



Original Reports

Increased Salience Network Connectivity Following Manual Therapy is Associated with Reduced Pain in Chronic Low Back Pain Patients

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Abstract: Chronic low back pain (cLBP) has been associated with changes in brain plasticity. Non-pharmacological therapies such as Manual Therapy (MT) have shown promise for relieving cLBP. However, translational neuroimaging research is needed to understand potential central mechanisms supporting MT. We investigated the effect of MT on resting-state salience network (SLN) connectivity, and whether this was associated with changes in clinical pain. Fifteen cLBP patients, and 16 matched healthy controls (HC) were scanned with resting functional Magnetic Resonance Imaging (fMRI), before and immediately after a MT intervention (cross-over design with two separate visits, pseudorandomized, grades V 'Manipulation' and III 'Mobilization' of the Maitland Joint Mobilization Grading Scale). Patients rated clinical pain (0–100) pre- and post-therapy. SLN connectivity was assessed using dual regression probabilistic independent component analysis. Both manipulation (Pre: 39.43 ± 16.5 , Post: 28.43 ± 16.5) and mobilization (Pre: 38.83 ± 17.7 , Post: 31.76 ± 19.4) reduced clinical back pain ($P < .05$). Manipulation (but not mobilization) significantly increased SLN connectivity to thalamus and primary motor cortex. Additionally, a voxelwise regression indicated that greater MT-induced increase in SLN connectivity to the lateral prefrontal cortex was associated with greater clinical back pain reduction immediately after intervention, for both manipulation ($r = -0.8$) and mobilization ($r = -0.54$). Our results suggest that MT is successful in reducing clinical low back pain by both spinal manipulation and spinal mobilization. Furthermore, this reduction post-manipulation occurs via modulation of SLN connectivity to sensorimotor, affective, and cognitive processing regions.

Perspective: MT both reduces clinical low back pain and modulates brain activity important for the processing of pain. This modulation was shown by increased functional brain connectivity between the salience network and brain regions involved in cognitive, affective, and sensorimotor processing of pain.

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Key Words: Functional connectivity, chronic low back pain, clinical pain, manual therapy, salience network, somatomotor network.

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Introduction

Chronic Low Back Pain (cLBP) is the leading cause of disability in the world with a prevalence of 9.4%.²¹ Given its prevalence, combined with the lack of efficacious long-term treatments, there has been a growing interest in complementary nonpharmacological therapies to treat a variety of pain disorders,³⁹ including cLBP. Manual Therapy (MT) is a nonpharmacological therapy used to treat a range of neuromusculoskeletal and chronic pain disorders. In the last 15 years, there has been an increase in research assessing the effectiveness of MT for cLBP. A review published in 2004 included the results of 69 randomized controlled trials using MT, and found evidence that its effects are stronger than placebo and general care.¹⁰ In a multi-site study conducted with 1,334 cLBP patients in the United Kingdom, those who were randomized to receive “best care” of general practice treatment in combination with spinal manipulation MT and exercise experienced a significant reduction in LBP intensity and disability scores at the three month and one year follow-up.⁴⁸ However, the mechanisms supporting MT are less clear and further research is needed.

There are a number of theories that attempt to explain the mechanisms through which MT provides therapeutic benefits. These include local joint function improvements, reflexive relaxation of local muscle tension, local spinal reflex activity, and pain modulation through stimulation of joint capsules and periarticular muscles. More recently it has been hypothesized to act via neurophysiological mechanisms, through both the direct evoked response to MT, as well as an immediate or even longer-lasting response, potentially due to consequences of a change in biomechanics.³⁷ In fact, MT as a treatment for cLBP patients found that participants who received MT showed inhibited temporal summation to thermal pain post-treatment, concluding a central pain processing mechanism which suggests neuroplastic changes post-MT.⁷ Alongside temporal summation, there are several other neurophysiological factors that have been cited as being impacted by MT (ie, changes in pain sensitivity, somatosensory evoked potentials) suggesting a mechanism of response via the central nervous system.⁶ Recently, neuroimaging research has suggested that cLBP is characterized by altered brain structure and function, suggesting a need for a better understanding of the underlying brain-focused neural mechanisms supporting nonpharmacological treatment modalities for this condition.^{3,22} As such, there has been an increase in neuroimaging research to assess cortical alterations post-MT for pain. A small fMRI study assessing evoked-pain in ten healthy controls pre- and post- mid-thoracic spine thrust manipulation found reductions in brain activity in regions associated with pain processing (ie, insular cortex, thalamus, S1, S2, etc.) as well as a significant reduction in perception of pain intensity of evoked stimuli.⁴⁴ In a larger cohort of experimentally-induced low back pain subjects, MT was found to immediately alter resting-state connectivity between brain regions implicated in

sensory and affective components of pain processing.¹⁶ Our group recently found that a single session of MT reduced the engagement of salience and social cognition brain circuitries in response to videos depicting exercises perceived as painful in cLBP patients.¹⁴ This suggests that altered brain activity following MT may underlie its hypoalgesic effects and more neuroimaging research is needed to better elucidate the specific mechanisms. Furthermore, a large meta-analysis conducted on 129 Randomized Controlled Trials of MT found evidence of improvement for psychological variables following treatment (ie, fear avoidance beliefs, depression).⁵² Therefore, MT, which also includes cognitive and affective components of therapy, may also impact cognitive and affective dimensions of pain, which should be further explored in mechanistic studies.

Recently, our group found that compared to healthy controls, cLBP patients demonstrated altered resting-state functional Magnetic Resonance Imaging (rs-fMRI) connectivity for the salience (SLN) which was linked with greater low back pain severity.²³ Moreover, we found that SLN connectivity can be modulated with maneuvers that exacerbate back pain.²⁸ Such functional connectivity analyses may also suggest how connectivity networks are modulated by MT, and which changes are associated with post-treatment reduction in back pain. Historically, the pain experience has been imaged via block-design evoked-experimental pain paradigms, which offer a way to assess hyperalgesia, an important characteristic of clinical pain. However, there are challenges that come with assessing clinical pain itself in a controlled setting, given the variability in clinical pain states from subject to subject and difficulty in experimentally controlling clinical pain severity. Our group has previously linked clinical pain intensity to intrinsic brain connectivity in chronic pain, including cLBP patients.^{28,33,34} As such, our group and others have now shown that rs-fMRI can be a useful tool to measure the neural mechanisms underlying clinical pain and an important step in understanding the brain's processing of chronic pain.

