18 participants identified as Caucasian (CLBP = 10), 14 identified as African American (CLBP = 7), and 1 HC identified as Asian American. The Institutional Review Board at the University of Florida approved the study, and all participants provided written informed consent.

2.2. Data collection procedures

For this study, participants completed 2 study visits, including a screening evaluation (visit 1) and an MRI session (visit 2). Visit 1 occurred 1 week before visit 2.

2.2.1. Visit 1

After completing screening measures (BDI-II and Mini Mental Status Examination), participants underwent a 10-minute mock MRI session. The mock scan was conducted to promote data quality by reducing participants' scanner-related anxiety and movement while lying down, and was used to further screen for participants who were ineligible to complete visit 2 (eg, difficulty remaining still, elevated anxiety to the mock MRI environment that did not habituate). Participants deemed eligible for MRI scanning were provided with instructions to complete the mood induction during visit 2 (see "Mood Induction Paradigm"). For the happy mood induction, both groups were asked to describe a time in which they felt particularly elated, such as a special occasion (eg, wedding or birthday). For the sad mood induction, participants were asked to think of an affectively salient memory to describe aloud related to an autobiographical event in which pain caused sadness, whereas HC participants were asked to think about an event involving acute pain (eg, inability to complete an

Table 1

Comparison of descriptive statistics for demographic information and questionnaire scores between chronic low back pain and healthy controls.

	Healthy controls (n = 16), mean (SD)	Chronic low back pain (n = 17), mean (SD)
Age (y)	41.0 (12.11)	47.82 (13.57)
Chronic low back pain duration (y)	—	4.29 (2.76)
Average pain intensity (0-100)	—	44.35 (18.19)
Beck Depression Inventory-II	4.0 (3.46)	7.65 (7.17)
Pain vigilance and attention questionnaire	37.44 (8.31)	46.82 (12.39)*
Mini mental status examination	29.13 (0.89)	29.36 (0.93)

* Chronic low back pain > healthy controls ($P < .05$).

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important athletic venture because of strained muscle), patients with CLBP were asked to think about an event involving their clinical pain (eg, missing an important family function because of CLBP).

2.2.2. Visit 2

Magnetic resonance imaging scanning took place during visit 2, and included 4 resting-state fMRI scans. For each resting-state scan, participants were instructed to fixate their eyes on a projected crosshair, remain as still as possible, and to let their minds wander. **Figure 1** demonstrates fMRI scanning procedures. To minimize carryover effects between the 2 mood manipulations, inductions were conducted before the second and fourth resting-state scans using counterbalanced moods (ie, happy and sad) across participants; results from the second baseline scan (ie, scan 3) and happy mood induction were not included in the present analyses. Individuals were asked to rate their current mood before and after each scan and induction. Using a verbal rating scale (0 = "no level of the mood", 100 = "highest amount of the mood imaginable"), participants rated the following emotions: happy, sad, angry, anxious, and neutral. In addition, participants rated their current level of low back pain (0 = "no current low back pain", 100 = "greatest intensity of low back pain imaginable"). Only self-report data related to sadness, happiness, and pain were used in the present analyses.

2.2.3. Mood induction paradigm

This study used a modified version of the mood induction paradigm described by Harrison et al.,[31] which measured differences in DMN FC among HCs before and after undergoing sad mood induction. In addition, this procedure has been used successfully in other PET and fMRI studies to significantly alter mood.[16,51] The version of this paradigm was modified, however, to include a sad mood induction specific to recall of a painful experience. We chose this induction specifically to act as a clinically relevant model of fluctuations in pain-related affect. During visit 1, participants were given instructions for the mood induction procedures used in visit 2. Specifically, they were asked to think of 2 stories related to happy and sad autobiographical events, respectively, and attempt to reexperience the emotions during these events while telling the stories. Several steps were taken to increase the likelihood that the desired mood was induced during visit 2: (1) participants were instructed to provide true autobiographical events, rather than contrive events, (2) participants were encouraged to describe very detailed aspects of the events including sensory experiences (eg, smells, sounds, etc.) and thoughts at the time of the event (eg, "My pain will never go away," "I am a failure," etc.), and (3) participants were asked to write down the detailed stories before visit 2 and bring the written version to the scanning session.

