View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Harvard University - DASH

DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD
DASH.HARVARD.EDU

HARVARD LIBRARY
Office for Scholarly Communication

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

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation	Ichesco, Eric, Tobias Schmidt-Wilcke, Rupal Bhavsar, Daniel J. Clauw, Scott J. Peltier, Jieun Kim, Vitaly Napadow, et al. 2014. "Altered Resting State Connectivity of the Insular Cortex in Individuals With Fibromyalgia." The Journal of Pain 15 (8) (August): 815–826.e1. doi:10.1016/j.jpain.2014.04.007.
Published Version	10.1016/j.jpain.2014.04.007
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:36640549
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP

NIH Public Access
Author Manuscript
J Pain. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:
J Pain. 2014 August ; 15(8): 815–826.e1. doi:10.1016/j.jpain.2014.04.007.

Altered resting state connectivity of the insular cortex in individuals with fibromyalgia

Eric Ichesco[1,*], **Tobias Schmidt-Wilcke**[1,7,*], **Rupal Bhavsar**[1,2], **Daniel J. Clauw**[1], **Scott J. Peltier**[3], **Jieun Kim**[4], **Vitaly Napadow**[4,5,6], **Johnson P. Hampson**[1], **Anson E. Kairys**[1,8], **David A. Williams**[1], and **Richard E. Harris**[1]

[1]Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

[2]Neurology Department, University of Pennsylvania, Philadelphia, PA, USA

[3]Functional MRI Laboratory, University of Michigan, Ann Arbor, USA

[4]MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA

[5]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[6]Department of Radiology, Logan College of Chiropractic, Chesterfield, MO, USA

[7]Department of Neurology, Bergmannsheil, Ruhr University Bochum, Bochum, Germany

[8]Department of Psychology, University of Colorado Denver, Denver, CO, USA

Abstract

The insular (IC) and cingulate cortices (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. Here we more thoroughly evaluate the degree of resting state connectivity to multiple regions of the IC in individuals with FM and healthy controls (HC). 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 HC using

© 2014 The American Pain Society. Published by Elsevier Inc. All rights reserved.

Corresponding author: Eric Ichesco, B.S., Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, MI 48105, USA, eichesco@med.umich.edu.
*Both authors contributed equally to this manuscript.

Disclosures
This study was funded in part by NIH/National Center for Complementary and Alternative Medicine grant K01-AT-01111-01 and in part by a grant from Pfizer Incorporated, Groton, Connecticut. Tobias Schmidt-Wilcke was supported by a grant of the DFG (Deutsche Forschungsgemeinschaft, GZ: SchM 2665/1-1). Richard Harris is supported by grants from the Dana foundation and the Department of Defense (Army grant: DAMD-W81XWH-07-2-0050), and has previously consulted for Pfizer Inc. Daniel Clauw has previously consulted for Pfizer Inc. Vitaly Napadow was supported by NCCAM, NIH (R01-AT004714 (Napadow), P01-AT002048 (Rosen)). All other authors have no conflicts of interest to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

pre-defined 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 the left CC; and (3) right anterior IC and left superior temporal gyrus. HCs displayed greater connectivity between: left anterior IC and the bilateral medial frontal gyrus/ACC; and left posterior IC and the 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 playing 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 fibromyalgia.

Keywords

Fibromyalgia; chronic pain; resting state connectivity; insular cortex; cingulate cortex

Introduction

The insular (IC) and cingulate cortices (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 co-activation 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 evidence by human brain imaging studies[36].

Fibromyalgia (FM) is a chronic pain state characterized by widespread non-articular 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 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 MRI (fcMRI), a non-invasive technique applied in awake humans either at rest (i.e. resting state connectivity) or during task. With resting state analyses, low frequency (<0.1Hz) 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 ACC in patients when compared to healthy controls (HC)[22]. Our recent studies in FM have suggested that resting connectivity between the IC and DMN, a constellation of brain regions activated during self-referential thinking,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

was correlated to current clinical pain at the time of the scan[30, 31]. Additionally, we reported in two longitudinal trials 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, and 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: (1) the anterior IC was connected to both posterior ACC, and anterior mid cingulate cortex (MCC) regions; (2) the mid/posterior IC was connected to the posterior MCC and PCC.

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 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 upon 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 (mean ± SD age 35.8 ± 12.0 years) and 18 age- and sex-matched healthy controls (mean ± SD 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 different hypotheses than included in the present study[30, 31]. Inclusion criteria for FM patients were: 1) having met the 1990 American College of Rheumatology (ACR) criteria for FM[50], 2) had a disease duration of at least 1 year, and reported the continued presence of pain for more than 50% of each day, 3) were older than age 18 years and younger than age 75 years, 4) were right-handed, and 5) were capable of giving their 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) a history of substance abuse, 3) concurrent autoimmune or inflammatory disease that cause 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) had a psychiatric illness

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(e.g., current schizophrenia, major depression with suicidal ideation, or substance abuse within the past 2 years), or currently had major depression.

Healthy control (HC) subjects were age- and sex-matched to the FM patients. Inclusion criteria for HCs were: 1) between the ages of 18 and 75, 2) were right-handed, 3) were capable of giving their written informed consent, and 4) were willing to complete all study procedures. Exclusion criteria for the healthy control subjects were: 1) having met the 1990 ACR criteria for FM, 2) having any chronic medical illness, including a psychiatric disorder (e.g., psychosis, schizophrenia, or delusional disorder), 3) diagnosed to have a chronic pain disorder, and 4) current pregnancy. All FM patients and HCs had no contraindications for participating in an fMRI scan.

Behavioral data

The following clinical features were assessed: demographics (i.e., age, duration of FM, and life-time illness burden), clinical pain (i.e., current pain at the time of study visit), experimental pain (random noxious thumbnail pressure stimuli), and allied mood and illness attributions (i.e., depression and anxiety).

Demographics—A standardized demographics form was used to record age and sex (i.e., all female in this study) as well as medical status (e.g., duration of FM in years). Lifetime illness burden was assessed using the Complex Medical Symptom Inventory (CMSI)[49] a 48-symptom checklist of co-morbid symptoms common to FM.

Clinical Pain—The clinical pain experience of patients with FM was assessed using the Visual Analogue Scale (VAS) and the Pain Rating Index (PRI) from the Short Form McGill Pain Questionnaire (SF-MPQ) [29]. When completing the SF-MPQ, participants were asked to answer questions within each section pertaining to their current pain. The VAS consists of a 10-cm line anchored on the left with “No Pain” and on the right with “Worst Possible Pain”. Participants in the study were asked to rate their present FM pain by placing a tick along this line. The PRI component of the SF-MPQ consisted of 15 word descriptors (11 sensory and 4 affective). Participants rated these descriptors as either “none”, “mild”, “moderate” or “severe”, giving a score of 0, 1, 2 or 3, respectively, for each descriptor. The measures were added to yield sensory, affective and total scores.

Mood and illness attributions—Depression in the FM cohort was assessed with either the Hospital Anxiety and Depression Scale (HADS) (n = 7) or the Center for Epidemiologic Studies Depression Scale (CES-D) (n = 11)[39, 51]. FM patients were categorized to a low versus high level of depression by defining a high level as ≥ 8 symptoms on the HADS and ≥ 16 on the CES-D. State Anxiety was assessed using the State-Trait Personality Inventory (STPI Form Y)[42], a refinement of the State-Trait Anxiety Inventory.

