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Cold Water Pressor Test Differentially Modulates Functional Network Connectivity in Fibromyalgia Patients Compared with Healthy Controls

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Abstract

Fibromyalgia is a multifaceted chronic pain condition of unknown etiology. Conditioned pain modulation (CPM) such as cold water pressor test of the foot, is widely documented as being disrupted in patients with fibromyalgia. To date, the mechanisms underlying such dysregulation of the descending control of pain in fibromyalgia remain poorly understood. In this study, we used ICA-based network analysis to comprehensively compare differences in functional network connectivity among relevant (nonartifactual) intrinsic connectivity brain networks during the resting state before and after cold pressor test in patients with fibromyalgia and healthy controls. The results revealed significant differences in functional connectivity between the two groups that included the networks that integrate cognitive control and attention systems with memory, emotion and brainstem regions. Specifically, functional connectivity involving central executive network was absent in patients with fibromyalgia compared with controls. Patients showed significant functional connectivity changes involving subcortical and brainstem networks with the sensorimotor and dorsal attention networks. Accordingly, aberrant CPM in patients with fibromyalgia may be due to the differences in functional connectivity involving the subcortical/brainstem regions, and is facilitated by the recruitment of the dorsal attention network in lieu of the central executive network. Future research replicating the present findings with larger sample size can shed more light on neurobiology of endogenous pain modulation in fibromyalgia.

I. INTRODUCTION

Fibromyalgia is a chronic pain condition characterized by widespread pain and tenderness, often accompanied by fatigue, cognitive and mood disturbances [1]. Dysregulation of the descending control mechanisms (e.g., cortical, subcortical and brainstem areas) of pain is thought to be a potential contributor to the ongoing pain and symptoms of allodynia (pain felt in response to normally non-painful stimuli) and hyperalgesia (increased pain felt in response to normally painful stimuli). Altered central nervous system activity has been demonstrated in fibromyalgia from a variety of studies using fMRI, PET, and other imaging modalities, both during resting state conditions as well as in response to painful and non-

painful stimulation [2]. Additionally, alterations in the autonomic nervous system may occur in patients with fibromyalgia [3]. Conditioned pain modulation (CPM) is a physiological phenomenon whereby pain evoked at one region of the body (e.g., foot) reduces pain perceived at another body location (e.g., hand) under healthy physiological conditions. CPM involves central nervous system processes at cortical, subcortical and brainstem levels [4]. This phenomenon is widely documented as being disrupted in patients with chronic pain, particularly patients with fibromyalgia, and is a primary indicator of dysregulated descending control of pain. Previously, altered functional connectivity of the midbrain periaqueductal gray (PAG) has been documented in patients with fibromyalgia, and the altered PAG connectivity is correlated with disrupted (lack of) CPM in the patients [5].

Our goal was to expand upon the limited findings of altered brain responses to CPM-like conditions in fibromyalgia using ICA-based network analysis, to clarify how dysregulated pain control mechanisms contribute to fibromyalgia. While typically the CPM response is tested with a conditioning stimulus (e.g., cold water pressor test of the foot) and a test stimulus (e.g., heat or pressure pain administered to the contralateral hand), the central nervous system response evoked by the conditioning stimulus / cold pressor test would be expected to be similar with or without the presence of the test stimulus. We therefore used a classic version of the cold pressor test administered to the foot during the middle of a resting state fMRI scan to investigate functional network connectivity changes evoked by the cold pressor test in patients with fibromyalgia as compared with controls. Functional network connectivity is a measure of the statistical dependencies (e.g., cross-correlation) among intrinsic brain networks [6]. We hypothesized that functional connectivity changes occurring after the cold pressor test stimulus would be more pronounced in the patients with fibromyalgia and involve sensorimotor, cognitive / attention, and subcortical networks. We expected that the connectivity changes observed in patients would potentially parallel enhancement of pain facilitatory (and reduced pain inhibitory) systems after the cold pressor test as compared with controls who would be expected to demonstrate network changes paralleling enhanced pain inhibitory systems (and reduced pain facilitation).

II. MATERIALS AND METHODS

A. Participants and Paradigm Description

Study participants were eight right-handed female patients with fibromyalgia (mean age = 40.36 ± 9.91 years), and a comparison group of eleven right-handed female healthy controls (mean age = 43.13 ± 13.70 years). Patients with fibromyalgia met the American College of Rheumatology criteria for fibromyalgia [7], experienced average pain intensity greater than 2 on a 0–10 scale (0 = no pain; 10 = the worst pain), and had suffered persistent pain for more than 6 months. The study was approved by Stanford School of Medicine IRB and written consent forms were collected.

The paradigm is described in more detail previously [8]. Briefly, participants were instructed to rest with their eyes closed in the scanner during the 12-minute scan. Before the scan, a plastic container was filled with cold water. The water temperature was determined for each participant during the quantitative sensory testing visit prior to the scan with target Visual Analogue Scale (VAS) pain rating of 3. Midway through the resting state scan, a staff

member lifted the participant's bent right leg and placed it into the cold water container. At the end of the one-minute cold pressor test, the staff member lifted the foot out of the water.

