Research Paper

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Somatotopically specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain

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Abstract

Although several studies have found that chronic pain is characterized by increased cross-network connectivity between salience network, sensorimotor network, and default mode network (DMN), a large sample-size investigation allowing for a more reliable evaluation of somatotopic specificity and subgroup analyses with linkage to clinical pain intensity has been lacking. We enrolled healthy adults and a large cohort of patients (N = 181) suffering from chronic low back pain (cLBP). To specifically link brain connectivity with clinical pain intensity, patients were scanned at baseline and after performing physical maneuvers that exacerbated pain. Compared with healthy adults, patients with cLBP demonstrated increased connectivity between the functionally localized back representation in the primary somatosensory cortex ($S1_{back}$) and both salience network and DMN. Pain exacerbation maneuvers increased $S1_{back}$ connectivity to salience network regions, but decreased connectivity to DMN, with greater pain intensity increase associated with greater shifts in these connectivity patterns. Furthermore, only in patients with cLBP reporting high pain catastrophizing, DMN connectivity was increased to a cardinal node of the salience network, anterior insula cortex, which was correlated with increased postmaneuver pain in this cLBP subgroup. Hence, increased information transfer between salience processing regions, particularly anterior insula, and DMN may be strongly influenced by pain catastrophizing. Increased information transfer between the salience network and S1 likely plays an important role in shifting nociceptive afference away from self-referential processing, reallocating attentional focus, and affective coding of nociceptive afference from specific body areas. These results demonstrate S1 somatotopic specificity for cross-network connectivity in encoding clinical back pain and moderating influence of catastrophizing for DMN/insula connectivity.

Keywords: Functional connectivity, Clinical pain, Primary somatosensory cortex, Pain catastrophizing, Chronic low back pain, Cross-network connectivity

1. Introduction

Chronic pain is a highly prevalent and debilitating disorder,[21] and neuroimaging research has strongly associated chronic pain severity and suffering with altered brain physiology. Multiple studies have demonstrated altered functional magnetic resonance imaging (fMRI) brain connectivity in numerous neuropathic and functional pain disorders,[2,18,28,30,37,50] including increased cross-network connectivity between several canonical resting-state networks (eg, salience network [SN], sensorimotor network, and default mode network [DMN]). Although multiple studies of patients with chronic pain have converged on similar findings, a large sample-size investigation allowing for a more reliable evaluation of somatotopic specificity and subgroup analyses with linkage to clinical pain intensity has been lacking.

The SN is a bilateral network that activates during novel stimulus-driven attention allocation, ie, when a stimulus stands out from background afference, and is deemed "salient".[43,45] The SN is strongly linked with a ventral attention network and typically encompasses anterior insula/frontal operculum, anterior mid-cingulate cortex, dorsolateral prefrontal cortex (dlPFC), and anterior temporoparietal junction (TPJ).[27,34,49] Spontaneously flaring clinical pain is a highly salient perception, potentially leading to altered SN connectivity. In addition, the sensorimotor network, which includes primary somatosensory (S1) cortical representations for different body regions, may receive excessive excitatory input under clinical pain and be important for coding location and severity of this pain. Our prior study demonstrated reduced resting connectivity between different S1 cortical representations for patients with fibromyalgia.[23] In fact, several

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resting-state fMRI (rs-fMRI) studies have suggested that both fibromyalgia and chronic back pain patients exhibit increased cross-network connectivity between SN, sensorimotor network, and DMN.[18,30,37] However, which aspects of chronic pain pathology, such as pain catastrophizing—a psychosocial construct strongly linked with self-referential DMN processing,[29] contribute to such cross-network connectivity is unknown.

Furthermore, state properties (ie, stability) of aberrant cross-network connectivity are important to assess, as alterations in connectivity may be relatively immutable and reflect a fairly stable trait (eg, linked to living with daily chronic pain) or be a more labile, fluctuating state (eg, linked to spontaneously flaring clinical pain), and researchers have ascribed both trait and state properties to functional connectivity.[7] Regarding state-like properties of pain, our previous neuroimaging studies in both healthy adults[24] and patients with fibromyalgia[23] have shown that experimental nociceptive stimuli increase connectivity between SN regions (eg, anterior insula) and contralateral somatotopically specific S1 cortical representations. Whether clinical pain exerts similar state-like alterations remains to be seen.

Here, we tested the hypothesis that both location and intensity of chronic, clinical pain are encoded by increased connectivity between DMN or SN processing brain regions and somatotopically specific S1 subregions. We contrasted a large cohort of patients suffering from chronic low back pain (cLBP), one of the most common chronic pain disorders,[20] with healthy adults. To experimentally manipulate clinical pain states and test the stability of cross-network connectivity, we adopted a modified version of our model for clinical back pain exacerbation.[46] We then explored the association between altered connectivity and exacerbation-induced changes in clinical pain intensity, further probing how, and under what conditions, the clinical pain state modulates resting-state brain connectivity.

2. Methods

Although most of the data came from a single study (N = 174; cLBP = 135 [78 females] and healthy control [HC] = 39 [20 F]), to further bolster the sample size and power of our analyses, we also included data from patients with cLBP and HC subjects (N = 36; cLBP = 17 [11 F] and HC = 19 [12 F]) acquired in a prior 3.0 T fMRI study,[26] which used similar inclusion and exclusion criteria and the same cLBP phenotype and similar study design. Collectively, rs-fMRI data from 152 patients with cLBP and age- and sex-matched HCs (N = 58) were available for data analyses. All rs-fMRI data were collected using 3.0 T Siemens MRI scanners at the Martinos Center for Biomedical Imaging, Charlestown, MA. This study was conducted in accordance with the Partners Human Research Committee, and informed consent was obtained from all participants.

2.1. Participants and back pain exacerbation maneuvers

Inclusion criteria for patients with cLBP were as follows: (1) aged 18 to 60 years, (2) cLBP meeting Quebec Task Force Classification System categories I to II (ie, patients were unlikely to have significant nerve root involvement, stenosis, or mechanical instability[1,31]) as confirmed by the study physician and/or review of medical records with the use of previous x-ray reports, (3) duration of LBP greater than 6 months, (4) severity of LBP averaging at least 4 on a 0 to 10 pain intensity scale (0 = no pain and 10 = most intense pain imaginable) over the past 2 weeks, and (5) ability to temporarily exacerbate their LBP using individually calibrated physical maneuvers. Exclusion criteria for patients with cLBP included the following: (1) back pain due to cancer, fracture, or infection, (2) constant radicular pain radiating below the knee, (3) complicated chronic back syndromes (eg, prior back surgery and ongoing medicolegal issues), (4) active substance abuse disorder in the past 2 years, (5) history of cardiac, respiratory, or nervous system disease that may impact MRI, (6) use of prescription opioids exceeding 60-mg morphine equivalents per day or steroids for pain, (7) acupuncture contraindications (eg, coagulopathy) or history of acupuncture treatment (because of aims of a separate longitudinal study), and (8) presence of typical contraindications for MRI scanning. Healthy controls aged 18 to 60 years demographically matched to cLBP patients were also enrolled, with exclusion criteria as for cLBP above, in addition to any low back or other acute/chronic pain disorder.

