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Sustained deep-tissue pain alters functional brain connectivity

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ABSTRACT

Recent functional brain connectivity studies have contributed to our understanding of the neurocircuitry supporting pain perception. However, evoked-pain connectivity studies have employed cutaneous and/or brief stimuli, which induce sensations that differ appreciably from the clinical pain experience. Sustained myofascial pain evoked by pressure cuff affords an excellent opportunity to evaluate functional connectivity change to more clinically relevant sustained deep-tissue pain. Connectivity in specific networks known to be modulated by evoked pain (sensorimotor, salience, dorsal attention, frontoparietal control, and default mode networks: SMN, SLN, DAN, FCN, and DMN) was evaluated with functional-connectivity magnetic resonance imaging, both at rest and during a sustained (6-minute) pain state in healthy adults. We found that pain was stable, with no significant changes of subjects' pain ratings over the stimulation period. Sustained pain reduced connectivity between the SMN and the contralateral leg primary sensorimotor (S1/M1) representation. Such SMN–S1/M1 connectivity decreases were also accompanied by and correlated with increased SLN–S1/M1 connectivity, suggesting recruitment of activated S1/M1 from SMN to SLN. Sustained pain also increased DAN connectivity to pain processing regions such as mid-cingulate cortex, posterior insula, and putamen. Moreover, greater connectivity during pain between contralateral S1/M1 and posterior insula, thalamus, putamen, and amygdala was associated with lower cuff pressures needed to reach the targeted pain sensation. These results demonstrate that sustained pain disrupts resting S1/M1 connectivity by shifting it to a network known to process stimulus salience. Furthermore, increased connectivity between S1/M1 and both sensory and affective processing areas may be an important contribution to interindividual differences in pain sensitivity.

1. Introduction

Neuroimaging analyses of functional brain connectivity have significantly impacted our understanding of brain function and the networks supporting perception of pain. Resting functional connectivity magnetic resonance imaging (fcMRI) examines intrinsic connectivity, which may be important for maintenance of synaptic connectivity, follows known structural monosynaptic and polysynaptic pathways [11,40,72], and likely reflects meaningful neurophysiological activity [54,81] within known primary sensory, executive, and associative networks [29]. Both the magnitude and extent of connectivity within these networks appear to be modulated by perceptual states, including clinical pain [49,50].

While pain studies using healthy volunteers typically evaluate responses to experimentally induced pain, they might also have important implications for understanding the pathophysiology underlying chronic pain in patients. However, previous analyses have not yet evaluated how functional connectivity is altered during sustained experimentally induced pain in otherwise healthy subjects. This is an important step in understanding how the experience of persistent pain alters brain function, since differences between chronic pain and healthy control groups may be shaped by dozens of potentially confounding factors such as medical comorbidities, medication history, physical inactivity, and emotional processes.

In healthy adults, Peltz et al. found that insular connectivity was altered in scans where experimental pain stimuli are presented in blocks, though this study was unable to evaluate connectivity

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changes during continuous noxious stimulation [53]. Interestingly, insular connectivity immediately preceding liminal (pain-threshold) stimuli determines whether such stimuli are perceived as painful [55]. Multiple studies have suggested that resting brain connectivity is altered in chronic pain patients [3,13–15,44,50,70], and connectivity between the brain's default mode network [10,60,65] and insula may specifically relate to clinical pain intensity [42,49,50]. Functional connectivity has not yet been evaluated during sustained experimental pain, most likely because continuous administration of many experimentally applied pain stimuli (eg, heat) risks permanent tissue damage. Thus, it is unknown if the altered resting connectivity noted in chronic pain patients differs from sustained pain state connectivity in healthy adults.

Additionally, it is also unknown how functional connectivity during sustained pain relates to pain sensitivity, which is known to vary widely between individuals [52]. Neuroimaging markers, such as pain-evoked activations, have been noted to track with individual difference in subjects' sensitivity to pain stimuli [18]. However, functional brain connectivity during sustained pain has never been explored for this purpose, and might inform our understanding of the neurophysiology underlying interindividual differences in pain sensitivity.

In this study, we hypothesized that sustained pain alters functional connectivity for brain networks known to respond to experimental pain stimuli. Functional brain connectivity was evaluated at rest and during a sustained pain state evoked by cuff pressure algometry, a technique that allows for a continuous, deep-receptor pain stimulus. Compared to most cutaneous pain techniques, deep tonic pain may better mimic clinical pain [22,62] and can be sustained for minutes without significant risk of tissue damage [57]. We also hypothesized that intersubject differences in cuff pain sensitivity could be predicted by variability in functional brain connectivity present in the sustained pain state.

2. Methods

This study evaluated functional brain connectivity during sustained cuff pain, and compared this response to resting brain connectivity, evaluated in the same subjects.

2.1. Participants

Eighteen right-handed, healthy volunteers were enrolled in this study. All participants gave written informed consent in accordance with the Human Research Committee of the Massachusetts General Hospital. Of these subjects, one was excluded after the training session due to unreliable pain ratings and another was disqualified following the MRI session due to excessive motion artifacts. Data from 16 subjects (11 male; age 28 ± 9.7 years, mean ± SD) were analyzed. Exclusion criteria for our healthy adults included: age below 18 years, chronic or acute pain, neurological disorders including peripheral neuropathy, history of significant head injury, serious cardiovascular disease, current use of medications and/or recreational drugs, and standard contraindications for MRI.

