

# Altered hypothalamus functional connectivity with limbic system in fibromyalgia and the modulation effect of intervention

Jian Kong (✉ [JKONG2@mgh.harvard.edu](mailto:JKONG2@mgh.harvard.edu))

Yiting Huang

Massachusetts General Hospital <https://orcid.org/0000-0002-7231-6341>

Jiao Liu

Massachusetts General Hospital

Siyi Yu

Massachusetts General Hospital

Ming Cheng

Massachusetts General Hospital

Helen Chen

Massachusetts General Hospital

Georgia Wilson

Massachusetts General Hospital

William Harvey

Tufts University School of Medicine

Wen Li

Florida State University Department of Psychology

Chenchen Wang

Tufts University School of Medicine

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## Research article

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# Abstract

**Background:** This study aims to investigate the resting state functional connectivity (rsFC) changes of the hypothalamus in Fibromyalgia patients and the modulation effect of effective treatments.

**Methods:** Fibromyalgia patients and matched healthy controls (HC's) were recruited. Resting state fMRI data were collected from fibromyalgia patients before and after a 12-week Tai Chi intervention and once from HC's.

**Results:** Data analysis showed that fibromyalgia patients displayed significantly decreased medial hypothalamus (MH) rsFC with the thalamus and amygdala when compared to HC's at baseline. After the intervention, fibromyalgia patients showed increased (normalized) MH rsFC in the thalamus and amygdala. Effective connectivity analysis showed disrupted MH and thalamus interaction in fibromyalgia, which nonetheless could be partially restored by Tai Chi.

**Conclusions:** Elucidating the role of the diencephalon and limbic system in the pathophysiology and development of fibromyalgia may facilitate the development of new treatment methods for this prevalent disorder.

**Trial registration:** Trial registration ClinicalTrials.gov Identifier: NCT02407665. Registered 3 April 2015 - Retrospectively registered, <https://clinicaltrials.gov/ct2/show/NCT02407665>

## Introduction

Fibromyalgia is a complex disorder characterized by chronic and widespread musculoskeletal pain, fatigue, sleep disturbance, psychological distress, functional impairment, and exercise intolerance<sup>[1]</sup>. Although still under investigation, accumulating evidence has suggested that the central nervous system plays a pivotal role in the pathophysiology of fibromyalgia<sup>[2-5]</sup>. As a result, brain imaging tools have been utilized extensively to investigate the pathophysiology<sup>[3, 4, 6-14]</sup> and treatment of fibromyalgia<sup>[5, 15-17]</sup>.

Resting state functional connectivity (rsFC) is a widely used brain imaging tool in pain research. Investigators have found that brain oscillations and synchrony, which can be measured by rsFC, can provide information about the intrinsic functional organization of the brain<sup>[18, 19]</sup> and may play a crucial role in the information flow of pain processing and modulation<sup>[20-22]</sup>.

The first aim of this study is to investigate alterations in hypothalamus rsFC between fibromyalgia patients and healthy controls. We focused on the hypothalamus because it is a functionally diverse region of the brain that regulates vital bodily functions such as stress, immune responses, and autonomic and endocrine functions<sup>[23, 24]</sup>. Literature suggests that hypothalamic subregions are functionally connected to their associated neural networks (limbic system) for the integration of sensory and affective information. As the initial point of hypothalamic-pituitary-adrenal axis activation, the hypothalamus has

been found to exert regulatory effects on the inflammatory response<sup>[23, 25]</sup>, which may play an important role in the pathophysiology of fibromyalgia<sup>[26]</sup>. Brain imaging studies suggest that it may also be involved in chronic pain. For example, studies have found activation within the hypothalamic region during spontaneous bouts of chronic pain<sup>[27]</sup>.

The second aim of this study is to investigate how non-pharmacological treatment (Tai Chi) can modulate altered hypothalamus rsFC changes in patients with fibromyalgia. We chose to investigate Tai Chi, as our previous study demonstrated that Tai Chi can significantly improve clinical outcomes in patients with fibromyalgia<sup>[28, 29]</sup>.

We believe that the combination of two studies (aims) will help us to deepen our understanding of the central mechanism of fibromyalgia. For instance, one area that remains unclear is if the brain regions that showed differences between fibromyalgia patients and healthy control subjects (HC's) are also sensitive to symptom reduction after treatments. Theoretically, brain regions that show structural/functional differences in fibromyalgia patients compared to HC's may be used as potential biomarkers for distinguishing fibromyalgia patients from HC's. Additionally, brain regions that are sensitive to pain intensity changes may have potential for fibromyalgia severity monitoring and may act as an objective measurement for treatment response<sup>[30]</sup>.

