BIOLOGICAL EFFECTS OF SPINAL MANIPULATION IN CHRONIC NON-SPECIFIC LOW BACK PAIN PATIENTS

By

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BIOLOGICAL EFFECTS OF SPINAL MANIPULATION IN CHRONIC NON-SPECIFIC LOW BACK PAIN PATIENTS

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Abstract

Low back pain (LBP) affects up to 85% of the adult population imposing an economic burden of $86 billion annually *or* 1% of the US gross domestic product. Traditionally, acute spinal pain has been considered as self-resolving with chronic low back pain (pain > 3 months duration) only accounting for 5% of those individuals with low back pain. Though, more recent literature has contested this view point by citing that between one-third and two-thirds of those patients with *acute* spinal pain do *not* improve, but instead transition to *chronic* pain. Thus, determining and using efficacious interventions for low back pain may prevent or improve the disability associated with chronic low back disorders. One viable treatment option for low back pain is spinal manipulative therapy (SMT).

However, insufficient evidence exists to explain the mechanisms of pain reduction and improved function associated with SMT, although SMT appears to be an advocated intervention for managing low back pain patients. If the biological mechanisms of SMT were understood, clinicians could determine *a priori* which patients may respond to SMT, perhaps improving clinical outcomes and reducing health care costs. Thus, our study sought to improve the understanding of the biological mechanisms associated with spinal manipulation.

This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with chronic non-specific low back pain (CNSLBP). We enrolled and randomly assigned 29 subjects (n = 29) to spinal manipulation (SMT) or sham spinal manipulation (sham SMT) groups. After group allocation, we conducted testing including pressure pain threshold (PPT) and kinematic analyses (angular displacement and velocity), along with clinical outcomes (Numeric Pain Rating Scale and Oswestry Disability Index).

This is the first study that demonstrates the effect of SMT on PPT at local, regional, and remote testing sites in chronic low back patients. Furthermore, the results demonstrate that SMT and sham SMT can lead to significant improvements in pain and patient-reported disability along with trunk kinematics in CNSLBP patients. Though not significant, the SMT group showed more favorable improvements in trunk angular displacement in the SMT group than the sham SMT group at 3-weeks post-intervention. It is therefore recommended to use the standard SMT in the clinical setting, even though some technique variations may influence trunk kinematics. Lastly, our results indicated that the relationship between SMT-induced changes in biological outcome measures appears limited.

Results of this study support the use of SMT or its variation in patients with CNSLBP. Furthermore, the specific technique of *how* spinal manipulation is conducted may be less important, as long as a mechanical load is applied to the spine. Overall, the presented work stipulates acquiescent evidence that SMT is an effective intervention in patients with CNSLBP. Nevertheless, further study with a larger sample size and longer-term outcome is required to better appreciate the biological mechanisms associated with SMT.

Acknowledgments

This body of work represents a culmination of seemingly ceaseless hours of effort over the past few years. However, I could not have reached this finale without the time, effort, encouragement, and support from many people. I would like to take the opportunity to acknowledge and express my gratitude to these individuals.

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CHAPTER 1:

Introduction

1.1 Background

Since World War II, there has been an epidemic of low back disability.[1] However, low back *pain* has been documented in medical literature since about 1,500 BC.[1] Clinical practice guidelines (CPGs) for the management of low back pain recommend using medications, exercise, physical modalities, and surgery.[2] In addition, present clinical practice guidelines recommend spinal manipulative therapy (SMT) as a *primary* intervention for low back pain.[2-4] SMT may reduce pain and disability in chronic low back pain (CLBP) patients.[5,6] However, a systematic review concluded that improvement in pain and function following SMT might *not* be considered clinically relevant.[7] It appears that the clinical efficacy of SMT for managing CLBP requires further clarification. The clinical predictors of CLBP patients likely to respond to SMT remain largely elusive. A possible reason for this limited application of SMT may be a poor understanding of the neurophysiological mechanisms associated with pain modulation. Thus, there is still a large group of CLBP patients that fail to achieve overall clinical success over time.[8,9]

1.2 Epidemiology of Low Back Pain

Low back pain affects up to 85% of the adult population imposing an economic burden of $86 billion annually *or* 1% of the US gross domestic product.[10-12] Traditionally, acute spinal pain has been considered as self-resolving with CLBP (pain > 3 months duration) only accounting for 5% of those individuals with low back pain.[10,11] However, more recent literature has contested this view point by citing that between one-third and two-thirds of those patients with *acute* spinal pain do *not* improve, but instead transition to *chronic* pain.[8,9,13] Chronic low back pain represents 75% of the total treatment costs associated with managing low back pain and is associated with

significant physical and psychological disability, representing *the* major cause of absenteeism from the workplace worldwide.[10,11,14] Thus, determining and using efficacious interventions during the *early* stages (acute and/or subacute) of low back pain may prevent or improve the disability associated with chronic low back disorders.[15,16] One viable treatment option for CLBP is spinal manipulative therapy (SMT).

1.3 Definition of Nonspecific Low Back Pain

The biopsychosocial model of low back pain proposes that pain may be the result of complex interaction between biological, psychological, and sociological influences.[17] The majority of persons (80-90%) with low back pain are described as "nonspecific" since a precise cause or tissue cannot be identified as the source of pain.[18,19] According to scientific literature examining the role of medical imaging studies in low back pain, there appears a weak relationship between imaging findings and patient symptomatology.[3,18,20,21] For example, anatomic defects (i.e., herniated or bulging discs) detected through imaging studies are common in healthy, asymptomatic individuals[20], while only 15% of low back pain diagnoses can be related to a specific imaging indicators.[22] Also, overutilization of imaging may lead to inappropriate diagnoses or interventions, labeling effects (i.e., patient anxiety or dependence), unnecessary exposure to ionizing radiation, and unwarranted financial expenditure.[20,21] Thus, centered on these imaging outcomes, non-specific low back pain (NSLBP) may be defined by the absence of a specific or identifiable pathology such as a fracture, tumor or physical deformity.[18] Hence, since most cases of low back pain do not present with an identifiable pathology, categorizing and/or managing low back pain patients based upon biological, psychological, and sociological characteristics appears appropriate.

According to scientific literature, the duration of pain associated low back disorders may be used as a staging system.[23] Generally, "chronic" low back pain is defined as a duration > 3 months, while the "acute" phase is defined as pain < 3 months.[23] However, the transition between "acute" and "subacute" low back pain has been *subjectively* defined at several cut-off points including 2, 3, 4, and 6 weeks.[15] Kovacs et al[15] used regression analyses to *objectively* predict a cut-off point of 14 days for the subacute stage based on changes in determinants of disability and quality of life and on the risk of developing chronic disability.[15] Thus, efficacious interventions such as SMT might be contemplated after 14 days (cut-off for subacute phase) to prevent or improve the disability associated with spinal disorders, especially chronic conditions.[15]

The Quebec Task Force (QTF) represents a diagnostic classification system for spinal disorders.[24,25] According to the QTF, patients with low back pain may be categorized based upon the clinical presentation (pain and neurologic examination information) into at least four classifications: (1) low back pain without radiation (QTF 1), (2) low back pain with proximal radiation/above the knee (QTF 2), (3) low back pain with distal radiation/below the knee (QTF 3), or (4) low back pain with distal radiation and neurologic signs (QTF 4).[24,25] For the purpose of our study, we will recruit subjects with chronic (> 12 weeks) low back pain limited to QTF 1 and QTF 2.

1.4 Definition of Spinal Manipulation

Spinal manipulation therapy (SMT) is an intervention advocated and implemented by several professions including osteopathic physicians, medical doctors, physical therapists, and chiropractors.[2,26-28] However, scientific literature has estimated that between 75% and 94% of

spinal manipulative procedures in the United States (US) are performed by chiropractors.[29-31] According to the American Chiropractic Association (ACA), manipulation may be defined as:[32]

> "A manipulation is a passive manual maneuver during which the three-joint complex may be carried beyond the normal voluntary physiological range of movement into the paraphysiological space without exceeding the boundaries of anatomical integrity. The essential characteristic is a thrust—a brief, sudden, and carefully administered 'impulsion' that is given at the end of the normal passive range of movement."

As mentioned, physical therapists may use joint manipulation to manage musculoskeletal conditions. The American Physical Therapy Association (APTA) Manipulation Task Force delineates that the terms mobilization and manipulation are interchangeable and defines these procedures as:[33]

> "A manual therapy technique comprising a continuum of skilled passive movements to the joints and/or related soft tissue that are applied at varying speeds and amplitudes, including a small-amplitude/high-velocity therapeutic movement."

Also, the American Physical Therapy Association (APTA) Manipulation Task Force characterized thrust manipulation as, "high velocity, low amplitude therapeutic movements within or at end range of motion."[33]

1.5 Effectiveness of Spinal Manipulation for Low Back Pain

One non-surgical approach that has improved patient clinical outcomes for chronic non-specific low back pain (CNSLBP) is SMT. As reported by Dagenais et al,[2] recent clinical practice guidelines from several countries support and extend the use of SMT for effectively managing low back pain (Table 1).

Table 1: International Clinical Practice Guidelines Recommendations for Managing Low Back Pain with Spinal Manipulation.[2]

	Spinal Manipulative Therapy Recommendation			*Evidence Studied to Support Clinical Practice Guidelines*					
	Acute LBP	**Chronic LBP**	**Neurologic**	**Clinical practice guidelines**	**Systematic reviews**	**Randomized clinical trials**	**Observational studies**	**Health technology assessments**	**Economic evaluations**
Belgium[34]	----	Yes	Yes	X	X	X		X	X
Europe[35,36]	Yes	Yes	----	X	X	X	X		X
Italy[37]	Yes	Yes	No	X	X	X			X
United Kingdom[38]	----	Yes	----		X	X		X	X
United States[39]	Yes	Yes	Yes		X	X			X

Up to date, it is unclear whether or not SMT can improve self-reported pain and low back-related disability in *chronic* LBP patients. Conclusions from clinical trials, as well as review articles, reported a significant effect of SMT in CLBP patients.[5,6,40,41] However, other studies concluded that SMT had no significant clinical effect on pain and/or function in CLBP patients.[7,42] A systematic review concluded that SMT and mobilization provided effective short-term clinical improvement as compared to placebo and general practitioner care, and in the long-term matched to physical therapy.[40] In addition, for both short and long-term disability outcomes, limited to moderate data revealed that SMT is superior to physical therapy and home exercise.[40] Another systematic review stated that moderate to strong evidence substantiated a short-term effect of SMT in comparison to sham for pain, function and overall health.[41] Also, SMT combined or not with other interventions, including exercise, may improve clinical outcomes for CNSLBP patients.[41] Recent clinical trials[5,6] reported that CLBP subjects receiving SMT significantly improved pain and function scores compared to sham SMT. However, a systematic review by Rubinstein et al[7]

concluded that SMT for CLBP produces changes in pain and function that might *not* be considered clinically relevant according to group mean differences in outcome measures and established clinically important threshold values.[7] A large clinical trial (n = 301) examined the effects of SMT, home exercise, and supervised exercise on CLBP subjects.[42] Bronfort et al[42] stated that the short- and long-term differences between the groups for self-reported pain and disability consistently favored the supervised exercise group compared to home exercise and SMT groups. Because of the conflicting information above, we identified a gap in the scientific literature related to the clinical efficacy of SMT for managing CNSLBP patients. Thus, our study sought to investigate the effect of SMT on clinical outcomes in CNSLBP patients.

Based upon a review of the available scientific literature, it is also unclear whether or not SMT can improve self-reported pain and low back-related disability in *acute* back pain patients. Again, conclusions from clinical trials, as well as review articles, reported a significant effect of SMT in acute low back pain patients.[40,41] However, other studies concluded that SMT had no significant clinical effect on pain and/or function in acute low back pain patients.[40,43,44] Bronfort et al[40] identified 31 randomized clinical trials (RCTs) with 5,202 subjects that met their inclusion criteria for a systematic review. For *acute* low back pain, moderate evidence advocated that SMT provides superior short-term relief compared to mobilization and placebo.[40] Another review by Hidalgo et al[41] concluded that strong evidence supports a short-term effect of SMT on pain and function in acute low back pain patients when compared to sham. A systematic review, including a meta-analysis, by Rubinstein et al[43] identified 20 RCTs with a total of 2674 subjects that satisfied their inclusion criteria. Rubinstein et al[43] concluded that SMT is no more effective than sham SMT as adjunct therapy for patients with acute low back pain; also SMT does not emerge as more beneficial than other proposed interventions. According to Rubinstein et al[43], the outcomes

associated with their systematic review might be limited by a relatively small number of investigations. Similar to the findings associated with CLBP, the effects of SMT in the *acute* low back pain population appear to derive conflicting conclusions.

1.6 Scientific Models of Spinal Manipulation in Managing Musculoskeletal Pain

Over recent decades, numerous authors have endorsed scientific models attempting to explain the therapeutic effects associated with SMT.[45-52] These scientific theories have evolved over time according to the available scientific evidence along with the beneficial clinical results reported with SMT. In general, the proposed models incorporate biomechanical and/or neurophysiological therapeutic effects related to SMT. Shekelle[53] suggested one of the first modern "mechanical" models attempting to explain the clinical benefits of SMT:

> "There are four main hypotheses for lesions that respond to manipulation: (1) release of entrapped synovial folds or plica, (2) relaxation of hypertonic muscle by sudden stretching, (3) disruption of articular or periarticular adhesions, and (4) unbuckling of motion segments that have undergone disproportionate displacements."

A narrative review by Evans[48] examining the scientific literature available to support these four hypotheses refuted the plausibility of disrupting adhesions and unbuckling of motion segments as "mechanical" explanations of the observed clinical effects of SMT on pain. However, Evans[48] stated that the release of entrapped synovium remained a feasible mechanical mechanism of pain relief associated with SMT, but that the scientific evidence supporting the relaxation of hypertonic muscle by SMT should considered a "neurophysiologic" (non-mechanical) effect. Thus, Evans[48] concluded that a valid theory explaining the therapeutic mechanisms of SMT must account for "mechanical" *and* "neurophysiologic" effects associated with manipulation.

Triano[47] hypothesized a systematic model, primarily biomechanical, that reported SMT influences a manipulable lesion commonly referred to as a functional spinal lesion (Figure 1). This biomechanical model assumes that the functional spinal unit (FSU) is influenced by forces and moments, thus making the FSU vulnerable to "zig-zag" collapse or "buckling" behavior.[47]

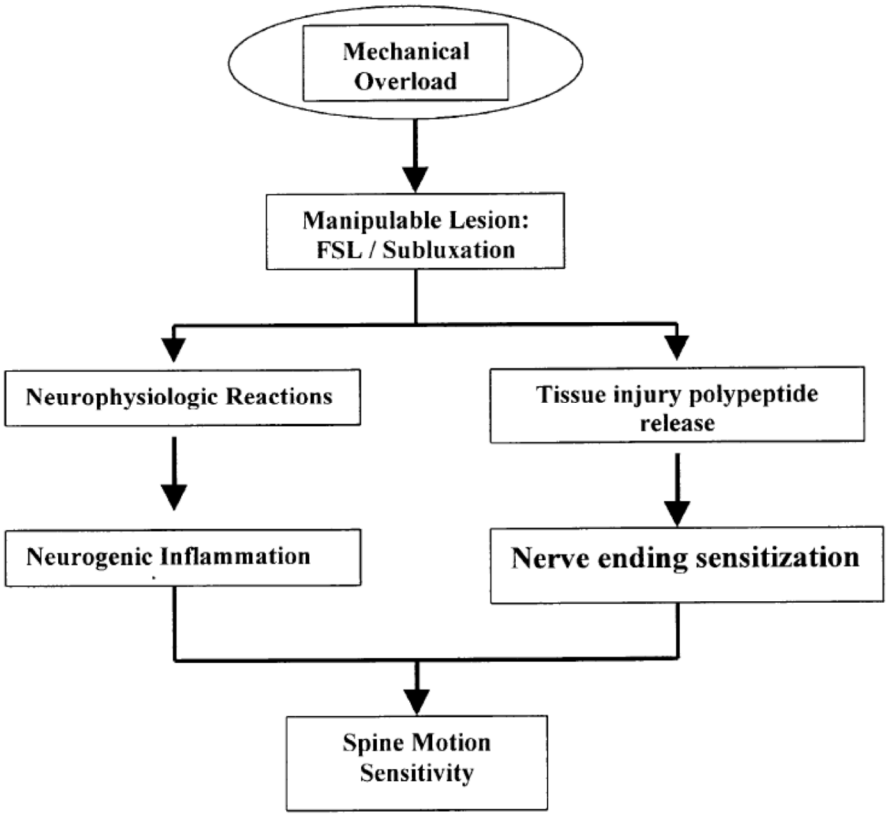

Figure 1: A theoretical mechanistic model depicting events producing clinical symptoms associated with a functional spinal lesion.[47] Copyright 2001 by Elsevier. Reprinted with permission.

According to Triano[47], segmental buckling of spinal joints are restrained by muscular forces, but mechanical overload as the result of a single traumatic occurrence or repeated events may produce an injury or functional spinal lesion:

> "When a critical buckling load is reached, the linear force-displacement behavior is interrupted by a disproportionately large displacement. The total distance, however, remains within the normal intersegmental range. That is, when buckling occurs, the affected area of the spine reaches its maximum range under lower load

> conditions and is operating at its extreme, out of phase with the demands of the task. It is assumed that such a functional configuration may result in altered stress distribution within the FSU."

As a result of the mechanical overload, neurophysiological and biochemical cascades lead to inflammation and nerve sending sensitization, thus yielding spine motion sensitivity along with local and/or remote symptoms.[47] Triano[47] states that SMT has a biomechanical therapeutic effect on a functional spinal lesion:

> "Spinal manipulation uses controlled forces and moments applied to the spine along with inertial forces generated by acceleration of relevant body segment mass. The algebraic sum of these loads are transmitted to the spine in a controlled manner and are designed to "unbuckle" motion segments and reduce local mechanical stresses within the functional spinal unit."

However, Triano[47] cautioned that the proposed biomechanical model remains theoretical since it is based on limited scientific and clinical observations.

Pickar[45] proposed a theoretical model outlining the relationship amongst SMT, segmental biomechanics, the nervous system, and end-organ physiology (Figure 2). According to Pickar,[45] biomechanical changes associated with SMT may produce neurophysiological responses thereby influencing nociceptive, motor, and autonomic neuronal pools:

> "A biomechanical alteration between vertebral segments hypothetically produces a biomechanical overload the effects of which may alter the signaling properties of mechanically or chemically sensitive neurons in paraspinal tissues. These changes in sensory input are thought to modify neural integration either by directly affecting reflex activity and/or by affecting central neural integration within motor, nociceptive and possibly autonomic neuronal pools. Either of these changes in sensory input may elicit changes in efferent somatomotor and visceromotor activity. Pain, discomfort, altered muscle function or altered visceromotor activities comprise the signs or symptoms that might cause patients to seek spinal manipulation. Spinal manipulation, then, theoretically alters the inflow of sensory signals from paraspinal tissues in a manner that improves physiological function."

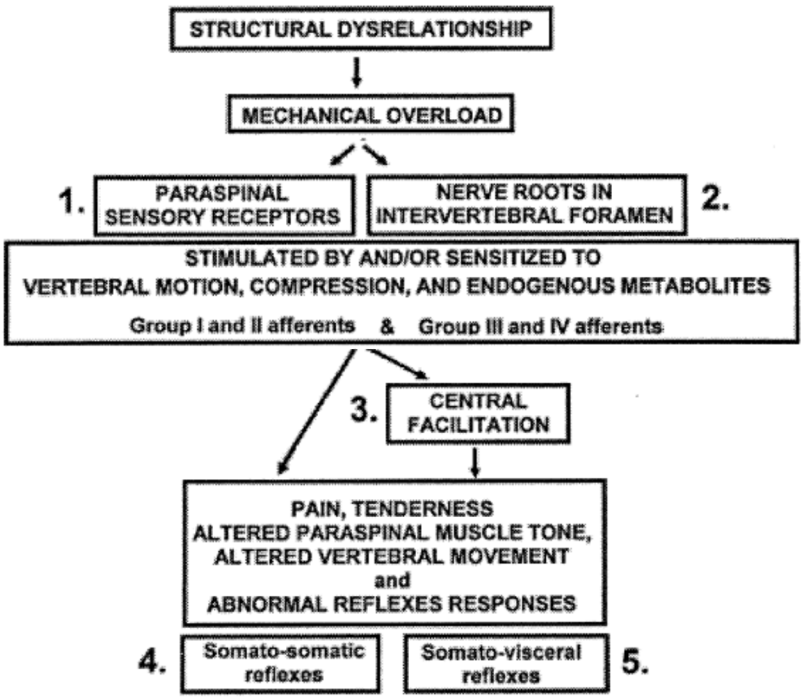

Figure 2: A theoretical model illustrating the potential neurophysiological effects of SMT. This model establishes that biomechanical changes caused by SMT may elicit neurophysiological changes at any of the numbered boxes.[45] Copyright 2002 by Elsevier. Reprinted with permission.

Pickar[45] concluded that scientific evidence supports the influence of SMT on proprioception, pain perception, and motor control systems. However, the therapeutic effects of SMT may likely be attributed to multiple mechanisms, including biomechanical and neurophysiological influences.[45]

Evans[51] proposed a *general* model of manipulation that requires the features of spinal manipulation include specific "actions" applied to the recipient by the clinician and "mechanical responses" that ensue within the recipient. The specific actions associated with joint manipulation include a force applied to the recipient and the line of action of the applied force is perpendicular to the joint surface.[51] The mechanical responses that occur within the recipient include the applied force producing movement within a joint followed by articular separation ("gapping") and

cavitation within the affected joint.[51] As described by Evans,[48] the "cracking" sound or cavitation associated with SMT is:

> "……the term used to describe the formation and activity of bubbles (or cavities) within fluid through local reduction in pressure."

According to Bialosky et al,[46] a theoretical model recognizing the potential for a combined effect of biomechanical and neurophysiological mechanisms associated with manual therapy is crucial to integrate the existing knowledge base and guide future investigation. Bialoksy et al[46] defined manual therapy to include joint-biased (manipulation and mobilization), soft tissue-biased (Swedish, deep tissue, trigger point and Shiatsu massage), and nerve-biased (neural dynamics) techniques. Bialosky et al[46] stated that a mechanical stimulus elicits a cascade of potential neurophysiological effects thereby accounting for the therapeutic benefits associated with manual therapy. The proposed model explains the nociceptive experience associated with musculoskeletal disorders by acknowledging that the neurophysiological effects of manual therapy comprise the peripheral and central nervous system mechanisms, including spinal cord and/or supraspinal pathways (Figure 3).[46]

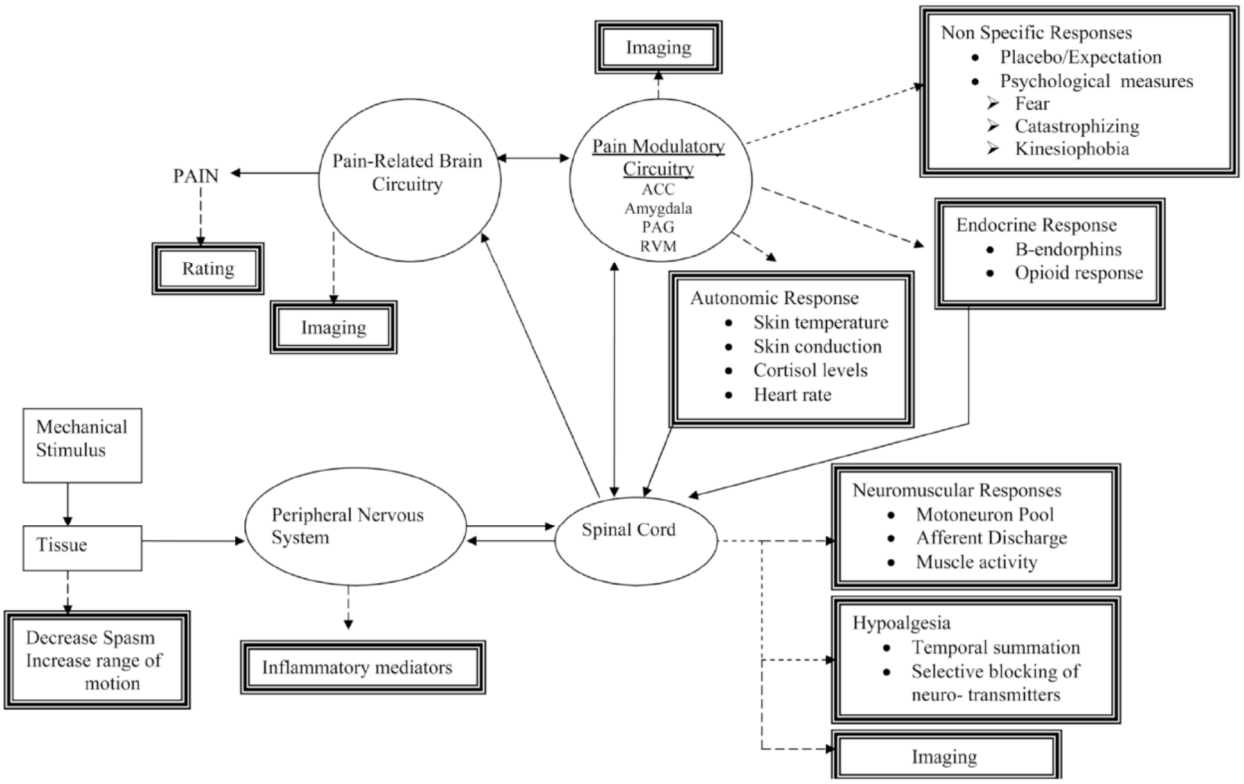

Figure 3: Bialosky et al[46] proposed a theoretical model illustrating the mechanisms of manual therapy. The model proposes that a mechanical stimulus elicits a cascade of potential neurophysiological effects. According to Bialosky et al[46], the solid arrows indicate a direct effect, while the broken arrows suggest an associative relationship between a construct and its measure. ACC = anterior cingulate cortex; PAG = periaqueductal grey; RVM = rostral ventral medulla.[46] Copyright 2009 by Elsevier. Reprinted with permission.