B. Image Acquisition and Analysis

Scans were acquired at the Stanford Lucas Center on a 3T GE Discovery MR750 MRI scanner (GE Medical Systems, WI) with a standard 8-channel head coil. Functional scans were acquired using gradient echo spiral in/out pulse sequence with the following parameters [TR/TE = 2000/30 ms, FoV = 26.0 cm, acquisition matrix = 64×64 , flip angle = 76° , slice thickness = 4 mm, gap = 0.5 mm, 31 slices, and ascending acquisition]. Collected resting state data from each participant were split into two data sets (each containing 155 volumes; 310 time points): (i) resting state data before the cold pressor test, and (iii) resting state data after the cold pressor test. Both data sets were preprocessed using SPM12. Data were motion and slice-time corrected, spatially normalized into standard MNI space, spatially smoothed with a 6-mm FWHM Gaussian kernel, and intensity normalized to improve ICA accuracy. Group ICA was performed on preprocessed fMRI data using Group ICA of fMRI Toolbox (GIFT) software (Medical Image Analysis Lab, University of New Mexico; version 4.0b) [9]. Minimum description length (MDL) criterion was used to estimate the optimal dimensionality of the data. ICA Infomax algorithm was repeated 100 times in ICASSO followed by GICA3 back reconstruction method to extract subject-specific spatial maps and their corresponding time courses [10].

The FNC toolbox (Medical Image Analysis Lab, University of New Mexico) was used for the functional network connectivity analysis. A constrained maximal time-lagged correlation method was used to compute Pearson's correlation values following the method explained in [6]. The maximal lag was set to 4 seconds ($2 \times TR$, $TR = 2$ seconds). The pairwise correlation values were normalized with Fisher r -to- z transformation [11]. A two-sample t -test was performed to examine the differences in the functional network connectivity between the two groups. A paired t -test was also used to compare before and after cold water pressor resting state data for each group. An uncorrected p -value of 0.05 and Bonferroni-corrected p -threshold of 0.05 were used to define statistical significance.

III. RESULTS

We performed group ICA with 52-IC decomposition (as determined by MDL criterion), and identified ten relevant networks for functional network connectivity analysis (Fig. 1). Mean maximal time-lagged Pearson's correlation differences between the two groups for the resting state before, and after the cold pressor test are displayed in Figures 2A, and 2B, respectively. Fig. 3 shows the results of the paired t -test for resting state data before and after cold pressor test in fibromyalgia patients (Fig. 3A) and controls (Fig. 3B). Corresponding correlation matrices for all conditions are illustrated in Fig. 4. Significant functional network connectivity differences for all conditions are summarized in Table 1.

IV. DISCUSSION AND CONCLUSION

In this study, we used ICA-based network analysis to identify differences in functional network connectivity among intrinsic connectivity brain networks in the resting state data

before and after cold pressor test in patients with fibromyalgia and controls. We examined temporal dependencies between networks by computing maximal lagged temporal correlation between the network time courses. Statistical analysis showed several networks pairs differed significantly between the two groups in terms of functional network connectivity.

During the resting state before the application of the cold pressor test, we observed functional network connectivity differences in two network pairs when we compared the two groups: (i) IC 26 (ventral somatosensory network) and IC 44 (sensorimotor network comprised of bilateral supramarginal areas), and (ii) IC 38 (dorsal somatosensory network) and IC 43 (subcortical / brainstem network encompassing the bilateral parahippocampal gyri, amygdala / hippocampus, midbrain, and pons). Thus, at the baseline resting state patients with fibromyalgia displayed functional connectivity alterations between the sensorimotor networks, and between the sensorimotor and subcortical / brainstem areas when compared with healthy controls.

Comparison of the functional network connectivity between the two groups for the resting state after the cold pressor test revealed functional connectivity alterations in the following network pairs: (i) IC 30 (central executive network) and IC 44 (sensorimotor network), (ii) IC 30 (central executive network) and IC 49 (more anterior dorsal attention network), (iii) IC 43 (subcortical / brainstem network) and IC 34 (a more posterior dorsal attention network), (iv) IC 38 (dorsal somatosensory network) and IC 26 (ventral somatosensory network), (v) IC 26 (ventral somatosensory network) and IC 44 (sensorimotor network comprised of supramarginal areas). Notably, changes in connectivity associated with the cold pressor test included the networks that integrate cognitive control and attention systems with memory, emotion, and brainstem regions [12]–[14].