2.2. Pain stimulation and experimental protocol

Participants received a painful pressure stimulus on their left lower leg (over the gastrocnemius muscle) continuously for 6 minutes. Pressure stimuli were delivered with a Velcro-adjusted pressure cuff (SC12D; Hokanson Inc, Bellevue, WA, USA) connected to a rapid cuff inflator (E20 AG101; Hokanson), which inflated the cuff to a constant, individually tailored pressure level. This type of cuff pressure algometry is a recently characterized method that is now included in many quantitative sensory testing evaluations [33]. One advantage to the application of cuff algometry is that, unlike more superficial methods of evaluating mechanical sensitivity, cuff pain responses are only marginally affected by sensitization or desensitization of the skin, indicating that this procedure primarily assesses sensitivity in muscle and other deep tissues [56,57]. Moreover, cuff pain at high intensities can be safely applied for extended periods of time (as much as 20 minutes, see [57]) without producing tissue damage.

Prior to imaging, subjects participated in a training session to familiarize themselves with the stimuli and rating procedures. The pressure level that produced a pain intensity rating of ~50/100 was determined for each subject during the training session, and recalibrated just before the imaging session.

The fcMRI session included a 6-minute resting state scan run (REST), which was followed by a 6-minute run with continuous pressure pain stimulation (PAIN). The cuff inflator was initiated at least 10 seconds before fcMRI data were collected in order to remove any brain response due to a generalized startle reflex. The cuff was fully inflated within 2~3 seconds after initiation by button press. The order was not counter-balanced to assure that any lingering pain sensation experienced during the PAIN run would not interfere with resting brain connectivity during REST. For both REST and PAIN, subjects were instructed to relax and lie still with their eyes open.

After the PAIN run, subjects were asked to rate the intensity and unpleasantness of pain from the cuff. Subjects provided ratings for each of the 2-minute blocks at the beginning, middle, and end of the 6-minute procedure in order to retrospectively evaluate potential sensitization or adaptation to the lengthy pain stimulus. A 0-100 numeric pain rating scale was used, where 0 was labeled "no pain" for the pain intensity and "neutral" for the pain unpleasantness, and 100 was labeled "the most intense pain tolerable" for the pain intensity and "extremely unpleasant" for the pain unpleasantness. Subjects were trained to distinguish intensity and unpleasantness of pain using a brief text similar to that employed by Price and colleagues [58], a method shown to allow dissociation between sensory and affective components of the pain experience [43,75,76]. A repeated-measures analysis of variance was used to compare ratings from the 3 2-minute periods of the 6-minute pain stimulus (SPSS, PASW Statistics 18.0; IBM, Armonk, NY, USA). We also performed post hoc testing using Dunnett's test in order to compare the first 2-minute period with the middle and last 2-minute periods in order to evaluate sensitization or adaptation to pain stimulation. All results were reported significant at $P < 0.05$.

The REST and PAIN runs were separated by 3 functional runs during which a series of calibrated cuff stimuli were delivered. The brain responses to these stimuli allowed us to identify regions responding linearly and nonlinearly to pain (see [41] for details), and these results were also used to define seeds for functional connectivity analyses on data from the 6-minute REST and PAIN scans.

2.3. MRI and physiological data collection

Functional MRI (fMRI) data were acquired using a 3T Siemens TIM Trio MRI system (Siemens Medical, Erlangen, Germany) equipped for echo planar imaging with a 32-channel head coil. A whole brain T2*-weighted gradient echo blood oxygenation level-dependent (BOLD) pulse sequence (repetition time [TR]/echo time [TE] = 2000/30 ms, field angle = 90°, 32 anterior commissure-posterior commissure (AC-PC) aligned axial slices, voxel size = 3.1 × 3.1 × 4 mm) was used. Anatomical data were also collected using a multi-echo magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) pulse sequence (TR/TE1/TE2/TE3/TE4 = 2530/1.64/3.5/5.36/7.22 ms, field angle = 7°, voxel size = 1 × 1 × 1 mm^3).

Physiological data were collected simultaneously to the fMRI data, as cardiorespiratory fluctuation is known to influence fMRI intrinsic connectivity estimation within several brain networks [6,16,17]. The electrocardiogram data were collected with an MRI-compatible Patient Monitoring system (Model 3150, Invivo Research Inc., Orlando, FL, USA) through MRI-compatible electrodes (VerMed, Bellows Falls, VT, USA) on the chest. Respiration data were collected using a custom-built MR-compatible belt placed around the subject's ribcage [5]. All physiological signals were collected at 400 Hz using Chart Data Acquisition Software on a laptop using the PowerLab System (ADInstruments Inc, Colorado Springs, CO, USA).

2.4. MRI data preprocessing

fMRI data were preprocessed using the validated FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl/), AFNI (afni.nimh.nih.gov/afni), and FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) software packages. Data were corrected for cardiorespiratory artifacts using RETROICOR [32]. Cardiac beat annotation and respiratory volume calculation were performed using custom scripts in MATLAB (The MathWorks, Natick, MA, USA). The electrocardiogram traces and respiration data were resampled at 40 Hz to be used in RETROICOR, and the cardiac and respiratory response functions were calculated to use as nuisance regressor [16,32].