Experimental pain assessment—Prior to scanning pressure-pain values eliciting “faint” pain (0.5 on the Gracely Box Scale [GBS], see below and Figure S1), “mild” pain (7.5 on the GBS), and “slightly intense” pain (13.5 on GBS) were determined for every subject using the multiple random staircase (MRS) method as described previously[19, 34]. The GBS is a numerical scale that is used to evaluate present pain intensity. This scale is

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

comprised of 21 boxes, sequentially numbered beginning with 0 and ending with 20. Descriptive words are arranged next to the numbers corresponding with varying levels of pain[15]. To elicit the GBS ratings, discrete pressure stimuli were applied to the subject's right thumbnail using a hydraulic system connected to a hard 1cm^2 hard, rubber, circular probe[16, 19].

Data Acquisition

Resting state fMRI data were acquired using a custom T2*-weighted spiral-in sequence [TR = 2.0 s, TE = 30 ms, FA= 90°, matrix size 64×64 with 43 slices, FOV = 20 cm and 3.13×3.13×3 mm voxels], using a General Electric (GE) 3.0 T Signa scanner 9.0, VH3 with quadrature birdcage transmit-receive radio frequency coil. During the 6 min resting state fMRI acquisition period (180 scans) the subjects were asked to remain awake with their eyes open. A fixation cross was presented on the screen. Subjects were told to lie still and fixate on the cross throughout the scan. Minimal cognitive tasks such as staring at a cross typically do not disrupt resting state networks[18]. Physiologic data was collected simultaneously with fMRI data because cardiorespiratory fluctuations are known to influence fMRI intrinsic connectivity within several brain networks[3, 7]. Respiratory volume data were collected by securing a GE magnetic resonance-compatible chest plethysmograph around each subject's abdomen. Cardiac data were collected using an infrared pulse oximeter (GE) attached to the subject's right middle finger. Participants' motion was minimized using foam pads placed around the head along with a forehead strap. In addition high resolution structural images were acquired [TR = 10.5ms, TE = 3.4ms, TI= 200ms, FA = 25°, 24 cm FOV, 256×256 matrix, 0.94×0.94×1.5 mm voxels, yielding 106 slices] using a spoiled gradient echo (SPGR) inversion recovery sequence. Inspection of individual T1 MR-images revealed no gross morphological abnormalities for any patient or subject.

Data Analysis

Data were pre-processed and analyzed using FSL (www.fmrib.ox.ac.uk/fsl) and SPM (Statistical Parametric Mapping) software packages, version 5 (Functional Imaging Laboratories, London, UK), as well as the functional connectivity toolbox *Conn* (Cognitive and Affective Neuroscience Laboratory, Massachusetts Institute of Technology, Cambridge, USA) running on Matlab 7.5b (Mathworks, Sherborn, MA, USA)[47]. Upon collection of the functional data, cardiorespiratory artifacts were corrected for using the RETROICOR[21, 37] algorithm in FSL. Pre-processing steps included motion correction (realignment to the first image of the time series), normalization to the Montreal Neurological Institute (MNI) average brain included in the SPM software (generating 2×2×2 mm resolution images) and smoothing (convolution with a 6 mm FWHM Gaussian Kernel). Subject head motion was assessed by evaluating three translations and three rotations for each scan. Translational thresholds were set to ± 2 mm, while rotational thresholds were limited to ± 1°. A subject was to be excluded from the analysis if head motion exceeded either of the thresholds in one of the six dimensions.

Based on the approach by Taylor et al.[43], six seed regions were defined within the anterior, middle and posterior IC bilaterally; seed regions were created as spheres (6 mm diameter) using MarsBaR-software (http://marsbar.sourceforget.net). For details on center coordinates

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and volumes see Figure 1. Seed regions' time-series were extracted; white matter and CSF signal, as well as realignment parameters were entered into the analysis as covariates of no interest. A band pass filter (frequency window: 0.01 – 0.1 Hz) was applied, thus removing linear drift artifacts and high frequency noise. First level analyses were performed correlating seed region signal with voxel signal throughout the whole brain, thereby creating seed region to voxel Fisher transformed r to z connectivity maps (six maps for each individual). Connectivity maps were then used for second level (random effects) analyses.

Analysis 1—In a first step, main effects were calculated for each group separately, by performing one sample t-tests. Due to the expectancy for highly correlated connectivity maps, results were thresholded at an uncorrected voxel-level threshold of $p < 0.00001$, and deemed significant based on a corrected value of $p < 0.05$ on the cluster level.

Analysis 2—We were then interested whether there were differences in connectivity between groups. To this end, two sample t-tests (controlling for age) for each seed region were performed. Since we were specifically looking for differences between groups within the pain system and in brain areas involved in pain modulation we allowed for these regions a less stringent threshold; differences were deemed significant, on the cluster level corrected for multiple comparisons ($p < 0.05$, derived from an uncorrected $p < 0.001$ on the voxel level, with a cluster extent of 69 contiguous voxels (552 mm^3) as estimated by the 3dClustSim application). 3dClustSim was implemented in the Analysis of Functional Neuroimages (AFNI) software (http://afni.nimh.nih.gov/afni/), based on a Monte Carlo simulation (1000 simulations) applied to a whole brain mask. Since we were specifically interested in IC – CC connectivity, a second mask, just covering the cingulum (anterior, middle and posterior, bilaterally) was created using the WFU_PickAtlas (http://www.nitrc.org/projects/wfu_pickatlas). Monte Carlo simulation using that mask resulted in a lower extent threshold: 28 contiguous voxels (224 mm^3) ($p < 0.001$, uncorrected, on the voxel level), yielding correction for multiple comparisons on the cluster level (within that mask).

Analysis 3a—Resultant significant connectivity maps from Analysis 2 were further evaluated with correlation analyses to assess the behavioral and clinical relevance to the group differences. Parameter estimates were extracted (yielding one parameter estimate per subject) and were correlated with pain measures (VAS, McGill Pain Questionnaire affective, sensory, and total measures) and MRS pressure pain thresholds (faint, mild and slightly intense) by means of a correlation analysis in SPSS, version 19. Significant results were found using a threshold of $p < 0.05$, but were deemed significant at $p < 0.025$ after a Bonferroni correction accounting for the two domains of pain (clinical pain and experimental pain).

Analysis 3b—To further evaluate the behavioral/clinical relevance of altered IC connectivity, we performed in a third step, regression analyses with pain measures (VAS, McGill Pain Questionnaire affective, sensory, and total measures) and MRS pressure pain thresholds as predictors and fcMRI as the outcome variable within the FM group (controlling for age). Similarly, regression analyses with experimental pain measures were

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

performed including experimental pressure pain thresholds within the HC group (controlling for age). Again a threshold on the cluster level corrected for multiple comparisons ($p < 0.05$, derived from an uncorrected $p < 0.001$ on the voxel level, with a cluster extent of 69 contiguous voxels) was applied. One subject was omitted from correlational analyses with the SF-MPQ AFF measure because of the classification of an outlier greater than 2 standard deviations from the mean. The resulting clusters were further analyzed by extracting parameter estimates from group level results (yielding one parameter estimate per subject) and performing the regression analyses with the pain measures in SPSS, version 19. During this analysis step, we evaluated the parameter estimates to assess for outliers which could be driving the significant results. The Automated Anatomical Labeling (aal) atlas[45] and xjView viewing program for SPM (http://www.alivelearn.net/xjview8/) were used to label anatomical regions for all analyses.