Our study assessed SLN connectivity response to MT in both cLBP patients and healthy controls (HC). In 2 separate imaging sessions, cLBP patients underwent rs-fMRI before and after the application of 2 MT techniques (Spinal Manipulation [MANIP], and Spinal Mobilization [MOBIL]). Because of our previous findings of altered connectivity in cLBP, and prior imaging results for MT, we hypothesized that MT, a forceful mechanical intervention, would increase SLN connectivity to brain regions along the somatosensory and/or motor pathway. Furthermore, we hypothesized that altered SLN connectivity to pain modulatory regions would be associated with post-MT hypoalgesia in cLBP patients. Additionally, because of our previously published manuscripts linking Default Mode Network (DMN) connectivity to spontaneous clinical pain in chronic pain populations, we then explored changes in DMN connectivity post- vs pre- MANIP and MOBIL.^{28,33,34}

Table 1A. Subject Characteristics and Mean Scores for Psychophysical Questionnaires

	<i>cLBP (MEAN ± SD)</i>	<i>HC (MEAN ± SD)</i>	<i>P</i>
Age (years)	37.7 ± 9.7	38.5 ± 10.1	.57
Pain Catastrophizing Scale	13.6 ± 10.2	6.2 ± 6.8	.026
Beck Depression Inventory	4.1 ± 4.1	1.9 ± 2.7	.18
Clinical pain at MRI scan (0-100)	44.2 ± 18.6	0.3 ± 1.2	<.001
Brief Pain Inventory – Severity (0-10)	4.5 ± 1.4	0.3 ± 0.4	<.001
Brief Pain Inventory – Interference (0-10)	3.2 ± 2.1	0.1 ± 0.2	<.001
Low back pain bothersomeness	5.0 ± 1.7	0.5 ± 1.3	<.001

Methods

Participants

We enrolled fifteen cLBP patients (37.7 ± 9.7 [M ± SD] years old) and sixteen age- and sex-matched HC (38.2 ± 10.4 years old) [Table 1A]. Given that there have not been many similar studies assessing clinical pain outcomes with neuroimaging post-MT, our sample size is based on the novelty of the approach, and on the same order of previous MT neuroimaging studies.^{14,16} All participants completed pre-screening to assess eligibility. Inclusion criteria for cLBP were as follows: 1) between 21 and 65 years of age, 2) cLBP meeting Quebec Task Force Classification System categories I-II (i.e. patients were unlikely to have significant nerve root involvement, stenosis, or mechanical instability^{1, 29} as confirmed by the study clinician and/or review of medical records with the use of previous x-ray reports (where available), 3) pain duration greater than 6 months prior to enrollment, and 4) on-going pain averaging to at least 4 (0–10) during the week prior to enrollment. Exclusion criteria were: 1) radicular pain (pain extending below the knee), 2) neural deficit in the lower extremity, 3) positive dural tension signs, 4) surgery within the past year related to back pain, 5) pain management procedures during the study period, 6) contraindications to MRI scanning, 7) current or past history of a major medical, neurological, or psychiatric illness other than chronic pain, 8) peripheral nerve injury, 9) diabetes, 10) pregnancy, breast feeding, or less than six months postpartum, 11) history of head trauma, 12) high blood pressure, 13) use of opioid medication, 14) self-reported use of recreational drugs, and 15) back pain due to cancer, fracture, or infection. In addition to these, exclusion criteria for HC included chronic or acute low back pain. Several of our cLBP patients and 1 HC reported taking over the counter pain medication as needed, such as Ibuprofen (cLBP: n = 8; HC: n = 1), Acetaminophen (n = 1) and Naproxen (n = 1). One cLBP patient reported taking Imitrex for occasional headaches. Additionally, 1 cLBP patient reported taking Hydrocodone and/or Acetaminophen on a very limited basis as needed. Two of our cLBP patients reported taking SSRIs such as Fluoxetine (n = 1) and Venlafaxine (n = 1). This study was approved by the Human Research Committee of Massachusetts General Hospital (Protocol #2013P001614) and conducted in accordance with the Declaration of Helsinki.

Study Design

All study participants attended an initial behavioral session for consenting, familiarization of study procedures and questionnaires. CLBP patients attended two MRI scans, one including MOBIL and one visit including MANIP¹⁸ performed at the lumbar spine. It is composed of five grades based on resistance of the joint being manipulated.³⁰ MOBIL (Grade III–IV of the Maitland Joint Mobilization Scale) is a large amplitude movement that is performed up to the limit of available range, while MANIP (Grade V) is a small amplitude high velocity thrust that is typically performed at the end of the available passive motion range.¹⁸ The order of MT was counterbalanced across subjects, and participants were blinded to the type of intervention they were receiving, as they were told they would receive two types of MT for their low back pain (mean interval between MRI scans- 24.7 ± 22.9 days). HCs attended the initial behavioral session and one MRI visit with MANIP. MANIP was performed with an identical protocol for all participants, regardless of patient or control status. Clinicians were not blinded to the status of the participant, as the participants inclusion in the study was contingent upon an examination with the clinician. There was no MOBIL visit for HC as there were no expectations around clinical outcomes for these subjects, and therefore we chose to utilize only one MT technique as a control for more generalized contextual and/or physical contact induced changes in brain connectivity outside the clinical pain patient and/or clinician interaction. As MANIP is a more forceful (and perhaps salient) form of MT, fMRI response to MANIP was used to assess between-group (cLBP vs HC) differences, whereas MOBIL was used as a within-subjects comparison (cLBP only) (Fig 1 for study schematic).