Head motion correction used FSL-MCFLIRT [37]. As recent studies suggest that head motion during scanning may influence functional connectivity [73], computation of head motion metrics was performed using the same methods reported previously by Van Dijk et al. [73]. The mean translation was computed as the root-mean-square of the estimated motion translation parameters in x, y, and z directions, while mean rotation was computed using Euler angle from the estimated motion angular components. The difference in mean translation (REST: 0.02 ± 0.01 mm, mean ± SD; PAIN: 0.03 ± 0.02) and mean rotation (REST: 0.33 ± 0.11 radians × 1000, mean ± SD; PAIN: 0.37 ± 0.14) between REST and PAIN was not statistically significant (mean translation: $P = 0.39$, rotation: $P = 0.11$). Brain extraction was performed using FSL-BET [66]. Cortical surface reconstruction was completed to perform improved structural-functional co-registration using FreeSurfer's bbregister tool [34]. Functional data were then registered to standard Montreal Neurological Institute (MNI) space using FMRIB's nonlinear co-registration tool (FNIRT). Functional data were smoothed using a Gaussian kernel of full width at half maximum (FWHM) 6 mm, and high-pass temporal filtering (f = 0.008 Hz) was performed.

2.5. Functional connectivity: independent component analysis (ICA)

Functional connectivity MRI analysis was performed using the validated dual-regression independent component analysis (ICA) approach [28,82]. This approach uses the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (FSL-MELODIC) tool, and our application was similar to our past published studies [49,50].

This approach consists of 3 stages. First, a probabilistic ICA (pICA, MELODIC, FSL) was applied on concatenated, preprocessed functional data from both REST and PAIN runs from all subjects. We limited the number of independent components (ICs) to 25, as in previous publications using the dual regression approach [28,49,50]. From the pool of 25 ICs, we selected functionally relevant ICs using spatial correlation with previously defined templates provided by Beckmann et al. [4]. In the second stage, these independent spatial maps were used in a general linear model (spatial regression model) as a spatial regressor for each individual subject. The temporal dynamics were calculated for each IC of interest at the subject level.

In the third stage of dual regression, this fMRI time series from each subject was variance normalized and used in a subject-level general linear model (temporal regression model) to reconstruct spatial maps for each subject. In order to limit any residual shared variance with nonneuronal response, nuisance regressors were included in this model: 1) fMRI time series from white matter and ventricular regions; 2) motion correction time series for the 6 translation/rotation parameters reflecting rigid body head motion correction; and 3) cardiorespiratory artifacts defined by convolving the heart rate and respiratory variation time series with appropriate cardiac and respiratory transfer functions, as defined by Chang et al. [16] and Birn et al. [7], respectively. No global signal regression was used in this analysis. Reconstructed independent spatial maps were then input into our higher-level analyses for within- and between-subject group analyses.

Our analyses were focused on several pain-related resting state network: the salience network (SLN), sensorimotor network (SMN), dorsal attention network (DAN), frontoparietal control network (FCN), and the default mode network (DMN). The SLN is known to be encompassed by bilateral anterior insula and dorsal anterior cingulate areas [64], regions commonly activated by experimental pain stimuli [2]. The SMN includes pre- and postcentral gyri and supplementary motor area [8], regions also commonly activated by somatosensory stimuli, including pain. The DAN includes regions in the frontal eye fields, superior parietal lobule, intraparietal sulcus, and middle temporal area [12,30,77]. The FCN is composed of rostrolateral prefrontal cortex, middle frontal gyrus, lateral parietal, and anterior insula/frontal operculum [13,67,68,77]. The DMN is known to include medial frontal cortex, posterior cingulate cortex and precuneus, inferior parietal lobule, lateral temporal cortex, and hippocampal formation [10,60]. This network is typically deactivated by evoked pain and other external stimuli, and its connectivity is altered in chronic pain conditions in a clinical pain intensity-dependent manner [49,50]. Individuals' reconstructed resting state networks were then passed up to group-level analyses, performed using FLAME (FMRIB's Local Analysis of Mixed Effects). All maps were thresholded using cluster correction for multiple comparisons with a cluster-forming threshold of $Z > 2.3$, and cluster-size significance of $P < 0.05$.

As we found that sustained pain decreased SMN connectivity to primary sensory/motor cortex (S1/M1) and increased SLN connectivity to the same region (see Results), an intersubject correlation analysis explored whether subjects with decreased SMN connectivity were the same as those with increased SLN connectivity. Peak response from the SMN and SLN difference map was extracted and entered into a one-tailed Pearson's correlation test, reported significant at $P < 0.05$.

2.6. Functional connectivity: seed-based correlation analysis

As our dual-regression ICA approach identified altered SMN and SLN connectivity to contralateral (right) S1/M1, at the level of the paracentral lobule (ie, sensorimotor representation of the leg), we chose this S1/M1 area as a seed to further explore how sustained pain alters connectivity between this region and the rest of the brain. We used a functional localizer taken from different scans – that is, the contralateral somatotopic S1/M1 cluster demonstrating linearly increasing fMRI response to linearly increasing cuff pain stimuli, as reported in our previous study [41]. The S1/M1 correlation maps were produced by extracting the fMRI time series from the preprocessed fMRI data with a 4-mm radius sphere centered at MNI coordinates: x = 10, y = 36, z = 68 mm. The extracted fMRI time series, variance normalized, was used as a regressor in a general linear model for the REST and PAIN data.

