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Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis

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ABSTRACT

Spinal manipulation (SMT) is commonly used for treating individuals experiencing musculoskeletal pain. The mechanisms of SMT remain unclear; however, pain sensitivity testing may provide insight into these mechanisms. The purpose of this systematic review is to examine the literature on the hypoalgesic effects of SMT on pain sensitivity measures and to quantify these effects using meta-analysis. We performed a systematic search of articles using CINAHL, MEDLINE, PsycINFO, and SPORTDiscus from each databases' inception until May 2011. We examined methodological quality of each study and generated pooled effect size estimates using meta-analysis software. Of 997 articles identified, 20 met inclusion criteria for this review. Pain sensitivity testing used in these studies included chemical, electrical, mechanical, and thermal stimuli applied to various anatomical locations. Meta-analysis was appropriate for studies examining the immediate effect of SMT on mechanical pressure pain threshold (PPT). SMT demonstrated a favorable effect over other interventions on increasing PPT. Subgroup analysis showed a significant effect of SMT on increasing PPT at the remote sites of stimulus application supporting a potential central nervous system mechanism. Future studies of SMT related hypoalgesia should include multiple experimental stimuli and test at multiple anatomical sites.

1. Introduction

In the United States, spinal manipulation (SMT) is a commonly used intervention for the treatment of individuals experiencing pain (Nahin et al., 2009). SMT is effective for some individuals experiencing musculoskeletal pain (Childs et al., 2004). However, despite the clinical effectiveness, the mechanisms by which SMT reduces pain and disability remain largely unknown. Mechanistic research on SMT suggests that biomechanical and neurophysiological changes occur with the application of SMT (Bialosky et al., 2009a; Evans, 2002; Pickar, 2002; Vernon, 2000; Wright, 1995). Studies using pain sensitivity testing for measuring responses to SMT are appropriate in considering potential mechanisms of SMT.

Reductions in pain sensitivity, or hypoalgesia, following SMT may be indicative of a mechanism related to the modulation of afferent input or central nervous system processing of pain. Characterizing this mechanism may provide some insight into how SMT produces clinical benefit (Staahl et al., 2009a,b). For example, Bialosky et al. (2009b) reported an immediate hypoalgesic response to a specific noxious thermal stimulus (temporal summation of pain) and not other noxious thermal stimuli following lumbar SMT in patients with low back pain. In this study, the reduction in pain sensitivity was observed in the lower extremity and not the upper extremity. The authors theorized the observed effect related to modulation of pain primarily at the level of the spinal cord since (1) these changes were seen within lumbar innervated areas and not cervical innervated areas and (2) the findings were specific to a measure of pain sensitivity (temporal summation of pain), and not other measures of pain sensitivity, suggesting an effect related to attenuation of dorsal horn excitability and not a generalized change in pain sensitivity.

The example illustrated above highlights principal information related to the methodology of pain sensitivity testing, especially in terms of elucidating potential mechanisms of SMT. The characteristics of pain sensitivity measures include the sensory modality

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used, the psychophysical response, and the location of stimulus application (Arendt-Nielsen and Yarnitsky, 2009; Staahl and Drewes, 2004). Pain sensitivity is measured through the application of different sensory modalities, such as thermal, mechanical, electrical, ischemic and chemical stimuli, to different tissues of the body such as skin, muscle, and viscera (Arendt-Nielsen and Yarnitsky, 2009; Staahl and Drewes, 2004). The psychophysical response to a quantifiable amount of stimulus is assessed by methods such as the minimal amount of stimulus to generate pain (threshold), or the change in pain sensitivity to repeated stimulation (temporal summation) or multiple locations of stimulation (spatial summation) (Arendt-Nielsen and Yarnitsky, 2009; Staahl and Drewes, 2004). The location of stimulus can be measured at regions local or remote to the injured area or area where the intervention will be applied. In mechanistic studies of SMT, pain sensitivity may be assessed before and immediately following an intervention to assess the immediate effects (Bialosky et al., 2009b; Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007; George et al., 2006), or throughout a course of treatment to assess the relationship to clinical outcomes (Valencia et al., 2011; Werner et al., 2010).

Vernon (2000) previously conducted a qualitative review of studies investigating SMT-induced hypoalgesia and noted few articles investigating the hypoalgesic effects of SMT. The review proposed several objectives for future investigations including, but not limited to: (1) identifying where in the CNS pain modulation is occurring, (2) identifying the neurochemical mechanisms involved in pain modulation, (3) investigating the cumulative effects of SMT, and (4) elucidating if certain elements of the SMT procedure such as location and cavitation are directly related to hypoalgesia (Vernon, 2000). In that review, a systematic appraisal of study quality was not conducted, nor was a pooled effect size estimate generated for a specific pain sensitivity measure such as pressure pain threshold. The latter may not have been possible at the time due to few studies utilizing similar pain sensitivity measures. These two factors are important because the quality of the studies helps in the interpretation of the findings and a pooled estimate from multiple studies could provide a more valid indicator of the effect size for SMT on pain sensitivity.

The purpose of this systematic review and meta-analysis was to synthesize the growing literature on the relationship between SMT and pain sensitivity and examine the hypoalgesic effect of SMT. Specifically, we were interested in the changes in pain sensitivity following SMT. Further, we hoped to assess whether the observed effect of SMT differed based on sample population or location of assessment. Studies of pain sensitivity in response to SMT have included both healthy (Bishop et al., 2011; Fernandez-de-las-Penas et al., 2007; George et al., 2006) and clinical samples (Bialosky et al., 2009b; Fernandez-Carnero et al., 2008; Vernon et al., 1990). Differences in pain sensitivity responses to SMT may exist considering chronic pain states are associated with altered pain sensitivity (Blumenstiel et al., 2011; Chua et al., 2011; Staud, 2010; Wallin et al., 2011). For example, chronic low back pain is associated with generalized enhanced pressure pain sensitivity as compared to individuals without low back pain (Giesecke et al., 2004; O'Neill et al., 2007). Therefore, we were interested in whether any observed changes differed by population (clinical vs. healthy). Finally, we were interested in whether SMT related changes in pain sensitivity differed by the location of the stimulus assessment (local to SMT application vs. remote to SMT application). Changes in pain sensitivity at the site of application of SMT, but not at remote regions, would indicate the effects of SMT are specific to the location of application. On the other hand, remote changes may be indicative of a more general effect, one mediated through modulation of nociceptive afferent processing within the central nervous system.

2. Methods

This review was conducted in accordance with guidelines from Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) and the Cochrane Back Review Group (Furlan et al., 2009; Liberati et al., 2009).

2.1. Eligibility criteria

2.1.1. Study type

We included published randomized-controlled trials (RCT) that investigated the effects of SMT on pain sensitivity. Designs could include parallel (two or more groups) or crossover (one group) trials. We excluded case reports, case series, and single-case study designs.

2.1.2. Participants

The sample populations of interest were asymptomatic (e.g. healthy) and symptomatic (e.g. reporting a current musculoskeletal pain complaint) human participants of any age or sex. We did not limit the sample to participants with a specific clinical condition, as SMT is applied to those with various musculoskeletal conditions including extremity disorders (Iverson et al., 2008; Mintken et al., 2010). We excluded studies investigating the effect of SMT on non-musculoskeletal conditions (e.g. asthma).

2.1.3. Intervention

The intervention of interest was SMT and we operationally defined this as a high-velocity, low-amplitude thrust technique targeted to a spinal region that may or may not result in an audible cavitation of a joint(s). Other synonymous terms for SMT used in studies include grade V mobilization, thrust mobilization/manipulation, or spinal adjustment. The SMT technique could be applied by the practitioner's hand or with an instrument. The technique(s) could be provided multiple times to the same spinal region or to various spinal regions during a single session or over multiple sessions. Co-interventions could also be included within the treatment session if these same co-interventions were implemented in the comparison group. This allows for differences in treatment effect to be attributed to the addition of SMT in the experimental group. Conversely, we excluded studies in which SMT was provided with multiple co-interventions where the exclusive effect of SMT could not be established. For example, we excluded studies using multi-modal treatments (exercise + SMT + medication) compared to other forms of management.

2.1.4. Comparison

The comparison group could include any form of active or non-active intervention. Active interventions included exercise, patient education, and other forms of manual therapy. Non-active interventions included sham techniques (manual contact or detuned modalities) and quiet rest.

2.1.5. Outcome measure

The primary outcome of interest was a pain sensitivity measure assessing a participant's response to the application of a quantifiable amount of experimental stimulus. The characteristics of the pain sensitivity measure include the experimental sensory modality used, the psychophysical response, and the location of stimulus application. The experimental sensory modality could include chemical, electrical, ischemic, mechanical (e.g. pressure, vibration), and thermal (e.g. cold, heat) stimuli. Further, these measures could be either static (e.g. threshold or tolerance) or dynamic (e.g. temporal summation) measures of pain processing. Finally, the location of the experimental stimulus application was considered, specifically in relation to the region where SMT was applied. We did not limit inclusion to a specific experimental pain modality as there is no universal stimuli protocol or accepted technique.