Mood inductions were conducted before the second and fourth resting-state scans while the participant was lying in the scanner, but without actual scanning taking place. As each participant recounted their stories, music played through MR-compatible headphones (Avotec, Stuart, FL). For the happy mood induction, the musical piece "Coppelia" by Debiles played during the recall period for both groups.[50] For the sad mood induction, the musical piece "Russia under the Mongolian Yoke" by Prokofiev played during the recall period for both groups.[31,68] Participants were instructed to continue telling their story for at least the duration of each musical piece (approximately 4-5 minutes), but could exceed this time if needed to finish the story. To maintain the integrity of the resting-state paradigm, no audio stimuli played during fMRI data collection, and participants were only provided with typical resting-state instructions before each scan (ie, they were not instructed to try to remain in each mood for the duration of the scan).

2.2.4. Data acquisition parameters

Functional and structural MRI data were acquired with a research-dedicated whole-body scanner (Philips Achieva, 3.0T, Philips Medical Systems, Best, the Netherlands) using a standard head 32-channel radio frequency coil. High-resolution, three-dimensional anatomical images were collected using a T1-weighted MP-RAGE protocol (176 1 mm-sagittal slices; repetition time = 7 ms, echo time = 3.2 ms, flip angle = 8°, 240 × 240 mm matrix; field of view = 240 × 240 × 176 mm). Functional images of the whole brain were collected using an echo planar imaging sequence (42 interleaved, transverse slices; repetition time = 2250 ms; echo time = 30 ms; flip angle = 90°; 80 × 80 matrix; field of view = 240 × 240 × 126 mm; 3 mm^3 isotropic voxels with 0 mm slice gap). Each scan lasted 8 minutes 12.7 seconds to collect a total of 213 volumes.

2.3. Statistical analyses

2.3.1. Functional magnetic resonance imaging data preprocessing

SPM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) in MATLAB 2011b (MathWorks, Sherbon, MA) was used to preprocess fMRI data. Preprocessing procedures

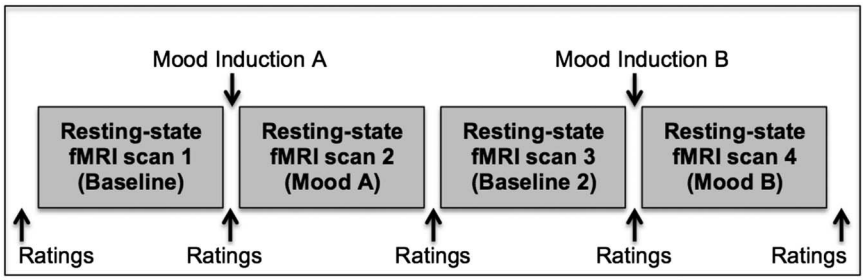

Figure 1. The protocol for functional magnetic resonance imaging scanning included 4 resting-state functional magnetic resonance imaging scans, with 2 mood inductions (ie, happy and sad moods) completed between these scans. The 2 inductions occurred before the second and fourth resting-state scans, and were counterbalanced across participants. The second baseline (ie, scan 3) and happy mood scans were not analyzed for this study. Mood and pain ratings were collected before and after each scan and mood induction.

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included (1) slice-timing correction for interleaved data collection, (2) three-dimensional motion correction with realignment to the middle volume of each scan, (3) coregistration to the individual's structural MRI, (4) normalization to an Montreal Neuological Institute template, and (5) spatial smoothing (6 mm^3 Gaussian kernel [full width at half maximum]).

In addition, we used the artifact detection tool (ART, www.nitrc.org/projects/artifact_detect/) to identify outlier time points in the data that might confound FC results. Outliers were defined as rotational displacement greater than 0.02 radians from the previous volume, or head displacement greater than 4 mm from the previous volume.[14] Average motion (Euclidean norm = $t(31) = -1.2$, $P = 0.24$) and data outliers ($t(31) = -0.9$, $P = 0.38$) across all runs were not significantly different between groups.

Importantly, resting-state FC can be confounded by physiological nuisance variables, such as respiration and cardiac output.[54] Although this has traditionally been corrected through regressing out cardiac and respiration data collected at the time of scanning, more recent work has demonstrated that applying anatomical segmentation in a general linear model is more effective in regressing out physiological noise.[4] As such, structural data were segmented into gray matter, white matter, and cerebrospinal fluid masks to be used as regressors in the FC analysis pipeline.