In this manuscript, we first investigated alterations of hypothalamus (medial and lateral separately) rsFC in fibromyalgia patients (compared to HC's). Then, we studied hypothalamus rsFC changes after non-pharmacological treatment (Tai Chi). We hypothesized that 1) fibromyalgia patients will be associated with altered hypothalamus rsFC with limbic system, and 2) some altered hypothalamus functional connectivity changes as detected above will normalize after intervention in patients with fibromyalgia.

## Materials And Methods

This study was registered on ClinicalTrials.gov. The full details of the study are reported in a previous study, in which we investigated dorsal lateral prefrontal cortex (DLPFC) rsFC differences between fibromyalgia and healthy control patients and the modulation effect of Tai Chi exercise<sup>[5]</sup>. In this study, we investigated the rsFC of the lateral and medial hypothalamus between the fibromyalgia and healthy controls and the modulation effect of Tai Chi on hypothalamus connectivity, which has not been previously published.

## Participants

Based on American College of Rheumatology (ACR) 1990 classification criteria and the ACR 2010 diagnostic criteria for fibromyalgia, 24 patients ( $\geq 21$  years old) with fibromyalgia and 24 healthy controls matched for age, gender, and body mass index (BMI) participated in the study. The main exclusion criteria were: (1) diagnosed with medical conditions that are known to contribute to

fibromyalgia symptomatology, (2) unable to pass the Physical Activity Readiness Questionnaire, (3) a score of less than 24 on the Mini-Mental State Examination; (4) if the patient presented any contraindications to fMRI scanning or had prior experience with Tai Chi training; and 5) similar types of complementary and alternative medicine in the past year.

## Intervention

All participants in the Tai Chi group attended a 60-minute practice session twice a week for 12 weeks at Tufts Medical Center using a standardized Tai Chi protocol developed for patients with fibromyalgia [29]. Each component of the program was derived from the condensed version of the classical Yang-style, 108-posture Tai Chi for the 12-week intervention program. Participants were also instructed to practice at least 30 minutes a day at home. 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 physician visits throughout the course of the study.

## Outcome measurements

The primary outcome for this study was resting state functional connectivity (rsFC) of the medial and lateral hypothalamus. Secondary outcomes included: 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 the Martinos Center for Biomedical Imaging of Massachusetts General Hospital with a 32-channel head coil and 3.0 T Siemens (Skyra syngo) scanner. Magnetization-Prepared Rapid Gradient Echo (MPRAGE) T1-weighted images were collected (voxel size  $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ ). The blood oxygen level dependent (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 =  $64 \times 64$ , voxel size =  $2.6 \times 2.6 \times 2.6 \text{ mm}^3$ , 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

Clinical data analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). A threshold of  $p < 0.05$  (2-tailed) was applied. T-test and Chi square tests were conducted to compare the baseline characteristics of participants between groups.

## Seed based functional connectivity analysis

Resting state functional connectivity analysis was conducted using the CONN toolbox v18b<sup>[31]</sup> (<http://www.nitrc.org/projects/conn>). Preprocessing was performed using a standard pipeline in CONN. During the preprocessing, images were realigned, segmented, co-registered to each subject's high-resolution T1 scan, and normalized to the standard Montreal Neurological Institute (MNI) template. Images were also smoothed using a 6 mm full-width at half-maximum Gaussian kernel and filtered with a frequency window of 0.008–0.09 Hz. In addition, we employed segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas for the removal of temporal confounding factors (white matter and CSF)<sup>[31]</sup>.

Data was also subjected to motion correction using the artifact detection toolbox ([http://www.nitrc.org/projects/artifact\\_detect/](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 six other regular motion parameters<sup>[32]</sup>.

Similar to previous studies<sup>[24, 33]</sup>, the bilateral medial hypothalamus (MH) (MNI coordinates:  $x = \pm 4$ ;  $y = -2$ ;  $z = -12$  plus 2 mm sphere) and lateral hypothalamus (LH) (MNI coordinates:  $x = \pm 6$ ;  $y = -9$ ;  $z = -10$  plus 2 mm sphere) were selected as seeds using WFU-Pick Atlas software. 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 increase normality and allow for improved second-level general linear model analyses.