Results

Patients and behavioral data

All 36 subjects enrolled in this study were included in the analyses. Of the 18 FM patients, 7 were categorized to have a high level of depression (6 of the 7 FM patients had CES-D scores > 16, and the seventh scored > 8 on the HADS questionnaire). All 18 of the HC subjects were assessed for depressive symptoms using the CES-D measure – none of which were categorized to have a high level of depressive symptoms.

As expected the FM cohort was found to have significantly higher clinical pain report scores compared to the HC group. However, the two groups did not differ statistically with respect to experimental pressure pain thresholds. Demographics and pain ratings for both patients and controls are displayed in Table 1.

Functional connectivity during resting state

Analysis 1—The location and size of each IC seed region is shown in Figure 1. Supplementary Table S1 shows the fcMRI main effect clusters for the six IC seed regions in the FM and HC groups separately. Connectivity maps were thresholded using a corrected cluster-level Family Wise Error value of $p < 0.05$. From this analysis, we were able to partially replicate the findings by Taylor et. al.: namely anterior to posterior topographical connectivity between the IC and the CC. In both patients and controls the anterior IC was connected to the anterior CC and the mid IC was connected to the mid CC, however, we were not able to replicate the posterior IC to posterior CC connectivity in either group[43].

Analysis 2—For between group comparisons FM patients had: greater connectivity compared to HCs between the *right anterior IC seed* and the right superior temporal gyrus (peak voxel: x = −46, y = −26, z = −2; z-score = 4.69; Table 2), greater connectivity between the *right mid IC seed* and both the right mid insular cortex (peak voxel: x = 38, y = 2, z = 0; z-score = 4.27, Table 2 and Figure 2) and right mid/posterior CC (peak voxel: x = 2, y = −16, z = 44; z-score = 3.85, Table 2, and Figure 2). Patients also displayed greater connectivity between the *right posterior IC seed* and both the left mid CC (peak voxel: x =

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

−2, y = 10, z = 30; z-score = 4.03, Table 2, and Figure 2) and the posterior CC (peak voxel: x = 0, y = −24, z = 46; z-score = 3.88, Table 2 and Figure 2).

Decreased connections in FM patients compared to HCs were also found. FM patients were found to have less connectivity between the *left anterior IC seed* and both the right medial frontal gyrus (peak voxel: x = 10, y = 40, z = 40; z-score = 4.48, Table 2 and Figure 3) and the left medial frontal gyrus (peak voxel: x = −12, y = 46, z =22; z-score = 4.25; Table 2 and Figure 3), and the *left posterior IC seed* and the right superior frontal gyrus ((STG) peak voxel: x = 26, y = 20, z = 50; z-score = 4.43; Table 2 and Figure 3).

Analysis 3a—IC to CC connectivity within the FM patients was found to be related to experimental pressure-pain thresholds. The right posterior IC, which showed increased connectivity to the posterior CC in FMs compared to HCs, was found to have a strong negative correlational trend to “mild pain” MRS pressure threshold values ($r = -0.50$, $p = 0.04$; Table 3a). Furthermore, FM patients were found to have correlational trends between this same right posterior IC – posterior CC connectivity with the two other experimental pressure-pain thresholds (“faint pain”: $r = -0.34$, $p = 0.16$ and “slightly intense pain”: $r = -0.38$, $p = 0.12$). Additionally, IC-STG connectivity within the FM patients was found to be related to clinical pain. The right anterior IC, found to have increased connectivity within the FM group compared to HCs, was significantly positively correlated to clinical pain: greater IC-STG connectivity was associated with greater affective scores from the SF-MPQ ($r = 0.61$, $p = 0.01$; Table 3a) and the total score of the SF-MPQ resulted in a strong trend ($r = 0.51$, $p = 0.03$, Table 3a). No significant correlations to clinical and experimental pain report were found amongst the HC group within these regions.

Analysis 3b—Within the FM group, the functional connectivity of the *right mid IC seed* and both the left precuneus and right precuneus were positively correlated with the sensory component of the SF-MPQ (left precuneus: $z = 3.79$, $p < 0.001$; right precuneus: $z = 4.48$, $p < 0.001$; Table 3b and Figure 4); i.e. FM patients with higher sensory pain component scores had higher connectivity between the right mid IC and both the left and right precuneus regions.

FM patients were found to have several negative correlations between experimental pain thresholds and IC connectivity: greater functional connectivity was associated with lower pressure pain thresholds. The *left mid IC seed* and the left mid CC connectivity was negatively correlated with slightly intense pressure thresholds ($z = 3.67$, $p = 0.001$; Table 3b and Figure 5); the *left mid IC seed* and the right mid CC connectivity was negatively correlated with faint pressure thresholds $z = 3.58$; $p < 0.001$, Table 3b and Figure 5); and the *right posterior IC seed* and the left mid/anterior CC was negatively correlated with faint pressure thresholds ($z = 4.42$, $p < 0.001$; Table 3b and Figure 5).

HC subjects were only found to have one significant correlation between connectivity and experimental pressure-pain measures. Within this group, connectivity between the *right anterior IC seed* and the right posterior CC was negatively correlated with mild pressure thresholds ($r = -0.53$, $p = 0.024$; Table 3b).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Discussion

The main objective of this work was to systematically test whether FM patients displayed regional differences within the IC with respect to their connectivity to other brain regions compared to pain free HCs. In a first step, we were able to comparatively reproduce the results by Taylor et al. showing topographically distributed and highly correlated low frequency oscillations between specific IC and CC subdivisions[43] (i.e. IC–CC connectivity was detected along the anterior - middle axis) in both HCs and FM patients. These findings are also in line with a study by Kong et al. reporting resting state fcMRI between the anterior IC and the ACC/MCC in healthy subjects[24]. Interestingly, our group comparison between the FM and HC groups yielded significantly increased connectivity between the IC and CC regions within the FM patients, whereas other regions showed increased connectivity in the controls. Largely these findings showed that patients had increased connectivity of the right insula whereas controls had increased connectivity of the left insula. Previous studies have shown that there is lateralized cerebral function with regards to the processing of pain, where the right hemisphere has been shown to have more involvement in pain perception and sensitivity compared to the left hemisphere[28, 33, 40]. Furthermore, Kucyi et al. reported right hemisphere lateralization in intrinsic functional connectivity between the temporoparietal junction, a brain region involved in salient stimulus detection, and the right mid IC[25]. In this study we found augmented right hemisphere lateralization resting state connectivity including the IC in FM patients compared to HCs. The chronification process within these patients very well could have strengthened this relationship in the right hemisphere and caused this increased connectivity of pronociceptive regions while at rest. Additionally, when comparing correlation measures between the FM and HC groups, it appears that FM patients have formed significant new connections between the right IC and CC regions (Figure 2), and added deficits between the left IC and MFG regions (Figure 3) when compared to controls seemingly no significant connection exists.