Behavioral Visit

After informed consent procedures, all study participants met with a chiropractic physician for either a clinical evaluation of their pain symptoms (cLBPs) or to exclude the presence of back pain (HCs). Participants then filled out a set of questionnaires and were given instructions of the procedures for each MRI session. Validated questionnaires included the Pain Catastrophizing Scale,⁴⁵ the Beck Depression Inventory,⁴ and the Brief Pain Inventory.⁴⁶

Study Flow Schematic

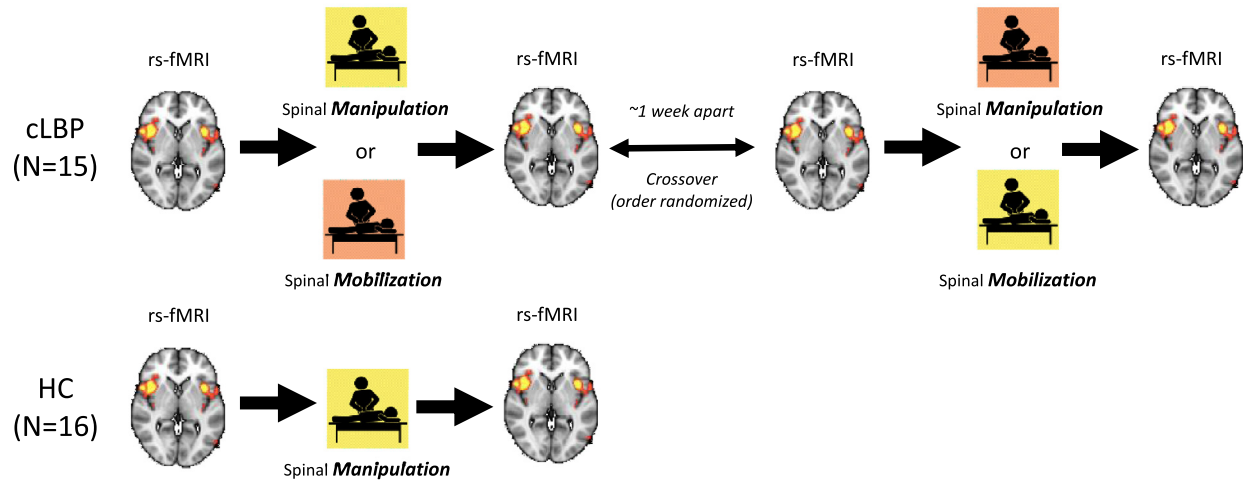


Figure 1. Schematic of the flow of the study. CLBP patients participated in 2 MRI scan sessions, 1 with MANIP and 1 with MOBIL, in a randomized order and separated by ~1 week. HC subjects participated in a single MRI scan session, with MANIP. Resting state fMRI (rs-fMRI) was completed before and after the MT intervention at all scan sessions.

MRI Session

All MRI data were collected at the Athinuola A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, on a 3T Siemens Skyra MRI scanner using a 32-channel head coil (Siemens, Erlangen, Germany). Participants were scanned utilizing rs-fMRI during each MRI visit. During scans, participants were instructed to remain still and keep their eyes open. Before and after each rs-fMRI scan, participants rated the intensity of their clinical low back pain. Following the pre-MT rs-fMRI, participants were temporarily removed from the MRI bore to undergo MT (MANIP or MOBIL) by the chiropractic physician. Immediately following MT, they were placed back inside the bore for the post-MT rs-fMRI scan. To explore the impact of expectancy on clinical pain outcomes, expectancy for relief was assessed using a 0–10 Numerical Rating Scale (0: does not work at all, 10: complete pain relief). In order to assess clinical low back pain changes following treatment, subjects reported the intensity of low back pain before and after all MT procedures on a 0–100 Numerical Rating Scale. Additionally, ratings of back pain bothersomeness (0–10 VAS) over the previous week were collected at each visit.

Brain Imaging Acquisition and Preprocessing

Structural MRI data were collected using a T1-weighted 3-dimensional magnetization-prepared rapid gradient-echo pulse sequence (repetition time and/or echo time (TR/TE = 2530ms/1.69ms, flip angle = 7°, field of view = 256 × 256mm, 176 axial slices, voxel size = 1mm isotropic). Functional images were acquired with a T2*-weighted gradient-echo BOLD pulse sequence with multi-band and/or simultaneous multislice acceleration (TR/TE = 1.25s/33ms, flip angle = 65°, number of slices = 75, voxel size = 2mm isotropic, SMS factor = 5, acquisition time = 6 minutes and 15 seconds).

Functional MRI data were preprocessed using FEAT (FMRI Expert Analysis Tool) Version 6.0 of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Data preprocessing steps were as follows: slice timing correction, motion correction (FSL-MCFLIRT), fieldmap unwarping (FSL-PRELUDE and FSL-FUGUE), skull stripping (FSL-BET), spatial smoothing (FWHM = 5mm), and temporal high-pass filtering ($f = 0.008\text{Hz}$). The structural MRI volume was aligned to functional volumes using boundary-based registration (BBREGISTER, Freesurfer Version 5.3.0), after which both structural and functional data were co-registered to the standard Montreal Neurological Institute space using non-linear registration prior to group analyses.

Statistical Analysis

We previously reported an analysis of variance (ANOVA) assessing the combined MANIP and MOBIL induced pain reduction in cLBP following both interventions.¹⁴ Here, we used a repeated measures ANOVA to assess clinical pain reduction for Group (MANIP vs MOBIL) by Time (post-MT vs pre-MT) interaction. Additionally, we performed a post-hoc paired T-test to further assess clinical pain reduction for the different MT interventions, as this is a greater focus in the present study. In order to estimate connectivity between specific brain networks, a dual regression⁵ independent component analysis (ICA) approach was used on concatenated 4D datasets collected from cLBP (post- vs pre-MANIP & post- vs pre-MOBIL) and HC (post- vs pre-MANIP) subjects (MELODIC, FSL). Twenty-five components were identified as a result of the ICA and of these the SLN and DMN were identified as in many of our prior publications.^{27,28,23,33,34} Group-level spatial maps were used as a set of spatial regressors onto each subject's rs-fMRI dataset using a General Linear Model (GLM), resulting in a set of time courses for each subject, which was then used to generate subject specific spatial maps.

