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RESEARCH ARTICLE

Association of Fine Motor Loss and Allodynia in Fibromyalgia: An fNIRS Study

Aykut Eken [1], Didem Gökçay[2], Cemre Yılmaz[3], Bora Baskak[4,5], Ayşegül Baltacı[6], Murat Kara[7]

[1]Biomedical Engineering Department, Düzce University, Düzce, Turkey. [2]Medical Informatics Department, Informatics Institute, Middle East Technical University, Ankara, Turkey. [3]Neuroscience Graduate Program, Bilkent University, Ankara, Turkey. [4]Department of Psychiatry, Ankara University Faculty of Medicine, Ankara, Turkey. [5]Ankara University Brain Research Center, Ankara, Turkey. [6]Department of Physical and Rehabilitation Medicine, Yenimahalle Research Hospital, Yıldırım Beyazıt University Ankara, Turkey. [7]Department of Physical and Rehabilitation Medicine, Hacettepe University Medical School, Ankara, Turkey.

ABSTRACT. Recent studies showed that fine motor control dysfunction was observed in fibromyalgia (FM) syndrome as well as allodynia. However, brain signatures of this association still remain unclear. In this study, finger tapping task (FTT) and median nerve stimulation (MNS) were applied to both hands of 15 FM patients and healthy controls (HC) to understand this relationship. Hemodynamic activity was measured simultaneously using functional near-infrared spectroscopy (fNIRS). Experiments were analyzed separately by using 2x2 repeated measures ANOVA. Results for the FTT experiment revealed that HC showed higher activity than FM patients in bilateral superior parietal gyrus (SPG), left supramarginal gyrus (SMG) and right somatosensory cortex (SI). Furthermore, right-hand FTT resulted in higher activity than left-hand FTT in left SPG, left SI and right motor cortex (MI). In the MNS experiment, FM patients showed higher activity than HC in bilateral SPG, right SMG, right SI and right middle frontal gyrus (MFG). Negative correlation was observed in left SPG between FTT and MNS activities. Besides, MNS activity in left SPG was negatively correlated with left-hand pain threshold.This study revealed that left SPG might be an important indicator to associate fine motor loss and allodynia in FM.

Keywords: fNIRS, Fibromyalgia, Fine Motor Loss

Introduction

Fibromyalgia (FM) is a widespread pain syndrome diagnosed during physical examination on several tender points of the body that has a considerable negative effect on accuracy and speed of motor responses (Reyes Del Paso, Montoro, & Duschek, 2015) and performance of motor skills such as gait (Rasouli, Fors, Borchgrevink, Ohberg, & Stensdotter, 2017). Previous studies focused on motor skill loss in FM by using electromyography (EMG) (Casale et al., 2009), magnetic stimulation (Salerno et al., 2000), self-reporting using standard questionnaires (Watson, Buchwald, Goldberg, Noonan, & Ellenbogen, 2009), Purdue Pegboard test (Perez-de-Heredia-Torres, Martinez-Piedrola, Cigaran-Mendez, Ortega-Santiago, & Fernandez-de-Las-Penas, 2013; Rasouli et al., 2017), Jebsen–Taylor hand function test (Perez-de-Heredia-Torres et al., 2013), and Box and Blocks test (Canny, Thompson, & Wheeler, 2009). According to studies focusing on fine motor loss, in women with FM, there is no significant difference between FM and healthy groups in the Purdue Pegboard test (Rasouli et al., 2017), but the one-hand pin placement subtest of the Purdue Pegboard test showed that FM patients had lower test scores than controls (Perez-de-Heredia-Torres et al., 2013). The Jebsen–Taylor hand function test showed that the nondominant hand needed more time performing subtests (Perez-de-Heredia-Torres et al., 2013). Besides, women with FM had lower manual dexterity than healthy women by using the Box and Blocks test (Canny et al., 2009). Also, FM patients had lower handgrip strength results than healthy controls (HC) (Aparicio et al., 2010, 2011; Dombernowsky, Dreyer, Bartels, & Danneskiold-Samsoe, 2008; Koklu, Sarigul, Ozisler, Sirzai, & Ozel, 2016).

On another front, allodynia is defined as augmented responsiveness of the nervous system to nonpainful stimuli. Allodynia is a result of excessive tenderness in the body due to central sensitization (Woolf, 2011). A recent review revealed that region-specific alterations in cerebral gray matter decreased functional connectivity pattern in pain modulation within the descending somatosensory system and increased brain activity in FM patients might be related to central sensitization (Cagnie et al., 2014).

To our best knowledge, there is neither a behavioral nor a neuroimaging study that directly focuses on relationship between fine motor loss and pain perception in the FM syndrome. However, there are some studies that directly focus on motor cortex (MI) stimulation using transcranial direct current stimulation (tDCS) for treatment of fibromyalgia (Fregni et al., 2006; Villamar et al., 2013). These studies revealed that stimulating MI using tDCS causes significant pain reduction in FM patients. Based on these studies, a recent hypothetical work directly claimed that MI may modulate pain in FM patients, despite not being mentioned in the "pain matrix" (Saavedra, Mendonca, & Fregni, 2014). On the other hand, some functional neuroimaging studies focused on pain perception in FM by applying

Correspondence address: Aykut Eken, Biomedical Engineering Department, Düzce University, Konuralp Campus, 81620 Düzce, Turkey. e-mail: aykuteken@duzce.edu.tr

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painful stimulation revealed an MI activation (Cook et al., 2004; Pujol et al., 2009). These findings showed that a possible bidirectional relationship might be available between pain perception and motor activity.

The association between pain and fine motor loss can be explained through the pain-adaption model (Lund, Donga, Widmer, & Stohler, 1991) or vicious cycle model (Johansson & Sojka, 1991; Peck, Murray, & Gerzina, 2008). In the pain-adaptation model, it is proposed that pain reduces the contraction ability of muscles. On the other hand, in the vicious cycle model, a cycle that begins with an initial abnormality in movement, posture, or structure that might cause pain is assumed. However, to our best knowledge, there is no neural evidence that proves the validity of these models. A recent review showed that there are several factors other than pain that may affect motor functioning, such as lack of somatosensory input and loss of muscle targets, and it was reported that pain and MI interactions are complicated and a causal relationship is still unclear (Mercier & Leonard, 2011). In a recent functional neuroimaging study focusing on multisensory hemodynamic responses of FM patients, results showed that no difference was observed in primary motor and somatosensory cortices (Lopez-Sola et al., 2014) during tactile finger opposition task. Neuroimaging studies on the relationship of fine motor loss and pain perception in the FM syndrome are scarce.