For each group (condition), a one sample t-test was applied to explore the positive and negative rsFC of pre- and post-treatment in fibromyalgia patients and HC's respectively. Then, the baseline medial and lateral hypothalamus rsFC of fibromyalgia patients and HC's 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. 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 amygdala, rostral anterior cingulate cortex, and thalamus in the pathophysiology of fibromyalgia and pain modulation, we defined these regions as regions of interest [using the Automated Anatomical Labeling (AAL) template]. For predefined ROIs, Monte Carlo

stimulations using 3dFWHMx and 3dClustSim [in the Analysis of functional NeuroImages program (<https://afni.nimh.nih.gov>) released in July 2017] were applied, and voxel-wise  $p < 0.005$  and  $p < 0.05$  at cluster level were corrected for the minimum voxel. The cluster-size threshold ( $k$ ) for the corrected region was shown in the results.

## Effective connectivity of medial hypothalamus (MH)

In this study, we found that rsFC between the MH and right thalamus was decreased in fibromyalgia patients, but normalized after mind-body intervention (see Results section for details). We thus performed a spectral dynamic causal modeling (DCM) analysis using DCM 12<sup>[34]</sup> and implemented in SPM12, with the bilateral medial hypothalamus and right thalamus (i.e., overlapping areas of two contrasts: fibromyalgia vs healthy control and pre vs post Tai Chi) as regions of interest (ROIs). The following 3 models were specified: MH influencing thalamus (model 1), thalamus influencing MH (model 2), and a fully connected model of bidirectional effective connectivity between the MH and thalamus (model 3). Fixed effects (FFX) Bayesian Model Selection (BMS) was conducted to determine the best model for each group. For the best model, the Bayesian Model Averaging (BMA) was conducted to analyze the connectivity parameters in the group level. The probability weighted values of the model parameters were also obtained from BMA and compared across the three conditions after controlling for effects of age and gender if needed (all conditions have same best model).

## Results

The study was completed with 21 fibromyalgia patients and 20 healthy controls. One healthy control was excluded due to brain atrophy and one fibromyalgia patient was excluded from the rsFC analysis due to excessive head movement during the scan. There were no significant differences in age, gender, race, or BMI between the fibromyalgia and healthy control subjects included in the fMRI data analysis.

FIQR scores demonstrated moderate to severe fibromyalgia in the majority of fibromyalgia subjects with an average score of  $45.2 \pm 17.8$  (mean  $\pm$  SD). BDI-II scores revealed moderate depression with an average score of  $17.7 \pm 9.3$  in the fibromyalgia group, and a two-sample t-test showed significant differences ( $p < 0.0001$ ) between the fibromyalgia and healthy control groups in BDI-II scores ( $4.2 \pm 3.2$ ). Paired t-tests showed significant pre- and post-Tai Chi differences in general FIQR scores (Pre:  $45.9 \pm 17.6$ , post:  $36.3 \pm 20.3$ ,  $p = 0.001$ ) and three sub scores: Function ( $p = 0.001$ ), Overall Impact ( $p = 0.05$ ), and Symptoms, ( $p = 0.017$ ). Analysis of BDI-II scores demonstrated a significant difference between pre- and post-treatment scores in fibromyalgia patients (pre:  $17.7 \pm 9.3$ , post:  $10.8 \pm 9.2$ ,  $p = 0.0005$ ). There was also a significant association between FIQR score changes and BDI score changes ( $p = 0.003$ ).

## Medial hypothalamus (MH) rsFC results

The MH rsFC of fibromyalgia (pre- and post-intervention) and HC is presented in Fig. 1. The results showed that both fibromyalgia and HC are associated with positive MH rsFC in brain regions that belong to the default mode network (medial prefrontal cortex (MPFC) / anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) / precuneus) and bilateral thalamus. Of the three conditions, fibromyalgia (pre-treatment) was associated with the most robust positive MH rsFC.

Compared to the healthy controls, fibromyalgia patients at baseline showed significantly increased rsFC between the medial hypothalamus and bilateral subcallosal cingulate cortex and decreased rsFC between the medial hypothalamus and bilateral cerebellum, amygdala ( $k = 2$ ), and right thalamus ( $k = 5$ ) compared to healthy controls at baseline.