The averaged fMRI signal from ROIs placed in white-matter, cerebrospinal fluid, as well as 6 (translation, rotation) head motion parameters were used as nuisance regressors in this subject-level GLM. Parameter estimates and their variance were then passed up to the group-level GLM. The results of group-level analyses were cluster corrected for multiple comparisons ($z > 2.3$, $P < .05$). In order to assess MT-induced changes in SLN connectivity within both groups (cLBP vs HC) at both time points (post- vs pre-MT), we defined spherical ROIs by placing a 5mm sphere at the peak voxel location for clusters demonstrating significant SLN connectivity difference following MANIP. ROIs were selected from the MANIP voxelwise contrast for cLBP, as we primarily wanted to find robust response for this condition, and secondarily evaluate if these brain regions were also modulated for control conditions: ie, MANIP between groups (cLBP vs HC) and within cLBP (MANIP vs MOBIL). SLN to ROI connectivity values were extracted from each subject and used in repeated measure analyses of variance (rmANOVA) in order to investigate the group (cLBP vs HC) by time (post- vs pre-MANIP) interaction and the treatment (MANIP vs MOBIL) by time (post- vs pre-MT) interaction in response to MT.

In order to address potential ROI-selection bias based on cLBP MANIP response, and in support of our original hypothesis that MT would increase cLBP SLN connectivity along the somatosensory and/or motor pathway, we took anatomically and functionally-defined ROIs of somatomotor processing regions based on the intersection of the Yeo 7-network brain atlas for the sensorimotor network⁵³ and the Harvard-Oxford Probabilistic Atlas.¹³ These regions included primary somatosensory cortex (S1), secondary somatosensory cortex (S2), primary motor cortex (M1), thalamus, posterior insula, and supplementary motor area. To define these regions, labels from the Harvard-Oxford probabilistic atlas¹³ were thresholded at 30% and then binarized before being intersected with the Yeo-7 sensorimotor network atlas⁵³ for greater precision and relevance to sensorimotor functional activity. Individual subject SLN connectivity values were extracted from these ROIs and used in a rmANOVA to again assess group x time (cLBP vs HC) and within-cLBP treatment by time interactions (post- vs pre-MT). Additionally, a linear voxelwise regression was run in order to assess the association between post-MANIP change in low back pain intensity and change in SLN connectivity. Furthermore, in order to link changes in clinical low back pain with functional connectivity, Pearson Correlation coefficients were calculated to assess the association between post-MT changes in low back pain intensity and SLN connectivity results (Post-MT vs Pre-MT). Analyses were performed using RStudio (Version 1.1.456).

To explore DMN connectivity changes within and between groups, we repeated the same approach of defining spherical ROIs at the peak voxel location for clusters demonstrating significant DMN connectivity difference following MANIP. For this analysis we used a 4mm sphere to extract ROIs due to subcortical clusters. These connectivity values were again extracted from

each subject and used in repeated measure analyses of variance (rmANOVA) in order to investigate the group by time interaction and the treatment by time interaction in response to MT.

Results

All subjects tolerated the MT procedures without adverse events. Average expectancy of post-treatment pain relief did not differ between MT procedures ($t = 1.43$, $P = .17$). Expectancy ratings were not correlated with pain reduction following neither MANIP ($r = -0.16$, $P = .6$), nor MOBIL ($r = -0.47$, $P = .08$), however the latter group demonstrated trending significance. Furthermore, perceived credibility of MT did not differ between cLBP and HC, as previously reported¹⁴ [Table 1B]. ANOVA results showed a significant main effect for Time in clinical low back pain reduction ($f = 13.34$, $P = .003$), but no effect for Group x Time interaction ($f = 0.22$, $P = .65$), as low back pain intensity was reduced following both MANIP (Pre: 39.43 ± 16.5 , post: 28.43 ± 16.5 , $P = .005$) and MOBIL (Pre: 38.83 ± 17.7 , post: 31.76 ± 19.4 , $P = .02$), while the magnitude of change did not differ between MT approaches [See Fig 2]. Additionally, a paired T-test assessing differences between pre-scan low back pain levels between the two different conditions (MANIP vs MOBIL) showed no significant differences ($P = .8$). Patients ranged in low back pain bothersomeness, from 2 to 7 (0–10, visual analog scale), as rated for the week prior to the MRI session. Analyses of functional brain connectivity are highly susceptible to head motion effects, and average Root Mean Square (RMS) values were calculated for each subject and each scan. These values were used in a repeated measures ANOVA to assess potential differences in head motion between conditions. There were no significant effects of group (cLBP vs HC, $P = .37$), time (post-MANIP vs pre-MANIP, $P = .69$), or group x time interaction ($P = .83$) for MANIP, and no significant effects of treatment (MANIP vs MOBIL, $P = .9$), time (post vs pre, $P = .3$), or treatment x time interaction ($P = .7$) for cLBP patients. These results suggest that head motion did not contribute significantly to our rs-fMRI connectivity findings.