For patients with cLBP, a clinical/behavioral session before the MRI sessions was used to determine which back-targeted physical maneuvers reliably exacerbated their LBP. The maneuvers were an individualized, dynamic procedure that controlled the level of movements to briefly increase the intensity of cLBP in an objective, measured, and reproducible manner such that it would remain at this elevated level during the scan session. First, the experimenter and the participant discussed maneuvers that would potentially exacerbate back pain. Participants were informed that they did not have to perform maneuvers if they felt their pain was too severe at the baseline pain state. Next, the participant performed a set of typical maneuvers (eg, toe touches, facet-joint loading twists, sit-ups, back arches, and pelvic tilts), and the experimenter recorded parameters (eg, number of repetitions, extension, and angular deviation) of each maneuver, as well as the change in pain severity. If these typical maneuvers were unsuccessful in exacerbating pain, subjects then chose an experience from their daily lives that exacerbated pain (eg, one study participant experienced intense pain while putting on socks, so the participant performed repeated movements mimicking this action, to exacerbate back pain). This procedure has been adapted after several prior neuroimaging studies using similar techniques to exacerbate clinical LBP.[26, 30, 46]

Subjects were also asked to complete several self-report assessments: LBP bothersomeness over the past week, current LBP intensity, Beck Depression Inventory,[3] Back Pain Specific Disability,[41,42] Patient-Reported Outcomes Measurement Information System (PROMIS) scale,[11] and Pain Catastrophizing Scale (PCS).[44]

Demographic and clinical data were compared between cLBP and HC groups using independent samples *t* tests, whereas state variables recorded before vs after LBP exacerbation maneuvers in cLBP were contrasted with paired sample *t* tests (SPSS v.22). The Pearson χ^2 test was used to assess the difference in sex ratio (male:female) between cLBP and HC. Statistical significance was determined at $P < 0.05$.

2.2. Resting-state functional magnetic resonance imaging data acquisition

Brain imaging data were acquired using 3.0 T MRI systems (Siemens, Erlangen, Germany), equipped with a 32-channel head coil (N = 169 were acquired using a Siemens Skyra system, whereas N = 41 were acquired using a Siemens Trio system). All rs-fMRI data from the prior study[26] were acquired using a Siemens Trio system. Structural MRI was used for standard space coregistration and applied T1-weighted pulse sequences (Skyra MEMPRAGE: repetition time [TR]/echo time [TE]1/TE2/TE3/TE4 = 2530/1.69/3.5/5.36/7.22 ms, flip angle = 7°, voxel

size = 1 mm isotropic; Trio MPRAGE: TR/TE = 2200/1.54 ms, flip angle = 7°, voxel size = 1.2 mm isotropic). Resting-state fMRI data were collected using T2*-weighed gradient-echo BOLD EPI pulse sequences (Skyra: TR/TE = 3000/30 ms, flip angle = 90°, 44 tilted axial slices, voxel size = 2.6 × 2.6 × 3.1 mm; Trio: TR/TE = 3000/30 ms, flip angle = 85°, 47 tilted axial slices, voxel size = 3.0 × 3.0 × 3.0 mm).

All participants were instructed to keep their eyes open and remain still during the 6-minute rs-fMRI runs. After a baseline run ($cLBP_{pre}$), patients with cLBP were removed from the scanner and performed customized physical maneuvers to temporarily increase their LBP. Following back pain exacerbation, patients were placed back inside the scanner and a second 6-minute rs-fMRI run was acquired ($cLBP_{post}$). Our previous study showed that similar physical maneuvers did not induce pain or significantly alter cerebral blood flow in HCs[46]; hence, HCs did not perform maneuvers. Subjects verbally rated LBP intensity on a 0 to 100 scale (0 = no pain and 100 = worst pain imaginable) before and after each of the $cLBP_{pre}$ and $cLBP_{post}$ fMRI scans.

Physiological/autonomic data were also collected during Siemens Skyra fMRI scans. Cardiac activity was assessed with electrocardiogram (ECG amplifier ECG100C-MRI; Biopac Systems Inc, Goleta, CA) and finger pulse (ADInstruments, Colorado Springs, CO) data. Respiration data were collected using a custom-built pneumatic MRI-compatible belt system with air pressure transducer (PX138-0.3D5V; OMEGA Engineering Inc., Norwalk, CT). In-house scripts were used to filter, process, and annotate the physiological signals. All physiological data were collected at 500 Hz. Low-pass filtering was applied to remove MRI gradient and radiofrequency noise in both cardiac and respiration data (cutoff frequency: 50 Hz). We then applied the MATLAB (R2016b; MathWorks, Natick, MA) software library's peakfinder function to annotate cardiac traces, and algorithm-detected peaks were confirmed by visual inspection.

We excluded fMRI data of 19 patients with cLBP and 4 HCs because of excessive head motion with the following criteria: (1) greater than 3 mm translation/rotational motion from initial time-point or (2) relative framewise displacement[38,39] greater than 2 mm. In addition, data from 6 individuals with cLBP were excluded because they were not able to perform physical maneuvers during the MRI session. Resting-state fMRI data from a total of 127 patients with cLBP and 54 HCs were available for analyses.

2.3. Functional S1-seed localization functional magnetic resonance imaging

At a separate MRI visit, to localize the S1 representation for the low back (body region related to pain pathology) and fingers (pain-free body region used as control) for localization and seed connectivity analyses, subjects scanned with the Siemens Skyra also completed evoked pain fMRI scans (TR/TE = 3000/30 ms, flip angle = 90°, 44 tilted axial slices, voxel size = 2.6 × 2.6 × 3.1 mm). To avoid bias in analyses, seed localization was determined in a combined sample of patients with cLBP and HCs. Cutaneous electrical stimulation was delivered to the right lower back (over erector spinae muscles) or a control location on the right hand (second and third fingers) in separate fMRI scans. Before this fMRI scan, the intensities (electrical current, mA) for painful and nonpainful electrical stimuli were individually tailored using the method of limits to evoke 40/100 pain (P40, 0 = no pain and 100 = worst pain imaginable) and 7/10 moderate but not painful sensation (P0, 0 = no sensation and 10 = on the verge of pain), respectively. For each 4-minute fMRI scan, these 2 current intensities were used for 13 P40 and 13 P0 (2-second duration, 25 Hz, electrical current: P40 = 3.5 ± 2.9 mA, P0 = 1.5 ± 1.4 mA) stimulus blocks, applied in a randomized order. The interstimulus interval was jittered from 6 to 12 seconds. Preprocessing included RETROICOR,[16] motion correction (MCFLIRT-FSL), susceptibility-induced distortion correction (TOPUP-FSL), resampling to 2 × 2 × 2 mm (3Dresample-AFNI), skull stripping (BET-FSL), and functional-to-functional coregistration (FLIRT-FSL). Following spatial smoothing (full width at half maximum = 5 mm), and temporal filtering (high-pass frequency = 1/42 seconds), general linear modeling (GLM with FEAT-FSL) yielded individual-subject response maps for P40 and P0. A second level fixed-effects analysis calculated the P40 − P0 difference map for each individual, and these parameter estimates and their variances were then coregistered to MNI-space (BBREGISTER-Freesurfer) and passed up to a group analysis computing the P40 vs P0 difference map. This P40 − P0 difference map was calculated for each stimulus location (low back and finger) separately, across both patients with cLBP and HCs. These combined-group P40 vs P0 difference maps were used for S1 localization of low back and finger representations for nociceptive afference, as well as to define consistent seeds in connectivity analyses (see below).

