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Immediate Changes After Manual Therapy in Resting-State Functional Connectivity as Measured by Functional Magnetic Resonance Imaging in Participants With Induced Low Back Pain

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Abstract

Objective: The purposes of this study were to use functional magnetic resonance imaging to investigate the immediate changes in functional connectivity (FC) between brain regions that process and modulate the pain experience after 3 different types of manual therapies (MT) and to identify reductions in experimentally induced myalgia and changes in local and remote pressure pain sensitivity.

Methods: Twenty-four participants (17 men; mean age ± SD, 21.6 ± 4.2 years) who completed an exercise-injury protocol to induce low back pain were randomized into 3 groups: chiropractic spinal manipulation (n = 6), spinal mobilization (n = 8), or therapeutic touch (n = 10). The primary outcome was the immediate change in FC as measured on functional magnetic resonance imaging between the following brain regions: somatosensory cortex, secondary somatosensory cortex, thalamus, anterior and posterior cingulate cortices, anterior and poster insula, and periaqueductal gray. Secondary outcomes were immediate changes in pain intensity, measured with a 101-point numeric rating scale, and pain sensitivity, measured with a handheld dynamometer. Repeated-measures analysis of variance models and correlation analyses were conducted to examine treatment effects and the relationship between within-person changes across outcome measures.

Results: Changes in FC were found between several brain regions that were common to all 3 MT interventions. Treatment-dependent changes in FC were also observed between several brain regions. Improvement was seen in pain intensity after all interventions ($P < .05$) with no difference between groups ($P > .05$). There were no observed changes in pain sensitivity, or an association between primary and secondary outcome measures.

Conclusion: These results suggest that MTs (chiropractic spinal manipulation, spinal mobilization, and therapeutic touch) have an immediate effect on the FC between brain regions involved in processing and modulating the pain experience. This suggests that neurophysiologic changes after MT may be an underlying mechanism of pain relief. (J Manipulative Physiol Ther 2014;37:614-627)

Key Indexing Terms: *Magnetic Resonance Imaging; Musculoskeletal Manipulations; Neurophysiology Brain; Chiropractic*

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Improvements in pain intensity and pain sensitivity are often reported after manual therapy (MT).[1–4] Research has demonstrated the following: (1) neurophysiologic changes are observed after MT, and (2) reductions in pain intensity and pain sensitivity are associated with functional changes in central nervous system.[5–8] A current assumption is that neurophysiologic changes after MT may underlie clinical improvement.

Functional magnetic resonance imaging (fMRI) research includes several different approaches to estimate cortical function. Several of these approaches have demonstrated functional changes associated with pain relief. One such measure is functional connectivity (FC). Functional connectivity has been defined as "the temporal correlation of a neurophysiologic index measured in different brain areas" (see Fig 1).[9] Recently, Letzen et al[6] used FC between the default mode network and brain regions associated with pain processing to investigate lidocaine-induced analgesia, whereas Zyloney et al[10] used FC between the Periaqueductal Gray (PAG) and cortical regions to investigate differential effects underlying analgesia from of genuine and sham electroacupuncture. With the evidence supporting efficacy of MT to reduce pain intensity and pain sensitivity, it is reasonable to assume that the underlying therapeutic effect of MT is likely to include a higher cortical component.[1,4,11,12]

Although models explaining the therapeutic effects of MT on pain and pain sensitivity include the potential for a higher cortical mechanism, the extent that MT exert effects on higher brain centers is not fully understood.[13–16] Thus far, only one study has used fMRI to assess changes in cortical function after MT.[17] Unlike the studies by Letzen et al and Zyloney et al, the study by Sparks et al[17] used a different approach. They used peak blood-oxygen-level–dependent (BOLD) contrast imaging to estimate of cortical function associated with a task. In their study, pain-free volunteers processed thermal stimuli applied to the hand before and after thoracic spinal manipulation (a form of MT). What they found was that after thoracic manipulation, several brain regions demonstrated a reduction in peak BOLD activity. Those regions included the cingulate, insular, motor, amygdala and somatosensory cortices, and the PAG.

The purpose of this study was to investigate the changes in FC between brain regions that process and modulate the pain experience after MT. The primary outcome was to measure the immediate change in FC across brain regions involved in processing and modulating the pain experience and identify if there were reductions in experimentally induced myalgia and changes in local and remote pressure pain sensitivity.

Methods

Study Design

This study is made up of a subset of participants who have completed a larger, ongoing, preclinical trial (NCT01406847). A randomized study design with blinded assessment was implemented with 3 groups, measured at 2 time points. Pain-free volunteers completed an exercise protocol to induce myalgia in the low back. Forty-eight hours after completion of the exercise protocol, participants returned and underwent preintervention assessment. Preintervention assessment included collection of pain intensity, local and remote pressure pain measures, and fMRI data by a blinded assessor. Participants were then randomized to receive 1 of 3 MT interventions. Sealed opaque envelopes were used to inform the treatment provider of assignment. Interventions were performed by either a licensed physical therapist or chiropractor. The randomization sequence was generated by an individual no responsible for determining study eligibility, outcome assessment, or intervention. After the intervention, participants underwent the same assessment (postintervention) performed by the same blinded assessor.

Participants

Seventy-five volunteers read and signed the informed consent form approved by the University of Florida Institutional Review Board. Enrolled participants were recruited from the campuses of the University of Florida and UF Health Hospital and the local surrounding community. Participants were eligible to participate in the study if they were between the ages of 18 and 44 years and currently not experiencing back pain. Participants were excluded from participating in the study if they met any of the following criteria: previous participation in a conditioning program specific to trunk extensors, any current back pain, any chronic medical conditions that may affect pain perception (eg, diabetes, high blood pressure, fibromyalgia, and headaches), kidney dysfunction, muscle damage, or major psychiatric disorder; history of previous injury including surgery to the lumbar spine, renal malfunction, cardiac condition, high blood pressure, osteoporosis, or liver dysfunction; and performance of any intervention for symptoms induced by exercise and before the termination of their participation of the protocol. To be included in these analyses, participants needed to undergone the exercise-injury protocol and have completed resting-state fMRI scans at both time points.

Exercise Injury Model to Induce Low Back Pain

Prior to exercise, all participants completed a 5-minute warm-up consisting of riding a stationary bicycle. After the 5-minute warm-up, participants then performed an isometric test to establish a baseline measure of torque.[18] Participants then performed repetitions of dynamic resisted exercise. Resistance was individualized to each participant using a weight load. Weight loads were equal to 90% of the peak torque measured during the baseline isometric test. Each repetition was performed through the full available range of motion. Participants performed sets of 15 repetitions or until

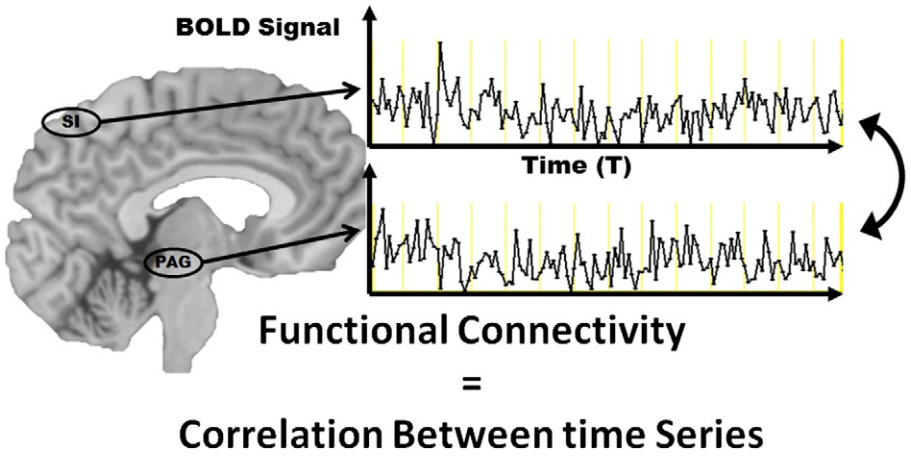

Fig 1. *Functional connectivity is defined as the temporal correlation of a neurophysiologic index measured in different brain areas. This term has been applied to fMRI, where the changes in BOLD signal over time are compared between 2 ROIs. The correlation between the time series equals the estimated FC.*

volitional fatigue. After each set, torque was reestimated. Using a criterion of 50% drop in torque, participants either completed another set if the torque was greater than 50% or ended if the reestimated torque was 50% or less than the baseline. After the exercise, participants were instructed not to initiate any medication or apply any intervention to the lumbar spine to reduce painful symptoms. This human model of acute endogenous low back pain has been previously described in greater detail elsewhere.[19,20]

Manual Therapy Interventions

Interventions were performed by health care professionals who were selected from a pool based on availability and who were not involved with the assessment of the participant. The pool consisted of health care professionals who had an active license (either physical therapy or chiropractic), were currently or previously practiced, were comfortable providing MT for musculoskeletal pain conditions, and underwent training (with M.D.B.) on the specific techniques performed in this study. The amount of "hands-on" and personal contact was equivalent between interventions. Prior to the intervention, all participants were given similar verbal instructions regarding the techniques performed. Each intervention met the criteria to be categorized as a "Mind and Body"–based therapy by the National Center of Complementary and Alternative Medicine.[21] In this study, each intervention was considered an MT technique and is briefly described below.