When contrasting SLN connectivity post- vs pre-MANIP for HC, no significant differences were found. However, for the cLBP group, SLN connectivity was significantly increased to the thalamus, primary motor cortex (M1), right intraparietal sulcus (rIPS), and right occipital, and significantly decreased to the left occipital, and right superior temporal gyrus (rSTG) after MANIP [Table 2A]. While the group (cLBP vs HC) by time

Table 1B. Mean cLBP Subject Scores for Expectancy for Relief and Credibility of Treatment for Both MANIP and MOBIL

	cLBP; MT-MANIP	cLBP; MT-MOBIL	P
Expectancy for relief (0-10)	5.1 ± 2.5	5.9 ± 2.7	.17
Credibility of treatment	1.8 ± 0.6	1.94 ± 0.7	.46

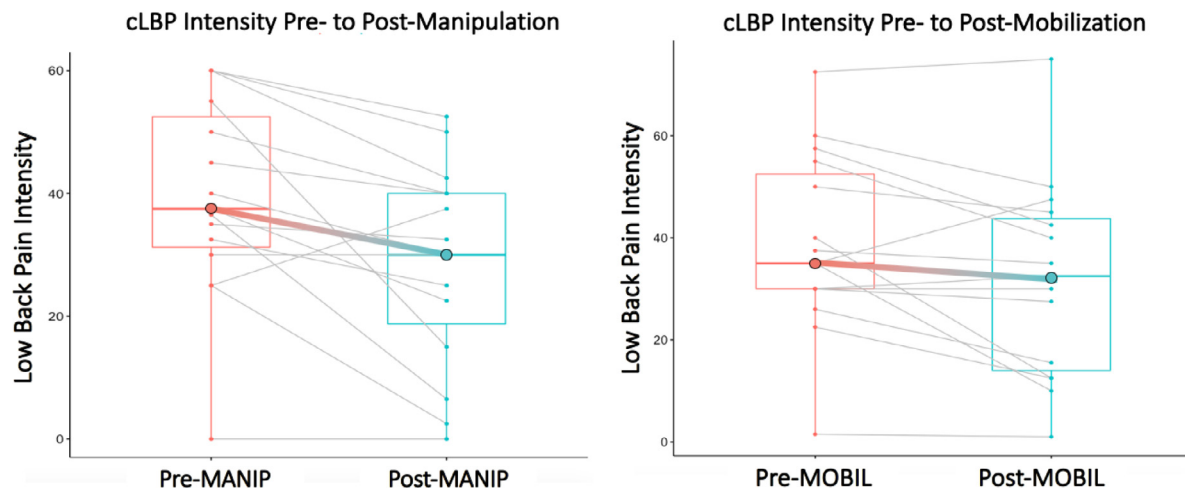


Figure 2. Low back pain intensity in cLBP patients was reduced following high MANIP ($P = .005$, left) and MOBIL ($P = .02$, right).

Table 2A. Regions Showing Significant SLN Connectivity Changes Post- versus Pre-MANIP and Their Corresponding Z-stats for Post- versus Pre-MANIP and Post- versus Pre-MOBIL in cLBP Patients, and for Post- versus Pre-MANIP in HC

SALIENCE NETWORK								
REGION	SIDE	SIZE [MM ³]	MNI COORDINATES [MM]			Z-STAT (CLBP)		Z-STAT (HC)
			X	Y	Z	POST- VS PRE-MANIP	POST- VS PRE-MOBIL	POST- VS PRE-MANIP
Thalamus	L	1,232	-12	-14	14	3.58 [*] , [†]	-0.72	0.72
Primary motor Cortex (M1)	L	1,384	-8	-30	72	4.02 [*] , [†]	1.34	0.14
Intraparietal sulcus	R	1,384	30	-53	28	3.97 [*] , [†]	-0.69	-0.91
Occipital cortex	R	1,472	26	-88	24	4.92 [*] , [†]	-0.06	-0.92
Superior temporal gyrus	L	1,352	-36	-84	-12	3.88 [*] , [†]	-0.39	0.18
Superior temporal gyrus	R	1,152	56	-56	20	3.88 [*] , [†]	1.67	0.07

(post-MANIP vs pre-MANIP) interactions were not significant in the voxelwise analyses, follow-up ROI analyses using regions identified in the post- minus pre-MANIP map yielded a significant effect for both thalamus ($P = .001$), and M1 ($P = .001$) [Fig 3].

Following our anatomical ROI selection, a rmANOVA found a significant treatment x time effect in thalamus ($p = 0.02$) and trending effect in M1 ($P = .06$) for within group (cLBP) contrasts assessing pre-MT vs post-MT for MANIP and MOBIL. There were no significant group x time interactions nor treatment by time interactions for S1, S2, posterior insula, or supplementary motor area. The between group (cLBP vs HC) contrast assessing pre-MANIP vs post-MANIP found a significant effect of group within the Thalamus ($P = .0009$) and M1 ($P = .008$), however no significant group x time interaction [Fig 4].

We also performed a voxelwise, whole-brain linear regression analysis for pre- to post-MANIP change in SLN connectivity versus change in low back pain and found a significant cluster in the left prefrontal cortex (LPFC). Specifically, greater post-MANIP reduction in clinical pain was associated with greater post-MANIP increase in SLN to LPFC connectivity. While this region was defined using post-MANIP change in SLN

connectivity, post-MOBIL change in SLN to LPFC connectivity was also correlated with the post-MOBIL change in low back pain intensity ($r = -0.54$, $P = .04$) [Fig 5].

In our exploratory analysis contrasting DMN connectivity post- versus pre-MANIP for HC, no significant differences were found. However, in the cLBP group post- versus pre-MANIP contrast, DMN connectivity was significantly increased to the left caudate and left nucleus accumbens [Table 2B]. A rmANOVA for within group (cLBP) contrast of pre-MT versus post-MT for MANIP and MOBIL in the left caudate found a significant effect of time ($P = .03$), but not treatment nor treatment x time interaction (Supplementary Fig 1). There were no significant within-group, nor between group treatment x time interactions for the left nucleus accumbens.