In this study, we performed two different experimental paradigms, finger tapping task (FTT) and median nerve stimulation (MNS), to observe the association between fine motor loss and allodynia via hemodynamic activity of the brain. Finger tapping task is widely used to observe motor activity in functional neuroimaging studies (Witt, Laird, & Meyerand, 2008) and studies related to motor function evaluation (Aoki & Kinoshita, 2001; Cousins, Corrow, Finn, & Salamone, 1998; Giovannoni, van Schalkwyk, Fritz, & Lees, 1999; Jobbagy, Harcos, Karoly, & Fazekas, 2005). After collecting the data for both paradigms, correlations between brain activity profiles and clinical data are also investigated in our study.

Methods

Participants

Seventeen healthy controls and 19 FM patients who were diagnosed according to ACR 1990 criteria (Wolfe et al., 1990) were enrolled. All participants were right handed according to the Edinburgh Handedness Inventory (EHI). Before the experiments, all participants filled the Beck Depression Inventory (BDI). Participants with major depression were excluded from the experiments. Pain threshold values for both thumbs were collected by using an electronic von Frey (eVF) anesthesiometer. Level of education and proximity of menstruation were also recorded before the experiments. Fibromyalgia Impact Questionnaire (FIQ) scores, tender point counts, and disease durations were also recorded among FM patients. All participants were informed about the study protocol that was approved by the Ethical Board Committee of Ankara University (No. 04-178-14) and signed the informed consent form. Participants did not take any medication at least 12 hours before the experiment. Clinical and demographic information of participants is shown in Table 1.

Pain Threshold Measurements

We obtained individual pain thresholds from every participant. To obtain this value, we applied the quantitative sensory testing (QST) method. We used the eVF anesthesiometer (Ugo Basile Co., Varese, Italy) to carry out pain threshold measurements. The eVF anesthesiometer is a precise and accurate equipment used in several studies (Ambalavanar et al., 2006; KuKanich, Lascelles, & Papich, 2005; Tena et al., 2012; Vivancos et al., 2004) for measuring

TABLE 1. Demographic and clinical characteristics of the participants

Variable	FM patients ($N = 19$)	Healthy controls ($N = 17$)	Statistical results
Age (years)	37.7 ± 5.8	36.2 ± 9.0	$p = .537$
Gender (M/F)	2/17	2/15	$p = .906$
BDI score	19.6 ± 10.1	9.2 ± 8.8	$p = .004$
Pain threshold (gf)			
Right thumb	208.9 ± 54.0	244.8 ± 46.8	Group: $p = .009$
Left thumb	183.3 ± 56.7	242.5 ± 41.7	Hand: $p = .025$
Number of tender points	14 (11–16)	-	
Disease duration (years)	4.3 ± 5.9	-	
FIQ score	61.3 ± 13.9	-	

Data are given as mean ± *SD*, ratio, or median (min–max). FM: fibromyalgia; F: female; M: male; BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; gf: gram-force; RHS: right-hand stimulation; LHS: left-hand stimulation.

pressure pain thresholds. The eVF pressure pin has a diameter of 0.5 mm and the measurement range of the system is 1–1000 gram-force with 0.1 gram-force increments.

In the QST method, while the stimulation was being applied in linearly increasing intensity trend, participants gave a verbal sign when the stimulation induces an unpleasant feeling. This procedure was applied five times in order to obtain an accurate threshold value. The mean result of five measurements was considered as the individual pain threshold value. Between every measurement, there is a 20 s interval to prevent habituation. Instead of a discrete measurement, continuous measurement gives a higher resolution of response to painful stimuli. All measurements were taken from the dip joint between distal and proximal phalanx of left and right thumbs.

Experimental Design

Experimental tasks were performed in the following order: right-hand FTT, right-hand MNS, left-hand FTT, and left-hand MNS. Between every task, participants were required to rest for 5 min. Experimental timing was the same for both FTT and MNS as shown Figure 1. In each experiment, after an initial 20 s resting period, a 20 s FTT and 20 s resting period was repeated three times.

Experiment 1: Finger Tapping Task

Participants were asked to tap their fingers according to a visual stimulus shown on a monitor. In FTT paradigm, participants were required to tap their fingers self-paced without counting during ON stages of the experimental design. Visual stimuli for FTT and experimental timing were presented electronically using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

Experiment 2: Median Nerve Stimulation

We used the Intelect TENS device (Chattanooga Co., Tennessee, USA) with conventional TENS parameters: a pulse width of 60 μs and a frequency of 115 Hz. TENS was applied via two square Dura-Stick Plus Self-Adhesive Electrodes with 5 cm size. For every participant, a 30 mA amplitude, 60 μs pulse width, and 115 Hz frequency stimulus was tested before the experiment and it was observed that these parameters cause a nonpainful tingling effect when applied during the ON condition of the experiment. Electrodes were directly positioned on anterior forearms over median nerve trace of subjects.

Functional Near-Infrared Imaging

Functional near-infrared spectroscopy (fNIRS) scans were acquired at a sampling rate of 10 Hz using a Hitachi ETG-4000 continuous-wave near-infrared spectroscopy system at Ankara University Brain Research and Application Center (AÜBAUM). In this system, near-infrared wavelengths of 695 and 830 nm were used to observe the hemodynamic activity through concentration changes of oxyhemoglobin (ΔHbO_2) and deoxyhemoglobin (ΔHb). Optical light was sent to the head surface via a source optode and captured by a detector optode attached to a cap or grid. Optical light signals were converted to ΔHbO_2 and ΔHb by using the modified Beer–Lambert law (Cope & Delpy, 1988).

Probe Positioning and Channel Configuration

To maximize the spatial accuracy, we utilized the EEG 10–20 electrode positioning system (Jasper, 1958) to position the source and detectors onto the head surface. In this positioning system, half of the distance from nasion to inion (Nz–Iz) corresponds to the channel Cz. After defining the position of Cz, we set the 3 $\times$ 3 probe holders for both hemispheres over the line of right ear and left ear, by calculating two spots: C3 and C4. We defined the positions of C3 and C4 by measuring the distance between right tragus and left tragus. Thirty percent of this distance gives us the position of C3 from

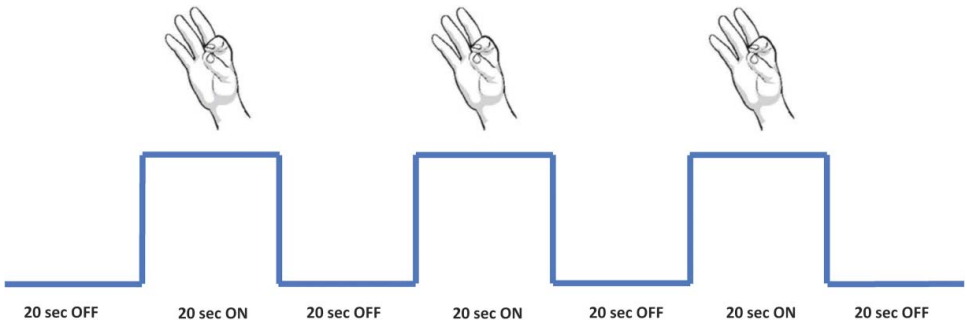

FIGURE 1. Experiment design of FTT.