To identify the role of spinal manipulation in chronic non-specific low back pain patients, we will objectively test a central hypothesis that SMT will reduce hypersensitivity to mechanical stimuli applied at local, regional and remote sites and improve clinical outcomes in chronic non-specific low back pain patients. Our hypothesis has been formulated upon the basis of previous studies establishing the clinical efficacy of SMT in managing acute and chronic low back pain patients.[2-4,54-56]

1.7 Mechanical Characteristics of Spinal Manipulation

In recent decades, basic science researchers have quantified the mechanical properties of spinal manipulative therapy.[45,47,57] Scientific literature has established mechanical characteristics associated with SMT such as force-time profiles and displacement properties.[45] In general, according to Pickar et al,[58] SMT is mechanically quantified by a high velocity (duration < 150 ms), low amplitude (segmental translation < 2 mm; rotation < 4°) impulse thrust (applied force 220-889 N).

The force-time profile of high-velocity low-amplitude SMT includes three phases: pre-load, thrust, and resolution (Figure 4).[57,59] Pre-loading represents the phase of the force-time profile that consists of the clinician applying a load to the anatomical segment of interest and moving the region to the end its physiological range of motion. Also, the duration of the pre-load phase may be upwards of 5 seconds and include up to 25% of the thrust force.[58]

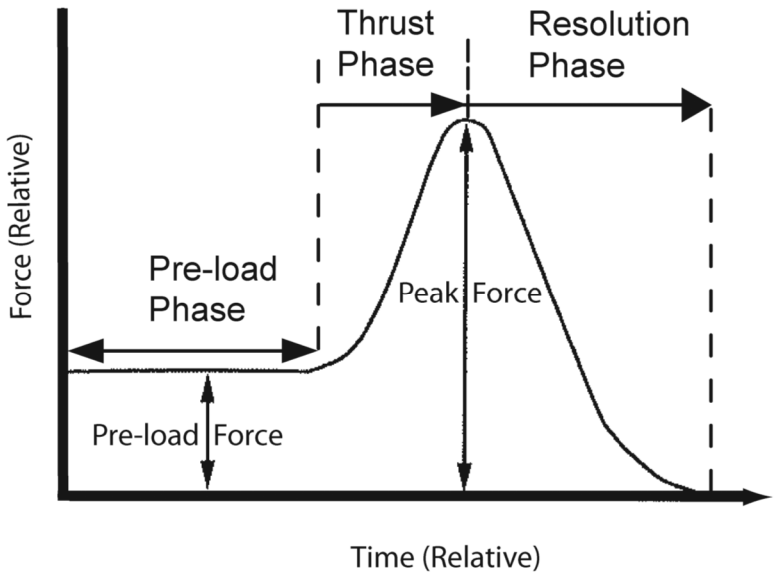

Figure 4: Force-time profile for high-velocity low-amplitude SMT, including pre-load, thrust, and resolution phases.[59] Copyright 2012 by Elsevier. Reprinted with permission.

The thrust and resolution phases of SMT have the visual appearance of half a sine wave (Figure 5).[58] Depending upon the anatomical region, peak forces associated with SMT may range between 108 to 399 N (Table 2).[57] Peak forces applied during cervical spine manipulation appear considerably less than the peak forces associated with the thoracic and lumbopelvic spinal regions (Figure 5).[57] Also, the thrust phase increases to a peak load in < 150 milliseconds during SMT applied to the thoracic and lumbar regions.[58] Again, depending upon the anatomical region, the rate of force application ranges between 132 to 2660 N/s (Table 2).[57] According to Pickar[45] and Triano,[47] transmitted loads associated with lumbar spine SMT emerge below the threshold of injury and closely match forces produced during activities of daily living. As previously mentioned, SMT is associated with small amplitude displacement of intervertebral segments; translation within a principal plane is usually < 2 mm while rotation about an axis is < 4°.[58]

Table 2: Mechanical characteristics of SMT applied to the cervical, thoracic, and sacroiliac regions.[57] N = Newton; ms = millisecond; N/s = Newton per second

	Spinal Region		
	Cervical	**Thoracic**	**Sacroiliac**
Pre-load forces (N)	27	139	88
Peak forces (N)	108	399	323
Thrust duration (ms)	81	150	150
Rate of force application (N/s)	132	2660	2153

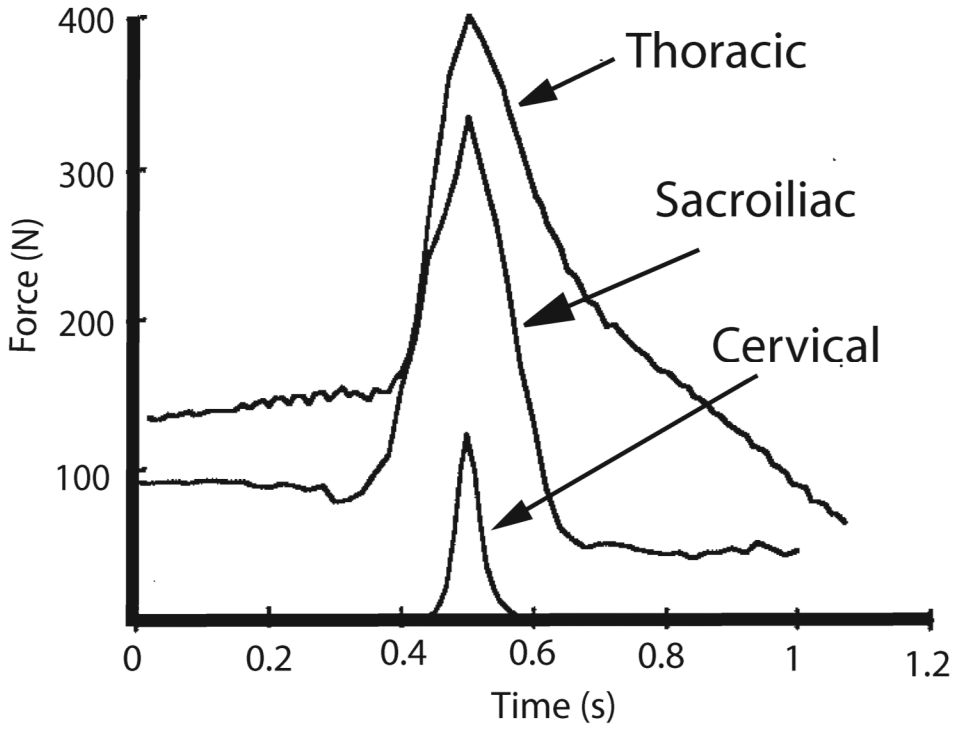

Figure 5: Mean force-time profiles for SMT applied to cervical, thoracic, and sacroiliac spinal regions.[59] Copyright 2012 by Elsevier. Reprinted with permission.

1.8 Biomechanical Mechanisms of Spinal Manipulation

As outlined earlier, scientific models attempting to explain the therapeutic effects of SMT have recognized mechanical responses concomitant with manipulation.[45-51,53] As asserted by Evans,[51] the forces accompanying spinal manipulation should create *motion* within a joint along with cavitation and separation of articular surfaces. Previous scientific literature supports the resultant movement within a joint following SMT.[51,58,60-62] SMT is defined as a high-velocity *low-amplitude* procedure, and thus the resultant joint movements associated with manipulation are relatively minor.[45,60-62] Clinically, an improvement in regional mobility has been reported following SMT,[63-66] including a systematic review by Millan et al[67] that reported manipulation may have a small effect on range of motion, particularly the cervical spine.

As mentioned, a *second* mechanical feature of manipulation includes *separation* or "gapping" of articular surfaces following SMT. Gapping or changes in the dimension of spinal zygapophyseal joints may break fibrous adhesions and/or release of entrapped synovial folds or plica that form after joint hypomobility, thus leading to improved *mobility* following SMT (Figure 6).[48,50,68]

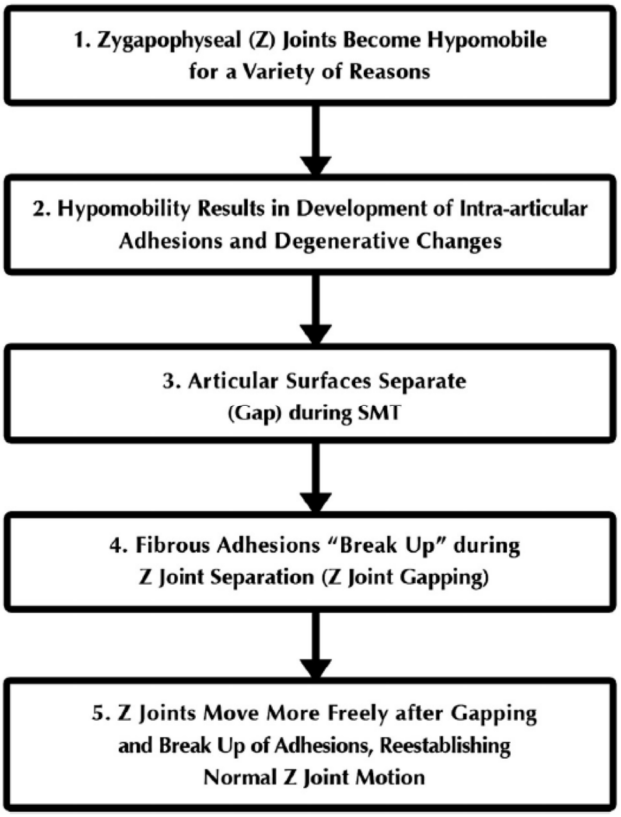

Figure 6: Cramer et al[68] proposed a theoretical model illustrating joint hypomobility followed by formation of fibrous adhesions and degenerative changes. SMT produces gapping within the spinal zygapophyseal joints, thus breaking adhesions and restoring joint mobility.[68] Copyright 2013 by Elsevier. Reprinted under Creative Commons.

Using a small animal model, Cramer et al[69] demonstrated mechanical fixation induced *hypomobility* within the lumbar spine region of rats, ultimately leading to *degenerative* adaptations within the spine. Reported outcome measures included degenerative changes of the intervertebral disks and vertebral bodies, along with zygapophyseal joint osteophyte formation and zygapophyseal joint articular surface degeneration. Compared to spinal regions without fixation

(control), regions undergoing fixation (hypomobility) demonstrated more degenerative changes. Results indicated minimal degenerative changes within the intervertebral disks and vertebral bodies, while the zygapophyseal joints displayed significant osteophyte formation and articular surface degeneration. In addition, for all zygapophyseal joint outcomes, the fixed regions exhibited more degenerative changes than the non-fixed regions. Finally, Cramer et al[69] reported a time-dependent effect of fixation with more osteophyte formation and articular surface degeneration at a threshold between 1 and 8 weeks. Cramer et al[69] concluded that degenerative changes ensue hypomobility of the zygapophyseal joints and clinicians should consider applying interventions such as joint manipulation that target movement of hypomobile segments *early* or prior to this threshold, thus averting or reversing degeneration.

In addition to the hypomobility-induced degenerative changes of zygapophyseal joints, Cramer et al[70] used the previously[69] reported small animal (rat) model to examine the effects of mechanical fixation (hypomobility) on the formation of fibrous *adhesions*. Zygapophyseal joints of control (non-fixed) and experimental (fixed) animals were evaluated for the existence of connective tissue adhesions or "bridges" within the joint space. Cramer et al[70] defined an adhesion as, "connective tissue material located within the Z joint space and completely connecting two distinct Z joint structures (i.e., superior articular process to inferior articular process, superior articular process to a synovial fold, or inferior articular process to a synovial fold)." Based upon visual inspection, adhesions were quantified according to size (small, medium or large) and location within the joint space. As reported by Cramer et al,[70] animals from control and experimental groups demonstrated the presence of small and medium adhesions, while large adhesions were detected only in animals undergoing 8, 12, or 16 weeks of mechanical hypomobility. Also, 16-week control (non-fixed) and experimental (fixed) animals exhibited

significant differences for small, medium, and large adhesions. According to Cramer et al,[70] hypomobility-induced zygapophyseal joints adhesions appear time-dependent with the formation of medium and large adhesions closely related to the duration of hypomobility. Cramer et al[70] concluded that joint hypomobility leads to increased adhesion formation. Again, clinicians should contemplate using interventions such as spinal manipulation that target movement of hypomobile segments, perhaps preventing or breaking adhesions.[70]

Cramer et al[71] conducted a randomized clinical trial with *healthy* subjects comparing the effects of lumbar spine side-posture *positioning* and lumbar spine side-posture *manipulation* on the separation or "gapping" of articular surfaces. Magnetic resonance imaging (MRI) scans (pre- and post-intervention) measuring the anterior to posterior dimensions of the zygapophyseal joints were compared following side-posture positioning and side-posture manipulation. Cramer et al[71] reported high reliability (ICCs > .90) for inter-observer and intra-observer measurements of gapping. Results indicated that gapping of the zygapophyseal joints occurred following side-posture positioning and side-posture manipulation, but side-posture manipulation produced greater gapping of the zygapophyseal joints than side-posture positioning. Lumbar spine manipulation may increase the synovial space of the zygapophyseal joints by up to 0.7 mm.[71] This increased joint space may persist beyond the duration of the manipulation itself, thus possibly straining connective tissues that span the joint. Cramer et al[71] concluded that gapping of the lumbar spine zygapophyseal joints proposes evidence substantiating a therapeutic mechanism associated with spinal manipulation (Figure 6).

In addition to gapping in *healthy* subjects, Cramer et al[68] conducted a randomized clinical trial with *acute* low back pain patients comparing the effects of lumbar spine side-posture *positioning* and lumbar spine side-posture *manipulation* on gapping of articular surfaces. Again,

MRI scans (pre- and post-intervention) measuring the anterior to posterior dimensions of the zygapophyseal joints were compared following side-posture positioning and side-posture manipulation; additional outcome measures included assessment of pain and function. Subjects underwent an initial MRI scanning session (pre- and post-intervention scans) followed by 2 weeks of treatment (1-3 visits per week as recommended by the treating clinician) and a second MRI scanning session (pre- and post-intervention scans). According to Cramer et al,[68] the side-posture positioning group demonstrated the greatest zygapophyseal joint gapping at the initial MRI session. During the second scanning session, after 2 weeks of treatment, the group experiencing spinal manipulation followed by side-posture positioning displayed the greatest amount of zygapophyseal joint gapping, followed by side-posture positioning alone. Cramer et al[68] concluded that side-posture positioning yielded an enhancing benefit to spinal manipulation with regard to pain modulation and zygapophyseal joint gapping (Figure 7).

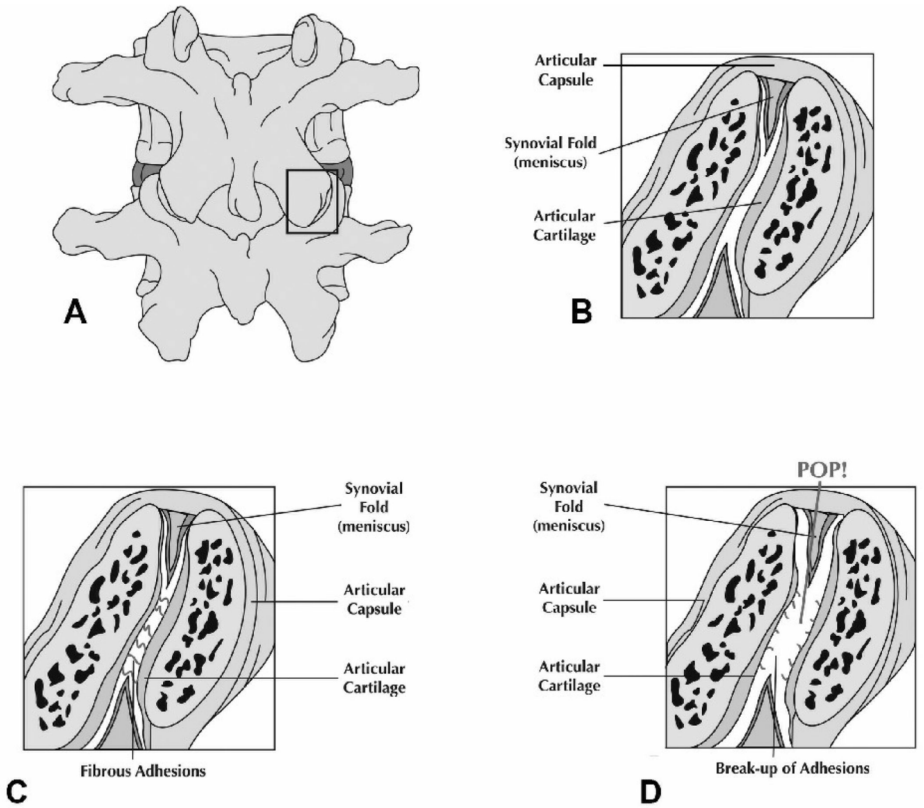

Figure 7: Theoretical model of cavitation with associated breaking of fibrous adhesions suggested by Cramer et al.[72] Copyright 2011 by Elsevier. Reprinted with permission.

A *third* feature of spinal manipulation as delineated by Evans[51] is *cavitation* or "audible release" within the affected joint. As mentioned, cavitation might be the result of gas suddenly entering a joint space followed by the formation a gas bubble created during *distraction* of the joint surfaces.[73] Another cavitation theory states that cavitation may be caused by gas bubble *collapse* within the joint space.[74] Using static and cine MRI images, Kawchuck et al[75] recently demonstrated *in-vivo* visual responses within the metocarpophalangeal joints during cavitation. According to Kawchuck et al,[75] joint cavitation appears consistent with tribonucleation:

> "Our results offer direct experimental evidence that joint cracking is the result of cavity inception within synovial fluid rather than collapse of a pre-existing bubble. These observations are consistent with tribonucleation, a known process where opposing surfaces resist separation until a critical point where they separate rapidly resulting in vapor cavities that do not collapse instantaneously."

Relative to the therapeutic mechanisms associated with SMT, scientific knowledge has postulated that gapping or separation of articular surfaces may be related to the cavitation phenomena, thus interrupting connective tissue adhesions and/or stimulating neurophysiological responses (Figure 8).[72] Brodeur[76] proposed that the separation of the articular surfaces caused by SMT creates elastic recoil within the zygapophyseal joint capsules, thus producing a cavitation response. In addition, Brodeur[76] asserted that beneficial neurological reflex responses such as pain reduction and muscle relaxation were instigated by the capsular recoil. Cramer et al[72] stated that the mechanical and neurophysiological pathways associated with SMT are *not* mutually exclusive and predisposing hypomobility and joint pathology may *not* be necessary to elicit neurophysiological effects. Briefly, the neurophysiologic affects associated with SMT include pain modulation,[46,77-80] along with stimulation of mechanoreceptors,[45,58,59,81-84] and somatic[45] and/or visceral[45] efferents.

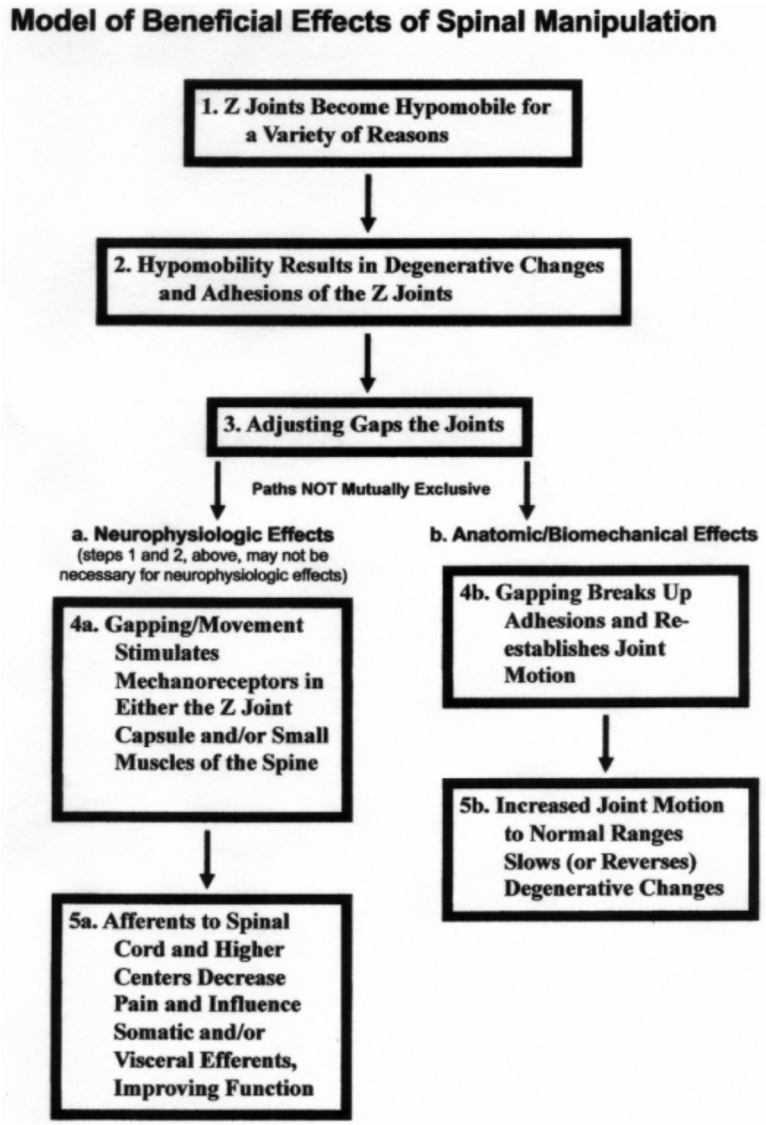

Figure 8: Cramer et al[72] proposed a theoretical model outlining the potential mechanical and neurophysiological effects of SMT. Note that the pathways are *not* mutually exclusive and hypomobility and joint pathology may not be necessary to elicit neurophysiological effects. Copyright 2011 by Elsevier. Reprinted with permission.

Cramer et al[72] reported a case series examining the relationship between cavitation and zygapophyseal joint gapping during side-posture spinal manipulation in healthy subjects. Using MRI scans (pre- and post-intervention) and accelerometers, zygapophyseal joint gapping and cavitation were determined following spinal manipulation. According to Cramer et al,[72] zygapophyseal joints experiencing spinal manipulation (0.5 ± 0.6 mm) demonstrated greater gapping than zygapophyseal joints *not* experiencing spinal manipulation (–0.2 ± 0.6 mm). Also,

greater gapping occurred in the spinal joints that cavitated (0.8 ± 0.7 mm) compared to those spinal joints that did not cavitate (0.4 ± 0.5 mm).

Cramer et al[85] conducted a randomized clinical trial with *healthy* subjects comparing the effects of lumbar spine side-posture *positioning* and lumbar spine side-posture *manipulation* on gapping of articular surfaces along with concomitant cavitation. As outlined earlier, magnetic resonance imaging (MRI) scans (pre- and post-intervention) measuring the anterior to posterior dimensions of the zygapophyseal joints were compared following side-posture positioning and side-posture manipulation. In addition, nine accelerometers placed on specific lumbar spinous processes captured spinal joint cavitation events. Results indicated that spinal joints experiencing cavitation gapped more than spinal joints not undergoing cavitation (0.56 vs. 0.22 mm, $p = 0.01$).[85] Cramer et al[85] concluded that compared to side-posture positioning, greater gapping occurred in zygapophyseal joints receiving side-posture manipulation. Also, cavitation may be considered indicative of spinal joint gapping, but cavitation cannot quantify joint gapping.

