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Spinal Manipulative Therapy–Specific Changes in Pain Sensitivity in Individuals With Low Back Pain (NCT01168999)

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Abstract: Spinal manipulative therapy (SMT) is effective for some individuals experiencing low back pain; however, the mechanisms are not established regarding the role of placebo. SMT is associated with changes in pain sensitivity, suggesting related altered central nervous system response or processing of afferent nociceptive input. Placebo is also associated with changes in pain sensitivity, and the efficacy of SMT for changes in pain sensitivity beyond placebo has not been adequately considered. We randomly assigned 110 participants with low back pain to receive SMT, placebo SMT, placebo SMT with the instructional set "The manual therapy technique you will receive has been shown to significantly reduce low back pain in some people," or no intervention. Participants receiving the SMT and placebo SMT received their assigned intervention 6 times over 2 weeks. Pain sensitivity was assessed prior to and immediately following the assigned intervention during the first session. Clinical outcomes were assessed at baseline and following 2 weeks of participation in the study. Immediate attenuation of suprathreshold heat response was greatest following SMT (P = .05, partial η^2 = .07). Group-dependent differences were not observed for changes in pain intensity and disability at 2 weeks. Participant satisfaction was greatest following the enhanced placebo SMT. This study was registered at www.clinicaltrials.gov under the identifier NCT01168999.

***Perspective:** The results of this study indicate attenuation of pain sensitivity is greater in response to SMT than the expectation of receiving an SMT. These findings suggest a potential mechanism of SMT related to lessening of central sensitization and may indicate a preclinical effect beyond the expectations of receiving SMT.*

***Key words:** Central sensitization, manual therapy, low back pain, placebo, spinal manipulation.*

Low back pain (LBP) is a significant public health problem, with lifetime incidence rates up to 90%[89] and loss of work production estimated at $7.4 billion for workers in the United States between the ages of 40 and 65.[70] Chronic LBP, similar to other chronic pain conditions (eg, fibromyalgia), is associated with altered pain processing,[42,63] suggesting a mechanism related to central sensitization of pain.[56,76] Specifically, chronic LBP is associated with generalized pain sensitivity[42] and cortical responses to painful stimuli differing from those observed in healthy individuals.[2,28] Central sensitization is considered a factor in the progression of acute pain to chronic pain and the maintenance of chronic pain.[71] Subsequently, attenuation of central sensitization may represent a treatment target.[81]

Spinal manipulative therapy (SMT) is an effective[13-15,31] complementary and alternative medicine intervention for some individuals experiencing LBP. SMT is recommended by many LBP clinical practice guidelines[21]; however, not

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all clinical practice guidelines support SMT and variability exists between those that do, suggesting a need for stronger evidence.[57] Improved understanding of the mechanisms of SMT could enhance clinical effectiveness and clarify the variability in the present literature. LBP is a heterogenous condition for which the anatomical basis is commonly unidentifiable.[26] Consequently, a pathoanatomical diagnosis is generally not helpful for guiding treatment,[24] and identifying subgroups of individuals with LBP most likely to benefit from a specific intervention is a research priority.[27] Clarifying the mechanisms of SMT could assist in identifying key features of individuals with LBP likely to respond to these interventions, allowing more efficacious clinical application.

SMT is associated with changes in pain sensitivity,[19,61] suggesting a mechanism related to attenuation of central sensitization.[10] SMT results in increased mechanical pain thresholds in individuals with neck pain[23,88] and lateral epicondylalgia[30] and attenuation of suprathreshold heat response.[8,9,38] Consequently, the clinical effectiveness of SMT could result from lessening of central sensitization.

Placebo is associated with robust analgesia[85] enhanced by expectation for pain relief.[66] For instance, saline is associated with analgesia in patients with fibromyalgia[69] and irritable bowel syndrome[86] believing they received a pain-relieving drug. Clinical outcomes related to interventions for pain result from both intervention-specific and placebo mechanisms.[91] This point is exemplified in open-hidden paradigm studies in which a known analgesic agent is provided in an open manner or through hidden infusion, resulting in greater analgesia when openly administered.[5,16] Expectation is also influential in outcomes related to complementary and alternative medicine interventions. For example, a study comparing the efficacy of massage and acupuncture for individuals with LBP observed a moderating effect of expectation.[54] Participants expecting more relief with acupuncture demonstrated better outcomes when receiving acupuncture, whereas those expecting more relief with massage demonstrated better results when receiving massage.[54] Furthermore, active acupuncture is associated with similar analgesic properties as placebo acupuncture in participants following dental surgery.[3] However, participants believing they received acupuncture reported significantly less pain than those believing they received the placebo acupuncture.[3] Collectively, these studies suggest that placebo mechanisms related to expectation are influential in clinical outcomes for complementary and alternative medicine interventions, yet rigorous assessment in SMT is lacking.

The primary purpose of this mechanistic trial was to consider a potential mechanism of SMT by determining the efficacy of SMT upon pain sensitivity. We have observed immediate lessening of pain sensitivity in response to SMT,[8,9,38] and the current study was designed to extend these findings by determining whether lessening of pain sensitivity is specific to SMT or the expectation of receiving SMT. As a secondary purpose, we considered the clinical efficacy of SMT and the influence of expectation upon these outcomes.