When comparing our correlational findings with experimental pain reports, we found strong negative associations between posterior IC-posterior CC connectivity and experimental pain thresholds in pain patients. Since pain thresholds are effectively the inverse of pain sensitivity, these findings are showing that increased pain sensitivity (i.e. hyperalgesia/ allodynia) is associated with increased connectivity between these regions. Moreover, we found additional negative correlations between experimental pain and IC connectivity to nociceptive regions. These results included increased connectivity between the bilateral mid IC seed regions and the mid CC and contralateral posterior IC target regions (i.e. IC-CC and IC-IC connectivity), which corresponded with decreased experimental pressure-pain thresholds within FM patients.

Insular involvement in processing and modulation of pain has been widely reported as it is one of the most commonly activated pain regions in neuroimaging studies of pain[1]. Previously, FM patients were reported to have increased IC connectivity when compared to HC subjects, and FM patients were found to have positive correlations between current clinical pain intensities and intrinsic connectivity between the IC and both Default Mode Network and Executive Attention Network[30, 31]. It has been suggested that bilateral IC

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

activation is essential for pain perception, as opposed to non-painful somatosensory perception. In 2007, Seifert and Maihöfner displayed bilateral IC activation in a sample of HC subjects when undergoing an fMRI scan with a cold allodynia stimulus application[41]. A more recent study of HC subjects that used arterial spin labeling (ASL) reported results of increased cerebral blood flow to the bilateral IC in response to increased intramuscular infusion of hypertonic saline into the brachioradialis muscle[32]. Within HCs, high connectivity has been displayed between the IC and the contralateral insula during a resting state[5, 43]. Here, FM patients were found to have increased resting state fcMRI compared to HC volunteers. This amplified connectivity between the insular regions in these FM patients could contribute to the widespread non-articular pain that is symptomatic of this disorder.

It has been suggested that the anterior IC – ACC system integrates interoceptive input with its emotional salience in contrast to the mid-/posterior IC – MCC system, which is thought to be more related to environmental monitoring and response selection[43]. With respect to pain perception there is strong evidence that the posterior IC, as part of the lateral pain pathway, together with the primary and secondary somatosensory cortex, encodes pain intensity, laterality and somatotopy, while the anterior IC, as part of the medial pathway, together with the ACC, has a unique role in affective pain processing and learning[44].

Although there is an increasing body of evidence that suggests that the IC flexibly connects attention and emotional brain areas, and that these connections are in fact an important determinant of pain experience [38], the literature on the capability of the mid CC to modulate IC activity in pain conditions, or vice versa, is sparse. In this study, we observed augmented mid/posterior IC – mid/posterior CC connectivity within FM patients compared to HCs. Moreover, these regions with increased IC-CC connectivity displayed correlations with experimental pressure-pain thresholds. FM patients were found to have decreased pressure-pain tolerances (slightly intense pain) and thresholds (faint pain) when displaying increased mid IC – mid CC connectivity as well as posterior IC – mid IC connectivity. When this comparison was assessed in HC subjects, no such correlation existed. While we did not see significant behavioral differences in experimental pressure-pain between groups in this study, this correlation result falls in line with differences in experimental pressure-pain thresholds between HC and FM patients seen in other studies[35], and associates the sensation of pain with the underlying neurobiological mapping within these FM patients.

Another intriguing result from an *a priori* hypothesis, was that FM patients were found to have IC to default mode network (DMN) region connectivity correlated with clinical pain report. Within the FM cohort, increased connectivity between the right mid IC and bilateral precuneus regions were both positively associated with the sensory aspect of pain (i.e. the stronger the connectivity between these two regions, the higher the level of pain reported). The precuneus is a region that contributes to the DMN, a network of regions throughout the brain that has been found to be engaged in self-referential thinking, which is disengaged during a variety of task conditions[4, 14]. Previously, our group reported that patients with FM have increased connectivity between the IC and the DMN at rest, and that this connectivity is associated with increased current clinical pain[31]. The current finding appears to support this finding that patients with FM have hyperactive IC – DMN connectivity and increased associated clinical pain as previously reported by our group[30, 31].

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Interestingly, while not an *a priori* hypothesis, we noted that FM patients were found to have increased connectivity between the right anterior insula and the contralateral superior temporal gyrus (STG). This heightened connectivity result for the FM patients was found to be positively correlated with clinical pain (increased connectivity was associated with increased pain scores); both with the affective (significant) and total (trend) scores from the SF-MPQ. The role of the STG in pain is not well established, but this region has been shown to be active during evoked painful stimuli in both HC and FM patients[17]. While the mechanism of the STG in pain processing may not be fully understood, it is possible that this region could be contributing to the augmented affective experience of pain in FM patients, as we have found this increased anterior IC to STG connectivity to be positively correlated with affective pain report scores. Furthermore, FM patients were found to have a negative correlation displaying increased connectivity between the posterior IC and STG, with decreases in experimental pressure-pain thresholds (faint pain).

Limitations

Although our trial found significant differences in IC – CC connectivity in FM, there are certain limitations that need to be highlighted. One possible confounder in our study was age. Although not statistically different, the FM group was slightly older than the HCs. To control for this potential confound, age was added as a covariate to all second level analyses. Another limitation in our study was the cross-sectional design and its inability to resolve conclusively the pre-existing versus acquired nature of the observed alterations. From our results it is unclear whether chronic widespread pain leads to the changes in connectivity or if changes in IC connectivity predispose someone to developing chronic pain. Another potential weakness to our design is that we used standardized seed regions. Subtle albeit natural differences in functional anatomy across subjects and differences in brain size and subsequent normalization might have had an influence on connectivity maps. However we would assume that variation in functional anatomy is equally distributed between groups and the fact that images had been smoothed prior to analysis helped to control for such differences. Indeed we were able to partially replicate the findings of Taylor et al. suggesting consistent findings[43]. A minor limitation for this study was that when confirming handedness, a validated tool like the Edinburgh Handedness Inventory was not included. While all participants reported they were right-handed, an instrument to confirm this measure would prove useful for validation in an fcMRI study. Finally, fcMRI allows no assumptions on causality, or on directedness of influence: namely we cannot tell if the IC is sending pain information to the CC or vice versa. Against this background it is conceivable that fcMRI between two regions may also be driven by a third region, not identified in the analysis. More sophisticated approaches exploring effective connectivity and the relationship between functional and structural connectivity[12] will help to overcome such methodological shortcomings in future studies.

Conclusions and outlook

The investigation of resting-state networks is a promising approach and might in fact turn out to be a stronger tool than approaches using evoked pain paradigms, when it comes to the exploration of subjective states, such as clinical pain. Our main goal was to explore regional differences in IC connectivity to the rest of the brain in individuals with FM as compared to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

HCs. Our analyses reveal increased IC-CC and IC-IC connectivity in FM and in addition we find both positive and negative relationships between IC connectivity to other brain regions and multiple pain domains. These findings are indicative of a disturbed IC connectivity in FM patients which may be related to the subjective enhanced pain that they experience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Keith Newnham for MRI technical assistance.