1.9 Neurophysiological Mechanisms of Spinal Manipulation

To date, the neurophysiological mechanisms of the clinical success associated with SMT in low back pain patients remains inadequate. A theoretical construct proposed by Bialosky et al[46] suggests that manual therapies, including SMT along with soft-tissue and neural dynamic interventions, may demonstrate therapeutic benefits in managing musculoskeletal pain via: (1) peripheral, (2) spinal cord, and (3) supraspinal mechanisms. Based upon this model, outcome measures such as changes in mobility, inflammatory mediators, hypolagesia, neuromuscular

responses, and imaging, may capture the resultant activity in the pain modulatory circuitry following the application of therapeutic mechanical stimuli (or manual therapy) to local tissue.[46]

Scientific evidence supporting a *peripheral* mechanism associated with SMT includes the modulation of the inflammation and nociception following musculoskeletal injury.[78] Teodorczyk-Injeyan et al[86] reported that compared to sham SMT or control groups, healthy subjects receiving SMT demonstrated a significant reduction in blood and serum inflammatory cytokine levels. Also, Degenhardt et al[87] described post-manipulation changes in nociceptive biomarkers including beta-endorphin, serotonin, anandamide, and N-palmitoylethanolamide. Lastly, healthy subjects exhibited altered serum levels of endogenous cannabinoids post-manipulation.[88] Together, this scientific data suggests that the peripheral nervous system may be a pathway for pain modulation associated with joint manipulation.

Bialosky et al[46] also postulated a *spinal cord* pathway associated with spinal manipulation. Boal & Gillette[89] suggested that SMT stimulates co-activation of low-threshold (Aβ/group II) and high-threshold (Aδ/group III, C/group IV) mechanosensitive afferents, thus acting as a ‘‘counter-irritant’’ via the gate theory of pain. In addition, spinal manipulation may stimulate the central nervous system through sensory information transmitted through proprioceptors.[45,48] As previously stated, direct and indirect measures offer scientific evidence that SMT influences the spinal cord. Indirect evidence suggests that SMT is associated with motoneuron pool activity,[90,91] afferent discharge,[84,92-94] muscle activity,[95-98] and hypoalgesia.[78,79,99,100] Malisza et al[101] demonstrated direct evidence of a spinal cord effect associated with joint manipulation using functional MRI (fMRI) in an animal model. After injecting capsaicin into the rodent limb, fMRI measured the spinal cord response to light touch stimuli. Subsequent to manipulation of the limb, fMRI revealed a trends towards reduced activation of the dorsal horn.

Based upon this model, neuroimaging such as fMRI may capture the resultant activity in the pain modulatory circuitry following the application of therapeutic mechanical stimuli (or manual therapy) to local tissue.[46] During the past decade, scientific literature exploring the neural mechanisms associated with pain has demonstrated exponential growth. For example, the number of publications examining pain using imaging increased from approximately 250 papers between 1993-1996 to over 6000 papers between 2005-2008.[102] Functional imaging techniques for examining chronic pain include functional magnetic resonance imaging (fMRI) whereby the blood oxygen level-dependent (BOLD) signal represents an indirect measure of neuronal activity via change in the local concentration of deoxyhemoglobin.[103] Other imaging techniques for investigating chronic pain include voxel-based morphometry, diffuse tensor imaging, magnetic resonance spectroscopy, near-infrared spectroscopy, and magnetoencephalography.[102] However, this discussion will focus on fMRI, including discussion of *evoked* and *spontaneous* pain as related to low back pain.

Evoked-stimuli fMRI has been used to examine pain networks because of the convenience of presenting controlled, objective stimuli during the scanning session.[102] Based upon findings from evoked-stimuli fMRI, it appears that the acute pain related to painful stimulation demonstrates a consistent and reliable activation within defined brain regions.[104,105] Also, healthy control subjects and CLBP patients appear to have similar brain activations in response to painful stimuli.[104,106] Activation of these regions during acute painful stimulation has been described as the "pain matrix" or "neuromatrix".[107] Generally, the regions activated during painful stimulation of CLBP patients include the somatosensory, insular, cingulate and prefrontal cortical areas along with the thalamus.[104-106,108] Thus, it appears that the brain regions activated in response to acute pain are associated with sensory processing (somatosensory and insular cortices and thalamus),

emotional/affective processing (cingulate cortices) and cognitive/integrative function (prefrontal cortex).[102]

Previous literature has established that CLBP patients experience spontaneous pain even in the absence of a mechanical or thermal stimuli.[104,109-111] However, the neural pathway associated with spontaneous CLBP does not simply reflect augmented activity within the "neuromatrix" defined for acute pain.[107] Rather, the neural pathway associated with CLBP represents a network distinct from acute pain. In addition, different clinical conditions such as CLBP, knee osteoarthritis, and post-herpetic neuralgia seem to elicit neural responses unique to the specific clinical disorder.[112-115] Based upon MRI data examining functional connectivity (fcMRI), the brain resting states, including the default mode network (DMN), appear disrupted in CLBP patients.[109-111,116] More specifically, the brain regions affected by CLBP include the dorsolateral prefrontal cortex (DLPFC), medioprefrontal cortex (mPFC), cingulate cortices (ACC and PCC), basal ganglia, insula, amygdala, and caudate nucleus along with frontal (middle) and temporal gyri (superior and middle).[102,104,109-111,116] Thus, it emerges that the neuronal regions affected by CLBP are associated with sensory processing (insula), emotional/affective processing (mPFC, ACC, PCC, and amygdala) and cognitive/integrative function (prefrontal cortex).[102]

Although limited, previous scientific research has reported *supraspinal* effects associated with SMT. Using a fMRI animal model, noxious stimuli in rats produced brain activation in the anterior cingulate, frontal and somatosensory cortices.[117] Moreover, manual joint mobilization of painful limb resulted in decreased activation in these brain regions.[117] A recent case series published by Sparks et al[118] demonstrated that supraspinal mechanisms may be associated with thoracic SMT and hypoalgesia. Ten healthy subjects experienced painful stimulation of the index finger while undergoing an initial fMRI scan. Following the baseline fMRI scan, subjects received

SMT applied to the mid-thoracic spine. Post-SMT, a second fMRI recorded brain activity during noxious stimuli. Additionally, subjects were asked to rate their pain perception to the noxious stimuli using an 11-point numeric pain rating scale (NPRS). *Pre*-manipulation, painful stimuli produced significant activation in the left and right cerebellum, amygdala, thalami, periaqueductal gray, insular cortex, ACC, somatosensory cortices, supplementary motor area, and premotor areas.[118] However, *post*-manipulation fMRI scans exhibited reduced activation in the ascribed regions.

Recent studies utilizing somatosensory evoked potentials (SSEPs) demonstrated an immediate central effect associated with SMT in patients with a history of neck pain.[119,120] Passmore et al[121] defined a SSEP as the electrical activity response recorded at the cutaneous surface after precise peripheral nerve stimulation, most often electrical stimuli. Joint manipulation of the cervical spine immediately (20-30 minutes post-SMT) altered cortical somatosensory processing and sensorimotor integration.[119,120] The authors concluded that the changes in SSEPs following SMT provide evidence of transient neural plasticity. Also, transcranial magnetic stimulation (TMS) studies in patients with a history of neck pain studies have reported cervical SMT directly alters sensorimotor integration.[122,123] Collectively, findings from these imaging studies suggest a supraspinal mechanism associated with SMT.

In summary, much of the understanding of the proposed neurophysiological mechanisms associated with SMT remains to be further explored, even though recent research findings indicate the possible role of spinal cord pathways and potential involvement of supraspinal mechanism. Until scientific evidence can clearly demonstrate the neurophysiological mechanisms associated with spinal manipulation, it is neither possible to establish the definitive clinical efficacy of SMT, nor to gain ubiquitous acceptance of SMT among the scientific and healthcare communities.[124,125]

1.10 Effects of Spinal Manipulative Therapy on Pain Sensitivity

As previously outlined, SMT may elicit a pain-modulating effect through one *or* more neurological and/or mechanical mechanisms.[45,46,48,53,68] Bialosky et al[46] suggested experimental pain testing procedures such as pressure pain threshold (PPT) may be used as indirect measures of *peripheral* and *central* sensitization for musculoskeletal disorders. Peripheral and central sensitization may be differentiated by comparing experimental pain responses at sites *local* and *remote* to the primary area of injury.[126,127] Peripheral mechanisms such as sensitization of tissue nociceptors may elucidate *local* tissue hyperalgesia, while central sensitization reflects widespread hyperalgesia at *remote* (distant to the tissue pathology) anatomical locations.[127] As reported by Graven-Nielsen and Arendt-Nielsen[127], *descending inhibitory pain mechanisms* (DIPM) modulating dorsal horn neurons may explain the diminished response or hypoalgesia to nociceptive stimuli at *remote* testing sites.

Scientific models acknowledge that the neurophysiological effects associated with SMT comprise three fundamental pathways.[46] These neural pathways reflect SMT influences within *local tissues* along with *spinal cord* and/or *supraspinal* pathways.[46] Pain-reducing effects of SMT at the local tissue level (peripheral pathways) may be the result of decreased sensitivity within muscles spindles.[45,128] According to Clark et al[129], the "pain-spasm-pain" model of CLBP advocates that pain produces muscular overactivity, thereby causing pain. The pain-spasm-pain model postulates that a hyperactive spinal stretch reflex establishes the basis of the cycle.[129,130] Specifically, stimulation of nociceptive afferents may influence the gamma-motoneurons increasing the sensitivity of muscles spindles to stretch, thereby exciting alpha-motoneurons.[129,130] Subsequently, this excitation of alpha-motoneurons leads to increased muscle activation.[129,130]

SMT may alter the pain-spasm-pain cycle by modulating nociception and subsequently attenuating the muscle stretch reflex, thus reducing muscle activity.[129] A short-latency stretch reflex ensues following rapid stretch of a muscle, thus exciting Ia afferents within the muscle spindles.[129] Clark et al[129] found that SMT alters the short-latency stretch reflex within the erector spinae muscles. According to Clark et al[129], SMT functions mechanistically by modulating the sensitivity of muscle spindles within the erector spinae muscles, thereby influencing local nociception. In addition, scientific evidence from animal models substantiates the stimulation of primary afferents in the spinal tissues following SMT.[45,58,59,82,83,93,131]

Secondly, pain-reducing effects of SMT may be influenced by effects on the spinal cord, specifically the dorsal horn.[78,79] Dorsal horn neurons with receptive fields in the lumbar paraspinal tissues receive more convergent information from types III and IV afferents compared to dorsal horn neurons with receptive fields in the extremities.[125,132] In addition, nociceptive neurons within the superficial dorsal horn of the spinal segments communicate with receptive fields with the deep and superficial tissues of the lumbar spine and *lower extremities*.[125,132] Thus, segmental innervation from the lumbar spine includes tissues in the lower extremities.[125] After nociceptive neurons project to the dorsal horn, they diverge into ascending and descending fibers forming the dorsolateral tract of Lissauer.[133] According to Purves et al[133], axons in the Lissauer tract project caudal and cephalad one or two spinal cord segments prior to entering the grey matter of the dorsal horn. Presuming a sufficient duration to transition from an acute to chronic pain condition, SMT may influence regional or referred pain by removing subthreshold mechanical stimuli from paraspinal tissues through pain gate mechanisms.[45,127,128,134]

Thirdly, scientific literature supports that SMT may influence central sensitization of dorsal horn neurons through supraspinal pathways including the descending inhibitory pain mechanisms

(DIPM) via the periaqueductal gray (PAG) region.[134-141] Savva et al[134] suggested that activation of the PAG modulates nociception at the spinal cord, thus producing an analgesic effect on musculoskeletal pain. Within the neural pathways from the PAG to the spinal cord, distinct descending systems exist including non-adrenergic and serotonergic control systems.[134,140,141] The noradrenergic system uses noradrenaline to inhibit *mechanical* stimuli, while the serotonergic system uses serotonin to raise the *thermal* nociceptive threshold.[134,140,141] Also, the noradrenergic descending system instigates excitation of the sympathetic nervous system, while the serotonergic system triggers sympathoinhibition.[134] Scientific literature from animal models reveals altered mechanical withdrawal thresholds in *remote* anatomical regions following manual therapy suggesting a central influence on sensory processing via the DIPM.[137,140-142] Specifically, activation of the DIPM following SMT may inhibit nociceptive afferent input at the spinal cord producing hypoalgesia, thereby increasing pressure pain threshold.[128,134,139] According to Skyba et al,[137] blockage of non-opioid receptors at the spinal cord prevented the hypoalgesic effect of manual therapy at a *remote* site using an animal model. In contrast, blockage of opioid receptors at the spinal cord did not influence the anti-nociceptive effect of manual therapy.[137] Thus, activation of the DIPM, which uses noradrenaline and serotonin, produced the mechanical hypoalgesia that followed application of manual therapy to a remote site.[134,137] Because manual therapy produced mechanical hypoalgesia at location remote to the site of injury, this limits the likelihood that SMT could facilitate recovery or alter the chemical environment of the injured region.[134] Thus, central neural mechanisms including the DIPM appear to stimulate the hypoalgesic effect associated with SMT.[134] Central sensitization of dorsal horn neurons in the spinal cord may be an influence in the transition from acute to chronic pain and play a role in the

maintenance of chronic pain.[16,79,143] Thus, therapeutic interventions such as SMT that potentially influence central sensitization are worth further exploration.[79]

Depending on the measurement site, the examined effect of SMT on pressure pain threshold in CLBP patients may reflect local tissue, spinal cord and/or supraspinal biological pathways.[144] Previous studies testing the consequences of *lumbopelvic* manipulation on pain sensitivity have reported applying stimuli to numerous anatomical locations.[78,79,99,145-148] Coronado et al[144] published a systematic review and meta-analysis that concluded future research designs should include *multi-regional* application of stimulus following SMT to differentiate local, specific effects versus general hypoalgesia. Hypoalgesia at a *local* testing site following SMT might modulate pain via stimulation of peripheral muscle spindles and/or central segmental reflex pathways.[128,129] A *regional* testing site might be considered an anatomical region within the same or overlapping dermatomes as those influenced by SMT.[99] For example, testing for hypoalgesia following lumbopelvic manipulation only in anatomical locations innervated by lumbosacral nerve roots.[79,145] George et al[99] reported that pain sensitivity testing *only* at remote anatomical locations cannot distinguish whether or not the hypoalgesia following SMT is a large, general effect or a specific effect localized to the spinal levels associated with the manipulation. Also, paraspinal muscle reflexes along with motoneuron excitability may be influenced by SMT, perhaps affecting reflex neural output to spinal musculature.[45,128] Thus, modulation of PPT at regional sites following SMT seems likely modulated through central neural mechanisms, however peripheral mechanisms may also influence the regional pain effects of SMT.[45,128] A systematic review and meta-analysis concluded that increased PPT at *remote* anatomical sites suggests a general or widespread effect of SMT on central sensitization.[144] In addition, evidence from fMRI imaging suggests that reduced

PPT (i.e., hyperalgesia) at a *remote* site indicates a *central*, rather than peripheral, cause for CLBP.[149]

As mentioned, multi-regional application of stimulus following SMT may help to distinguish the biological pathways associated with pain modulation following SMT. For example, changes in pain sensitivity over the upper extremity (remote site) following lumbopelvic SMT, but not at the paraspinal musculature (local site), might suggest a general effect of SMT on central sensitization via descending inhibitory pain mechanisms (DIPM). Alternatively, a change in pain sensitivity over the paraspinal musculature (local site) following lumbopelvic SMT, but not at the upper extremity (remote site) or lower extremity (regional site), might imply a local effect of SMT via stimulation of peripheral muscle spindles.

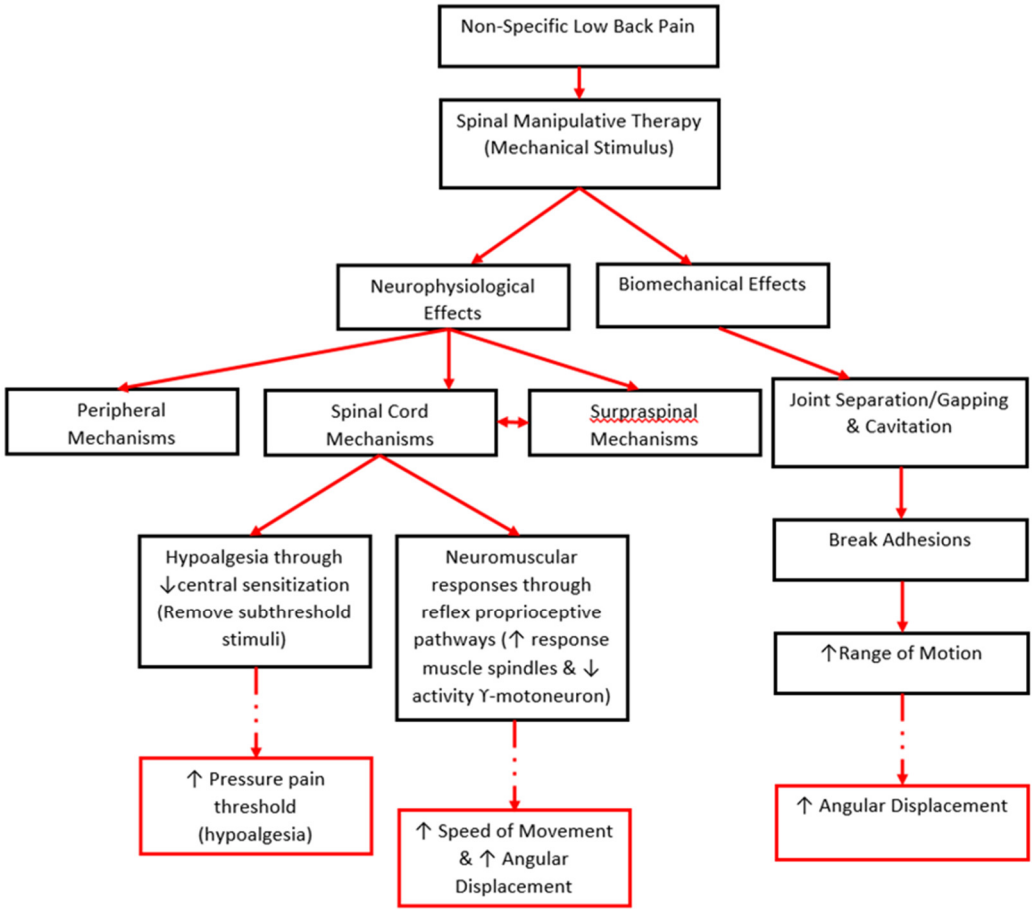

Figure 9: Proposed mechanisms and pathways producing the therapeutic effects associated with SMT. Red boxes and broken lines represent the measurable constructs for this study.

A systematic review and meta-analysis concluded that SMT exhibited a favorable effect on increasing pressure pain threshold compared to other interventions.[144] However, this meta-analysis by Coronado et al[144] *only* included *one* study that examined the effect of SMT on PPT in *low back pain* patients, while the remaining nine studies reported the outcomes of SMT on PPT in either neck pain or asymptomatic subjects. Scientific studies have measured pain sensitivity following joint manipulation applied to the cervical,[100,135,136,150-153] thoracic,[80,154,155] and lumbopelvic,[78,79,99,145-148] spinal regions, along with the peripheral joints.[156-158] Depending on the measurement site, the examined effect of SMT on pressure pain threshold in *CNSLBP* patients may reflect *local tissue*, *spinal cord* and/or *supraspinal* biological pathways.[144] Based upon past

studies of *lumbopelvic* manipulation on pain sensitivity (Table 3),[78,79,99,145-148] mixed results on changes in PPT after SMT were reported. Past studies have reported varied results on changes in PPT after lumbopelvic SMT related to the anatomical *site* of the applied mechanical stimuli in healthy and low back pain subjects.[145-148,159] Studies in *healthy*, *asymptomatic* subjects examining the effects of lumbopelvic SMT on PPT reported *significant* changes in PPT at local, regional, and remote sites[159] along with conflicting results reporting *no significant* change in PPT at a local site.[146] Past studies in *low back pain* patients evaluating the effects of lumbopelvic SMT on PPT described *no significant* changes in PPT at regional locations,[145,148] while other studies reported *significant* changes in PPT at a local site.[145,147] Up to date, it is unclear whether SMT can reduce PPT in CNSLBP, and if it does, which pain pathway, peripheral or central, is responsible for changes in PPT. The current investigation embodies a novel design by examining the effects of SMT on PPT across *multiple* anatomical testing locations (local, regional, and remote) in *chronic* non-specific low back pain patients.

Table 3: Effects of Lumbopelvic Spinal Manipulative Therapy on Pain Sensitivity. RCT = randomized, controlled trial; HVLA = high-velocity low amplitude; PSIS = posterior superior iliac spine; PPT = pressure pain threshold

Article	*Design & Participants*	*Interventions*	*Duration/ Number of Interventions*	*Pain Modality*	*Location of Applied Pain Modality*	*Summary of Results*
Bialosky et al[79] (2014)	RCT with low back pain of any duration (n=110).	Group1: Lumbar HVLA. Group 2: Standard placebo SMT. Group 3: Enhanced placebo SMT Group. 4: No treatment.	Therapy duration: 6 sessions over 2-week period.	Mechanical: Suprathreshold pain (6 kg). Thermal: Suprathreshold temporal summation (C-fiber).	PSIS (local) and dominant foot (regional) for mechanical pain, Dominant foot for thermal pain.	No significant changes in mechanical pain sensitivity. Significant ↓ thermal pain sensitivity observed only in SMT group.
de Oliveira et al[145] (2013)	RCT with chronic low back pain (n=148).	Group 1: Lumbar (region-specific) rotational HVLA. Group 2: Thoracic (non-region specific) "global" HVLA.	Therapy duration: 1 session.	Mechanical: Pressure pain threshold (rate 5 N/s).	Bilateral lumbar (local) paraspinal and tibialis anterior muscles (regional).	No significant between-group differences or changes in region-specific group. Non–region specific group ↑ PPT at lumbar.
Yu et al[159] (2012)	RCT with healthy, asymptomatic (n=30).	Group 1: Lumbosacral instrument-assisted manipulation. Group 2: Sham (no force) manipulation.	Therapy duration: 1 session.	Mechanical: Pressure pain threshold (rate 0.5 kg/s).	Bilateral L5 joint, L5 dermatome, and first dorsal interossei (hand)	SMT produced significant ↑ PPT at all testing sites, and trend toward ↑ PPT compared to sham.
Bialosky et al[78] (2009)	RCT with low back pain of any duration (n=36).	Group 1: Lumbar HVLA (supine). Group 2: Lumbar extension press-up exercise. Group 3: Stationary bike.	Therapy duration: 1 session.	Thermal: 1. Suprathreshold (Aδ) pain. 2. Temporal summation (C-fiber).	Non-dominant forearm (remote) and posterior calf (suprathreshold). Non-dominant palm of hand (remote) and plantar region of foot (temporal summation).	No hypoalgesia for Aδ-fiber pain in either region. Significant hypoalgesia (↓) of temporal summation in lumbar region of SMT, but not other interventions. All subjects ↓ in temporal summation in upper extremity.
Thomson et al[146] (2009)	RCT with healthy,	Group 1: Lumbar HVLA (side-lying). Group 2:	Therapy duration: 1 session.	Mechanical:	Lumbar spinous process (most tender).	No significant changes in PPT over time for

	asymptomatic (n=50).	Lumbopelvic mobilization (prone). Group 3: Sham laser lumbar region (prone).		Pressure pain threshold (rate 1 kg/s).		any intervention.
George et al[99] (2006)	RCT with healthy, asymptomatic (n=60).	Group 1: Lumbar HVLA (supine). Group 2: Lumbar extension press-up exercise. Group 3: Stationary bike.	Therapy duration: 1 session.	Thermal: 1. Suprathreshold (Aδ-fiber) pain. 2. Temporal summation (C-fiber).	Non-dominant forearm (remote) and posterior calf (suprathreshold). Non-dominant palm of hand (remote) and plantar region of foot (temporal summation).	Significant effect of Aδ-fiber hypoalgesia for all groups in lower extremity. SMT larger ↓ in temporal sensation at lower extremity than stationary bike, but not extension exercise.
Shearar et al[147] (2005)	RCT with sacroiliac joint syndrome (n=60).	Group 1: Lumbosacral HVLA. Group 2: Lumbosacral mechanical-assisted manipulation.	Therapy duration: 4 sessions over 2-week period.	Mechanical: Pressure pain threshold (rate 1 kg/cm^2/s).	Sacroiliac joint (symptomatic and asymptomatic sides).	For both groups, PPT increased from 1st to 3rd assessments.
Cote et al[148] (1994)	RCT with chronic low back pain (n=30).	Group 1: Lumbar HVLA (side-lying). Group 2: Knee-to-chest mobilization.	Therapy duration: 1 session.	Mechanical: Pressure pain threshold (rate 100 g/s).	Symptomatic-side erector spinae muscles, PSIS, and gluteal regions.	No significant changes in PPT after either intervention at any location or time at times 0, 15, 30 minutes.