A direct comparison of before and after intervention in fibromyalgia patients indicated an increased medial hypothalamus rsFC with the left amygdala ( $k = 2$ ), rACC ( $k = 5$ ), cerebellum, right DLPFC/operculum, thalamus ( $k = 5$ ), and occipital area after Tai Chi intervention. No reduced MH rsFC was found after Tai Chi intervention at the threshold we set.

Interestingly, we found that increased MH-thalamus and MH-amygdala rsFC after intervention overlapped with decreased MH-thalamus rsFC when compared with the healthy control group, indicating that the treatment can normalize decreased FC. Exploratory analysis showed a significant correlation between MH-thalamus connectivity changes and FIQR function sub score percent changes before and after intervention ( $r = -0.48$ ,  $p = 0.03$ ).

## Lateral hypothalamus (LH) rsFC results

LH rsFC of fibromyalgia and HC is presented in Fig. 1. Results showed that HC's were associated with positive LH rsFC with the thalamus and occipital cortex, while fibromyalgia was associated with LH rsFC with the insula and brain regions belonging to the default mode network, including the ACC / MPFC and precuneus. This pattern was similar after intervention, but the connectivity was more robust.

Compared with HC, fibromyalgia patients (at baseline) showed significantly increased rsFC between the LH and right temporal pole and decreased rsFC between the lateral hypothalamus and right occipital inferior gyrus/cerebellum.

Comparisons before and after intervention in fibromyalgia patients indicate an increased rsFC between the lateral hypothalamus and bilateral rostral anterior cingulate cortex (rACC) and MPFC, as well as the left PCC and right middle temporal gyrus/ superior temporal gyrus after Tai Chi intervention. There was no significant rsFC reduction after Tai Chi intervention.

## Effective connectivity of medial hypothalamus (MH)

The results of effective connectivity analysis at the group level are shown in Fig. 3. For healthy subjects, the best model at the group level was Model 2. For patients with fibromyalgia, Model 3 was the best for pre-intervention, while Model 1 was the best for post-intervention.

## Discussion

In this study, we investigated medial and lateral hypothalamus functional connectivity in fibromyalgia patients and connectivity changes following a non-pharmacological intervention. We found that 1) compared to healthy controls, fibromyalgia patients were associated with decreased MH rsFC with the thalamus and amygdala; 2) the MH rsFC with the thalamus and amygdala increased (normalized), and the MH-thalamus rsFC was significantly associated with clinical outcome changes; and 3) there was an MH / LH rsFC increase with the rACC. In addition, we found different MH-thalamus effective connectivity between the fibromyalgia patients and HC's, as well as before and after treatment. Our results suggest that fibromyalgia is associated with altered functional connectivity within the limbic system, and some of these changes are sensitive to intervention.

The hypothalamus is a small but functionally diverse region of the brain, exerting vital regulatory influences over the central and peripheral nervous system. As a key region of the limbic system, it has direct connections with the frontal lobes, hippocampus, amygdala, thalamus, and brain stem, and it regulates many autonomic processes.

In this study, we found two overlapping but distinct neural networks from the LH and MH using resting-state FC analyses. Our results are consistent with the findings from a previous study on healthy subjects using an identical seed as the current study [24].

One major finding of our study is the decreased MH-thalamus rsFC in fibromyalgia patients and the increased MH-thalamus rsFC after intervention. Both the hypothalamus and thalamus belong to the diencephalon, and there are bidirectional connections between these two structures. The thalamus is a key region for central processing and integration of nociceptive inputs. It acts as a relay center for handling incoming sensory information and motor impulses between the spinal cord, medulla oblongata, and cerebrum. Specifically, the thalamus receives nociceptive signals via two major ascending pathways: the spinothalamic tract (STT) and the spinoreticulothalamic tract (SRT). The STT conveys noxious information from the dorsal horn to both the lateral thalamus and medial thalamus, while the SRT mainly relays nociceptive information to the medial thalamus via an additional synaptic relay within the medullary reticular formation of the brainstem [35].

Further studies suggest that the thalamo-cortical pathways / interactions may underlie the perception of pain as an unpleasant sensory and emotional experience. The lateral thalamocortical pathway is involved in coding the sensory discriminative aspects of pain, while the medial thalamocortical pathway codes the emotional qualities of pain [35]. Literature suggests that the anatomical and biochemical alterations in thalamocortical circuits may be responsible for the development of chronic pain [35–37]. The

thalamus observed in our study extends from the medial portion to the lateral portion, suggesting alterations of both sensory and emotional aspects in the pathophysiology of fibromyalgia.