Abbreviations

ACC	anterior cingulate cortex
ACR	American College of Rheumatology
BA	Brodmann Area
BOLD	blood oxygenation level dependent
CC	cingulate cortex
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
fcMRI	functional connectivity
FM	fibromyalgia
FWHM	full width at half maximum
HC	healthy controls
IC	insular cortex
ICA	independent component analysis
IPL	inferior parietal lobule
MCC	mid cingulate cortex
MFG	medial frontal gyrus
MNI	Montreal Neurological Institute
PRI	pain rating index
S1	primary somatosensory cortex
SF-MPQ	Short-Form McGill Pain Questionnaire
SFG	superior frontal gyrus
SMA	supplementary motor area
STG	superior temporal gyrus

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

VAS visual analogue scale

Literature

1. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005; 9:463–484. [PubMed: 15979027]
2. Birn RM. The behavioral significance of spontaneous fluctuations in brain activity. Neuron. 2007; 56:8–9. [PubMed: 17920009]
3. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage. 2006; 31:1536–1548. [PubMed: 16632379]
4. Buckner RL, Vincent JL. Unrest at rest: default activity and spontaneous network correlations. Neuroimage. 2007; 37:1091–1096. discussion 1097–1099. [PubMed: 17368915]
5. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. Neuroimage. 2011; 55:8–23. [PubMed: 21111053]
6. Cauda F, Sacco K, D'Agata F, Duca S, Cocito D, Geminiani G, Migliorati F, Isoardo G. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in diabetic neuropathic pain. BMC Neurosci. 2009; 10:138. [PubMed: 19941658]
7. Chang C, Glover GH. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. Neuroimage. 2009; 47:1448–1459. [PubMed: 19446646]
8. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol. 2004; 31:364–378. [PubMed: 14760810]
9. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002; 3:655–666. [PubMed: 12154366]
10. Craig AD. How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci. 2009; 10:59–70. [PubMed: 19096369]
11. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci. 2004; 7:189–195. [PubMed: 14730305]
12. Damoiseaux JS, Greicius MD. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct Funct. 2009; 213:525–533. [PubMed: 19565262]
13. Davis KD, Taylor KS, Hutchison WD, Dostrovsky JO, McAndrews MP, Richter EO, Lozano AM. Human anterior cingulate cortex neurons encode cognitive and emotional demands. J Neurosci. 2005; 25:8402–8406. [PubMed: 16162922]
14. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8:700–711. [PubMed: 17704812]
15. Gracely RH, Kwilosz DM. The Descriptor Differential Scale: applying psychophysical principles to clinical pain assessment. Pain. 1988; 35:279–288. [PubMed: 3226757]
16. Gracely RH, Lota L, Walter DJ, Dubner R. A multiple random staircase method of psychophysical pain assessment. Pain. 1988; 32:55–63. [PubMed: 3340422]
17. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002; 46:1333–1343. [PubMed: 12115241]
18. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003; 100:253–258. [PubMed: 12506194]
19. Harris RE, Gracely RH, McLean SA, Williams DA, Giesecke T, Petzke F, Sen A, Clauw DJ. Comparison of clinical and evoked pain measures in fibromyalgia. J Pain. 2006; 7:521–527. [PubMed: 16814691]
20. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, Sundgren PM, Foerster B, Petrou M, Schmidt-Wilcke T, Clauw DJ. Pregabalin Rectifies Aberrant Brain Chemistry, Connectivity,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and Functional Response in Chronic Pain Patients. Anesthesiology. 2013; 119:1453–1464. [PubMed: 24343290]

21. Hu X, Le TH, Parrish T, Erhard P. Retrospective estimation and correction of physiological fluctuation in functional MRI. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 1995; 34:201–212.
22. Ichesco E, Quintero A, Clauw DJ, Peltier S, Sundgren PM, Gerstner GE, Schmidt-Wilcke T. Altered Functional Connectivity Between the Insula and the Cingulate Cortex in Patients With Temporomandibular Disorder: A Pilot Study. Headache. 2011
23. Ichesco E, Schmidt-Wilcke T, Clauw D, Peltier S, Williams D, Harris R. Altered resting connectivity between the insula and cingulate cortex is related to chronic fibromyalgia pain. The Journal of Pain. 2012; 13:S29.
24. Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. Pain. 148:257–267. [PubMed: 20005043]
25. Kucyi A, Hodaie M, Davis KD. Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks. Journal of neurophysiology. 2012; 108:3382–3392. [PubMed: 23019004]
26. Limongi R, Sutherland SC, Zhu J, Young ME, Habib R. Temporal Prediction Errors Modulate Cingulate-insular Coupling. Neuroimage. 2013
27. Loggia ML, Kim J, Gollub RL, Vangel MG, Kirsch I, Kong J, Wasan AD, Napadow V. Default mode network connectivity encodes clinical pain: an arterial spin labeling study. Pain. 2013; 154:24–33. [PubMed: 23111164]
28. Lugo M, Isturiz G, Lara C, Garcia N, Eblen-Zaijur A. Sensory lateralization in pain subjective perception for noxious heat stimulus. Somatosensory & motor research. 2002; 19:207–212. [PubMed: 12396577]
29. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987; 30:191–197. [PubMed: 3670870]
30. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum. 2012; 64:2398–2403. [PubMed: 22294427]
31. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010; 62:2545–2555. [PubMed: 20506181]
32. Owen DG, Clarke CF, Bureau Y, Ganapathy S, Prato FS, St Lawrence KS. Measuring the neural response to continuous intramuscular infusion of hypertonic saline by perfusion MRI. J Magn Reson Imaging. 2012; 35:669–677. [PubMed: 21953816]
33. Pauli P, Wiedemann G, Nickola M. Pain sensitivity, cerebral laterality, and negative affect. Pain. 1999; 80:359–364. [PubMed: 10204749]
34. Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain. 2003; 105:403–413. [PubMed: 14527701]
35. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. Eur J Pain. 2005; 9:325–335. [PubMed: 15862482]
36. Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin. 2000; 30:263–288. [PubMed: 11126640]
37. Pfeuffer J, Van de Moortele PF, Ugurbil K, Hu X, Glover GH. Correction of physiologically induced global off-resonance effects in dynamic echo-planar and spiral functional imaging. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2002; 47:344–353.
38. Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Flexible Cerebral Connectivity Patterns Subserve Contextual Modulations of Pain. Cereb Cortex.
39. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977:385–401.
40. Sarlani E, Farooq N, Greenspan JD. Gender and laterality differences in thermosensation throughout the perceptible range. Pain. 2003; 106:9–18. [PubMed: 14581105]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