1.11 Effects of Spinal Manipulative Therapy on Kinematics

Individuals with low back pain showed changes in kinematic parameters including diminished lumbar range of motion (ROM) in all cardinal planes,[22,160-163] slower lumbar movement,[22,161,163,164] and worse proprioception.[160,165-167] SMT may produce beneficial effects on ROM.[45,46,68,168] Cramer et al[68] proposed that gapping or changes in the dimension of spinal zygapophyseal joints may break fibrous adhesions and/or release of entrapped synovial folds or plica that form after joint hypomobility, thus leading to improved mobility or ROM following

SMT (**Figure 9**). In addition, paraspinal muscle reflexes along with motoneuron excitability may be influenced by SMT, perhaps affecting reflex neural output to spinal musculature, thereby improving trunk kinematics (**Figure 9**).[45,128] However, investigations examining the effects SMT on lumbar mobility demonstrate an inconsistent effect on ROM (**Table 4**).[65,169-172] Results of a systematic review indicated that SMT may have a small effect on ROM in the cervical region, but no effect on ROM in the lumbar region.[67] However, *limitations* related to their conclusions include questionable construct validity or *precision* of the ROM measuring *devices*. Also, SMT may not have a large effect on total ROM, but may instead influence kinematics or "how the spine moves."[67] Past studies have also used different measurement devices including electromagnetic tracking, inclinometers, and finger-tip-floor excursion.[65,169,170] Currently, it is unclear whether SMT can improve trunk kinematics in patients with spinal pain. Specifically, while using a *precision* measuring device for *multiple* planes of movement, it is uncertain whether *SMT* can influence trunk kinematics in *chronic non-specific low back pain* patients.

Table 4: Effects of Manual Therapy on Lumbar Spine Range of Motion. HVLA = high-velocity low amplitude; ROM = range of motion

Article	*Design*	*Participants*	*Interventions*	*Measurement Outcomes and Device*	*Summary of Results*
Stamos-Papastamos et al[170] (2011)	Crossover	Asymptomatic (n=32).	- Lumbar HVLA (rotational). - Lumbar mobilization (central posteroanterior).	Bending stiffness and lumbar ROM (flexion/extension) using electromagnetic tracking device.	No significant effect of manipulation and mobilization on lumbar ROM, but individual differences based on initial ROM.
Konstantinou et al[65] (2007)	Crossover	Chronic low back pain (n=26).	- Lumbar mobilization (posteroanterior). - Placebo (lying in self-prescribed comfortable position).	Lumbar ROM (flexion/extension) using double inclinometer.	Small changes in ROM associated with mobilization.
Goodsell et al[169] (2000)	Crossover	Mixed (acute & chronic)	- Lumbar mobilization (posteroanterior).	Lumbar ROM (flexion/extension)	No effect of mobilization and

	low back pain (n=26).	- No intervention (lying down).		using fingertips-to-floor and inclinometer.	control on lumbar ROM.

1.12 Significance of the Proposed Research

According to the World Health Organization (WHO), low back pain has reached epidemic proportions, reported worldwide by about 80% of people at some point in their life.[173] The functional prognosis for CLBP is poor with only 50% of patients returning to work after 6 months and almost none after 2 years.[174] Thus, a large number of CLBP patients *fail* to realize significant improvements in pain and function. CLBP is associated with significant physical and psychological disability, representing *the* major cause of absenteeism from the workplace worldwide.[14] Present clinical practice guidelines recommend SMT as a *primary* intervention for CLBP.[2-4] SMT improves clinical outcomes, including pain and disability in low back pain patients.[5,6,41,175,176] Also, scientific literature demonstrates the cost effectiveness of SMT in managing spinal pain, but not a clear understanding of its biological mechanisms.[124]

Presently, it is unclear whether SMT can reduce PPT in CNSLBP, and if so, which pain pathway, local or central, is responsible for changes in PPT. Until these questions are answered, it is neither possible to establish objective neurophysiological evidence of the mechanisms of SMT, nor to gain ubiquitous acceptance of SMT among the scientific and healthcare communities.[124,125] Depending on the measurement site, the examined effect of SMT on pressure pain threshold in *CNSLBP* patients may reflect *local*, *regional* or *remote* neurophysiological mechanisms.[144] The immediate, widespread or *remote* hypoalgesia associated with SMT has been ascribed to changes in central pain processing including stimulation of the *descending inhibitory pain mechanisms*

(DIPM) via the PAG.[134-141,177] Moreover, changes in PPT at *local* and/or *regional* sites following SMT may be associated with reduced sensitivity within local muscles spindles or influenced by effects on the dorsal horn through the removal of subthreshold mechanical stimuli via pain gate mechanisms.[45,79,127,128,134]

As an outcome of the proposed research, we expect to contribute to the scientific understanding of the improvements in pain and movement associated with SMT in CNSLBP patients. *This contribution is significant because it is likely to add to the clinical knowledge establishing objective biological evidence of the mechanisms of SMT, perhaps helping to gain ubiquitous acceptance of SMT among the scientific and healthcare communities.* Scientific research has suggested that SMT influences the peripheral and central nervous systems.[45,46,119,120,122,123] However, insufficient evidence exists to explain the mechanisms of pain reduction and improved function associated with SMT, although SMT appears to be an advocated intervention for managing CLBP patients.[2] If the biological mechanisms of SMT were understood, clinicians could determine *a priori* which patients may respond to SMT, perhaps improving clinical outcomes and reducing health care costs. It is also expected that the information learned from this research may contribute to improvement of patient clinical outcomes, specifically pain and function.

1.13 Innovation of the Proposed Research

This is an *innovative* project because it may establish biological therapeutic mechanisms of SMT for chronic non-specific low back pain patients. Although clinicians (*e.g.*, physical therapists, orthopedic surgeons, chiropractors) currently recommend SMT for low back pain patients, the biological mechanisms associated with SMT remain unclear. Immediate reduction in pain sensitivity at *remote* anatomical locations following SMT has been ascribed to changes in

central pain processing including stimulation of the *descending inhibitory pain mechanisms* (DIPM) via the PAG.[134-141,177] Moreover, changes in PPT at *local* and/or *regional* sites following SMT may be associated with reduced sensitivity within local muscles spindles or influenced by effects on the dorsal horn through the removal of subthreshold mechanical stimuli via pain gate mechanisms.[45,78,79,127,128,134] However, it is unclear whether SMT can reduce PPT in *CNSLBP*, and if it does, which pain pathway, peripheral or central, is responsible for changes in PPT. The present study represents an innovative design by examining the effects of SMT on PPT across *multiple* anatomical testing locations (local, regional, and remote) in *chronic* non-specific low back pain patients.

Previous investigations examining the effects SMT on lumbar mobility demonstrate an inconsistent effect on ROM.[65,169-172] Past studies have used different measurement devices including electromagnetic tracking, inclinometers, and finger-tip-floor excursion.[65,169,170] Currently, it is unclear whether SMT can improve trunk kinematics in low back pain patients. Specifically, while using a *precision* measuring device for *multiple* planes of movement, it is uncertain whether *SMT* can influence trunk kinematics in *chronic non-specific low back pain* patients.

Thus, our study will involve a novel design using *pressure pain threshold* and *kinematic* procedures to determine the biological effects of SMT in *chronic non-specific* low back pain patients. The results of this research may provide insight into therapeutic recommendations that improve clinical outcomes in low back pain patients. The outcomes may have an important positive health impact because this vertical step in rehabilitation may contribute to the resolution of an enduring and pervasive health problem.

1.14 Specific Aims

Experimental pain tests such as pressure pain threshold (PPT) may be used as indirect measures of peripheral and/or central sensitization for musculoskeletal pain.[46] Peripheral and central sensitization may be differentiated by comparing experimental pain responses at sites *local* and *remote* to the primary area of injury.[126,127] Peripheral mechanisms such as sensitization of tissue nociceptors may elucidate *local* tissue hyperalgesia, while central sensitization reflects widespread hyperalgesia at *remote* anatomical locations.[127] SMT may influence peripheral tissue hyperalgesia through decreased sensitivity within muscles spindles[45,128] and central sensitization of dorsal horn neurons through the descending inhibitory pain mechanism (DIPM) via the periaqueductal gray (PAG) region.[134,137-141] Depending on the measurement site, the examined effect of SMT on PPT in *chronic* LBP patients may reflect *local*, *regional* or *remote* neurophysiologic mechanisms.[128,144] Past studies have reported mixed results on changes in PPT after SMT related to the anatomical site of the applied mechanical stimuli in healthy and low back pain subjects.[145-148,159] Studies in *healthy*, *asymptomatic* subjects examining the effects of SMT on PPT reported *significant* changes in PPT at local, regional, and remote sites[159] along with conflicting results reporting *no significant* change in PPT at a local site.[146] Investigations in *low back pain* patients evaluating the effects of SMT on PPT described *no significant* changes in PPT at regional locations[145,148], while other studies reported *significant* changes in PPT at a local site.[145,147] Presently, it is unclear whether SMT can reduce PPT in chronic LBP, and if it does, which pain pathway, local or central, is responsible for changes in PPT. Until these questions are answered, it is neither possible to establish objective neurophysiological evidence of the mechanisms of SMT, nor to gain ubiquitous acceptance of SMT among the scientific and healthcare communities.[124,125] The *long-term goal* of our study is to improve the understanding of

the biological mechanisms associated with spinal manipulation. *The overall objective of this research is to examine the effect of SMT on PPT at different anatomical sites and clinical outcomes. Its central hypothesis is that SMT will reduce hypersensitivity to mechanical stimuli applied at local, regional and remote sites and improve clinical outcomes in chronic non-specific low back pain patients*. We will meet the overall objective through four specific aims described in the following:

Specific Aim #1: To investigate the effect of SMT on pressure pain threshold in chronic non-specific low back pain patients. (Chapter 2)

Primary Hypothesis: Experimental spinal manipulation group will demonstrate a significantly greater increase in pressure pain threshold at three different body sites than that in the control group. Pressure pain threshold will be measured by a digital algometer at three anatomical sites related to local, regional and remote areas in reference to low back pain.

Specific Aim #2: To investigate the effect of SMT on trunk movements as measured by kinematics of trunk in chronic non-specific low back pain patients. (Chapter 3)

Secondary Hypothesis: Experimental spinal manipulation group will demonstrate a significantly greater improvement in trunk motions than that in the control group. Trunk angular displacement and velocity will be measured using a kinematic measurement system.

Specific Aim #3: To investigate the effect of SMT on clinical outcomes in chronic non-specific low back pain patients. (Chapter 2)

Secondary Hypothesis 2: Experimental spinal manipulation group will demonstrate a significantly greater improvement in clinical outcomes than that in the control group. Clinical outcomes will be measured by the Numerical Pain Rating Scale and the Oswestry Disability Index.

Specific Aim #4: To investigate the relationship between SMT-induced changes in biological outcome measures in the intervention group. (Chapter 4)

Secondary Hypothesis 3: Following SMT, there will be a significant correlation between the change in clinical scores and change in pressure pain threshold.

Secondary Hypothesis 4: Following SMT, there will be a significant correlation between the change in kinematics and change in pressure pain threshold.

CHAPTER 2:

Effect of Spinal Manipulative Therapy on Mechanical Pain Sensitivity in Patients with Chronic Non-Specific Low Back Pain: A Randomized, Controlled Trial

2.1 Abstract

The *long-term* goal of our study is to improve the understanding of the biological mechanisms associated with spinal manipulative therapy (SMT). This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with chronic non-specific low back pain (CNSLBP). We examined the effect of SMT on clinical outcomes and pressure pain threshold (PPT) at different anatomical sites. We screened 51 individuals for the study and 29 (n = 29) signed an informed consent form agreeing to participate. Our findings suggest that SMT and sham SMT reduced hypersensitivity (increased PPT) at local and regional anatomical sites at 3-weeks, as shown in a significant main effect for time. Furthermore, a significant main effect for time was observed for reduced pain and disability. However, no between-group differences were observed in measures of PPT, clinical pain, or disability over the three weeks of the study between the SMT and sham SMT groups. In summary, our findings indicate that SMT or sham SMT may influence peripheral and/or central pain pathways in CNSLBP patients, independent of *how* the spinal manipulation was applied.

Keywords: Manipulation; Spinal; Manual Therapy; Low Back Pain; Pain Threshold; Treatment Outcome

2.2 Introduction

Low back pain affects up to 85% of the adult population imposing an economic burden of $86 billion annually *or* 1% of the United States gross domestic product.[10-12] Chronic low back pain (pain duration > 3 months), although only accounting for 5% of those with low back pain, represents 75% of the total treatment costs.[10,11] Present clinical practice guidelines recommend spinal manipulative therapy (SMT) as a *primary* intervention for low back pain.[2-4] SMT may reduce pain and disability in chronic low back pain patients.[5,6] However, a systematic review concluded that improvement in pain and function following SMT, in comparison with other interventions, might *not* be considered clinically relevant due to limited level of improvement and small effect size.[7]

Researchers have investigated changes in pressure pain threshold (PPT) in an attempt to understand *how* and *why* SMT impacts peripheral and/or central biological pathways in low back pain, but the findings have not been conclusive.[128,134,144] PPT testing may be used as an indirect measure of peripheral and/or central sensitization for musculoskeletal pain.[46] Peripheral and central sensitization may be differentiated by comparing experimental pain responses at sites *local* and *remote* to the primary area of injury.[126,127] Peripheral mechanisms such as sensitization of tissue nociceptors may elucidate *local* tissue hyperalgesia, while central sensitization reflects widespread hyperalgesia at *remote* anatomical locations.[127] SMT may influence peripheral tissue hyperalgesia through decreased sensitivity within muscles spindles[45,128] and central sensitization of dorsal horn neurons through the descending inhibitory pain mechanism (DIPM) via the periaqueductal gray (PAG) region.[134,137-141] Depending on the measurement site, the examined effect of SMT on PPT in *chronic* LBP patients may reflect *local*, *regional* or *remote*

neurophysiological mechanisms.[128,144] Past studies have reported mixed results on changes in PPT after SMT related to the anatomical site of the applied mechanical stimuli in healthy and low back pain subjects.[145-148,159] Studies in *healthy*, *asymptomatic* subjects examining the effects of SMT on PPT reported *significant* changes in PPT at local, regional, and remote sites[159] along with conflicting results reporting *no significant* change in PPT at a local site.[146] Investigations in *low back pain* patients evaluating the effects of SMT on PPT described *no significant* changes in PPT at regional locations,[145,148] while other studies reported *significant* changes in PPT at a local site.[145,147] Presently, it is unclear whether SMT can reduce PPT in chronic low back pain, and if it does, which pain pathway, local or central, is responsible for changes in PPT. Until these questions are answered, it is neither possible to establish objective neurophysiological evidence of the mechanisms of SMT, nor to gain ubiquitous acceptance of SMT among the scientific and healthcare communities.[124,125]

The *long-term* goal of our study is to improve the understanding of the biological mechanisms associated with SMT. As our *primary* objective, we examined the effect of SMT on PPT at different anatomical sites and specific clinical outcomes. Our *central* hypothesis was that SMT would reduce hypersensitivity to mechanical stimuli applied at local, regional and remote sites and improve clinical outcomes in chronic non-specific low back pain (CNSLBP) patients.

2.3 Methods

2.3.1 General Design

This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with CNSLBP (Figure 10). Subjects were

randomly assigned to spinal manipulation (SMT) or sham spinal manipulation (sham SMT) groups. We enrolled 29 (n = 29) subjects out of 51 patients who were assessed for inclusion/exclusion criteria. Clinical evaluations and biomechanical analyses were performed at a university research lab. Prior to starting treatment, each subject underwent physical and neurological examinations. Physical examination procedures included vital signs, orthopedic testing, palpation, and range of motion testing. Neurological examination comprised testing of muscle strength, deep tendon reflexes, pathological reflexes, and sensation.

2.3.2 Participants

We recruited persons with CNSLBP between January 2016 and April 2016 from campuses of two universities. Subjects were screened for fulfilling the inclusion and exclusion criteria. If a subject met these criteria, they were asked to sign an informed consent form approved by the human protection committees of two institutions. Patients with low back pain were included in this study if they met the following criteria: 1) chronic non-specific (> 12 weeks duration) low back pain rated ≥ 3/10 at its worst over the past 24 hours on a numeric rating scale (NRS) (0 = no pain at all, 10 = worst pain imaginable); 2) male or female subjects between the ages of 18 and 60 years; 3) ability to read and understand English; 4) currently not involved in litigation. Chronic low back pain patients were excluded if they reported any of the following criteria: 1) previous low back surgery; 2) severe structural spinal deformity; 3) neurological compromise/spinal cord compression; 4) severe spinal instability; 5) severe osteoporosis/osteopenia; 6) head trauma (recent); 7) spinal infection (recent); 8) known neurological, neuromuscular, systemic or orthopedic problems that might prevent them from participating in manual therapy interventions; 9) pregnancy; 10) obesity; 11) pain or paresthesia below the knees; 12) systemic illness known to

affect sensation i.e. diabetes; 13) acute and/or chronic pain condition unrelated to low back pain; 14) spinal manipulation within the past 4 weeks.

2.3.3 Randomization and Blinding

A computerized random number generator created a random allocation sequence list. Using this list, subjects were randomly allocated to either SMT or sham SMT group. This list was stored in a locked file cabinet with access limited to research personnel. After subject enrollment, a designated research assistant opened the correct numbered, sealed, opaque envelope. Each subject was assigned a unique identification number and the research assistant registered the subject's name and identification number in a log. This was the only information connecting the patient's identifying information with study records. Clinicians delivering the intervention were aware of group assignment, but the assessor was blinded to group allocation. A single assessor evaluated all outcome measures. Also, subjects were blinded to group allocation and advised to avoid discussing study details with the outcome assessor.

2.3.4 Procedures for Clinical Assessment

After signing an informed consent, investigators collected information regarding medications, past medical history, education, and demographic data from each subject. We gathered information related to attendance, medications, adverse events, and treatment sessions during the trial. The study coordinator monitored data quality on a weekly basis. In the event of improper data collection, there was immediate resolution of the recognized irregularity. A clinician

performed a standard physical examination including vital signs and mobility testing. In addition, subjects underwent a neurological examination.

During the baseline evaluation, subjects completed clinical outcome measures capturing pain and self-reported disability. Information related to pain and disability was ascertained through the Numerical Pain rating Scale (NPRS) and Oswestry Disability Index (ODI). Clinical changes over 3-weeks (assessed at pre-first intervention and 3-weeks on visit 7) on measures of pain (NPRS) and disability (ODI) served as clinical outcomes. While using the NPRS, subjects rated their pain intensity using an 101-point scale, with "0" indicating no pain and "100" indicating the worst pain imaginable.[178] The reliability and validity of NPRSs has been established in the scientific literature.[179,180] The ODI is an efficient (~ 10 minutes) and generalizable outcome measure.[181] This self-reported measure consists of ten sections that ask questions about pain and function such as sleeping, self-care, and social life.[182] The reliability and validity of the ODI has been reported in the scientific literature.[182-185] The ODI has been found the most sensitive index to detect an improvement in disability associated with manual therapy, yielding large-sized improvements across many studies.[178,183,184,186] Minimal clinically important difference (MCID) scores for the ODI range from a 5 to 6 point change,[185,187] while the NPRS has a MCID of 1.25[187] points (on an 11-point NPRS scale) or a 27.9% reduction[188] (raw change/baseline x 100) for subjects with chronic low back pain.

2.3.5 Assessment of Pain Sensitivity

During the first visit, CNSLBP subjects underwent *pre* and immediately *post-treatment* pressure pain threshold (PPT) assessment. In addition, subjects underwent PPT assessment at the follow-up visit (visit 7). We determined PPT by applying pressure with a digital algometer

(Wagner Instruments, Greenwich, Connecticut) to three anatomical regions considered as local, regional, or remote. The digital algometer had a 1 cm^2 rubber-tipped probe that was applied perpendicular to skin at a rate of 1 kilogram per second (kg/s).[146] Marks were placed on the belly (middle third) of the dominant tibialis anterior muscle (regional)[145] and dominant lateral epicondyle of the elbow (remote).[136] Also, we marked a point 5 cm lateral to the spinous process of L5 (local) on the dominant side.[145] These three anatomical landmarks for pressure application were been chosen based on high reliability values reported from previous studies.[136,145] Scientific literature has reported using dominant regions[79] for PPT testing, while a systematic review by Millan et al[128] reported that SMT consistently demonstrates a bilateral hypoalgesic effect. Thus, we selected the dominant-side for PPT testing.

Subjects were asked to say "stop" the moment the sensation changed from feeling *pressure* to feeling *pain*. The pain threshold was defined as the least pressure intensity at which subject's perceived pain. The pressure threshold in kilograms (kg) causing the perception of pain was recorded for data analysis. Three measurements were collected for each anatomical region with 30 seconds of rest in between pressure applications. The mean value of the three threshold measurements was used for data analysis.[145,146] Before testing, each subject received three practice measurements with pressure applied to the dorsal aspect of their dominant hand.[146] Previous scientific literature has demonstrated the rest-retest reliability of PPT measurements.[145,189,190] Prior to data collection, an assessor blinded to group allocation undertook training with the digital algometer to ensure adherence to the specified rate of pressure application and cessation of pressure.[146,190] PPT has been used in previous clinical trials as an outcome measure for response to spinal manipulation.[79,100,128,136,144,147,148,191] Previous scientific literature has established that a 15% reduction in PPT may be considered a clinically relevant change.[157,192]

2.3.6 Treatment Protocols

After completion of the screening and baseline assessments, both the SMT and sham SMT groups commenced the assigned treatment protocols. The SMT and sham SMT procedures were administered and supervised by licensed clinicians. Subjects received three treatments per week for two consecutive weeks (6 treatments) with one additional follow-up visit less than 1-week post-intervention (visit 7). A written log of attendance, medications, health changes, and injuries/adverse events was maintained for each subject. Subjects were required to attend at least 80% (5 of the 6) of the clinical sessions during the study. If attendance was < 80%, the subject's data was not analyzed for this study because our aim was to investigate the explanatory effects of SMT.

2.3.7 Manual Interventions

SMT involved the patient lying supine with the spine in a position of lateral bending and rotation followed by a high-velocity low-amplitude force applied to the lumbopelvic region (Figure 11). This SMT procedure has demonstrated clinical efficacy in previous clinical trials involving low back pain patients.[193-196] This treatment protocol adheres to current United States clinical practice guidelines for managing low back pain with SMT.[197] Thus, a 2-week (6 treatments) intervention appears sufficient to determine the potential effects of SMT in chronic non-specific low back pain patients. As reported in previous studies,[78,79,99] each subject received

two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides.

Previous clinical trials have used placebo SMT or sham SMT as a comparison group.[79,198,199] Sham SMT placed the patient in the supine position, but without accompanying lateral bending and rotation of the spine (neutral spine position) followed by a high-velocity low amplitude force applied to the table (Figure 11). As reported in previous studies,[78,79,99] each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides. Both the lumbopelvic SMT and sham SMT procedures were administered by two licensed clinicians (physical therapist and/or chiropractor) with greater than 8 years of manual therapy experience.

2.3.8 Data Analyses

We used individual *t*-tests and chi-square tests to assess for post-randomization group differences in demographic measures, clinical measures, and pain sensitivity measures. We set our significance at .05 and performed all analyses using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL).

Our primary aim consisted of investigating the effect of SMT on PPT in CNSLBP patients. We checked for normality (Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test). Based on meeting the assumption of normality, we used a mixed analysis of variance to test for a group (SMT, sham SMT) x time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction for pressure pain threshold. Interaction terms may be considered comparable to the *between*-group differences or the effect of the intervention. If testing revealed a significant group x time interaction, we performed contrasts to determine *within*-group changes.