left tragus and C3 from the right tragus. According to several studies, C3 and C4 positioned in this fashion correspond to the left and right postcentral gyri, respectively (Koessler et al., 2009; Okamoto et al., 2004). We used the 2 × 3 × 3 optode configuration that includes 10 sources, 8 detectors, and 24 channels as shown in Figure 2. The channels are the spaces between source and detector pairs. Channels 1–12 and 13–24 were located in left and right hemispheres, respectively. Optodes 18 and 13 were placed onto the C3 and C4 spots in left and right hemispheres, respectively. After probe holder placement, we marked optode positions by using a 3D digitizer (Polhemus Co., Vermont, USA) to determine the exact position of every channel. For every participant, we obtained fNIRS probe positions and registered them onto MNI space via fNIRS Analysis Package (NAP) (Fekete, Rubin, Carlson, & Mujica-Parodi, 2011). Then, we averaged coordinate values of all participants (Tsuzuki & Dan, 2014). To obtain brain regions corresponding to MNI coordinates, we used LONI Probabilistic Brain Atlas (Shattuck et al., 2008). Averaged MNI coordinates with corresponding cortical regions are shown in Table 2.

Data Preprocessing

We used MATLAB for preprocessing (MathWorks, Inc., Natick, MA, USA). Preprocessing pipeline included baseline correction, detrending to eliminate low-frequency drift, filtering for removal of systemic artifacts, removal of the channels that include motion artifacts, and averaging of blocks in the same condition. Initially, baseline correction was applied to remove DC component from time series. A wavelet-based detrending filter was used to remove the activity trend (Jang et al., 2009). We applied amplitude thresholding to remove out the channels that include motion artifacts. Finally, a low-pass filter with a cutoff at 0.05 Hz was applied to remove high-frequency noise.

Statistical Analysis of Clinical Data

Statistical analyses were performed with SPSS 20.0. We used the Shapiro–Wilk test for normality of variables. We applied a 2 × 2 [Group (FM patients and healthy controls) × Hand (right and left)] ANOVA to compare pain thresholds between the groups. The Pearson correlation coefficient was used to associate the mean value of the

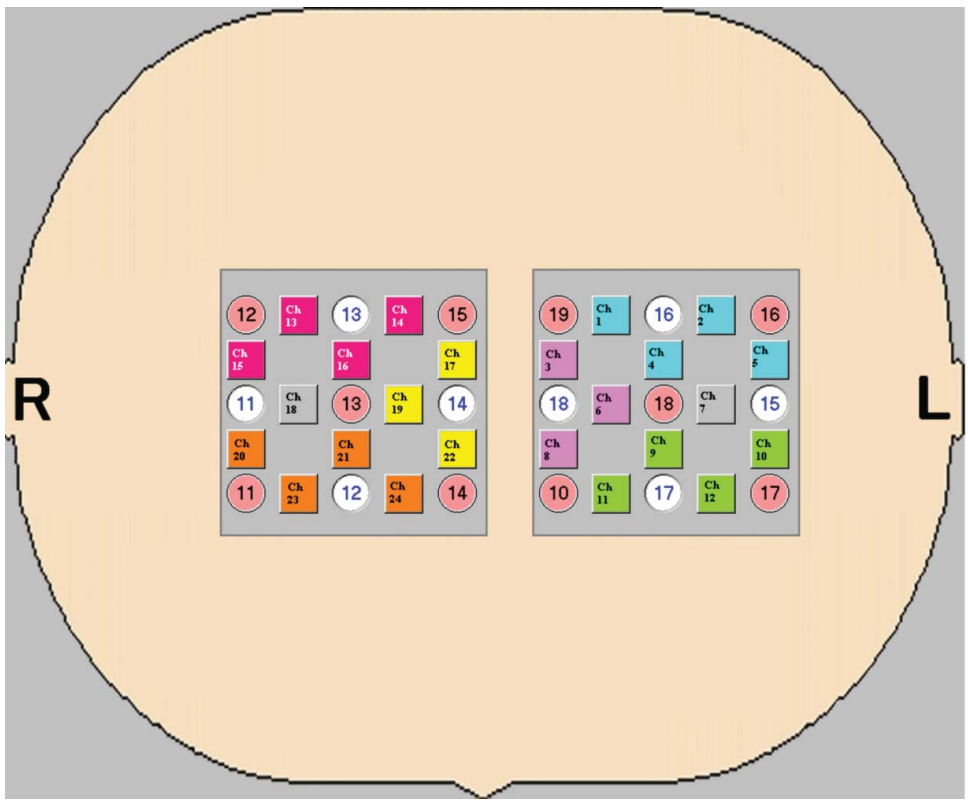

FIGURE 2. Channel and optode configuration of 2 × 3 × 3 probe setting. In this figure, locations that are represented as squares are channels. White circles that include numbers in blue are detectors. Pink circles that include numbers in black are sources (R: right; L: left).

TABLE 2. Channel numbers and average coordinate positions with corresponding cortical structures registered onto MNI space after using LPBA 40 cortical atlas

Channel number	Mean *X*	Mean *Y*	Mean *Z*	*SD*	Corresponding cortical structure
1	−40.77	−48.77	64.97	10.48	L superior parietal gyrus
2	−59.55	−49.44	44.52	9.41	L angular gyrus
3	−31.02	−35.25	72.91	10.9	L superior parietal gyrus
4	−53.88	−33.41	56.97	9.99	L supramarginal gyrus
5	67.22	−34.77	30.55	8.70	L supramarginal gyrus
6	−44.22	−20	65.22	11.12	L postcentral gyrus
7	−62.38	−19.16	43.66	9.33	L postcentral gyrus
8	−29.55	−5.38	70.33	11.96	L precentral gyrus
9	−52.63	−5.02	52.94	10.42	L precentral gyrus
10	−65.38	−5.44	25.66	9.43	L postcentral gyrus
11	−39.11	9.83	59.52	11.66	L middle frontal gyrus
12	−57.27	9.75	35.80	10.00	L precentral gyrus
13	61.02	−50.91	43.69	8.30	R angular gyrus
14	42.13	−49.30	64.44	9.31	R superior parietal gyrus
15	69	−36.58	30.69	7.94	R supramarginal gyrus
16	56.25	−34.80	56.77	9.40	R supramarginal gyrus
17	32.63	−34.97	72.94	10.31	R superior parietal gyrus
18	64.94	−20.97	44.27	9.36	R supramarginal gyrus
19	46.36	−20.33	65.16	10.88	R postcentral gyrus
20	68.02	−6.55	27.5	8.55	R postcentral gyrus
21	55.50	−6	53.02	10.47	R postcentral gyrus
22	31.94	−5.11	69.75	11.50	R precentral gyrus
23	59.86	8.86	37.05	9.54	R precentral gyrus
24	42.13	9.97	59.02	10.95	R middle frontal gyrus

Probability values were obtained from LPBA 40 cortical atlas (L: left; R: right).

block-averaged ΔHbO_2 signal and the pain threshold value. A p-value $\leq .05$ was considered for statistical significance.