2.2. Data Sources

Studies were identified by performing a comprehensive systematic literature search for relevant articles in Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE (PubMed), PsycINFO, and SPORTDiscus from each database's inception until May 2011. Only manuscripts published in English were included. No limit was placed on the time of publication. Search terms used in the databases included "musculoskeletal manipulations", "orthopedic manipulation", "osteopathic manipulation", "chiropractic manipulation, "manual therapy", "pain", "pain measurement", "pain threshold", "thermal pain", "pressure pain", "mechanical pain", "experimental pain", and "exercise-induced pain". MESH terms (PubMed) and Major Headings (CINAHL) were used when available. Database searches were conducted on May 2, 2011. The search strategy used for the MEDLINE database is listed in Table 1. Additionally, to identify missed studies, we performed a manual search through the reference lists of all potentially relevant articles and previously published systematic reviews.

2.3. Study search and selection

The primary author (R.A.C.) screened all articles for eligibility from the search of the databases and reference lists. The initial screening step involved reviewing the article title for potential inclusion into this study. If the title did not provide adequate information for inclusion, abstracts were screened. Articles appearing to meet inclusion criteria based on the screening of title and abstract were considered potentially relevant. Articles deemed not relevant were excluded. After potentially relevant articles were identified, two authors (R.A.C. and C.W.G.) independently reviewed the full-texts of these articles for inclusion into the review. Any disagreements regarding article inclusion were resolved by consensus. If consensus could not be reached, a third author (J.E.B.) was recruited to resolve disagreement.

2.4. Data extraction

Two authors (R.A.C. and C.W.G.) blindly and independently extracted data from each of the included articles with the use of a standardized data extraction form. Results of each author's extraction were compared to ensure accuracy of the extracted data. Each article was reviewed for the following information: (1) type of clinical trial; (2) participant characteristics including age, sex, and clinical condition; (3) type of intervention within groups including co-intervention and duration of therapy; (4) pain sensitivity outcome and region in which stimulus was applied; (5) results of the study (pre- and post-mean values and standard deviation for each measure and each group). The primary author of the respective article was contacted if any of the above information was unobtainable. If the primary author of a study did not provide a response within 7 days of being contacted, the information was not included in the review. Three authors were contacted for information regarding study results and two of three authors provided responses (Bishop et al., 2011; Mansilla-Ferragut et al., 2009).

Table 1
MEDLINE search strategy.

1	Musculoskeletal manipulations [mesh; major topic]	6469
2	"Manual therapy"	1485
3	1 OR 2	7495
4	Pain [mesh; major topic]	168,081
5	Pain measurement [mesh; major topic]	7037
6	Pain threshold [mesh; major topic]	2769
7	"Thermal pain"	523
8	"Pressure pain"	869
9	"Mechanical pain"	338
10	"Experimental pain"	956
11	Exercise-induced pain	1507
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	172,382
13	Humans [mesh]	115,84,116
14	3 and 12 and 13	1512
15	Limits: english	1372
16	Limits: clinical trial, randomized controlled trial, clinical trial, Phase I, clinical trial, Phase II, clinical trial, Phase III, clinical trial, Phase IV, controlled clinical trial	465

2.5. Methodological Quality Assessment

The quality of each article was assessed using criteria reported in prior systematic reviews and recommended by the Cochrane Back Review Group (Furlan et al., 2009; Gross et al., 2002; Miller et al., 2010; Rubinstein et al., 2011). The 12-item criteria allows for assessment of the internal validity of each article (e.g. selection bias, performance bias, attrition bias, detection bias). Articles meeting 6 or more of the 12 items are considered as having low risk of bias (higher quality) (Furlan et al., 2009). Prior to assessing the quality of the included articles, two authors (R.A.C. and C.W.G.) independently scored two trial articles (not included in this analysis) to ensure understanding of the quality criteria. Once understanding was confirmed, the two authors independently rated the quality of each included article. After completion of independent grading, the authors met to finalize the scores for each article. Disagreements regarding article quality were resolved by consensus. If consensus could not be reached, a third author (J.E.B.) was recruited to resolve discrepancy.

2.6. Data analysis

Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and PASW Statistics, Version 18 (SPSS, Inc., Chicago, IL) were used to examine reviewer agreement and individual study descriptive statistics (e.g. mean, standard deviation). For meta-analytical procedures, Comprehensive Meta-Analysis, Version 2 (Biostat, Inc., Englewood, NJ) was utilized. Alpha was set at the 0.05 level for statistical significance.

Agreement for the final inclusion of articles (based on examination of full-text) was assessed by kappa statistic and 95% confidence interval for kappa. Agreement for article methodological quality was examined using the intraclass correlation coefficient (ICC) and 95% confidence interval. Both kappa and ICC values range from 0 to 1 with 0 representing no agreement and 1 perfect agreement. We deemed kappa values greater than 0.80 and ICC values greater than 0.75 as excellent (Landis and Koch, 1977; Portney and Watkins, 2009).

Individual effect size estimates (Hedges g) were generated for each group within each study using information provided in the articles. Each study's pain sensitivity outcome measure was considered for inclusion into the meta-analysis, however only the immediate effect of SMT on pressure pain threshold (PTT) had an adequate number of studies (e.g. >2) using similar methodology for further analysis. A random effects model was generated with the primary comparison being the difference in effect on PPT between the group receiving SMT and the comparison group. Hedges g effect size estimates and 95% confidence intervals (CI) were computed as the measure of effect. Effect size estimates were considered small (0.20), medium (0.50), or large (0.80) (Cohen, 1988).

Homogeneity of the estimated effects was tested using a measure of inconsistency (I^2) where large values of I^2 suggest heterogeneity. Several methods were used to address publication bias (Rothstein et al., 2005). Publication bias was first examined by observation of a funnel plot. The presence of bias would be indicated in the funnel plot by asymmetry in the effects of individual studies around the overall mean. Egger's regression method was used to quantify the bias observed. Alpha values <0.05 indicate significant publication bias. Rosenthal's failsafe *N*, the number of missing studies needing to be added to the analysis before the combined effect is non-significant, was computed to indicate whether the observed estimated effect was an artifact of bias. An adjusted overall effect size and 95% CI was computed using Duvall and Tweedie's trim and fill method.

Additionally, two subgroup analyses were performed. We stratified the results by population and location of outcome assessment. The population was categorized as 'healthy' (asymptomatic participants) or 'clinical' (symptomatic participants) based on the study description. We defined location of outcome assessment as 'local' if the pain sensitivity measure was obtained in the same anatomical region to where SMT was applied or 'remote' if the pain sensitivity measure was obtained in different anatomical regions from where SMT was applied. In some studies, multiple PPT outcomes were reported. In these cases, PPT measures were combined according to location so as to generate a single composite effect for either local or remote PPT using the methods for combining multiple outcomes described by Borenstein (2009).

3. Results

3.1. Study selection

Fig. 1 depicts a flow diagram of the study selection process with reasons for exclusion at each stage. A total of 1125 articles were identified from the systematic search of CINAHL, MEDLINE, PsycINFO, and SPORTDiscus and three articles from a review of reference lists. Once duplicates were removed, 997 articles remained to be assessed for inclusion. Of these, 958 articles were excluded after screening of either the title or abstract. The full-texts of 39 articles were selected to be screened by two independent reviewers. Nineteen articles were excluded based on (1) study design (Bialosky et al., 2010; Suter and McMorland, 2002), (2) inability to compare the effects of SMT (Bialosky et al., 2008), (3) inclusion of non-spinal manipulation or non-thrust manipulation (Brantingham et al., 2005; Fernandez-de-Las Penas et al., 2011; Gamber et al., 2002; Govender et al., 2007; La Touche et al., 2009; Tucker et al., 2003; Vernon et al., 2005; Vicenzino et al., 1996, 1998, 2001; von Piekartz and Ludtke, 2011), and (5) lack of experimental pain outcome (Glover et al., 1974; Godfrey et al., 1984; Hoehler et al., 1981; Keller and Colloca, 2000; Sloop et al., 1982). As a result, 20 articles representing 20 studies were identified as meeting the criteria for inclusion into this review. The agreement for the included studies was excellent (Kappa = 0.92 [95% CI = 0.83; 1.00]).

3.2. Characteristics of studies

Table 2 provides a full description of the key characteristics of each study including the characteristics of the sample population, SMT, and pain sensitivity outcome studied.