Methods

Participants

The study was approved by the institutional review board of the University of Florida. A sample of convenience was recruited from the general community of the University of Florida campus and Health Science Center by posted flyers and electronic distribution. Participants between the ages of 18 and 60 currently experiencing mechanical LBP rated ≥4/10 at its worst over the past 24 hours on a numeric rating scale (NRS) (0 = no pain at all to 10 = worst pain imaginable) were included in the study. We based the diagnosis of LBP on clinical presentation related to pain in the lumbar region rather than on imaging abnormalities because an anatomical cause is not identifiable in the majority of cases of LBP.[26] Participants were excluded for 1) pain or paresthesia below the knees; 2) potential nonmusculoskeletal causes of LBP as indicated by unexplained weight loss of greater than 10 pounds, fever corresponding to LBP, nonmechanical pain, and bowel or bladder dysfunction; 3) surgery to the low back within the past 6 months; 4) systemic illness known to affect sensation, that is, diabetes; 5) chronic pain condition unrelated to LBP; 6) fracture as the cause of LBP; and 7) pregnancy. Duration of LBP was not a consideration for inclusion/exclusion from the study because we wished to include a full range of individuals with LBP for ecological validity, whereas anticipating individuals with LBP more chronic in nature would predominate because of our recruitment strategy. We felt that our primary mechanistic aim related to central sensitization justified this approach and anticipated that any influence of duration upon the outcomes would be negated by the parallel group design. All individuals meeting the criteria for participation and providing informed consent were enrolled in the study.

Measures

Demographic and Clinical Characteristics

Demographic information was obtained at baseline through a questionnaire specific to age, sex, years of education, and duration of LBP.

Psychological Questionnaires

Psychological measures known to influence experimental pain[39,64] and LBP outcomes[33,48,74,75] were assessed as we wished to control for these factors in the event our randomization process did not evenly distribute them across the groups. Psychological measures included the Fear Avoidance Belief Questionnaire,[90] the Tampa Scale of Kinesiophobia,[92] and the Pain Catastrophizing Scale.[82]

Assessment of Pain Sensitivity

Measures of pain sensitivity served as primary outcomes reflective of SMT-related changes in central sensitization and included the following.

Mechanical Pain Sensitivity. Mechanical pain sensitivity lessens in response to SMT[19] and we wished to determine if similar changes occurred in the current

study. A pressure algometer (Pain Diagnostics & Treatment, Great Neck, NY) was used to determine suprathreshold mechanical pain sensitivity. Six kilograms of force was applied at a rate of 1 kg/sec through a 1-cm^2 application tip at the dominant-side posterior superior iliac spine to determine local changes in pain sensitivity and the web space of the dominant foot to determine remote changes in pain sensitivity because SMT is associated with both local and remote changes in mechanical pain sensitivity.[19] Mechanical pain sensitivity was quantified through a 100-mm mechanical visual analog scale anchored with "No pain" and "The most intense pain sensation imaginable." Mechanical visual analog scales are commonly used in the assessment of pain and have demonstrated sound psychometric properties, including the characteristics of a ratio scale.[65]

Thermal Pain Sensitivity. Thermal pain sensitivity was assessed for suprathreshold heat response and aftersensations. Participants underwent thermal pain assessment using the Medoc Neurosensory Analyzer (TSA-2001; Medoc, Ramat Yishai, Israel) with a hand-held, Peltier element–based stimulator.

Suprathreshold Heat Response. Suprathreshold heat response assessment used previously established protocols for temporal summation[69,80] at 51°C applied to the plantar surface of the dominant foot with an interstimulus interval of .33 seconds. A 101-point NRS anchored with "no pain" and "the most intense pain sensation imaginable" quantified the pain experienced with each heat pulse, and participants were instructed to rate their "second pain." We have previously observed moderate within-session stability of this protocol in both healthy participants and those experiencing pain conditions.[1] The rating provided for the fifth pulse in this temporal summation protocol is considered primarily C-fiber mediated[67] and corresponds most highly to clinical pain.[84] We selected the rating provided for the fifth pulse as our measure of suprathreshold heat response based on its translational potential because of the established relationship to clinical pain.

Aftersensation. Participants quantified pain they continued to feel 15 seconds following the tenth pulse in the suprathreshold heat response protocol using an NRS.[78] Aftersensation is considered primarily C-fiber mediated.[67,69,77] We elected to consider aftersensation as a competing measure of C-fiber-mediated pain and because of its relationship to clinical pain in other chronic pain conditions.[78-80] We have previously observed good within-session reliability of the assessment of aftersensation in both healthy participants and those experiencing pain conditions.[1]

Clinical Outcomes

Clinical Pain Intensity

Clinical pain intensity was assessed for changes over the 2 weeks of the study using the NRS for "usual pain over the past week" from the Pain-Centered Outcomes Questionnaire. NRSs are reliable and valid[37,52] and a common measure of clinical pain intensity.

LBP-Related Disability

LBP-related disability was assessed through the Oswestry Disability Index (ODI). The ODI is a 10-item questionnaire specific to LBP. Each item contains a 6-point adjectival scale scored from 0 to 5. We doubled the total score as is commonly done[29] to provide a percentage, with higher scores indicating greater perceived disability. The ODI is a commonly used measure of disability in the study of LBP and has demonstrated strong reliability and validity.[12,29,34,35]

Participant Satisfaction

Satisfaction is related to expectation,[4,49] and unmet expectations may lead to dissatisfaction.[4] We included satisfaction as a secondary outcome measure to determine whether differing group-related expectations were associated with differences in satisfaction separate from changes in clinical outcomes. We used 2 questions from the North American Spine Society Lumbar Spine Outcome Assessment[22] indicative of satisfaction.[40] Participants were asked the following questions: 1) "Would you have the same intervention you received in this study again for low back pain?" Possible responses ranged from 1 = definitely not to 5 = definitely yes. 2) "How would you rate the overall results of the intervention you received in this study for low back pain?" Possible responses ranged from 1 = terrible to 6 = excellent.

Interventions

All interventions (Fig 1) were performed by a licensed physical therapist (J.E.B. or M.E.H.).

The SMT group received an SMT previously shown to be effective in the treatment of some individuals experiencing LBP.[13,31] Furthermore, we have previously observed the attenuation of suprathreshold heat response in response to the studied SMT.[8,38] Similar to our prior studies, the SMT was performed 2 times on each side.[8,38] Participants receiving the SMT were instructed through the informed consent process that they would receive either a studied SMT or a placebo intervention and were provided no additional information regarding which intervention they received.