Spinal Manipulative Therapy

Participants randomized to the spinal manipulative therapy (SMT) group received a high-velocity, low-amplitude thrust (grade V) technique previously described in the literature and commonly used for the treatment of low back pain by several health care professions.[22–28] This particular technique was selected because it was used in low back pain–clinical prediction rule studies involving patients with acute and subacute pain[23] and was the same technique used by our group, which reported immediate pain sensitivity changes in healthy and low back pain participants.[24,25]

Spinal Mobilization

Participants randomized to spinal mobilization (MOB) received a "grade III" mobilizing force applied and released to the lumbar spine, directed posterior to anterior at a rate of 1 Hz for 2 minutes, followed by a 1-minute rest, and then the mobilizing force again for 2 minutes. This particular technique was selected because it was used in a recent clinical trial involving patients with acute or subacute pain,[29] and commonly used for the treatment of low back pain.

Therapeutic Touch Control

Participants randomized to therapeutic touch control (TT) lay prone. The therapist placed both hands in contact with the participants' pelvis across the top of the posterior aspect of the sacrum and ilia. Light pressure was applied for 5 minutes.

Primary Outcome (Functional Imaging)

Acquisition. Functional magnetic resonance imaging was performed using a research dedicated, Phillips Achieva 3 Tesla MRI Scanner (Phillips Healthcare, Andover, MA), fitted with a 32-channel head coil. Each resting-state fMRI scan was 5 minutes and 42 seconds long. One resting-state scan was taken before and after the assigned intervention. Functional data were collected in the transaxial orientation using an EPI sequence (XYZ dimension = 80 * 80 * 38; field

of view [RL (right-to-left direction), AP (anterior-to-posterior direction), FH (foot-to-head direction)—mm] = 240, 240, 114; slice thickness [mm] = 3; gap thickness = 0; voxel dimension [mm] = 3 * 3 * 3; repetition time [milliseconds] = 2000), which is consistent with recommended resting functional scanning parameters.[30] Structural data consisted of a high-resolution 3-dimensional (3D) structural T1 collected in sagittal orientation (XYZ dimension = 256 * 256 * 180; field of view [AP, FH, RL—mm] = 240, 240, 180; slice thickness [mm] = 1; gap thickness = 0; voxel dimension [mm] = 1 * 1 * 1; repetition time/echo time (TR/TE) [milliseconds] = 8.1/3.7). During the functional scan, physiological measures (eg, pulse oximeter and respirations) were recorded simultaneously using built-in recording equipment that is part of the Philips system. During scanning, participants remained in the supine position with their heads cushioned to reduce motion. Participants were instructed to remain awake, with their eyes open and fixated on a cross hair, "not to think about anything in particular," and to remain as still as possible. Participants wore earplugs throughout the experiment to attenuate MRI noise.

Processing. Functional data were preprocessed in SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Images were (1) slice-time corrected, (2) realigned and resliced into 3-mm isotropic voxels, (4) co-registered to the high-resolution 3D anatomic volume, (5) warped into Montreal Neurological Institute standard space using the deformations used to realign the 3D anatomical data into Montreal Neurological Institute space, and (6) spatially smoothed using a 6-mm full-width half-maximum Gaussian kernel. Data were spike corrected to reduce the impact of artifacts using the postprocessing Artifact Detection Tool toolbox for fMRI data (http://www.nitrc.org/projects/artifact_detect). Time points, where the mean global signal changed by above 3 SDs, translation movement exceeded 0.5 mm or rotational movement exceeded 0.01°, were identified and later removed during first level general linear model. The final processing steps were then carried out using the FC toolbox Conn (http://www.nitrc.org/projects/conn) that implements the component-based noise correction method strategy for physiological and other noise source reduction, which included the following: (1) temporal (band-pass) filtering set between 0.01 and 0.1 Hz and (2) removal of several sources of nonspecific variance by regression of nuisance variables. Those nuisance variables included the following: (1) the signal averaged over the lateral ventricles, (2) the signal averaged over the deep cerebral white matter, (3) the 6 parameters obtained by motion correction, and (4) the outlier data points identified with the Artifact Detection Tool toolbox.

Regions of Interest. Within the brain, the pain experience is subserved by an extended network of brain regions including the thalamus (THA), primary and secondary somatosensory, cingulate, and insular cortices.[31–33] Collectively, these regions are referred to as the *pain processing network* (PPN) and encode the sensory discriminate and cognitive and emotional components of the pain experience.[33,34] Perception of pain is dependent not merely on the neural activity within the PPN but also on the flexible interactions of this network with other functional systems, including the descending pain modulatory system.[35,36] The descending pain modulatory system includes subcortical regions such as the PAG.[37,38] Because of this, we choose to investigate 8 brain regions bilaterally (16 total). Those regions are as follows: anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), anterior insular cortex (aINS), posterior insular cortex (pINS), THA, primary and secondary somatosensory cortex (SI, SII), and the PAG. We used previously published coordinates to center our regions of interest (ROIs). Those coordinates come from pain studies that included patients with back pain[39–41] and healthy volunteers.[42,43] With the coordinates as the center, 9-mm spheres were created for each ROI, except for the THA and PAG, which were 6 mm each. Each ROI sphere was overlaid with a gray-matter mask to include only gray-matter voxels. The ROI time series was then estimated by the spatial average of the BOLD time series over all voxels within the generated spherical region and gray-matter mask.

Functional Connectivity. Functional connectivity was estimated using the "Conn Toolbox" (www.nitrc.org/projects/conn)[44] and represents the bivariate correlation between 2 ROIs' time series. See Figure 1 for a schematic of FC. The FC between each possible ROI-to-ROI connection was estimated twice (120 total connections): once before the intervention and again immediately after the intervention. Bivariate correlations were converted to normally distributed z scores using the Fisher transformation. The difference (post-FC − pre-FC) in FC was estimated and used as the change in FC between each ROI-to-ROI connection.

Secondary Outcomes (Behavioral Measures)

Pain Intensity. Participants used the 101-point numerical rating scale to provide a measure of the current intensity of their lower back pain.[45] The numeric rating scale is anchored with 0 = "no pain" and 100 = "worst pain imaginable." The therapist who performed the intervention collected participants' ratings. The therapist asked for the rating immediately before and after the participants received their assigned intervention. The immediate effect on pain intensity was the difference between ratings given at the 2 time points (ie, post − pre).