3.2.1. Sample population

A total of 974 participants (58% female) were enrolled in the included studies. Eleven studies (n = 695, 59% female) included asymptomatic participants and nine studies (n = 279, 54% female) included symptomatic participants. The clinical conditions examined within the nine studies with symptomatic participants were lateral epicondylalgia (one study) (Fernandez-Carnero et al., 2008), low back pain (two studies) (Bialosky et al., 2009b; Cote et al., 1994), neck pain (five studies) (Maduro de Camargo et al., 2011; Mansilla-Ferragut et al., 2009; Parkin-Smith and Penter,

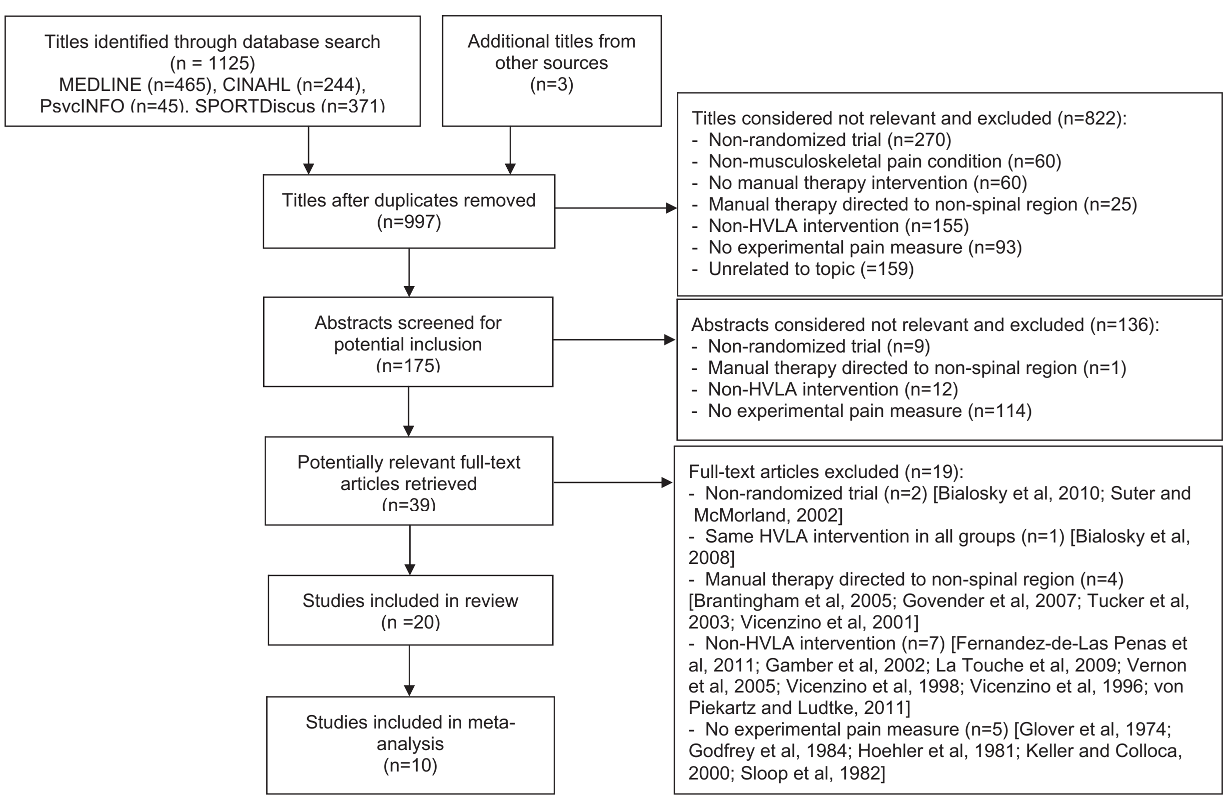

Fig. 1. Flow chart of study identification, selection, and inclusion.

Table 2
Characteristics of Included Studies.

Article	Design	Participants	Interventions	Pain sensitivity measure	Summary of Results	Values*
Bialosky et al. (2009b)	Randomized-controlled trial	36 Individuals with low back pain Number of females: 26 Mean age (SD): 32.39 (12.63)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the anterior superior iliac spine in an anterior to posterior and inferior direction with the participant in supine. Group B (comparison): passive, participant-generated low back extension press-up exercise with the participant in prone. Group C Comparison: Seated stationary bike activity. Co-interventions: None Duration of therapy: 1 session	Thermal: *Heat suprathreshold (A-delta) pain* Temperature: 35–47, 49 °C Stimulus applied to forearm and posterior calf. *Heat temporal summation* Temperature: 35–51 °C Stimulus applied to palm of hand and plantar surface of foot	Changes over time were noted for TS measured in the upper extremity, indicating an overall decrease in pain sensitivity over time with no group effect. Those who received SMT showed a decrease in TS measured in the lower extremity with no changes in the other groups	*TS (foot)* A: Pre: 28.5 (24.8) Post: 19.9 (21.6) B: Pre: 42.9 (31.7) Post: 40.3 (30.9) C: Pre: 29.6 (20.1) Post: 33.3 (25.6) ES: A: -0.34 B: -0.08 C: 0.14
Bishop et al. (2011)	Randomized-controlled trial	90 Healthy, asymptomatic individuals Number of females: 66 Mean age (SD): 22.9 (2.7)	Group A (SMT): high-velocity, low-amplitude thrust manipulation through the patient's elbows to the upper thoracic spine in an anterior to posterior direction with the participant in supine. Group B (comparison): active cervical chin tuck exercise with the patient in supine. Group C (Comparison): Quiet rest with the participant in supine. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to web space of 1st and 2nd fingers and 1st and 2nd toes. Thermal: *Heat suprathreshold (A-delta) pain* Temperature: 35–45, 47, 49, 51 °C Stimulus applied to forearm and posterior calf. *Heat temporal summation* Temperature: 35–50 °C Stimulus applied to palm of hand and plantar surface of foot	Significant increases in PPT were found for all groups in both the upper and lower extremities. HPST at 47 °C and 49 °C were lower for all groups over time in both the upper and lower extremity. SMT experienced greater reductions in TS than cervical exercise or control. Differences in cervical exercise and the control group were not significant	*PPT (hand):* A: Pre: 2.2 (1.2) Post: 2.5 (1.3) B: Pre: 2.2 (1.3) Post: 2.2 (1.2) C: Pre: 1.9 (1.3) Post: 2.0 (1.3) ES: A: 0.23 B: -0.04 C: 0.04 *PPT (foot):* A: Pre: 3.3 (1.6) Post: 3.6 (1.8) B: Pre: 3.0 (1.2) Post: 3.4 (1.5) C: Pre: 2.6 (1.4) Post: 2.9 (1.6) ES: A: 0.16 B: 0.23 C: 0.17 *HPST 47 °C (forearm):* A: Pre: 3.5 (2.3) Post: 2.7 (2.1) B: Pre: 3.9 (1.9) Post: 2.8 (1.7) C: Pre: 3.4 (2.4) Post: 2.8 (2.0) ES: A: -0.35 B: -0.59 C: -0.26 *HPST 47 °C (calf):* A: Pre: 3.2 (2.4) Post: 2.1 (2.0) B: Pre: 3.4 (1.9) Post: 2.5 (1.5) C: Pre: 3.3 (2.4) Post: 2.8 (2.2) ES: A: -0.44 B: -0.46 C: -0.19 *HPST 49 °C (forearm):* A: Pre: 5.0 (2.4) Post: 4.5 (2.7) B: Pre: 5.2 (1.8) Post: 4.2 (2.0) C: Pre: 4.8 (2.4) Post: 4.1 (2.8) ES: A: -0.20 B: -0.50 C: -0.25 *HPST 49 °C (calf):* A: Pre: 4.5 (2.8) Post: 3.8 (2.7) B: Pre: 4.8 (2.2) Post: 4.5 (2.2) C: Pre: 4.6 (2.4) Post: 4.2 (3.2) ES: A: -0.24 B: -0.13 C: -0.11 *TS (hand):* A: Pre: -1.9 (15.9) Post: -9.4 (15.2) B: Pre: -6.1 (20.2) Post: -2.1 (19.2) C: Pre: -0.1 (16.3) Post: 1.3 (13.0) ES: A: -0.47 B: 0.20 C: 0.08 *TS (foot):* A: Pre:1.1 (19.3) Post: -4.3 (10.5) B: Pre: 1.0 (15.9) Post: 5.6 (14.0) C: Pre: 0.3 (16.3) Post: 1.8 (13.9) ES: A: -0.26 B: 0.29 C: 0.09