2.4. Resting functional magnetic resonance imaging data preprocessing

Resting fMRI data were corrected for the physiological artifact (RETROICOR-AFNI), head motion (MCFLIRT-FSL), susceptibility-induced distortion (TOPUP-FSL), and skull-stripped (BET-FSL). Collectively, 68.8% of scans (cLBP: 70.1% and HC: 63.0%) contributed physiological data to correct for cardiorespiratory artifacts in fMRI data using RETROICOR.[16] The proportion of missing physiological data did not differ between cLBP and HC groups (Pearson $\chi^2 = 1.3$, $P = 0.25$). Additional sources of artifact were then removed using a GLM. Heart rate and respiratory volume data convolved with cardiorespiratory response functions,[12,13] white matter and cerebrospinal fluid signal regressors identified with the top 5 principal components using the CompCor algorithm[5,47] with FAST-FSL tissue segmentation, 6 translational/rotational motion correction parameters, and a censoring confound matrix of head motion outliers (fsl_motion_outliers-FSL) were included in the GLM as nuisance regressors. Importantly, the global signal was not included in this GLM. The residual signal after regressing out these nuisance signals was then transferred to the MNI space (BBREGISTER-Freesurfer), spatially smoothed (full width at half maximum = 6 mm), temporally high-pass filtered (high pass = 0.006 Hz as in previous publications,[19,23,37] 3dBandpass-AFNI), and used for connectivity analyses. This resting fMRI data analysis pipeline is displayed in supplementary Fig. 1, available at http://links.lww.com/PAIN/A763.

2.5. Resting functional magnetic resonance imaging connectivity: whole-brain analyses

Dual-regression independent component analysis (ICA) and seed-voxel correlation analyses were used. The dual-regression ICA approach uses data-driven methods to explore SN and DMN level connectivity. For dual-regression ICA,[14,51] temporally concatenated fMRI data from $cLBP_{pre}$, $cLBP_{post}$, and HCs were entered in a group ICA (MELODIC-FSL), without predefined dimensionality constraint. From the group ICs (N = 10), the best-fit ICs for the SN and DMN were selected by calculating spatial correlation with a canonical Beckmann 8 template[4] and visualized

Table 1

Baseline demographic and clinical data.

	cLBP (n = 127)	HC (n = 54)	*P*
Age (y)	39.3 ± 11.8	39.5 ± 11.2	0.92
Sex (male/female)	55/72	25/29	0.75*
Pain duration (y)	7.6 ± 7.0	N/A	—
% Using opioids	7.8	0	<0.001
BDI	6.6 ± 6.9	2.5 ± 4.2	<0.001
BPSD†	8.6 ± 4.5	N/A	—
PROMIS-physical function†	42.3 ± 5.1	56.3 ± 2.8	<0.001
PROMIS-pain interference†	59.3 ± 5.8	41.6 ± 0.0	<0.001
PCS†	12.5 ± 8.8	4.1 ± 6.0	<0.001
Back pain bothersomeness†	5.1 ± 2.0	N/A	—

* Pearson χ^2 test (2-sided, 0 cells have expected count less than 5).
† Data available for large subset of subjects (cLBP: n = 114 and HC: n = 36).
BDI, Beck Depression Inventory II (0-63 scale); BPSD, Back Pain Specific Disability (0-10 scale); cLBP, chronic low back pain; HC, healthy control; PCS, Pain Catastrophizing, Back pain bothersomeness (0-10 scale); PROMIS, Patient-Reported Outcomes Measurement Information System.

to confirm adequate independent component definitions (see supplementary Fig. 2 for DMN and SN group independent component maps with their respective template; available at http://links.lww.com/PAIN/A763).

Seed-voxel correlation analyses were used to evaluate whole-brain connectivity maps for a priori–defined regions of interest. Specifically, our seed connectivity analysis was inspired by the results of the dual-regression ICA, which found increased SN connectivity to $S1_{back}$. For this seed connectivity analysis, we first defined an $S1_{back}$ seed using results from the stimulus-evoked back pain fMRI scan described above. A bilateral $S1_{back}$ mask was created by centering a 6-mm radius sphere on the left (contralateral to the right back stimulation site) $S1_{back}$ peak activation voxel (MNI (x, y, z) = −18, −38, 72 mm) and mirroring this sphere across the midsagittal plane. Averaged fMRI signal from this $S1_{back}$ mask was used as a GLM regressor for each individual.

For both dual-regression ICA and seed-voxel connectivity analyses, resultant connectivity parameter estimate and variance maps for each individual were passed up to group-level difference analyses. Connectivity was then contrast between $cLBP_{pre}$ and $cLBP_{post}$ using a paired sample *t* test, whereas patients with cLBP and HC groups were contrast with an independent samples *t* test. We used FMRIB's Local Analysis of Mixed Effects (FLAME 1 + 2) to improve mixed-effects variance estimation. We also performed whole-brain linear regression analyses within the cLBP group to assess the association between functional connectivity and subjective measures of clinical pain intensity at the time of the scan. For these analyses, the postmaneuver minus premaneuver parameter estimate difference map was calculated for each subject, whereas variance maps were summed for the FLAME 1 + 2 linear regression analysis.

Although head motion was addressed by several correction algorithms during data preprocessing, we also compared head motion in cLBP and HC groups using different metrics. The number of high motion timepoints censored from the fMRI timeseries did not differ significantly between groups ($cLBP_{pre}$ = 6.6 ± 3.2, HC = 5.5 ± 3.3, $P = 0.15$) nor between baseline and postmaneuver scans in cLBP ($cLBP_{post}$ = 6.2 ± 3.0, $P = 0.23$). All individual rs-fMRI data sets included more than 4 minutes of uncensored data as recommended by Parkes et al.[38] (the maximum number of censored volumes for any data set was 16 for $cLBP_{pre}$, 15 for $cLBP_{post}$, and 14 for HC at TR = 3 seconds). We also calculated root-mean-square (RMS) relative head motion estimates. The head motion RMS metric did not differ between cLBP and healthy groups ($cLBP_{pre}$ = 0.039 ± 0.022, 0.012∼0.119 (mean ± SD, range), HCs = 0.038 ± 0.027, 0.009∼0.140; *t* test $P = 0.91$), but was greater in patients with cLBP following maneuvers ($cLBP_{post}$ = 0.047 ± 0.029, 0.008∼0.190) compared with the baseline pain state ($cLBP_{post}$ vs $cLBP_{pre}$ paired *t* test, $P < 0.001$) and was trending when compared with HCs ($cLBP_{post}$ vs HC unpaired *t* test, $P = 0.053$). Thus, analyses were adjusted for this frame-to-frame relative head motion metric (RMS), as well as age and sex, by including these variables as regressors in the GLM. Correction for multiple comparisons was performed using GRF cluster correction ($Z > 2.3$) and corrected $P < 0.05$.

2.6. Resting functional magnetic resonance imaging connectivity: region of interest analyses

Follow-up region of interest (ROI) analyses were performed to evaluate whether SN connectivity increased to somatotopically specific brain regions. S1 localizations for the back and finger (similarly determined $S1_{finger}$, MNI(x, y, z) = −42, −20, 56 mm) were used in follow-up ROI analyses, in addition to another control S1 localization for the face ($S1_{face}$), whose location was drawn from a previous evoked-stimulation fMRI study.[35] We also performed follow-up ROI analyses to evaluate which specific SN subregions showed altered connectivity with the $S1_{back}$ seed. Candidate SN subregions included the following right and left

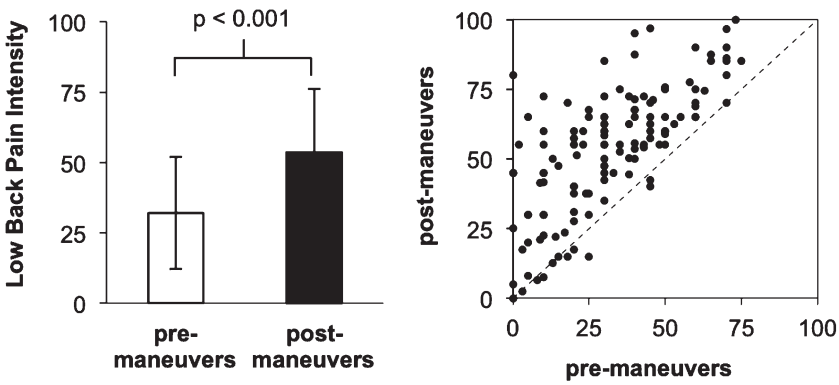

Figure 1. Low back pain intensity (0-100, numerical rating scale) was significantly increased in patients with cLBP following physical maneuvers ($P < 0.001$, the paired *t* test for postmaneuvers vs baseline). Error bars represent SD. cLBP, chronic low back pain.