Pressure Pain Threshold. Pressure pain thresholds (PPT) were assessed by a blinded assessor using a Microfet 2 handheld dynamometer (Hoggan Health Industries, Inc, West Jordan, UT). The tip of the dynamometer is equipped with a rubber foot-plate of 1-cm diameter. During testing, participants were positioned prone and pressure was slowly applied until the participant reported that the sensation changed from pressure to pain. At that point when participants reported pain, the applied force was recorded. Threshold measures were evoked in the paraspinal muscles bilaterally 2.5 cm from the spinous processes of L1, L5, and S2 and over the dorsum of the hand and foot, in the web-

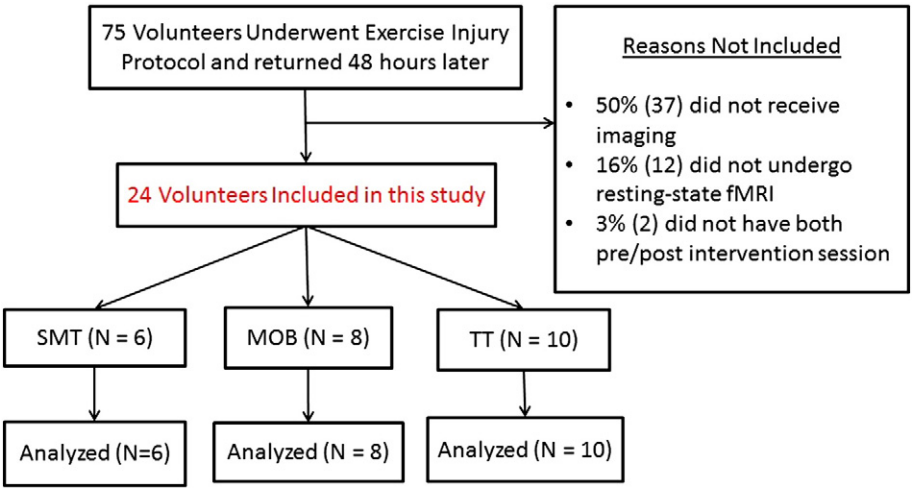

Fig 2. *The data used for this study were obtained from a subgroup of volunteers derived from the preclinical trial. fMRI, functional magnetic resonance imaging; MOB, spinal mobilization theory; SMT, spinal manipulative therapy; TT, therapeutic touch control.*

space between the first and second toe/finger. Local PPTs were a composite measure of the average threshold over the 3 paraspinal muscle locations assessed bilaterally. Remote PPTs were a composite measure of the average threshold assessed on the dorsum of the foot and hand.

Statistics

For all measures, means and SDs were created at each time point. Pearson correlation coefficients were estimated to assess the relationships across variables at each time point (ie, preintervention and postintervention). To establish within- and between-group changes over time, we used repeated-measures analysis of variance (RM-ANOVA). Separate RM-ANOVAs were used to assess for the main effect of time and for group by time interactions for each ROI-to-ROI connection, pain intensity, and pressure pain sensitivity. In each RM-ANOVA, the dependent variable was the postrandomization value, the baseline value was a covariate, and intervention assignment was the between-participant factor. We corrected for the number of separate RM-ANOVAs conducted for across the 120 ROI-to-ROI pairs by using a P value less than .01 as significant. Lastly, residual change scores were used to put all outcome measures into a standard metric of change. Pearson correlation coefficients were used to estimate the relationship of within-person change between the different outcomes measured (ie, primary and secondary outcomes). All data analyses were performed using SPSS v21 (SPSS, Chicago, IL).

Results

Of the 75 volunteers, 24 (mean ± SD age, 21.6 ± 4.2 years; 17 women) met the inclusion criteria and were included in these analyses. Figure 2 shows the derivation of the included sample. The imaging subgroup did no differ in age, percent female, or other behavioral measures from the remainder of the nonimaged study population (see Table 1 for more details).

Randomization of the imaging subgroup resulted in 6 participants receiving SMT, 8 participants receiving MOB, and 10 participants receiving TT. Characteristics of the imaging subgroup, separated by randomization assignment, are summarized in Table 2. Preintervention, postintervention, and raw change scores are presented for FC measures between each ROI-to-ROI connection, as well as the correlation to behavioral measures at the same time point, in Tables 3, 4, and 5 for right hemisphere connections, left hemisphere connections, and cross-hemisphere connections, respectively.

Primary Outcome Measure

Common FC Changes for All MT groups. The RM-ANOVAs found a main effect for time in 2 left hemisphere connections and 1 cross-hemisphere connection (see Fig 3). In the left hemisphere, the connections between the PCC and aINS ($P = .001$) and pINS and PAG ($P = .005$) significantly changed over time. Prior to MT, the left PCC and left aINS showed a weak inverse (negative) relationship (FC = −0.02, SD = 0.17). After MT, the relationship flipped, showing a weak positive relationship (FC = 0.15, SD = 0.21). The relationship between the left pINS and left PAG showed an overall increase over time going from 0.03 (SD = 0.21) to 0.17 (0.21). The cross-hemisphere connection between the left SI and right pINS decreased over time ($P = .005$). These regions shared a moderately strong positive relationship prior to intervention (FC = 0.36, SD = 0.26) that became weaker overtime (FC = 0.20, SD = 0.26).

Table 1. *Comparison of Characteristics of the Subgroup Included to Those Not Included in the Current Analysis*

Variable	Imaging Subgroup (n = 24)	No Imaging Subgroup (n = 51)	Mean Difference Between Groups	*P*
Age (y), mean (SD)	21.6 (4.2)	22.7 (4.0)	1.1	.27
Sex	71% (17 women)	73% (37 women)	2%	.84
Pain intensity (Pre)	10.5 (15.2)	12.1 (13.4)	1.6	.64
Pain intensity (Post)	6.6 (11.9)	9.0 (9.7)	2.5	.35
ΔPain intensity	−3.9 (6.9)	−3.5 (9.5)	0.3	.88
Local PPT (Pre)	14.9 (6.4)	18.6 (9.3)	3.7	.08
Local PPT (Post)	14.9 (6.6)	18.0 (9.2)	3.1	.14
ΔLocal PPT	−0.0 (3.7)	−0.4 (2.9)	−0.3	.68
Remote PPT (Pre)	13.6 (5.6)	16.0 (9.5)	2.5	.24
Remote PPT (Post)	13.4 (5.2)	14.9 (8.3)	1.5	.41
ΔRemote PPT	−0.2	−0.9	−0.7	.36

Pain intensity values are presented as mean (SD) rating using 101-point numerical rating system. PPT values are presented as mean (SD) force kg/cm^2*. Post,* after MBB therapy; *PPT*, pressure pain thresholds; *Pre*, prior to MBB therapy; *Δ*, change score (post minus pre).

Table 2. *Characteristics of Imaging Subgroup Separated by MBB Therapy*

Variable/Group	SMT	MOB	TT	Total
No. of participants	6	8	10	24
Age (y), mean (SD)	20.7 (1.8)	21.1 (3.2)	22.5 (5.9)	21.6 (4.2)
Female, no. (%)	5 (83)	7 (88)	5 (50)	17 (71)
Pain intensity (Pre)	11.8 (13.7)	14.5 (22.1)	6.4 (8.5)	10.5 (15.2)
Pain intensity (Post)	5.5 (8.1)	10.1 (18.2)	4.4 (7.2)	6.6 (11.9)
ΔPain intensity	−6.3 (8.8)	−4.4 (8.5)	−2.0 (3.5)	−3.9 (6.9)
Local PPT (Pre)	12.9 (4.8)	12.4 (4.3)	18.2 (7.5)	14.9 (6.4)
Local PPT (Post)	11.8 (4.6)	11.2 (2.9)	19.7 (7.0)	14.9 (6.6)
ΔLocal PPT	−1.1 (0.8)	−1.2 (3.8)	1.5 (4.2)	−0.02 (3.7)
Remote PPT (Pre)	10.1 (3.4)	12.7 (3.7)	16.4 (6.8)	13.6 (5.6)
Remote PPT (Post)	10.2 (3.7)	11.6 (3.1)	19.7 (7.0)	13.4 (5.2)
ΔRemote PPT	0.1 (1.0)	−1.1 (3.9)	0.4 (3.0)	−0.2 (3.0)

Pain intensity values are presented as mean (SD) rating using 101-point numerical rating system. PPT values are presented as mean (SD) force kg/cm^2*. MOB,* spinal mobilization theory; *Post*, after MBB therapy; *PPT*, pressure pain thresholds; *Pre*, prior to MBB therapy; *SMT*, spinal manipulative therapy; *TT*, therapeutic touch control; *Δ*, change score (post minus pre).

