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BRIEF REPORT

Decreased Intrinsic Brain Connectivity Is Associated With Reduced Clinical Pain in Fibromyalgia

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Objective. **A major impediment to the development of novel treatment strategies for fibromyalgia (FM) is the lack of an objective marker that reflects spontaneously reported clinical pain in patients with FM. Studies of resting-state intrinsic brain connectivity in FM have demonstrated increased insular connectivity to the default mode network (DMN), a network whose activity is increased during nontask states. Moreover, increased insular connectivity to the DMN was associated with increased spontaneous pain levels. However, as these analyses were cross-sectional in nature, they provided no insight into dynamic changes in connectivity or their relationship to variations in self-reported clinical pain. The purpose of this study was to evaluate longitudinal changes in the intrinsic brain connectivity of FM patients treated with nonpharmacologic interventions known to modulate pain levels in this patient population, and to test the hypothesis that the reduction of DMN–insula connectivity following therapy would correlate with diminished pain.**

Methods. **Seventeen FM patients underwent resting-state functional magnetic resonance imaging at baseline and following 4 weeks of a nonpharmacologic intervention to diminish pain. Intrinsic DMN connectivity was evaluated using probabilistic independent components analysis. Longitudinal changes in intrinsic DMN connectivity were evaluated by paired analysis, and correlations between longitudinal changes in clinical pain and changes in intrinsic DMN connectivity were investigated by multiple linear regression analysis. Changes in clinical pain were assessed with the short form of the McGill Pain Questionnaire (SF-MPQ).**

Results. **Clinical pain as assessed using the sensory scale of the SF-MPQ was reduced following therapy ($P = 0.02$). Intrinsic DMN connectivity to the insula was reduced, and this reduction correlated with reductions in pain (corrected $P < 0.05$).**

Conclusion. **Our findings suggest that intrinsic brain connectivity can be used as a candidate objective marker that reflects changes in spontaneous chronic pain within individual FM patients. We propose that intrinsic connectivity measures could potentially be used in either research or clinical settings as a complementary, more objective outcome measure for use in FM.**

Fibromyalgia (FM) is a functional chronic pain syndrome characterized by diffuse hyperalgesia and spontaneous widespread pain (1). Multiple studies have characterized functional, structural, and neurochemical brain changes in patients with FM (2). Since most of these studies have been cross-sectional in nature, they do not address whether the changes in brain structure, function, and neurochemistry are a cause of the pain, a consequence, or simply factors associated with chronic pain. In most of the studies that used functional magnetic resonance imaging (fMRI) to assess changes in response to pain stimuli, information about hyperalgesia

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was provided, but information on ongoing spontaneous pain was not. Recently, we reported that use of an fMRI technique that assesses resting or intrinsic brain connectivity provides neurobiologic correlates to self-reported spontaneous clinical pain in patients with FM (3). Results of fMRI showed that FM patients displayed greater connectivity between the insula and the default mode network (DMN), and the degree of connectivity was directly associated with the intensity of ongoing spontaneous pain. However, that cross-sectional analysis did not assess whether the connectivity could have potential as a brain imaging marker that reflects dynamic longitudinal changes in pain in FM patients undergoing therapy.

For FM and chronic pain in general, effective analgesic therapies and better understanding of the pathophysiology underlying chronic pain syndromes are needed. Indeed, these two factors are likely related: a better understanding of the mechanistic pathways underlying specific pathology in subgroups of patients could be used to optimize and enhance therapy for specific individuals with FM. Subjective self-reports of pain symptoms most likely lack the specificity needed to identify phenotypes of specific pathologic factors in individual patients; however, as FM is increasingly characterized as a disorder in central nervous system functioning (1), a noninvasive neuroimaging marker could greatly improve our ability to characterize and track pain symptoms in FM patients in longitudinal trials.