The same nuisance regressors adopted in the dual regression analyses (see above) were included in this model as well. Group brain maps were thresholded ($Z > 2.3$) using cluster correction with cluster significance of $P < 0.05$.

2.7. Correlation between S1/M1 functional connectivity and stimulus intensity

In order to investigate the link between primary sensorimotor functional connectivity and individual differences in cuff pressure used to reach the targeted pain sensation, we performed a linear regression with S1/M1 functional connectivity data from the PAIN run as dependent variable, and cuff-pressure levels (in mm Hg) individually determined to produce the 50/100 pain intensity as the independent variable. Results were reported significant at cluster corrected $P < 0.05$.

3. Results

All subjects who completed the fMRI session tolerated the cuff stimulus for the full duration of 6 minutes. All subjects reported that the cuff pain had abated within 30 seconds following cuff deflation.

3.1. Psychophysical response to sustained pain

A repeated-measure analysis of variance on the ratings from 3 2-minute periods revealed no statistically significant changes over time in either cuff pain intensity or unpleasantness [$F(2, 30) = 1.50$, $P = 0.24$ for pain intensity; $F(2, 30) = 1.21$, $P = 0.31$ for pain unpleasantness]. Dunnett's test was performed using the first 2-minute period as reference timepoint to evaluate sensitization or adaptation to sustained pain stimulation. There was no statistically significant changes between the first 2-minute and second 2-minute periods ($P = 0.36$ for pain intensity and 0.75 for pain unpleasantness), nor between the first 2-minute and last 2-minute periods ($P = 0.75$ for pain intensity and 0.48 for pain unpleasantness; Fig. 1).

3.2. Functional brain connectivity response to sustained pain

The ICA group maps for SMN, SLN, DAN, FCN, and DMN were successfully identified and were very similar to networks previously described [4,64] (Supplementary Fig. 1). Connectivity maps across experimental conditions revealed that functional connectivity was altered during PAIN, compared to REST. While connectivity between SMN and a cluster within the S1/M1 was reduced during PAIN, the connectivity between the SLN and a near-identical S1/M1 cluster was increased (Fig. 2, Table 1). This S1/M1 cluster was located at the level of the right paracentral lobule, that is, the contralateral somatotopic location of the left lower leg, where the cuff was placed. A significant correlation ($r = -0.46$, $P < 0.05$) was found between decreased SMN-S1/M1 connectivity and increased SLN-S1/M1 connectivity (Fig. 3).

Other networks were also significantly modulated by sustained pain. During PAIN, the DAN showed greater correlation (or less anticorrelation; see Table 1) to pre-supplementary motor area (pre-SMA), mid-cingulate cortex, left posterior insula, and left putamen, as well as midbrain (nuclei raphe dorsalis/nuclei cuneiform), pontine, reticular formation (consistent with locus ceruleus), and cerebellar (bilateral lobule VI l) nuclei. Greater anticorrelation between right FCN and both S1/M1 and precuneus was also found during PAIN (Fig. 4, Table 1). A whole brain analysis contrasting DMN connectivity between PAIN and REST did not yield any significant clusters.

The changes in functional connectivity during sustained pain, as resolved with the network-based ICA analysis were also broadly supported by our contralateral S1/M1 seed connectivity analysis (see Methods). During PAIN, contralateral leg-region S1/M1 connectivity to bilateral S1/M1 areas outside of this leg region was significantly decreased (ie, broadly consistent with decreased SMN connectivity to contralateral leg-region S1/M1) (Fig. 5, Table 1). However, contralateral leg-region S1/M1 connectivity to right anterior insula was significantly increased (i.e. broadly consistent with increased S1/M1 connectivity to SLN, while specifically implicating the right anterior insula node of this network) (Fig. 5, Table 1).

3.3. Stimulus intensity was associated with S1/M1 connectivity during pain

Cuff pressure was individually tailored to evoke a 50/100 pain intensity in all subjects. Cuff pressure ranged from 110 to 410 mm Hg (253.81 ± 75.76, mean ± SD), which indicates that subjects exhibited a wide range of cuff pressure. In order to determine whether somatotopic (leg region) S1/M1 functional connectivity during sustained pain could, in part, explain such heterogeneity, linear regression analysis was performed using the cuff pressure as explanatory variable. We found that higher cuff pressure eliciting 50/100 pain was associated with less somatotopic S1/M1 connectivity to a significant cluster including left putamen, thalamus, amygdala, and posterior insula (Fig. 6, Table 2). Thus, less sensitive participants (ie, those experiencing higher cuff pressures) demonstrated less contralateral S1/M1 connectivity to these brain areas.