We tested *within*-group pressure pain threshold differences using a paired-samples *t*-test. We repeated these same measures for each pressure pain testing location (lumbar paraspinal musculature, elbow lateral epicondyle, and tibialis anterior muscle).

Our secondary aim consisted of investigating the effect of SMT on clinical outcomes in CNSLBP patients. We checked for normality (Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test). Based on meeting the assumption of normality, we used a mixed analysis of variance to test for a group (SMT, sham SMT) x time (pre-first intervention to 3-weeks) interaction for clinical outcomes (NPRS and ODI). If testing revealed a significant group x time interaction, we performed contrasts to determine *within*-group changes. We tested *within*-group (pre- and post-intervention) clinical differences using a paired-samples *t*-test.

2.3.9 Sample Size Estimation

Our primary aim was to examine the changes after SMT in pressure pain threshold examined at a three different body sites. Bialosky et al[78] reported an effect size (Cohen's d) of 1.20 on thermal pain threshold measured on upper limb after spinal manipulation in comparison to a control group. We assumed that the pressure pain threshold measured at the upper limb may show similar changes after our SMT intervention compared to the control group. Assuming 80% statistical power and .05 alpha level, a sample size of 12 was required for each group in our study. Presuming a drop-out rate of 20%, we needed to recruit a total of 30 subjects.

2.4 Results

2.4.2 Baseline Demographics and Characteristics

We screened 51 individuals for the study and 29 (n = 29) signed the informed consent form (Figure 10). Within our sample 38% of the subjects were females with a mean age of 23.86 (SD = 5.74) years (Table 5). Individual groups did not differ by baseline demographic measures, clinical measures, or pain sensitivity measures.

2.4.2 Pain Sensitivity

We did not observe group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) differences in PPT assessed at the dominant-side lumbar paraspinal musculature ($p = .76$) (Table 6). However, we observed a significant main effect for time with PPT at the lumbar paraspinal musculature ($p < .01$) *Post-hoc* pairwise comparisons revealed significant ($p = .049$) within-group differences from pre-first intervention to 3-weeks (Figure 12). We did not observe group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) differences in PPT assessed at the dominant-side lateral epicondyle ($p = 0.93$) nor did we observe a main effect for time ($p = .11$). We did not observe group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) differences in PPT assessed at the dominant-side tibialis anterior muscle ($p = .68$). However, we observed a significant main effect for time with PPT at the tibialis anterior muscle ($p < .01$). *Post-hoc* pairwise comparisons revealed significant ($p = .013$) within-group differences from immediately post-first intervention to 3-weeks. (Figure 13)

2.4.3 Clinical Outcomes

We did not observe a significant group (SMT, sham SMT) × time (baseline to 3-weeks) interaction for low back pain over the 3-weeks of the study ($p = .75$). However, we observed a significant main effect for time with low back pain ($p < .001$). Regardless of group assignment, we observed a mean decrease in low back pain of 11.64 (SD = 14.11) across subjects in the study. We did not observe a group (SMT, sham SMT) × time (baseline to 3-weeks) interaction for low back pain-related disability ($p = .84$). However, we observed a significant main effect for time with disability ($p < .05$). Regardless of group assignment, we observed a mean decrease in low back pain-related disability of 2.64 (SD = 5.55) across participants in the study.

2.5.1 Additional Outcomes

We recorded additional clinical information including adverse events, change in medication, spinal joint cavitation, onset of new injuries/exacerbations, and believability of group assignment. A single adverse event of transient (< 48 hours) local, mild joint discomfort was reported in the SMT group, while participants in the sham SMT group related no adverse events during the clinical trial. In addition, no changes in medication were conveyed for participants in either group throughout the study.

As reported by clinician perception, spinal joint cavitation occurred at 60% (47/78 occasions) and 2.2% (2/90 occasions) frequencies in the SMT and sham groups, respectively. For the sham SMT group, 8/15 (53.3%) of subjects reported an exacerbation of low back pain related to activity at 3-week follow-up session, while only 3/13 (23.1%) of subjects in the SMT group reported an exacerbation during the trial. Based upon a two-sample test for proportions, there was no significant difference ($p = .778$) between the groups for subjects who felt they received an active

form of treatment. Within the SMT group, 38.5% of participants believed that they received an active form of therapy, while 33.3% of subjects in the sham group thought that they received active treatment. Thus, our results indicate that we achieved adequate blinding for both groups and knowledge of treatment did not likely affect outcomes since both groups were similar in perception that they received an active form of intervention.

2.5 Discussion

2.5.1 Pain Sensitivity

As outlined, our primary aim was to investigate the effect of SMT on PPT in chronic non-specific low back pain patients, thereby exploring the neurophysiological mechanisms associated with SMT. We tested PPT at three anatomical locations including the lumbar paraspinal musculature[145] (local), tibialis anterior muscle[145] (regional), and lateral epicondyle of the elbow[136] (remote). The application of a mechanical stimuli across multiple anatomical regions following SMT may help to differentiate the biological pathways, peripheral and/or central, associated with pain modulation following SMT. The current investigation embodied a novel design by examining the effects of SMT on PPT across *multiple* anatomical testing locations (local, regional, and remote) in *chronic* non-specific low back pain patients.

Based upon our findings, both SMT and sham SMT reduced hypersensitivity (increased PPT) at a local anatomical site from pre-intervention to 3-weeks. In addition, both SMT and sham SMT reduced hypersensitivity at a regional location from post-first intervention to 3-weeks. Our results are similar to some previous studies[135,136,147,159] that reported reduced hypersensitivity to mechanical stimuli following SMT. Yu et al[159] reported that lumbopelvic SMT performed on

asymptomatic volunteers produced an immediate, significant reduction in hypersensitivity at local, regional, and remote anatomical locations, thus signifying local and widespread hypoalgesia.

Scientific models acknowledge that the neurophysiological effects associated with SMT comprise three fundamental pathways.[46] These neural pathways reflect SMT influences within *local tissues* along with *spinal cord* and/or *supraspinal* pathways.[46] Pain-reducing effects of SMT at the local tissue level (peripheral pathways) may be the result of decreased sensitivity within muscles spindles.[45,128] According to Clark et al,[129] the "pain-spasm-pain" model of CLBP advocates that pain produces muscular overactivity, thereby causing pain. The pain-spasm-pain model postulates that a hyperactive spinal stretch reflex establishes the basis of the cycle.[129,130] Specifically, stimulation of nociceptive afferents may influence the gamma-motoneurons increasing the sensitivity of muscles spindles to stretch, thereby exciting alpha-motoneurons.[129,130] Subsequently, this excitation of alpha-motoneurons leads to increased muscle activation.[129,130] SMT may alter the pain-spasm-pain cycle by modulating nociception and subsequently attenuating the muscle stretch reflex, thus reducing muscle activity.[129] A short-latency stretch reflex ensues following rapid stretch of a muscle, thus exciting Ia afferents within the muscle spindles.[129] Clark et al[129] found that SMT alters the short-latency stretch reflex within the erector spinae muscles. According to Clark et al,[129] SMT functions mechanistically by modulating the sensitivity of muscle spindles within the erector spinae muscles, thereby influencing local nociception. In addition, scientific evidence from animal models substantiates the stimulation of primary afferents in the spinal tissues following SMT.[45,58,59,82,83,93,131]

Secondly, pain-reducing effects of SMT may be influenced by effects on the spinal cord, specifically the dorsal horn.[78,79] Dorsal horn neurons with receptive fields in the lumbar paraspinal tissues receive more convergent information from types III and IV afferents compared to dorsal

horn neurons with receptive fields in the extremities.[125,132] In addition, nociceptive neurons within the superficial dorsal horn of the spinal segments communicate with receptive fields with the deep and superficial tissues of the lumbar spine and *lower extremities*.[125,132] Thus, segmental innervation from the lumbar spine includes tissues in the lower extremities.[125] After nociceptive neurons project to the dorsal horn, they diverge into ascending and descending fibers forming the dorsolateral tract of Lissauer.[133] According to Purves et al,[133] axons in the Lissauer tract project caudal and cephalad one or two spinal cord segments prior to entering the grey matter of the dorsal horn. Presuming a sufficient duration to transition from an acute to chronic pain condition, SMT may influence regional or referred pain by removing subthreshold mechanical stimuli from paraspinal tissues through pain gate mechanisms.[45,127,128,134]

Scientific literature supports that SMT may influence central sensitization of dorsal horn neurons through supraspinal pathways including the descending inhibitory pain mechanisms (DIPM) via the periaqueductal gray (PAG) region.[134-141] Savva et al[134] suggested that activation of the PAG modulates nociception at the spinal cord, thus producing an analgesic effect on musculoskeletal pain. Within the neural pathways from the PAG to the spinal cord, distinct descending systems exist including non-adrenergic and serotonergic control systems.[134,140,141] The noradrenergic system uses noradrenaline to inhibit *mechanical* stimuli, while the serotonergic system uses serotonin to raise the *thermal* nociceptive threshold.[134,140,141] Also, the noradrenergic descending system instigates excitation of the sympathetic nervous system, while the serotonergic system triggers sympathoinhibition.[134] Scientific literature from animal models reveals altered mechanical withdrawal thresholds in *remote* anatomical regions following manual therapy suggesting a central influence on sensory processing via the DIPM.[137,140-142] Specifically, activation of the DIPM following SMT may inhibit nociceptive afferent input at the spinal cord

producing hypoalgesia, thereby increasing pressure pain threshold.[128,134,139] According to Skyba et al,[137] blockage of non-opioid receptors at the spinal cord prevented the hypoalgesic effect of manual therapy at a *remote* site using an animal model. In contrast, blockage of opioid receptors at the spinal cord did not influence the anti-nociceptive effect of manual therapy.[137] Thus, activation of the DIPM, which uses noradrenaline and serotonin, produced the mechanical hypoalgesia that followed application of manual therapy to a remote site.[134,137] Because manual therapy produced mechanical hypoalgesia at location remote to the site of injury, this limits the likelihood that SMT could facilitate recovery or alter the chemical environment of the injured region.[134] Thus, central neural mechanisms including the DIPM appear to stimulate the hypoalgesic effect associated with SMT.[134]

Depending on the measurement site, the examined effect of SMT on pressure pain threshold in CLBP patients may reflect local tissue, spinal cord and/or supraspinal biological pathways.[144] Previous studies testing the consequences of *lumbopelvic* manipulation on pain sensitivity have reported applying stimuli to *local*, *regional*, and/or *remote* anatomical locations.[78,79,99,145-148] Coronado et al[144] published a systematic review and meta-analysis that concluded future research designs should include *multi-regional* application of stimulus following SMT to differentiate local, specific effects versus general hypoalgesia. Hypoalgesia at a *local* testing site following SMT might modulate pain via stimulation of peripheral muscle spindles and/or central segmental reflex pathways.[128,129] A *regional* testing site might be considered an anatomical region within the same or overlapping dermatomes as those influenced by SMT.[99] For example, testing for hypoalgesia following lumbopelvic manipulation only in anatomical locations innervated by lumbosacral nerve roots.[79,145] George et al[99] reported that pain sensitivity testing *only* at remote anatomical locations cannot distinguish whether or not the hypoalgesia following

SMT is a large, general effect or a specific effect localized to the spinal levels associated with the manipulation. Also, paraspinal muscle reflexes along with motoneuron excitability may be influenced by SMT, perhaps affecting reflex neural output to spinal musculature.[45,128] Thus, modulation of PPT at regional sites following SMT seems likely modulated through central neural mechanisms, however peripheral mechanisms may also influence the regional pain effects of SMT.[45,128] A systematic review and meta-analysis concluded that increased PPT at *remote* anatomical sites suggests a general or widespread effect of SMT on central sensitization.[144] In addition, evidence from fMRI imaging suggests that reduced PPT (i.e., hyperalgesia) at a *remote* site indicates a *central*, rather than peripheral, cause for CLBP.[149]

As discussed, multi-regional application of stimulus following SMT may help to distinguish the biological pathways associated with pain modulation following SMT. For example, changes in pain sensitivity over the upper extremity (remote site) following lumbopelvic SMT, but not at the paraspinal musculature (local site), might suggest a general effect of SMT on central sensitization via descending inhibitory pain mechanisms (DIPM). Alternatively, a change in pain sensitivity over the paraspinal musculature (local site) following lumbopelvic SMT, but not at the upper extremity (remote site) or lower extremity (regional site), might imply a specific, local effect of SMT via stimulation of peripheral muscle spindles.

To our knowledge, this paper represents the first investigation reporting the effects of SMT on PPT across local, regional, and remote locales in CNSLBP patients. In addition to quantifying the immediate (< 30 minutes) effects of SMT on PPT, our novel design measured the effects of repeated (6 interventions) SMT on PPT at 3-weeks. In our study, we did not find immediate or 3-week hypolagesia at a remote testing site, implying that SMT may not have a significant widespread hypoalgesic effect on CNSLBP patients.[99] In addition, our findings of 3-week

hypoalgesia at local and regional sites advocates that SMT may diminish sensitivity within local muscles spindles and/or influence the dorsal horn by means of the removal of subthreshold mechanical stimuli via pain gate mechanisms.[45,79,127,128,134] Based upon previous scientific literature,[79,127,128] our findings of local and regional hypoalgesia infer a *primarily* central-mediated analgesic effect of SMT at the spinal cord, but peripheral mechanisms cannot be excluded from modulating spinal pain. Similar to our results, a previous study reported a local hypoalgesic effect following lumbopelvic SMT in *healthy* subjects, but no significant widespread hypoalgesic effect on a remote testing site (cervical spine).[99]

Hypolagesia at 3-weeks post-SMT suggests a prolonged analgesic effect beyond the brief, immediate period post-intervention reported by previous investigations.[99,147,159] Boal and Gillette[89] suggested that SMT may produce hypoalgesia through stimulation of mechanosensitive afferents that modulate pain via central-mediated pathways. Long-term depression (LTD), initiated by the activation of mechanosensitive afferents, may reverse long-term potentiation (LTP) in dorsal horn neurons through neuronal plasticity.[89] LTD may influence dorsal horn neurons for protracted time intervals, thereby mitigating spinal pain for minutes or hours, and perhaps even for days or weeks.[89] Accordingly, our findings of SMT-induced hypolagesia at 3-weeks implies that manual therapy may modulate pain for an extended period of time through central-mediated neuronal plasticity.

However, interpretation of our results requires a caution. It appears that our SMT and sham SMT had a similar effect on PPT at 3-weeks post-intervention. The sham SMT has been previously reported effective in blinding participants.[79] Bialosky et al[79] compared the effects of SMT in low back pain patients to placebo SMT, "enhanced" placebo SMT, and control groups. Although not significant, Bialosky et al[79] reported limited, immediate hypoalgesia to mechanical stimuli applied

to the posterior superior iliac spine after low back pain subjects received SMT, sham SMT and enhanced sham SMT. The sham SMT used for our experimental design aimed to apply a thrust into the table with the spine positioned in neutral (without trunk lateral bending), unlike the SMT procedure that applied a thrust into rotation with accompanying trunk lateral bending. Bialosky et al[79] conceded that the sham SMT applied a *mechanical load* to the spine. Scientific models associated with SMT postulate that a *mechanical stimulus* may elicit a cascade of potential neurophysiological effects, thereby accounting for the therapeutic benefits associated with manual therapy.[45,46,72] Our findings that both SMT and sham SMT produced hypoalgesia at sites local and distant to the region of pain indicated that the application of a *mechanical load* to the spine elicited a neurophysiological response, but suggests less importance on *how* the force is applied.

Our outcomes indicate a small, but potentially clinically relevant change in PPT following SMT in CNSLBP patients. At 3-weeks post-intervention, the SMT group demonstrated a 15.2% (± 1.75 SE) increase (hypoalgesia) in PPT at the local site, and a 19.7% (± 2.11 SE) increase in PPT at the regional location (Figure 14). Consequently, both of these PPT testing locations reached the 15% change in threshold established as clinically relevant for patient populations.[157] However, at 3-weeks post-intervention, both the SMT and sham SMT groups failed to achieve at least a 15% increase in PPT at the remote location, while the sham SMT group did not meet the established clinical threshold at the local (12.5%) and regional (9.4%) locations. Also, immediately post-first intervention (Figure 15), both intervention groups did not realize the 15% clinically relevant threshold at any of the three PPT testing locations (local, regional, and remote).

2.5.2 Clinical Outcomes

Similarly, our results did not show group-related differences, but a main effect for time in measures of clinical pain and disability over the three weeks of the study. Despite some past clinical trials[5,6] reporting that SMT appears efficacious for managing low back disorders, our results were similar to a previous clinical trial.[79] Bialosky et al[79] did not observe group-related differences over a 2-week study examining the effects of SMT on clinical pain and disability. However, a significant main effect for time was observed for reduced pain and disability.[79] They cautioned that the design of their trial may have been underpowered to detect clinical treatment effects since their number of subjects were limited across four arms (total n = 110 or ~ 27 per group). Based upon our *post-hoc* analyses, we obtained an observed power value < 80% for clinical outcomes (NPRS and ODI) between-subjects effects, thus we acknowledge the possibility of a type II error.

Our results signified small, but potentially meaningful changes in patient-rated outcomes. A reduction of 14.3 points (or 1.43 points on an 11-point NPRS scale) in the NPRS score within the SMT group met the MCID of 1.25[187] points for low back pain patients (Figure 16). However, a reduction of 9.33 points (or 0.933 points on an 11-point NPRS scale) in the NPRS score within the sham SMT group indicated a score below the stated MCID threshold. Alternatively, the SMT group demonstrated a 34.9% reduction in the NPRS score, thereby meeting the MCID of 27.9% reduction[188] (raw change/baseline x 100) for CLBP patients. Again, the sham SMT group failed to achieve the defined MCID with a reduction of 25.3% in the NPRS score. There were 6 (46.2%) subjects in the SMT group and 7 (46.7%) in the sham SMT group that had a pain reduction greater than the MCID.

2.5.3 Limitations

Pressure may be considered a non-specific stimuli that elicits a response from mechanoreceptors and nociceptors in surrounding tissues.[200] Pressure pain threshold (PPT) may be used as an *indirect* measure of peripheral and central sensitization for musculoskeletal disorders.[46] In addition, a slow, gradual application of pressure until a pain threshold is reached might reflect a different neural pathway than rapidly applied stimuli.[200] This investigation only examined the effect of SMT in response to mechanical stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT.

The placebo SMT used for our experimental design aimed to apply a thrust into the table with the spine positioned in neutral (without trunk lateral bending). However, our sham SMT produced improvements in clinical and neurophysiological outcome measures. Bialosky et al[79] conceded that this sham SMT applied a *mechanical load* to the spine. Thus, a *mechanical stimulus* following sham SMT may elicit a cascade of potential biological effects, thereby accounting for the therapeutic effects associated with our sham intervention.[45,46,72] Therefore, our results suggest that the application of a mechanical load to the spine elicited a neurophysiological response, but *how* the load is applied appears less important.

There may be potential bias in the recruited sample, especially for a small sample. Scientific literature has suggested that within low back patients there may be sub-groups that respond differently to specific interventions.[19,193] For example, a clinical decision rule outlining acute low back patients likely to respond to spinal manipulation reported several predictor criteria, including symptom location (proximal to knee).[193] As an attempt to adhere to predictors of response to spinal manipulation, our study criteria limited the sample population to CLBP with *no distal* symptoms.

In addition, the mean age of our sample at 23.86 (± 5.74) years may not be representative of the CNSLBP population. Previous scientific literature has reported the mean ages of CNSLBP patients seeking SMT ranging from 31.68 (± 11.85)[79] to "middle-aged".[7] Thus, our study sample may have been younger than reported in previous studies examining the effects of SMT, perhaps limiting the generalizability of our results. However, our baseline pain (NPRS) and low back-related disability (ODI) values across both study groups were similar to a previous study[79] investigating the effects of SMT on pain sensitivity.

This study may have been more clinically meaningful if we had monitored our subjects at some further time interval (6 months or 1 year). Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, long-term follow-up may have provided us with a more consequential measure of the effect of SMT on CNSLBP, thereby contributing to the development of more comprehensive evidence-based practice guidelines for managing low back disorders.

2.5.4 Future Directions

Based upon our study results, the biological mechanisms associated with SMT appear multifaceted and complex. Thus, we propose additional extensions of this body of work to address these complexities. Though the effectiveness of SMT on clinical outcomes has been previously investigated, there remains controversy as to the suitable dosage of SMT for low back disorders. Future investigations may study the effect of dosage on biological outcome measures to determine appropriate or optimal prescriptions. Also, our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations

manifest over a longer duration. Thus, future studies should include longer-term follow-up of biological outcomes, thereby improving the clinical applicability of the effects of SMT on spinal disorders. This investigation only examined the effect of SMT in response to *mechanical* stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT. According to Coronado et al,[144] limited investigations have combined more than one stimulus modality. By implementing this, future research could determine whether SMT alters modality-specific sensitivity.[144]

2.5.5 Conclusions

Following a 3-week course of SMT or sham SMT in CNSLBP patients, we found hypoalgesia at local and remote sites along with improved pain and low back-related disability. However, there was no difference between the two interventions in terms of PPT or clinical outcomes (NPRS and ODI) indicating that the *method* of SMT force application might be irrelevant to the outcomes. Overall, the current study contributes to the understanding of the biological mechanisms associated with pain modulation following neurophysiological stimulation of the spine in CNSLBP subjects by indicating that hypoalgesia may be related to peripheral and/or central pain pathways.

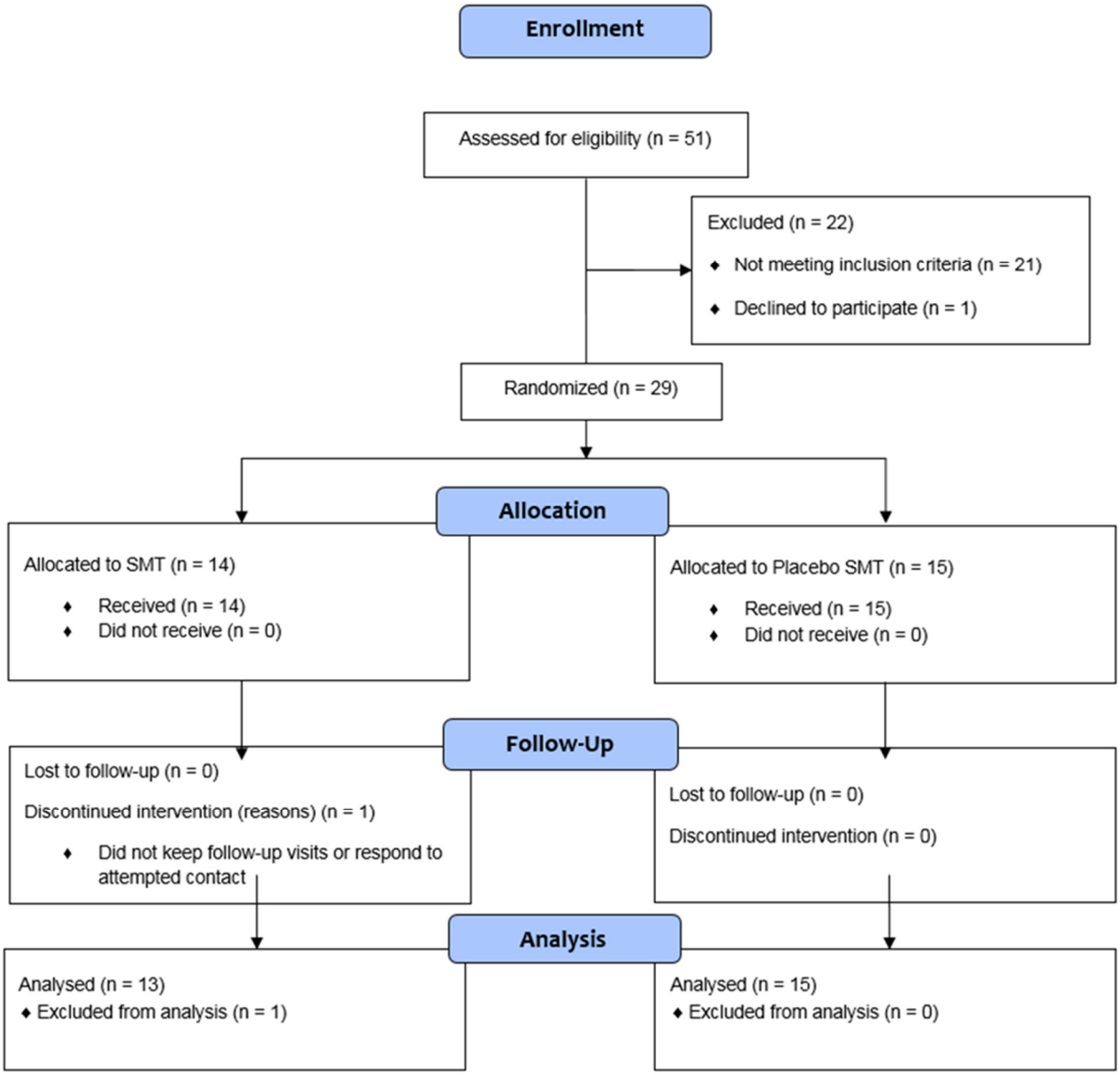

Figure 10: Overview of recruitment, enrollment, randomization, follow-up, and analysis for study. SMT = spinal manipulative therapy.