2.3.2. Functional connectivity analyses

To assess DMN FC, we used the CONN toolbox[84] implemented through MATLAB. This toolbox predominantly uses seed-based correlations to assess task-based or resting-state FC among regions. Preprocessed structural and functional images were entered into the toolbox's processing pipeline, which includes temporal processing (ie, denoising), first-level analyses, and second-level analyses. In addition, conditions were specified by the mood associated with each fMRI run (eg, baseline, sad). Temporal processing was conducted using CONN's CompCor algorithm to remove physiological noise, such as outlier data detected in ART and signal within white matter/cerebral spinal fluid (CSF; ie, proxy for cardiac and respiration confounds).[4] Using principal component analysis, the following nuisance variables were regressed out: 5 principal components from white matter and CSF masks, head motion parameters with first-order temporal derivatives, outliers detected during ART, and linear trends. Data were also band-pass filtered (0.008-0.09 Hz).[84]

Processed time series data were subsequently used in first-level FC analyses. CONN's default processing pipeline includes an atlas of a priori regions of interest (ROIs), from which time series data were extracted. Specifically, time series data were extracted from 10-mm spheres around peak coordinates of midline DMN hubs [ie, medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)] to be used in the seed-based FC analyses.[14] We chose the mPFC and PCC as our DMN seed regions given their roles as key hubs in the DMN,[9] which we combined into 1 ROI for seed-to-voxel analyses (MNI coordinates: mPFC = −1, 47, −4, PCC = −5, −49, 40). The ROIs used in this study are standard within the CONN toolbox and were generated from a previous study by Fox et al.,[26] which examined intrinsic organization of functional networks.

Seed-to-voxel analyses measure FC strength between seed a priori ROIs and all other voxels in the brain. For first-level seed-to-voxel analyses, bivariate temporal correlations were conducted among individuals' time series data from a priori ROIs and all other voxels in the brain for each fMRI run. As standardized within the toolbox, correlation coefficients were Fisher Z-transformed to improve assumptions of normality.[84]

Second-level seed-to-voxel analyses were then completed to allow for group-level comparisons. We conducted 2 repeated-measures analysis of variance (ANOVA) (2-factorial design) using group (CLBP > HC) and condition (sadness > baseline; happiness > baseline) as factors. Significance thresholds were estimated through Monte Carlo simulations (Alphasim, http://afni.nih.gov/afni/docpdf/AlphaSim.pdf) using the resultant F maps (cluster connection radius: 12.1 mm, iterations: 10,000). Significance with multiple comparisons correction ($P_{FDR} < 0.05$) was determined as a voxel threshold of $P < 0.01$ with a contiguous cluster size > 118 voxels. Individual-level values for clusters identified at this significance threshold using the omnibus model were extracted and entered into SPSS to determine the main effects of group and condition, as well as group × condition interaction effects.

3. Results

3.1. Behavioral ratings and questionnaires

A 2-way repeated-measures ANOVA (group × condition) of sadness ratings indicated that there was a significant main effect of condition ($M_{Baseline} = 11.37$, SD = 17.81; $M_{Sadness} = 40.12$, SD = 31.88; $F_{1,31} = 32.02$, $P < 0.001$, $\eta^2_P = 0.5$), so that sadness ratings increased in both groups after sad mood induction. However, there was not a significant group × condition interaction effect ($M_{CLBP} = 32.62$, SD = 20.58; $M_{HC} = 18.88$, SD = 20.59; $F_{1,31} = 0.79$, $P = 0.38$), or main effect of group ($F_{1,31} = 0.2.88$, $P = 0.1$). The impact of group (CLBP > HC) and condition (baseline > happiness) on happiness ratings was also measured using a 2 × 2 ANOVA (Baseline: $M_{CLBP} = 70.69$, SD = 19.33; $M_{HC} = 77.32$, SD = 19.33; Happiness: $M_{CLBP} = 83.71$, SD = 20.26; $M_{HC} = 83.38$, SD = 24.30). Across all participants, there was a significant main effect of condition ($F_{1,31} = 4.51$, $P = 0.04$), so that happiness ratings increased after the induction; however, there were no significant group ($F_{1,31} = 0.33$, $P = 0.57$) or group × condition interaction effects ($F_{1,31} = 0.49$ $P = 0.49$).