Cote et al. (1994)	Randomized-controlled trial	30 Individuals with low back pain Number of females: 14 Mean age (SD): 31 (7.15)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the lumbosacral region in a rotational direction with the participant in sidelying. Group B (comparison): passive, clinician-assisted knee-to-chest exercise with the participant in supine. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 100 g/s Stimulus applied to gluteal, low back, and sacroiliac region	Significant changes in PPT were not found at any of the three sites following either intervention immediately or at 15 and 30 min	*PPT (gluteal)* A: Pre: 5.0 (3.4) Post: 5.3 (2.1) B: Pre: 5.0 (2.0) Post: 5.0 (2.3) ES: A: 0.09 B: -0.01 *PPT (low back)* A: Pre: 5.4 (1.8) Post: 5.4 (2.3) B: Pre: 5.9 (2.4) Post: 5.3 (2.4) ES: A: 0.00 B: -0.26 *PPT (sacroiliac)* A: Pre: 5.1 (2.1) Post: 5.8 (2.6) B: Pre: 6.1 (2.6) Post: 5.8 (2.7) ES: A: 0.26 B: -0.10
Fernandez-Carnero et al. (2008)	Randomized cross-over trial	10 Individuals with lateral epicondylalgia Number of females: 5 Mean age (SD): 42 (6)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the cervical C5-C6 region in a rotational direction with the participant in supine. Group B (comparison): manual contact by clinician in a pre-manipulative position (similar to Group A) without thrust. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 30 kPa/s Stimulus applied to lateral epicondyle. Thermal: *Cold pain threshold* Temperature: 32–4.5 °C Stimulus applied to lateral epicondyle. *Heat pain threshold* Temperature: 32–50 °C Stimulus applied to lateral epicondyle	Greater increase in PPT over the lateral epicondyle bilaterally for the SMT group	*PPT (lateral epicondyle):* A:Pre: 2.9 (0.5) Post: 4.1 (0.1) B:Pre: 3.2 (0.1) Post: 3.4 (0.2) ES: A: 1.74 B: 0.63 *CPT:* A: Pre: 17.5 (7.5) Post: 17.8 (5.1) B: Pre: 18.2 (7.4) Post: 19.7 (6.8) ES: A: 0.04 B: 0.19 *HPT:* A: Pre: 41.3 (3.4) Post: 42.5 (4.0) B: Pre: 41.1 (3.4) Post: 41.8 (1.3) ES: A: 0.29 B: 0.16
Fernandez-de-las-Penas et al. (2008)	Randomized-controlled trial	30 Healthy, asymptomatic individuals Number of females: 17 Mean age (SD): 26 (5)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the cervical C7-T1 region in a translational direction from right to left with the participant in prone. Group B (SMT): High-velocity, low-amplitude thrust manipulation to the cervical C7-T1 region in a translational direction from left to right with the participant in prone. Group C (comparison): manual contact by clinician in a pre-manipulative position (similar to Group A) without thrust. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 30 kPa/s Stimulus applied to cervical region	Both SMT groups showed equal increases in PPT in the cervical region that was not found in the control group. Males showed greater increases in PPT compared to females	*PPT (right cervical):* A: Pre: 3.4 (0.8) Post: 4.0 (0.7) B: Pre: 3.1 (0.1) Post: 4.0 (0.4) C: Pre: 3.2 (0.5) Post: 3.2 (0.5) ES: A: 0.67 B: 1.34 C: -0.05 *PPT (left cervical):* A: Pre: 3.4 (0.7) Post: 3.9 (0.5) B: Pre: 3.2 (0.2) Post: 3.7 (0.3) C: Pre: 3.2 (0.3) Post: 3.2 (0.3) ES: A: 0.64 B: 1.71 C: -0.13
Fernandez-de-las-Penas et al. (2007)	Randomized crossover trial	15 Healthy, asymptomatic individuals Number of females: 8 Mean age (SD): 21 (2)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the cervical C5-C6 region in a rotational direction with the participant in supine. Group B (comparison): manual contact by clinician in a pre-manipulative position (similar to Group A) without thrust. Group C (comparison): participant-generated motion in a pre-manipulative position (similar to Group A) without thrust or manual contact. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold*Rate: Not reported Stimulus applied to lateral epicondyle	SMT demonstrated an increase in PPT over the lateral elbow region bilaterally, where as the sham and control groups did not	*PPT (ipsilateral lateral epicondyle):* A: Pre: 2.1 (0.5) Post: 2.9 (0.6) B: Pre: 2.3 (0.4) Post: 2.3 (0.5) C: Pre: 2.2 (0.5) Post 2.2 (0.4) ES: A: 1.33 B: 0.00 C: 0.19 *PPT (contralateral lateral epicondyle):* A: Pre: 2.2 (0.5) Post: 2.8 (0.6) B: Pre: 2.3 (0.5) Post: 2.3 (0.6) C: Pre: 2.3 (0.5) Post: 2.3 (0.5) ES: A: 1.00 B: 0.00 C: 0.00
Fryer et al. (2004)	Randomized-controlled trial	96 Healthy, asymptomatic individuals Number of females: 57 Mean age (SD): NR	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the middle or upper thoracic region in a posterior to anterior direction with the participant in sitting. Group B (comparison): non-thrust mobilization to the middle or upper thoracic region in a posterior to anterior direction with the participant in sitting.	Mechanical: *Pressure pain threshold* Rate: 30 kPa/s Stimulus applied to thoracic region	PPT increased in both intervention groups but not the control group over time	*PPT (thoracic)* A: Pre: 2.1 (0.9) Post: 2.2(0.9) B: Pre: 2.2 (0.9) Post: 2.5 (1.0) C: Pre: 2.5 (1.0) Post: 2.5 (0.9) ES: A: 0.13 B: 0.28 C: 0.01

(*continued on next page*)

Table 2 (*continued*)

Article	Design	Participants	Interventions	Pain sensitivity measure	Summary of Results	Values*
			Group C (comparison): sham laser acupuncture to the thoracic region with the participant in prone. Co-interventions: None Duration of therapy: 1 session			
George et al. (2006)	Randomized-controlled trial	60 Healthy, asymptomatic individuals Number of females: 40 Mean age (SD): 24 (NR)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the anterior superior iliac spine in an anterior to posterior and inferior direction with the participant in supine. Group B (comparison): passive, participant-generated low back extension press-up exercise with the participant in prone. Group C (comparison): seated stationary bike activity. Co-interventions: None Duration of therapy: 1 session	Thermal: *Heat suprathreshold (A-delta) pain* Temperature: 35–45, 47, 49, 51 °C Stimulus applied to forearm and posterior calf. *Heat temporal summation* Temperature: 35–47 °C Stimulus applied to palm of hand and plantar surface of foot	Changes in HPST at 47 °C or 49 °C over time were observed in the lower extremity for all groups but not the upper extremity. No change over time was observed for TS measured at the hand. SMT had a greater reduction in TS at the foot than stationary cycling but not significantly greater than lumbar extension exercises	*HPST 47 °C (calf):* A: Change: 13.2 (17.2) B: Change: 12.9 (7.9) C: Change: 23.5 (17.3)
Hamilton et al. (2007)	Randomized-controlled trial	90 Healthy, asymptomatic individuals Number of females: 61 Mean age (SD): 23 (5)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the cervical C0–C1 region in a rotation direction with the participant in supine. Group B (comparison): muscle energy technique to the suboccipital and trapezius muscles with the patient in supine. Group C (comparison): manual contact by clinician in a neutral position without thrust. Co-interventions: none Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 30 kPa/s Stimulus applied to cervical region	PPT in the cervical region increased in the MET and SMT groups at 5 min but not the control group. At 30 min only the MET group showed an increase in PPT	*PPT (cervical)*: A: Pre: 3.7 (1.4) Post: 4.1 (1.4) B: Pre: 3.5 (1.7) Post: 3.9 (1.6) C: Pre: 3.6 (1.6) Post: 3.8 (2.1) ES: A: 0.29 B: 0.25 C: 0.08
Maduro de Camargo et al. (2011)	Randomized-controlled trial	37 Individuals with neck pain Number of females: 15 Mean age (SD): 29.9 (NR)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the cervical C5–C6 region in a rotational direction with the participant in sitting. Group B (Comparison): quiet rest with the participant in sitting. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to cervical region, upper trapezius, and deltoid muscle	There was an increase in PPT over the deltoid muscle bilaterally and C5 spinous process for the SMT group compared to the control group	*PPT (cervical)* A: Pre: 2.3 (1.2) Post: 2.4 (1.2) B: Pre: 2.3 (1.1) Post: 2.2 (0.9) ES: A: 0.08 B: -0.09 *PPT (ipsilateral upper trapezius)* A: Pre: 3.4 (1.8) Post: 3.6 (1.9) B: Pre: 3.4 (1.3) Post: 3.7 (1.4) ES: A: 0.10 B: 0.21 *PPT (contralateral upper trapezius)*: A: Pre: 3.3 (1.9) Post: 3.7 (2.0) B: Pre: 3.6 (1.5) Post: 3.7 (1.5) ES: A: 0.19 B: 0.06 *PPT (ipsilateral deltoid)* A: Pre: 3.2 (2.1) Post: 3.5 (2.5) B: Pre: 3.2 (1.6) Post: 3.0 (1.5) ES: A: 0.12 B: -0.12 *PPT (contralateral deltoid)*: A: Pre: 3.2 (2.1) Post: 3.4 (2.2) B: Pre: 3.1 (1.5) Post: 2.9 (1.3) ES: A: 0.09 B: -0.13
Mansilla-Ferragut et al. (2009)	Randomized-controlled trial	37 Individuals with neck pain Number of females: 37 Mean age (SD): 35 (8)	Group A (SMT): high-velocity, low-amplitude thrust manipulation to the atlanto-occipital region in a distraction direction with the participant in supine. Group B (Comparison): Manual contact by	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to sphenoid bone	There was a significant group x time interaction where the SMT group showed an increase in PPT compared to the control group	*PPT (Sphenoid)* A: Pre: 0.8 (0.3) Post: 0.9 (0.4) B: Pre: 0.8 (0.3) Post: 0.7 (0.4) ES: A: 0.25 B: -0.25