A. SMT B. Placebo SMT

Figure 11: Spinal manipulative therapy and sham spinal manipulative therapy.[79]

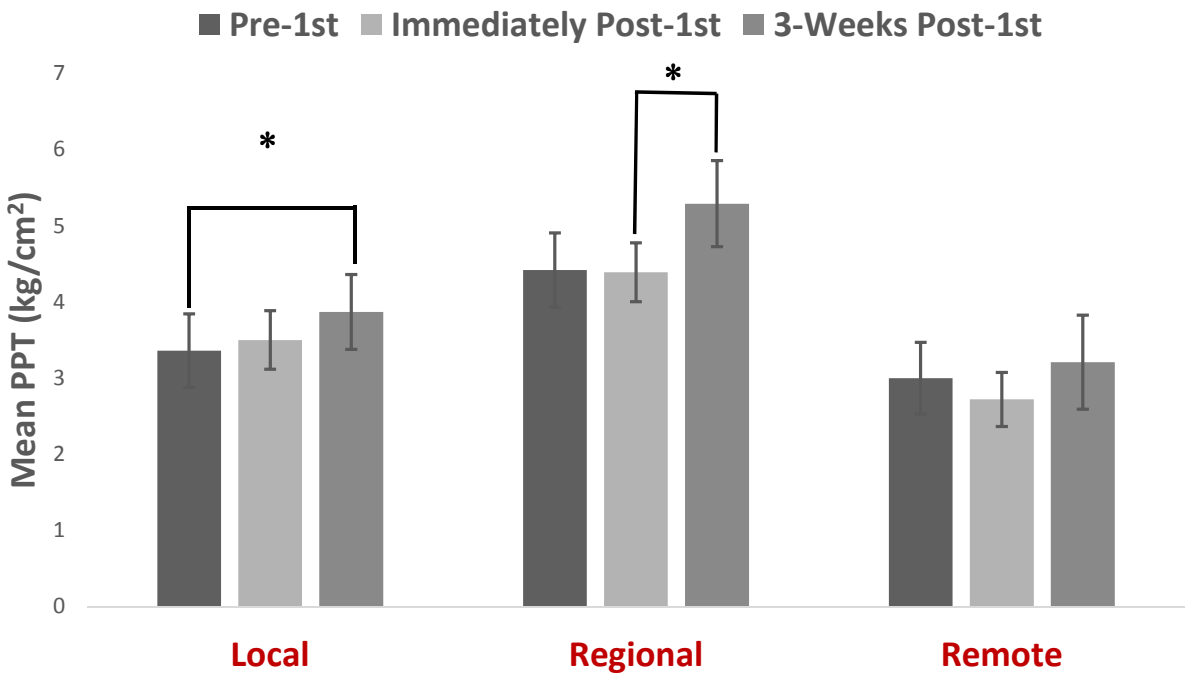

Figure 12: Change in PPT from pre-1st intervention to immediately post-1st intervention and 3-weeks post-1st intervention for the *SMT* group at local, regional, and remote testing locations. We observed a significant main effect of time at the local and regional testing sites, but neither outcome was dependent upon group assignment. SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. Error bars = standard error. *significant *within*-group differences ($p < .05$).

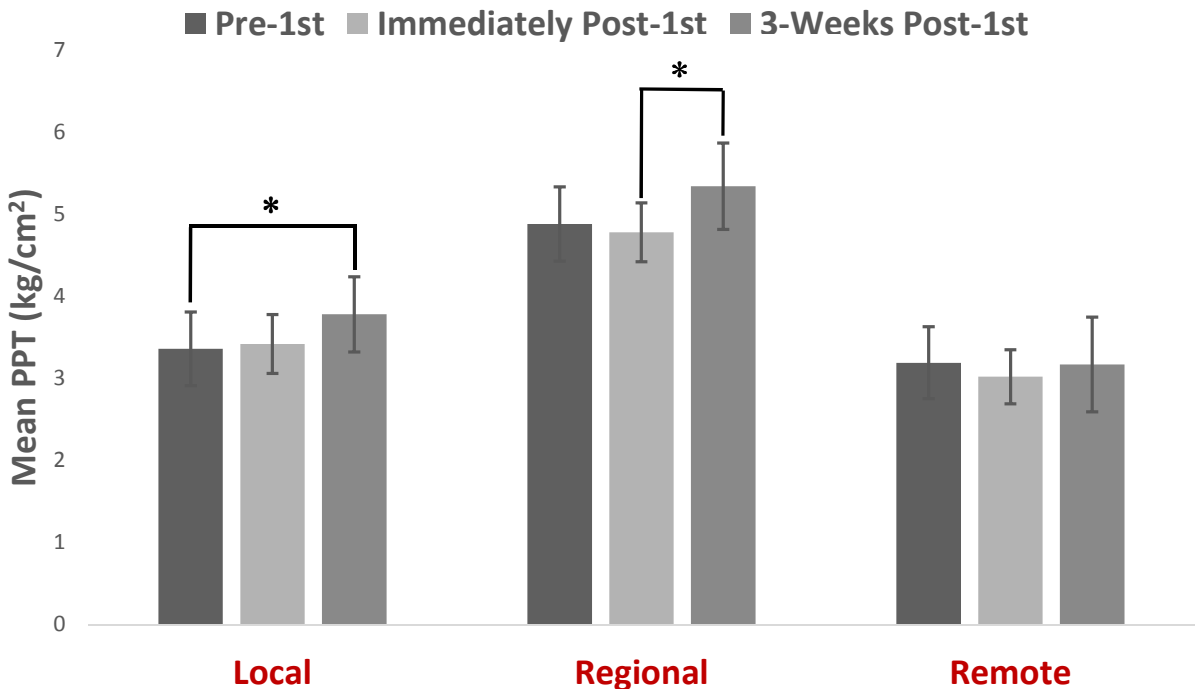

Figure 13: Change in PPT from pre-1st intervention to immediately post-1st intervention and 3-weeks post-1st intervention for the *sham* SMT group at local, regional, and remote testing locations. We observed a significant main effect of time at the local and regional testing sites, but neither outcome was dependent upon group assignment. SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. Error bars = standard error. *significant *within*-group differences ($p < .05$).

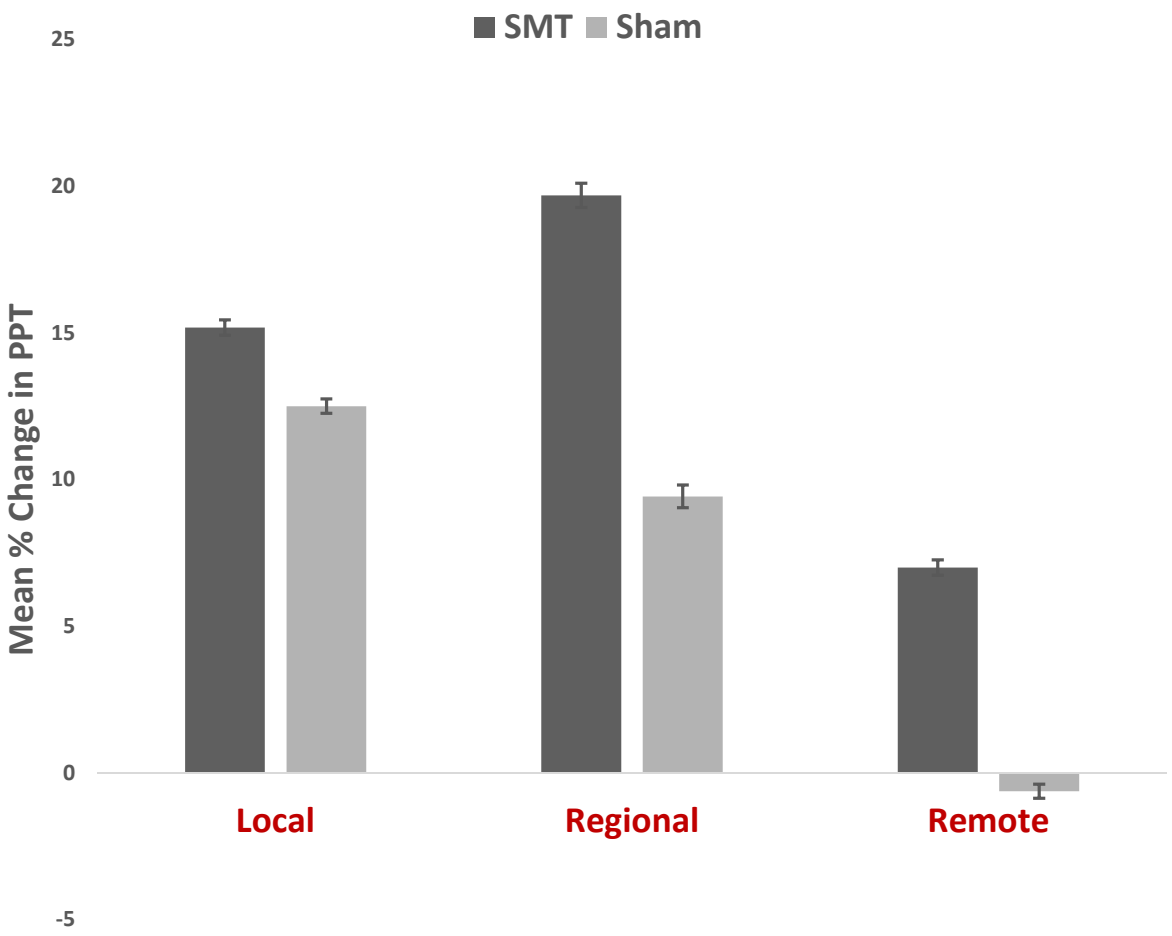

Figure 14: Mean percentage change in PPT from pre-1st intervention to 3-weeks post-1st intervention for chronic non-specific low back pain subjects at local, regional, and remote testing locations. For *within-group* comparisons, negative values indicate reduced PPT (hyperalgesia), while positive values indicate increased PPT (hypoalgesia). A 15% change in PPT may be considered clinically relevant.[157] SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. Error bars = standard error.

Figure 15: Mean percentage change in PPT from pre-1st intervention to immediately post-1st intervention for chronic non-specific low back pain subjects at local, regional, and remote testing locations. For *within-group* comparisons, negative values indicate reduced PPT (hyperalgesia), while positive values indicate increased PPT (hypoalgesia). A 15% change in PPT may be considered clinically relevant.[157] SMT = spinal manipulative therapy. PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. Error bars = standard error.

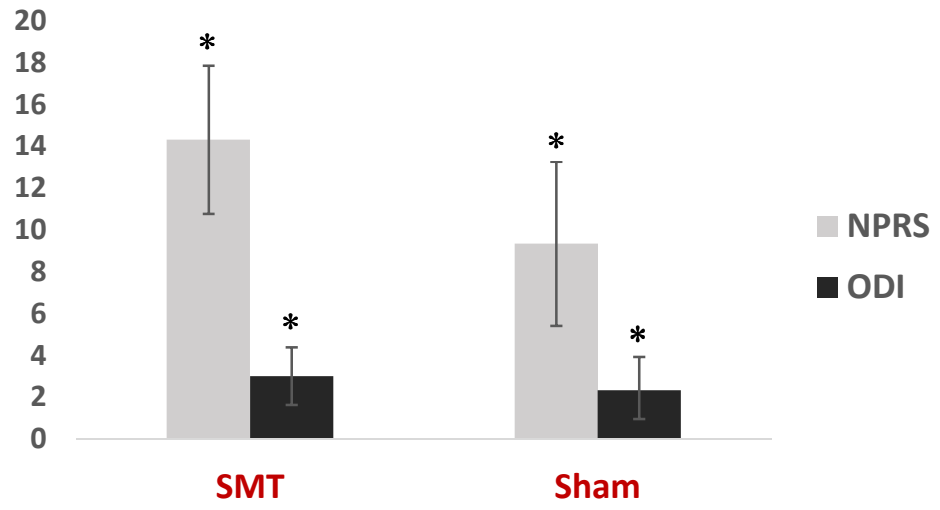

Figure 16: 3-week mean change in low back-related pain intensity and disability. Bars signify change in scores (pre-first intervention to 3-weeks post-intervention) with positive numbers on the y-axis signifying declining pain and disability following intervention. We observed a significant main effect of time for pain and disability, but neither clinical outcome was dependent upon group assignment. NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). ODI = Oswestry Disability Index (0 – 100% with smaller numbers representing less disability). *significant *within*-group differences ($p < .05$). SMT = spinal manipulative therapy. Error bars = standard error

Table 5. Baseline Comparison of Intervention Groups.

	SMT	*Sham*	*Total Sample*	*p-value for difference*
Gender (% female)	6/14 (43)	5/15 (33)	11/29 (38)	.60
Age (years)	24.29 (7.33)	23.47 (3.94)	23.86 (5.74)	.71
Education (years)	17.00 (1.92)	17.20 (1.47)	17.10 (1.68)	.76
Duration of LBP (months)	45.07 (29.77)	43.00 (27.40)	44.00 (28.07)	.85
ODI	15.93 (6.23)	15.07 (6.79)	15.48 (6.91)	.74
NPRS	41.64 (12.70)	36.87 (17.25)	39.17 (15.15)	.41
PPT Local	3.39 (2.02)	3.36 (1.36)	3.37 (1.68)	.96
PPT Regional	4.36 (1.78)	4.88 (1.71)	4.63 (1.74)	.44
PPT Remote	2.95 (1.33)	3.19 (1.55)	3.08 (1.35)	.64

All data reported as mean (standard deviation) values. LBP = low back pain. ODI = Oswestry Disability Index (0 – 100% with smaller numbers indicating less disability). NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle.

Table 6. Changes in PPT.

	Time	*PPT Lumbar Paraspinal Musculature (Local)*	*PPT Tibialis Anterior Muscle (Regional)*	*PPT Lateral Epicondyle (Remote)*
SMT	Pre-First Intervention	3.36 (2.10)	4.42 (1.84)	3.00 (1.38)
	Immediately Post-First Intervention	3.50 (2.02)	4.39 (2.09)	2.72 (1.04)
	3-Weeks Post-First Intervention	3.87 (1.81)*	5.29 (2.08)$^{\delta}$	3.21 (1.33)
Sham	Pre-First Intervention	3.36 (1.36)	4.88 (1.71)	3.19 (1.39)
	Immediately Post-First Intervention	3.42 (1.49)	4.78 (1.99)	3.02 (1.64)
	3-Weeks Post-First Intervention	3.78 (1.59)*	5.34 (2.35)$^{\delta}$	3.17 (1.23)
Total Sample	Pre-First Intervention	3.36 (1.71)	4.67 (1.76)	3.10 (1.36)
	Immediately Post-First Intervention	3.46 (1.72)	4.60 (2.00)	2.88 (1.38)
	3-Weeks Post-First Intervention	3.82 (1.67)	5.32 (2.19)	3.19 (1.25)

All data reported as mean (standard deviation) values. We observed a significant main effect of time for PPT at the paraspinal and tibialis anterior testing locations, but neither outcome was dependent upon group assignment. *significant *within*-group differences ($p < .05$) between pre-first intervention and 3-weeks. $^{\delta}$significant *within*-group differences ($p < .05$) between post-first intervention and 3-weeks.

CHAPTER 3:

Effect of Spinal Manipulative Therapy on Trunk Kinematics in Patients with Chronic Non-Specific Low Back Pain: A Randomized, Controlled Trial

3.1 Abstract

The *long-term* goal of our study is to improve the understanding of the biological mechanisms associated with spinal manipulative therapy (SMT). This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with chronic non-specific low back pain (CNSLBP). We examined the effect of SMT on trunk kinematics within the sagittal and transverse planes in patients with CNSLBP. We screened 51 individuals for the study and 29 (n = 29) signed an informed consent form agreeing to participate. Following a 3-week course of SMT or sham SMT in CNSLBP patients, we found no significant improvements in trunk range of motion (ROM) within the sagittal plane, while changes in trunk angular velocity, either improved or diminished, dependent upon the spinal region. Also, the sham SMT group exhibited an improvement in trunk rotational ROM, while SMT did not significantly increase transverse plane (rotation) trunk ROM. Finally, there was no difference between the two interventions in terms of trunk ROM or angular velocity, except upper lumbar spine (ULS) ROM in the SMT group compared to the sham SMT group.

Keywords: Manipulation; Spinal; Manual therapy; Low Back Pain; Biomechanics; Range of Motion

3.2 Introduction

According to the World Health Organization (WHO), low back pain has reached epidemic proportions, reported worldwide by about 80% of people at some point in their life.[173] The functional prognosis for *chronic* low back pain remains poor with only 50% of patients returning to work after 6 months, and almost none after 2 years.[174] Thus, a large number of low back pain patients *fail* to realize significant improvements in pain and function. Chronic low back pain represents 75% of the total treatment costs associated with managing low back pain and is associated with significant physical and psychological disability, representing *the* major cause of absenteeism from the workplace worldwide.[10,11,14] Therefore, determining and using efficacious interventions may limit or improve the disability associated with *chronic* low back disorders.[15,16] According to clinical practice guidelines, spinal manipulative therapy (SMT) is a viable treatment option for low back disorders.[2-4,54-56]

Individuals with low back pain demonstrate changes in kinematic parameters including diminished lumbar range of motion (ROM) in all cardinal planes,[22,160-163] slower lumbar movement,[22,161,163,164] and worse proprioception.[160,165-167] SMT may produce beneficial effects on ROM.[45,46,68,168] Cramer et al[68] proposed that gapping or changes in the dimension of spinal zygapophyseal joints may break fibrous adhesions and/or release of entrapped synovial folds or plica that form after joint hypomobility, thus leading to improved mobility or ROM following SMT. In addition, paraspinal muscle reflexes along with motoneuron excitability may be influenced by SMT, perhaps affecting reflex neural output to spinal musculature, thereby improving trunk kinematics.[45,128] However, investigations examining the effects SMT on lumbar mobility demonstrate an inconsistent effect on ROM.[65,169-172] Results of a systematic review indicated that SMT may have a small effect on ROM in the cervical region, but no effect on ROM

in the lumbar region.[67] However, limitations related to their conclusions include questionable construct validity or *precision* of the ROM measuring *devices*. Also, SMT may not have a large effect on total ROM, but may instead influence kinematics or "how the spine moves."[67] Past studies have also used different measurement devices including electromagnetic tracking, inclinometers, and finger-tip-floor excursion.[65,169,170] Currently, it is still unclear whether SMT can improve trunk kinematics in patients with spinal pain. Specifically, while using a *precision* measuring device for *multiple* planes of movement, it is uncertain whether *SMT* can influence trunk kinematics in *chronic non-specific low back pain* patients.

The long-term goal of our study is to improve the understanding of the biological mechanisms associated with SMT. As our *primary* objective, we examined the effect of SMT on kinematics of sagittal and transverse plane trunk movements in patients with chronic non-specific low back (CNSLBP) pain. Our *central* hypothesis postulated that SMT would significantly improve trunk kinematics in CNSLBP patients.

3.3 Methods

3.3.1 General Design

This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with CNSLBP (Figure 17). We enrolled 29 subjects (n = 29) out of 51 patients who were screened for inclusion/exclusion criteria. Subjects were randomly assigned to spinal manipulation (SMT) or sham spinal manipulation (sham SMT) groups. Prior to starting treatment, each subject underwent physical and neurological examinations. Physical examination procedures included vital signs, orthopedic testing, palpation,

and range of motion testing. Neurological examination comprised testing of muscle strength, deep tendon reflexes, pathological reflexes, and sensation.

3.3.2 Randomization and Blinding

A computerized random number generator created a random allocation sequence list. Using this list, subjects were randomly allocated to either SMT or sham SMT group. This list was stored in a locked file cabinet with access limited to research personnel. After subject enrollment, a designated research assistant opened the correct numbered, sealed, opaque envelope. Each subject was assigned a unique identification number and the research assistant registered the subject's name and identification number in a log. This was the only information connecting the patient's identifying information with study records. Clinicians delivering the intervention were aware of group assignment, but the assessor was blinded to group allocation. A single assessor evaluated all outcome measures. Also, subjects were blinded to group allocation and advised to avoid discussing study details with the outcome assessor.

3.3.3 Participants

We recruited persons with CNSLBP between January 2016 and April 2016 from the two educational institutions. Subjects were screened for fulfilling the inclusion and exclusion criteria. If a subject met these criteria, they were asked to sign an informed consent form approved by human protection committees of both institutions. Patients with low back pain were included in this study if they met the following criteria: 1) chronic non-specific (> 12 weeks duration) low back pain rated ≥ 3/10 at its worst over the past 24 hours on a numeric rating scale (NRS) (0 = no

pain at all, 10 = worst pain imaginable); 2) male or female subjects between the ages of 18 and 60 years; 3) ability to read and understand English; 4) currently not involved in litigation. Chronic low back pain patients were excluded if they reported any of the following criteria: 1) previous low back surgery; 2) severe structural spinal deformity; 3) neurological compromise/spinal cord compression; 4) severe spinal instability; 5) severe osteoporosis/osteopenia; 6) head trauma (recent); 7) spinal infection (recent); 8) known neurological, neuromuscular, systemic or orthopedic problems that might prevent them from participating in manual therapy interventions; 9) pregnancy; 10) obesity; 11) pain or paresthesia below the knees; 12) systemic illness known to affect sensation i.e. diabetes; 13) acute and/or chronic pain condition unrelated to low back pain; 14) spinal manipulation within the past 4 weeks.

3.3.4 Treatment Protocols

After completion of the screening and baseline assessments, both the SMT and sham SMT groups commenced the assigned treatment protocols. The SMT and sham SMT interventions were administered and supervised by licensed clinicians. Subjects received three treatments per week for two consecutive weeks (6 treatments) with one additional follow-up visit less than 1-week post-intervention (visit 7). We collected information related to attendance, medications, adverse events, and treatment sessions during the trial and the study coordinator monitored data quality on a weekly basis. In the event of improper data collection, there was immediate resolution of the recognized irregularity. Subjects were required to attend at least 80% (5 of the 6) of the clinical sessions during the study. If attendance was < 80%, the subject's data was not analyzed for this study because our aim was to investigate the explanatory effects of SMT.

3.3.5 Manual Interventions

SMT involved the patient lying supine with the spine in a position of lateral bending and rotation followed by a high-velocity low-amplitude force applied to the lumbopelvic region (Figure 18). This SMT procedure has demonstrated clinical efficacy in previous clinical trials involving low back pain patients.[193-196] This treatment protocol adheres to current United States clinical practice guidelines for managing low back pain with SMT.[197] Thus, a 2-week (6 treatments) intervention appears sufficient to determine the potential effects of SMT in chronic non-specific low back pain patients. As reported in previous studies,[78,79,99] each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides.

Previous clinical trials have used placebo SMT or sham SMT as a comparison group.[79,198,199] Sham SMT placed the patient in the supine position, but without accompanying lateral bending and rotation of the spine (neutral spine position) followed by a high-velocity low amplitude force applied to the table (Figure 18). As reported in previous studies,[78,79,99] each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides. Both the lumbopelvic SMT and sham SMT procedures were administered by two licensed clinicians (physical therapist and/or chiropractor) with greater than 8 years of manual therapy experience.

