Published in final edited form as:
Brain Imaging Behav. 2019 April ; 13(2): 482–492. doi:10.1007/s11682-018-9875-3.

Altered resting state functional connectivity of the cognitive control network in fibromyalgia and the modulation effect of intervention

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Abstract

This study examines altered resting state functional connectivity (rsFC) of the cognitive control network (CCN) in fibromyalgia patients as compared to healthy controls, as well as how effective interventions, such as Tai Chi, can modulate the altered rsFC of the CCN. Patients with fibromyalgia and matched healthy subjects were recruited in this study. Fibromyalgia patients were scanned 12 weeks before and after intervention. The bilateral dorsolateral prefrontal cortex (DLPFC) was used as a seed to explore the rsFC of the CCN. Data analysis was conducted with 21 patients and 20 healthy subjects. Compared to healthy subjects, fibromyalgia patients exhibited increased rsFC between the DLPFC and the bilateral rostral anterior cingulate cortex (rACC) and medial prefrontal cortex (MPFC) at baseline. The rsFC between the CCN and rACC/MPFC further increased after Tai Chi intervention, and this increase was accompanied by clinical improvements. This rsFC change was also significantly associated with corresponding changes in the Overall Impact domain of the Revised Fibromyalgia Impact Questionnaire (FIQR). Further analysis showed that the rACC/MPFC rsFC with both the PAG and hippocampus significantly decreased following Tai Chi intervention. Our study suggests that fibromyalgia is associated with altered CCN rsFC and that effective treatment may elicit clinical improvements by further increasing this altered rsFC. Elucidating this mechanism of enhancing the allostasis process may deepen our understanding of the mechanisms underlying mind-body intervention non-pharmacological treatment of fibromyalgia and facilitate the development of new pain management methods.

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Conflict of interest

Jian Kong holds equity of a start-up Inc (MNT). All authors declare that they have no competing financial interests.

Keywords

Resting state functional connectivity; fibromyalgia; cognitive control network; dorsal lateral prefrontal cortex; Tai Chi; anterior cingulate cortex; mind-body intervention

Introduction

Fibromyalgia (FM) is a multidimensional complex disorder characterized by chronic widespread musculoskeletal pain, and physical and psychological limitations (Sumpton & Moulin, 2014). The neuropathology of fibromyalgia remains unclear, but previous studies have suggested that the central nervous system may play an important role in the development and maintenance of fibromyalgia (Jensen, Loitoile, et al., 2012; K. B. Jensen et al., 2013; Tracey & Bushnell, 2009).

Recently, functional magnetic resonance imaging (fMRI) has been used to investigate the pathophysiology (K. Jensen et al., 2013; Jensen, Loitoile, et al., 2012; Loggia et al., 2014; Truini et al., 2016) and treatment of fibromyalgia (Cummiford et al., 2016; Flodin et al., 2015). These studies suggest that patients with fibromyalgia exhibit significant changes in brain function and structure, further endorsing the role of brain in the neuropathology of fibromyalgia. For instance, studies show that fibromyalgia patients exhibit reductions in cortical thickness, brain volume (K. B. Jensen et al., 2013; Kuchinad et al., 2007; Lutz et al., 2008; Robinson, Craggs, Price, Perlstein, & Staud, 2011), and measures of functional connectivity (K. B. Jensen et al., 2013) in the rostral anterior cingulate cortex (rACC) and medial prefrontal cortex (MPFC) compared to healthy controls, demonstrating the important role of rACC/MPFC in the development of FM.

Although these studies significantly enhance our understanding of fibromyalgia, the physiological implications of these brain functional and morphometry changes remain unclear. One possible explanation is that some of these changes may reflect an adaptation process of the brain to fibromyalgia, specifically through allostasis, the process of achieving homeostasis through physiological or behavioral changes. Based on the theory of allostasis, the human body, including the brain, adapts to the altered conditions caused by a disorder, such as persistent pain (Borsook, Maleki, Becerra, & McEwen, 2012). This can be carried out by means of alteration in the hypothalamus – pituitary – adrenal (HPA) axis hormones, the autonomic nervous system, as well as through brain functional and structure changes (McEwen & Wingfield 2003). For example, to adapt and cope with consistent pain, fibromyalgia patients may employ an involuntary distraction strategy through a cognitive control mechanism. In support of this hypothesis, studies have demonstrated that attention can significantly modulate pain perception (Legrain et al., 2009; Lobanov, Quevedo, Hadsel, Kraft, & Coghill, 2013; Torta, Legrain, Mouraux, & Valentini, 2017); that is, focusing on pain may enhance pain responses, while distraction from pain can significantly reduce one’s pain experience (Valet et al., 2004). Further studies suggest that the descending pain modulation system, including the periaqueductal gray (PAG), cingulate cortex, and dorsal lateral prefrontal cortex, may play an important role in the attention regulation of pain (H. Fields, 2004; H. L. Fields, Basbaum, & Heinricher, 2005; Kong, Tu, Zyloney, & Su, 2010).