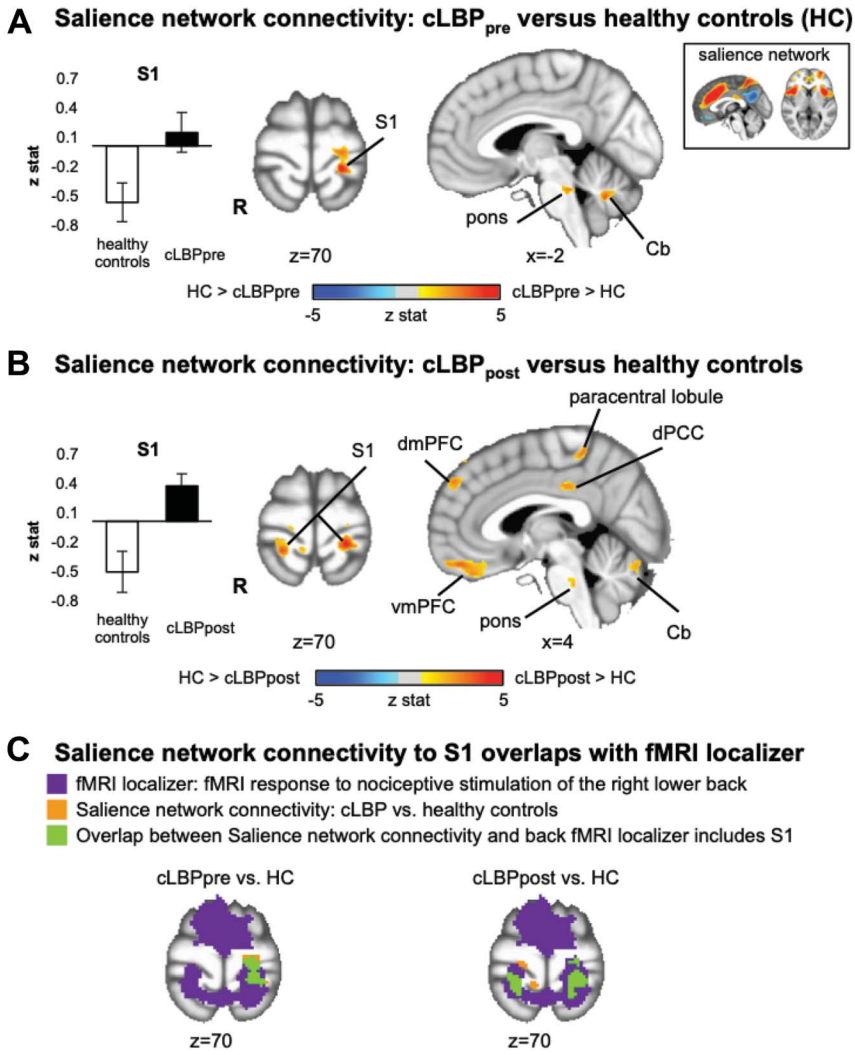

Figure 2. Dual-regression ICA found that resting salience network connectivity is altered by chronic low back pain. (A) Compared with healthy controls, patients with cLBP exhibited increased salience network connectivity to S1. (B) Following physical maneuvers that increased patients' clinical low back pain, salience network connectivity was further increased to S1, as well as to several default mode network regions (dPCC, dmPFC, and vmPFC). Note that healthy controls did not perform any maneuvers. (C) A conjunction analysis found that the S1 subregion noted in A and B partially overlapped (*green*) with the primary sensorimotor cluster found with fMRI-localized response to nociceptive stimulation of the right lower back. cLBP, chronic low back pain; dmPFC, dorsomedial prefrontal cortex; dPCC, dorsal posterior cingulate cortex; fMRI, functional MRI; ICA, independent component analysis; S1, primary somatosensory cortex; vmPFC, ventromedial prefrontal cortex.

nodes: anterior insula (MNI (x, y, z) = ±32,20, −2 mm), dlPFC (MNI (x, y, z) = ±26, 42, 32 mm), and anterior TPJ (MNI (x, y, z) = ±60, −32, 32 mm), with locations drawn from the $S1_{back}$ connectivity difference map contrasting exacerbated pain ($cLBP_{post}$) vs HCs (see Results). Functional connectivity data were extracted from centering a 4-mm radius sphere on the voxel for each ROI and were compared between cLBP and HC groups using independent samples *t* tests, whereas $cLBP_{pre}$ and $cLBP_{post}$ were contrasted with paired sample *t* tests at the $P < 0.05$ level of significance (SPSS v.22).

2.7. Pain catastrophizing subgroup analyses

Our prior cLBP study[30,37] with a high pain catastrophizing chronic pain cohort (mean PCS was 23, adjust to consistent 0-4 rating scale) linked elevated DMN-insula connectivity with increased clinical pain intensity following physical maneuvers. Our current study enrolled a much larger sample with heterogeneous but, on average, relatively low pain catastrophizing scores (mean PCS was 12.5). Thus, we followed up the above analyses to evaluate DMN connectivity in different pain catastrophizing subgroups. For patients with cLBP for whom PCS scores were collected (N = 114, **Table 1**), PCS scores ranged from 0 to 38. We divided patients with cLBP into equal sample size low-, mid-, and high-PCS tertile subgroups with nonoverlapping score ranges (ie, low PCS: 3.12 ± 1.93, 0∼7 (mean ± SD, range), mid PCS: 11.53 ± 1.91, 8∼15, and high PCS: 23.32 ± 6.07, 16∼38). To test whether PCS status influenced clinical pain–linked DMN connectivity, we evaluated for each PCS subgroup, DMN connectivity changes following physical maneuvers, which were also associated with change in clinical pain following these maneuvers, using identical methods as above.

3. Results

3.1. Demographic and clinical characterization

Compared with HCs, patients with cLBP demonstrated significantly higher Beck Depression Inventory, PROMIS (pain interference), and PCS scores (**Table 1**). Patients performed

Table 2

Salience network connectivity in healthy controls vs cLBP patients, pre- and post-physical maneuvers, which temporarily exacerbated clinical pain.