3.3.6 Assessment of Trunk Kinematics

During the initial visit, CNSLBP subjects underwent *pre* and immediate *post-treatment* trunk kinematic assessment. As part of the kinematic evaluation, we quantified trunk angular

displacement and trunk angular velocity. In addition, subjects underwent a third session of trunk kinematic assessment at the follow-up visit (visit 7). Kinematic testing for this study used a protocol previously reported as reliable and valid for healthy and low back pain subjects.[22] Subjects were asked to perform three trunk movement tasks comprising the entire spine at a non-imposed speed.[22] These three trunk motions tasks consisted of flexion and axial rotation (left and right) movements. These movements were chosen based on literature supporting the ability of these motions to discriminate healthy subjects from low back patients.[22] Subjects performed each of the movement tasks 15 times per session (recorded 10 trials). At the first visit, two sessions (*pre* and *post intervention*) were recorded using an opto-electronic motion measurement system (Vicon T-series, Denver, Colorado) consisting of eight cameras sampling at a frequency of 100 Hz. Nine reflective markers were placed on standardized bony landmarks by a blinded assessor (and experienced clinician) including five markers on the spinous processes of S2, L3, T12, T7, and C7; two markers on the right and left anterosuperior iliac spines; and two markers on the right and left acromioclavicular (AC) joints. Based on the position of the markers, we used a lab-made program in MATLAB (MathWorks, Natick, MA) to calculate mean values for ROM (angular displacement) and angular velocity at six spinal regions for each subject. Data analyses of kinematic parameters used the mathematical models and equations described in a previous report.[165]

In order to limit the effects of hip motion, pelvic asymmetry, hamstring overactivity, and emphasize lumbar movement, all of the trunk movements were performed while seated on a stool.[22] Also, to preserve a normal physiological curvature from the starting position for each subject, the height of the stool was adjusted to establish a 120° angle between the thigh and trunk.[22]As suggested by Hidalgo et al[22], subjects followed four rules during the trunk movements.

These instructions included beginning and ending movements with a normal physiological curve, moving at a non-imposed speed as far as possible, keeping continuous contact between the ischial tuberosities and stool, and only moving within the stipulated plane of motion.[22] Also, investigators provided each subject with a more detailed instruction set for the movement tasks as stipulated by Hidalgo et al.[22]

As outlined in previous report,[22] a kinematic spine model was constructed including the pelvic and shoulder regions. We considered each segment as rigid and homogenous and delimited by proximal and distal markers. The spine and shoulder were divided into six segments including the upper thoracic spine (UTS: C7-T7), lower thoracic spine (LTS: T7-T12), upper lumbar spine (ULS: T12-L3), lower lumbar spine (LLS: L3-S2), total lumbar spine (TLS: T12-S2), and shoulder segment (SS: LR-RR). As per the recommendations from Millan et al[67], all subjects were tested in the same location and room temperature along with the same warm-up protocol.

3.3.7 Data Analyses

We used individual *t*-tests and chi-square tests to assess for post-randomization group differences in demographic measures, clinical measures, and pain sensitivity measures. We set our significance at .05 and performed all analyses using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL).

Our primary aim consisted of investigating the effect of SMT on trunk kinematics in CNSLBP patients. We checked for normality (Kolmogorov-Smirnov test) and homogeneity of variance of independent variables (Levene's test). Based on meeting the assumption of normality, we used a mixed analysis of variance to test for a group (SMT, sham SMT) x time (pre-first intervention, immediately post-first intervention to 3 weeks) interaction for trunk kinematics

variables. If testing revealed a significant group x time interaction, we performed contrasts to determine within-group changes. We tested within-group (pre- and post-intervention) trunk kinematic (angular displacement and velocity) differences using a paired-samples *t*-test. In addition, we repeated these tests for the six spinal regions (UTS, LTS, ULS, LLS, TLS, and SS) including two planes of motion (flexion and axial rotation).

3.4 Results

3.4.1 Baseline Demographics and Characteristics

We screened 51 individuals for the study and 29 (n = 29) signed the informed consent form (Figure 17). Within our sample, 38% of participants were female with a mean age of 23.86 (SD = 5.74) years. Individual groups did not differ by baseline demographic measures, clinical measures, or kinematic measures (Table 7).

3.4.2 Trunk Kinematics

3.4.2.1 Angular Displacement

There was no significant group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction in LLS ROM ($p = .07$) nor a main effect for time ($p = .68$) (Table 8). There was a significant interaction between group (SMT, sham SMT) and time (pre-first intervention, immediately post-first intervention to 3-weeks) for ULS ROM ($p = .03$). At 3-weeks post-intervention, *post-hoc* testing revealed a mean difference of 12.58° (95%

CI [-1.47, 26.63], $p = .08$) in ULS ROM between the SMT and sham groups (Table 9). Also, *post-hoc* testing revealed a significant reduction of -7.96° (95% CI [1.43, 14.49], $p = .01$) in ULS ROM between pre-first intervention and 3-weeks post-first intervention for the sham group. Thus, the sham group exhibited a significant reduction in ULS ROM during the clinical trial, while the SMT group demonstrated only a slight change in ULS ROM. There was a significant interaction between group (SMT, sham SMT) and time (pre-first intervention, immediately post-first intervention to 3-weeks) for TLS ROM ($p = .04$). At 3-weeks post-intervention, *post-hoc* testing revealed a mean difference of 12.25° (95% CI [-1.29, 25.80], $p = .07$) in TLS ROM between the SMT and sham groups.

However, when interpreting the mean difference of lumbar spine flexion ROM (LLS, ULS, TLS) between SMT and sham SMT at 3-weeks post-intervention, we advise caution as the pre-first intervention mean difference in lumbar spine ROM between the groups was considerable (~ 3.5° to 7.0°). Further *post-hoc* analyses (Figure 19) examining the group mean *change* in TLS ROM between pre-first intervention and 3-weeks post-intervention revealed a mean difference of 6.64° (95% CI [-0.80, 14.07], $p = .078$). In addition, the group mean *change* in ULS between pre-first intervention and 3-weeks post-intervention revealed a significant mean difference of 9.06° (95% CI [1.36, 16.75], $p = .023$). However, these changes in TLS and ULS ROM do not surpass previously reported minimal detectable change (MDC) values for CNSLBP subjects.[22]

There was no group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction in LTS ROM ($p = .09$) nor did we observe a main effect for time ($p = .42$). There was no significant group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction in UTS ROM ($p = .15$) nor did we observe a main effect for time ($p = .81$).

There was no group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction in LR ROM (p = .12) or RR ROM (p = .13) (Table 10). However, we observed a significant main effect for time with LR ROM (p = .001) and RR ROM (p = .01). For the sham group, *post-hoc* testing revealed a significant increase of 6.08° (95% CI [2.30, 9.86], p = .001), in LR ROM between pre-first intervention and 3-weeks, and 7.51° (95% CI [2.31, 12.72], p = .003) between post-first intervention and 3-weeks. Also, the sham group significantly improved RR ROM by 5.96° (95% CI [0.41, 11.50], p = .032) from immediately post-first intervention to 3-weeks. Thus, the sham SMT group exhibited significantly improved LR ROM and RR ROM during the clinical trial, while the SMT group demonstrated a change in LR ROM and RR ROM, but did not achieve statistical significance.

3.4.2.2 Angular Velocity

There was no group (SMT, sham SMT) by time (pre-first intervention, immediately post-first intervention to 3-weeks) interaction in LLS (p = .38), ULS (p = .68), TLS (p = .84), LTS (p = .70), or UTS trunk velocities (p = .12) (Table 11). However, we observed a significant main effect for time with LLS (p = .001), ULS (p = .001), TLS (p = .001), LTS (p = .001), and UTS trunk velocities (p = .001). *Post-hoc* testing revealed significant increases of 13.18 °/second (95% CI [9.43, 16.94], p = .001) and 6.52 °/second (95% CI [4.80, 8.24], p = .001) in LLS velocity, and 16.54 °/second (95% CI [11.98, 21.10], p = .001) and 20.77 °/second (95% CI [13.87, 27.68], p = .001) in UTS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the SMT group. Also, there were significant increases of 15.01 °/second (95% CI [11.51, 18.51], p = .001) and 7.24 °/second (95% CI [5.64, 8.84], p = .001) in LLS

velocity, and 20.45 °/second (95% CI [16.21, 24.69], $p = .001$) and 26.81 °/second (95% CI [20.38, 33.23], $p = .001$) in UTS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the sham SMT group. Thus, the both the SMT and sham SMT groups exhibited significantly *improved* LLS and UTS velocity during the clinical trial.

Post-hoc testing revealed a significant *decrease* of 13.18 °/second (95% CI [-32.37, -17.22], $p = .001$) in ULS velocity between pre-first intervention and 3-weeks for the SMT group. Also, *post-hoc* testing revealed a significant increase of 3.48 °/second (95% CI [0.97, 5.98], $p = .004$) and a significant *reduction* of 22.46 °/second (95% CI [-29.511, -15.41], $p = .001$) in ULS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the sham group. Thus, the both the SMT and sham groups exhibited significantly *reduced* LLS velocity during the clinical trial.

Post-hoc testing showed a significant *reduction* of 7.61 °/second (95% CI [-9.70, -5.51], $p = .001$) and a significant increase of 9.62 °/second (95% CI [6.49, 12.76], $p = .001$) in TLS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the SMT group. Further *post-hoc* testing exhibited a significant *reduction* of 7.24 °/second (95% CI [-9.19, -5.30], $p = .001$) and a significant increase of 10.34 °/second (95% CI [7.42, 13.26], $p = .001$) in TLS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the sham group. Thus, the both the SMT and sham groups initially exhibited significantly *reduced* TLS velocity, followed by *improved* TLS velocity at 3-week follow-up.

Post-hoc testing demonstrated significant *reductions* of 23.13 °/second (95% CI [-30.76, -15.49], $p = .001$) and 9.96 °/second (95% CI [-17.71, -2.12], $p = .009$) in LTS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the

SMT group. Also, *post-hoc* testing showed significant *reductions* of 25.24 °/second (95% CI [-32.35, -18.14], $p = .001$) and 11.34 °/second (95% CI [-18.55, -4.12], $p = .001$) in LTS velocity between pre-first intervention, and immediately post-first intervention and 3-weeks, respectively, for the sham group. Thus, the both the SMT and sham groups exhibited significantly *reduced* LTS velocity during the clinical trial.

3.4.3 Additional Outcomes

We recorded additional clinical information including adverse events, change in medication, spinal joint cavitation, onset of new injuries/exacerbations, and believability of group assignment. A single adverse event of transient (< 48 hours) local, mild joint discomfort was reported in the SMT group, while participants in the sham SMT group related no adverse events during the clinical trial. In addition, no changes in medication were conveyed for participants in either group throughout the study.

As reported by clinician perception, spinal joint cavitation occurred at 60% (47/78 occasions) and 2.2% (2/90 occasions) frequencies in the SMT and sham groups, respectively. For the sham SMT group, 8/15 (53.3%) of subjects reported an exacerbation of low back pain related to activity at 3-week follow-up session, while only 3/13 (23.1%) of subjects in the SMT group reported an exacerbation during the trial. Based upon a two-sample test for proportions, there was no significant difference ($p = .778$) between the groups for subjects who felt they received an active form of treatment. Within the SMT group, 38.5% of participants believed that they received an active form of therapy, while 33.3% of subjects in the sham group thought that they received active treatment. Thus, our results indicate that we achieved adequate blinding for both groups and

knowledge of treatment did not likely affect outcomes since both groups were similar in perception that they received an active form of intervention.

3.5 Discussion

The primary aim of the current study was to examine the effect of SMT on trunk kinematics in chronic non-specific low back pain patients. Specifically, we measured trunk kinematics, including angular displacement (ROM) and angular velocity, for the sagittal (flexion) and transverse planes (rotation). Based upon our findings, SMT did not significantly improve sagittal plane (flexion) trunk ROM for each spinal region (LLS, ULS, TLS, LTS, UTS) from pre-intervention to immediately post-first intervention or 3-weeks, while the sham SMT group demonstrated a *reduction* in trunk flexion ROM for the ULS and LTS regions from pre-first intervention to 3-weeks. A possible explanation for the reduction in trunk flexion ROM for the sham group may be related to the method of force application or manual technique. While the SMT group received the high-velocity low amplitude (HVLA) thrust *after* being taken through a large, passive trunk ROM (lateral bending coupled with axial rotation), the sham group received the HLVA force without accompanying trunk lateral bending, and only slight rotational trunk positioning. Consequently, the sham group may *not* have elongated or "stretched" spinal tissues (i.e., spinal musculature) because of limited ROM during the application of the intervention. Previous studies have established that patients with low back pain demonstrate increased spinal stiffness,[201] and SMT-responders experience reduced spinal stiffness following intervention related to changes in lumbar multifidus muscle thickness.[202] Following SMT in low back pain patients, diminished spinal stiffness may facilitate improvements in trunk ROM.[203] Thus, the sham group may have exhibited

a reduction in trunk flexion ROM because of the absence of changes in muscular thickness related to trunk positioning during the intervention.

Also, the sham SMT group exhibited an improvement in left and right trunk rotational ROM at 3-weeks. However, SMT did not significantly increase transverse plane (rotation) trunk ROM from pre-first intervention to immediately post-first intervention or 3-weeks. Again, this change in trunk rotation within the sham group may be related to the method of force application or manual technique. Although the sham group did not receive a HVLA thrust while positioned in lateral bending, it seems plausible that the sham group experienced some *rotational* forces during the intervention. Our outcomes are similar to previous studies[65,67,169,170] that reported either small or no improvement in trunk ROM following manual therapy applied to the lumbopelvic region. Accordingly, our results indicate that the biological effects of SMT may not include an immediate, large improvement in trunk ROM for CNSLBP patients.

Our findings suggest that SMT and sham SMT produced a variable effect on sagittal plane (flexion) trunk angular velocity, with certain spinal regions (LLS, TLS, UTS) demonstrating an improvement in velocity, while other spinal regions (ULS, LTS) exhibited a reduction in velocity at 3-weeks. Our outcomes are similar to previous scientific literature[172] that reported improved trunk velocity following manual therapy applied to the lumbopelvic region. Mieritz et al[172] reported that lumbopelvic SMT performed on CLBP patients produced a significant improvement in lumbar flexion velocity, with patients exhibiting an improvement of 3.8 °/second (10.5%) at 12-week follow-up.[172] Consequently, our results indicate that the biological effects of SMT and sham SMT may include either improved trunk angular velocity or reduced trunk angular velocity, contingent on the spinal region.

Scientific literature postulates that SMT may elicit a therapeutic effect through one *or* more neurological and/or biomechanical mechanisms.[45,46,48,53,68] The sham SMT used in our experimental design aimed to apply a thrust into the table with the spine positioned in neutral (without trunk lateral bending), unlike the SMT procedure that applied a thrust into rotation with accompanying trunk lateral bending.[79] However, Bialosky et al[79] conceded that the *sham* SMT applied a *mechanical load* to the spine. Thus, the mechanical stimulus applied to the spine within the sham group may have produced neurological and/or biomechanical effects, explaining the kinematic changes associated with the sham group. Consequently, our findings that both SMT and sham SMT improve trunk kinematics suggests that the application of a mechanical load to the spine seems to elicit a biological response, but implies less importance on *how* the force is applied to the spine.

3.5.1 Limitations

Although we met our sample size estimation (n = 29), our study may be underpowered to detect *kinematic* changes in CNSLBP patients after SMT. Based upon our *post-hoc* analyses, we obtained an observed power value < 80% for our kinematic parameters (trunk angular displacement and velocity) between-subjects effects, thus we acknowledge the possibility of a type II error.

There may be potential bias in the recruited sample, especially for a small sample. Scientific literature has suggested that within low back patients there may be sub-groups that respond differently to specific interventions.[19,193] For example, a clinical decision rule outlining acute low back patients likely to respond to spinal manipulation reported several predictor criteria, including symptom location (proximal to knee).[193] As an attempt to adhere to predictors of

response to spinal manipulation, our study criteria limited the sample population to CLBP with *no distal* symptoms.

This study may have been more clinically meaningful if we had monitored our subjects at some further time interval (6 months or 1 year). Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, long-term follow-up may have provided us with a more consequential measure of the effect of SMT on CNSLBP, thereby contributing to the development of more comprehensive evidence-based practice guidelines for managing low back disorders.

Another limitation of the current study was that the design of the study did not help us determine whether or not the differences we observed in the dependent variables were present in the subjects before the onset of pain or after low back pain developed. There may have been adaptations in spinal tissues such as muscle and/or joint stiffness, and specific nervous system characteristics, such as individual variance in perception of pain that might have affected our results. However, we attempted to lessen the influence of these factors through random allocation of subjects to either intervention or control groups.

3.5.2 Future Directions

Based upon our study results, the biological mechanisms associated with SMT appear multifaceted and complex. Thus, we propose additional extensions of this body of work to address these complexities. Though the effectiveness of SMT on clinical outcomes has been previously investigated, there remains controversy as to the suitable dosage of SMT for low back disorders. Future investigations may study the effect of dosage on biological outcome measures to determine

appropriate or optimal prescriptions. The application of manual therapy or SMT has many differing techniques and nuances including patient position, clinician hand contact, force application (rate, duration, amplitude, direction), and patient contact (spinous process, transverse process). For example, future studies may examine the biological effects of SMT applied to patient side-posture positioning to patient supine positioning. Finally, our study only examined the *immediate* effect of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, future studies should include longer-term follow-up of biological outcomes, thereby improving the clinical applicability of the effects of SMT on spinal disorders.

3.5.3 Conclusions

Following a 3-week course of SMT or sham SMT in CNSLBP patients, we found no significant or clinically relevant improvements in trunk ROM within the sagittal plane, while changes in trunk angular velocity, either improved or diminished for both groups, dependent upon the spinal region. Also, the sham SMT group exhibited an improvement in trunk rotational ROM, while the SMT group did not significantly increase transverse plane (rotation) trunk ROM. Finally, there was no difference between the two interventions in terms of trunk ROM or angular velocity, except ULS ROM improved in the SMT group compared to a reduction within the sham SMT group.

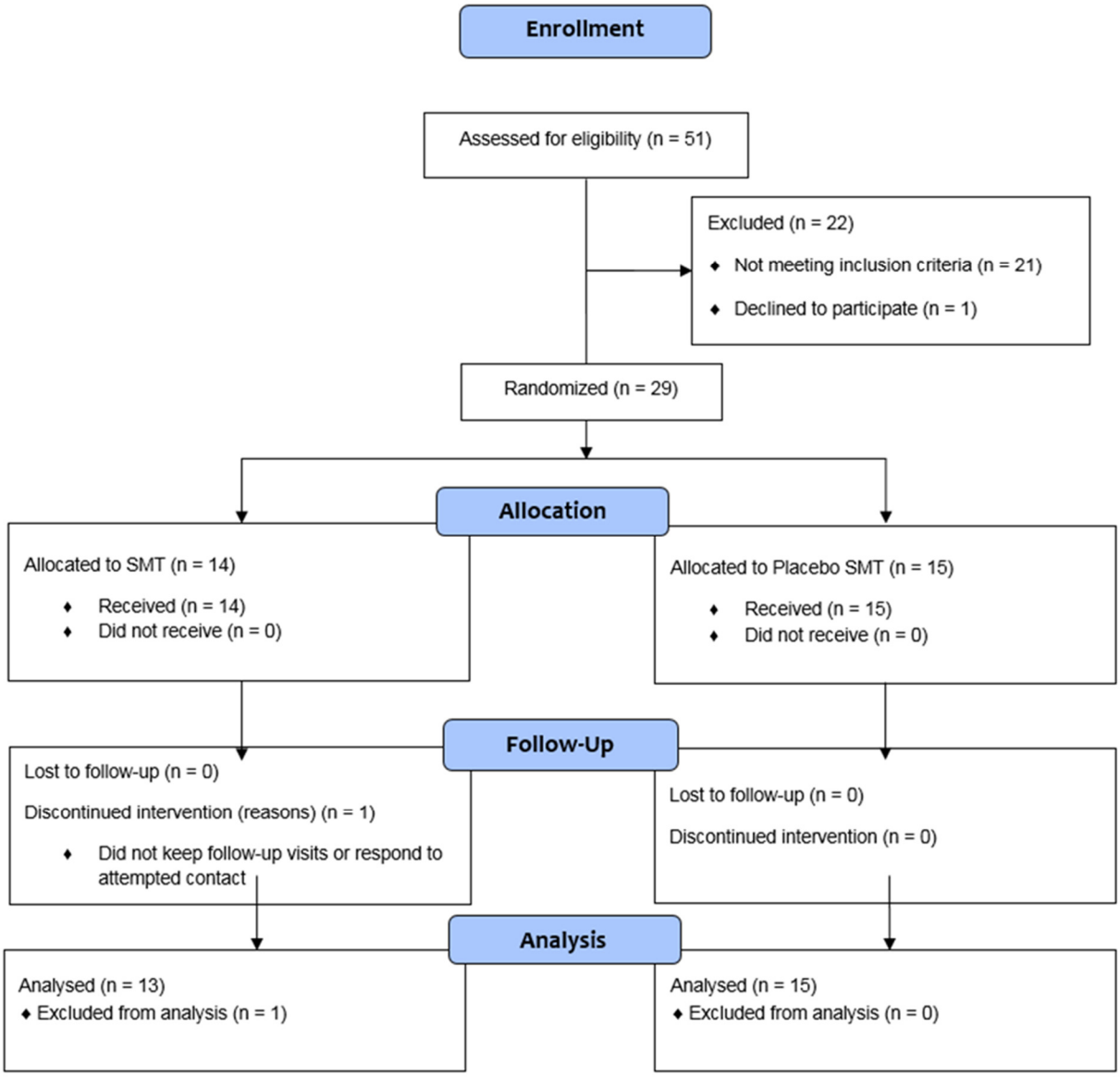

Figure 17: Overview of recruitment, enrollment, randomization, follow-up, and analysis for study. SMT = spinal manipulative therapy.

A. SMT B. Placebo SMT

Figure 18: Spinal manipulative therapy and sham spinal manipulative therapy.[79]

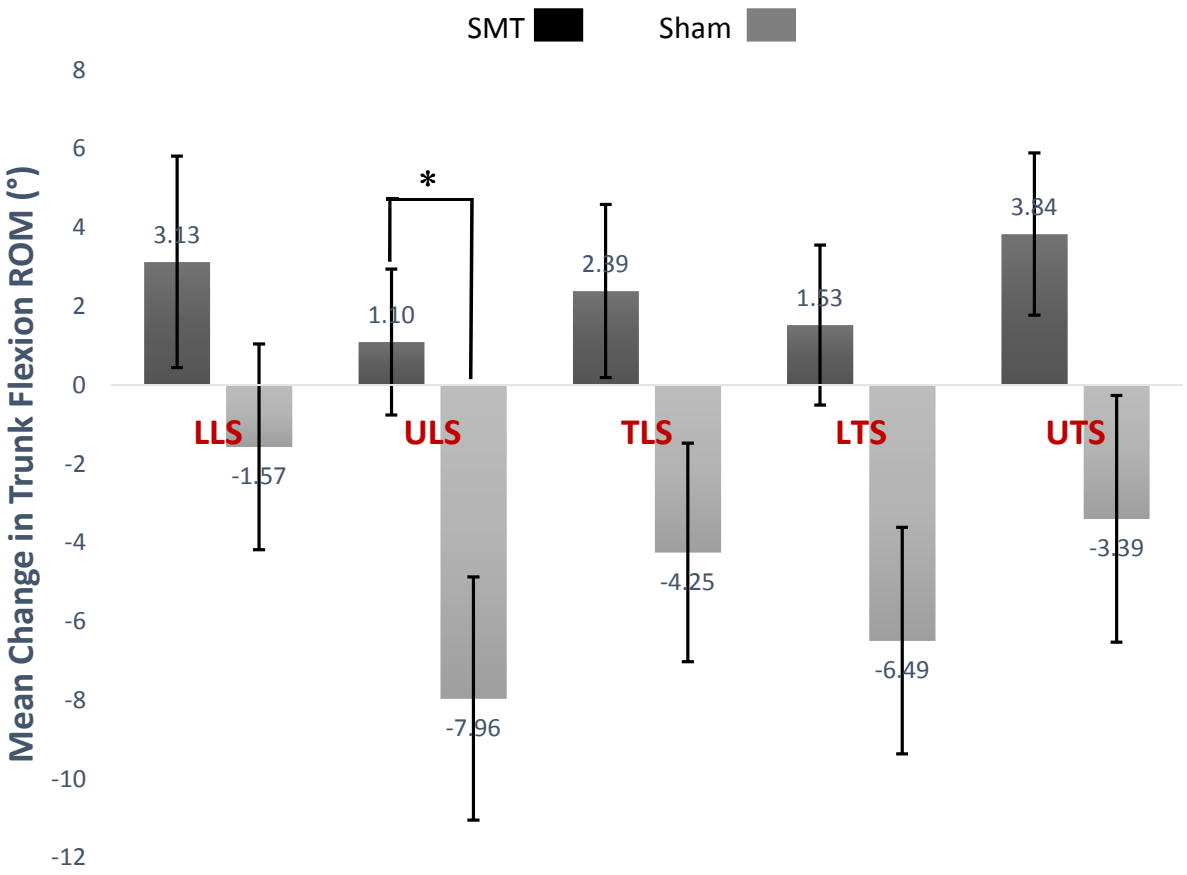

Figure 19: Mean Change in Trunk Flexion ROM (°). Bars signify mean change in scores (pre-first intervention to 3-weeks post-intervention) with positive numbers on the y-axis signifying increased ROM, while negative values indicate reduced ROM. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. ROM° = range of motion in degrees. SMT = spinal manipulative therapy. *significant *between*-group differences ($p < .05$). Error bars = standard error.