Cognitive control refers to the set of brain processes necessary for goal-directed thought and action (Cole & Schneider, 2007), which plays a crucial role in the top-down modulation of attention–memory interactions (Cole & Schneider, 2007; Rosen, Stern, Michalka, Devaney, & Somers, 2015; Sheline, Price, Yan, & Mintun, 2010), decision-making, and conflict resolution (Sheline et al., 2010). A key factor in cognitive control processing is attention, a mechanism by which sensory input is selected to enter into awareness and which can regulate one's pain experience (Bushnell, Ceko, & Low, 2013; Torta et al., 2017; C. Villemure & Bushnell, 2002; C. Villemure & Schweinhardt, 2010; Wiech, 2016; Zeidan et al., 2015; Zeidan, Grant, Brown, McHaffie, & Coghill, 2012). Thus, cognitive control may represent an interesting aspect of allostasis in FM patients.

The brain network most closely related to cognitive executive functioning is the cognitive control network (CCN), which includes the frontal gyrus, parietal gyrus, and anterior cingulate cortex (Petersen & Posner, 2012; Zanto & Gazzaley, 2013). A large body of evidence indicates that the dorsolateral prefrontal cortex (DLPFC) is a key region of the CCN, playing an important role in cognitive control processes (Cieslik et al., 2013; Legrain et al., 2009; Miller & Cohen, 2001; Sheline et al., 2010; Tracey & Mantyh, 2007). Previous studies have also suggested that using the bilateral DLPFC as a seed can be a valuable tool for exploring the function of the CCN using resting state fMRI (Cieslik et al., 2013; J. W. Hwang et al., 2015; Legrain et al., 2009; Miller & Cohen, 2001; Sheline et al., 2010; Tao, Chen, Egorova, et al., 2017; Tracey & Mantyh, 2007).

In this study, in addition to investigating the difference in the CCN between fibromyalgia patients and healthy controls, we also attempted to explore how effective treatment (Tai Chi) can modulate the rsFC in fibromyalgia patients. We believe investigating rsFC changes after effective treatment, as well as the association between these rsFC changes and accompanying clinical symptom reduction, will help us understand the significance of brain functional changes observed in FM patients when compared to healthy controls. We chose Tai Chi intervention because pharmacological treatment of FM only achieves limited success with a significant risk of adverse effects that cannot be tolerated by many patients (Goldenberg, Burckhardt, & Crofford, 2004; Lautenschlager, 2000). Previous randomized controlled trials have shown that Tai Chi, a multicomponent intervention that incorporates physical, psychosocial, emotional, spiritual, and behavioral elements, is a potentially useful therapy for patients with fibromyalgia (C. Wang et al., 2010). Meta-analyses indicate that Tai Chi can enhance cognitive function in older adults, particularly in the realm of executive functioning (Wayne et al., 2014). Imaging studies have also shown that Tai Chi can significantly modulate the function and structure of brain regions associated with cognitive control (Tao, Chen, Egorova, et al., 2017; G. X. Wei, Dong, Yang, Luo, & Zuo, 2014; G. X. Wei, Gong, Yang, & Zuo, 2017; G.X. Wei et al., 2013), further endorsing the role of the CCN in Tai Chi intervention.

In this study, we first compared the resting state functional connectivity (rsFC) of the DLFPC between fibromyalgia patients and healthy subjects to characterize the brain pathophysiology of fibromyalgia, and then investigated how the rsFC of the DLPFC are modulated when symptoms are relieved after longitudinal intervention. We hypothesized that fibromyalgia patients would show increased DLPFC – ACC/MPFC rsFC as a distraction/adaptation mechanism. Mind-body interventions may enhance this coping process by increasing DLPFC- ACC/MPFC connectivity, further triggering the descending pain modulation system to relieve clinical symptoms in fibromyalgia patients. This investigation, which combines both healthy controls and an intervention group, allows us to not only illustrate rsFC changes that are sensitive to symptom improvement or treatment, but also highlights the physiological implications of these changes.

Materials and Methods

Participants

From May 2015 to September 2015, we recruited 24 patients with fibromyalgia (≥21 years old) and 24 healthy controls matched for age, gender, and body mass index (BMI) to participate in the study. After describing the details of the study to interested and eligible subjects, written informed consent was obtained in accordance with the procedures established by Tufts Medical Center/Tufts University Human Institutional Review Board and the Medical Ethics Committee of Massachusetts General Hospital. The study rheumatologist (WFH) performed clinical examinations and confirmed that participants met the eligibility criteria. All FM patients participated in 12 weeks of Tai Chi training (NCT02407665).