41. Seifert F, Maihöfner C. Representation of cold allodynia in the human brain--a functional MRI study. Neuroimage. 2007; 35:1168–1180. [PubMed: 17360197]
42. Spielberger, CD. [Accessed 2010 March 18] http://mindgarden.com/products/stpi.htm
43. Taylor KS, Seminowicz DA, Davis KD. Two systems of resting state connectivity between the insula and cingulate cortex. Hum Brain Mapp. 2009; 30:2731–2745. [PubMed: 19072897]
44. Tracey I. Nociceptive processing in the human brain. Curr Opin Neurobiol. 2005; 15:478–487. [PubMed: 16019203]
45. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002; 15:273–289. [PubMed: 11771995]
46. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci. 2005; 6:533–544. [PubMed: 15995724]
47. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012; 2:125–141. [PubMed: 22642651]
48. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. J Pain. 2009; 10:777–791. [PubMed: 19638325]
49. Williams DA, Schilling S. Advances in the assessment of fibromyalgia. Rheum Dis Clin North Am. 2009; 35:339–357. [PubMed: 19647147]
50. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, Mccain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990; 33:160–172. [PubMed: 2306288]
51. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67:361–370. [PubMed: 6880820]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

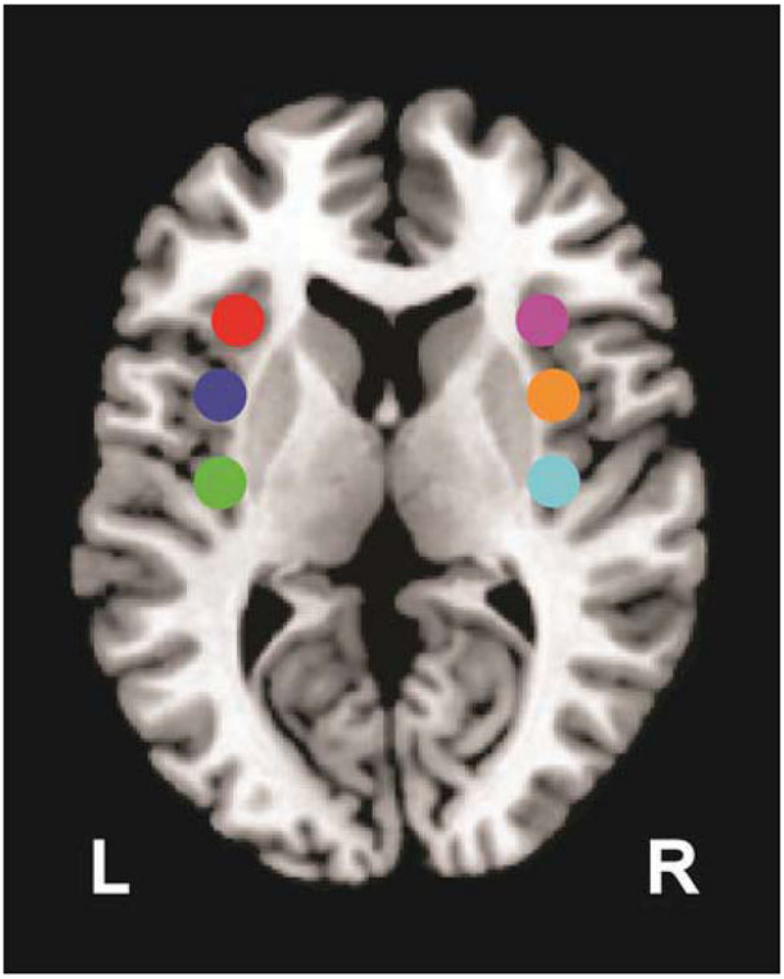

Figure 1. IC seeds used for functional connectivity analysis

Figure 1 displays the six seed regions used for functional connectivity analyses. Seed regions were spheres of 6 mm surrounding a peak voxel. MNI coordinates for each voxel include: left anterior IC (red): x = −32, y = 16, z = 6; left mid IC (dark blue): x = −38, y = 2 z = 8; left posterior IC (green): x = −39, y = −15, z = 1; right anterior IC (purple): x = 32, y = 16, z = 6; right mid IC (orange): x = 38, y = 2, z = 8; right posterior IC (light blue): x = 39, y = −15, z = 8. IC = insular cortex.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

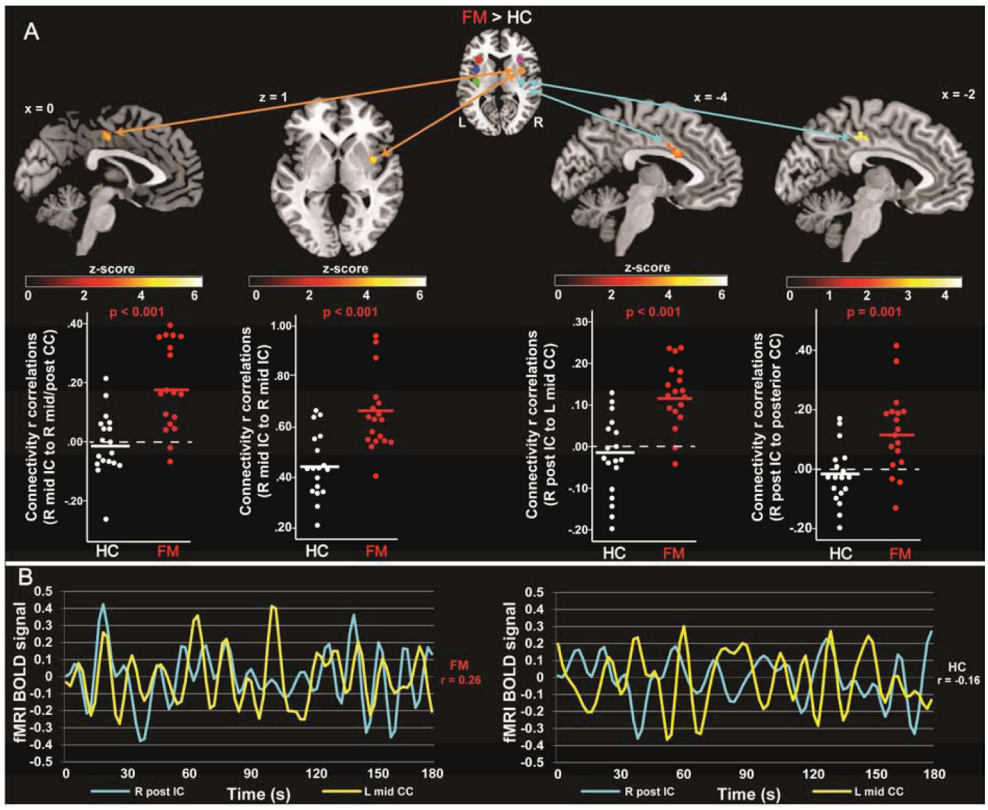

Figure 2. Greater IC connectivity in FM compared to HC

Figure 2A displays increased IC connectivity in FM patients compared to HCs. From left to right, increased connectivity in FM compared to HC subjects was found between the R mid IC seed and the right mid/post CC (far left), the R mid IC seed and the R mid IC (middle left), the R posterior IC seed and the L mid CC (middle left), and the R post IC seed and the posterior CC (far right). Scatter plots of connectivity r-value correlations for each cohort are displayed below brain figures. Figure 2B depicts two graphs of the fMRI BOLD signal time series for both seed (light blue) and connected region (yellow) from a representative FM subject and a HC subject. FM = fibromyalgia, HC = healthy controls, IC = insula cortex, CC = cingulate cortex, BOLD = Blood Oxygenation Level Dependent.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