Evaluation of intrinsic brain connectivity by fMRI is a relatively recent neuroimaging approach. Intrinsic connectivity assesses spontaneous neural and metabolic activity that occurs in a resting basal state since imaging is performed while subjects rest quietly in the scanner. We and others have proposed that this resting connectivity is related to the spontaneous chronic pain experienced by patients with FM (3). It may reflect synaptic neurotransmission as interregional correlations in the fMRI signal follow known structural monosynaptic and polysynaptic pathways (4). Thus, connectivity likely reflects neurophysiologically meaningful activity, and occurs within distinct networks of the brain. One such constellation is the DMN, an aggregate of the brain structures that have been associated with self-referential cognition and autobiographical memory (5). In addition to FM (3), altered intrinsic DMN connectivity has been detected in other chronic pain conditions (6). We found that the DMN demonstrated greater connectivity to the insula in FM patients compared to healthy adults, and, perhaps even more importantly, increasing DMN–insula connectivity was associated with increasing levels of spontaneous pain (3). These results suggested that intrinsic connectivity could serve as a brain biomarker for chronic pain, a hypothesis that would be bolstered if longitudinal changes in intrinsic DMN connectivity were associated with changes in the clinical pain state.

Our current study was designed to evaluate longitudinal changes in intrinsic brain connectivity in FM patients treated with a nonpharmacologic intervention that is known to modulate pain levels in this patient population (7). Subjects underwent scanning before and after therapy and were evaluated for intrinsic connectivity. We hypothesized that DMN–insula connectivity would be reduced following therapy and would correlate with diminished pain.

PATIENTS AND METHODS

Patients. As part of an ongoing study investigating nonpharmacologic treatment in FM, 17 female patients (mean ± SD age 46.4 ± 15.5 years) underwent MRI during 2 scanning sessions spaced a mean ± SD of 29.8 ± 4.0 days apart. Scanning sessions occurred before (mean ± SD 4.0 ± 2.4 days) and after (4.4 ± 3.8 days) 9 treatments of either acupuncture or sham acupuncture using a protocol that has been shown to decrease pain levels in FM patients (7,8). The treatment assignment was not considered during analyses, as we were not interested in any differences between treatment with acupuncture and sham acupuncture, but rather how changes in intrinsic brain connectivity are related to changes in pain. All subjects provided written informed consent, and protocols were approved by the University of Michigan Institutional Review Board.

Participant inclusion and exclusion criteria have been reported previously (3). Briefly, patients had FM that had met the 1990 American College of Rheumatology criteria for the diagnosis of FM (9) for at least 1 year, had continued presence of pain on >50% of days, and were willing to maintain their existing therapy and limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study.

Spontaneous clinical pain. Prior to scanning, subjects were asked to rate the intensity of their FM pain using the short form of the McGill Pain Questionnaire (SF-MPQ) (10). The sensory and affective subscales were contrasted between baseline and posttherapy time points by Student's *t*-test (significant at $\alpha = 0.05$).

Intrinsic connectivity fMRI data acquisition. Six minutes of resting-state fMRI data were collected as the first functional scan run in the session. We used a spiral in-out gradient echo T2*-weighted blood oxygenation level–dependent pulse sequence (repetition time [TR]/echo time [TE] 2,000/30 msec, 180 volumes, 43 slices parallel to the plane containing the anterior and posterior commissures, voxel size 3.13 × 3.13 × 4.0 mm) running on a 3T Signa Excite scanner (GE) equipped with an 8-channel head coil. Patients were instructed to close their eyes and to rest comfortably during the

functional scan without moving or falling asleep. Structural data were also collected using a spoiled gradient pulse sequence (TR/TE/inversion time 14/5.5/300 msec, flip angle 20°, 124 contiguous axial slices, voxel size 1.0 × 1.0 × 1.5 mm).

Physiologic data and fMRI data were collected simultaneously, as cardiorespiratory fluctuations are known to influence fMRI intrinsic connectivity estimation within several brain networks. Cardiac data were acquired using an infrared pulse oximeter (GE) attached to the right middle finger. Respiratory volume data were acquired using an MR-compatible belt (GE) placed around the subject's rib cage.