Inclusion criteria were: (1) age 21 years or older, (2) fulfillment of the American College of Rheumatology (ACR) 1990 classification criteria and the ACR 2010 diagnostic criteria for fibromyalgia, (3) willingness to complete a 12-week, twice-a-week Tai Chi exercise program, (4) willingness to undergo an fMRI scan at baseline and follow-up visits, and (5) fluent in English. Exclusion criteria were: (1) diagnosed with medical conditions that are known to contribute to fibromyalgia symptomatology, such as thyroid disease, inflammatory arthritis, systemic lupus erythematosus, rheumatoid arthritis, myositis, vasculitis, or Sjogren’s syndrome, (2) inability to pass the Physical Activity Readiness Questionnaire (PAR-Q), (3) score of less than 24 on the Mini-Mental State Examination; (4) plans to relocate from the region during the trial period; (5) verbal confirmation of pregnancy or planned pregnancy during the study period, (6) enrollment in any other clinical trial in the last 30 days, (7) presence of any contraindications to fMRI scanning, including but not limited to: cardiac pacemaker, metal implants, fear of enclosed spaces, pregnancy, and weight > 300 lbs., (8) prior experience with Tai Chi training, or similar types of complementary and alternative medicine (e.g. Qi Gong or yoga) in the past year, and (8) serious medical conditions limiting ability to participate in the Tai Chi training, including dementia, neurological disease, cancer, cardiovascular disease, pulmonary disease, metabolic disease, renal disease, liver disease, or other serious medical conditions, as determined by the study physicians.

Healthy controls were recruited and matched to enrolled fibromyalgia participants. Inclusion criteria were (1) age matched within 5 years (must be ≥ 21 years old), (2) gender and race matched, (3) BMI within 5 kg/m^2 (must be < 300 lbs.), and (4) willingness to attend a single evaluation. Exclusion criteria were (1) prior experience with Tai Chi training or similar types of complementary and alternative medicine, (2) chronic or acute pain (e.g. fibromyalgia, osteoarthritis), and (3) presence of any contraindications to fMRI scanning, including but not limited to: cardiac pacemaker, metal implants, fear of closed spaces, pregnancy, and weight > 300 lbs.

Intervention

All participants in the Tai Chi group attended a 60-minute practice session twice a week for 12 weeks at Tufts Medical Center. The instructor (RR), who has extensive experience conducting Tai Chi training programs, followed a standardized Tai Chi protocol developed for patients with fibromyalgia (C. Wang et al., 2010). Participants were also provided with printed materials on fibromyalgia and the Tai Chi mind-body program, including Tai Chi principles, practicing techniques, and safety precautions specifically for participants with fibromyalgia. Every session included the following components: (1) warm-up, (2) Tai Chi movement, (3) breathing techniques, and (4) relaxation. Each component of the program was derived from the classical Yang style Tai Chi 108 posture (1983) condensed for the 12-week intervention program.

All subjects were encouraged to maintain their usual physical activities and to perform no new additional strength training other than their Tai Chi exercises. Subjects were also allowed to continue taking regular medications and maintain routine visits to their physicians throughout the course of the study. Participants were also instructed to practice at least 30 minutes a day at home and to complete daily logs indicating the amount of time that they practiced Tai Chi exercises. Data on class attendance and home practice was recorded and verified using standard case report forms.

Outcome measurements

The primary outcome for the study was the resting state functional connectivity (rsFC) of the bilateral DLPFC (a key region of the cognitive control network). The secondary outcomes were: 1) Revised Fibromyalgia Impact Questionnaire (FIQR) including the three domains, i.e., Function, Overall Impact, and Symptom Severity, and 2) Beck Depression Inventory (BDI-II). All outcome measurements were collected at baseline and after 12 weeks of the intervention for the fibromyalgia cohort and at baseline for the healthy subjects.

MRI data acquisition

fMRI scans were performed at Massachusetts General Hospital at the Martinos Center for Biomedical Imaging. Each fibromyalgia subject participated in an identical fMRI scan before and after 12 weeks of Tai Chi exercise, whereas healthy controls were only scanned at baseline. The fMRI brain imaging acquisition was conducted on a 3.0 Tesla Siemens (Skyra syngo) scanner with a 32-channel head coil. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images were collected (flip angle= 7 degree, voxel size $1.0 \times 1.0 \times 1.0$ mm^3). The BOLD resting state functional images were obtained with echo-planar imaging (TR = 3000 ms, TE = 30 ms, flip angle = 85 degrees, slice thickness=2.6 mm, acquisition matrix = 64×64, voxel size = $2.6 \times 2.6 \times 2.6$ mm^3, 44 axial slices, scan time 8 min 21 sec). All patients were required to keep their eyes open during the resting state fMRI scan.