Conclusions

While there is a wealth of evidence that chronic pain alters brain structure and function, and evidence that MT can ameliorate cLBP, there is still a dearth of neuroimaging research to support potential underlying central mechanisms of MT for cLBP. Our study hypothesized

cLBP Post- versus Pre-Manipulation

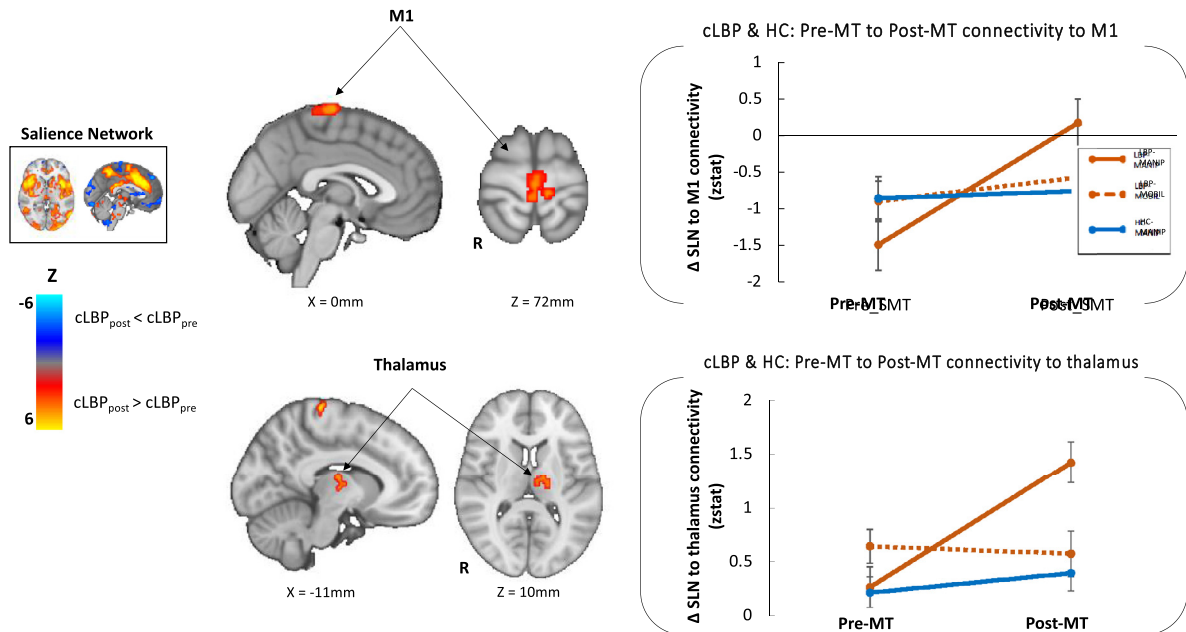


Figure 3. Whole brain results of SLN connectivity Post- versus Pre- MANIP in cLBP patients (left) and plots showing M1 and thalamus ROIs for MANIP and MOBIL in cLBP and MANIP in HC (right).

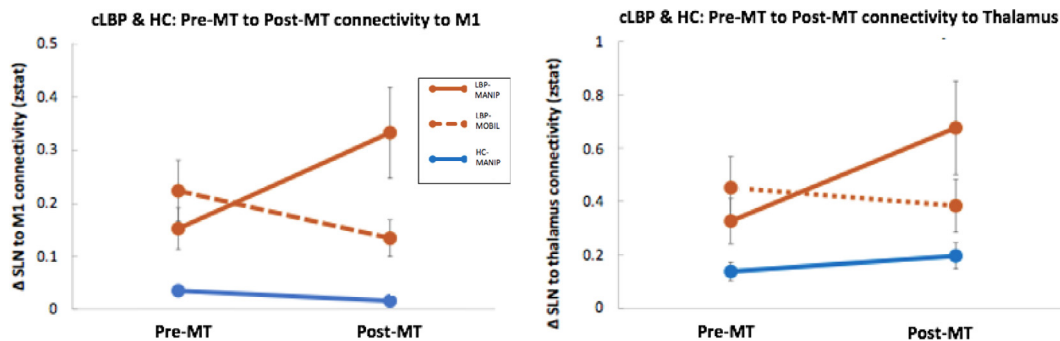


Figure 4. rmANOVA plots of SLN connectivity Post- versus Pre-MANIP and MOBIL in cLBP patients and Post- versus Pre-MANIP in HC in M1 (left) and Thalamus (right). ROIs were selected based on the intersection of the somatomotor network of the Yeo et al (2011) brain atlas and the Harvard-Oxford probabilistic atlas (Desikan, 2006).

that MT would modulate intrinsic brain functional connectivity for the SLN - a brain network recently demonstrated to link with pain severity in chronic pain patients.^{23,26} The function of the SLN is in fact essential in the processing of sensory stimuli, as the SLN plays a key role in the assessment of the inherent danger of such stimuli and how one should respond to them.⁸ Therefore, altered response in this network could be a contributing factor to the maintenance and chronicity of pain. Our results demonstrated that cLBP patients do in fact display unique SLN in comparison to healthy controls and that a single session of grade V manipulation immediately increases the integration of the SLN with both the thalamus and the motor cortex (M1).

The thalamus plays an important role in both somatosensory and affective components of pain.^{2,38} It has implications in both sensory and cognitive components of pain processing, which contribute to the modulation

of pain via an integration of sensory discrimination, attention, memories, etc.² Additionally, the thalamus plays a role in adaptive salience responses to sensory experiences.⁸ Therefore, post-MT increase in SLN to thalamus connectivity could reflect the modulation of brain responses in cLBP patients on both a sensory and a cognitive-affective dimension. For instance, dysrhythmia in thalamocortical connectivity has been suggested to support chronic, particularly central, pain.¹⁷ Our study found that SLN connectivity was upregulated to a cluster spanning the medial dorsal (MD), Ventral Posterior Lateral (VPL), and Ventral Lateral Posterior (VLp) nuclei of the thalamus³² [Fig 6]. The MD nucleus of the thalamus has been linked with the SLN⁴⁰ and plays a role in both limbic and/or emotional and cognitive (ie, memory) processing via communication with the Prefrontal Cortex.^{9,35,47} The VLp and VPL thalamic nuclei are known to be involved with both somatosensation and