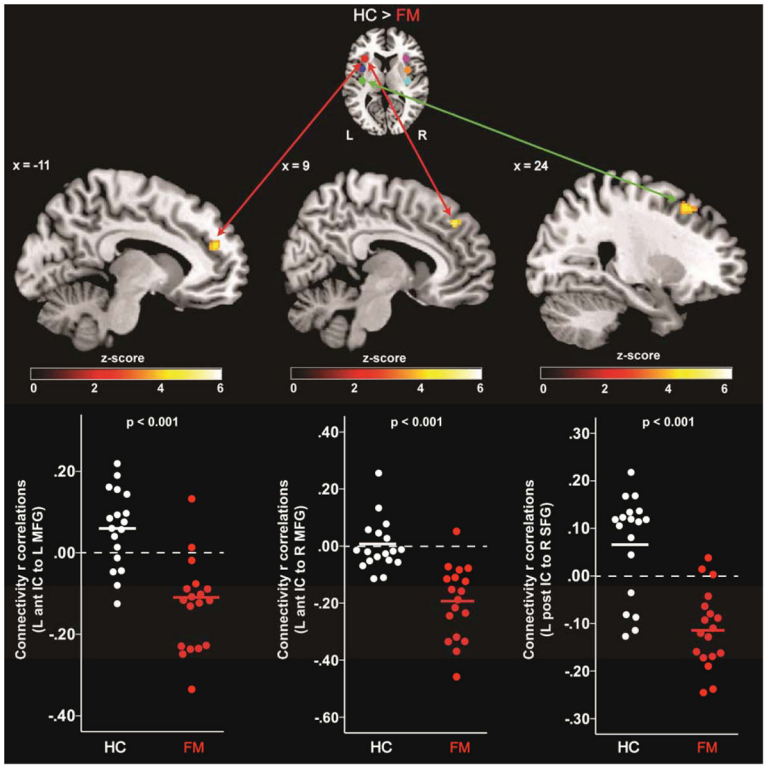

Figure 3. Regions of decreased connectivity in FM patients as compared to controls

Figure 3 depicts decreased connectivity for FM patients when compared to HC between: the L anterior IC seed and the L medial frontal gyrus (left), the L anterior IC seed and the R medial frontal gyrus (center), and the L posterior IC seed and the R superior frontal gyrus (right). Beneath each brain image is the corresponding scatter plot of the connectivity correlations for each cohort. FM = fibromyalgia, HC = healthy controls, IC = insula cortex, MFG = medial frontal cortex, SFG = superior frontal gyrus.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

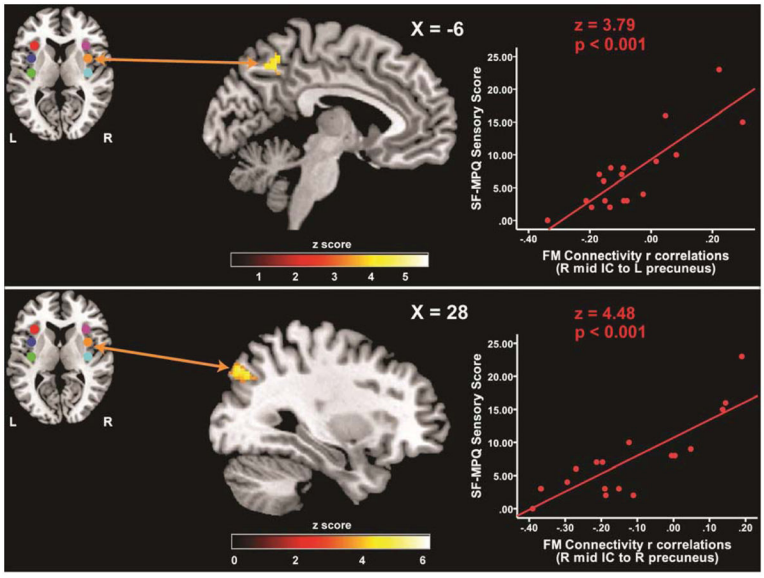

Figure 4. FM IC connectivity is associated with increased clinical pain

Figure 4 displays connectivity in FM patients between the IC and precuneus. Connectivity between the R mid IC seed and the L precuneus was positively associated with SF-MPQ sensory pain report (top). Also, connectivity between the R mid IC seed and the R precuneus was positively associated with SF-MPQ sensory pain report (bottom). In both cases, this result shows that FM patients display increased pain report as IC-precuneus connectivity increases. FM = fibromyalgia, IC = insula cortex, SF-MPQ = Short Form McGill Pain Questionnaire, L = left, R = right.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

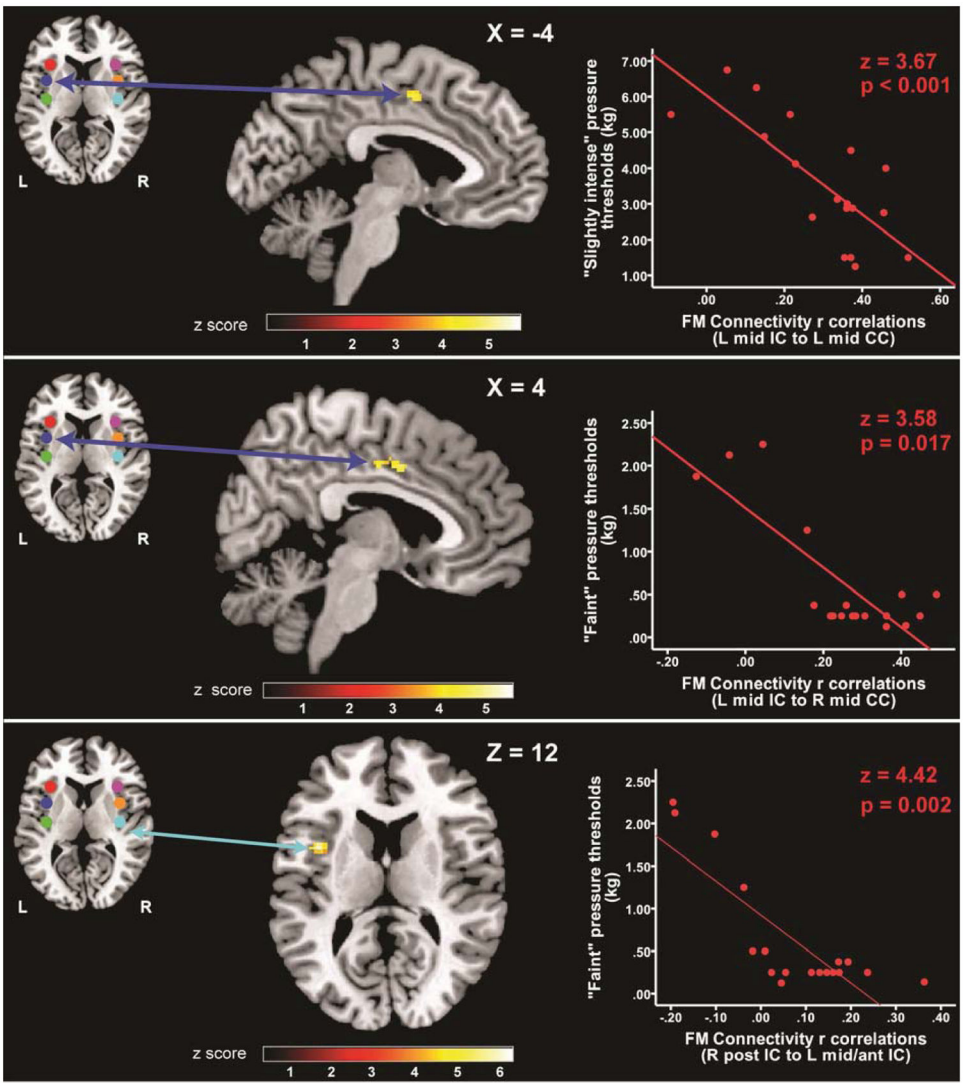

Figure 5. IC-CC connectivity is associated with decreased experimental pain thresholds in FM patients