Brain Activity Data Analysis

After preprocessing, we obtained the mean ΔHbO_2 value from the collected fNIRS data blocks. We ran 2 × 2 (Group × Hand) repeated measures ANOVA by using block-averaged mean ΔHbO_2 of activation condition. Post hoc analyses were performed for significant factors/interactions. For each channel, post hoc analyses were performed separately for significant factors/interactions by using Bonferroni correction as in previous studies (Schroeter, Zysset, Kupka, Kruggel, & Yves von Cramon, 2002; Uceyler et al., 2015). A p-value $\leq .05$ was considered for statistical significance.

Results

Clinical Data Analysis Results

Demographic and clinical characteristics of participants are shown in Table 1. Both groups are age and gender balanced ($p > .05$). There was one postmenopausal woman in each group, 14 premenopausal women (eight in luteal and six in follicular phases) in healthy controls, and 16 premenopausal women (eight in luteal and eight in follicular phases) among FM patients. BDI scores were significantly higher in FM patients than healthy controls ($t(34) = 3.3038$, $p = .004$).

For pain thresholds, there was a significant difference between FM patients and healthy controls ($F(1,34) = 7.788$, $p = .009$). Also, there was a significant difference between hands ($F(1,34) = 5.467$, $p = .025$). Post hoc analysis using Bonferroni adjustment showed that healthy controls had higher pain threshold than FM patients (243.7 ± 11.8 vs. 198.3 ± 11.2, mean difference = 45.4 ± 16.3, $p = .009$). Also, the dominant hand (right) had higher pain threshold than the nondominant (left) hand (226.9 ± 8.5 vs. 215.2 ± 8.6, mean difference = 11.8 ± 5.0, $p = .025$). Group × Hand interaction showed a marginally significant difference between hands ($F(1,16) = 3.817$, $p = .072$), such that the pain threshold difference between hands of the FM patients ($t(18) = -2.493$, $p = .028$) differed significantly.

Brain Activation Results for FTT

Group difference was observed in bilateral superior parietal gyrus (SPG) (channel 3: $F(1,33) = 4.947$, $p = .033$; channel 17: $F(1,33) = 4.633$, $p = .038$), left supramarginal gyrus (SMG) (channel 4: $F(1,33) = 4.081$, $p = .050$), and right somatosensory cortex (SI) (channel 21: $F(1,33) = 4.213$, $p = .048$). Channels that show significant group difference are shown in Figure 3. Post hoc comparison

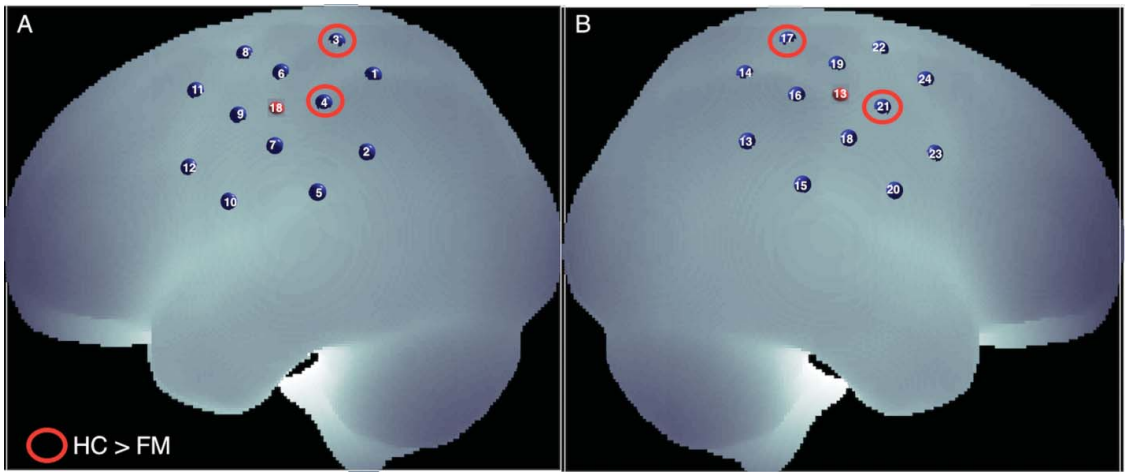

FIGURE 3. Channels that show Group main effect in finger tapping task marked on MNI space: (a) left hemisphere; (b) right hemisphere (L: left; R: right). Blue dots represent channels and red dots represent the sources that are considered as C3 and C4 in the EEG 10–20 system (13 and 18). The difference found in Group main effect is circled in red. FM: fibromyalgia patients; HC: healthy controls.

revealed that healthy controls had higher activation than FM patients in all of these aforementioned channels (i.e., channels 3, 4, 17, and 21 with $p < .05$).

Hand difference was observed in left SPG (channel 1: $F(1,33) = 6.175$, $p = .018$; channel 3: $F(1,33) = 8.494$, $p = .006$), left SI (channel 6: $F(1,33) = 4.633$, $p = .038$), and right MI (channel 22: $F(1,33) = 7.394$, $p = .010$). Channels that show significant hand difference are shown in Figure 4. Post hoc comparison revealed that right-hand tactile stimulation caused higher activation than left-hand tactile stimulation in left SPG (channel 1: $p = .018$; channel 3: $p = .006$), left SI (channel 6: $p = .038$), and right MI ($p = .010$). None of these channels showed a significant interaction between group and hand. Block-averaged time-series results of right-hand and left-hand stimulation are shown in the Appendix (Figures A1 and A2).