Statistical analysis

Clinical data analysis—Statistical analysis was performed using SPSS 19.0 Software (SPSS Inc., Chicago, IL, USA). A threshold of $p < 0.05$ (2-tailed) was applied. One-way ANOVA and Chi square tests were conducted to compare baseline characteristics of the participants between groups. There were no significant differences in age and gender between the fibromyalgia and matched healthy control groups.

Seed based functional connectivity analysis—Functional BOLD data were preprocessed using SPM 12 (Statistical Parametric Mapping. Welcome Department of Cognitive Neurology, London, UK; implemented by MATLAB R3012b, Math Works, Inc., Natick, MA, USA). During the preprocessing, images were realigned, segmented, and co-registered to each subject's high-resolution T1 scan, which was used to normalize to the standard Montreal Neurological Institute (MNI) template. Images were also smoothed using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel and filtered with a frequency window of 0.008–0.09 Hz. In addition to these steps, we employed segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas for the removal of temporal confounding factors (white matter and CSF) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Data were then submitted to motion correction using the artifact detection toolbox (http://www.nitrc.org/projects/artifact_detect/). For each subject, we treated images as outliers if the composite movement from a preceding image exceeded 0.5 mm or if the global mean intensity was greater than 3 standard deviations from the mean image intensity for the entire resting scan. Outliers were included as regressors in the first-level general linear model along with other six regular motion parameters (Redcay et al., 2013).

Resting state functional connectivity analysis was conducted using the CONN toolbox v15.g (Whitfield-Gabrieli & Nieto-Castanon, 2012) (http://www.nitrc.org/projects/conn). We used an a priori DLPFC seed (peak coordinate: ± 36, 27, 29, with 5 mm radius), which has been used in previous studies (J. Hwang et al., 2015; Sheline et al., 2010; Tao, Chen, Egorova, et al., 2017). Functional connectivity measures were computed between the seed and every other voxel in the brain. First-level correlation maps were produced by extracting the residual BOLD time course from the DLPFC and by computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were transformed into Fisher's 'Z' scores to increases normality and allow for improved second-level general linear model analyses.

The baseline DLPFC rsFC of fibromyalgia patients and healthy control subjects were compared using a two-sample t-test. The Tai Chi practice effect (post-practice minus pre-practice) on fibromyalgia patients was compared using a paired t-test. Additionally, we also compared the DLPFC rsFC of fibromyalgia patients after practicing Tai Chi to healthy controls using a two-sample t-test. Age, gender, and BDI scores were included as covariates. A threshold of voxel-wise $p < 0.005$ (uncorrected) and cluster-level $p < 0.05$ (family-wise error correction) were applied for data analyses. Given the important role of the periaqueductal grey in pain modulation, we defined the PAG as a region of interest and used small volume correction to correct the p value at a level of $p < 0.05$. Similar to previous studies (Eippert et al., 2009; Kong et al., 2013b), correction was based on peak coordinates (x, y, z: 1, −25, −12) with a 4 mm radius obtained from a previous PAG meta-analysis (Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012).

Results

The study was completed with 21 fibromyalgia patients and 20 healthy controls. One fibromyalgia patient was excluded from the rsFC analysis due to excessive head movement during scanning. Additionally, one healthy control was excluded due to brain atrophy.

The mean age of fibromyalgia subjects was 53.10 ± 11.58 (mean ± SD) and 52.90 ± 11.12 for control subjects (Table 1). There were no significant differences in age, gender, race, and BMI between the fibromyalgia and healthy control groups. FIQR scores demonstrated moderate to severe fibromyalgia in the majority of the fibromyalgia subjects with an average score of 45.1 ± 18.6. BDI-II scores revealed moderate depression with an average score of 19.71 ± 11.12 in the fibromyalgia group, and a two-sample t-test showed significant differences between the fibromyalgia and healthy control groups in BDI-II scores (2.75 ± 3.77) ($p < 0.0001$). Paired t-tests showed significant pre- and post-Tai Chi differences in general FIQR scores (mean ± SD, Pre: 45.1 ± 18.6, post: 35.8 ± 21.4, $p = 0.003$), as well as in the three FIQR domains: Function (pre: 12.1 ± 6.3, post: 8.5 ± 6.4, $p = 0.001$), Overall Impact (pre: 8.8 ± 6.4, post: 7.0 ± 5.7 $p= 0.05$), and Symptoms (pre: 25.1 ± 8.4, post: 20.8 ± 12, $p = 0.017$). Analysis of BDI-II scores showed a significant difference between pre- and post-treatment scores in the fibromyalgia patients (pre: 19.71 ±11.12, post: 9.95 ± 8.55, $p = 0.0027$).