The results of the paired *t*-test before and after cold water pressor test further revealed two major differences between the two groups. First, in controls the functional connectivity of IC 30 (central executive network) was significantly altered in relation with IC 44 (sensorimotor network), and IC 43 (subcortical / brainstem network). Interestingly, central executive network association was absent in patients with fibromyalgia. Instead, patients showed significant changes in functional connectivity between dorsal and ventral sensorimotor networks. Second, fibromyalgia patients showed significant connectivity changes between IC 43 (subcortical / brainstem network) and IC 34 (more posterior dorsal attention network) while controls displayed significant connectivity change between IC 43 (subcortical / brainstem network) and IC 49 (more anterior dorsal attention network).

Central executive network, also known as the frontoparietal control system, includes the bilateral dorsolateral prefrontal cortices as well as posterior parietal cortices [15]. It subserves processes related to decision making, working memory, and various cognitive functions [16], [17]. The dorsal attention network, on the other hand, includes intraparietal sulcus and the frontal eye fields [18]. It supports the external focus of attention during goal-directed, cognitively demanding tasks [19]. The alteration in functional connectivity involving the above-mentioned attention and cognitive networks in relation to the sensorimotor networks, and the subcortical / brainstem network with memory

(parahippocampal gyri), emotion (amygdala), and brainstem regions may indicate a disturbance in the pain inhibitory mechanism observed in fibromyalgia. Although we did not explicitly examine connectivity strength in relation to CPM responses from the sensory testing visit of the patients, it is reasonable to speculate that the involvement of IC 43 (subcortical / brainstem network) in functional network connectivity with sensorimotor and dorsal attention networks and lack of IC 30 (central executive network) involvement in patients may underpin aberrant CPM in fibromyalgia patients.

Some limitations of the present study must be noted. First, because each group had a relatively small sample size, the results are vulnerable to type I errors. Additionally, some of the group differences may be chance findings due to the lack of full correction for multiple comparisons. Future research replicating the present findings with larger sample size can shed more light on the nature of dysregulation of the descending control of pain in fibromyalgia.

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Fig. 1.
Spatial maps of selected intrinsic connectivity brain networks in neurological convention (right = right).

Fig. 2.

Functional network connectivity results. **A** Resting state data before the cold pressor test: (i) Functional network connectivity and time lags of fibromyalgia patients, (ii) Functional network connectivity and time lags of healthy controls, (iii) significant differences in functional network connectivity of fibromyalgia patients – healthy controls. **B** Resting state data after the cold pressor test: (i) Functional network connectivity and time lags of fibromyalgia patients, (ii) Functional network connectivity and time lags of healthy controls, (iii) significant differences in functional network connectivity of fibromyalgia patients – healthy controls. ($p < 0.05$). Direction of the arrows indicates the time lag between the pairs. Color bar shows lag in seconds.

Fig. 3. Resting state functional network connectivity results of paired *t*-tests comparing resting state connectivity before and after cold pressor test for **A** Fibromyalgia patients **B** Healthy controls ($p < 0.05$). Direction of the arrows indicates the time lag between the pairs. Color bar shows lag in seconds.

Fig. 4.

Correlation matrices for resting state functional network connectivity results. **A** Fibromyalgia patients – healthy controls before the cold pressor test. **B** Fibromyalgia patients – healthy controls after the cold pressor test. **C** Fibromyalgia patients before and after cold pressor test. **D** Healthy controls before and after cold pressor test. The lower half of matrix lists the mean correlation difference between network pairs. The upper half lists the t -values. (*) denotes uncorrected- $p < 0.05$, (**) denotes Bonferroni-corrected $p < 0.05$.

TABLE 1**RESTING STATE FUNCTIONAL NETWORK CONNECTIVITY RESULTS**

Condition	IC pairs	z	t-value	p-value
FM - HC (BEFORE)	IC 26 – IC 44	0.16	-2.73	0.014 [*]
	IC 38 – IC 43	-0.24	3.07	0.007 [*]
FM - HC (AFTER)	IC 26 – IC 38	0.17	-2.45	0.025 [*]
	IC 26 – IC 44	0.20	-3.15	0.006 [*]
	IC 30 – IC 44	0.14	-3.22	0.005 ^{**}
	IC 30 – IC 49	0.13	-2.37	0.030 [*]
	IC 34 – IC 43	-0.16	4.10	0.001 ^{**}
FM (BEFORE - AFTER)	IC 26 – IC 38	-0.14	-2.97	0.021 [*]
	IC 26 – IC 43	0.16	2.83	0.025 [*]
	IC 34 – IC 43	0.18	4.80	0.002 ^{**}
	IC 38 – IC 43	-0.16	-2.55	0.038 [*]
HC (BEFORE - AFTER)	IC 14 – IC 24	0.13	4.51	0.001 ^{**}
	IC 30 – IC 43	-0.09	-2.36	0.040 [*]
	IC 30 – IC 44	0.13	2.87	0.017 [*]
	IC 43 – IC 49	-0.09	-2.49	0.032 [*]

FM = patients with fibromyalgia, HC = healthy control, z = Pearson's correlation.

(^{*}) indicates significant at uncorrected $p < .05$ level.

(^{**}) indicates significant at Bonferroni-corrected $p < .05$ level.