Finally, we conducted a 2 × 2 mixed ANOVA (group × condition) for pain ratings. As expected, there was a significant main effect of group, so that participants with CLBP reported significantly higher LBP at baseline ($M_{CLBP} = 36.88$, SD = 29.72; $M_{HC} = 5.00$, SD = 5.58) and after sad mood induction ($M_{CLBP} = 35.88$, SD = 32.67; $M_{HC} = 2.93$, SD = 6.88; $F_{1,31} = 17.22$, $P < 0.001$, $\eta^2P = 0.36$). However, the group × condition interaction effect for pain ratings did not reach significance ($F_{1,31} = 0.07$, $P > 0.05$).

3.2. Default mode network functional connectivity after sad mood induction

A 2 × 2 mixed ANOVA was also conducted for FC data using combined mPFC and PCC ROIs as a seed representing the DMN with group (CLBP > HC) and condition (sadness > baseline) as factors (**Fig. 2**). Seven significant clusters were identified in the omnibus model as having significantly different FC to the DMN seed (**Table 2**, **Fig. 3**). Two clusters were identified as having a significant main effect of condition only: (1) ventral anterior cingulate cortex ([vACC]; $F_{1,31} = 23.35$, $P < 0.001$, $\eta^2P = 0.43$) and (2) right posterior insula ([pINS]; $F_{1,31} = 23.54$, $P < 0.001$, $\eta^2P = 0.43$). In both groups, DMN-vACC was positively correlated in the baseline condition and showed a similar magnitude of change in FC after sad mood induction (group ×

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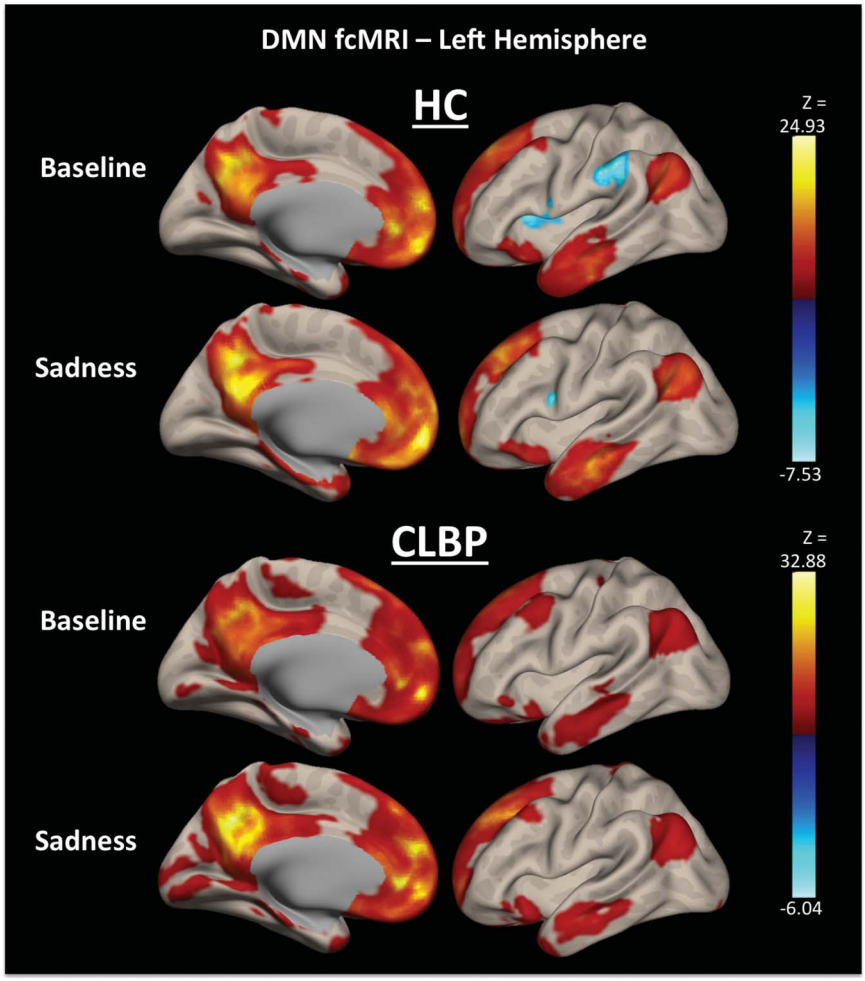

Figure 2. Left-hemisphere default mode network functional connectivity broken down by groups and conditions. The top 2 default mode network functional connectivity maps show mean static functional connectivity in healthy controls both in the baseline and sadness conditions, whereas the bottom 2 default mode network functional connectivity maps show mean static functional connectivity in participants with chronic low back pain during both conditions.

condition effect: $F_{1,31} = 0.01$, $P = 0.98$, $\eta^2P = 0.0$). However, both groups showed anticorrelated DMN-right pINS FC at baseline that became positively correlated after sad mood induction. Comparing the magnitude of change between groups, there was a trend for a greater increase in DMN-right pINS FC within the CLBP group (group × condition effect: $F_{1,31} = 3.0$, $P = 0.09$, $\eta^2P = 0.09$).