	Side	Size (mm^3)	MNI coordinates			Peak z-stat
			X (mm)	Y (mm)	Z (mm)	
$cLBP_{pre}$ vs healthy controls						
S1	L	5160	−20	−34	70	4.55
Cerebellum	R	1616	14	−58	−36	3.67
	L	13,832	−22	−76	−30	5.34
Pons/brainstem	R	4616	14	−34	−20	3.76
	L	6880	−10	−32	−20	4.12
$cLBP_{post}$ vs healthy controls						
S1	R	1160	22	−40	70	4
	L	848	−22	−36	70	4.51
Paracentral lobule	L	6040	−14	−34	56	4.62
vmPFC	R	5552	8	48	−18	4.02
dmPFC	L	3288	−4	52	38	4.7
	L	456	−4	42	52	3.08
dPCC	R	576	4	−28	34	3.49
Cerebellum	L	21,888	−36	−54	−28	4.5
Pons	R	816	6	−26	−30	3.21
$cLBP_{post}$ vs $cLBP_{pre}$						
Middle frontal gyrus	R	7144	54	−62	46	−4.52

cLBP, chronic low back pain; dmPFC, dorsomedial prefrontal cortex; dPCC, dorsal posterior cingulate cortex; S1, primary sensory cortex; vmPFC, ventromedial prefrontal cortex.

a range (and sometimes a combination) of physical maneuvers meant to exacerbate their clinical pain, with toe touches being most common (toe touches: 39.4%, facet-joint loading twists: 21.3%, leg raise: 19.7%, back arches: 18.1%, and simulated activities of daily life: 8.7%). Physical maneuvers significantly and robustly increased LBP intensity (premaneuvers: 31.9 ± 19.9 (mean ± SD) and postmaneuvers: 53.7 ± 22.5, $P < 0.001$) in most patients with cLBP (**Fig. 1**). We did not find significant differences in age ($P = 0.92$) or sex (Pearson $\chi^2 = 0.14$, $P = 0.75$) between patients with cLBP and HCs (**Table 1**). Although prescription medication use was not pervasive in our sample, the most common classes of medications in patients with cLBP included antidepressants (11.4%), benzodiazepines (3.5%), and opioids (8.8%) (supplementary Table 1, available at http://links.lww.com/PAIN/A763).

3.2. Independent component analysis–based network connectivity analysis: increased salience network connectivity to $S1_{back}$ in patients with chronic low back pain

Dual-regression ICA found that, compared with HCs, patients with cLBP exhibited increased SN connectivity to the pons, cerebellum, and an S1 cluster overlapping the fMRI-localized responses to nociceptive stimuli applied to the low back ($S1_{back}$, **Fig. 2A**). This increased SN connectivity to S1 was bilateral following physical maneuvers that robustly increased patients' LBP (**Figs. 2B and C**) compared with HCs. Furthermore, after physical maneuvers, patients with cLBP demonstrated increased SN connectivity to other brain regions: paracentral lobule, dorsal posterior cingulate cortex (dPCC), dorsomedial prefrontal cortex, ventromedial prefrontal cortex, pons, and cerebellum (**Table 2**). Specifically, group differences for SN connectivity to DMN regions (ie, dPCC, dorsomedial prefrontal cortex, and

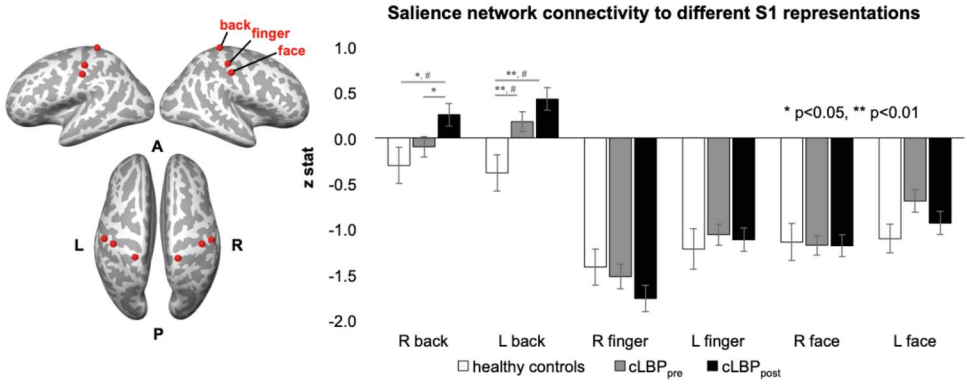

Figure 3. Salience network connectivity to S1 representations for different body regions. A region of interest (ROI) analysis found that salience network connectivity was increased to $S1_{back}$, but not to $S1_{finger}$ or $S1_{face}$ in cLBP patients compared with healthy controls. Furthermore, connectivity to $S1_{back}$ (but not $S1_{finger}$ or $S1_{face}$) was increased further in patients with cLBP following physical maneuvers that exacerbated their low back pain. # = significant with whole-brain voxelwise analysis with cluster-size correction for multiple comparisons. cLBP, chronic low back pain.

Table 3

$S1_{back}$ seed connectivity in healthy controls vs cLBP patients, pre- and post-physical maneuvers, which temporarily exacerbated clinical pain.

	Side	Size (mm^3)	MNI coordinates			Peak z-stat
			X (mm)	Y (mm)	Z (mm)	
$cLBP_{pre}$ vs healthy controls						
Inferior temporal gyrus	L	4040	−56	−70	−8	−3.86
Precuneus	R	3488	34	−76	40	−4.09
	L	10,632	−14	−76	48	−4.46
$cLBP_{post}$ vs healthy controls						
Anterior insula	L	11,704	−32	20	−2	4.43
Anterior TPJ	R	3736	60	−32	30	3.7
dlPFC	R	3976	28	40	44	4.09
	L	4840	−26	42	32	4.09
dmPFC	L	4544	−2	20	52	3.72
Striatum	R	1696	18	18	4	4.74
	L	1576	−28	−10	−2	3.25
Thalamus	R	776	10	−22	10	3.93
	L	488	−6	−8	−8	3.14
S1	R	3880	42	−28	64	−3.84
Paracentral lobule	L	3560	−42	−24	66	−3.82
Inferior temporal gyrus	R	3400	42	−62	0	−4.26
$cLBP_{post}$ vs $cLBP_{pre}$						
dlPFC	R	7000	46	8	40	4.31
Anterior TPJ	R	4776	60	−38	34	3.85
SMA	R	4008	10	−6	68	5.45
S1	L	1696	−14	−36	54	3.9
Precuneus	R	4288	12	−76	48	4.53
S1/M1	R	18,744	46	−16	62	−5.4
	L	16,880	−42	−14	60	−4.53
Inferior temporal cortex/parahippocampal gyrus	R	5680	42	−12	−42	−4.08
Superior temporal cortex	L	4680	−52	16	−18	−3.77

cLBP, chronic low back pain; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; S1, primary sensory cortex; SMA, supplementary motor area; TPJ, temporoparietal junction.

ventromedial prefrontal cortex) revealed reduced anticorrelation in patients with cLBP compared with HC.

We also directly explored SN connectivity to other control body area representations in S1 (finger and face). First, an ROI analysis found that even in HCs, compared with $S1_{back}$, the $S1_{finger}$ and $S1_{face}$ fMRI signal showed greater anticorrelation with the SN (eg, the paired *t* test for right $S1_{back}$ vs right $S1_{finger}$, $P < 0.001$; the paired *t* test for right $S1_{back}$ vs right $S1_{face}$, $P = 0.006$), whereas SN connectivity to $S1_{finger}$ vs $S1_{face}$ was not different (the paired *t* test for $S1_{finger}$ vs $S1_{face}$, $P = 0.16$). Comparing groups, patients with cLBP demonstrated increased SN connectivity to $S1_{back}$, but not $S1_{finger}$ or $S1_{face}$ (**Fig. 3**). Moreover, although a voxelwise dual-regression SN ICA did not find altered connectivity between $cLBP_{post}$ and $cLBP_{pre}$, our more focused S1 ROI analysis did find that following physical maneuvers that exacerbated LBP, patients with cLBP showed increased SN connectivity to $S1_{back}$, but not to $S1_{finger}$ or $S1_{face}$.