Treatment-Dependent FC Changes. Two right hemisphere and 1 cross-hemisphere ROI-to-ROI connections demonstrated significant ($P < .01$) treatment-dependent differences in the rate of FC change (see Fig 4). In the right hemisphere, the strength of the positive connection between SI and aINS increased in the SMT group (ΔFC = 0.28), whereas it deceased in the MOB (ΔFC = −0.04) and TT (ΔFC = −0.14) groups. Also in the right hemisphere, the strength between SI and PAG increased in the SMT (ΔFC = 0.04) and MOB (ΔFC = 0.19) groups, whereas it decreased in the TT group (ΔFC = −0.17). The cross-hemisphere connection between the right aINS and left PCC increased in the SMT (ΔFC = 0.21) and MOB (ΔFC = 0.05) groups, whereas it decreased the TT group (ΔFC = −0.06).

Secondary Outcome Measure

On average, the pain intensity in our sample significantly decreased overtime (mean pain reduction, 3.88; 95% confidence interval [CI], 0.98-6.77; $F_{1,21} = 8.60$, $P < .01$), regardless of the particular intervention received. No significant differences were observed in change of pain intensity across the MT groups as evidenced by group by time interaction ($F_{2,21} = 0.77$, $P = .50$). No significant change was observed in local or remote pressure pain sensitivity over time or for particular MT treatments (mean local PPT change, −0.02 [95% CI, −1.57 to 1.52]; mean remote PPT change, −0.17 [95% CI, −1.41 to 1.08]; $P > .05$).

Discussion

This study assessed the relationship of brain activity between regions of the PPN before and after MT. Using this approach, we found common and treatment-dependent changes in FC. These results provide further support to speculations that neurophysiologic mechanisms may be involved in the clinical benefit after MT.[15] Current speculation contends that the biomechanical aspect of MT induces neurophysiologic effects that underlie clinical improvement. Our study is unique in our neurophysiologic measure because we used resting-state fMRI in conjunction with FC analyses. Our results are in agreement with studies that have found immediate changes using other neurophysiologic outcomes, such as Hoffman-reflex and motor-neuron excitability,

Table 3. *Right Hemisphere ROI-to-ROI Connections*

ROI-to-ROI Pair	(Pre) FC	ρ (Pre) Pain Intensity	ρ (Pre) Local PPT	ρ (Pre) Remote PPT	(Post) FC	ρ (Post) Pain Intensity	ρ (Post) Local PPT	ρ (Post) Remote PPT	ΔFC	ρ ΔPain Intensity	ρ ΔLocal PPT	ρ ΔRemote PPT
R_ACC-to-R_PCC	0.26 (0.28)	0.053	0.282	0.456 [a]	0.17 (0.24)	0.271	0.062	0.204	−0.08 (0.30)	0.008	−0.129	0.118
R_ACC-to-R_aINS	0.26 (0.24)	0.204	0.302	0.389	0.30 (0.22)	−0.424 [a]	0.185	0.115	0.04 (0.30)	0.127	0.142	−0.117
R_ACC-to-R_pINS	0.29 (0.22)	0.214	−0.116	0.169	0.22 (0.27)	−0.370	−0.019	−0.041	−0.07 (0.30)	0.141	0.220	−0.187
R_ACC-to-R_SI	0.30 (0.25)	0.033	0.185	0.289	0.25 (0.24)	−0.214	0.124	0.043	−0.05 (0.28)	−0.093	0.153	0.053
R_ACC-to-R_SII	0.31 (0.22)	−0.011	0.360	0.604 [b]	0.29 (0.24)	−0.397	−0.007	−0.102	−0.02 (0.33)	−0.105	0.052	0.008
R_ACC-to-R_THA	0.09 (0.19)	0.062	0.151	0.129	0.13 (0.19)	0.339	−0.291	−0.031	0.04 (0.27)	0.039	−0.018	−0.255
R_ACC-to-R_PAG	0.18 (0.22)	0.088	0.014	0.248	0.20 (0.17)	−0.049	−0.031	0.070	0.10 (0.31)	−0.143	−0.139	0.216
R_PCC-to-R_aINS	−0.00 (0.17)	0.275	0.145	0.432 [a]	0.04 (0.14)	−0.178	0.164	0.074	0.04 (0.18)	0.062	−0.208	−0.218
R_PCC-to-R_pINS	0.16 (0.22)	0.282	0.089	0.432 [a]	0.09 (0.19)	−0.333	−0.051	−0.104	−0.07 (0.29)	0.249	−0.070	0.064
R_PCC-to-R_SI	0.16 (0.30)	−0.080	0.267	0.498 [a]	0.08 (0.26)	−0.085	0.021	0.177	−0.08 (0.35)	−0.073	−0.305	0.467 [a]
R_PCC-to-R_SII	0.16 (0.31)	0.041	0.322	0.587 [b]	0.11 (0.23)	−0.266	0.020	0.116	−0.05 (0.32)	0.070	−0.271	0.125
R_PCC-to-R_THA	0.18 (0.25)	0.180	0.006	0.137	0.16 (0.18)	−0.093	0.110	0.173	−0.02 (0.26)	0.569 [b]	−0.018	−0.277
R_PCC-to-R_PAG	0.22 (0.25)	0.259	0.067	0.239	0.23 (0.18)	−0.140	0.293	0.244	0.01 (0.28)	0.237	−0.200	−0.240
R_aINS-to-R_pINS	0.50 (0.31)	−0.139	−0.039	0.103	0.52 (0.30)	−0.262	−0.052	0.036	0.02 (0.28)	0.560 [b]	0.009	−0.030
R_aINS-to-R_SI	0.13 (0.16)	−0.016	0.016	0.276	0.13 (0.22)	−0.239	0.004	−0.317	−0.00 (0.28)	0.093	−0.208	−0.300
R_aINS-to-R_SII	0.34 (0.21)	0.058	−0.098	0.055	0.35 (0.29)	−0.338	−0.094	−0.126	0.01 (0.27)	0.174	0.287	−0.204
R_aINS-to-R_THA	0.12 (0.16)	−0.232	−0.028	0.134	0.04 (0.14)	−0.210	0.026	0.147	−0.08 (0.20)	0.192	−0.078	0.164
R_aINS-to-R_PAG	0.09 (0.16)	−0.196	0.042	0.225	0.11 (0.20)	−0.449 [a]	0.121	0.168	0.01 (0.16)	0.226	0.204	−0.089
R_pINS-to-R_SI	0.34 (0.25)	−0.097	−0.314	0.102	0.28 (0.21)	0.105	−0.101	−0.351	−0.05 (0.27)	−0.300	−0.417 [a]	−0.047
R_pINS-to-R_SII	0.60 (0.26)	−0.076	0.012	0.313	0.61 (0.25)	−0.015	0.170	0.009	0.01 (0.25)	−0.031	−0.115	−0.219
R_pINS-to-R_THA	0.23 (0.16)	0.214	0.026	−0.008	0.25 (0.18)	−0.383	0.104	0.111	0.02 (0.24)	−0.070	0.000	−0.092
R_pINS-to-R_PAG	0.12 (0.20)	0.006	−0.093	0.215	0.15 (0.22)	−0.221	−0.150	−0.267	0.03 (0.22)	0.099	−0.124	0.134
R_SI-to-R_SII	0.45 (0.22)	0.114	0.234	0.254	0.48 (0.25)	0.067	−0.056	−0.257	0.03 (0.27)	−0.046	−0.312	0.090
R_SI-to-R_THA	0.06 (0.18)	0.069	0.216	0.177	0.04 (0.27)	0.366	−0.314	−0.059	−0.02 (0.30)	−0.178	0.172	0.156
R_SI-to-R_PAG	0.09 (0.22)	0.138	0.289	0.359	0.09 (0.14)	0.199	−0.531 [b]	−0.390	0.00 (0.25)	0.001	−0.093	−0.120
R_SII-to-R_THA	0.17 (0.21)	0.271	−0.020	0.069	0.13 (0.13)	0.199	−0.531	−0.390	−0.04 (0.24)	−0.015	−0.159	0.076
R_SII-to-R_PAG	0.14 (0.24)	0.153	0.060	0.317	0.12 (0.18)	0.070	−0.218	−0.112	−0.02 (0.25)	0.055	−0.420 [a]	−0.009
R_THA-to-R_PAG	0.16 (0.19)	−0.004	0.134	0.339	0.15 (0.16)	−0.214	0.029	0.060	−0.00 (0.25)	0.049	−0.148	0.204

FC values are presented as mean (SD) Fisher transformed zero-order estimate.