Figure 5 displays connectivity in FM patients between the IC and mid CC and IC. Connectivity between the L mid IC seed and the L MCC was negatively associated with “slightly intense” pressure thresholds (top). Also, connectivity between the L mid IC seed and the R MCC was negatively associated with “faint” pressure thresholds (middle). Finally, connectivity between the R posterior IC seed and the left mid IC was negatively correlated with “faint” pressure thresholds (bottom). In all cases, this result shows that FM patients display decreased experimental pain thresholds as IC-CC and IC-IC connectivity increases. CC = cingulate cortex, FM = fibromyalgia, IC = insula cortex, L = left, R = right.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Demographics and Behavioral Data

	FM	HC	p value
Age	35.8 ± 12.0	32.3 ± 11.3	0.375
SF-MPQ TOT	9.7 ± 7.3	0.3 ± 0.4	< **0.001**
SF-MPQ SEN	7.2 ± 5.9	0.2 ± 0.4	< **0.001**
SF-MPQ AFF	2.5 ± 3.3	0.1 ± 0.3	**0.007**
SF-MPQ VAS	4.4 ± 2.3	0.1 ± 0.3	< **0.001**
MRS low (kg/cm^2)	0.6 ± 0.7	0.8 ± 0.8	0.505
MRS med (kg/cm^2)	2.3 ± 1.3	2.6 ± 1.4	0.481
MRS high (kg/cm^2)	3.6 ± 1.7	4.1 ± 1.8	0.347
Disease Duration (yrs)	3.9 ± 3.7	-	-

Table 1 includes behavioral data for all 36 subjects enrolled in this study (18 FM versus 18 HC). FM = fibromyalgia, HC = healthy control. SF-MPQ AFF = Short Form McGill Pain Questionnaire affective component, SF-MPQ SEN = Short Form McGill Pain Questionnaire sensory component, SF-MPQ TOT = Short Form McGill Pain Questionnaire total score, SF-MPQ VAS = Short Form McGill Pain Questionnaire Visual Analogue Scale. MRS = multiple random staircase.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 2

Differences in resting state functional connectivity between FM and controls

Seed region	Connectivity region	Brodmann Area	Cluster size (# of voxels)	z-score (peak value)	Coordinates (MNI)		
					x	y	z
FM>HC (ANCOVA with age as covariate of no interest)							
R ant IC	L superior temporal gyrus	22	81	4.69	−46	−26	−2
R mid IC	R mid IC	13	81	4.27	38	2	0
	R mid/post CC	24/31	57	3.85	2	−16	44
R post IC	L mid CC	24	123	4.03	−2	10	30
	Posterior CC	31/24	40	3.88	0	−24	46
HC>FM (ANCOVA with age as covariate of no interest)							
L ant IC	R medial frontal gyrus	6	101	4.48	10	40	40
	L medial frontal gyrus	9	70	4.25	−12	46	22
L post IC	R superior frontal gyrus	8	79	4.43	26	20	50

Table 2 details group differences between FM and HC subjects. FM = fibromyalgia, HC – healthy control, CC = cingulate cortex, IC = insular cortex, S1 = primary somatosensory cortex, ANCOVA = analysis of covariance, MNI = Montreal Neurological Institute, L = left, R = right.

J Pain. Author manuscript; available in PMC 2015 August 01.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 3a

Results of resting state functional connectivity group differences correlated with clinical and experimental pain in FM patients

fcMRI group difference	Seed region	Connectivity region	Behavioral correlate	p value	Corr. r
FM>HC	R ant IC	L superior temporal gyrus	SF-MPQ AFF	0.01	0.61*
FM>HC	R ant IC	L superior temporal gyrus	SF-MPQ TOT	0.03	0.51
FM>HC	R post IC	Posterior CC	MRS med	0.04	−0.50

Table 3a displays correlations between fcMRI group differences (identified in Table 2) and behavioral measures within the FM group. Correlations were deemed significant at a threshold of $p < 0.025$ based on a Bonferroni correction. Strong trends with a $p < 0.05$ are also reported. No significant correlations to experimental pain report were found amongst the HC group within these same regions. FM = fibromyalgia, HC = healthy controls, IC = insula cortex, CC = cingulate cortex, MRS = multiple random staircase, R = right, L = left, SF-MPQ AFF = Short Form McGill Pain Questionnaire affective component, SF-MPQ TOT = Short Form McGill Pain Questionnaire total score.

*One subject was removed due to a response being an outlier > 2 standard deviations from the mean.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 3b

Results of behavioral correlations with whole brain resting state functional connectivity

Seed region	Connectivity Region	Behavioral Correlate	BA	Cluster size (# of voxels)	z-score	Coordinates (MNI) x	y	z
FM – Positive Correlations								
R mid IC	R precuneus	SF-MPQ SEN	19	136	4.48	28	−78	42
	R SMA	SF-MPQ AFF*	6	80	4.03	24	14	62
	L precuneus	SF-MPQ SEN	7	71	3.79	−6	−54	50
FM – Negative Correlations								
L mid IC	L mid CC	MRS high	24	29	3.67	−4	−2	48
	R mid CC	MRS low	24	56	3.58	4	4	40
R mid IC	Mid CC	SF-MPQ AFF*	24	42	4.12	0	−10	48
	L posterior IC	SF-MPQ AFF*	13	45	3.97	−42	−4	2
R post IC	L precuneus	MRS low	19	223	4.74	−6	−76	38
	L mid/anterior IC	MRS low	13	42	4.42	−40	6	12
	R STG	MRS low	13/22	95	4.19	54	−42	18
HC – Positive Correlations								
R ant IC	R posterior CC	MRS med	31	57	4.20	10	−32	44

Table 3b includes correlation results between whole brain resting state fcMRI and experimental and clinical pain measures. BA = Brodmann area, FM = fibromyalgia, HC = healthy control, IC = insular cortex, CC = cingulate cortex, STG = superior temporal gyrus, MRS = multiple random staircase, SF-MPQ AFF = Short Form McGill Questionnaire affective component, SF-MPQ SEN = Short Form McGill Pain Questionnaire sensory component, L = left, R = right.

* One subject was removed due to a response being an outlier > 2 standard deviations from the mean.