3.3. Seed-based connectivity analysis: increased $S1_{back}$ connectivity to specific salience network nodes in chronic low back pain

Following up on results from SN analyses, the fMRI-localized $S1_{back}$ region was also used in a whole-brain seed connectivity analysis. A whole-brain voxelwise $S1_{back}$ seed connectivity analysis did not find increased $S1_{back}$ connectivity for patients with cLBP at baseline compared with HCs. However, following LBP exacerbation by physical maneuvers, patients with cLBP demonstrated increased $S1_{back}$ connectivity to several SN brain regions: anterior insular cortex, dlPFC, and anterior TPJ (**Table 3** and **Fig. 4A**). Furthermore, $S1_{back}$ connectivity was decreased to nonback representation areas within the primary somatosensory/motor cortex (S1/M1). We also found that compared with cLBP patients at baseline, following physical maneuvers these patients demonstrated increased $S1_{back}$ connectivity to anterior TPJ, supplementary motor area (SMA), and decreased connectivity to nonback representation areas within the S1/M1 (**Fig. 4B**). A follow-up ROI analysis found increased $S1_{back}$ connectivity to the bilateral anterior insula and dlPFC for patients with cLBP at baseline compared with healthy adults (**Fig. 4C**). Following physical maneuvers in patients with cLBP, there was increased $S1_{back}$ connectivity to the left anterior insula and bilateral anterior TPJ.

3.4. Association between $S1_{back}$ and salience network connectivity and clinical pain

To more closely link changes in functional brain connectivity with clinical pain intensity, we performed whole-brain linear regression analyses in patients with cLBP. Increased LBP intensity following individualized, back-targeted maneuvers was correlated with increased $S1_{back}$ connectivity to a cluster centered on the left anterior insula ($r = 0.36$, **Fig. 5**). Although this was the only cluster present in the whole-brain analysis, we also evaluated associations for other SN ROI's that

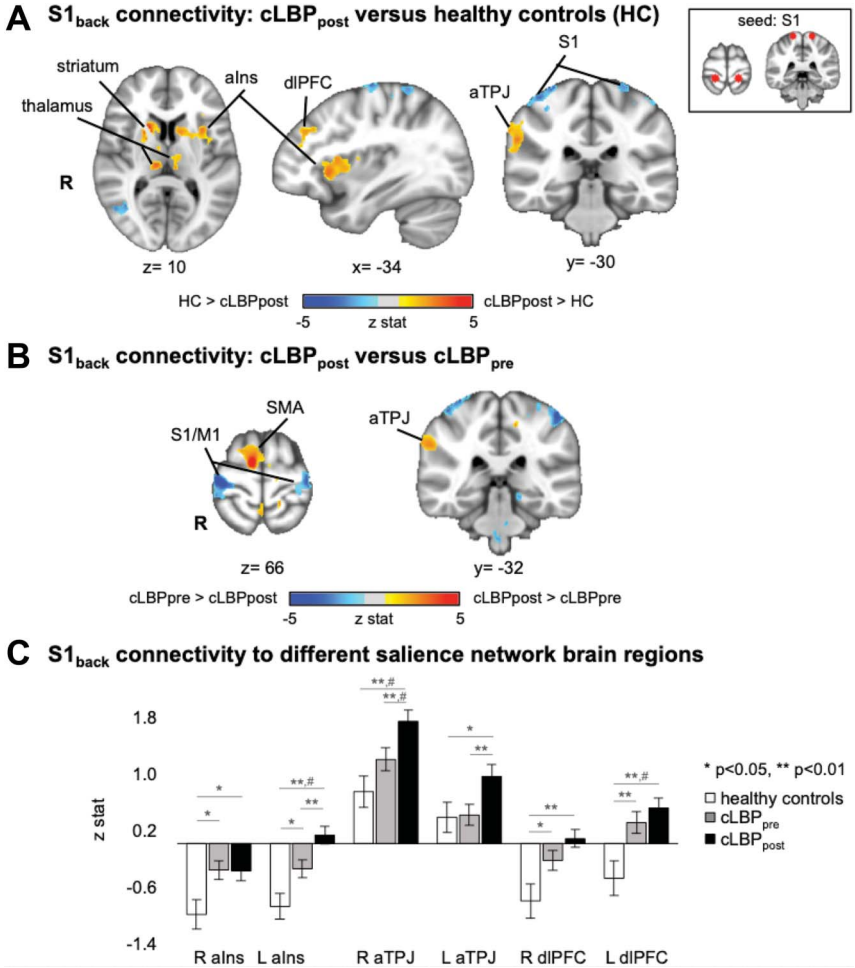

Figure 4. $S1_{back}$ seed-voxel connectivity is altered by exacerbated low back pain in patients with cLBP. (A) Compared with healthy controls, patients with cLBP in an exacerbated low back pain state demonstrated increased $S1_{back}$ connectivity to several salience network brain regions: anterior insular cortex (aIns), dorsolateral prefrontal cortex (dlPFC), and anterior temporoparietal junction (aTPJ). Note that healthy controls did not perform any maneuvers. (B) Compared with cLBP patients at baseline, following physical maneuvers, $S1_{back}$ seed-voxel connectivity was increased to the aTPJ (a salience network subregion). (C) $S1_{back}$ connectivity to specific salience network brain regions was increased in cLBP patients compared with healthy adults. # = significant with whole-brain voxelwise analysis with cluster-size correction for multiple comparisons. cLBP, chronic low back pain; SMA, supplementary motor area.

demonstrated increased $S1_{back}$ connectivity postmaneuvers vs premaneuvers (from **Fig. 4C**), and found that $S1_{back}$ connectivity to these other SN regions was not correlated with changes in LBP intensity (*R* aIns: $r = 0.11$, $P = 0.23$; *R* TPJ: $r = 0.09$, $P = 0.33$; L TPJ: $r = 0.04$, $P = 0.63$; *R* dlPFC: $r = -0.07$, $P = 0.41$; L dlPFC: $r = 0.00$, $P = 1.00$), highlighting the role of the left anterior insula in encoding clinical pain intensity.

3.5. Increased default mode network connectivity to $S1_{back}$ in patients with chronic low back pain and response to maneuvers

Compared with HCs, patients with cLBP at baseline demonstrated increased DMN connectivity to a S1 subregion, consistent with the cortical representation of the back (ie, $S1_{back}$) and leg (**Fig. 6A** and **Table 4**). Low back pain exacerbation following physical maneuvers decreased DMN connectivity to $S1_{back}$ and increased within-DMN connectivity to the medial prefrontal cortex (mPFC) (**Fig. 6B**). Furthermore, change in DMN-S1 connectivity following maneuvers was negatively correlated with change in clinical pain intensity ($R = -0.18$, $P = 0.04$), thus greater increase in pain following maneuvers was linked with greater reduction in DMN/S1 connectivity.