We also found that fibromyalgia patients are associated with decreased MH rsFC in the amygdala. After intervention, the MH rsFC in the amygdala significantly increased. The amygdala is a key region in the limbic system that plays an important role in emotion processing, fear and anxiety response, and the influence of negative emotions on pain [38]. The amygdala is also part of the descending pain modulation system, directly projecting to the PAG [39]. A previous study showed that chronic low back pain evoked brain activity increases in the amygdala and rACC / MPFC [40] and is associated with volume decreases in the amygdala [41]. A more recent study found higher incidences of white matter and functional connections within the MPFC–amygdala–accumbens circuit, with smaller amygdala volume accounting for 60% of the variance for chronic low back pain persistence [42]. Our results agree with these findings, suggesting that the linkage between the MH and amygdala plays an important role in the pathophysiology and development of fibromyalgia.

We also found that MH and LH rsFC increased with rACC after intervention. This result is consistent with a previous study using the same data set, in which we found that DLPFC rsFC with the rACC significantly increased after Tai Chi [5]. Similar results have been observed after various exercise interventions (Tai Chi, Baduanjin, and stationary cycling) in patients with knee osteoarthritis and after transcutaneous vagus nerve stimulation in patients with depression [33].

As a key region of the limbic system, default mode network, and descending pain modulation system, the involvement of the rACC in the pathophysiology of chronic pain has been well documented [3, 30, 43–46]. Previous studies have suggested close functional connectivity between the PAG, a key region of the descending pain modulation system, and the rACC [47], and alterations in PAG-rACC functional connectivity in patients with fibromyalgia [3].

Literature suggests that the hypothalamus has direct ascending and descending connections with the PAG [27]. In this study, we did not observe the hypothalamus rsFC changing with the periaqueductal gray at the threshold we set. Nevertheless, at a less conservative threshold of  $p < 0.005$  (voxel wise uncorrected), we did detect a MH-PAG rsFC decrease (peak MNI coordinate 4, -28, -8, 8 voxels) in fibromyalgia patients when compared to HC and an MH-PAG rsFC increase after intervention (peak MNI coordinate - 2, -24, -12, 12 voxels). Taken together, we speculate that Tai Chi intervention may work by modulating the linkages between key regions of the limbic system, including the hypothalamus, rACC, amygdala, and thalamus, and by modulating the functional connectivity of key regions between the limbic and descending pain modulation systems such as the PAG. It is worth noting that the rACC and amygdala are key regions of both the limbic system and descending pain modulation system [39, 47, 48], which provide further support for our hypothesis.

Our findings of clinical improvement after 12-weeks of Tai Chi exercise are consistent with a previous study demonstrating the positive effects of Tai Chi [29] and exercise [15] 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 [49–56] and chronic pain patients [57, 58]. Nevertheless, 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 hypothalamus in fibromyalgia patients and how these rsFC’s changed following effective treatment with symptom relief. We believe this study may shed light on our understanding of the pathophysiology and development of fibromyalgia. We also acknowledge that pharmacological medication (all participants were allowed to continue their regular medication during the experiment) and other unknown factors may have contributed to the clinical improvements observed.

Finally, DCM analyses indicated different MH - thalamus connectivity patterns between the fibromyalgia and healthy control groups, as well as before and after Tai Chi mind-body intervention. In healthy subjects, the connectivity pattern appeared to be the thalamus driving the MH. In fibromyalgia patients, the pre-treatment connectivity was the MH driving the thalamus, while the post-treatment connectivity was bidirectional with the MH and thalamus influencing each other. These results suggest that fibromyalgia is associated with reverse causal connectivity between the MH and thalamus (i.e., the presence of MH-to-thalamus influence and the absence of thalamus-to-MH influence). Nonetheless, Tai Chi treatment can restore the thalamus-to-MH influence (present in controls) even though the MH-to-thalamus influence (absent in controls) remains.

In conclusion, we found that compared to healthy controls, fibromyalgia patients showed altered functional connectivity within the limbic system and diencephalon (hypothalamus, thalamus, amygdala, and ACC). After the intervention, the altered functional connectivity between the hypothalamus, thalamus, and amygdala normalized. Effective connectivity analysis showed that MH and thalamus interaction was disrupted in fibromyalgia patients, which nonetheless could be partially restored by Tai Chi intervention. Elucidating the role of the extended hypothalamus network in fibromyalgia may shed light on the pathophysiology and development of this prevalent disorder and facilitate the development of a new treatment for chronic pain.