Three clusters showed a significant main effect of condition, as well as a group × condition interaction effect: (1) left pINS ($F_{1,31} = 5.59$, $P = 0.03$, $\eta^2P = 0.15$), (2) left parietal operculum/postcentral gyrus ([ParOper/PostGyr]; $F_{1,31} = 16.73$, $P < 0.001$, $\eta^2P = 0.35$), and (3) right ParOper/PostGyr ($F_{1,31} = 8.84$, $P = 0.006$, $\eta^2P = 0.22$). Both groups showed anticorrelated FC among these 3 clusters and the DMN at baseline. After sad mood induction, HCs showed a greater magnitude of change for DMN-left pINS and ParOper/PostGyr FC compared with participants with CLBP. Conversely, participants with CLBP showed a greater magnitude of change in DMN-right ParOper/PostGyr FC compared with HCs after sad mood induction.

Finally, 2 clusters showed significant group × condition interaction effects only: (1) frontal pole ($F_{1,31} = 26.05$, $P < 0.001$, $\eta^2P = 0.46$) and (2) cerebellum ($F_{1,31} = 18.8$, $P < 0.001$, $\eta^2P = 0.38$). Across both clusters, groups showed inverse patterns of change in FC after sad mood induction, whereas HCs showed a decreased in DMN cerebellum and frontal pole FC comparing sad mood to baseline conditions, CLBP showed an increase in FC between the DMN and these 2 clusters.

3.3. Default mode network functional connectivity after happy mood induction

A 2 × 2 mixed ANOVA was also conducted using group (CLBP vs HC) and condition (baseline vs happiness). One significant cluster was identified, which spanned a portion of the cerebellum (**Table 2**). This region showed a main effect of condition, so that there was decreased DMN cerebellum FC after happy mood induction in both groups ($F_{1,31} = 24.18$, $P < 0.001$, $\eta^2P = 0.44$). The magnitude of change was not significantly different between groups ($F_{1,31} = 2.29$, $P = 0.14$, $\eta^2P = 0.07$).

4. Discussion

Pain perception is always subjective,[53] and myriad trait (eg, personality characteristics, chronic mood disturbance) and state (eg, negative mood, distraction) factors have been shown to influence pain self-report and associated brain activity.[12,23,24,72,78,81,82,85,87]

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Table 2

Significant clusters identified in an omnibus test for two 2 × 2 repeated-measures analysis of variance using group (chronic low back pain > healthy controls) and condition (sadness > baseline; happiness > baseline) as factors.

Model	Hemisphere	Cluster coordinates	Cluster size	$F_{1,31}$	Cluster *P* (<0.05 FDR)	Cluster regions	Voxels per region
Chronic low back pain > healthy controls, sadness > baseline	Left	−44, −28, 20	453	11.59	0.000	Parietal operculum	169
						Postcentral gyrus	86
						Supramarginal gyrus	33
						Planum temporale	20
						Heschl gyrus	6
	Right	58, −18, 26	363	14.69	0.000	Parietal operculum	117
						Supramarginal gyrus	127
						Postcentral gyrus	76
						Planum temporale	23
	Left	−30, 2, −4	315	15.64	0.000	Posterior insula	124
						Putamen	74
						Heschl gyrus	39
						Central opercular cortex	21
						Planum polare	10
	Midline	4, 28, 24	128	12.36	0.05	Anterior cingulate cortex	128
	Left	−38, −42, −36	125	8.77	0.05	Cerebellum	67
						Fusiform gyrus	25
						Inferior temporal gyrus	24
	Left	−24, 52, 34	124	13.17	0.05	Frontal pole	124
	Right	34, 4, 0	119	12.55	0.05	Posterior insula	50
						Putamen	15
Chronic low back pain > healthy controls, happiness > baseline	Right	28, −82, −40	208	24.18	0.013	Cerebellum	208

These clusters were shown to have altered functional connectivity with key hubs of the default mode network [ie, medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)] after mood inductions. FDR, false discovery rate.