			clinician in a pre-manipulative position (similar to Group A) without thrust. Co-interventions: None Duration of therapy: 1 session			
Mohammadian et al. (2004)	Randomized crossover trial	20 Healthy, asymptomatic individuals Number of females: 6 Mean age (SD): 27 (NR)	Group A SMT: High-velocity, low-amplitude thrust manipulation to the thoracic region at vertebral levels determined by clinician based on examination and with the patient in various positions. Group B (Comparison): Manual contact by clinician in a pre-manipulative position (similar to Group A) without thrust. Co-interventions: None Duration of therapy: 1 session	Chemical: *Capsaicin allodynia and hyperalgesia* Concentration: 1% capsaicin cream applied to forearm	The area of allodynia and hyperalgesia induced by capsaicin was less for the SMT versus sham treatment group. The intensity of spontaneous pain induced by capsaicin was less for the SMT versus sham group	Chemical: *Area of allodynia (forearm)* ES: A vs. B 1.546 *Area hyperalgesia (forearm)* ES: A vs. B 1.381 *Intensity of pain (forearm)* ES: A vs. B 1.239
Oliveira-Campelo et al. (2010)	Randomized-controlled trial	122 Healthy, asymptomatic individuals Number of females: 91 Mean age (SD): 20 (3)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the atlanto-occipital region in a distraction direction with the participant in supine. Group B (Comparison): Muscle inhibition technique to the suboccipital muscles with the participant in supine. Group C Comparison: Quiet rest with the participant in supine. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to masseter and temporalis muscle	The SMT group demonstrated an increase in PPT in the masseter and temporalis muscles, while those receiving the sham and control treatments did not	*PPT (masseter):* A: Pre: 2.6 (0.7) Post: 2.8 (0.7) B: Pre: 2.7 (0.6) Post: 2.7 (0.8) C: Pre: 2.8 (0.7) Post 2.7 (0.7) ES: A: 0.28 B:0.00 C:-0.14 *PPT (temporalis)*: A: Pre: 2.6 (0.7) Post: 2.8 (0.7) B: Pre: 2.7 (0.7) Post: 2.9 (0.9) C: Pre: 2.8 (0.9) Post: 2.7 (0.8) ES: A: 0.28 B: 0.23 C: -0.11
Parkin-Smith and Penter (1998)	Randomized-controlled trial	30 Individuals with neck pain Number of females: 11 Mean age (SD): 35.4 (NR)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the cervical region at vertebral levels determined by clinician based on examination and with the patient in various positions. Group B (SMT): High-velocity, low-amplitude thrust manipulation to the cervical and thoracic region at vertebral levels determined by clinician based on examination and with the patient in various positions. Co-interventions: Undetermined Duration of therapy: Up to 6 sessions	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to cervical region	Statistically significant improvements were noted in PPT from the 1st to 6th assessments for both groups. No differences were noted between groups	*PPT (cervical)* A:Pre: 3.6 (1.8) Post: 4.9 (1.8) B:Pre: 3.0 (0.8) Post: 4.1 (1.0) ES:A: 0.67 B: 1.09
Ruiz-Saez et al. (2007)	Randomized-controlled trial	72 Healthy, asymptomatic individuals Number of females: 46 Mean age (SD): 31 (10)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the cervical C3-C4 region in a rotational direction with the participant in supine. Group B (Comparison): Manual contact by clinician in a pre-manipulative position (similar to Group A) without thrust. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to upper trapezius muscle	The SMT group showed an increase in PPT in the upper trapezius muscle, whereas the control group showed a decrease	*PPT (upper trapezius)* A: Pre:1.3 (0.5) Post: 1.4 (0.5) B: Pre:1.3 (0.4) Post: 1.3 (0.4) ES: A: 0.16 B: -.017
Shearar et al. (2005)	Randomized-controlled trial	60 Individuals with sacroiliac syndrome Number of females: 29 Mean age (SD): 39.1 (12.2)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the lumbosacral region with the participant in sidelying. Group B (SMT): Mechanical-force, manually-assisted manipulation to the lumbosacral region with an Activator Adjusting Instrument (Activator Methods International, Ltd, Phoenix, AZ) and with the participant in prone.	Mechanical: *Pressure pain threshold* Rate: 1 kg/cm^2/s Stimulus applied to sacroiliac region	PPT increased from the 1st to 3rd assessments for both groups	*PPT (Sacroiliac Region)* A: Pre: 4.8 (NR) Post: 6.5 (NR) B: Pre: 5.0 (NR) Post: 6.8 (NR)

(*continued on next page*)

Table 2 (*continued*)

Article	Design	Participants	Interventions	Pain sensitivity measure	Summary of Results	Values*
			Co-interventions: None Duration of therapy: Up to 4 sessions			
Terrett and Vernon (1984)	Randomized-controlled trial	50 Healthy, asymptomatic individuals Number of females: 0 Mean age (SD): 28.6 (NR)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the thoracic region in a posterior to anterior direction at vertebral levels determined by clinician based on examination and with the participant in prone. Group B (Comparison): Non-thrust mobilization to the thoracic region in a posterior to anterior direction with the participant in prone. Co-interventions: None Duration of therapy: 1 session	Electrical: *Electrical pain tolerance* Current: 0.2–5.0 mA Stimulus applied to thoracic region	Electrical pain tolerance over the most tender thoracic area increased for those receiving SMT versus those who did not	*Electrical pain tolerance*: A: Pre: 1.4 (0.8) Post: 2.1 (1.1) B: Pre: 1.6 (1.1) Post: 1.5 (0.9) ES: A: 0.62 B: -0.14
Thomson et al. (2009)	Randomized-controlled trial	50 Healthy, asymptomatic individuals Number of females: 21 Mean age (SD): 27 (6)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the lumbar L3-L4 region in a rotational direction with the participant in sidelying. Group B (Comparison): Non-thrust mobilization to the lumbopelvic region in a rotational direction with the participant in prone. Group C Comparison: Sham laser treatment to the lumbar region with the participant in prone. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 1 kg/s Stimulus applied to low back region	Mechanical PPT did not significantly change at the most tender lumbar spinous process over time for any intervention	*PPT Pre-Post Change:* A: -0.17 (0.48) B: 0.43 (0.55) C: -0.11 (0.42)
van Schalkwyk and Parkin-Smith (2000)	Randomized-controlled trial	30 Individuals with neck pain Number of females: 10 Mean age (SD): 30.4 (11.7)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the cervical region in a translational direction with the participant in supine. Group B (Comparison): High-velocity, low-amplitude thrust manipulation to the cervical region in a rotational direction with the participant in supine. Co-interventions: Undetermined Duration of therapy: 10 sessions	Mechanical: *Pressure pain threshold* Rate: not reported Stimulus applied to the cervical region	Significant changes in mechanical PPT were not found for either group comparing 1st consultation and either follow-up consultations. (Unusual findings for group B)	*PPT (cervical)*: A Pre: 2.9 (2.7) Post: 3.3 (0.8) B Pre: 2.8 (1.8) Post: 3.8 (1.8) ES: A: 0.14 B: 0.54
Vernon et al. (1990)	Randomized-controlled trial	9 Individuals with neck pain Number of females: 3 Mean age (SD): 30 (NR)	Group A (SMT): High-velocity, low-amplitude thrust manipulation to the cervical region in a rotational direction with the participant in supine. Group B (Comparison): Non-thrust mobilization to the cervical region in a rotational direction with the participant in supine. Co-interventions: None Duration of therapy: 1 session	Mechanical: *Pressure pain threshold* Rate: 1 kg/s Stimulus applied to cervical region	There was a significant group x time interaction where the SMT group showed increased PPT in the cervical region, while those receiving the sham treatment did not	*PPT (ipsilateral cervical below)*: A: Pre: 3.4 (1.3) Post: 4.9 (2.3) B: Pre: 2.8 (1.7) Post: 2.8 (1.7) ES: A: 0.51 B: 0.00 *PPT (ipsilateral cervical above)*: A: Pre: 3.4 (1.7) Post: 4.8 (2.2) B: Pre: 2.3 (1.9) Post: 2.3 (1.7) ES: A: 0.54 B: 0.00 *PPT (contralateral cervical below)*: A: Pre: 3.5 (1.0) Post: 4.9 (2.8) B: Pre: 2.4 (1.5) Post: 2.6 (1.5) ES: A: 0.34 B: 0.10 *PPT (contralateral cervical above)*: A: Pre: 3.3 (0.5) Post: 5.2 (3.2) B: Pre: 2.3 (1.4) Post: 2.4 (1.7) ES: A: 0.34 B: 0.05

Abbreviations: CPT – cold pain threshold, ES – effect size, HPST – suprathreshold heat pain, HPT – heat pain threshold, NR – not reported, PPT – pressure pain threshold, SMT – spinal manipulative therapy, TS – temporal summation.
* Values expressed in mean (SD). Not all values able to be extracted from studies. Only pre- and immediate post-measures reported in table.

1998; van Schalkwyk and Parkin-Smith, 2000; Vernon et al., 1990), and sacroiliac pain (one study) (Shearar et al., 2005). The mean age range in studies with asymptomatic participants was 21–31 years while the mean age range in studies with symptomatic participants was 30–42 years.