ACC, anterior cingulate cortex; *aINS*, anterior insular cortex; *FC*, functional connectivity; *L*, left; *PAG*, periaqueductal gray; *PCC*, posterior cingulate cortex; *pINS*, posterior insular cortex; *Post*, after MBB therapy; *PPT*, pressure pain threshold; *Pre*, prior to MBB therapy; *R*, right; *SI*, primary somato-sensory cortex; *SII*, secondary somato-sensory cortex; *THA*, thalamus; *Δ*, change score (post minus pre); *ρ*, Pearson product-moment correlation coefficient.

[a] $P < .05$.

[b] $P < .01$.

Table 4. *Left Hemisphere ROI-to-ROI Connections*

ROI-to-ROI Pair	(Pre) FC	ρ (Pre) Pain Intensity	ρ (Pre) Local PPT	ρ (Pre) Remote PPT	(Post) FC	ρ (Post) Pain Intensity	ρ (Post) Local PPT	ρ (Post) Remote PPT	ΔFC	ρ ΔPain Intensity	ρ ΔLocal PPT	ρ ΔRemote PPT
L_ACC-to-L_PCC	0.18 (0.26)	−0.09	0.32	0.59	0.17 (0.22)	0.13	0.20	0.17	−0.01 (0.27)	−0.020	−0.232	0.229
L_ACC-to-L_aINS	0.30 (0.21)	0.02	0.39	0.38	0.33 (0.24)	0.09	0.05	−0.09	0.03 (0.24)	0.097	−0.149	−0.278
L_ACC-to-L_pINS	0.29 (0.29)	0.06	0.02	0.34	0.23 (0.21)	−0.29	0.42	0.28	−0.06 (0.30)	−0.041	0.123	−0.082
L_ACC-to-L_SI	0.25 (0.26)	0.08	0.08	0.21	0.18 (0.22)	−0.19	0.10	−0.04	−0.07 (0.26)	0.052	0.007	0.064
L_ACC-to-L_SII	0.34 (0.19)	−0.18	0.18	0.36	0.37 (0.24)	−0.10	0.01	−0.15	0.03 (0.29)	−0.224	0.193	0.078
L_ACC-to-L_THA	0.14 (0.24)	0.05	−0.01	0.09	0.25 (0.16)	0.48	−0.37	−0.18	0.11 (0.25)	−0.028	−0.030	0.100
L_ACC-to-L_PAG	0.12 (0.22)	−0.05	0.02	0.33	0.22 (0.22)	0.17	0.02	0.09	0.09 (0.30)	−0.174	−0.135	0.223
L_PCC-to-L_aINS	−0.02 (0.17)	0.14	0.13	0.30	0.15 (0.21)	0.05	−0.01	−0.01	0.17 (0.23)	0.08	−0.17	0.07
L_PCC-to-L_pINS	0.11 (0.22)	−0.16	0.24	0.61	0.16 (0.17)	−0.12	−0.24	−0.17	0.05 (0.27)	−0.13	−0.23	0.38
L_PCC-to-L_SI	0.15 (0.27)	−0.231	0.131	0.357	0.12 (0.25)	−0.131	−0.246	−0.140	−0.04 (0.34)	−0.07	−0.28	0.37
L_PCC-to-L_SII	0.12 (0.31)	−0.15	0.32	0.57	0.11 (0.21)	0.11	−0.06	−0.08	−0.01 (0.33)	−0.23	−0.36	0.38
L_PCC-to-L_THA	0.12 (0.27)	0.20	−0.01	0.11	0.23 (0.20)	0.17	0.03	−0.06	0.11 (0.29)	0.29	0.02	−0.11
L_PCC-to-L_PAG	0.23 (0.24)	0.30	0.17	0.19	0.26 (0.17)	0.29	0.14	−0.01	0.04 (0.27)	0.24	−0.04	−0.18
L_aINS-to-L_pINS	0.62 (0.29)	−0.244	0.007	0.034	0.54 (0.31)	−0.305	0.234	0.240	−0.08 (0.28)	−0.167	0.033	−0.268
L_aINS-to-L_SI	0.18 (0.21)	−0.167	0.192	0.133	0.18 (0.26)	0.021	−0.060	−0.191	−0.00 (0.32)	−0.209	−0.285	−0.201
L_aINS-to-L_SII	0.39 (0.23)	0.251	−0.056	−0.154	0.29 (0.29)	−0.114	0.005	0.035	−0.10 (0.35)	0.066	0.370	−0.063
L_aINS-to-L_THA	0.04 (0.18)	0.221	−0.010	0.119	0.07 (0.21)	0.065	0.011	−0.051	0.03 (0.25)	0.146	−0.007	−0.293
L_aINS-to-L_PAG	0.05 (0.17)	0.115	0.215	0.409 [a]	0.17 (0.20)	−0.065	0.094	0.006	0.12 (0.26)	−0.081	−0.390	−0.205
L_pINS-to-L_SI	0.35 (0.28)	−0.029	0.214	0.273	0.35 (0.27)	0.047	0.255	−0.003	−0.01 (0.31)	0.207	−0.189	−0.065
L_pINS-to-L_SII	0.61 (0.26)	−0.186	0.439 [a]	0.324	0.49 (0.30)	0.036	0.413 [a]	0.182	−0.12 (0.25)	0.008	0.208	0.097
L_pINS-to-L_THA	0.04 (0.26)	0.129	−0.089	−0.001	0.14 (0.24)	0.373	−0.206	0.000	0.10 (0.29)	−0.047	0.101	0.058
L_pINS-to-L_PAG	0.03 (0.21)	0.106	−0.053	0.345	0.17 (0.21)	−0.093	0.060	0.203	0.13 (0.21)	0.052	−0.244	−0.210
L_SI-to-L_SII	0.48 (0.31)	−0.077	0.299	0.400	0.37 (0.31)	−0.051	0.220	0.120	−0.12 (0.33)	0.332	−0.196	−0.038
L_SI-to-L_THA	−0.06 (0.24)	0.230	−0.006	0.127	0.01 (0.20)	0.489 [a]	−0.225	−0.045	0.07 (0.30)	0.294	−0.042	0.220
L_SI-to-L_PAG	0.02 (0.21)	0.079	0.025	0.306	0.10 (0.16)	0.057	−0.242	−0.128	0.08 (0.22)	−0.065	−0.388	−0.109
L_SII-to-L_THA	0.08 (0.24)	0.045	−0.006	−0.078	0.15 (0.20)	0.687 [b]	−0.348	−0.098	0.06 (0.28)	−0.283	0.164	0.222
L_SII-to-L_PAG	0.03 (0.22)	0.046	−0.027	0.298	0.11 (0.19)	0.173	0.055	0.092	0.08 (0.23)	−0.201	−0.241	0.246
L_THA-to-L_PAG	0.32 (0.24)	0.064	0.080	0.177	0.32 (0.16)	0.152	−0.117	−0.033	0.00 (0.29)	0.425 [a]	−0.184	0.202

FC values are presented as mean (SD) Fisher transformed zero-order estimate.

ACC, anterior cingulate cortex; *aINS*, anterior insular cortex; *FC*, functional connectivity; *L*, left; *PAG*, periaqueductal gray; *PCC*, posterior cingulate cortex; *pINS*, posterior insular cortex; *Post*, after MBB therapy; *PPT*, pressure pain threshold; *Pre*, prior to MBB therapy; *R*, right; *SI,* primary somato-sensory cortex; *SII*, secondary somato-sensory cortex; *THA*, thalamus; *Δ*, change score (post minus pre); *ρ*, Pearson product-moment correlation coefficient.

[a] $P < .05$.

[b] $P < .01$.