Intrinsic connectivity fMRI data analysis. Data analysis was performed using FSL (www.fmrib.ox.ac.uk/fsl). Data were corrected for motion artifact (MCFLIRT) and for cardiorespiratory artifacts using the RETROICOR algorithm. FSL BET was used to perform brain extraction on functional data (i.e., to remove non-brain tissue from the image). Data were smoothed using a full width half maximum Gaussian kernel of 6 mm and a temporal high-pass filter (f = 0.008 Hz).

Resting-state fMRI data on individual patients were analyzed using the previously validated dual-regression independent components analysis (ICA) through MELODIC. Importantly, this approach has been reported to have moderate-to-high test–retest reliability both short term (within the scanning session) and long term (several weeks after the scanning session) in healthy adults (11). We used the same approach in our previous cross-sectional study investigating the relationship between pain and intrinsic brain connectivity in FM patients (3). Dual-regression ICA allows for voxelwise comparisons of resting-state functional connectivity by first temporally concatenating resting fMRI data from all subjects, followed by back-reconstructing the group intrinsic connectivity networks (ICNs) for individual subjects, which are then used for within- and between-subject group and difference maps. We limited the number of independent components to 25 and used our previous goodness-of-fit tests (3,12) to identify different ICNs. Our analysis was focused on the DMN network, as resting connectivity within this network was found to be altered in FM patients compared to healthy adults (3), while acupuncture has been shown to modulate resting-state DMN connectivity (12). As in our previous analyses, the generalized linear model included multiple temporal regressors of no interest, including time series from white matter and ventricular regions, and cardiac and respiratory variability defined by convolving the heart rate time series and respiratory variations with appropriate cardiac and respiratory transfer functions. This was done to limit any residual shared variance with non-neuronal (e.g., cardiorespiratory physiologic) processes. No global signal regression was used.

Mixed-effects group analyses were used to contrast intrinsic DMN connectivity at baseline and posttherapy. To more closely link changes in resting DMN connectivity with analgesic response, multiple linear regression analysis was performed using the change in DMN connectivity and the change in spontaneous pain rating (sensory/affective subscores of the SF-MPQ). This pain score was adjusted for age by including this variable in the model, as age is known to influence ICN connectivity. Results were determined to be significant using cluster correction for multiple comparisons (corrected P values less than or equal to 0.05 considered significant).

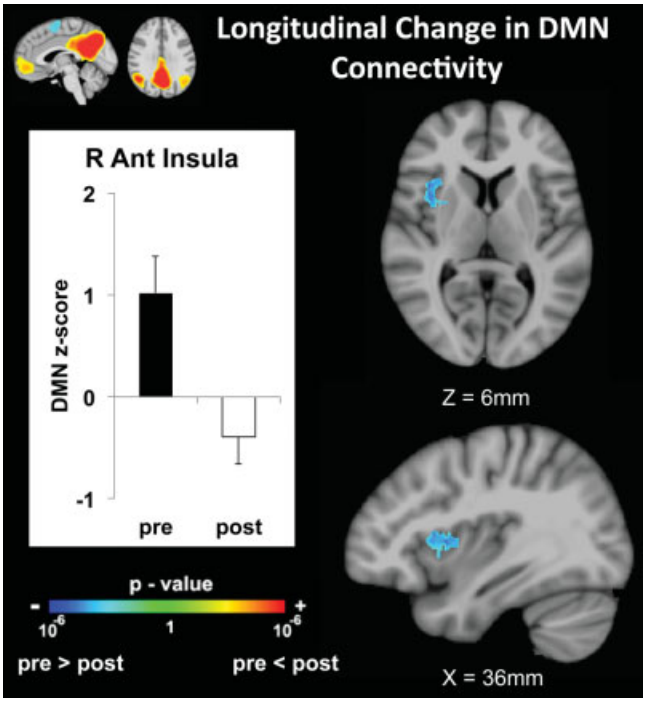

Figure 2. Default mode network (DMN) connectivity to the anterior insula in fibromyalgia patients before and after therapy. DMN connectivity was positive at baseline, and was significantly reduced following therapy. Bars show the mean ± SEM. R Ant Insula = right anterior insula. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131.