Functional connectivity results

rsFC analysis indicated that fibromyalgia patients showed significantly greater rsFC between the DLPFC and both the bilateral rostral anterior cingulate cortex (rACC) and medial prefrontal cortex (MPFC) compared to healthy controls at baseline. There were no significant DLPFC rsFC decreases in fibromyalgia patients compared to healthy subjects at baseline. The comparison between healthy controls and fibromyalgia patients after intervention showed significant CCN rsFC increases at the bilateral rACC MPFC and temporal pole, and rsFC decreases at the left superior parietal lobule and postcentral gyrus in fibromyalgia patients (Table 2).

A direct comparison between the DLPFC before and after intervention in FM patients indicate a significant rsFC increase with the bilateral rACC/MPFC, frontal gyrus, precuneus, occipital gyrus, cerebellum; left temporal lobe, angular/supramarginal gyrus; and right operculum and precentral gyrus, and a significant rsFC decrease at the brain stem after Tai Chi.

To explore the association between the CCN rsFC changes after intervention and the corresponding Overall Impact domain score changes (a domain reflecting the cognitive aspect of the FIQR), we extracted the Fisher z value of the rACC/MPFC cluster and applied a regression analysis, including age, gender, and BDI-II score as covariates. We found a significant positive association between CCN and rACC/MPFC rsFC changes and corresponding Overall Impact domain score changes ($p = 0.01$) (Figure 1).

Given the importance of the rACC/MPFC in pain modulation and pathophysiology of chronic pain (H. Fields, 2004; Li et al., 2016; Yu et al., 2014), we extracted the overlapping areas of the rACC/MPFC (contrasts of fibromyalgia post intervention > healthy and fibromyalgia post intervention > fibromyalgia pre-intervention) as an ROI. We defined the ROI using the overlapping area so that we could target the area reflecting both the neuropathology of fibromyalgia and the area that would be modulated by Tai Chi intervention. We then compared the rsFC of the rACC/MPFC before and after Tai Chi using the same method as the ROI of the DLPFC and found that after Tai Chi practice, FM patients showed significant rsFC decreases between the rACC/MPFC and the left hippocampus, parahippocampus, fusiform, cerebellum, right PAG, and caudate, and bilateral inferior temporal gyrus (Table 3, Figure 2). There were also significant rsFC increases between the rACC/MPFC and bilateral MPFC, precuneus, middle frontal gyrus, middle cingulate cortex, supplementary motor cortex, operculum; left middle frontal gyrus, postcentral gyrus/supramarginal gyrus; and right precentral gyrus (Table 3).

Discussion

In this study, we found that compared to matched healthy controls, the CCN of fibromyalgia patients showed increased rsFC with the bilateral rACC/MPFC prior to Tai Chi practice. After intervention, fibromyalgia patients demonstrated further increased rsFC between the CCN and the bilateral rACC and MPFC, which was significantly associated with a decrease in Overall Impact domain scores on the FIQR. Further rsFC analyses using the rACC/MPFC as a seed found that, after Tai Chi, the rsFC between the rACC/MPFC and both the PAG and hippocampus was significantly decreased.

Our findings are consistent with a previous study demonstrating the effects of Tai Chi (C. Wang et al., 2010) and exercise (Flodin et al., 2015) in fibromyalgia patients. In addition, our results are consistent with previous brain imaging studies, which demonstrated a significant modulation effect of Tai Chi on brain function and structure in healthy human subjects (Fong, Chi, Li, & Chang, 2014; Tao, Chen, Liu, et al., 2017; Tao, Chen, Egorova, et al., 2017; Tao et al., 2016; Tao, Liu, et al., 2017; G. X. Wei et al., 2014; G. X. Wei et al., 2017; G.X. Wei et al., 2013) and of exercise on brain responses to heat pain (Ellingson, Stegner, Schwabacher, Koltyn, & Cook, 2016). Our results are also similar with other studies that explore resting state functional connectivity of pain-related brain regions (Flodin et al., 2015) in patients with fibromyalgia.

The DLPFC is a brain region in the dorsal pathway (stream) that is associated with reactions to various stimuli, including pain. Lorenz and colleagues (Lorenz, Minoshima, & Casey, 2003) suggest that the DLPFC exerts active control on pain perception by modulating cortico-subcortical and cortico-cortical pathways. Napadow et al. (Napadow et al., 2010) found a negative association between the right frontoparietal network and both the PAG and hippocampus (greater right frontoparietal network connectivity in relation to lower pain levels) in fibromyalgia patients with greater spontaneous pain. In one of our previous studies, we found significant fMRI signal increases in the bilateral DLPFC and MPFC/ACC during both anticipation and the application of pain within a placebo analgesia conditioning paradigm (Kong et al., 2013a). We also found that the baseline rsFC between the right frontoparietal network and the rACC could significantly predict placebo analgesia.