Brain Activation Results for Median Nerve Stimulation

Results showed that there is a significant group difference in left and right SPG (channel 3: $F(1,33) = 5.10$, $p = .030$; channel 17: $F(1,33) = 7.37$, $p = .010$), right

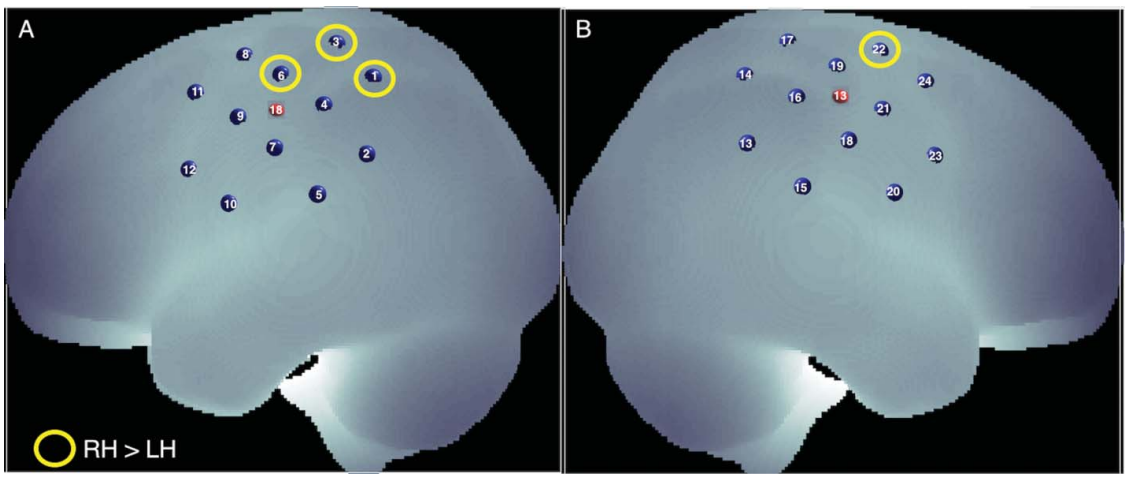

FIGURE 4. Channels that show Hand main effect in finger tapping task marked on MNI space: (a) left hemisphere; (b) right hemisphere (L: left; R: right). Blue dots represent channels and red dots represent the sources that are considered as C3 and C4 in the EEG 10–20 system (13 and 18). The difference found in Hand main effect is circled in yellow. FM: fibromyalgia patients; HC: healthy controls.

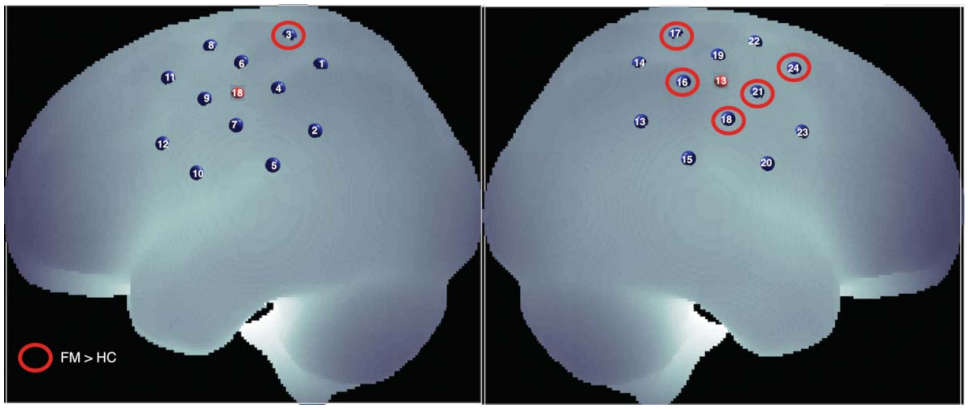

FIGURE 5. Channels that show Group main effect in median nerve stimulation with TENS marked on MNI space: (a) left hemisphere; (b) right hemisphere (L: left; R: right). Blue dots represent channels and red dots represent the sources that are considered as C3 and C4 in the EEG 10–20 system (13 and 18). The difference found in Group main effect is circled in red. FM: fibromyalgia patients; HC: healthy controls.

supramarginal gyrus (channel 16: $F(1,33) = 5.92$, $p = .021$; channel 18: $F(1,33) = 6.98$, $p = .012$), right postcentral gyrus (channel 21: $F(1,33) = 5.77$, $p = .022$), and right middle frontal gyrus (MFG) (channel 24: $F(1,33) = 8.11$, $p = .007$). Channels that show group difference are shown in Figure 5. Pairwise comparison showed that FM patients showed higher activity than healthy controls in left SPG (channel 3: $p = .030$), right SPG (channel 17: $p = .010$), right supramarginal gyrus (channel 16: $p = .021$; channel 18: $p = .012$), right postcentral gyrus (channel 21: $p = .022$), and right middle frontal gyrus (channel 24: $p = .007$). None of these regions showed significant difference in Hand main effect or Group × Hand interaction. Block-averaged time-series results of right-hand and left-hand stimulation are shown in the Appendix (Figures A3 and A4).

Brain Behavior Correlation Results

When left-hand MNS was applied, mean ΔHbO_2 of channel 3 (left SPG) showed a significant negative correlation with the measured left-hand pain threshold at the beginning of the experiment ($r = -.422$, $p = .012$). Similarly, again for the left-hand MNS, there was a strong negative correlation between left-hand pain threshold and mean ΔHbO_2 of channel 17 (right SPG) ($r = -.536$, $p = .001$). Correlation plots between behavioral and functional data are shown in Figure 6.

Correlation Between Brain Activity in FTT and MNS

When right-hand MNS was applied and right-hand FTT was performed, the brain activity data (mean ΔHbO_2) from

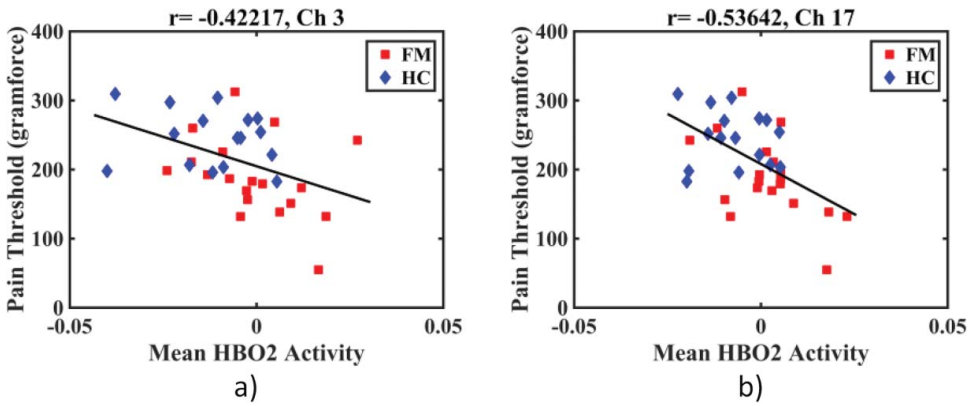

FIGURE 6. Correlation plots of (a) left-hand pain threshold and block-averaged mean ΔHbO_2 of left-hand MNS data for channel 3 (left superior parietal gyrus) and (b) left-hand pain threshold and block-averaged mean ΔHbO_2 of left-hand MNS data for channel 17 (right superior parietal gyrus).