3.2.2. Spinal manipulation

The region targeted for SMT included the cervical spine (11 studies) (Fernandez-Carnero et al., 2008; Fernandez-de-Las-Penas et al., 2008; Fernandez-de-las-Penas et al., 2007; Hamilton et al., 2007; Maduro de Camargo et al., 2011; Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010; Parkin-Smith and Penter, 1998; Rubinstein et al., 2011; van Schalkwyk and Parkin-Smith, 2000; Vernon et al., 1990), thoracic spine (five studies) (Bishop et al., 2011; Fryer et al., 2004; Mohammadian et al., 2004; Parkin-Smith and Penter, 1998; Terrett and Vernon, 1984), and lumbosacral spine (five studies) (Bialosky et al., 2009b; Cote et al., 1994; George et al., 2006; Shearar et al., 2005; Thomson et al., 2009). One study examined both cervical and thoracic manipulation (Parkin-Smith and Penter, 1998). There was variation between studies in the manipulation technique(s) used. Of the 11 studies on cervical manipulation, six studies (Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007; Maduro de Camargo et al., 2011; Ruiz-Saez et al., 2007; van Schalkwyk and Parkin-Smith, 2000; Vernon et al., 1990) examined a middle to lower cervical rotational manipulation while two studies (Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010) examined an upper cervical distraction manipulation. Of the five studies on lumbosacral manipulation, three studies (Cote et al., 1994; Shearar et al., 2005; Thomson et al., 2009) examined a sidelying rotational manipulation while the other two (Bialosky et al., 2009b; George et al., 2006) examined a supine lumbosacral manipulation. It appeared that no two studies incorporated the same thoracic manipulation technique.

3.2.3. Pain sensitivity outcome

There were different characteristics of the pain sensitivity outcome reported in studies. In terms of sensory modality used, studies investigated responses to chemical (Mohammadian et al., 2004), electrical (Terrett and Vernon, 1984), mechanical (Bishop et al., 2011; Cote et al., 1994; Fernandez-Carnero et al., 2008; Fernandez-de-Las-Penas et al., 2008; Fernandez-de-las-Penas et al., 2007; Fryer et al., 2004; Hamilton et al., 2007; Maduro de Camargo et al., 2011; Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010; Parkin-Smith and Penter, 1998; Ruiz-Saez et al., 2007; Shearar et al., 2005; Thomson et al., 2009; van Schalkwyk and Parkin-Smith, 2000; Vernon et al., 1990), and thermal stimuli (Bialosky et al., 2009b; Bishop et al., 2011; Fernandez-Carnero et al., 2008; George et al., 2006). The psychophysical responses examined were primarily a static measure of pain processing, such as a threshold response, while three studies (Bialosky et al., 2009b; Bishop et al., 2011; George et al., 2006) examined a dynamic measure, specifically temporal summation of pain.

In the studies that included a mechanical measure, there was similarity in that all these studies examined PPT. However, there was considerable variability in the region in which the pressure stimuli was applied. For example, some of the regions included the cervical spine (Fernandez-de-Las-Penas et al., 2008; Hamilton et al., 2007; Maduro de Camargo et al., 2011; Parkin-Smith and Penter, 1998; van Schalkwyk and Parkin-Smith, 2000; Vernon et al., 1990), elbow (Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007), head region (Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010), lumbar spine (Bishop et al., 2011; Cote et al., 1994; Shearar et al., 2005; Thomson et al., 2009), trapezius muscle (Maduro de Camargo et al., 2011), and web space of the fingers/toes (Bishop et al., 2011). All studies, except 3 (Parkin-Smith and Penter, 1998; Shearar et al., 2005; van Schalkwyk and Parkin-Smith, 2000), examined an immediate effect (only 1 session) of SMT.

3.3. Methodological quality

Table 3 summarizes the results for methodological quality of each study. Quality score agreement between the two primary raters (R.A.C. and C.W.G.) was excellent with an ICC = 0.79 [95% CI = 0.56; 0.90] and involvement of a third rater was not needed for disagreements. The median score for study quality was 7 with a range from 3–8. Three criteria were not met by any study: lack of blinding of the patient (Item 3); lack of blinding of care provider (Item 4); lack of blinding of assessor (Item 5). Information regarding selective outcome reporting (Item 8) for each study was unable to be obtained. Thus, we operationally chose to mark this item for each study as ‘‘unsure’’.

3.4. Meta-analysis results

Of the 20 studies included in this review, only 10 met the criterion for meta-analysis. All 10 studies (Bishop et al., 2011; Cote et al., 1994; Fernandez-de-Las-Penas et al., 2008; Fryer et al., 2004; Hamilton et al., 2007; Maduro de Camargo et al., 2011; Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010; Ruiz-Saez et al., 2007; Vernon et al., 1990) examined an immediate effect of SMT on PPT. The summary effect estimate suggested a small, but favorable effect of SMT on increasing PPT as compared to other interventions (Hedges $g = 0.315$ [95% CI = 0.078; 0.552], $p = 0.009$) (Fig. 2). However, heterogeneity was evidenced in the overall model ($I^2 = 46.9\%$, $p = 0.049$).

Six studies (Bishop et al., 2011; Fernandez-de-Las-Penas et al., 2008; Fryer et al., 2004; Hamilton et al., 2007; Oliveira-Campelo et al., 2010; Ruiz-Saez et al., 2007) included asymptomatic participants (healthy population) while four studies (Cote et al., 1994; Maduro de Camargo et al., 2011; Mansilla-Ferragut et al., 2009; Vernon et al., 1990) included symptomatic participants (clinical population). The summary effect estimate demonstrated a small favorable, but non-significant effect of SMT on increasing PPT in both the clinical (Hedges $g = 0.329$ [95% CI = −0.032; 0.691], $p = 0.074$) and healthy population (Hedges $g = 0.337$ [95% CI = −0.005; 0.679], $p = 0.053$) (Fig. 3). Heterogeneity was reduced in the clinical population ($I^2 = 0.0\%$, $p = 0.906$), but not in the healthy population ($I^2 = 69.271$, $p = 0.006$).

Five studies (Cote et al., 1994; Fernandez-de-Las-Penas et al., 2008; Fryer et al., 2004; Hamilton et al., 2007; Vernon et al., 1990) examined PPT at a local body region only, four studies (Bishop et al., 2011; Mansilla-Ferragut et al., 2009; Oliveira-Campelo et al., 2010; Ruiz-Saez et al., 2007) examined PPT at a remote body region only, and one study (Maduro de Camargo et al., 2011) examined PPT at both a local and remote body region. The summary effect estimate demonstrated a small favorable, but non-significant effect of SMT on increasing PPT at the local site (Hedges $g = 0.387$ [95% CI = −0.070; 0.844], $p = 0.097$) (Fig. 4). For the remote site, the summary effect estimate demonstrated a small, but significant effect for SMT on increasing PPT (Hedges $g = 0.287$ [95% CI = 0.073; 0.500], $p = 0.008$) (Fig. 4). Similar to the previous subgroup analysis, heterogeneity was reduced for the remote site studies ($I^2 = 0.0\%$, $p = 0.858$), but not for the local site studies ($I^2 = 68.057$, $p = 0.008$).

3.5. Publication bias

Asymmetry was apparent in the funnel plot (Fig. 5), especially for studies with less precision (located lower on *Y*-axis). However, Egger's test was non-significant ($p = 0.09$) with intercept = 2.43 [95% CI = −0.482; 5.348]. The failsafe *N* using a two-tailed criterion

Table 3
Methodological Quality Assessment of Included Studies.

Article	1	2	3	4	5	6	7	8	9	10	11	12	Total*
Bialosky et al. (2009b)	+	+	–	–	–	+	+	?	–	+	+	+	7
Bishop et al. (2011)(Bishop et al., 2011)	–	–	–	–	–	+	+	?	+	+	+	+	6
Cote et al. (1994)	+	+	–	–	–	+	+	?	–	+	+	+	7
Fernandez-Carnero et al. (2008)	–	+	–	–	–	+	+	?	+	+	+	+	7
Fernandez-de-las-Penas et al. (2008)	+	+	–	–	–	+	+	?	+	+	+	+	8
Fernandez-de-las-Penas et al. (2007)	+	+	–	–	–	+	+	?	+	+	+	+	8
Fryer et al. (2004)	+	+	–	–	–	+	+	?	–	+	+	+	7
George et al. (2006)	–	–	–	–	–	+	+	?	+	+	+	+	6
Hamilton et al. (2007)	+	+	–	–	–	+	+	?	+	+	+	+	8
Maduro de Camargo et al. (2011)	+	+	–	–	–	+	+	?	+	+	+	+	8
Mansilla-Ferragut et al. (2009)	+	+	–	–	–	+	+	?	+	+	+	+	8
Mohammadian et al. (2004)	+	+	–	–	–	+	+	?	–	+	+	+	7
Oliveira-Campelo et al. (2010)	+	+	–	–	–	+	+	?	+	+	+	+	8
Parkin-Smith and Penter (1998)	+	–	–	–	–	–	+	?	–	–	–	+	3
Ruiz-Saez et al. (2007)	+	+	–	–	–	+	+	?	+	+	+	+	8
Shearar et al. (2005)	+	–	–	–	–	–	+	?	+	+	–	+	5
Terrett and Vernon (1984)	–	–	–	–	–	+	–	?	+	+	+	+	5
Thomson et al. (2009)	–	+	–	–	–	+	+	?	+	+	+	+	7
van Schalkwyk and Parkin-Smith (2000)	+	–	–	–	–	–	+	?	–	+	–	+	4
Vernon et al. (1990)	–	–	–	–	–	+	+	?	–	+	+	+	5

(+) met criteria, (–) did not meet criteria, (?) unsure.
Criteria: 1 – was the method of randomization adequate?; 2 – Was the treatment allocation concealed?; 3 – Was the patient blinded to the intervention?; 4 – Was the care provider blinded to the intervention?; 5 – Was the outcome assessor blinded to the intervention?; 6 – Was the drop-out rate described and adequate?; 7 – Were all randomized participants analyzed in the group to which they were allocated?; 8 – Are reports of the study free of suggestion of selective outcome reporting?; 9 – Were the groups similar at baseline regarding the most important prognostic indicators?; 10 – Were co-interventions avoided or similar?; 11 – Was the compliance acceptable in all groups?; 12 – Was the timing of the outcome assessment similar in all groups?
* 1 Point for each item meeting criteria.

was 28. After adjusting for publication bias, the overall effect estimate still demonstrated a small, but significant effect for SMT on increasing PPT (Hedges $g = 0.269$ [95% CI = 0.106; 0.433].