The standard SMT placebo group received a placebo SMT. SMT interventions depend upon biomechanical approaches related to positioning and force application intended to isolate a vertebral segment or spinal region and impose motion.[41] The novel placebo was intended to mimic the studied SMT; however, it differed biomechanically. Specifically, the placebo maintained the lumbar spine in a neutral position (as opposed to contralateral side bending in the studied SMT). Participants were log-rolled toward the examiner and then returned to a supine position (as opposed to maintained in rotation as in the studied SMT). A thrust of similar force to the studied SMT was then applied to the contralateral anterior superior iliac spine of the pelvis directly into the table. The placebo SMT was designed to apply a thrust to a neutral spine and directly into the table rather than thrusting into rotation in a spine positioned in side bending and rotation as occurs in the studied SMT. We

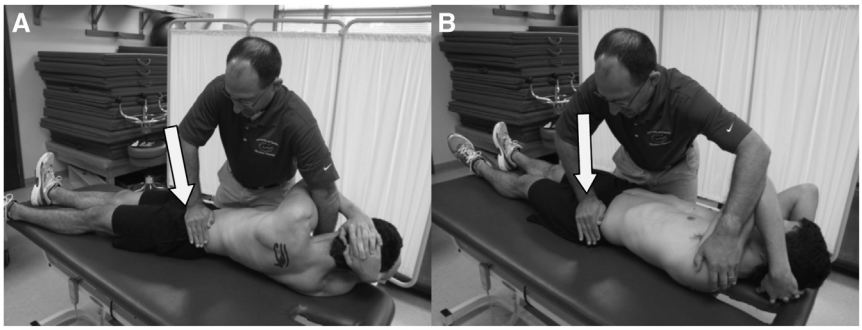

Figure 1. Illustration of the SMT and the placebo SMT. The SMT **(A)** is effective in the treatment of some individuals experiencing LBP and has been previously demonstrated to attenuate suprathreshold heat response. The participant was positioned with a neutral spine (ie, without apparent side-bending or rotation) for the placebo SMT **(B)**. A high-velocity, low-amplitude force was then applied through the pelvis to further rotate the lumbar spine. The participant was positioned with a neutral spine (ie, without apparent side-bending or rotation) for the placebo SMT. The participant was log-rolled into side-lying and then returned to supine. A thrust of similar magnitude of force as was applied during the SMT was then applied to the pelvis, which remained in contact with the table to prevent motion. Arrows indicate direction of the force.

acknowledge that load was applied to the spine with the placebo SMT; however, we believe this was necessary to provide a credible comparison because nonthrust placebo comparisons such as light touch are associated with lower treatment expectancies than SMT.[36] Additionally, the applied load was to a spine positioned vastly differently from typical clinical practice and not done with therapeutic intent. Similar to the studied SMT, the placebo SMT was performed 2 times on each side. Participants receiving the placebo SMT were instructed through the informed consent process that they would receive either a studied SMT or a placebo intervention and were provided no additional information regarding which intervention they received.

The enhanced SMT placebo group received the same placebo as the standard placebo group. Participants receiving the enhanced SMT placebo were instructed through the informed consent process they would receive either a studied SMT or a placebo intervention; however, they were told, "The manual therapy technique you will receive has been shown to significantly reduce low back pain in some people" immediately prior to the first intervention and subsequent intervention sessions. Similar instructional sets have been incorporated in mechanistic studies of placebo and are associated with enhanced placebo analgesia in subjects with irritable bowel syndrome.[68,86] Similar to the SMT and the standard placebo group, the enhanced placebo SMT group received the placebo SMT 2 times on each side.

The no-treatment control group sat quietly for 5 minutes during the initial session.

Procedures

Individuals agreeing to participate signed an informed consent form approved by the University of Florida Institutional Review Board and then completed the intake demographic form, psychological questionnaires, the Pain-Centered Outcomes Questionnaire, and the ODI. Participants next underwent baseline pressure and thermal pain testing and were randomly assigned to receive SMT, placebo SMT, enhanced placebo SMT, or no intervention. Randomization was computer generated with group assignment maintained in sealed, sequentially numbered, opaque envelopes. The envelopes were opened in sequential order based on entry in the study and after all baseline measures were completed for the participant.

We wished to ensure the appropriateness of the placebo SMT as indicated by the believability and resulting expectation for treatment effectiveness. Believability was assessed immediately following the application of the assigned intervention. Participants receiving the SMT, placebo, or enhanced placebo received the following instruction: "In this study you received either a manual therapy intervention or a placebo. Please indicate whether you believe you received the manual therapy intervention or the placebo." Participants were handed a form and asked to circle the intervention they believed they received (SMT or placebo). Expectation was also assessed immediately following the initial application of the assigned intervention. Participants were handed a form with the options of 1) more LBP, 2) less LBP, and 3) the same amount of LBP and asked to circle the option most reflective of their expected level of LBP upon completion of the study.

Next, participants underwent repeat mechanical and thermal pain sensitivity testing to consider an immediate, within-session change in pain sensitivity. Participants receiving the SMT and both placebo groups were scheduled for 5 additional sessions during the next 2 weeks to receive their assigned intervention. Participants in the SMT and standard placebo group were provided no information regarding their assigned intervention during any of the intervention sessions. Following the 2-week period of the study, all participants were seen for a final session in which clinical outcomes for pain intensity, disability, and satisfaction were assessed. Upon completion of the study, participants

were debriefed regarding their group assignment and the purpose of the study.

Data Analysis

Individual t-tests and chi-square tests were used to assess for postrandomization group differences. Significance was set at .05 and all analyses were performed using the SPSS statistical package, version 21.0 (SPSS Inc, Chicago, IL).