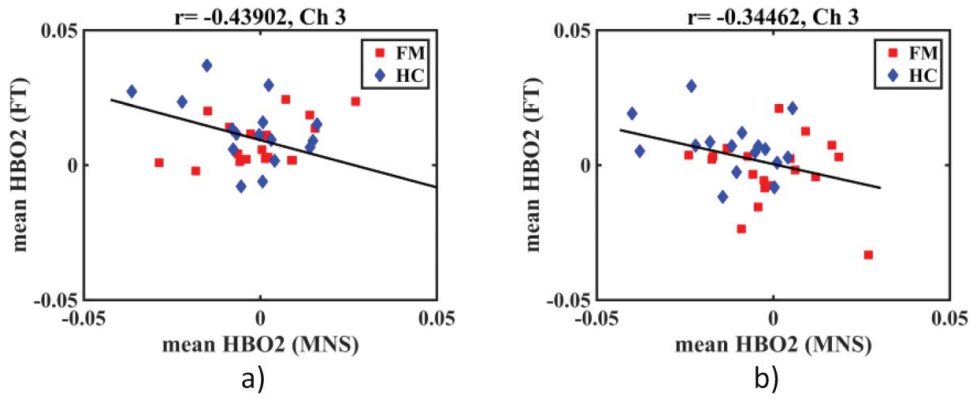

FIGURE 7. Correlation plots of (a) block-averaged mean ΔHbO_2 of right-hand FTT and right-hand MNS in channel 3 (left superior parietal gyrus) and (b) block-averaged mean ΔHbO_2 of left-hand FTT and left-hand MNS in channel 3 (left superior parietal gyrus).

channel 3 (left SPG) were strongly negatively correlated ($r = -.439$, $p = .008$) as seen in Figure 7a. When left-hand MNS was applied and left-hand FTT was performed, again a significant negative correlation was exhibited in channel 3 ($r = -.344$, $p = .042$) (Figure 7b). No other channel exhibited a significant correlation between the two tasks.

Discussion

In this study, we investigated the relationship between fine motor loss and pain perception in FM patients. Fine motor loss is a possible reflection of chronic pain diseases such as chronic fatigue syndrome (Rasouli et al., 2017). Our motivation to perform this study was to observe the relationship between fine motor loss and central sensitization through neuroimaging perspective.

FTT Experiment

Higher activity in healthy controls in FTT might show us a reflection of fine motor loss in FM patients. Several studies support our finding by using clinical tasks (Canny et al., 2009; Perez-de-Heredia-Torres et al., 2013; Rasouli et al., 2017). Also, we found that the dominant hand showed higher hemodynamic activity than the nondominant hand in different regions. There is only one study that analyzes the hand effects of fine motor loss in FM patients (Perez-de-Heredia-Torres et al., 2013). This study revealed that the nondominant hand needed relatively much more time to complete the subtests of the Jebsen–Taylor hand function test than the dominant hand for FM patients with respect to healthy controls. Perhaps, lower hemodynamic activity in FM patients reflects fine motor loss while performing FTT based on proprioceptive influences.

In an fMRI study (Lopez-Sola et al., 2014) that used nonpainful multisensory tactile stimulation including concurrent auditory, visual, and tactile stimulation on both FM patients and healthy controls, FM patients showed higher hemodynamic activity in insula and lingual gyrus and lower hemodynamic activity in primary/secondary visual and auditory cortices. However, in our study, we found augmented hemodynamic activity in right SI, left SMG, and left SPG in healthy controls in comparison to FM patients. This difference might be related to concurrent multisensory stimulation. Despite activation in SI for both groups that is strongly related to somatosensation, there is no difference between both groups. In our study, we applied a finger tapping paradigm instead of finger opposition task. Based on a recent fNIRS study performed on healthy participants, hand grasping and finger opposition tasks show similar hemodynamic responses (Kashou, Giacherio, Nahhas, & Jadcherla, 2016), so it is expected to observe similar findings between the study of Lopez-Sola et al. (2014) and our study. The discrepancy between our findings and those of Lopez-Sola et al. (2014) validates further investigation of the neural correlates of fine motor loss in FM patients.

MNS Experiment

We observed group difference in left and right superior parietal, right supramarginal, right postcentral, and right middle frontal gyri. Post hoc analysis revealed that FM patients showed higher activation than healthy controls. A similar study showed that FM patients showed greater activity than healthy controls in prefrontal, supplementary motor area, insular, and anterior cingulate cortices by using nonpainful warm stimuli applied via a thermal stimulator (Cook et al., 2004). Increased activation in FM patients compared with healthy controls is a general pattern that indicates that TENS-related activity in FM patients might increase due to central sensitization. Stimulating large Aβ nerve fibers that carry non-nociceptive stimulation causes allodynia in FM patients (Woolf, 2011). According to Cook et al. (2004), CNS dysregulation was found independent of stimulus type in FM patients. FM patients may perceive TENS stimulation as a nociceptive stimulation that may have introduced an additive effect in hemodynamic activation.

Lopez-Sola et al. (2014) explain that higher hemodynamic activity in FM patients during nonpainful stimulation may be a part of pathology in FM. A previous and similar MNS study in FM patients that used magnetoencephalography (MEG) (Lim et al., 2015) showed that FM patients had higher electrophysiological activity than healthy controls. Such higher activity in patients might indicate that these regions receive decreased intracortical inhibition from other areas of the brain (Lim et al., 2015). To understand brain signatures related to FM pathophysiology, further studies should be performed by using multimodal neuroimaging methods.

SPG, located in posterior parietal cortex, is known as sensory association area and it is found to be significantly active in MNS studies (Boakye, Huckins, Szeverenyi, Taskey, & Hodge, 2000; Klingner et al., 2011). Boakye et al. (2000) performed MNS on both hands of healthy participants and analyzed brain activity by using fMRI. They showed that posterior parietal cortex (BA 7: SPG; BA 40: supramarginal gyrus) was activated. Also, SI was found to be significantly active in healthy controls according to the several MNS studies (Boakye et al., 2000; Klingner et al., 2011; Spiegel, Tintera, Gawehn, Stoeter, & Treede, 1999). In the light of this literature, our findings in MNS demonstrate higher sensitivity in FM patients for non-nociceptive stimulation.

Correlation Between MNS and FTT Data

Strong correlation between MNS and FTT in left SPG showed that SPG might be an important marker to determine the relationship between fine motor loss and allodynia. Studies suggested that SPG has an important role for sensorimotor integration (Wolpert, Goodbody, & Husain, 1998). Lesions in this region may affect sensory processing and motor control (Freund, 2003). Such a relationship between both tasks in this region might be a possible reflection of a dysfunction in sensorimotor function in the FM group as reported earlier (McCabe, Cohen, & Blake, 2007; Montoya et al., 2005).

On the other hand, fibromyalgia patients have disrupted exteroceptive awareness. They overestimate their body size and this overestimation is correlated positively with pain and its impact on functionality (Valenzuela-Moguillansky, Reyes-Reyes, & Gaete, 2017). Such perceived body schema distortions can be detected as somatosensory differences and normalized with median nerve stimulation using electroacupuncture (Ho et al., 2014; Maeda et al., 2017). In the context of aforementioned studies and mechanisms, the detected motor loss in SPG in FM may be associated with alleviation of allodynia with MNS through normalization of distorted body schema, which is also detected at SPG during MNS.