Both DLPFC and ACC/MPFC play an important role in executive control processing (Petersen & Posner, 2012) and non-pharmacological therapeutic modalities such as mind-body intervention (Tang, Holzel, & Posner, 2015) and acupuncture (Chen et al., 2015; Chen, Spaeth, Retzepi, Ott, & Kong, 2014; X. Wang et al., 2016; Z. Wang et al., 2017), as well as placebo effects (Gollub et al., 2018; Kong et al., 2006; Petrovic, Kalso, Petersson, & Ingvar, 2002; Wager et al., 2004; Zubieta et al., 2005). Studies also suggest that the rACC/MPFC is a key region in the descending pain modulatory system (Eippert & Tracey, 2014; H. Fields, 2004; Kong et al., 2013a; Kucyi, Salomons, & Davis, 2013; Tracey et al., 2002; Yu et al., 2014), forming a core network with the PAG and rostral ventral medulla (RVM) for pain modulation (Kong et al., 2010). Patients with fibromyalgia have been shown to exhibit reduced connectivity during repeated pressure pain stimuli between the rACC and the amygdala, hippocampus, and brainstem (PAG) compared to healthy controls (Jensen, Loitoile, et al., 2012). Thus, we postulate that enhanced rsFC between the DLPFC and the rACC/MPFC in fibromyalgia patients at baseline may indicate that the brain employs a self-regulation mechanism to cope with repeated pain experiences.

Consistent with the aforementioned studies and our hypothesis, we found that after 12 weeks of Tai Chi intervention, the rsFC between the CCN and the rACC/MPFC rsFC was further enhanced, and this increase was associated with decreases in the Overall Impact domain score of the FIQR, suggesting that Tai Chi practice can further amplify this self-regulation process (Tang et al., 2015). Our finding is consistent with a previous study (Jensen, Kosek, et al., 2012) investigating the effects of cognitive behavioral therapy on fibromyalgia patients. Investigators found that rather than reducing pain responses in patients with fibromyalgia, cognitive behavioral therapy increased access to executive regions for the reappraisal of pain. These results are further supported by another brain imaging study (Li et al., 2017) on the effect of acupuncture treatment in patients with migraines, in which the investigators discovered decreased rsFC between the right frontoparietal network and bilateral precuneus in migraine patients when compared to healthy controls. After acupuncture treatment, the rsFC between the frontoparietal network and precuneus was further reduced, and this reduction was associated with headache intensity relief.

Taken together, we believe our results suggest the existence of allostasis in patients with fibromyalgia. Based on the allostasis theory proposed by McEwen and colleagues (McEwen & Stellar, 1993), physiological systems within the body fluctuate to meet demands from external forces to maintain homeostasis. In this context, allostasis represents the ability to protect the body through the altered activity of mediators that normally promote adaptation (Borsook et al., 2012). Most importantly, it seems that different treatment modalities, such as behavioral therapy, mind-body interventions, and acupuncture, can further enhance allostasis to promote self-regulation and adaptation, and this may represent a common mechanism underlying non-pharmacological treatments. Elucidating this mechanism might shed light on the development of new pain management methods.

To further explore the role of the rACC/MPFC in the development of FM and the associated clinical improvements, we compared the rsFC changes of the rACC/MPFC before and after intervention. We found that after 12 weeks of Tai Chi practice, the rsFC between the rACC/MPFC and both the hippocampus and PAG were significantly reduced. Recently, investigators have conceptualized chronic pain as a type of long-term learning (Apkarian, Hashmi, & Baliki, 2011), characterized by an accumulation of nociceptive memory (Yi & Zhang, 2011) and inability to extinguish negative emotional associations and anxiety (Mutso et al., 2014; Ploghaus et al., 2001; Vachon-Presseau et al., 2013; Vachon-Presseau et al., 2016). A recently proposed model of aversive prediction error in pain learning has suggested that the PAG is the primary hub in the pain learning neural network (Roy et al., 2014), relying on the rACC/MPFC and the hippocampus. We (Kong et al., 2018) found that the rsFC of the nucleus accumbens (NAc) showed significant increase with both rACC/MPFC and dorsolateral prefrontal cortex in the boosted acupuncture group using an expectancy manipulation (Kong et al., 2006) as compared to standard acupuncture group without such a manipulation. In another study, we found that acupuncture significantly increased the rsFC between the hippocampus and PAG (Egorova, Gollub, & Kong, 2015) and improved pain intensity in knee osteoarthritis patients, providing further support for the role of the hippocampus in pain modulation.