Table 5. *Cross-Hemisphere ROI-to-ROI Connections*

ROI-to-ROI Pair	(Pre) FC	ρ (Pre) Pain Intensity	ρ (Pre) Local PPT	ρ (Pre) Remote PPT	(Post) FC	ρ (Post) Pain Intensity	ρ (Post) Local PPT	ρ (Post) Remote PPT	ΔFC	ρ ΔPain Intensity	ρ ΔLocal PPT	ρ Δ Remote PPT
R_ACC-to-L_ACC	2.58 (0.25)	0.065	0.286	0.110	2.60 (0.34)	0.171	−0.115	−0.123	0.02 (0.35)	−0.083	−0.121	0.030
R_ACC-to-L_PCC	0.18 (0.26)	−0.074	0.309	0.551 [b]	0.18 (0.24)	0.140	0.197	0.185	−0.00 (0.28)	−0.002	−0.183	0.174
R_ACC-to-L_aINS	0.31 (0.22)	0.018	0.387	0.367	0.33 (0.25)	0.083	0.050	−0.048	0.03 (0.24)	0.070	−0.158	−0.279
R_ACC-to-L_pINS	0.29 (0.29)	0.039	0.026	v.309	0.24 (0.21)	−0.336	v.423 [a]	0.258	−0.05 (0.31)	−0.050	0.111	−0.091
R_ACC-to-L_SI	0.26 (0.26)	0.059	0.103	0.222	0.19 (0.22)	−0.207	0.103	−0.040	−0.07 (0.26)	0.043	−0.011	0.060
R_ACC-to-L_SII	0.34 (0.20)	−0.171	0.169	0.337	0.38 (0.25)	−0.124	−0.008	−0.162	0.04 (0.29)	−0.204	0.199	0.028
R_ACC-to-L_THA	0.13 (0.24)	−0.011	0.035	0.135	25 (0.16)	0.449 [a]	−0.348	−0.179	0.12 (0.26)	−0.051	−0.065	0.114
R_ACC-to-L_PAG	0.12 (0.23)	−0.022	0.018	0.354	0.22 (0.23)	0.145	0.038	0.138	0.10 (0.31)	−0.143	−0.139	0.216
R_PCC-to-L_ACC	0.26 (0.28)	0.033	0.302	0.506 [a]	0.17 (0.24)	0.277	0.073	0.197	−0.09 (0.30)	−0.014	−0.154	0.168
R_PCC-to-L_PCC	1.32 (0.20)	−0.027	0.067	0.019	1.28 (0.25)	−0.041	−0.358	−0.441 [a]	−0.04 (0.26)	0.003	0.043	−0.153
R_PCC-to-L_aINS	−0.02 (0.20)	0.132	0.185	0.408 [a]	0.09 (0.20)	0.148	0.017	0.055	0.11 (0.22)	−0.048	−0.132	0.072
R_PCC-to-L_pINS	0.06 (0.24)	−0.031	0.191	0.555 [b]	0.12 (0.17)	−0.126	−0.136	−0.117	0.06 (0.24)	0.027	−0.104	0.273
R_PCC-to-L_SI	0.12 (0.30)	−0.186	0.187	0.243	0.12 (0.21)	−0.141	−0.185	−0.087	0.00 (0.34)	−0.104	−0.232	0.325
R_PCC-to-L_SII	0.10 (031)	−0.078	0.282	0.490 [a]	0.09 (0.20)	0.101	−0.124	−0.080	−0.01 (0.32)	−0.225	−0.274	0.332
R_PCC-to-L_THA	0.12 (0.30)	0.275	−0.112	0.065	0.23 (0.25)	0.174	0.137	0.165	0.10 (0.27)	0.265	0.025	−0.138
R_PCC-to-L_PAG	0.24 (0.25)	0.301	0.020	0.087	0.26 (0.16)	0.145	0.139	0.213	0.02 (0.23)	0.199	0.029	−0.228
R_aINS-to-L_ACC	0.25 (0.23)	0.206	0.291	0.374	0.28 (0.22)	−0.414 [a]	0.145	0.066	0.03 (0.29)	0.138	0.120	−0.114
R_aINS-to-L_PCC	−0.04 (0.14)	0.205	0.181	0.386	−0.00 (0.17)	−0.159	0.039	−0.058	0.04 (0.18)	0.019	−0.099	−0.100
R_aINS-to-L_aINS	0.54 (0.27)	0.176	0.225	0.357	0.48 (0.30)	0.004	0.251	0.258	−0.06 (0.30)	−0.106	−0.270	0.088
R_aINS-to-L_pINS	0.26 (0.30)	−0.018	0.103	0.149	0.30 (0.21)	−0.391	0.243	0.282	0.03 (0.27)	0.338	−0.079	−0.253
R_aINS-to-L_SI	0.13 (0.19)	−0.043	0.308	0.328	0.07 (0.20)	−0.202	0.064	−0.241	−0.05 (0.28)	−0.160	−0.145	−0.373
R_aINS-to-L_SII	0.21 (0.23)	0.213	0.028	0.126	0.17 (0.25)	−0.476 [a]	.199	−0.025	−0.04 (0.34)	0.098	0.263	−0.263
R_aINS-to-L_THA	0.02 (0.21)	0.167	−0.242	−0.101	−0.03 (0.18)	−0.463 [a]	0.141	−0.045	−0.06 (0.27)	0.221	0.222	−0.005
R_aINS-to-L_PAG	0.06 (0.19)	−0.015	0.100	0.320	0.09 (0.20)	−0.631 [b]	0.266	0.181	0.03 (0.18)	0.316	−0.011	−0.145
R_pINS-to-L_ACC	0.28 (0.22)	0.237	−0.110	0.180	0.21 (0.27)	−0.386	0.007	−0.021	−0.07 (0.30)	0.170	0.231	−0.201
R_pINS-to-L_PCC	0.15 (0.21)	0.044	0.159	0.459 [a]	0.08 (0.22)	−0.168	−0.169	−0.168	−0.07 (0.30)	−0.036	−0.154	0.123
R_pINS-to-L_aINS	0.29 (0.19)	0.114	0.170	0.200	0.18 (0.27)	−0.252	0.028	0.002	−0.11 (0.30)	0.390	0.076	−0.304
R_pINS-to-L_pINS	0.54 (0.31)	0.018	0.365	0.292	0.50 (0.29)	0.284	0.028	0.043	−0.04 (0.36)	0.125	0.065	0.016
R_pINS-to-L_SI	0.36 (0.26)	−0.197	0.089	0.089	0.20 (0.26)	0.040	0.171	−0.056	−0.16 (0.26)	0.004	−0.188	−0.296
R_pINS-to-L_SII	0.43 (0.34)	−0.147	0.200	0.127	0.39 (0.27)	0.034	0.194	0.093	−0.05 (0.28)	−0.341	−0.048	−0.308
R_pINS-to-L_THA	0.01 (0.20)	0.197	−0.098	−0.174	0.03 (0.20)	0.016	−0.199	−0.197	0.02 (0.27)	0.058	0.212	0.118
R_pINS-to-L_PAG	0.10 (0.21)	0.301	−0.258	0.139	0.13 (0.22)	−0.220	−0.053	−0.147	0.03 (0.24)	0.272	−0.118	−0.034
R_SI-to-L_ACC	0.28 (0.26)	0.064	0.167	0.287	0.24 (0.23)	−0.212	0.126	0.036	−0.04 (0.27)	−0.061	0.129	0.041