However, studies proposing functional neuroimaging biomarkers of chronic pain have not adequately addressed these variables in their design, raising questions about the practical application of results. Our findings demonstrate that variables known to influence pain perception are highly important to consider in the development of functional neuroimaging biomarkers. Specifically, we found that mood altered FC of the DMN, which has been named as a candidate biomarker for a wide variety of clinical conditions,[3,8,28,37,61,79,92] including at least 5 chronic pain conditions.[13,48,55,73,91]

Although consistent resting-state networks have been identified across numerous studies, manipulation of mental state at the time of scanning has been shown to systematically influence patterns of connectivity within these networks in healthy individuals. Experimentally manipulated factors include cognitive focus before scanning,[44,45,75,83] maintaining eyes opened or closed during data collection,[57,90] and elevated level of temporary sad mood. Harrison et al.[31] demonstrated that increased reported sadness after negative mood induction was associated with decreased within-DMN FC in HC participants. The authors concluded that assessing mental state at the time of scanning is imperative for the interpretation of results in both scientific and clinical applications. In addition, experimental pain stimulation before resting-state scanning in patients with fibromyalgia subsequently resulted in increased FC between the thalamus and regions within the DMN (ie, precuneus/PCC).[33] The authors concluded that experimental pain altered the "neural signature of chronic pain" collected during resting-state fMRI, similarly highlighting the susceptibility of brain FC to behavioral manipulations, and raising concerns for the practical application of pain neuroimaging biomarkers.

Given that such factors have been shown to alter DMN FC in HCs and fibromyalgia patients, we aimed to determine whether alterations in a clinically relevant aspect of pain (ie, negative pain affect) could similarly alter the DMN in individuals with and without CLBP. Specifically, we used an empirically based mood induction protocol modified to function as a clinically relevant manipulation (ie, recall of an autobiographical story in which pain caused sadness). We chose to manipulate mood given the high prevalence of mood disturbance among patients with chronic pain,[1,24,32] impact of mood on pain perception,[72,78,82] and previous findings linking a key hub of the DMN to pain-related affect (ie, rumination[42]).

Sadness ratings significantly increased after negative mood induction, suggesting individuals experienced a heightened level of sadness during this condition compared with baseline. Furthermore, participants with CLBP reported increased LBP intensity associated with this change in mood, which is consistent with previous studies noting a relationship between mood and