We determined the appropriateness of our placebo comparison prior to consideration of our primary and secondary purposes. Separate chi-square analyses compared perceived group assignment (SMT, placebo SMT, placebo SMT with enhanced instructional set) to both actual assignment (SMT or placebo SMT) and categorized expectation for results (more, less, or the same amount of LBP). Significant group-related differences were observed in perception of group assignment immediately following the first intervention, $\chi^2(2, n = 81) = 10.02$, $P = .01$ (Table 1). More participants receiving the standard placebo SMT believed they received a placebo than did those receiving SMT ($P = .03$) or the enhanced placebo SMT ($P < .01$). Differences in perceived intervention were not found between participants receiving the SMT and the enhanced placebo SMT ($P = .36$). These findings suggest that participants found the enhanced placebo SMT to be equally believable as a rehabilitation intervention as they did the studied SMT. Significant group-related differences were observed in the expected 2-week changes in LBP immediately following the first intervention, $\chi^2(6, n = 110) = 20.91$, $P < .01$ (Table 2). A larger percentage of participants receiving the SMT and enhanced placebo SMT expected less pain than those receiving the standard placebo SMT and the no-treatment control group ($P < .05$). Expected LBP at 2 weeks in response to the intervention did not differ for participants receiving the SMT and enhanced placebo SMT ($P = .67$) or for participants in the no-treatment control and the standard placebo SMT group ($P = .23$). These findings suggest that the enhanced placebo SMT was associated with similar expectations for effectiveness as the studied SMT.

Pain Sensitivity

Separate mixed-model analyses of variance (ANOVAs) were used to test for a group (SMT, placebo SMT, enhanced placebo SMT, control) × time (pre- to immediately postintervention during the initial session) interaction for measures of mechanical and thermal pain sensitivity. In the event of a statistically significant group × time interaction, simple contrasts were performed to assess within-group changes. Changes in aftersensation were assessed only in participants reporting continued pain at 15 seconds following the last pulse in the suprathreshold heat response protocol at baseline.

Table 1. Validity of Placebo SMT: Believability

	Intervention Received		
Perceived Intervention	SMT	Standard Placebo SMT	Enhanced Placebo SMT
SMT	18	10	21
Placebo	9	17	6

NOTE. Significant group-related differences were observed in perception of group assignment immediately following the first intervention, $\chi^2(2, n = 81) = 10.02$, $P = .01$. Significantly more participants receiving the standard placebo group believed they were receiving a placebo than those receiving the SMT or enhanced placebo ($P < .05$). No differences were observed in perceived intervention in the participants receiving the SMT and the enhanced placebo ($P = .36$).

Table 2. Validity of Placebo SMT

Expectation	SMT	Standard Placebo SMT	Enhanced Placebo SMT	No Treatment
More pain	0	0	0	1
Less pain	15	7	16	3
Same pain	13	20	11	24

NOTE. Significant group-related differences were observed in categorized expectation for change in condition immediately following the first intervention, $\chi^2(6, n = 110) = 20.91$, $P < .01$. Significantly more participants receiving the SMT and the enhanced placebo reported expecting to have less pain following the study than those receiving the standard placebo or no treatment ($P < .05$). Differences were not observed in expected change in LBP between the SMT and enhanced SMT ($P = .67$) and the no-treatment control and the standard placebo SMT ($P = .23$).

Clinical Outcomes

Separate mixed-model ANOVAs were used to test for a group (SMT, placebo SMT, enhanced placebo SMT, control) × time (baseline to 2 weeks) interaction for clinical pain intensity and disability.

Participant Satisfaction

Separate chi-square analyses were used to compare group assignment (SMT, placebo SMT, enhanced placebo SMT, control) to the responses to the following questions: 1) "Would you have the same intervention you received in this study again for low back pain?" Possible responses ranged from 1 = definitely not to 5 = definitely yes and were further categorized with individuals answering "definitely not," "probably not," and "completely uncertain" combined into one category and those answering "probably yes" and "definitely yes" combined into a second category. 2) "How would you rate the overall results of the intervention you received in this study for low back pain?" Possible responses ranged from 1 = terrible to 6 = excellent and were further categorized with individuals answering "terrible," "poor," and "fair" combined into one group and those responding "good," very good," or "excellent" grouped separately.

Influence of Expectation Upon Clinical Outcomes

Participants were categorized by whether they expected more, less, or the same amount of LBP immediately following the initial intervention. Separate mixed-model ANOVAs were used to test for a group (expect more, less, or the same amount of LBP) × time (baseline to 2 weeks) interaction for clinical pain