4. Discussion

We conducted a comprehensive systematic review and meta-analysis on the hypoalgesic effects of SMT on measures of pain sensitivity. Our meta-analysis results suggest SMT has a favorable effect on increasing PPT, or reducing pain sensitivity, when compared to other forms of intervention. This effect on PPT was largest when measured at a remote anatomical region. These results have implications on potential neurophysiological mechanisms and for areas of future research.

Prior reviews have considered the potential role of SMT on pain processing (Bialosky et al., 2009a; Pickar, 2002; Vernon, 2000). Many of the studies included in this review were published after the narrative reviews by Pickar (2002) and Vernon (2000). Our systematic review expands upon these prior works as we were able to (1) include recent studies published after the reviews by Pickar (2002) and Vernon (2000), (2) provide information on the quality of SMT studies, and (3) quantitatively assess the effect of SMT. Overall, we reached a similar conclusion: SMT has a favorable effect on pain sensitivity.

When examining the effect of SMT based on population, there did not appear to be a different effect when studied in healthy versus clinical samples. This is noteworthy as some musculoskeletal conditions have been associated with altered pain sensitivity (Arendt-Nielsen et al., 2010; Fernandez-Carnero et al., 2009; O'Neill et al., 2007). This difference in pain state does not seem to affect the response to SMT. Studies involving both healthy and clinical participants are important in establishing the mechanisms of SMT. Only 9 of the 20 studies that have evaluated SMT on pain sensitivity responses were assessed among clinical participants. It is imperative that mechanistic studies include clinical participants to link changes in pain sensitivity to changes in a pertinent clinical outcome.

One of the primary questions posed by both Pickar (2002) and Vernon (2000) was whether SMT elicits a general response on pain sensitivity or whether the response is specific to the area where SMT is applied. For example, changes in pain sensitivity over the cervical facets following a cervical spine SMT would indicate a local and specific effect while changes in pain sensitivity in the lumbar facets following a cervical spine SMT would suggest a general effect. We observed a favorable change for increased PPT when measured at remote anatomical sites and a similar, but non-significant change at local anatomical sites. These findings lend support to a possible general effect of SMT beyond the effect expected at the local region of SMT application.

Studies of changes in pain sensitivity in response to SMT indicate potential mechanisms to account for the clinical effectiveness. The mechanisms of SMT are theorized to result from both spinal cord mediated mechanisms (Boal and Gillette, 2004) and supraspinal mediated mechanisms (Wright, 1995). A recent model of the mechanisms of manual therapy suggests changes in pain related to SMT result from an interaction of neurophysiological responses related to the peripheral nervous system and the central nervous system at the spinal and supraspinal level (Bialosky et al., 2009a). Prior studies provide support for such an interaction. For example, we have previously observed diminished pain sensitivity to a behavioral measure of dorsal horn excitability (temporal summation of pain) in response to lumbar SMT indicating a spinal cord mediated mechanism (Bialosky et al., 2009b; George et al., 2006). Interestingly, these findings were reversed in a subsequent study when healthy participants were instructed to expect more pain following the SMT (Bialosky et al., 2008).Collectively these studies suggest an interaction between a spinal cord mediated mechanism of SMT related hypoalgesia (temporal summation) and a supraspinal mediated mechanism related to expectation. Future mechanistic studies of SMT related changes in pain sensitivity should consider and control for potential peripheral, spinal, and supraspinal mechanisms and their potential interaction.

Caution is recommended when interpreting the potential clinical relevance of these findings. While a majority of these studies demonstrated low risk of bias (high quality), 17 of the 20 studies

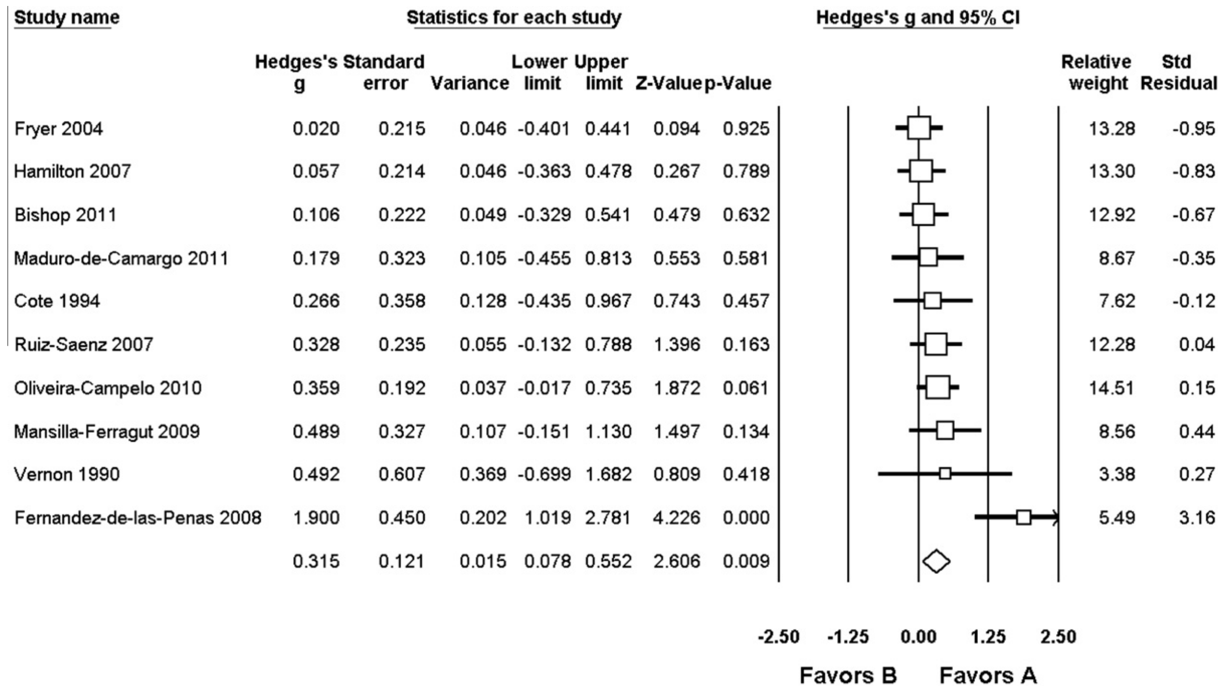

Fig. 2. Meta-analysis results for the effects of spinal manipulation on pressure pain threshold. A = SMT; B = Comparison.

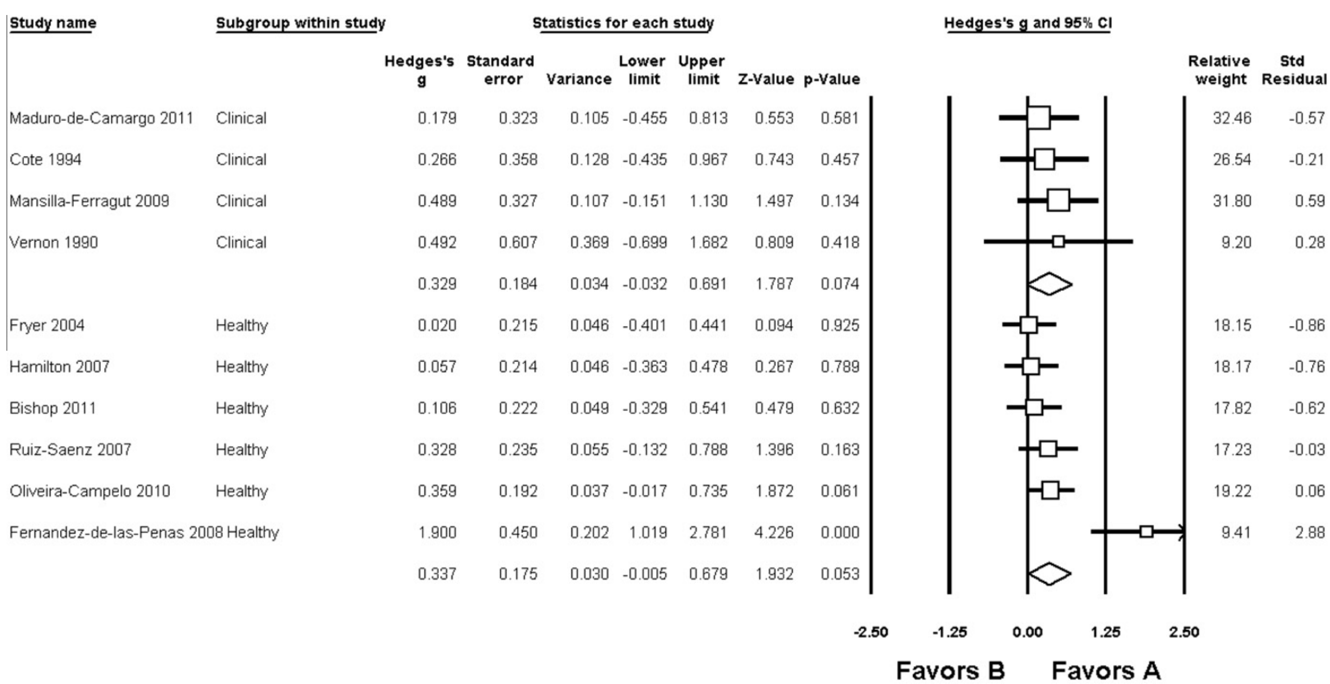

Fig. 3. Meta-analysis results for the effects of spinal manipulation on pressure pain threshold based on clinical or healthy population. A = SMT; B = Comparison.