## Abbreviations

rsFC

Resting-State functional connectivity

HC

Healthy Control

ACR

American College of Rheumatology

BMI

Body Mass Index  
BDI-II  
Beck Depression Inventory  
FIQR  
Revised Fibromyalgia Impact Questionnaire  
MPRAGE  
Magnetization-Prepared Rapid Gradient Echo  
MNI  
Montreal Neurological Institute  
BOLD  
Blood Oxygen Level Dependent  
AAL  
Automated Anatomical Labeling  
CSF  
Cerebrospinal fluid  
ROI  
Region of Interest  
DLPFC  
Dorsolateral prefrontal cortex  
PAG  
Periaqueductal gray  
rACC  
Rostral anterior cingulate cortex  
MPFC  
Medial prefrontal cortex  
PCC  
Posterior cingulate cortex  
MH  
Medial hypothalamus  
LH  
Lateral hypothalamus  
DCM  
Dynamic causal modeling  
FFX  
Fixed effects  
BMS  
Bayesian Model Selection  
BMA  
Bayesian Model Averaging  
STT

Spinothalamic tract  
SRT  
Spinoreticulothalamic tract

## **Declarations**

### **Ethics approval and consent to participate**

Ethics approval and 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. All the subjects signed the consent forms before the experiments started.

### **Consent for publication**

All the subjects agreed their data being used for publication during the consent process.

### **Availability of data and materials**

The data that support the findings of this study are available on request from the corresponding author JK and CW. The data are not publicly available due to IRB restriction.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

JK and CW contributed to study design and draft manuscript; YH and WL contributed to analyze data and prepare manuscript; JL, SY and MC contributed to analyze data; HC and GW contributed to prepare manuscript; WH and CW contribute to collect data

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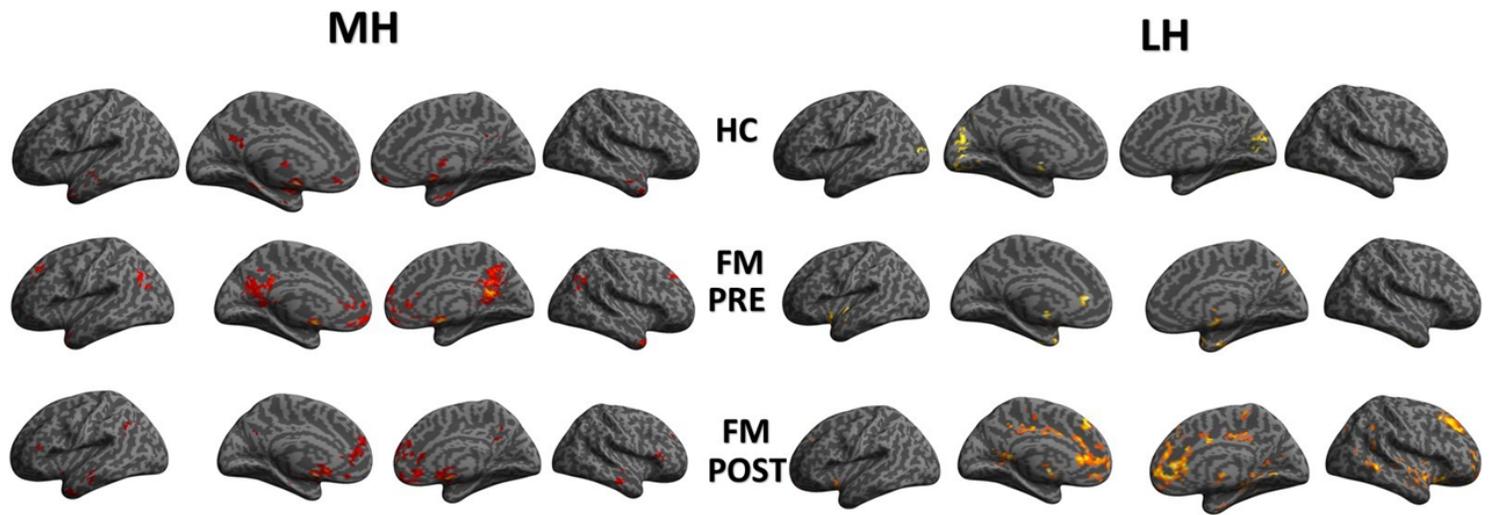
## Table 1