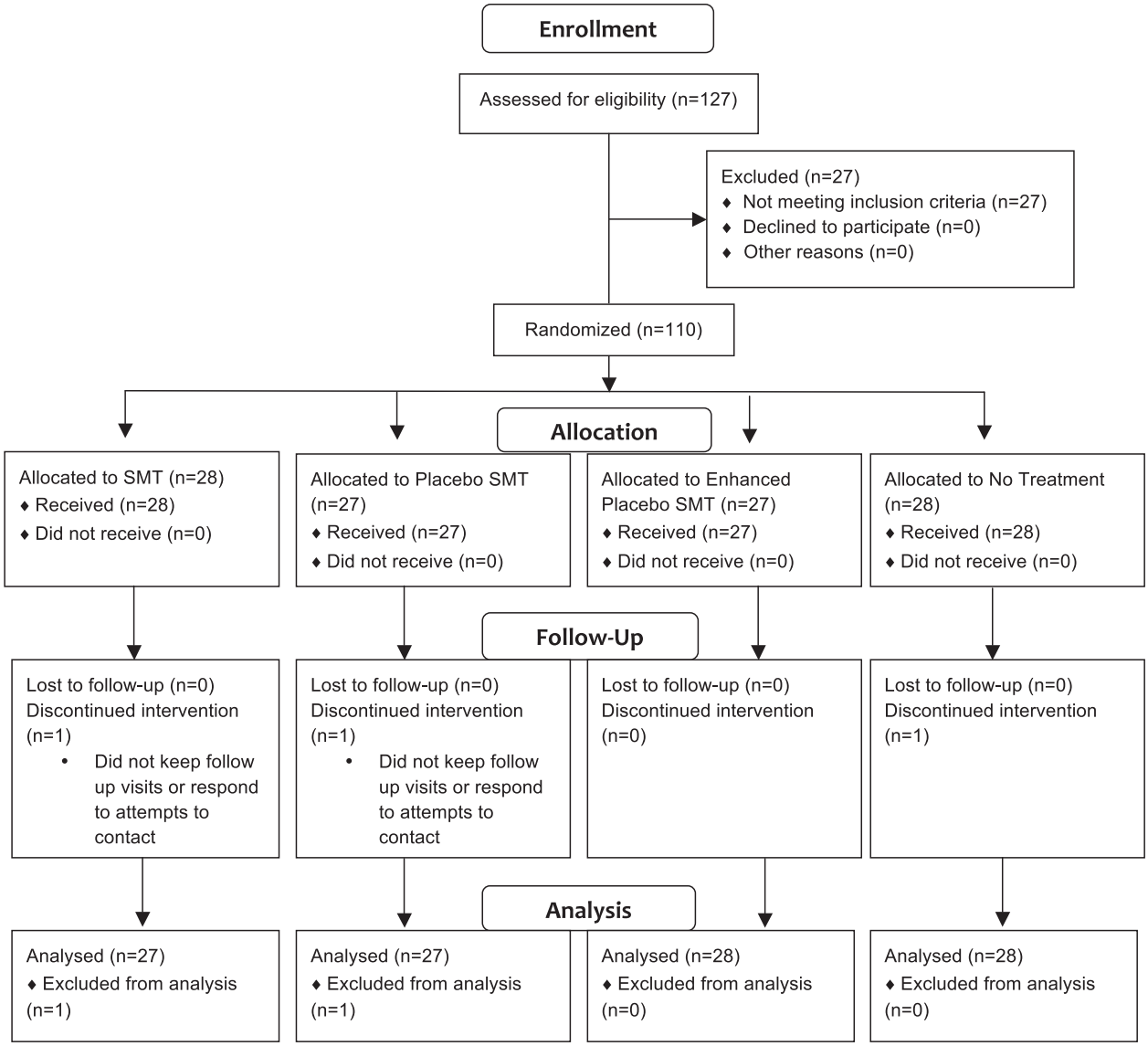

Figure 2. Summary of recruitment, enrollment, randomization, follow-up, and analysis for study.

intensity and disability. In the event of a statistically significant group × time interaction, pairwise comparisons were performed to assess within-group changes.

Sample Size Determination

Sample size was determined based on reduction in suprathreshold heat response by using effect sizes from our prior studies comparing the same technique to other common physical therapy interventions for LBP.[8,38] We used a conservative analgesic effect size of measures of suprathreshold heat response from our previous studies (η^2 = .17), a 2-tailed null hypothesis, and an alpha of .05 (to account for the multiple comparisons) to generate a conservative estimate of power. Twenty participants per treatment group were determined to provide greater than 95% power to detect a group × time interaction in the proposed ANOVA model. We oversampled to 28 subjects per treatment group to account for potential dropouts and allow for extra power if smaller than anticipated effect sizes were observed.

Results

One hundred twenty-seven individuals were screened for the study, and 110 signed the informed consent form and agreed to participate (Fig 2). Seventy percent of participants were female and mean age was 31.68 (standard deviation = 11.85) years. Baseline measures of the sample as a whole and by group assignment are presented in Table 3. Individual groups did not differ by baseline demographic measures, clinical measures, psychological measures, or pain sensitivity measures.

Pain Sensitivity

Group × time (pre–first intervention to immediately post–first intervention) differences were not observed in mechanical pain sensitivity assessed at the posterior

Table 3. Baseline Comparison of Intervention Groups

	SMT	Placebo	Enhanced Placebo	No-Treatment Control	Total Sample	P Value for Difference
Sex (% female)	21/28 (75.0)	17/27 (63.0)	20/27 (74.1)	19/28 (68.0)	77/110 (70.0)	.74
Age	32.07 (10.98)	33.22 (13.29)	31.56 (11.85)	29.85 (12.09)	31.68 (11.85)	.78
Education (years)	16.04 (2.33)	15.59 (2.50)	15.89 (2.38)	16.57 (2.60)	16.03 (2.45)	.51
Duration of LBP (weeks) (median, interquartile range)	12 (164.50)	24 (100)	36 (543)	4 (108)	16.03 (153)	.43
ODI	17.04 (9.17)	14.22 (8.56)	17.92 (13.31)	20.04 (15.27)	17.32 (11.95)	.35
Usual pain	45.26 (26.21)	43.78 (22.45)	37.89 (22.13)	33.93 (26.21)	40.16 (23.33)	.24
FABQ-PA	12.78 (4.89)	11.74 (3.05)	12.41 (5.21)	13.50 (5.68)	12.61 (4.80)	.59
FABQ-W	10.92 (8.05)	10.42 (7.44)	9.23 (9.39)	12.32 (8.07)	10.75 (8.22)	.59
TSK	23.27 (6.25)	22.46 (4.88)	20.54 (5.04)	22.42 (6.02)	22.17 (5.59)	.35
PCS	16.08 (8.51)	13.88 (9.66)	14.88 (11.04)	12.75 (11.67)	14.37 (10.25)	.68

Abbreviations: FABQ, Fear Avoidance Belief Questionnaire; PA, personal activities; W, work; TSK, Tampa Scale of Kinesiophobia; PCS, Pain Catastrophizing Scale.
NOTE. All data are reported as mean (standard deviation) ratings unless otherwise noted. Duration of LBP in weeks presented as median, interquartile range, because of nonnormal distribution. ODI = 0–100%, with smaller numbers indicating less disability. Suprathreshold heat response expressed as the rating of the fifth pulse in the suprathreshold heat response protocol using an NRS with 0 = no pain to 100 = worst pain imaginable.

superior iliac spine ($F_{3,104} = 1.14$, $P = .34$, partial $\eta^2 = .03$), nor was a main effect for time ($F_{1,104} = 3.65$, $P = .06$, partial $\eta^2 = .03$; Table 4). Group × time (pre–first intervention to immediately post–first intervention) differences were not observed in mechanical pain sensitivity assessed at the web space of the foot ($F_{3,104} = .93$, $P = .43$, partial $\eta^2 = .03$), nor was a main effect for time ($F_{1,104} = 2.31$, $P = .13$, partial $\eta^2 = .02$). Group × time (pre–first intervention to immediately post–first intervention) differences were observed in suprathreshold heat response ($F_{3,106} = 2.63$, $P = .05$, partial $\eta^2 = .07$). Statistically significant lessening of pain sensitivity was observed only in response to the SMT ($P < .05$; Fig 3). Thirty-eight of the 110 participants (34.5%) reported continued pain 15 seconds following the 10th pulse in the suprathreshold pain protocol and were considered in the analysis of aftersensation.