R_SI-to-L_PCC	0.16 (0.28)	−0.058	0.274	0.619 [b]	0.06 (0.26)	0.048	−0.001	0.169	−0.09 (0.35)	−0.015	−0.339	0.478 [a]
R_SI-to-L_aINS	0.15 (0.20)	−0.148	0.170	0.290	0.12 (0.21)	−0.152	0.108	−0.034	−0.03 (0.29)	−0.090	−0.130	−0.137
R-SI-to-toL_pINS	0.29 (0.17)	0.012	0.000	0.288	0.30 (0.25)	−0.075	0.269	−0.115	0.00 (0.28)	0.073	0.001	−0.348
R_SI-to-L_SI	0.65 (0.29)	−0.029	0.254	0.321	0.66 (0.30)	−0.230	0.286	0.092	0.01 (0.29)	0.241	−0.035	−0.168
R_SI-to-L_SII	0.42 (0.24)	−0.183	0.301	0.333	0.44 (0.28)	−0.017	0.175	0.118	0.01 (0.26)	−0.157	−0.259	0.109
R_SI-to-L_THA	−0.03 (0.21)	0.188	−0.026	0.012	0.03 (0.21)	0.312	−0.102	0.239	0.05 (0.25)	0.000	0.258	0.224
R_SI-to-L_PAG	0.03 (0.21)	0.011	0.310	0.340	0.13 (0.15)	0.144	−0.073	0.071	0.1 (0.23)	−0.067	−0.004	−0.042
R_SII-to-L_ACC	0.31 (0.22)	0.011	0.365	0.633 [b]	0.30 (0.23)	−0.392	0.010	−0.078	−0.02 (0.33)	−0.095	0.049	0.021
R_SII-to-L_PCC	0.16 (0.30)	−0.047	0.383	0.570 [b]	0.09 (0.24)	−0.115	0.046	0.086	−0.06 (0.33)	−0.001	−0.253	0.213
R_SII-to-L_aINS	0.26 (0.19)	0.141	0.095	0.106	0.15 (0.25)	−0.387	0.090	−0.044	−0.11 (0.28)	0.044	0.146	−0.163
R_SII-to-L_pINS	0.40 (0.20)	0.094	0.333	0.374	0.36 (0.24)	−0.205	0.195	−0.104	−0.04 (.025)	0.271	0.041	−0.234
R_SII-to-L_SI	0.38 (0.19)	−0.202	0.265	0.131	0.32 (0.22)	−0.429 [a]	0.265	−0.148	−0.07 (0.28)	0.027	−0.035	−0.335
R_SII-to-L_SII	0.63 (0.29)	0.157	0.412 [a]	0.189	0.54 (0.31)	−0.193	0.400	0.138	−0.09 (0.34)	−0.273	0.127	−0.349
R_SII-to-L_THA	0.07 (0.22)	0.287	−0.078	−0.062	0.01 (0.20)	0.055	−0.338	−0.198	0.05 (0.26)	−0.040	0.110	0.039
R_SII-to-L_PAG	0.12 (0.23)	0.204	−0.033	0.129	0.11 (0.18)	−0.025	0.089	0.173	−0.01 (0.25)	0.090	−0.189	−0.083
R_THA-to-L_ACC	0.08 (0.19)	0.117	0.115	0.089	0.13 (0.18)	0.313	−0.326	−0.048	0.05 (0.26)	0.052	−0.039	−0.305
R_THA-to-L_PCC	0.14 (0.24)	0.082	0.058	0.170	0.12 (0.19)	−0.222	0.217	0.135	−0.01 (030)	0.426 [a]	0.046	−0.261
R_THA-to-L_aINS	0.04 (0.18)	0.078	0.216	0.158	−0.01 (0.15)	−0.119	0.129	0.116	−0.05 (0.26)	0.221	0.254	−0.319
R_THA-to-L_pINS	0.05 (0.19)	0.368	0.035	0.060	0.07 (0.19)	−0.058	0.080	0.163	0.03 (0.22)	0.225	0.461 [a]	−0.375
R_THA-to-L_SI	0.02 (0.18)	0.244	0.398	0.344	−0.01 (0.15)	0.324	−0.124	0.003	−0.03 (0.23)	0.298	0.335	0.036
R_THA-to-L_SII	0.03 (0.20)	0.194	0.184	0.159	0.07 (0.20)	0.180	0.043	0.096	0.04 (0.28)	0.087	0.189	−0.188
R_THA-to-L_THA	0.47 (0.22)	−0.146	0.027	0.224	0.48 (0.20)	−0.411 [a]	0.252	−0.009	0.01 (0.25)	0.265	0.269	−0.259
R_THA-to-L_PAG	0.16 (0.21)	0.100	−0.095	0.407 [a]	0.16 (0.20)	−0.006	0.097	0.249	0.00 (0.27)	0.080	−0.198	0.279
R_PAG-to-L_ACC	0.18 (0.22)	0.065	0.028	0.269	0.19 (0.16)	−0.067	−0.007	0.030	0.02 (0.27)	0.164	−0.077	0.049
R_PAG-to-L_PCC	0.19 (0.26)	0.327	0.134	0.341	0.22 (0.16)	−0.011	0.216	−0.134	0.03 (0.30)	0.265	−0.237	−0.210
R_PAG-to-L_aINS	0.07 (0.20)	−0.124	0.250	0.279	0.15 (0.20)	−0.190	−0.043	−0.095	0.08 (0.26)	−0.058	−0.182	−0.267
R_PAG-to-L_pINS	0.04 (0.20)	−0.145	0.123	0.481 [a]	0.14 (0.25)	−0.033	−0.246	−0.113	0.10 (0.26)	−0.160	−0.204	0.123
R_PAG-to-L_SI	0.06 (0.25)	0.132	0.076	0.327	0.08 (0.18)	−0.017	−0.449 [a]	−0.395	0.01 (0.27)	−0.003	−0.329	−0.120
R_PAG-to-L_SII	0.09 (0.22)	−0.053	0.006	0.356	0.08 (0.15)	0.038	−0.313	−0.296	−0.01 (0.23)	−0.240	−0.369	0.208
R_PAG-to-L_THA	0.28 (0.21)	−0.060	0.065	0.132	0.27 (0.17)	−0.050	−0.058	0.011	−0.01 (0.26)	0.297	−0.155	0.187
R_PAG-to-L_PAG	1.00 (0.28)	0.034	−0.103	0.050	1.10 (0.26)	−0.051	−0.307	−0.139	0.08 (0.34)	−0.167	−0.168	−0.105

FC values are presented as mean (SD) Fisher transformed zero-order estimate.

ACC, anterior cingulate cortex; *aINS*, anterior insular cortex; *FC*, functional connectivity; *L*, left; *PAG*, periaqueductal gray; *PCC*, posterior cingulate cortex; *pINS*, posterior insular cortex; *Post*, after MBB therapy; *PPT*, pressure pain threshold; *Pre*, prior to MBB therapy; *R*, right; *SI,* primary somato-sensory cortex; *SII*, secondary somato-sensory cortex; *THA*, thalamus; *Δ*, change score (post minus pre); *ρ*, Pearson product-moment correlation coefficient.

[a] $P < .05$.

[b] $P < .01$.

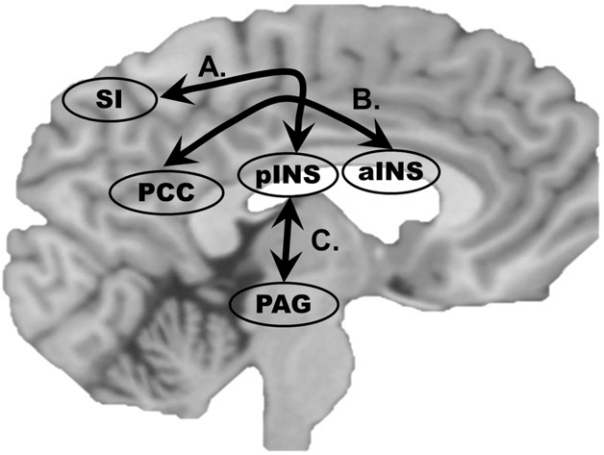

Fig 3. *A, After MT, a decrease in FC between the left somatosensory cortex (SI) and the right pINS was observed. B, The left aINS and left PCC showed increased FC over time. C, After MT, the left pINS and left PAG showed increased FC. aINS, anterior insular cortex; INS, posterior insular cortex; PAG, periaqueductal gray; PCC, posterior cingulate cortex; SI, primary somato-sensory cortex.*

