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Original Reports

Altered Resting State Connectivity of the Insular Cortex in Individuals With Fibromyalgia

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Abstract: The insular cortex (IC) and cingulate cortex (CC) are critically involved in pain perception. Previously we demonstrated that fibromyalgia (FM) patients have greater connectivity between the insula and default mode network at rest, and that changes in the degree of this connectivity were associated with changes in the intensity of ongoing clinical pain. In this study we more thoroughly evaluated the degree of resting-state connectivity to multiple regions of the IC in individuals with FM and healthy controls. We also investigated the relationship between connectivity, experimental pain, and current clinical chronic pain. Functional connectivity was assessed using resting-state functional magnetic resonance imaging in 18 FM patients and 18 age- and sex-matched healthy controls using predefined seed regions in the anterior, middle, and posterior IC. FM patients exhibited greater connectivity between 1) right mid IC and right mid/posterior CC and right mid IC, 2) right posterior IC and left CC, and 3) right anterior IC and left superior temporal gyrus. Healthy controls displayed greater connectivity between left anterior IC and bilateral medial frontal gyrus/anterior cingulate cortex; and left posterior IC and right superior frontal gyrus. Within the FM group, greater connectivity between the IC and CC was associated with decreased pressure-pain thresholds.

***Perspective:** These data provide further support for altered resting-state connectivity between the IC and other brain regions known to participate in pain perception/modulation, which may play a pathogenic role in conditions such as FM. We speculate that altered IC connectivity is associated with the experience of chronic pain in individuals with FM.*

***Key words:** Fibromyalgia, chronic pain, resting-state connectivity, insular cortex, cingulate cortex.*

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The insular cortex (IC) and cingulate cortex (CC) play pivotal roles in integrating multimodal information involved in sensorimotor, emotional, and homeostatic functions.[9,11,46] Functional brain imaging studies in humans often show a coactivation of IC and CC in a variety of tasks, including attention, decision making, self-recognition, and time perception.[10,13,26] Both regions are critically involved in pain perception as evidenced by human brain imaging studies.[36]

Fibromyalgia (FM) is a chronic pain state characterized by widespread nonarticular pain, stiffness, sleep and mood disturbances, and fatigue.[50] Impaired antinociception and augmented central processing of nociceptive input have been considered to be partially responsible for pain in FM.[48] Support for FM's being a predominantly centrally mediated pain state comes from quantitative sensory testing and functional neuroimaging studies using experimentally induced pain stimuli, indicating both diffuse hyperalgesia and allodynia.[8,17] Despite their heuristic value, these earlier studies examined primarily experimentally induced pain rather than ongoing clinical pain.

With the emergence of advanced neuroimaging methods, new approaches to neurobiological correlates of ongoing clinical pain have been developed. One such method is functional connectivity magnetic resonance imaging (fcMRI), a noninvasive technique applied in awake humans either at rest (ie, resting-state connectivity) or during task. With resting-state analyses, low-frequency (<.1 Hz) temporal correlations in the MRI signal are assessed across various brain regions. These low-frequency fluctuations are thought to be functionally relevant indices of connectivity between brain regions subserving similar or related brain functions.[2]

Currently, fcMRI has been investigated in few chronic pain states.[6] When investigating fcMRI in patients with temporomandibular disorders, we found greater resting-state fcMRI between the anterior IC and the pregenual anterior cingulate cortex (ACC) in patients when compared to healthy controls (HCs).[22] Our recent studies in FM have suggested that resting connectivity between the IC and default mode network (DMN), a constellation of brain regions activated during self-referential thinking, was correlated to current clinical pain at the time of the scan.[30,31] Additionally, we reported in 2 longitudinal trials that decreases in IC to DMN connectivity in FM patients were associated with reductions in clinical pain.[20,30] Although whole brain searches were performed, our findings were largely restricted to connectivity between the DMN and the IC in FM patients. In support of our model, greater DMN-IC connectivity, as well as strong association between this connectivity and clinical pain, was also noted in chronic low back pain patients.[27]

Taylor and colleagues recently investigated IC connectivity in a sample of HCs to systematically explore IC connectivity to other brain regions.[43] Predefined seed regions were placed in the IC, and functional connectivity analyses showed that 1) the anterior IC was connected to both posterior ACC and anterior midcingulate cortex (MCC) regions, and 2) the mid/posterior IC was connected to the posterior MCC and posterior CC.

Here we investigate whether these IC-CC connectivity patterns are also seen in FM patients and whether these relationships are related to the hyperalgesia/allodynia these patients experience. We used an approach similar to that of Taylor et al, looking specifically at seed-based IC-CC and IC-IC connectivity in a sample of FM patients compared to HCs. This analysis expands on our previously published connectivity results by applying the Taylor et al seeds[30,31] to FM and linking connectivity to evoked pain data. Given previous findings, we hypothesized that differences in IC-CC and IC-IC connectivity would be detected in FM and that this might provide further insights into the central neural correlates of chronic pain.

Results from this manuscript were previously presented at the 2012 Annual Scientific Meeting of the American Pain Society.[23]

Methods

Subjects

This study was approved by the medical institution review board of the University of Michigan, and all subjects read and signed an informed consent form prior to participation. Using the fcMRI protocol described in detail (see below), we investigated 18 female FM patients (age, 35.8 ± 12.0 years) and 18 age- and sex-matched HCs (32.3 ± 11.3 years). A subset of these FM patients and HCs had been part of a previously reported study using different methodologies to investigate hypotheses different from those included in the present study.[30,31] Inclusion criteria for FM patients were as follows: 1) met the 1990 American College of Rheumatology criteria for FM,[50] 2) disease duration of at least 1 year and continued presence of pain for more than 50% of each day, 3) age between 18 and 75 years, 4) right-handedness, and 5) capable of giving informed written consent. Participants were excluded from analysis if any new treatments were introduced between consenting and imaging time points. Exclusion criteria for FM patients included 1) current use or history of taking opioid or narcotic analgesics; 2) history of substance abuse; 3) concurrent autoimmune or inflammatory disease that caused pain, such as rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease; 4) concurrent participation in other therapeutic trials; 5) pregnant or currently a nursing mother; and 6) history of psychiatric illness (eg, current schizophrenia, major depression with suicidal ideation, or substance abuse within the past 2 years) or current major depression.

HC subjects were age- and sex-matched to the FM patients. Inclusion criteria for HCs were 1) age between 18 and 75, 2) right-handedness, 3) capable of giving written informed consent, and 4) willingness to complete all study procedures. Exclusion criteria for the HC subjects were as follows: 1) met the 1990 American College of Rheumatology criteria for FM, 2) any chronic medical illness, including a psychiatric disorder (eg, psychosis, schizophrenia, or delusional disorder), 3) a chronic pain