We also found that after the intervention, fibromyalgia patients showed increased rsFC between the rACC/MPFC and the middle/inferior prefrontal gyrus, middle cingulate, and postcentral gyrus/operculum. It is well known that these regions are involved in the cognitive, affective, and sensory aspects of pain, respectively (Tracey & Mantyh, 2007). The increased rsFC between the rACC/MPFC and these regions may reflect the enhanced modulation effects and therapeutic benefits of Tai Chi.

Although our results may provide some novel insights into the mechanisms underlying the effectiveness of Tai Chi, the lack of a control condition has significantly limited our ability to identify the precise mechanism behind Tai Chi’s therapeutic effects. We would like to emphasize here that the aim of this study was to investigate the rsFC alterations of the CCN in FM patients and how these rsFC changes following effective treatment were associated with symptom relief. These findings have the potential to shed light on our understanding of the pathophysiology and development of FM. We acknowledge that pharmacological medication (all participants were allowed to keep their regular medication during experiment) and other unknown factors may have also contributed to the clinical improvements observed. Nevertheless, this paradigm has been used in previous studies (Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009). Additional controls should be applied in future studies to elucidate the specific effect of Tai Chi.

In summary, we found that fibromyalgia patients showed increased resting state functional connectivity between the cognitive control network and the rACC/MPFC, which may reflect an adaptive brain response to fibromyalgia. Effective interventions such as Tai Chi can further enhance the cognitive control network and rACC/MPFC rsFC and relieve the clinical symptoms in fibromyalgia patients. Finally, we found the rACC/MPFC rsFC with both the PAG and hippocampus were significantly reduced after the intervention. Our findings suggest the existence of allostasis in patients with fibromyalgia. A novel effective pain management intervention such as Tai Chi may further enhance allostasis to promote self-regulation and adaptation mechanisms and ultimately, provide significant therapeutic benefit to FM patients.

Acknowledgments

This study was supported by the National Center for Complementary and Integrative Health of the National Institutes of Health (R01 AT005521, R01 AT006367 and K24 AT007323, R01AT006364, R01 AT008563, R21AT008707, R61 AT009310, and P01 AT006663 from NIH/NCCIH), the National Center for Research Resources, National Institutes of Health (UL1 RR025752) and the National Center for Advancing Translational Sciences, National Institutes of Health (UL1TR000073 and UL1TR001064).

Dr. Chenchen Wang is supported by R01 AT005521, R01AT006367 and K24AT007323, the National Center for Research Resources, National Institutes of Health (UL1 RR025752) and the National Center for Advancing Translational Sciences, National Institutes of Health (UL1TR000073 and UL1TR001064). Dr. Jian Kong is supported by R01AT006364, R01AT008563, R61 AT009310, R21AT008707, and P01 AT006663 from NIH/NCCIH. We also thank Courtney Lang for her help in manuscript revision and proof reading.

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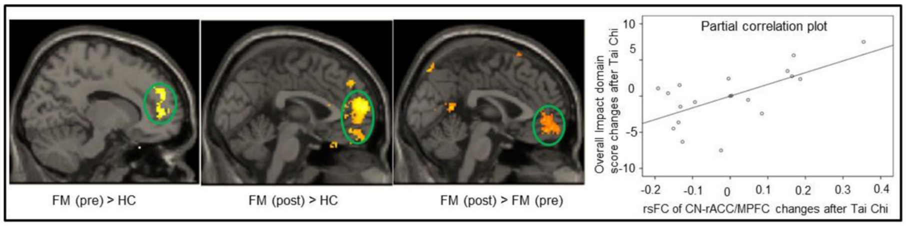

Figure 1.

Comparison of dorsal lateral prefrontal cortex (DLPFC) connectivity maps in fibromyalgia patients and healthy controls. The partial correlation scatter indicates a regression analysis between the Overall Impact domain score and DLPFC-rACC/MPFC rsFC changes.

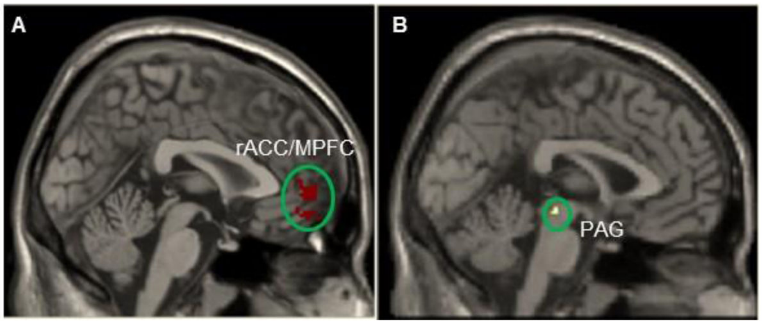

Figure 2.