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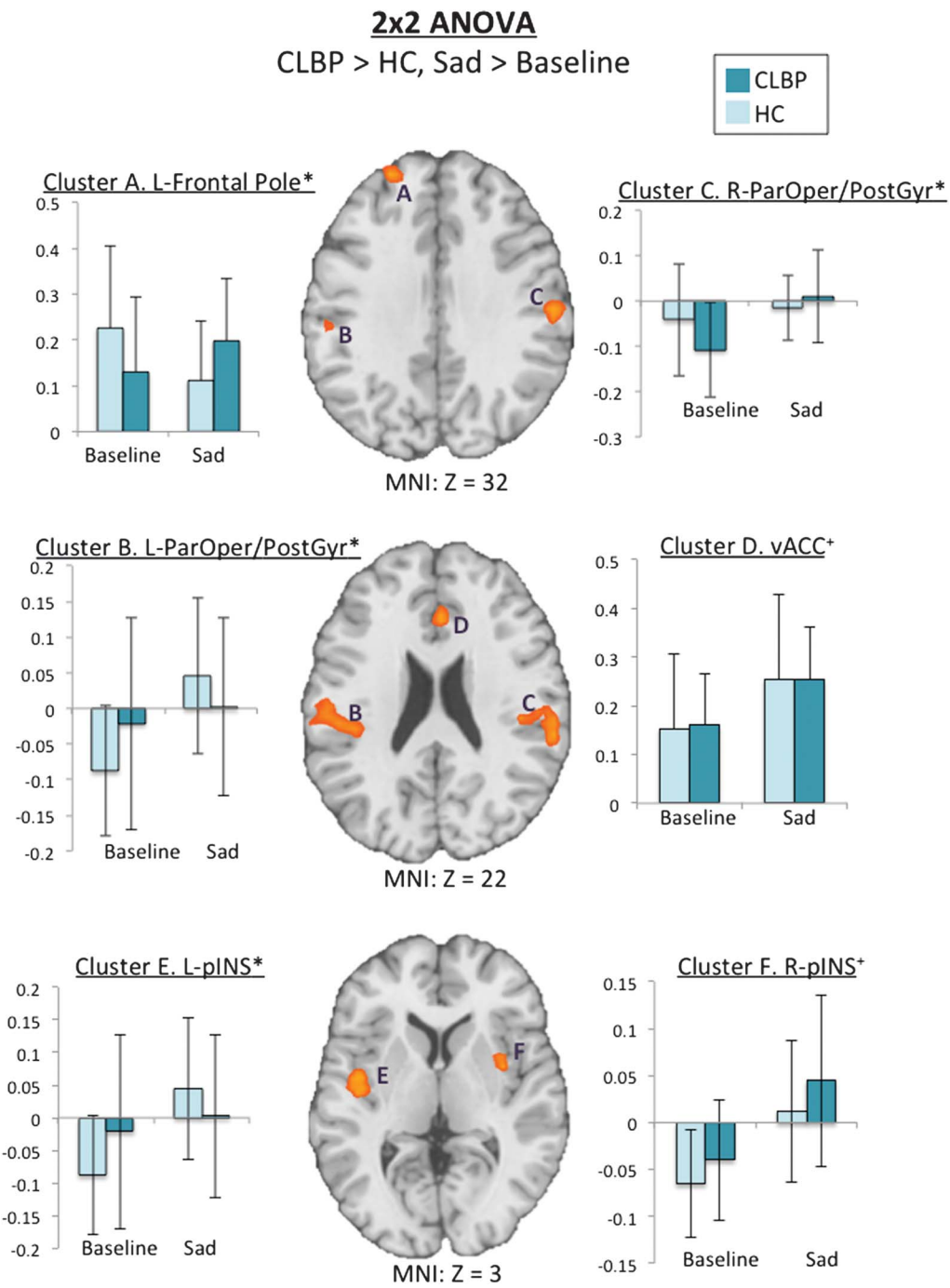

Figure 3. Axial slices of omnibus results from a 2 × 2 repeated-measures analysis of variance using the factors group (chronic low back pain > healthy controls) and condition (sadness > baseline). Level is indicated by the Z-plane MNI coordinate below each slice. Bar graphs represent mean functional connectivity values of each cluster, which are labeled by letters. Light bars represent healthy controls and dark bars represent participants with chronic low back pain. Group × condition interaction effects were identified in clusters (A) (frontal pole), (B) (left ParOper/PostGyr), (C) (right ParOper/PostGry), (E) (left posterior insula), and cerebellum (not pictured)], so that chronic low back pain participants showed increased functional connectivity between these clusters and the default mode network after sad mood induction. In addition, there was a main effect of condition only in clusters (D) (ventral anterior cingulate cortex) and (F) (right posterior insula). *Group × condition interaction effect, $^{+}$main effect of condition.

pain. It is important to note that because participants recalled autobiographical stories related to pain, attentional focus before resting-state scanning was specific to a previous pain experience across all participants.

Overall, we found differences in DMN FC based on condition (ie, baseline vs sadness, and baseline vs happiness) and group × condition interaction effects for sadness only. There was increased DMN FC to the vACC, bilateral pINS, and bilateral ParOper/PostGyr across both groups after sad mood induction. Whereas HC participants showed a greater magnitude of change in DMN FC to the left pINS and ParOper/PostGyr, there a greater magnitude of change in DMN FC to right ParOper/PostGyr (and trend for right pINS) in participants with CLBP. Two additional clusters were identified showing opposite patterns of FC with the

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DMN between groups (ie, cerebellum and frontal pole), so that HCs showed a decrease in FC after sad mood induction, and participants with CLBP showed an increase in FC with the DMN. After the happiness induction, there was decreased DMN FC with a portion of the cerebellum across both groups.

Previous research has described vACC, pINS, ParOper/PostGyr, and cerebellum in the context of pain processing,[34,38,58] as well as imagined pain.[22,36] Both vACC and INS are included within limbic[64] and paralimbic circuitry,[30] respectively. Specifically, vACC has been linked to the affective-motivational dimension of pain,[63] and is activated during the retrieval of autobiographical pain memories.[36] The pINS has been associated with pain processing[69] and negative affect.[7] Among subregions of the INS, pINS shows resting-state FC with primary and secondary somatosensory cortices, which is consistent with our findings of increased DMN ParOper (ie, S2,[20]) and PostGyr (ie, S1,[35]) FC after sad mood induction. Furthermore, both vACC and ParOper/PostGyr activation were linked to modulation of affect in sensory perception,[66] suggesting that the pattern of FC identified in this study was associated with modulated affect.