3.6. Increased default mode network connectivity to the insula in chronic low back pain patients with high pain catastrophizing

For the whole cLBP patient (N = 127) cohort, DMN connectivity to the insula did not differ significantly between cLBP and HC groups, nor for cLBP before vs after pain exacerbation maneuvers. However, when the cLBP cohort was broken up into low-, mid-, and high-PCS cLBP subgroups, the low-PCS subgroup demonstrated elevated DMN connectivity to the mPFC following physical maneuvers, which was correlated with increasing pain intensity following maneuvers ($r = 0.35$, $P = 0.04$). Default mode network connectivity decreased to the dlPFC and cuneus following maneuvers for the mid-PCS subgroup, but these changes were not associated with changes in pain intensity. However, high-PCS cLBP patients demonstrated increased DMN connectivity to the right anterior/midinsula (**Fig. 6C**) following maneuvers, and this increase was correlated with postmaneuver change in LBP intensity ($r = 0.43$, $P = 0.01$). A subsequent ROI analysis found

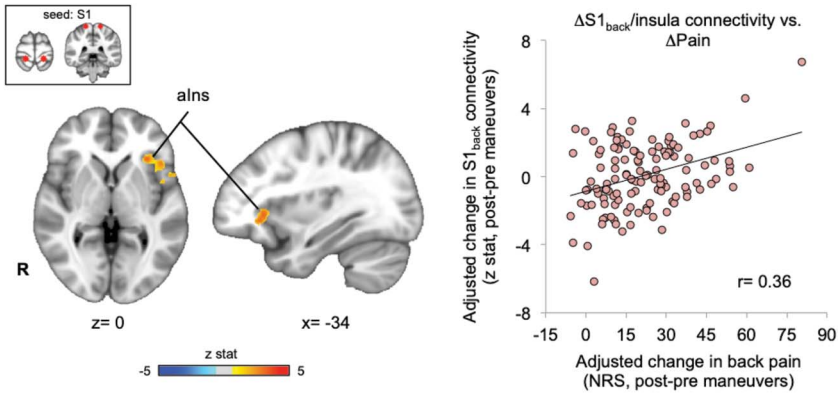

Figure 5. Maneuver-induced change in $S1_{back}$ connectivity to the anterior insula was associated with change in clinical pain. A whole-brain seed-voxel analysis found that physical maneuver–induced increase in low back pain was correlated with increased $S1_{back}$ connectivity to the left anterior insula cortex. This linear regression analysis was adjusted to control for age, sex, and head motion. aIns, anterior insular cortex; NRS, numerical rating scale.

that correlation between change in DMN-a/mIns connectivity and change in LBP intensity was not found for the low- and mid-PCS subgroups (low PCS: $r = 0.22$, $P = 0.21$; mid PCS: $r = -0.14$, $P = 0.42$). Importantly, the magnitude of postmaneuver increase in clinical pain after physical maneuvers did not differ between these PCS subgroups (analysis of variance, $F(2) = 1.42$, $P = 0.25$) and was thus unlikely to influence DMN-a/mIns connectivity results.

4. Discussion

Improved understanding of how clinical pain states are encoded by brain connectivity aids our understanding of the neurophysiology supporting clinical pain perception, how the neurophysiology of clinical pain differs from evoked experimental pain, and even biomarker development, by introducing candidate quantitative imaging metrics that track clinical pain severity, enhancing our ability to diagnose and treat chronic pain. Evaluation of a large sample (N = 127) of patients with cLBP found that compared with healthy adults, patients demonstrated increased $S1_{back}$ connectivity to both SN and DMN. Pain exacerbation maneuvers increased $S1_{back}$ connectivity to SN regions, but decreased connectivity to DMN, with greater pain intensity increase linked with greater shifts in these connectivity patterns. Furthermore, only in patients with cLBP reporting high pain catastrophizing, DMN connectivity was increased to a cardinal node of the SN, anterior/middle insula cortex, which was also correlated with the magnitude of increased clinical pain intensity following physical maneuvers. These results aid our understanding of how cross-network connectivity encodes clinical pain intensity and how pain catastrophizing might mediate pain encoding.

Compared with healthy adults, patients with cLBP demonstrated augmented SN connectivity to $S1_{back}$, which was further increased following pain exacerbation maneuvers. Salience network processing has been associated with reallocation of attentional resources toward a salient stimulus such as pain.[10,25,33] In turn, S1 is a critical component of the nociceptive pathway and is known to receive and process afference to encode body location and intensity of nociceptive stimuli.[8] Our previous study found that blood flow to S1 was increased following LBP exacerbation,[46] and patients with cLBP show increased S1 cortical thickness compared with healthy adults.[26] Localizing pain within the body should significantly influence attentional focus, and we thus posit that attentional reallocation is at least partially mediated by greater information transfer between the SN and the somatotopically specific S1 representation of the lower back. Increased $SN/S1_{back}$ connectivity in $cLBP_{pre}$ (ie, baseline, resting state), compared with HCs, might reflect trait-like persistence in altered *intrinsic* connectivity. However, exacerbating clinical pain further amplified $SN/S1_{back}$ connectivity, suggesting that shifts in information transfer dynamics clearly have state-like properties and likely occur throughout patients' daily experience of flaring and abating pain. In general, altered S1 organization[15,32] and connectivity[23] have been noted in multiple chronic pain populations, and maladaptive reorganization has been hypothesized to influence behavioral/perceptual deficits such as tactile acuity.[9]

Within the SN, $S1_{back}$ connectivity following cLBP exacerbation was specifically increased to the anterior insula and linked with increase in back pain intensity. The anterior insula is a key node of the SN and has been implicated in the salience/affective dimension of pain processing,[48] as well as stimulus-driven bottom-up control of attentional resources.[45] Interestingly, our previous study[23] evaluated brain connectivity response to evoked, deep pressure pain applied over the lower leg of patients with chronic pain, and found that increased $S1_{leg}$ connectivity to the left anterior insula was correlated with self-reported scores of attention to the pain stimulus. Thus, our reported linkage between postmaneuver increases in clinical pain and $S1_{back}$ connectivity to the left anterior insula in patients with cLBP may reflect increased attentional focus on the location of patients' pain—ie, low back region.

In addition, patients with cLBP at baseline (premaneuvers) showed increased DMN connectivity to $S1_{back}$, suggesting that patients with cLBP demonstrate greater intrinsic information transfer between self-referential processing regions and S1 regions coding for the location of nociceptive input. However, pain-exacerbating maneuvers *decreased* this $DMN/S1_{back}$ connectivity (in contrast to the increased $SN/S1_{back}$ connectivity), and greater DMN/S1 connectivity decrease was associated with greater pain intensity exacerbation. In addition, patients with cLBP, particularly in an exacerbated back pain state, demonstrated *decreased* $S1_{back}$ connectivity to other, nonback, S1 representations compared with healthy adults. Reduced $S1_{back}$ connectivity to nonback S1 areas was also seen when contrasting baseline and exacerbated pain states in patients with cLBP. Thus, we propose that when clinical pain is temporarily exacerbated, information transfer from S1 nociception processing regions switches from its "home" network(s), which for cLBP may include both the sensorimotor network and DMN, to SN