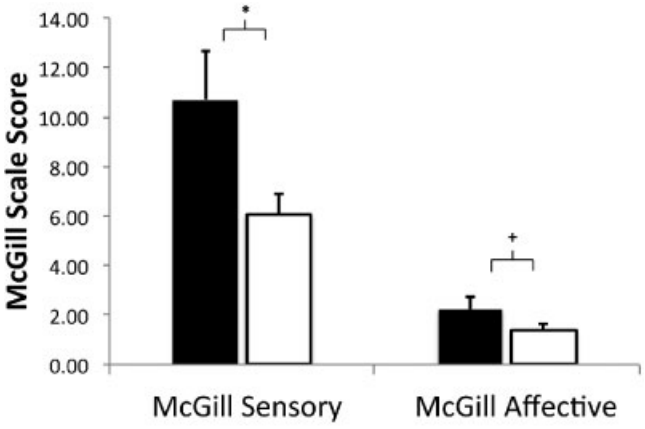

Figure 1. Levels of pain in fibromyalgia patients before therapy (solid bars) and after therapy (open bars) as assessed with the short form of the McGill Pain Questionnaire. Clinical pain levels were assessed just prior to functional magnetic resonance imaging. There was a significant reduction in pain on the McGill sensory subscale and a trend toward diminished pain on the McGill affective subscale following therapy. Bars show the mean ± SEM. * = P = 0.02; + = P = 0.09.

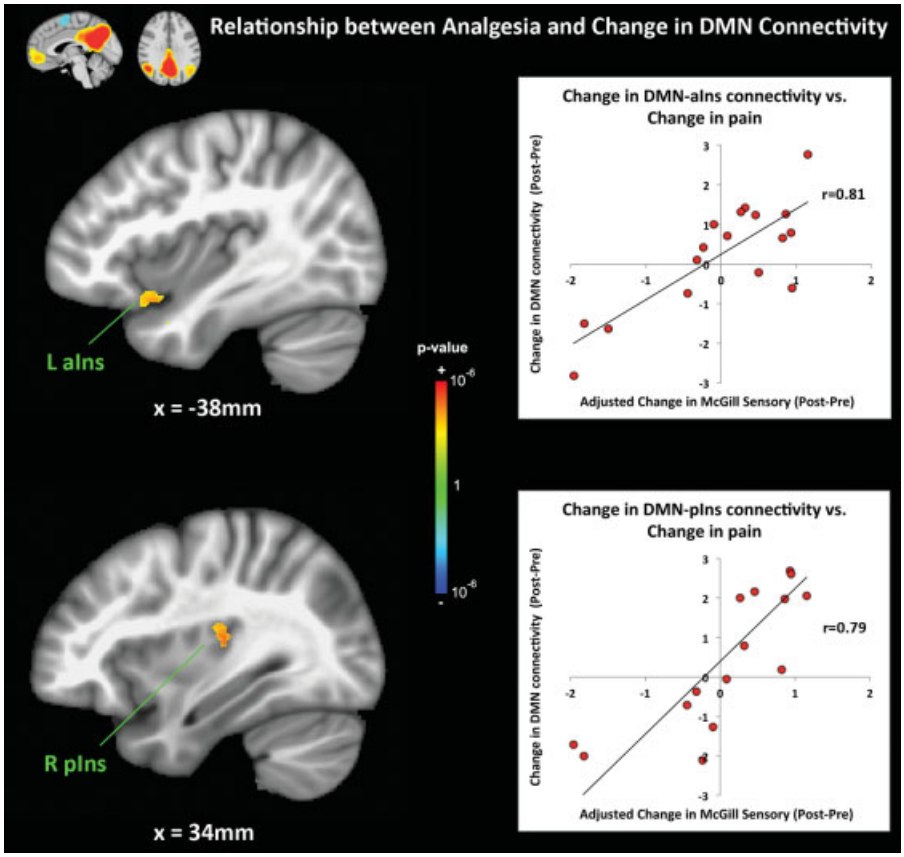

Figure 3. Relationship between changes in age-adjusted clinical pain and intrinsic default mode network (DMN) in patients with fibromyalgia. Multiple linear regression analysis demonstrated that the change in age-adjusted clinical pain at the time of functional magnetic resonance imaging correlated with reduced intrinsic DMN connectivity to the left anterior insula (L aIns). A subthreshold cluster was also found in the right posterior insula (R pIns).