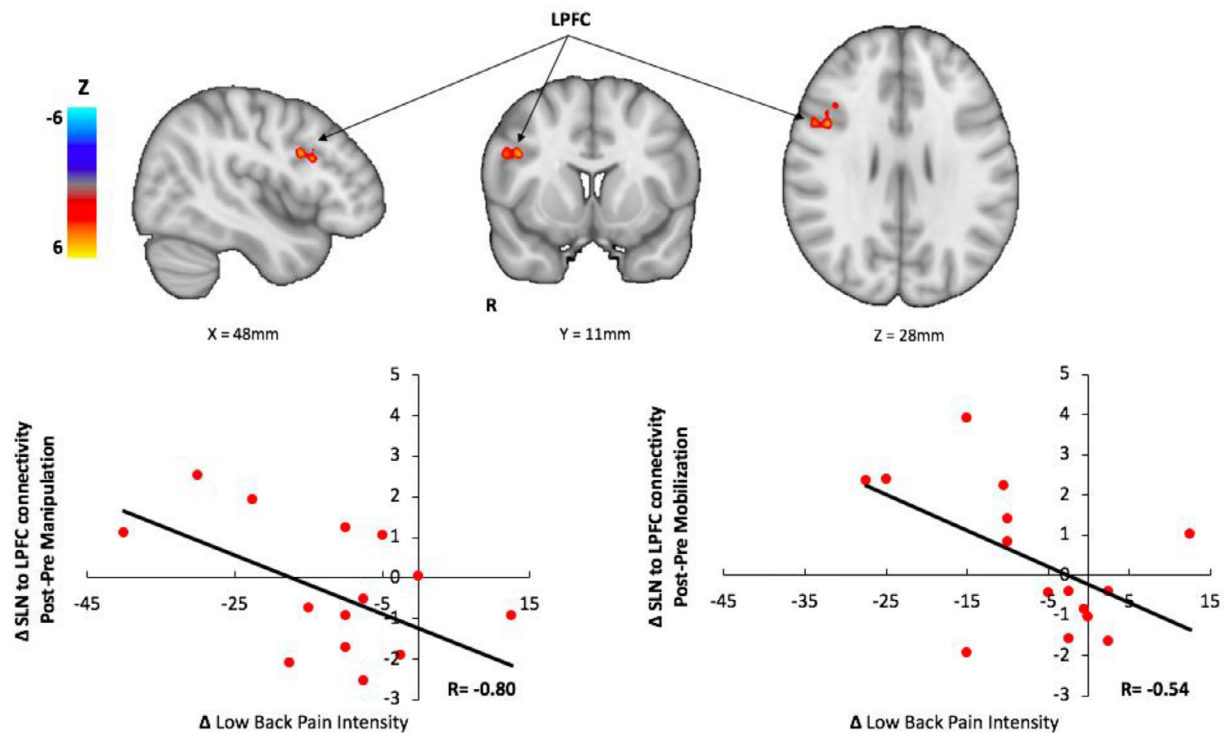


Figure 5. Whole-brain linear regression voxelwise analysis using post-intervention clinical pain change found that greater increase in SLN connectivity to lateral prefrontal cortex (LPFC) post- versus pre-MANIP was associated with greater reduction in low back pain. A similar association was found for post-MOBIL in the same patients (bottom right).

Table 2B. Regions Showing Significant DMN Connectivity Changes Post- versus Pre-MANIP and Their Corresponding Z-Stats for Post- versus Pre-MANIP and Post- versus Pre-MOBIL in cLBP patients, and for Post- versus Pre-MANIP in HC

DEFAULT MODE NETWORK								
T	SIDE	SIZE [MM ³]	MNI COORDINATES [MM]			Z-STAT (CLBP)		Z-STAT (HC)
			X	Y	Z	POST- VS PRE-MANIP	POST- VS PRE-MOBIL	POST- VS PRE-MANIP
Caudate	L	1320	-14	22	-2	3.62 [*] _⊠	0.39	1.71
Nucleus accumbens			-8	7	-10	3.61 [*] _⊠	0.07	1.61

*cLBP-MANIP > cLBP-MOBIL $P < .05$.

⊠cLBP-MANIP > HC-MANIP $P < .05$.

passive movement. Specifically, the VPL nucleus is important for relaying somatosensory afference to the primary S1,^{11,25,43} which is consistent with somatosensory aspects of the MT intervention. The VLp, in turn, is located slightly dorsal to the VPL nucleus and has been shown to activate with passive joint movement (eg, MT), acting as a relay center between the cerebellum and motor cortex.^{19,24} Thus, MT may contribute to somatosensory, affective, and cognition and/or memory components of pain processing by modulating salience processing and attentional resource allocation via SLN connectivity to the MD, VPL, and VLp nuclei of the thalamus.

It is known that pain can interfere with motor function, both on a movement-related and movement-anticipated basis.^{14,31} In fact, the motor cortex plays a role in controlling postural changes, and cLBP patients exhibit abnormal postural control, which could be due to the

reorganization of this cortex.⁴⁹ Several MRI studies have shown altered structure and function of M1 in chronic pain patients.^{12,42,50} Furthermore, research assessing cortical thickness in the motor cortex post-treatment showed improvements related to both decreased pain intensity and physical disability.⁴² Previously our group found that evoked pain modulated SLN connectivity to M1, and that sensitivity to painful stimuli was highly correlated with SLN to M1 functional connectivity changes.²⁸ Therefore, it is possible that the somatosensory component of MT, particularly of MANIP, helps alter the top-down processing of pain, immediately following the manipulation, through increased SLN connectivity to M1. Additionally, in our previous publication on this cohort, we found that both MANIP and MOBIL reduced patient's ratings of movement-expected pain associated with the performance of back