Finally, SPL has a role in updating the hand location (Granek, Pisella, Blangero, Rossetti, & Sergio, 2012). The participants' hands during the FTT or MNS experiment were hidden behind a curtain throughout the experiments. The participants might be involved in visualizing the treatment while the ON cycles were underway. Hence, the overlapping SPG activations during FTT and MNS may also be explained through this function, although separate studies are needed to justify why FM patients would have additional activity in this respect compared to healthy controls.

Limitations

Our study has a few limitations. The first limitation is that we did not administer any behavioral hand function test. This study was conducted as a part of a larger study that involved extensive pain testing. Due to that, administration of behavioral motor testing was not possible. In the future, our results should be verified along with behavioral results. Furthermore, we assumed all channels as independent time series while performing statistical analysis. Any possible cross-talk between channels was ignored. Finally, although patients were admitted to the study through screening of BDI scores to exclude patients with major depressive disorder, we did not scrutinize the admitted patients for antidepressant treatment. This might have introduced some variance to our findings. Major depressive disorder (MDD) is known to be accompanied by sensorimotor symptoms as well as psychomotor retardation (American Psychiatric Association, 2013). Some functional neuroimaging studies suggest that sensorimotor cortex may also be implicated in MDD (Northoff, 2016; Yin et al., 2017). Although we excluded subjects with clinically established diagnosis of MDD, depressive symptoms as ascertained by the BDI were significantly higher in the index than the control group and may indeed have interfered with the results. Nevertheless, mood symptoms are among the core features of fibromyalgia (Clauw, 2014) and depressive symptoms may rather be regarded as intrinsic to the fibromyalgia syndrome. We therefore preferred not to control the effect of depressive symptom scores in the statistical analyses.

Conclusion

In this study, we carried out two different experiments to find an association between fine motor skill loss and central sensitization. Although several areas in the brain exhibited differences between healthy controls and fibromyalgia patients for finger tapping and median nerve stimulation, among these areas, differences converged to left superior parietal gyrus. Our findings warrant future research for deriving a signature for motor skill loss in FM, especially by harvesting neuroimaging data from the superior parietal cortex.

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ORCID

Aykut Eken http://orcid.org/0000-0002-7023-7930

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Appendix

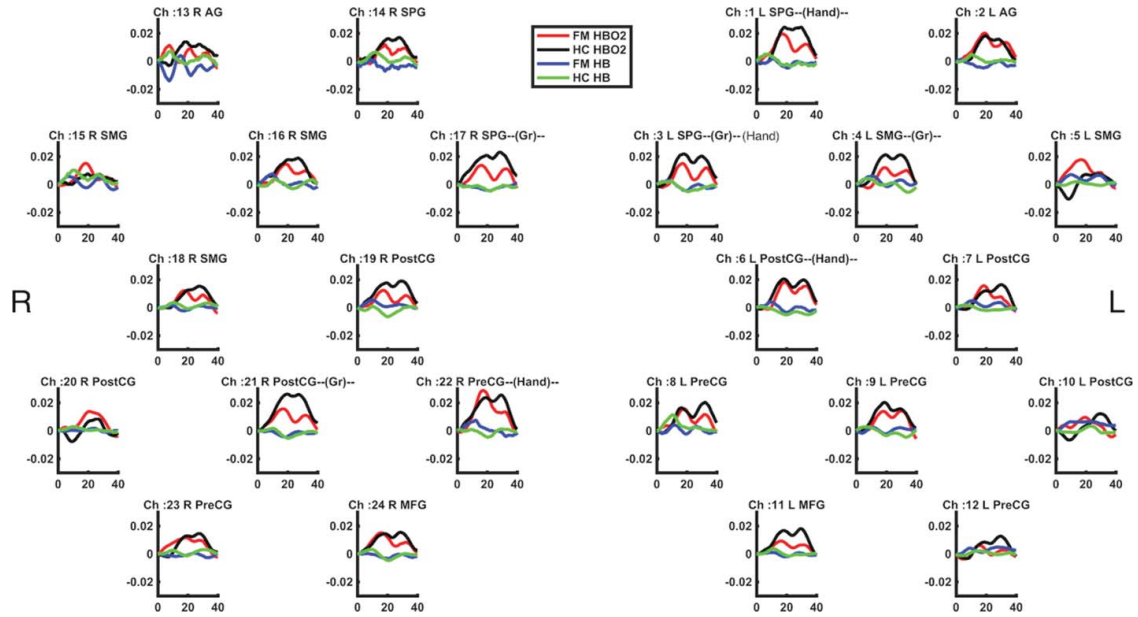

FIGURE A1. Block-averaged time-series results of right-hand FTT. R: right; L: left; Gr: channels that show group difference in 2 × 2 (Group × Hand) repeated measures ANOVA results; AG: angular gyrus; SPG: superior parietal gyrus; SMG: supramarginal gyrus; Pre CG: precentral gyrus; Post CG: postcentral gyrus; MFG: middle frontal gyrus; FM: fibromyalgia; HC: healthy controls; HBO_2: oxyhemoglobin activity; HB: deoxyhemoglobin activity.