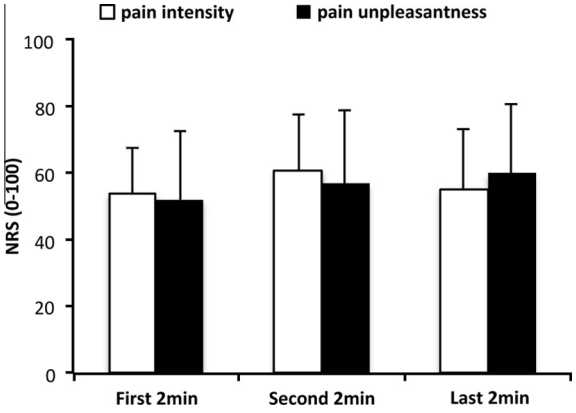

Fig. 1. Psychophysical results for pain intensity and unpleasantness. There was no significant change of pain ratings over the stimulation period. Error bars represent SD. NRS, numeric rating scale.

4. Discussion

Our study found that sustained pain led to a distinct shift in functional brain connectivity. The somatotopic representation of the noxiously stimulated leg in the primary sensorimotor cortex became less connected with other primary sensorimotor regions, and more connected to brain regions comprising the salience network (insula, mid-cingulate). Moreover, increased connectivity between somatotopically defined primary sensorimotor cortex and other sensory as well as affective brain areas may be an important contribution to interindividual differences in pain sensitivity.

When the brain is at rest, different S1/M1 cortical representation regions are in direct communication, leading to robust interconnectivity within the so-called sensorimotor network [4]. During somatosensory perception, a somatotopic representation in contralateral S1/M1 is activated. Our results demonstrated that when this S1/M1 somatotopic representation was processing

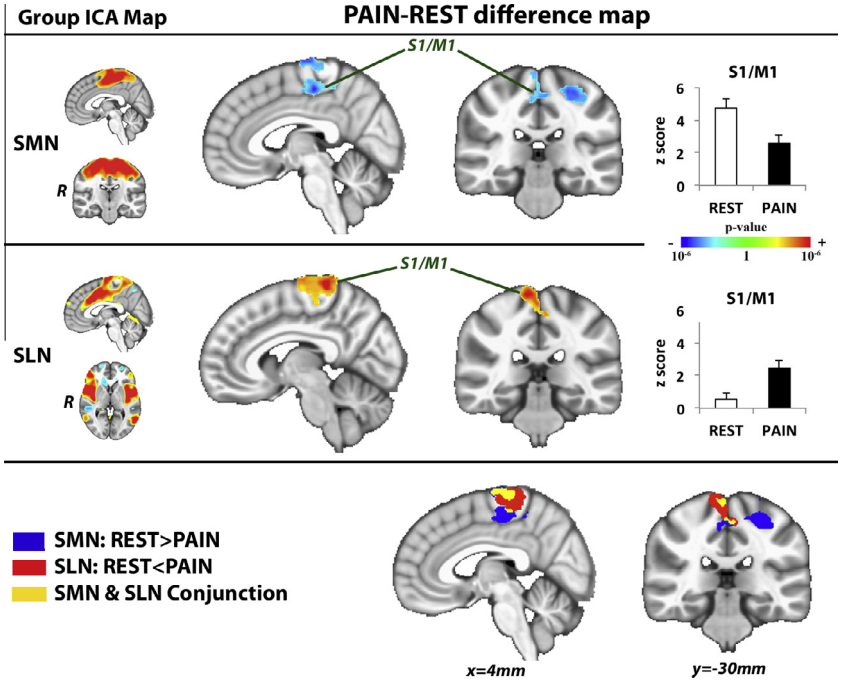

Fig. 2. S1/M1 connectivity shifts from SMN to SLN during sustained pain. Difference maps contrasting functional connectivity during PAIN vs REST noted increased SLN and reduced SMN connectivity to contralateral S1/M1. ICA, independent component analysis; M1, primary motor cortex; S1, primary sensory cortex; SLN, salience network; SMN, sensorimotor network. Plot error bars denote standard error of the mean.

Table 1
Sustained pain alters functional connectivity (PAIN–REST).

	Side	Size (mm^3)	MNI coordinates			Peak *z*-stat	*z*-Stat (mean ± SD)	
			X	Y	Z		REST	PAIN
Salience network (SLN)								
S1/M1	R	8128	10	−40	74	5.20	0.53 ± 1.39	2.45 ± 1.82
Sensorimotor network (SMN)								
S1/M1	R	4520	4	−22	52	−4.10	4.73 ± 2.26	2.59 ± 2.06
	L	3880	−28	−26	58	−3.98	5.73 ± 2.19	4.58 ± 2.26
Dorsal attention network (DAN)								
Cerebellum (VI *l*)	L	12672	−28	−60	−24	4.05	1.18 ± 1.56	3.00 ± 1.43
	R	6048	26	−52	−24	3.90	0.49 ± 1.28	2.08 ± 1.10
Pons	R	6048	2	−30	−40	2.99	−0.38 ± 1.40	0.91 ± 1.36
NRD/NCF	L	6048	−4	−30	−16	2.92	−0.67 ± 1.25	0.46 ± 1.47
Putamen	L	5176	−30	−24	14	3.58	−0.65 ± 1.44	0.87 ± 1.07
Posterior insula	L	5176	−40	−22	12	2.67	−1.65 ± 1.30	0.54 ± 1.48
MCC	R	4728	4	20	38	3.07	0.04 ± 1.13	1.81 ± 1.18
Pre-SMA	R	4728	4	2	58	3.16	−0.71 ± 1.31	0.77 ± 1.44
Right frontoparietal control network (rFCN)								
Precuneus	L	3264	−10	−52	60	−4.06	−1.02 ± 1.67	−2.88 ± 1.89
S1/M1	L	3264	−2	−36	58	−3.19	0.46 ± 1.39	−0.69 ± 1.54
Right (contralateral) S1/M1 seed connectivity								
Anterior insula	R	8088	44	8	0	3.89	1.45 ± 1.15	3.76 ± 1.81
S1/M1	R	14,056	32	−28	58	−4.51	15.57 ± 7.54	10.43 ± 4.18
	L	20,368	−12	−38	70	−3.79	11.14 ± 5.57	5.23 ± 2.67