Eight of 28 (29%) participants in the SMT group, 9 of 27 (33%) of participants in the placebo SMT group, 8 of 27 (30%) in the enhanced placebo SMT group, and 13 of 28 (46%) participants in the no treatment group reported aftersensation. Group × time (pre–first intervention to immediately post–first intervention) differences were not observed in aftersensation ($F_{3,34} = 1.42$, $P = .25$, partial $\eta^2 = .11$), nor was a main effect for time ($F_{1,34} = 1.88$, $P = .18$, partial $\eta^2 = .05$).

Clinical Outcomes

A group × time interaction was not observed for LBP over the 2 weeks of the study ($F_{3,103} = .51$, $P = .68$, partial

Table 4. Immediate Changes in Pain Sensitivity

	Mechanical Pain Sensitivity, PSIS	Mechanical Pain Sensitivity, Dorsum of the Foot	Suprathreshold Heat Response	Aftersensation
SMT				
Pre	19.12 (20.96)	22.14 (20.16)	36.57 (22.81)	13.75 (12.46)
Post	18.56 (23.18)	26.10 (26.77)	29.54 (23.64)*,†	6.00 (4.57)
Placebo				
Pre	26.48 (30.02)	23.22 (25.76)	31.04 (22.01)	12.67 (9.25)
Post	23.64 (28.93)	24.16 (27.00)	34.07 (24.37)	11.67 (13.69)
Placebo+				
Pre	18.81 (23.82)	15.24 (15.28)	27.00 (22.19)	6.75 (3.58)
Post	11.78 (16.67)	20.39 (29.14)	25.78 (22.78)	3.63 (2.39)
No treatment				
Pre	21.68 (26.46)	29.27 (27.92)	26.61 (24.92)	9.62 (11.09)
Post	21.23 (27.20)	28.19 (26.53)	29.54 (23.64)	11.69 (13.79)
Total sample				
Pre	21.55 (25.39)	22.60 (23.16)	30.33 (23.07)	10.61 (9.85)
Post	18.89 (24.60)	24.78 (27.12)	29.45 (22.90)	8.79 (10.94)

Abbreviation: PSIS, posterior superior iliac spine.
NOTE. All data are reported as mean (standard deviation). Placebo+ = placebo SMT provided with instructional set to enhance expectation. Suprathreshold heat response expressed as the rating of the fifth pulse in the suprathreshold heat response protocol using an NRS with 0 = no pain to 100 = worst pain imaginable. Aftersensation = pain report through an NRS with 0 = no pain to 100 = worst pain imaginable provided 15 seconds following the 10th pulse in the suprathreshold heat response protocol. Further, 38/100 (34.5%) of participants reported persistent pain 15 seconds following the 10th pulse in the suprathreshold heat response protocol. Aftersensation information is provided only for the participants who reported persistent pain.
*Significant between group differences ($P \leq .05$).
†Significant within group differences ($P \leq .05$).

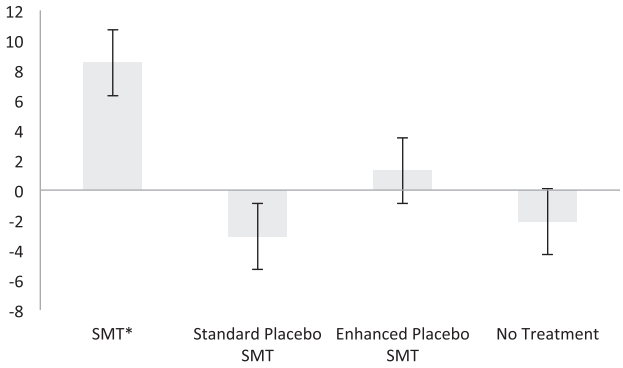

Figure 3. Immediate within-session changes in suprathreshold heat response. Immediate (preintervention to immediately postintervention) within-session changes in suprathreshold heat response. Bars represent change scores (pre- to postintervention), with positive numbers on the *y*-axis indicating a lessening of pain sensitivity in response to an intervention. A significant group × time interaction was observed (P = .05), indicating group-dependent changes in suprathreshold heat response. *Significant lessening of pain sensitivity (P = .05). Error bars = standard error of the mean. SMT = spinal manipulative therapy.

η^2 = .02; Fig 4). Significant main effect for time was observed with LBP ($F_{1,103}$ = 36.56, P < .01, partial η^2 = .26). A mean decrease in LBP of 10.27 (standard deviation = 18.22) was observed across participants in the study regardless of group assignment. A group × time interaction was not observed for LBP-related disability ($F_{3,102}$ = .43, P = .73, partial η^2 = .01). Significant main effect for time was observed with disability ($F_{1,102}$ = 13.86, P < .01, partial η^2 = .12). A mean decrease in LBP-related disability of 2.93 (standard deviation = 8.06) was observed across participants in the study regardless of group assignment.

Participant Satisfaction

Significant group-related differences were observed in response to the question "Would you have the same intervention you received in this study again for low back pain?" $\chi^2(3, n = 106) = 8.15$, P = .04 (Table 5). Significantly more participants receiving the enhanced placebo SMT indicated "probably to definitely yes" than the other groups individually (P < .05). Significant group-related differences were observed in response to the question "How would you rate the overall results of the intervention you received in this study for low back pain?" Significantly more participants receiving the enhanced placebo SMT indicated "good to excellent" than participants receiving the standard placebo SMT or no treatment (P < .05). A significant difference was not observed between participants receiving the SMT and the enhanced placebo SMT (P = .07).