RESULTS

Resting-state fMRI data were collected from all 17 female subjects, before and after therapy (mean ± SD 29.8 ± 4.0 days between scans). All subjects tolerated the intervention and there were no dropouts.

After therapy, there was significant diminishment of clinical pain as assessed according to the SF-MPQ sensory subscore (mean ± SEM 6.06 ± 0.85, versus 10.71 ± 1.93 at baseline; $P = 0.02$). Additionally, there was a trend toward diminished pain as assessed according to the SF-MPQ affective subscore (1.35 ± 0.31, versus 2.24 ± 0.47 at baseline; $P = 0.09$) (Figure 1).

Following therapy, reduced intrinsic brain connectivity between the DMN and the right anterior/middle insula was detected (z = −3.63; Montreal Neurological Institute [MNI] coordinates x, y, z = 39 mm, 7 mm, 5 mm, respectively) (Figure 2). Reduced connectivity between the DMN and right putamen was also noted posttreatment (z = −3.57; MNI coordinates x, y, z = 26 mm, 1 mm, 1 mm, respectively). Interestingly, diminished self-reported spontaneous clinical pain correlated positively with reduced connectivity between the DMN and left anterior insula (z = 3.21; MNI coordinates x, y, z = −38 mm, 12 mm, −18 mm, respectively) (Figure 3), as well as the left amygdala (z = 3.22; MNI coordinates x, y, z = −24 mm, 1 mm, −21 mm, respectively). A subthreshold cluster, which survived at an uncorrected P value of less than 0.005 (minimum cluster size 400 mm^2), was also found in the right posterior insula (z = 3.74; MNI coordinates x, y, z = 32 mm, −24 mm, 16 mm, respectively).

DISCUSSION

Our previous studies linked increased intrinsic DMN–-insula connectivity to spontaneous pain in FM patients (3). The current study demonstrates that DMN–insula connectivity is decreased following successful

longitudinal therapy. Furthermore, diminished pain correlated positively with reduced intrinsic connectivity between the DMN and anterior insula. These results provide preliminary support for the use of intrinsic brain connectivity as a candidate objective marker for the subjective experience of clinical pain in FM. Moreover, we have demonstrated the utility of using intrinsic connectivity as a surrogate objective outcome measure for interventional trials in FM, especially in early proof-of-concept trials.

Previous studies have demonstrated insular involvement in the multidimensional (sensory, affective, cognitive) pain state. The insula is one of the most commonly activated brain regions in neuroimaging studies of acute experimental pain (13). However, the insula does not just process pain signals, and has been associated with multiple aversive or otherwise salient experiential states, both interoceptive (14) and exteroceptive (15). As DMN processing has been attributed to self-referential cognitive processing, we could speculate that increased DMN–insula connectivity in FM may reflect a state of hyperawareness to pain, which has been incorporated into the patient's sense of self. Longitudinal reduction in DMN–insula connectivity may then follow, accompany, or even play a causal role in the reduction of pain experienced during analgesic intervention. At this time we cannot differentiate between these hypotheses.

The use of an insula-associated neuroimaging marker to track FM pain has been explored in previous studies. For instance, we have shown that insular glutamate levels as assessed with proton magnetic resonance spectroscopy were elevated in FM patients and were found to correlate positively with changes in clinical pain (8,16). The current study adds to our understanding of insular involvement in clinical pain reported by patients and shows again that longitudinal changes in pain in FM are related to longitudinal changes in insular physiology.

We used acupuncture as the nonpharmacologic therapy in this study. This intervention was used instead of pharmacologic intervention as there is less risk of modulating neurovascular coupling, and acupuncture (both real and sham) is known to reduce pain levels in FM patients (7). Our previous studies have also demonstrated that acupuncture increases intrinsic DMN connectivity to pain-modulatory and affective brain areas such as the anterior cingulate cortex, periaqueductal gray matter, and amygdala (12). The effect was short term (immediately following acupuncture stimulation), whereas our present study showed that more sustained therapy reduced DMN connectivity to the insula. It is not currently known whether the longitudinal changes found over multiple weeks in this trial are related to the more immediate stimulus-related change we observed previously. Future studies are needed to clarify this.