**Table 1. Regions showing significantly different functional connectivity with the medial hypothalamus (MH) and lateral hypothalamus (LH) in fibromyalgia patients (FM) and healthy controls, before and after three-month intervention.**

	Condition	Region	Cluster size	MNI coordinates			Peak z value
				X	Y	Z	
Seed							
MH	FM (pre) > HC	Bilateral subcallosal cingulate gyrus	125	-12	14	-16	3.85
	HC > FM (pre)	Bilateral cerebellum	155	0	-80	-28	3.82
		Left amygdala	70	-30	-8	-16	4.72
		Right amygdala	23	32	-8	-20	3.12
		Right thalamus	32	10	-14	0	3.54
	FM (post) > FM (pre)	Right DLPFC/Operculum	105	56	20	2	4.16
		Right occipital gyrus	180	22	-78	-6	4.23
		Left cerebellum	101	-12	-70	-20	3.96
		Left amygdala	24	-18	-12	-12	3.64
		Right thalamus	59	8	-18	2	4.19
		left rACC	23	-12	44	22	3.8
	FM (pre) > FM (post)	None					
LH	FM (pre) > HC	Right temporal pole	152	38	6	-42	3.54
	HC > FM (pre)	Right inferior occipital gyrus/cerebellum	213	40	-66	-8	3.93
	FM (post) > FM (pre)	Bilateral rACC	229	10	36	6	4.42
		Bilateral MPFC	180	8	46	-2	4.1
		Right middle temporal gyrus/superior temporal gyrus	185	60	0	-16	4.34
		Left PCC	106	-12	-36	34	4.09
	FM (pre) > FM (post)	None					

**Note:** FM (pre)=fibromyalgia pre-Tai Chi intervention, FM (post)=fibromyalgia post-Tai Chi intervention, HC=healthy control, DLPFC=dorsolateral prefrontal cortex, PAG=periaqueductal gray, rACC=rostral anterior cingulate cortex, MPFC= medial prefrontal cortex, PCC=posterior cingulate cortex

## Figures



**Figure 1**

Resting state functional connectivity of the medial hypothalamus (MH) and the lateral hypothalamus (LH) in fibromyalgia patients and healthy controls. A threshold of  $p < 0.005$  with 80 continuous voxels was applied.