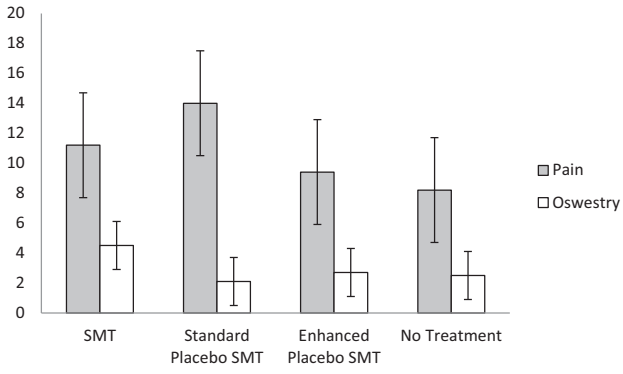

Figure 4. Two-week changes in clinical outcomes. Two-week changes in low back–related pain intensity and disability. Pain intensity was measured with a 101-point NRS anchored with 0 = no pain to 100 = worst pain imaginable for the "usual" pain over the past week. Disability was assessed with the ODI. Bars represent change scores (baseline to 2 weeks), with positive numbers on the *y*-axis indicating reductions in pain and disability in response to an intervention. A significant main effect for time was observed for both pain and disability; however, neither was dependent on group assignment. Error bars = standard error of the mean.

Influence of Expectation Upon Outcomes

A group (expect more LBP, less LBP, the same amount of LBP) × time (baseline to immediately following the first intervention) interaction was not observed for immediate change in suprathreshold heat response ($F_{2,107}$ = .32, P = .73, partial η^2 = .01). A group (expect more LBP, less LBP, the same amount of LBP) × time (baseline to 2 weeks) interaction was not observed for change in LBP ($F_{2,104}$ = .76, P = .47, partial η^2 = .01) or LBP-related disability ($F_{2,103}$ = 2.19, P = .12, partial η^2 = .04) over the 2 weeks of the study.

Discussion

Efficacy of SMT on Suprathreshold Heat Response

The present study extends our prior work related to the mechanisms of SMT. We have previously observed attenuation of suprathreshold heat response following SMT in both healthy participants[9,38] and those experiencing LBP.[8] Furthermore, we have observed heightened suprathreshold heat response following SMT in healthy participants expecting to experience more pain,[7] indicating an influence of expectation. The current study adds to these observations by indicating that the lessening of pain sensitivity accompanying SMT is likely specific to 1) SMT rather than the expectation of receiving SMT and 2) suprathreshold heat response and not other thermal or mechanical measures of pain sensitivity used in this study. Studies in anesthetized animals confirm windup of neurons in the dorsal horn of the spinal cord in response to repeated C-fiber stimulation.[20,43] Thus, we interpret our findings to reveal a mechanism of SMT related to modulation of dorsal horn excitability. Lessening of central sensitization as indicated by changes in suprathreshold heat response suggests a treatment target with potential relevance to clinical pain conditions.[81] Our SMT-specific changes in suprathreshold heat response suggest the potential for a clinically beneficial intervention if these effects are lasting and associated with clinical pain reduction. Furthermore, the specificity of this finding to SMT and not placebo SMT suggests a mechanism beyond the expectation of receiving SMT.

Table 5. Measures of Participant Satisfaction

	SMT	Placebo SMT	Enhanced Placebo SMT	No Treatment
A. Participant answer to "Would you have the same intervention you received in this study again for low back pain?"*				
Definitely not to completely uncertain	21	20	13	22
Probably to definitely yes	6	6	13	5
B. Participants answer to "How would you rate the overall results of the intervention you received in this study for low back pain?"†				
Terrible to fair	20	20	13	20
Good to excellent	7	6	13	1

*Significant group related differences were observed in response to the question "Would you have the same intervention you received in this study again for low back pain?" $\chi^2(3, n = 106) = 8.15$, $P = .04$. Significant group-related differences were observed with significantly more participants receiving the enhanced placebo SMT indicating "probably to definitely yes" than the other group individually ($P < .05$).

†Significant group-related differences were observed in response to the question "How would you rate the overall results of the intervention you received in this study for low back pain?" $\chi^2(3, n = 100) = 12.47$, $P = .01$. Group-related differences were observed with significantly more participants receiving the enhanced placebo SMT indicating "good to excellent" than participants receiving the placebo SMT or no treatment ($P < .05$). A significant difference was not observed between participants receiving the SMT and the enhanced placebo SMT ($P = .07$).

Clinical Outcomes

We did not observe group-related differences in clinical pain or disability over the 2 weeks of the study despite differences in blinding, expectation, and immediate within-session changes in pain sensitivity. These findings contrast with systematic reviews suggesting that SMT is an effective intervention for individuals with LBP.[14] LBP is a heterogeneous condition resulting in frequently small treatment effects in response to common interventions.[55] A more recent management approach advocates determining homogeneous groups of individuals with LBP likely to benefit from specific interventions.[27] Specific to SMT, a clinical cluster has been formulated[31] and validated[13] identifying individuals experiencing LBP likely to benefit from SMT. Additionally, SMT may be more effective for acute LBP[32] and when combined with exercise.[13,15,31] We did not base inclusion in our study on meeting the clinical cluster and included individuals with chronic LBP. Our primary purpose was mechanistic and specific to the efficacy of SMT on proxy measures of central sensitization of pain. Given that central sensitization is more likely to be prevalent in a chronic pain population, the inclusion of those with long-standing pain was justified. The results of this study will provide important foundational findings for future studies in more acute samples of individuals with LBP. Furthermore, we elected to only include SMT (rather than SMT and exercise) as we were interested in focusing on mechanisms specific to SMT. Clinical treatment effects may have been observed if we had powered the study to detect them, been more selective in our participant selection, or included an exercise intervention with SMT. Related to these limitations, our findings should not be interpreted as an indication of the efficacy of SMT but rather as complementary data to the more mechanistically inclined outcomes. Numerous studies have considered the immediate effects of manual therapy interventions upon neurophysiological responses such as changes in pain sensitivity. A methodological weakness of these studies is the failure to link the observed findings to clinical outcomes.[17] The clinical findings of the current study allow for interpretation of the clinical relevance of SMT-related changes in pain sensitivity.