In conclusion, our findings suggest that intrinsic brain connectivity can be used as a candidate objective marker that is sensitive enough to track pain levels in FM. Intrinsic connectivity can be used as a complementary, objective outcome measure in longitudinal clinical trials of different therapies in this patient population. Incorporation of this marker in future clinical trials may provide a better understanding of the mechanistic pathways underlying various interventions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Napadow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Napadow, Clauw, Harris.
Acquisition of data. Clauw, Harris.
Analysis and interpretation of data. Napadow, Kim, Clauw, Harris.

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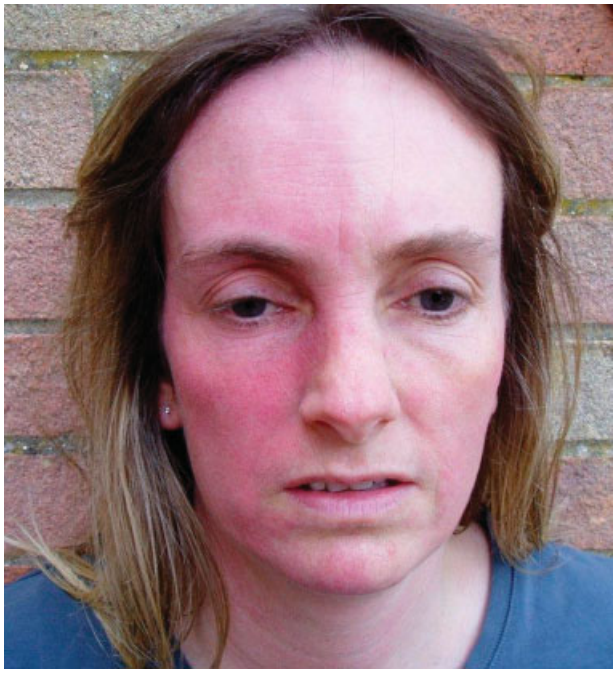
Clinical Image: The Harlequin sign—benign blush or the bearer of bad news?



The patient, a 41-year-old woman, presented to the rheumatology clinic. She reported that, for the past 3 years, she experienced unilateral facial flushing and coldness of the ipsilateral hand after vigorous exercise. Results of the neurologic assessment, including tests for autonomic function, were normal. Findings of magnetic resonance imaging of the patient's brain, neck, thoracic outlet, and chest were also normal. The patient mentioned that her son experienced similar symptoms, although he had not been formally assessed. A diagnosis of Harlequin syndrome was made in light of the patient's characteristic symptoms, which included unilateral flushing and hyperhidrosis after exercise (Wasner G, Maag R, Ludwig J, Binder A, Schattschneider J, Stingele R, et al. Harlequin syndrome—one face of many etiologies. Nat Clin Pract Neurol 2005;1:54–9). Harlequin syndrome results from disruption of sympathetic fibers at or distal to the sympathetic ganglia at T2–T3, with proximally located lesions associated with greater autonomic dysfunction. To date, 91 patients with Harlequin syndrome have been reported, and in 64% of these no cause was identified. In the remaining patients, mediastinal tumors, paravertebral thoracic blocks, and neck-mass resection accounted for the majority of the cases. In some cases of Harlequin syndrome there may be a generalized disorder of the autonomic nervous system constituting part of a spectrum of conditions involving generalized dysautonomia, such as Ross syndrome and Adie syndrome. Coldness of the ipsilateral arm, suggestive of multifocal involvement, was mentioned in only 1 other case report (Moon SY, Shin DI, Park SH, Kim JS. Harlequin syndrome with crossed sympathetic deficit of the face and arm. J Korean Med Sci 2005;20:329–30). Hereditary Harlequin syndrome has not yet been described. Management involves ruling out structural lesions in the paravertebral region, after which education, reassurance, and procedures to improve cosmesis form the mainstay of therapy.

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