MNI, Montreal Neurological Institute; NRD, nuclei raphe dorsalis; NCF, nuclei cuneiform; S1, primary sensory cortex; M1, primary motor cortex; MCC, mid-cingulate cortex; SMA, supplementary motor area.

peripheral noxious afference, its resting connectivity with neighboring S1/M1 sub-regions (ie, with the sensorimotor network) was disrupted. In addition, connectivity between this contralateral somatotopic S1/M1 subregion and the salience network, particularly the insula, was augmented. Thus, while canonical connectivity networks, such as the SMN and SLN, remain grossly intact during sustained pain processing, the extent of these networks is altered to exclude or include brain areas activated by the stimulus. The anterior insula and mid-cingulate cortices, as salience network areas [23,48,64], have been postulated to assign homeostatic relevance for both internal and external sensory inputs to the brain [20], and are key regions of affective and attentional processing of pain stimuli [61,79]. Moreover, linked activity within the anterior insula and mid-cingulate cortex may play a role in integrating cognitive, affective, and interoceptive processing in order to produce behavioral and autonomic motor response [46]. Hence, the increased connectivity between somatotopic S1 and salience network regions likely reflects a multidimensional attribution of

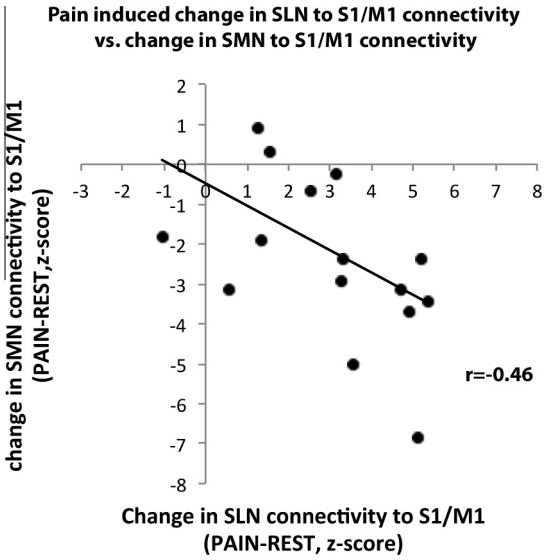

Fig. 3. Intersubject correlation between increased SLN connectivity to S1/M1 and decreased SMN connectivity to S1/M1. Subjects who responded to sustained pain with greater increased SLN connectivity to S1/M1 (positive *z*-scores in x axis represent greater SLN connectivity to S1/M1 during PAIN compared to REST), also demonstrated more decrease in SMN connectivity to S1/M1 (negative *z*-scores in y axis represent reduced SMN connectivity to S1/M1 during PAIN compared to REST). M1, primary motor cortex; S1, primary sensory cortex; SLN, salience network; SMN, sensorimotor network.

relevance to the ongoing painful stimulus. Similarly, increased DAN connectivity to known pain-processing regions such as the mid-cingulate cortex, midbrain (nuclei cuneiform), posterior insula, and putamen during PAIN likely also relate to the shifting of, in this case, more basic attentional resources toward processing of the ongoing pain stimulus.

Other nonpainful, unilateral sensorimotor tasks have been shown to produce similar disruptions in functional connectivity. For instance, reduction in left-right S1/M1 synchrony was found during unilateral continuous performance of a finger-tapping task [1,47,51]. Contralateral somatotopic M1 connectivity to mid-cingulate and insula was not reported by these studies, and this connectivity may prove to be more pronounced during tasks with arguably greater salience to the organism, such as evoked pain. However, reduced interhemispheric connectivity in response to a unilateral motor task is similar to our findings for unilateral pain, and suggests that such interhemispheric de-coupling is a consistent phenomenon across multiple unilateral tasks, which might underlie spatial localization [36] and/or suppression of irrelevant sensory information, thereby enhancing processing of signals expected to carry greater behavioral significance [24,35,38,39,78]. Future studies should also evaluate functional connectivity during a broader range of noxious and innocuous somatosensory stimuli as, for instance, SLN recruitment of S1/M1 may be modulated in an intensity-dependent manner.

Individual differences in pain sensitivity greatly influence diagnosis and treatment of chronic pain patients [18]. There are also important implications for pain chronification in healthy adults, although this is more controversial [26]. Neuroimaging studies have found that more sensitive individuals exhibited more frequent and more robust pain-induced activation in brain regions involved in affect as well as attention and decision-making [19]. However, functional connectivity during sustained pain has never been evaluated as a potential determinant of pain sensitivity.