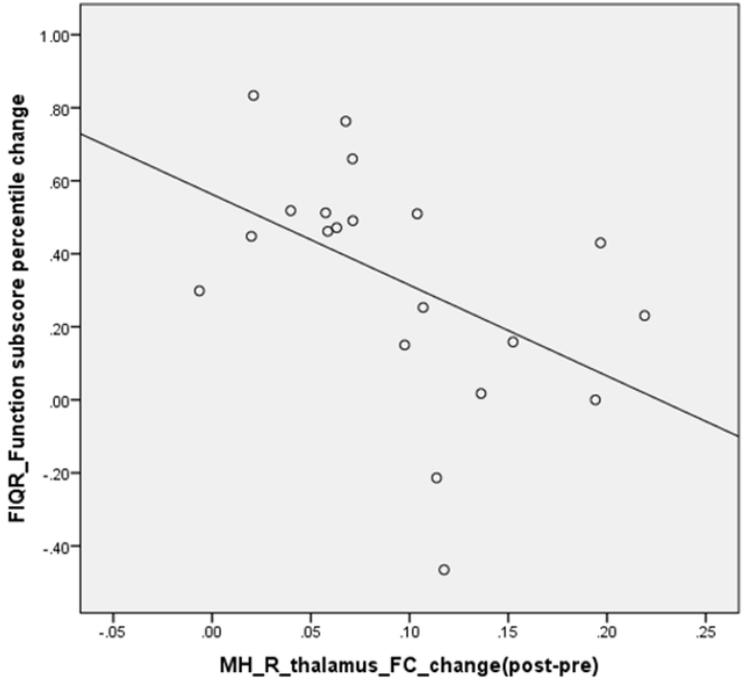
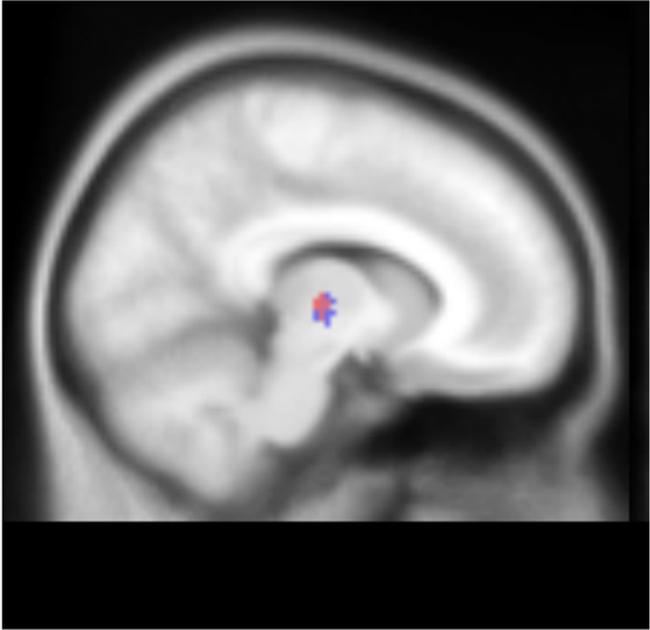
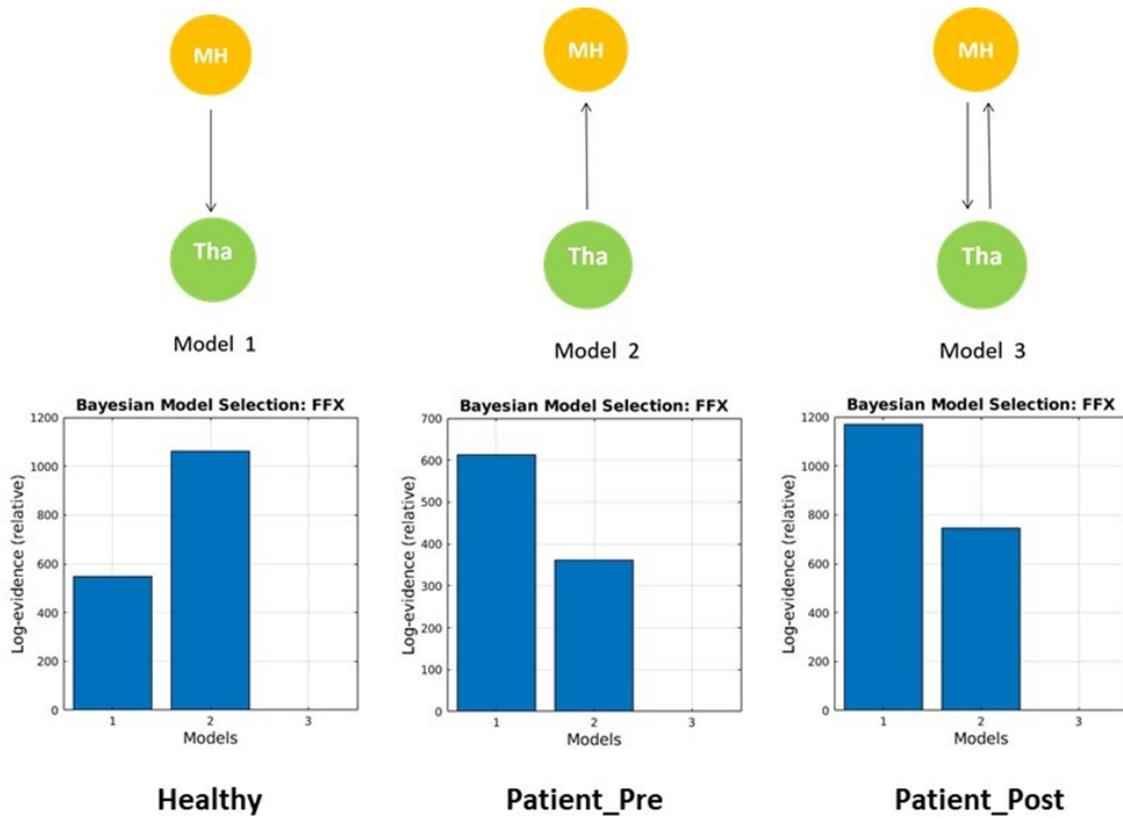


Figure 2

Medial hypothalamus functional connectivity decreased in the right thalamus in FM patients compared to healthy controls (red) and increased after 12-weeks of non-pharmacological intervention (blue). The scatter plot indicates the significant association between the MH-thalamus functional connectivity changes and the FIQR function sub-score changes.



**Figure 3**

Medial hypothalamus – thalamus effective connectivity model and results