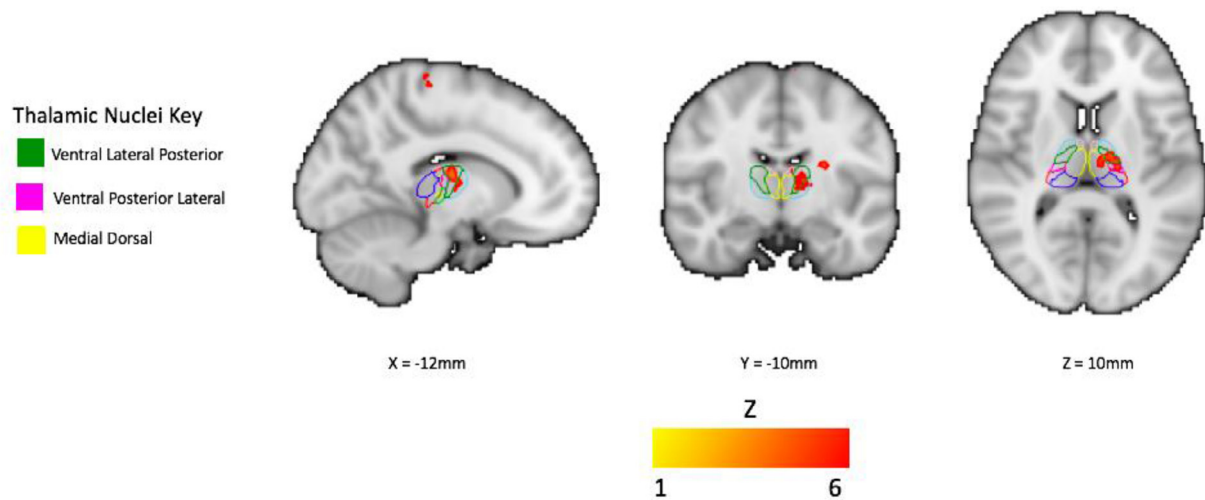


Figure 6. SLN connectivity to the thalamus was increased following MANIP (see Fig 3) and the thalamic cluster spanned important nuclei for pain modulation – ventral lateral posterior (VLP), ventral posterior lateral (VPL), and medial dorsal (MD), as evident by overlay with the canonical Morel thalamus atlas in MNI space.

straining exercises.¹⁴ Therefore, increased SLN to M1 connectivity may be related to decreased expectation of movement-induced pain.

Interestingly, our voxelwise analysis revealed significant activation in the LPFC which was associated with a decrease in low back pain post MANIP and MOBIL. The LPFC is known to play a role in emotion regulation and social cognition,¹⁵ and has been shown to have an impact on negative cognitive processes in clinical pain populations.^{27,41,51} Our previous results suggested a biopsychosocial mechanism underlying MT treatment for cLBP, as patients showed a post-treatment reduction in both clinical pain and fear of “back-straining” exercises, which were related to decreased BOLD response in various brain regions associated with emotion, cognition, and pain perception.¹⁴ Thus, our results suggest that SLN connectivity to LPFC supports MT-induced analgesia, which could be due to cognitive top-down processing of pain via anti-nociceptive pathways.

Our results showing both somatosensory and cognitive changes post-MT implicate the importance of elucidating the psychophysiological underpinnings of this therapeutic method in cLBP patients. The single-session modulation of SLN connectivity to Thalamus and M1 suggest an immediate effect of MT on a physiological level, however the reduction in clinical pain was not associated with this change. A longitudinal trial is necessary to further assess associations between clinical pain reduction and somatosensory regions such as M1 and Thalamus. However, the association with post-MT decrease in clinical pain and increased activation in LPFC suggest that higher-level cognitive processing plays an important role in the reduction of clinical pain immediately following a single session of MT.

Although our results only produced significant connectivity changes post- MANIP, MOBIL was similarly as successful in reducing clinical low back pain post-therapy. This is supported by previous research showing that both of these techniques helped attenuate temporal

summation to evoked heat pain, statistically different not from one another but from a control rest condition.³⁶ Therefore, both manipulation and mobilization play an analgesic role in the perception of low back pain. There are several challenges that still remain and need to be further examined. Firstly, our design utilized a between-groups control for only spinal manipulation, and not mobilization, which limits our capacity to fully compare the two conditions across cLBP and HC groups. “Furthermore, our analysis used a lower cluster-forming threshold ($Z > 2.3$) than the recently recommended standard ($Z > 3.1$). However, given the statistical power inherent to our sample size, we felt that our choice for thresholding was acceptable as it still complies with the assumptions underlying Gaussian Random Field theory. Nevertheless, our study was novel in design, and further research with larger cohorts may be needed in order to replicate our results.

Our outcomes focused on immediate brain responses to a single MT intervention. Future longitudinal studies should also assess longer-term responses following a course of therapy. Additionally, in this analysis we chose to focus on the Salience Network, as there was ample *a priori* evidence that this network is altered in chronic pain and may be targeted by MT. However, MT might also modulate additional resting state networks, which also contain known cognitive and limbic brain regions. Additionally, as SLN has been linked with autonomic processing²⁰ future analyses could attempt to link autonomic modulation by MT with altered connectivity for specific SLN subregions. Moreover, our ROI analyses focused on the results contrasted from post- vs pre-MANIP in our cLBP patient cohort, which could have biased the results towards both the patient population and the manipulation technique. Future studies should increase power in order to focus more on interactions between both groups and techniques at a voxelwise level. A larger powered study could better assess various aspects of clinical effectiveness in both MANIP and

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MOBIL. Dynamic connectivity models may prove useful, as superior temporal resolution with multiband accelerated fMRI data would allow for better linkage with time series of autonomic function.

In conclusion, this study found that MT's capacity to immediately reduce clinical low back pain, specifically after manipulation, may operate via modulation of SLN functional brain connectivity. Additionally, this modulation of salience connectivity occurs in regions associated with cognitive, affective and sensorimotor components

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of pain processing (ie, thalamus, M1). Furthermore, our result showing an association between increased SLN connectivity to the LPFC for both MANIP and MOBIL suggests that MT-induced hypoalgesia may also be sensitive to higher-order cognitive processing.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2020.11.007>.

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