Our findings may be viewed as paradoxical as we observed SMT-specific changes in pain sensitivity not reflected in changes in clinical outcomes over the 2 weeks of the study. We have parallel results in another manual therapy model (neurodynamic interventions) in individuals with signs and symptoms of chronic carpal tunnel syndrome.[6] Specifically, clinical outcomes did not correspond to changes in pain sensitivity observed over the 3 weeks of the study.[6] Suprathreshold heat response as obtained through the included protocol are believed to be a measure of neuroplastic changes in the nervous system in response to pain. One interpretation of these findings is that neuroplastic changes in pain sensitivity may be a precursor to subsequent changes in clinical outcomes that require more time to manifest. Manual therapy–related within-session changes in clinical pain are associated with longitudinal changes in clinical outcomes,[18,44] and immediate changes in pain sensitivity may provide similar predictive value given adequate follow-up time. Another competing interpretation of these findings is that favorable changes in pain sensitivity corresponding to SMT may not be directly linked to the studied clinical outcomes. Future studies with longer follow-up times are necessary to determine whether immediate positive changes in suprathreshold heat response are a precursor to improved clinical outcomes.

Significantly more participants receiving the enhanced placebo indicated satisfaction with the intervention *despite the lack of group-dependent differences in clinical outcomes.* Our findings are consistent with others who observed satisfaction as independent of clinical outcomes related to pain and function. For example, George and Hirsh found satisfaction with treatment delivery to differ from that of treatment effect,[40] and Breen and Breen observed "overall improvement" to explain only 57% of the variance for satisfaction in individuals seeking chiropractic care due to LBP.[11] All participants in the current study were instructed during the consent process that they could receive either a studied SMT or a placebo. Participants in the enhanced placebo SMT group were told they were receiving an effective intervention, whereas those receiving the SMT and the standard placebo received no instruction as to which

intervention they received and were left to their own conclusions. Participants receiving the enhanced placebo may have been more satisfied as the delivery met their expectations for treatment (ie, they received a perceived active and potentially effective intervention).[83] SMT is associated with high satisfaction.[50] Our findings suggest that SMT-related satisfaction is influenced by the context of the intervention and not necessarily the intervention itself or corresponding outcomes.

Influence of Expectation Upon Clinical Outcomes

We did not find expectation to influence immediate changes in suprathreshold pain response. We have previously observed worsening of suprathreshold heat response in healthy participants told to expect *more* pain.[7] Ethical considerations prevented us from providing an instructional set suggestive of worsening of LBP in the current study; however, suprathreshold heat response to SMT may be more susceptible to negative expectation. Additionally, our measure of expectation was specific to longitudinal changes in LBP and not suprathreshold heat response. Expectation-related changes in suprathreshold heat response may have been observed had we manipulated and measured expectation specific to the experimental pain protocol. Our findings of a lack of expectation-dependent change in clinical outcomes contrast with prior findings of expectation as influential in outcomes related to musculoskeletal pain conditions[51,62] and complementary and alternative medicine interventions.[54,59] Similar to the lack of treatment group–dependent changes in clinical outcomes, 2 weeks may have provided insufficient time to observe expectation–dependent changes in clinical outcomes in our sample.

A final finding of the study was the identification of a novel placebo comparison for SMT associated with similar believability and expectations for treatment effect as the studied SMT, but differing effects on pain sensitivity. A placebo control for SMT is inherently difficult as a consensus is lacking regarding the "active" agent of SMT and the appropriateness of prior SMT comparative placebo interventions questioned.[36,45,58] A valid placebo control should be indistinguishable from the studied intervention in a blinded design and create similar expectations for treatment effectiveness as the studied intervention.[47,87] Prior manual therapy comparative placebos[25,72] are associated with lower expectations or believability than comparative SMT.[36,60] Our enhanced placebo SMT was effective in blinding participants and creating similar expectations as the studied SMT with different effects on pain sensitivity. Therefore, the placebo SMT used in this study may merit future investigation in clinical trials for those interested in distinguishing the nonspecific effects of SMT.

Limitations

The current study has several limitations. First, we did not maintain blinding of the researcher providing the intervention and obtaining outcomes. Although researcher–participant interactions were scripted for consistency, we cannot be certain the lack of blinding did not bias our findings. Second, participants in the study were responding to a study advertisement and may differ from individuals with LBP seeking medical care. In fact, baseline measures of clinical pain intensity and disability were significantly lower in our sample than in those reported in studies of SMT in participants seeking care.[13,15,31] Our inclusion criteria required participants to rate their pain as ≥4/10, indicating moderate, more restrictive pain requiring treatment.[46,53,73] Consequently, we believe our cohort is representative of individuals with chronic LBP who may seek SMT, but we did not recruit them from a health care environment. A third limitation was the lack of a fully balanced design. Specifically, we did not include a group receiving the SMT with an enhanced instructional set (ie, "The manual therapy technique you will receive has been shown to significantly reduce low back pain in some people"). SMT is typically provided clinically by enthusiastic practitioners with instructional sets likely more similar to that provided to our participants receiving the enhanced placebo. We considered including an intervention group with SMT provided with the enhanced placebo instructional set; however, we elected against this because of the concern that the group would essentially receive 2 interventions (SMT + enhanced expectations). Future studies should consider whether an additive effect occurs when SMT is provided with an instructional set known to enhance placebo analgesia.[86]

In conclusion, we observed SMT-specific attenuation of suprathreshold heat response, suggesting an effect beyond only the expectation of receiving an SMT.

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