We noted that the cuff pressure necessary to evoke the same moderate pain intensity varied widely (from 110 to 410 mm Hg) across our healthy volunteer group. This wide variability would not allow for a stimulus-matched experimental design to explore interindividual differences in pain sensitivity, as no single pressure would be 1) painful and 2) tolerable for all subjects. Hence, we inferred pain sensitivity from our percept-matched analysis by using cuff pressure as an independent variable. We found that individuals highly sensitive to cuff pressure stimulation (ie, requiring lower cuff pressures) demonstrated greater contralateral somatotopic S1/M1 functional connectivity with brain regions known to process both the sensory and affective dimensions of pain (thalamus, posterior insula, putamen, and amygdala). The thalamus is commonly found to respond to evoked pain [2,25]. In our study, the specific localization of the thalamic cluster was likely the ventral posterolateral nucleus, which relays sensory-discriminative information to the primary somatosensory cortex [13], and shows reduced connectivity to S1 in diabetic neuropathic pain patients [14]. Similarly, the posterior insula responds to nociceptive afference and the sensory-discriminative dimension of pain [2,21,45], a contention supported by stimulus-response mapping in both neuroimaging [9] and intracranial evoked potential [31] studies. The putamen is also commonly activated in evoked pain studies [2] and may be

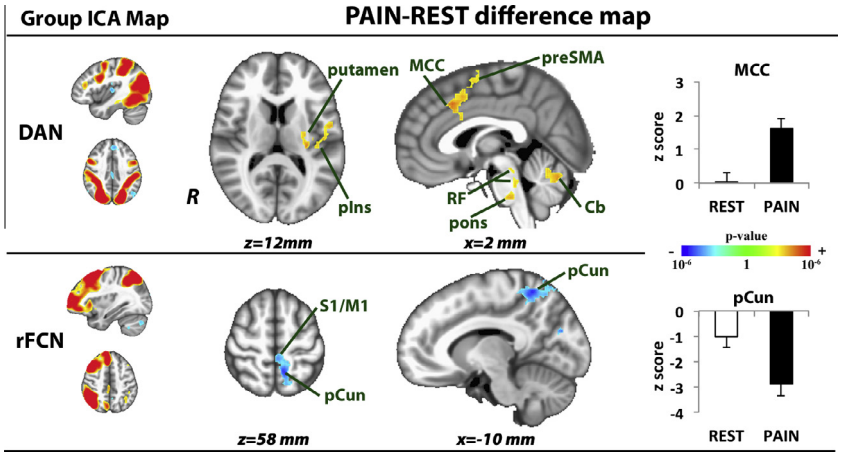

Fig. 4. Sustained PAIN alters dorsal attention (DAN) and frontoparietal control (FCN) network connectivity. During sustained pain, DAN showed greater correlation to pre-SMA, MCC, left posterior insula, left putamen, midbrain, pontine, reticular formation, and cerebellar nuclei. Greater anti-correlation between right FCN and both S1/M1 and precuneus was also found during PAIN. pre-SMA, pre-supplementary motor area; MCC, mid-cingulate cortex; pIns, posterior insula; RF, reticular formation; Cb, cerebellar nuclei; pCun, precuneus.

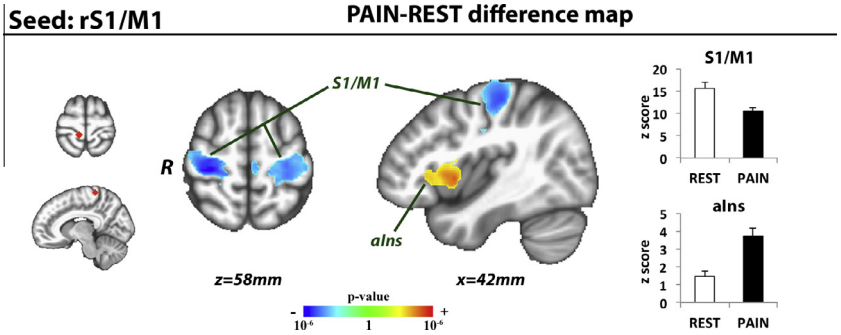

Fig. 5. Sustained pain modulates S1/M1 seed connectivity. Using a seed connectivity analysis approach, sustained pain increased connectivity between contralateral leg-region S1/M1 and right anterior insula. Pain also decreased connectivity between contralateral leg-area S1/M1 and bilateral S1/M1 subregions outside of this contralateral leg representation area. S1/M1, primary somatosensory/motor cortex; aIns, anterior insula.