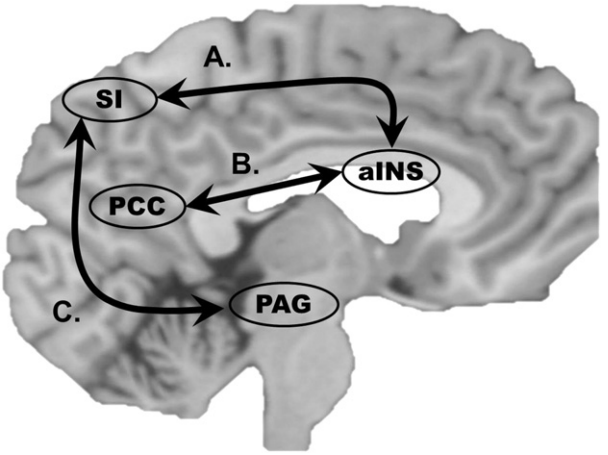

Fig 4. *A, The change in FC between the right aINS and right somatosensory cortex (SI) differed across the 3 MT groups. The SMT group showed an increase in FC (Δ= 0.28), whereas the MOB group (Δ= −0.04) and the TT group (Δ= −0.14) showed decreases in FC. B, The FC changes between the right aINS and left PCC differed across the 3 MT groups. The SMT group (Δ= 0.21) and the MOB (Δ= 0.05) showed increases, whereas the TT group (Δ= −0.06) showed a decrease. C, The FC changes between the right somatosensory cortex (SI) and right PAG increased in the SMT (Δ= 0.04) and MOB (Δ= 0.19) groups, whereas FC decreased in the TT group (Δ= −0.17). aINS, anterior insular cortex; INS, posterior insular cortex; PAG, periaqueductal gray; PCC, posterior cingulate cortex; SI, primary somato-sensory cortex.*

electroencephalography with somatosensory-evoked potentials, transcranial magnetic stimulation with motor evoked potentials, and task-based fMRI with peak BOLD response.[17,46–49]

Directly comparing our results with that of the only other fMRI study is difficult because of the different estimates of cortical function. We used FC estimated at rest, whereas they used peak BOLD activity while processing a thermal-stimulus task. Despite these differences, the results from these studies do show similarities. For example, they found reduced activity within the insular cortex, somatosensory cortices, and PAG. We found the interrelationship between some of these regions changed in the left hemisphere after MT. We also found treatment-dependent changes in the interrelationship between similar regions in the right hemisphere. The ROI-to-ROI FC changes that were common to all 3 interventions (ie, main effect of time) may represent shared neurophysiologic mechanisms. However, we cannot conclusively assume that these common shifts are more than natural history or that they are specific to an MT intervention, as these potential confounds were not controlled for in the study design. The timing of these changes (ie, < 1 hour) could be viewed as associative, but more work is needed in this area.

The treatment-dependent changes in ROI-to-ROI FC may be reflective of differing biomechanical attributes of the treatments. The 3 MT techniques used in our study differ in their force-duration profiles. Research has shown differences in the biomechanical and neurophysiologic responses that are force-duration dependent.[50–54] Although the 3 MT interventions showed similar pain relief in our study, there remains conflicting evidence as to the superiority of clinical outcomes after MT techniques with differing forcer-duration attributes.[3,29,55,56]

We found a significant reduction in exercised-induced pain intensity after MT. Our findings are consistent with a prior study that reported positive effects of MT on exercised-induced myalgia in the extensor muscles of the wrist.[57] In that study, there was an improvement in pain intensity with stretch seen in the 2 MT treatments over a no-treatment group. There was no difference between the 2 MT treatments. A reduction in resting pain intensity was seen over time; however, there was no difference between MT treatment groups and the no-treatment group. Because we did not include a no-treatment group to compare, caution is needed when attributing the pain relief in our study to the intervention.

We did not find immediate changes in remote or local pressure pain sensitivity. This is contrary to the previous study using MT on exercise induced myalgia in the wrist and recent systematic reviews looking at the immediate effect of MT on pressure pain sensitivity.[1,4,57] We suggest that our sample size is one possible reason for our results conflicting with previous findings. Given our relatively small sample size (n = 24), small main effects (η = 0.24) effects are likely to be obscured.

Limitations and Future Studies

Without a natural history group, attributing any change solely to the intervention is unsubstantiated at this point because all of our groups improved equally over time.

Additional analyses are needed to disentangle treatment-specific and natural improvement because our exercise-induced injury model has a favorable prognosis and resolution is expected naturally with time. Caution is needed when applying the findings in our model to chronic conditions because the acute pain and pain sensitivity increases in our model resolve quickly over time, whereas in chronic pain, it does not.

In this study, we did not control for the variability between providers, nor did we look for an interventionist effect within the analyses. However, we feel that this also strengthens our study because this increases the ability to generalize the mechanism beyond a single provider and increases the likelihood of findings can be replicated.

Although we found changes in FC, the within-person relationship across the primary and secondary outcomes was weak and inconsistent. Thus, interpretation of these findings to represent a mechanism of pain relief currently cannot be made. There is, however, some evidence suggesting that the FC between brain regions prior to a stimulus influences the perception of pain.[36,58,59] Those studies have shown that (1) the FC between the aINS and the PAG, measured prior to the evoked stimulus, was predictive of pain perception, and (2) prior to the evoked stimulus, fluctuations in FC between regions in the classic "pain network" and brain areas related to attention, emotion, and descending pain modulation subserve contextual modulations of pain intensity. In this context, our findings show that FC changes between the insula and somatosensory cortex and PAG may subserve the subsequent reductions in peak BOLD while processing stimuli.

The involvement of the insular cortex in our study is consistent with the close association between activity in this region and the subjective experience of pain. This brain region is extensively interconnected with various other brain regions and integrates sensory and contextual information to generate a higher-order representation of interoception.[60]

Our ROI-to-ROI approach has several limitations. On the positive side, this approach allows for a priori ROIs to be investigated. However, numerous brain regions were not included such as prefrontal, motor, reward, and aversion regions. Because measuring change in FC is a novel approach, future studies may consider a more exploratory approach where only a single seed region is used to identify other relevant brain regions. However, this approach is limited by the selection of the seed region. There are consequences to increasing the number of brain regions. With our limited ROI approach, 8 ROI bilateral, approximately 120 ROI-to-ROI comparisons we generated. We used a liberal correction ($P < .01$) for the number of planned comparisons. This liberal correction does increase the likelihood that some of our findings may be false positives. Thus, achieving the correct balance between the number of ROIs and correction for the number of comparisons needs to be taken into account.

Our sample size (n = 24) may obscure moderate to small group by time interactions. With our estimated partial η^2 ($\eta^2 = 0.068$) for the 3 group by 2 time point interaction, we would need a sample of 133 participants to be properly powered. We suggest that the sample size is a possible reason for our results that pose conflict with previous published findings suggesting that there are differential MT effects. Also, we investigated only the immediate effects, so extrapolating our findings beyond this cannot be made.

This study has implications for future mechanistic research. In addition to disentangling common vs shared cortical pathways, future research can build upon our results by using more sophisticated network modeling approaches. We found changes between sensory discriminate and sensory affective ROIs, as well as between these ROIs and pain modulatory brain areas. Our findings show that changes, albeit modest, can be expected in the interrelationships between these brain regions. Network modeling approaches, such as functional network connectivity and dynamic causal modeling, may provide additional insight into the central modulatory effects of MT therapy on cortical function. Continued research in this area is needed to address the extent to which these changes underlie pain relief.

Conclusion

This mechanistic study identified brain regions of the PPN where FC changed immediately after 3 different types of MT. Neurophysiologic changes after MT may be an underlying mechanism of pain relief.

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Contributorship Information

Concept development (provided idea for the research): C.W.G., M.E.R., S.Z.G., W.M.P., M.D.B.
Design (planned the methods to generate the results): C.W.G., M.E.R., S.Z.G., W.M.P., M.D.B.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): C.W.G., M.E.R., S.Z.G., W.M.P., M.D.B.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): C.W.G.

Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): C.W.G., M.E.R., S.Z.G., W.M.P., M.D.B.
Literature search (performed the literature search): C.W.G.
Writing (responsible for writing a substantive part of the manuscript): C.W.G., M.D.B.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): M.E.R., S.Z.G., W.M.P., M.D.B.

Practical Applications

- Resting-state fMRI in conjunction with FC analyses demonstrates common and treatment-dependent changes after 3 different types of MT.
- The intensity of experimentally induced myalgia is reduced after MT.
- Neurophysiologic changes after MT may be an underlying mechanism of pain relief.

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