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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).

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