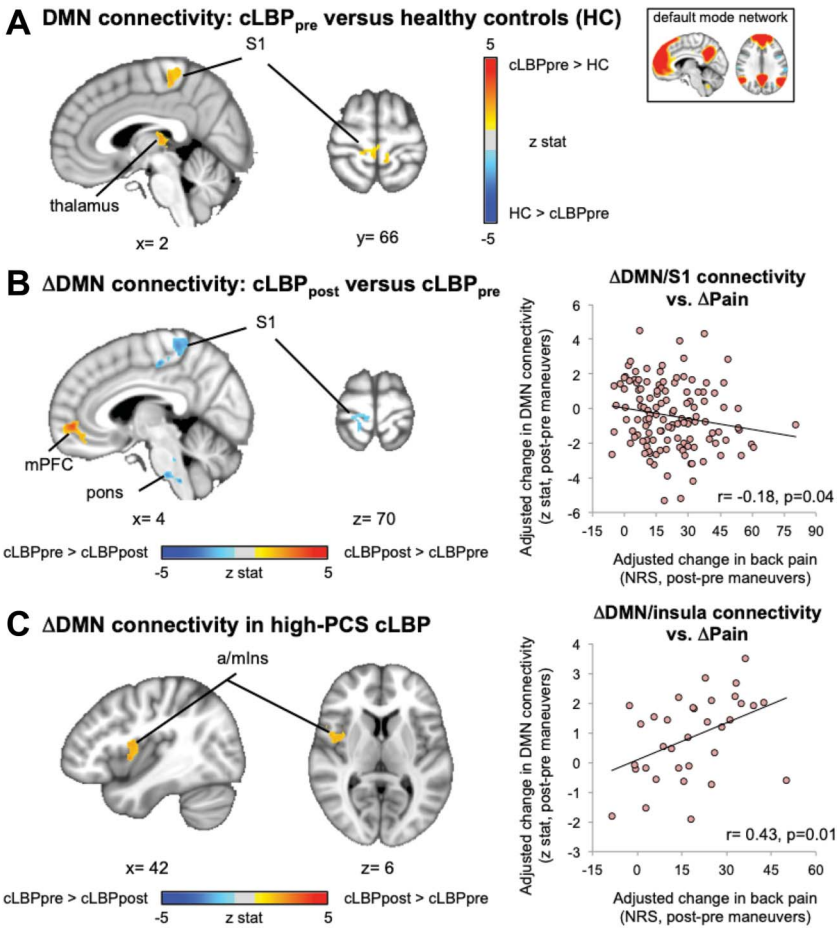

Figure 6. Default mode network connectivity was altered in patients with cLBP and linked with maneuver-induced change in clinical pain. (A) Compared with healthy controls, patients with cLBP at baseline exhibited increased DMN connectivity to $S1_{back}$. (B) Following physical maneuvers, DMN connectivity was decreased to $S1_{back}$ and increased to the mPFC. Decreased DMN-S1 connectivity was correlated with changes in clinical pain. (C) In a high-PCS cLBP subgroup, increased DMN connectivity to the insula after physical maneuvers was associated with postmaneuver increase in low back pain. Linear regression analyses were adjusted to control for age, sex, and head motion. cLBP, chronic low back pain; DMN, default mode network; mPFC, medial prefrontal cortex; NRS, numerical rating scale; PCS, Pain Catastrophizing Scale.

nodes such as the anterior insula, reflecting a switch toward salience processing of nociceptive afference from the pain-affected body region.

Moreover, we previously found that an evoked, experimental pain stimulus reduces connectivity between the S1 subregion activated by that stimulus and other S1 subregions.[23,24] We also previously noted reduced resting connectivity between multiple different S1 representations for patients with fibromyalgia, who suffer from widespread chronic pain.[23] In healthy adults, Riedl et al.[40] found the converse of this phenomenon: habituation to repeated noxious stimulation (ie, reduced pain perception) was accompanied by *increased* functional connectivity within the sensorimotor network. Taken together, our current findings support the hypothesis that sustained pain experience in a specific body location leads to a tonic level of elevated somatosensory processing, which then both *increase* resting-state connectivity between the specific S1 subregion coding for ongoing clinical pain (eg, low back) and DMN or SN areas, and *reduces* connectivity between this S1 subregion and other sensorimotor network subregions.

We also found that $cLBP_{post}$ (but not $cLBP_{pre}$) patients demonstrated increased SN connectivity (or decreased anti-correlation) to DMN regions including mPFC and dPCC, corroborating previous studies demonstrating that patients with chronic pain can exhibit increased overlap between SN regions and DMN.[18,30,37] Longitudinal therapy that reduces fibromyalgia pain also reduced DMN-a/mIns connectivity,[36] whereas greater pain reduction following pregabalin pharmacotherapy was associated with greater reduction in PCC/anterior insula connectivity.[17] Our large cohort in this study also allowed for a subgroup analysis to identify factors that might influence how cross-network connectivity encodes pain intensity. Although in the whole cLBP cohort, SN connectivity to DMN regions (or vice versa) was not altered by physical maneuvers or linked with the magnitude of postmaneuver pain increase, a high-PCS cLBP subgroup did demonstrate increased DMN connectivity to an anterior/midinsula cluster almost identical to that found by our prior studies,[30,37] and greater increase was directly associated with greater increase in postmaneuver clinical pain. Thus, given that on average our cLBP cohort reported a relatively low level of pain catastrophizing (mean PCS score of 12.5, compared with 23 in our prior cLBP study),[30] and given the previously described role of the SN and the known role of the PCC in autobiographical memory and self-referential cognition,[6] as well as demonstrated activation of the PCC in response to a cognitive pain catastrophizing task,[29] altered connectivity between SN and DMN regions may reflect the dominance of pain self-monitoring cognitions and affect in some patients with chronic pain. Thus, a direct linkage between DMN/insula connectivity and pain intensity is more evident when patients also suffer from high negative affect.

Table 4

Default mode network **(DMN) connectivity in healthy controls vs cLBP patients, pre- and post-physical maneuvers, which temporarily exacerbated clinical pain.**

	Side	Size (mm^3)	MNI coordinates			Peak z-stat
			X (mm)	Y (mm)	Z (mm)	
$cLBP_{pre}$ vs healthy controls						
S1	L	3744	−6	−24	54	3.64
Thalamus	L	3184	−18	−38	4	3.49
S1	L	3032	−62	−20	32	−3.83
$cLBP_{post}$ vs healthy controls						
Precuneus	R	7544	34	−76	34	3.63
$cLBP_{post}$ vs $cLBP_{pre}$						
All cLBP patients						
mPFC	R	3672	4	52	−4	4.34
MT+	R	7888	44	−80	10	4.56
S1/M1	R	5368	2	−36	66	−3.72
Pons	L	3424	−12	−24	−34	−3.81
High-PCS cLBP subgroup						
Anterior/midinsula	R	2992	40	4	0	3.34
Mid-PCS cLBP subgroup						
Cuneus		9248	0	76	14	−4.28
dlPFC	R	2792	46	44	8	−4.09
Low-PCS cLBP subgroup						
mPFC	R	4880	4	38	−12	4.63
S1/M1	R	4640	10	−28	72	−4.37

cLBP, chronic low back pain; dlPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; PCS, Pain Catastrophizing Scale; S1, primary sensory cortex.

Limitations of our study should also be noted. Although we attribute findings of altered functional connectivity to clinical pain and saliency/attention, we did not explicitly collect scores of attention regarding LBP. Future studies should evaluate this link directly using postscan ratings, as unfortunately online ratings during fMRI would require patients to use potentially overlapping cognitive resources, thereby confounding ratings of pain perception and brain response.[22] Another limitation was that although we found significant changes in brain connectivity using a large cohort of patients with cLBP, acquired data were pooled from 2 different MRI scanners. However, our main findings of increased SN connectivity to $S1_{back}$ and reciprocal increased $S1_{back}$ seed connectivity to SN brain regions were also evident in separate single-scanner analyses with subsamples of our data set (supplementary Fig. 3, available at http://links.lww.com/PAIN/A763), suggesting that our findings generalize across different scanners and data samples.

In conclusion, increased information transfer between S1 and SN regions, particularly the anterior insula, likely plays an important role in reallocating attentional focus and affective coding of somatic nociceptive afference from specific body areas. In addition, increased information transfer between the anterior insula and DMN in patients with cLBP, and its association with clinical pain, was strongly influenced by pain catastrophizing.

Conflict of interest statement

Ajay D. Wasan has a potential conflict of interest by consulting from Pfizer and Analgesic Solutions. The rest of authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A763.

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