A representative result of resting state functional connectivity using the rostral anterior cingulate cortex (rACC)/medial prefrontal cortex (MPFC) as a seed (ROI). A: seed region used in rsFC analysis. B: periaqueduct grey (PAG) showed significant rsFC decreases with rACC/MPFC after Tai Chi exercise.

Table 1

Baseline Characteristics and Health Outcome Variables of Study Participants, all values are mean (SD) unless otherwise noted.

Variable	Tai Chi (n=21)	Healthy Controls (n=20)
Female, no. (%)	20 (95.24)	19 (95.00)
Age, yr.	53.10 (11.58)	52.9 (11.12)
Race, no. (%)		
White	13 (61.90)	12 (60.00)
Black	6 (28.57)	6 (30.00)
Asian	2 (9.52)	2 (10.00)
Body Mass Index, kg/m^2	29.37 (6.96)	27.28 (3.58)
Beck Depression Inventory-II	19.71 (11.12)	2.75 (3.77)

Table 2

Regions with significantly different connectivity between the DLPFC and other brain regions in fibromyalgia patients (FM) and healthy controls before and after treatment.

			Cluster centroid (MNI)			
Conditions	**Brain Regions**	**mm^3**	**x**	**y**	**z**	**Z**
FM (pre) > HC	Bilateral rACC/MPFC	540	18	48	6	3.91
HC > FM (pre)	NA					
FM (post) > FM (pre)	Bilateral rACC/MPFC	312	−10	58	−4	3.89
	Bilateral middle frontal gyrus/superior frontal gyrus	1380	−16	28	38	5.61
	Left middle frontal gyrus	768	−36	26	28	4.68
	Left middle frontal/medial frontal gyrus	255	−20	42	18	4.59
	Right operculum	246	46	24	−2	4.22
	Left angular/supramarginal gyrus	235	−54	−58	22	4.27
	Right precentral gyrus	211	46	−8	40	4.71
	Left temporal lobe	202	−50	12	−30	3.96
	Bilateral middle occipital gyrus	1561	34	−72	22	5.57
	Bilateral precuneus	804	28	−72	−4	5.18
	Right cerebellum	378	40	−48	−40	4.92
	Left cerebellum	308	−22	−60	−54	4.73
	Left cerebellum/fusiform gyrus	209	−44	−46	−28	4.63
FM (pre) > FM (post)	Brainstem	253	8	−24	−56	4.52
FM(post) > HC	Bilateral rACC/MPFC	2650	18	42	26	4.76
	Left temporal pole	251	−52	16	−14	3.96
	Right temporal pole	190	42	24	−22	4.05
HC>FM(post)	Left superior parietal lobule/postcenral gyrus	449	−42	−44	56	4.22

Note: FM(pre)=Fibromyalgia pre-Tai Chi intervention, FM(post)=Fibromyalgia post-Tai Chi intervention, HC=Healthy control, DLPFC=dorsolateral prefrontal cortex, rACC=rostral anterior cingulate cortex, MPFC= medial prefrontal cortex.

Table 3

Regions with significantly different connectivity between the rACC/MPFC and other brain regions in FM and healthy controls before and after treatment.

			Cluster centroid (MNI)			
Conditions	**Brain Regions**	**mm^3**	**x**	**y**	**z**	**Z**
FM (post) > FM (pre)	Right middle frontal gyrus/precentral gyrus	811	42	12	38	6.10
	Left postcentral gyrus/supramarginal gyrus/operculum	1113	−44	−24	40	5.54
	Right middle frontal gyrus	227	40	54	2	4.39
	Bilateral middle cingulate cortex/MPFC/supplementary motor cortex	361	−4	26	36	4.07
	Left middle frontal gyrus	230	−36	40	46	4.41
	Left middle frontal gyrus	804	−38	48	8	5.65
	Bilateral precuneus	1238	−6	−68	46	5.03
	Right operculum	239	66	−16	16	3.76
FM (pre) > FM (post)	Left inferior temporal gyrus/fusiform gyrus/hippocampus/parahippocampus	212	−48	−18	−44	4.40
	Right PAG (small volume correction)	6	2	−22	−8	2.88
	Right caudate	264	22	−4	36	5.58
	Right inferior temporal gyrus	498	52	−24	− 38	5.02
	Left cerebellum gyrus	419	−20	−62	− 24	5.28

Note: FM (pre) = Fibromyalgia pre-Tai Chi intervention, FM (post)= Fibromyalgia post-Tai Chi intervention, HC=Healthy control, DLPFC= dorsolateral prefrontal cortex, rACC= rostral anterior cingulate cortex, MPFC= medial prefrontal cortex.