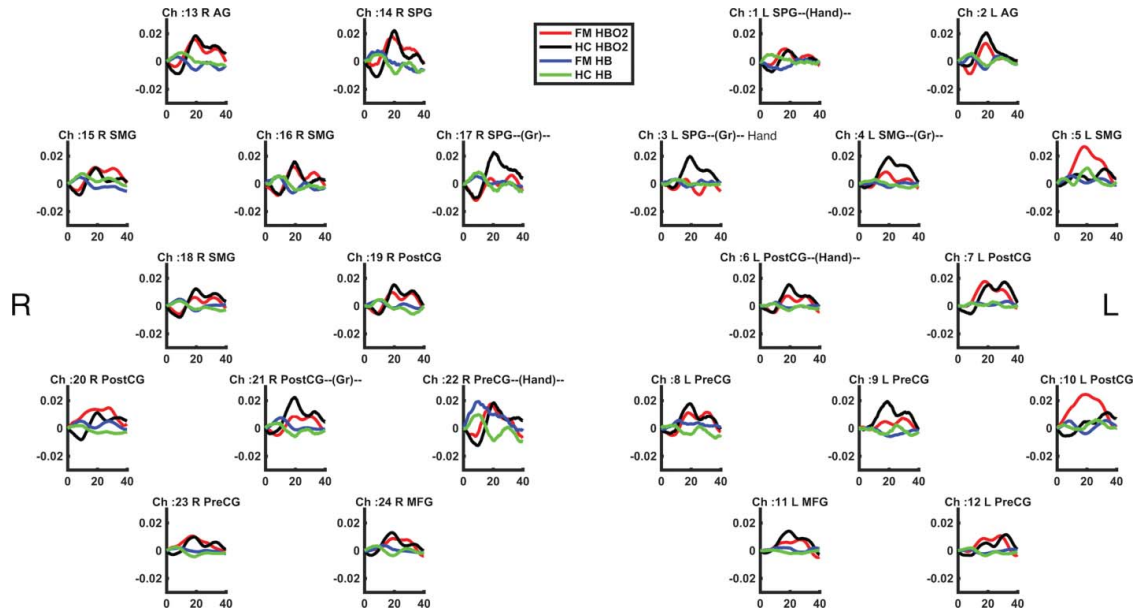

FIGURE A2. Block-averaged time-series results of left-hand FTT. R: right; L: left; Gr: channels that show group difference in 2 × 2 (Group × Hand) repeated measures ANOVA results; AG: angular gyrus; SPG: superior parietal gyrus; SMG: supramarginal gyrus; Pre CG: precentral gyrus; Post CG: postcentral gyrus; MFG: middle frontal gyrus.

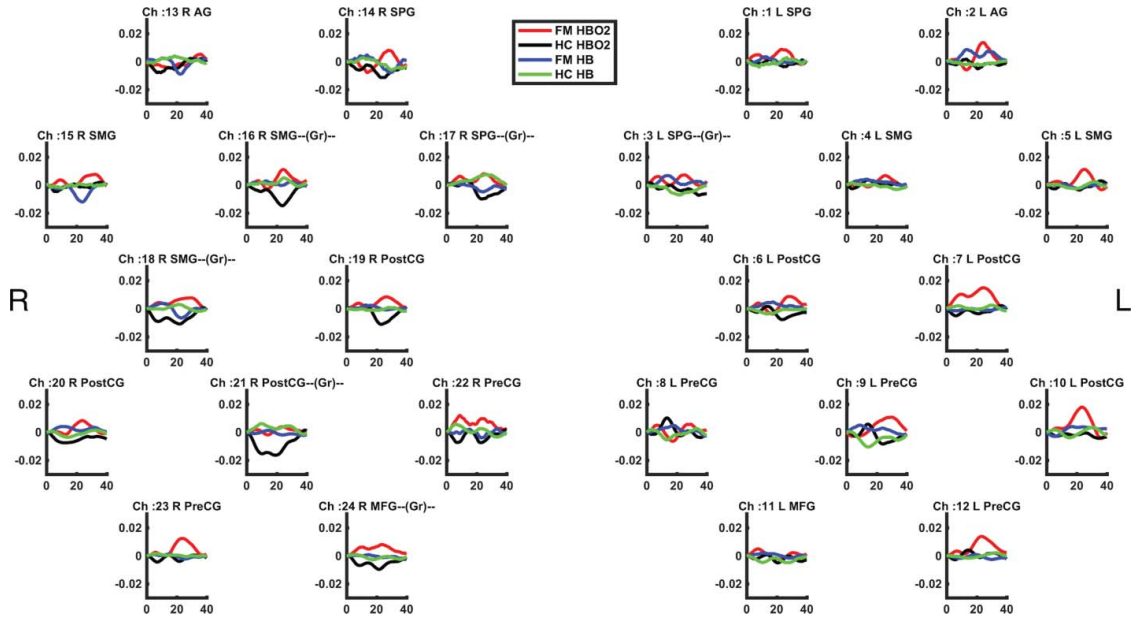

FIGURE A3. Block-averaged time-series results of right-hand TENS stimulation. R: right; L: left; Gr: channels that show group difference in 2 × 2 (Group × Hand) repeated measures ANOVA results; AG: angular gyrus; SPG: superior parietal gyrus; SMG: supramarginal gyrus; Pre CG: precentral gyrus; Post CG: postcentral gyrus; MFG: middle frontal gyrus; FM: fibromyalgia; HC: healthy controls; HBO_2: oxyhemoglobin activity; HB: deoxyhemoglobin activity.

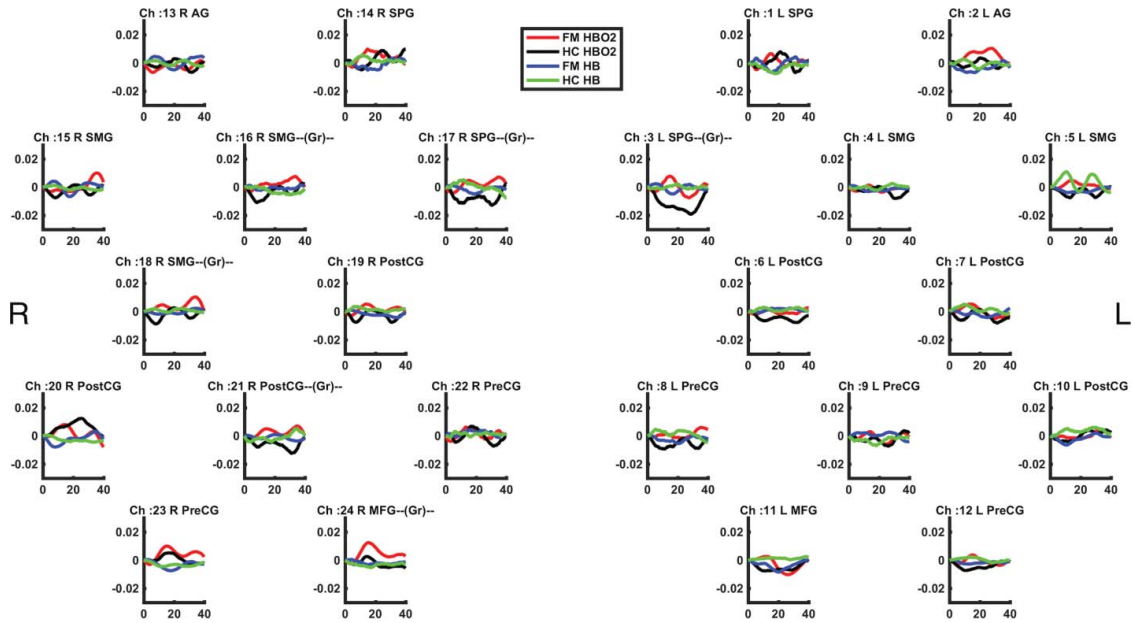

FIGURE A4. Block-averaged time-series results of left-hand TENS stimulation. R: right; L: left; Gr: channels that show group difference in 2 × 2 (Group × Hand) repeated measures ANOVA results; AG: angular gyrus; SPG: superior parietal gyrus; SMG: supramarginal gyrus; Pre CG: precentral gyrus; Post CG: postcentral gyrus; MFG: middle frontal gyrus; FM: fibromyalgia; HC: healthy controls; HBO_2: oxyhemoglobin activity; HB: deoxyhemoglobin activity.