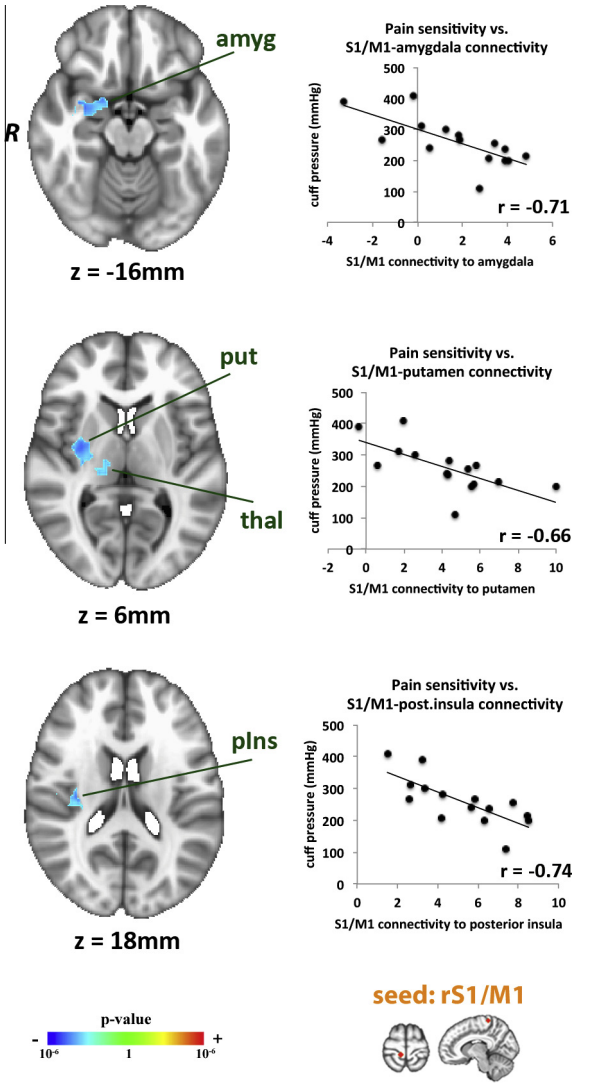

Fig. 6. S1/M1 connectivity during sustained pain predicted interindividual stimulus intensity. Stimulus intensity (ie, cuff pressure evoking 50/100 pain) was negatively correlated to contralateral (somatotopic leg-region) S1/M1 connectivity to the amygdala, putamen, and posterior insula during PAIN. Amyg, amygdala; put, putamen; thal, thalamus; pIns, posterior insula.

involved in sensory aspects of pain processing, as suggested by a recent human brain lesion study [69]. On the other hand, the amygdala is a key region for fear and emotion processing [80],

Table 2
S1/M1 connectivity during sustained pain is associated with stimulus intensity.

	Side	Size (mm^3)	MNI coordinates			Peak *z*-stat
			X	Y	Z	
Putamen	R	8424	32	−8	2	−3.65
Posterior insula	R	8424	34	−20	20	−3.38
Amygdala	R	8424	32	−2	−16	−3.29
Thalamus	R	8424	14	−18	4	−2.67

S1, primary sensory cortex; M1, primary motor cortex; MNI, Montreal Neurological Institute S1, primary sensory cortex; M1, primary motor cortex.

which likely supports the affective dimension of pain processing. Greater connectivity between this region and brain regions known to support the sensory-discriminative dimension of pain (ie, S1) might form the neurophysiological substrate underlying the greater pain and pain-related negative emotions [27] reported by highly sensitive individuals. In sum, while there exist multiple known factors that contribute to interindividual variability in pain sensitivity (eg, gender, age, genetics, and psychosocial functioning), interindividual variability in functional brain connectivity may also contribute to this heterogeneity in subjective pain report. Future studies may benefit from the application of fcMRI to help categorize and diagnose pain patients, as well as identifying individuals most likely to benefit from particular treatments.

In most pain neuroimaging studies, noxious stimulation has been delivered using thermal, laser, and electrical shock stimuli [2]. In general, due to the risk of tissue damage, such studies have been unable to apply tonic painful stimulation for a long enough period to evaluate pain-related changes in functional connectivity. Moreover, these methods stimulate, primarily or exclusively, cutaneous and superficial afferent fibers. In this study we utilized cuff pressure algometry. This technique stimulates muscle and other deep nociceptors [56,57] and can be safely applied for extended periods of time without damaging the underlying tissue. Thus, we were able, for the first time, to report on brain functional connectivity changes induced by a sustained, deep-tissue pain stimulus, which is known to better mimic clinical pain [22,62].

Several limitations to this study should be noted. For instance, gender is known to influence individual variability in pain sensitivity [59]. However, our study did not include enough subjects to separately evaluate males and females in regard to functional connectivity predictors for pain sensitivity. Additionally, we cannot state that all of our results are specific to evoked deep tissue pain, as we did not evaluate how, for example, a nonpainful somatosensory stimulation modulates functional brain connectivity. However, previous studies applying fcMRI during nonpainful sensorimotor tasks [1,51] did not report altered connectivity

outside of primary and secondary sensorimotor regions. Finally, after the 6-minute PAIN scan, subjects were asked to rate pain over 3 different temporal windows – a procedure that may have required greater cognitive effort than rating pain for a single shorter-duration stimulus provocation. We cannot rule out the possibility that increased working memory or cognitive load from this pain rating procedure influenced our results. However, our subjects were well trained in discriminating different pain intensities, and several studies using a variety of methodologies have noted that individuals are generally quite proficient at remembering pain intensity levels over spans of time ranging from minutes [12,74] to days [63,71].

In summary, the main findings of our study demonstrate that 1) sustained pain alters functional brain connectivity, shifting S1/M1 connectivity from the SMN to SLN brain regions; and 2) interindividual differences in pain sensitivity were associated with variability in sensorimotor functional connectivity evaluated during the sustained pain stimulus.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.04.016.

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