Owing to the pervasiveness of mood disturbance in patients with chronic pain,[17] it is imperative to ensure that biomarkers asserted to be pain intensity–specific are not resultant from changes in mood or pain-related affect. For example, patients with major depression show increased DMN FC with the vACC,[70] suggesting that mood impacts FC of the DMN to this region. Similarly, approximately 60% of neuroimaging studies manipulating mood through recall of an emotional autobiographical memory resulted in INS activation, which was suggested to support this region's role in evaluation of distressing cognitions and emotional processing.[59]

Previous work aimed at identifying patients with chronic pain (ie, biomarker development) has not examined the multicomponent nature of pain, and instead focused more on pain intensity, to the exclusion of affective or other components of clinical pain. The present findings are consistent with most definitions of clinical pain in that changes in mood or pain-related affect also impact pain intensity ratings. Clinically then, it is important to note that if the purpose of a biomarker is as a diagnostic tool, fluctuations in mood (from any cause) or pain-related affect can impact DMN FC. If the purpose of the biomarker is to provide mechanistic information and aid in treatment planning, then it is important to consider whether negative pain-related affect is contributing to the pattern of brain FC.

4.1. Implications for functional neuroimaging biomarker development

The present results support previous research demonstrating that brain FC associated with pain perception is not a static phenomenon,[41] but rather, a dynamic process that is susceptible to varied conditions at the time of scanning. With the rise in number of purported pain biomarkers, future studies should experimentally test whether such factors known to influence pain perception and its neural correlates also impact these markers, which will ultimately improve their clinical application. It is entirely possible that previously (or future) proposed biomarkers are representative of the clinical phenomenon in question; however, few have undergone substantial experimental testing to warrant such a label. It is not enough to conclude that a certain FC pattern is a pain-specific biomarker simply because 2 predetermined groups differ in FC. Empirical evaluation of biomarkers under different conditions and across time points is encouraged as common practice.[88]

Specific to studies using resting-state as a paradigm to derive biomarkers, it should be noted that the largest barrier to clinical translation of resting-state fMRI is moderate reproducibility of results within specific populations.[25] Consistent with previous research, our findings demonstrate that even "control" samples, used to make conclusions about aberrant FC in clinical samples, can show altered DMN FC based on varied conditions, such as increased negative affect and changes in previous cognitive task.[31,44,45,75,83,90] In a clinical setting, it is entirely possible that some patients might be primed to think about pain intensity or pain-related affect through clinical measures (eg, questionnaires) completed immediately before scanning, whereas others might be distracted from focusing on their clinical pain. Studies proposing biomarkers should account for the impact of previous cognitive task as a potential confound for results.

Of note are the study's limitations that future work should expand on. First, the patients with CLBP used in this study were specifically chosen to have subclinical symptoms of depression to avoid confounds of mood disorder; however, our sample was not fully representative of patients with CLBP seeking treatment for pain (ie, 52% meet criteria for clinical depression[15]). Future studies should determine whether patients with CLBP with comorbid mood disorders show further DMN FC differences. In addition, we only manipulated 1 variable known to influence pain perception for this study (ie, negative mood). Future studies should determine whether proposed biomarkers endure other factors that influence pain perception, such as attention or expectations for relief. Finally, we examined static, seed-based FC within the DMN; however, it will be important to determine whether potential chronic pain biomarkers derived from other analytic techniques (eg, graph theory, dynamic FC, and machine-learning) would similarly be affected by changes in behavioral factors.

5. Conclusion

The present findings suggest that behavioral factors that influence pain perception can influence DMN FC in both individuals with and without CLBP, raising practical concerns for the application of the DMN as a biomarker of pain intensity. Thorough empirical testing of brain FC under varying conditions is necessary in claiming candidate biomarkers of chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

This research was funded by the National Center for Complementary and Integrative Health through grants to MER (R01AT001424-05A2) and JEL (F31AT007898-03), as well as the National Institute of Nursing Research (1R01NR015314-01A1).

Article history:
Received 29 January 2016
Received in revised form 22 August 2016
Accepted 24 August 2016
Available online 31 August 2016

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