investigated short-term effects only. Collectively, these studies provide evidence that SMT has an immediate effect on reducing pain sensitivity, most notably at the remote region of stimulus assessment with similar results in clinical and healthy populations. Although this an important first step, Cook (2011) has highlighted the need for examining the effect of SMT beyond an immediate follow-up since (1) many interventions (including those considered ineffective) demonstrate a favorable immediate effect, and (2) it is undetermined how an immediate hypoalgesic effect relates to long-term clinical improvement (e.g. function). Additionally, many of these studies do not link the change in pain sensitivity to a meaningful change in clinical outcome limiting the potential for clinical relevance.

There was a lack of consistency in the pain sensitivity outcomes studied and this allowed for the assessment of effects on PPT only within the meta-analysis. The 20 RCTs included in this review examined the effects of SMT on responses to chemical ($n = 1$), electrical ($n = 1$), mechanical ($n = 15$), and thermal ($n = 4$) stimuli applied to the skin. However, we observed that only one pain sensitivity measure was consistently included in a majority of studies, pressure pain threshold (PPT). Further, the experimental stimuli tended to be applied and measured at one anatomical region only. Future studies

Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
Fryer 2004	Local	0.020	0.215	0.046	-0.401	0.441	0.094	0.925	21.64	-0.83
Hamilton 2007	Local	0.057	0.214	0.046	-0.363	0.478	0.267	0.789	21.66	-0.74
Maduro-de-Camargo 2011	Local	0.151	0.323	0.104	-0.482	0.785	0.468	0.640	17.56	-0.47
Cote 1994	Local	0.266	0.358	0.128	-0.435	0.967	0.743	0.457	16.32	-0.23
Vernon 1990	Local	0.492	0.607	0.369	-0.699	1.682	0.809	0.418	9.47	0.15
Fernandez-de-las-Penas 2008	Local	1.900	0.450	0.202	1.019	2.781	4.226	0.000	13.35	2.55
		0.387	0.233	0.054	-0.070	0.844	1.660	0.097		
Bishop 2011	Remote	0.106	0.222	0.049	-0.329	0.541	0.479	0.632	24.03	-0.93
Maduro-de-Camargo 2011	Remote	0.187	0.323	0.105	-0.447	0.821	0.577	0.564	11.30	-0.33
Ruiz-Saenz 2007	Remote	0.328	0.235	0.055	-0.132	0.788	1.396	0.163	21.46	0.20
Oliveira-Campelo 2010	Remote	0.359	0.192	0.037	-0.017	0.735	1.872	0.061	32.13	0.46
Mansilla-Ferragut 2009	Remote	0.489	0.327	0.107	-0.151	1.130	1.497	0.134	11.07	0.66
		0.287	0.109	0.012	0.073	0.500	2.635	0.008		

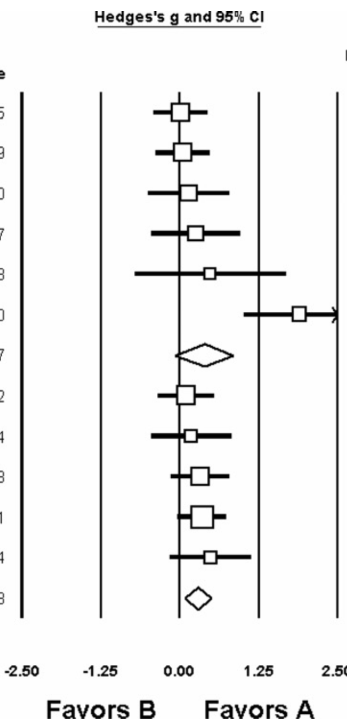

Fig. 4. Meta-analysis results for the effects of spinal manipulation on pressure pain threshold measured at local or remote body region. A = SMT; B = Comparison.

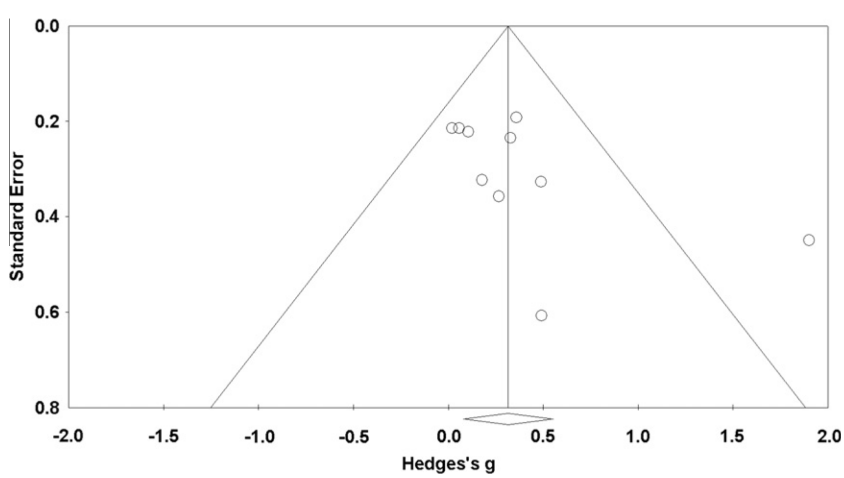

Fig. 5. Funnel plot for publication bias.

investigating the mechanisms of hypoalgesia related to SMT should consider assessing pain sensitivity with multiple experimental sensory stimuli at local and remote sites. These assessments are useful for characterizing whether SMT, and other forms of manual therapy, have (1) a robust hypoalgesic effect (e.g. across multiples sensory modalities), (2) effects that are specific to the location of application and/or the location of pain (for clinical samples), and (3) effects that include a central nervous system component of modulating afferent nociceptive signal (e.g. remote effects).

Our review has additional implications for future studies. First, while it was beyond the scope of this study to examine dosage, we noted that either too little information was provided by authors regarding dosage or no attempt was made to examine the effect of dosage on pain sensitivity responses. Understanding the effect of repeated SMT application is relevant as no optimal dosage has been appreciated in mechanistic or clinical studies. Second, there was no consensus among the studies on type of stimulus or parameters of stimulus application. Few studies incorporated more than one stimulus modality or multi-regional application of the stimulus. Using multiple stimuli for studying pain in both a clinical and research setting has been recommended by previous authors (Arendt-Nielsen and Yarnitsky, 2009; Hastie et al., 2005; Nijs et al., 2009). Pain sensitivity may differ based on type of stimulus and there is potential for clinical and healthy participants to exhibit different pain profiles (Hastie et al., 2005). By implementing this, future research could consider whether SMT results in a change in global pain sensitivity or modality-specific sensitivity.

4.1. Limitations

There are several limitations in this review. While most of the studies demonstrated low risk of bias, there is the potential for some of the scoring items to be irrelevant as 17 studies were immediate effect studies. For example, within an immediate effect study, there is little concern for drop-outs (Item 6), compliance (Item 11), and timing of assessment (Item 12). Thus, the qualitative scoring criteria may be overestimated for these studies. Another limitation includes the lack of unpublished studies entered into this review. It is undetermined how the inclusion of these reports would impact the overall results. Further, we did not obtain information regarding concomitant clinical pain reports following SMT. Our focus remained on pain sensitivity responses rather than clinical pain. Prior reviews have examined the effect of SMT and other forms of manual therapy on clinical pain complaints and thus this paper is best viewed as a mechanistic investigation. In this review, we chose to combine studies in the meta-analysis that exhibited some heterogeneity. For example, we aimed to examine the response of SMT globally on any site of PPT measure and we did not have enough studies to examine each region of SMT separately. Despite this, we did stratify the analysis by location of PPT.

5. Conclusion

The mechanism of SMT remains elusive, but SMT appears to modulate pain through both central and peripheral pathways. Studies have investigated the effect of SMT using variable experimental pain modalities including chemical, electrical, mechanical, and thermal stimuli. SMT demonstrated a favorable effect over other interventions on pressure pain thresholds (PPT). Additionally, subgroup analysis showed a significant effect of SMT on remote sites of pressure stimulus application further supporting a potential influence on higher levels within the central nervous system. Future studies using experimental pain testing to examine the mechanisms of SMT should include multiple stimuli and test at multiple anatomical sites if determining potential mechanisms is the goal.

Conflict of interest statement

None declared.

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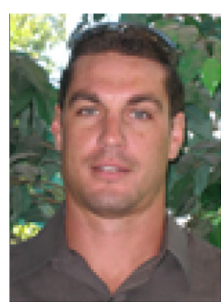

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