Table 7: Baseline Comparison of Intervention Groups.

	SMT	*Sham*	*Total Sample*	*p-value for difference*
Gender (% female)	6/14 (43)	5/15 (33)	11/29 (38)	.60
Age (years)	24.29 (7.33)	23.47 (3.94)	23.86 (5.74)	.71
Education (years)	17.00 (1.92)	17.20 (1.47)	17.10 (1.68)	.76
Duration of LBP (months)	45.07 (29.77)	43.00 (27.40)	44.00 (28.07)	.85
ODI	15.93 (6.23)	15.07 (6.79)	15.48 (6.91)	.74
NPRS	41.64 (12.70)	36.87 (17.25)	39.17 (15.15)	.41
LLS (°)	65.39 (15.05)	58.25 (17.89)	61.57 (16.73)	.27
ULS (°)	86.13 (16.07)	82.61 (21.77)	84.24 (19.07)	.64
TLS (°)	75.66 (14.96)	70.05 (19.14)	72.66 (17.25)	.40
LTS (°)	101.34 (16.78)	100.36 (22.52)	100.81 (19.71)	.90
UTS (°)	104.83 (16.08)	106.86 (21.16)	105.92 (18.66)	.78
LR (°)	64.41 (10.07)	65.85 (8.89)	65.18 (9.31)	.69
RR (°)	63.84 (12.57)	70.28 (9.84)	67.29 (11.45)	.14
LLS (°/s)	40.97 (11.50)	33.15 (14.88)	36.78 (13.76)	.14
ULS (°/s)	63.46 (13.39)	57.85 (20.49)	60.45 (17.48)	.41
TLS (°/s)	53.86 (12.66)	49.37 (17.73)	51.45 (15.47)	.45
LTS (°/s)	66.65 (15.42)	63.42 (17.71)	64.92 (16.46)	.61
UTS (°/s)	50.26 (12.02)	45.28 (17.72)	47.58 (15.28)	.40

All data reported as mean (standard deviation) values. SMT = spinal manipulative therapy. LBP = low back pain. ODI = Oswestry Disability Index (0 – 100% with smaller numbers indicating less disability). NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. LR = left rotation. RR = right rotation. ° = degrees. °/s = degrees per second.

Table 8: Sagittal Plane (Flexion) Changes in Mean Trunk Range of Motion**.**

	Time	*LLS (°)*	*ULS (°)*	*TLS (°)*	*LTS (°)*	*UTS (°)*
SMT	Pre-1st Intervention	65.39 (15.05)	86.13 (16.07)	75.66 (14.96)	101.34 (16.78)	104.83 (16.08)
	Immediately Post-1st Intervention	62.84 (16.93)	84.75 (18.88)	73.63 (17.05)	100.56 (18.81)	106.42 (17.36)
	3-Weeks Post-1st Intervention	68.53 (16.24)	87.23 (16.91)	78.05 (16.30)	102.87 (13.40)	108.67 (13.97)
Sham	Pre-1st Intervention	58.25 (17.89)	82.61 (21.77)	70.05 (19.14)	100.36 (22.52)	106.86 (21.16)
	Immediately Post-1st Intervention	59.28 (18.31)	81.62 (23.10)	70.14 (19.97)	98.51 (24.47)	103.43 (22.35)
	3-Weeks Post-1st Intervention	56.68 (18.13)	74.65 (18.96)*	65.80 (18.27)	93.87 (20.19)*	103.47 (19.06)
Total Sample	Pre-1st Intervention	61.57 (16.73)	84.24 (19.07)	72.66 (17.25)	100.81 (19.71)	105.92 (18.66)
	Immediately Post-1st Intervention	60.93 (17.45)	83.07 (20.92)	71.76 (18.41)	99.46 (21.65)	104.82 (19.88)
	3-Weeks Post-1st Intervention	62.18 (18.00)	80.49 (18.82)	71.49 (18.16)	98.04 (17.67)	105.88 (16.80)

All data reported as mean (standard deviation) values. SMT = spinal manipulative therapy. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. ° = degrees. *significant *within*-group differences ($p < .05$) between pre-first intervention and 3-weeks.

Table 9: Within-Group and Between-Group Changes in Mean Trunk Range of Motion**.**

	Analysis/Measure		*Pre-1st Intervention*	*Immediately Post-1st Intervention*	*p-value for difference*	*3-Weeks Post-1st Intervention*	*p-value for difference*
	Trunk flexion (°)						
	LLS						
		SMT		-2.56 (-7.68, 2.56)	.64	3.13 (-3.91, 10.18)	.80
		Sham		1.03 (-3.73, 5.80)	1.00	-1.57 (-8.12, 5.00)	1.00
	ULS						
		SMT		-1.38 (-6.40, 3.64)	1.00	1.10 (-5.92, 8.11)	1.00
Within-group		Sham		-0.99 (-5.66, 3.69)	1.00	-7.96 (-14.49, -1.43)∗	.01∗
change score	TLS						
from pre-1st		SMT		-2.03 (-6.73, 2.67)	.84	2.39 (-4.38, 9.16)	1.00
intervention		Sham		0.09 (-4.29, 4.47)	1.00	-4.25 (-10.55, 2.06)	.29
	LTS						
		SMT		-0.78 (-6.43, 4.88)	1.00	1.53 (-5.27, 8.32)	1.00
		Sham		-1.85 (-7.11, 3.42)	1.00	-6.49 (-12.81, -0.16)∗	.04∗
	UTS						
		SMT		1.59 (-4.17, 7.35)	1.00	3.84 (-3.43, 11.10)	.57
		Sham		-3.43 (-8.80, 1.93)	.34	-3.39 (-10.16, 3.37)	.63
	Trunk rotation (°)						
	LR						
Within-group		SMT		1.51 (-3.40, 6.42)	1.00	3.51 (-0.55, 7.57)	.11
change score		Sham		-1.44 (-6.01, 3.14)	1.00	6.08 (2.30, 9.86)∗	.001∗
from pre-1st	RR						
intervention		SMT		3.45 (-1.58, 8.48)	.27	4.35 (-1.04, 9.75)	.15
		Sham		-1.96 (-6.65, 2.72)	.88	3.99 (-1.03, 9.02)	.16

Between-group difference in change score	LLS	3.56 (-10.22, 17.33)	.60	11.84 (-1.62, 25.30)	.08
	ULS	3.13 (-13.43, 19.69)	.70	12.58 (-1.47, 26.63)	.08
	TLS	3.50 (-11.05, 18.04)	.63	12.25 (-1.29, 25.80)	.07
	LTS	2.05 (-15.12, 19.22)	.81	9.00 (-4.54, 22.55)	.18
	UTS	3.00 (-12.74, 18.73)	.70	5.20 (-7.97, 18.37)	.42
	LR	1.51 (-7.78, 10.79)	.74	-4.01 (-12.11, 4.08)	.32
	RR	-1.02 (-10.89, 8.84)	.83	-6.08 (-14.68, 2.53)	.16

All data reported as mean (95% confidence intervals) values. For *within-group* comparisons, negative values indicate reduced ROM, while positive values indicate increased ROM. For *between-group* comparisons, negative values indicate improvements in ROM that favor the *sham* group, while positive values indicate improvements in ROM that favor the *SMT* group. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. LR = left rotation. RR = right rotation. ° = degrees. *significant *within*-group differences ($p < .05$).

Table 10: Transverse Plane (Rotation) Changes in Mean Trunk Range of Motion**.**

	Time	***LR (°)***	***RR (°)***
SMT	Pre-1st Intervention	64.41 (10.07)	63.84 (12.57)
	Immediately Post-1st Intervention	65.92 (12.89)	67.29 (14.22)
	3-Weeks Post-1st Intervention	67.91 (11.90)	68.19 (12.26)
Sham	Pre-1st Intervention	65.85 (8.89)	70.28 (9.84)
	Immediately Post-1st Intervention	64.41 (11.02)	68.32 (11.15)
	3-Weeks Post-1st Intervention	71.92 (8.91)*δ	74.27 (9.89)δ
Total Sample	Pre-1st Intervention	65.18 (9.31)	67.29 (11.45)
	Immediately Post-1st Intervention	65.11 (11.72)	67.84 (12.44)
	3-Weeks Post-1st Intervention	70.06 (10.40)	71.45 (11.27)

All data reported as mean (standard deviation) values. SMT = spinal manipulative therapy. LR = left rotation. RR = right rotation. ° = degrees. *significant *within*-group differences ($p < .05$) between pre-first intervention and 3-weeks. δsignificant *within*-group differences ($p < .05$) between post-first intervention and 3-weeks.

Table 11: Within-Group and Between-Group Changes in Mean Trunk Angular Velocity.

	Analysis/Measure		*Pre-1st Intervention*	*Immediately Post-1st Intervention*	*p-value for difference*	*3-Weeks Post-1st Intervention*	*p-value for difference*
	Trunk flexion velocity (°/s)						
Within-group change score from pre-1st intervention	LLS						
		SMT		13.18 (9.43, 16.94)*	.001*	6.52 (4.80, 8.24)*	.001*
		Sham		15.01 (11.51, 18.51)*	.001*	7.24 (5.64, 8.84)*	.001*
	ULS						
		SMT		1.91 (-0.78, 4.60)	.24	-24.80 (-32.37, -17.22)*	.001*
		Sham		3.48 (0.97, 5.98)*	.004*	-22.46 (-29.51, -15.41)*	.001*
	TLS						
		SMT		-7.61 (-9.70, -5.51)*	.001*	9.62 (6.49, 12.76)*	.001*
		Sham		-7.24 (-9.19, -5.30)*	.001*	10.34 (7.42, 13.26)*	.001*
	LTS						
		SMT		-23.13 (-30.76, -15.49)*	.001*	-9.96 (-17.71, -2.21)*	.009*
		Sham		-25.24 (-32.35, -18.14)*	.001*	-11.34 (-18.55, -4.12)*	.001*
	UTS						
		SMT		16.54 (11.98, 21.10)*	.001*	20.77 (13.87, 27.68)*	.001*
		Sham		20.45 (16.21, 24.69)*	.001*	26.81 (20.38, 33.23)*	.001*
Between-group difference in change score	LLS			6.00 (-6.67, 18.67)	.34	7.11 (-4.26, 18.47)	.21
	ULS			4.04 (-9.51, 17.60)	.55	3.28 (-6.86, 13.41)	.51
	TLS			4.13 (-6.72, 14.99)	.44	3.78 (-9.29, 16.85)	.56
	LTS			5.34 (-6.09, 16.77)	.35	4.60 (-8.13, 17.34)	.46
	UTS			1.05 (-13.01, 15.11)	.88	-1.08 (-16.13, 13.98)	.88

All data reported as mean (95% confidence intervals) values. For *within-group* comparisons, negative values indicate reduced velocity, while positive values indicate increased velocity. For *between-group* comparisons, negative values indicate improvements in velocity that favor the *sham* group, while positive values indicate improvements in velocity that favor the *SMT* group. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. LR = left rotation. RR = right rotation. °/s = degrees per second. *significant *within*-group differences ($p < .05$).

CHAPTER 4:

Relationship between Spinal Manipulative Therapy-Induced Changes in Biological Outcome Measures in Chronic Non-Specific Low Back Pain Patients

4.1 Abstract

This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with chronic non-specific low back pain (CNSLBP). In the current study, we examined the relationship between SMT-induced changes in biological outcome measures in CNSLBP patients. We screened 51 individuals for the study and 29 (n = 29) signed an informed consent form agreeing to participate. Following a 3-week course of SMT in CNSLBP patients, changes in PPT did not significantly correlate to trunk angular velocity, and only correlated with a single trunk angular displacement (ROM) parameter. In addition, changes in PPT at the lateral epicondyle (remote testing site) by 3-weeks correlated to a patient-reported measure of disability (ODI) in CNSLBP patients. Collectively, our results suggest that mechanical pain sensitivity testing may have limited significance as a prognostic indicator for low back pain-related pain and function.

Keywords: Manipulation; Spinal; Manual Therapy; Low Back Pain; Pain Threshold; Biomechanics; Range of Motion

4.2 Introduction

Low back pain affects up to 80% of the adult population at some point in their life[173] imposing a fiscal burden of $86 billion annually *or* 1% of the United States gross domestic product.[10-12] *Chronic* low back pain (CLBP) accounts for 75% of the total treatment expenditures accompanying the management of low back disorders.[10] Furthermore, CLBP represents *the* major cause of absenteeism from the workplace worldwide, and is associated with considerable physical and psychological disability.[10,11,14,204] Hence, establishing and applying effective interventions may limit or improve the disability associated with chronic low back disorders.[15,16] According to numerous clinical practice guidelines, spinal manipulative therapy (SMT) is a viable therapy for lower back pain.[2-4,54-56] SMT may elicit a pain-modulating effect through one *or* more neurological and/or mechanical pathways.[45,46,48,53,68]

Previously reported outcome measures examining the therapeutic effects following SMT include *subjective* clinical outcomes such as pain and disability,[7,31,40,41,43] and *objective* biological assessments such as spinal kinematics,[65,169-172] and pressure pain threshold (PPT).[78,79,99,145-148] In addition to an outcome measure, pain sensitivity testing may be an important *prognostic* indicator for spinal pain,[205] although quantitative sensory testing is not presently a standard examination procedure in low back pain patients.[206] Scientific studies have measured pain sensitivity following joint manipulation applied to the cervical,[100,135,136,150-153] thoracic,[80,154,155] and lumbopelvic[78,79,99,145-148] spinal regions, along with the peripheral joints.[156-158] However, many of these investigations fail to establish the relationship between changes in pain sensitivity and significant changes in clinical outcomes, thus limiting the potential for clinical applicability.

Health care professionals involved with treating low back disorders often rely on patient-reported (subjective) measures of pain and disability to determine impairment levels and evaluate

clinical success.[178-180,183,184,186] Sensitization, peripheral or central, represents augmentation of neural signaling producing pain hypersensitivity or lowered pain threshold.[207] Bialosky et al[46] suggested experimental pain testing procedures such as PPT may be used as indirect measures of *peripheral* and *central* sensitization for musculoskeletal disorders. Peripheral and central sensitization may be differentiated by comparing experimental pain responses at sites *local* and *remote* to the primary area of injury.[126,127] Peripheral mechanisms such as sensitization of tissue nociceptors may elucidate *local* tissue hyperalgesia, while central sensitization reflects widespread hyperalgesia at *remote* (distant to the tissue pathology) anatomical locations.[127] If peripheral and/or central sensitization are fundamental neurophysiological mechanisms associated with CLBP, and presuming that PPT is a valid marker of sensitization, then a predictable, consistent relationship might exist between pain threshold and patient-reported pain/disability.[207] In other words, if a relationship exists between these parameters, changes in sensitization might account for or explain the therapeutic effects of SMT in CNSLBP patients.

Clinicians managing low back pain evaluate regional ROM to determine the severity of the condition or assign disability, along with use as outcome measure to determine treatment effectiveness.[208,209] Individuals with low back pain demonstrate changes in kinematic parameters including diminished lumbar range of motion (ROM) in all cardinal planes,[22,160-163] and slower lumbar movement,[22,161,163,164] perhaps due to local and/or central pain pathways. Limited spinal mobility in the form of restricted range of motion might be a contributor to patient-reported pain and/or disability.[208] SMT may produce beneficial effects on ROM.[45,46,68,168] Following successful SMT in CNSLBP patients, a significant correlation between reductions in PPT (hypolagesia) at local and/or remote anatomical regions and spinal kinematics (angular displacement and velocity) might suggest a relationship between diminished pain and improved trunk movements. For

example, a low back pain patient may be prescribed a course of SMT to improve regional spinal mobility, and if movement is restored, the patient may feel less pain.[208] Consequently, by remedying the primary biomechanical disorder, this will then diminish the pain intensity in a rather predictable way.[208]

In the current study, we examined the relationship between SMT-induced changes in biological outcome measures in chronic non-specific low back pain (CNSLBP) patients. We hypothesized that following SMT there would be a significant correlation between the change in clinical scores and change in pressure pain threshold. In addition, following SMT there would be a significant correlation between the change in kinematics and change in pressure pain threshold.

4.3 Methods

4.3.1 General Design

This pilot project involved a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with chronic non-specific low back pain (Figure 20). Subjects were randomly assigned to spinal manipulation (SMT) or sham spinal manipulation (sham SMT) groups. We enrolled 29 subjects (n = 29) out of 51 patients who were assessed for inclusion/exclusion criteria. Clinical evaluations and biomechanical analyses were performed at a university research lab. Prior to starting treatment, each subject underwent physical and neurological examinations. Physical examination procedures included vital signs, orthopedic testing, palpation, and range of motion testing. Neurological examination comprised testing of muscle strength, deep tendon reflexes, pathological reflexes, and sensation.

4.3.2 Randomization and Blinding

A computerized random number generator created a random allocation sequence list. Using this list, subjects were randomly allocated to either SMT or sham SMT group. This list was stored in a locked file cabinet with access limited to research personnel. After subject enrollment, a designated research assistant opened the correct numbered, sealed, opaque envelope. Each subject was assigned a unique identification number and the research assistant registered the subject's name and identification number in a log. This was the only information connecting the patient's identifying information with study records. Clinicians delivering the intervention were aware of group assignment, but the assessor was blinded to group allocation. A single assessor evaluated all outcome measures. Also, subjects were blinded to group allocation and advised to avoid discussing study details with the outcome assessor. We collected information related to attendance, medications, adverse events, and treatment sessions during the trial. The study coordinator monitored data quality on a weekly basis. In the event of improper data collection, there was immediate resolution of the recognized irregularity.

4.3.3 Participants

We recruited persons with chronic non-specific low back pain (CNSLBP) between January 2016 and April 2016 from campuses of two universities. Subjects were screened for fulfilling the inclusion and exclusion criteria. If a subject met these criteria, they were asked to sign an informed consent form approved by the human protection committees of two institutions. Patients with chronic low back pain were included in this study if they met the following criteria: 1) chronic non-specific (> 12 weeks duration) low back pain rated ≥ 3/10 at its worst over the past 24 hours

on a numeric rating scale (NRS) (0 = no pain at all, 10 = worst pain imaginable); 2) male or female subjects between the ages of 18 and 60 years; 3) ability to read and understand English; 4) currently not involved in litigation. Chronic low back pain patients were excluded if they reported any of the following criteria: 1) previous low back surgery; 2) severe structural spinal deformity; 3) neurological compromise/spinal cord compression; 4) severe spinal instability; 5) severe osteoporosis/osteopenia; 6) head trauma (recent); 7) spinal infection (recent); 8) known neurological, neuromuscular, systemic or orthopedic problems that might prevent them from participating in manual therapy interventions; 9) pregnancy; 10) obesity; 11) pain or paresthesia below the knees; 12) systemic illness known to affect sensation i.e. diabetes; 13) acute and/or chronic pain condition unrelated to low back pain; 14) spinal manipulation within the past 4 weeks.

4.3.4 Procedures for Clinical Assessment

After signing an informed consent, information regarding medications, past medical history, education, and demographic data was collected from each subject. We collected information related to attendance, medications, adverse events, and treatment sessions during the trial. The study coordinator monitored data quality on a weekly basis. In the event of improper data collection, there was immediate resolution of the recognized irregularity. A clinician performed a standard physical examination including vital signs and mobility testing. In addition, subjects underwent a neurological examination.

During the baseline evaluation, subjects completed clinical outcome measures capturing pain and self-reported disability. Information related to pain and disability was ascertained through the Numerical Pain Rating Scale (NPRS) and Oswestry Disability Index (ODI). Clinical changes over 3-weeks (assessed at pre-first intervention and 3-weeks on visit 7) on measures of pain

(NPRS) and disability (ODI) served as clinical outcomes. While using the NPRS, subjects rated their pain intensity using an 101-point scale, with "0" indicating no pain and "100" indicating the worst pain imaginable.[178] The reliability and validity of NPRSs has been established in the scientific literature.[179,180] The ODI is an efficient (~ 10 minutes) and generalizable outcome measure.[181] This self-reported measure consists of ten sections that ask questions about pain and function such as sleeping, self-care, and social life.[182] The reliability and validity of the ODI has been reported in the scientific literature.[182-185] The ODI has been found the most sensitive index to detect an improvement in disability associated with manual therapy, yielding large-sized improvements across many studies.[178,183,184,186]

4.3.5 Treatment Protocols

After completion of the screening and baseline assessments, both the SMT and sham SMT groups commenced the assigned treatment protocols. The SMT and sham SMT interventions were administered and supervised by licensed clinicians. Subjects received three treatments per week for two consecutive weeks (6 treatments) with one additional follow-up visit less than 1-week post-intervention (visit 7). Researchers documented written logs of attendance, medications, health changes, and injuries/adverse events for each subject. Subjects were required to attend at least 80% (5 of the 6) of the clinical sessions during the study. If attendance was < 80%, the subject's data was not analyzed for this study because our aim was to investigate the explanatory effects of SMT.

4.3.6 Manual Interventions

SMT involved the patient lying supine with the spine in a position of lateral bending and rotation followed by a high-velocity low-amplitude force applied to the lumbopelvic region (Figure 21). This SMT procedure has demonstrated clinical efficacy in previous clinical trials involving low back pain patients.[193-196] This treatment protocol adheres to current United States clinical practice guidelines for managing low back pain with SMT.[197] Thus, an intervention duration of 2 weeks (6 treatments) is of sufficient length to determine the potential effects of SMT in chronic non-specific low back pain patients. As reported in previous studies,[78,79,99] each subject received two high-velocity low-amplitude thrusts to both sides of the pelvis, alternating between the left and right sides.

Previous clinical trials have used placebo SMT or sham SMT as a comparison group.[79,198,199] Sham SMT placed the patient in the supine position, but without accompanying lateral bending and rotation of the spine (neutral spine position) followed by a high-velocity low amplitude force applied to the table (Figure 21). As reported in previous studies,[78,79,99] each subject received a total of four sham high-velocity low-amplitude thrusts, alternating between the left and right sides. Both the lumbopelvic SMT and sham SMT procedures were administered by two licensed clinicians (physical therapist and/or chiropractor) with greater than 8 years of manual therapy experience.

4.3.7 Assessment of Pain Sensitivity

During the first visit, CNSLBP subjects underwent *pre* and immediately *post-treatment* pressure pain threshold (PPT) assessment. In addition, subjects underwent pressure pain

threshold (PPT) assessment at the follow-up visit (visit 7). We determined PPT by applying pressure with a digital algometer (Wagner Instruments, Greenwich, Connecticut) to three anatomical regions considered as local, regional, or remote. The digital algometer had a 1 cm^2 rubber-tipped probe that was applied perpendicular to skin at a rate of 1 kilogram per second (kg/s).[146] Marks were placed on the belly (middle third) of the dominant tibialis anterior muscle (regional)[145] and dominant lateral epicondyle of the elbow (remote).[136] Also, we marked a point 5 cm lateral to the spinous process of L5 (local) on the dominant side.[145] These three anatomical landmarks for pressure application were been chosen based on high reliability values reported from previous studies.[136,145] Scientific literature has reported using dominant regions[79] for PPT testing, while a systematic review by Millan et al[128] reported that SMT consistently demonstrates a bilateral hypoalgesic effect. Thus, we selected the subject's self-reported dominant-side for PPT testing.

Subjects were asked to say "stop" the moment the sensation changed from feeling pressure to feeling pain. The pain threshold was defined as the least pressure intensity at which subject's perceived pain. The pressure threshold in kilograms (kg) causing the perception of pain was recorded for data analysis. Three measurements were collected for each anatomical region with 30 seconds of rest in between pressure applications. The mean value of the three threshold measurements was used for data analysis.[145,146] Before testing, each subject received three practice measurements with pressure applied to the dorsal aspect of their dominant hand.[146] Previous scientific literature has demonstrated the rest-retest reliability of PPT measurements.[145,189,190] Prior to data collection, an assessor blinded to group allocation undertook training with the digital algometer to ensure adherence to the specified rate of

pressure application and cessation of pressure.[146,190] PPT has been used in previous clinical trials as an outcome measure for response to spinal manipulation.[79,100,128,136,144,147,148,191]

4.3.8 Assessment of Trunk Kinematics

During the initial visit, CNSLBP subjects underwent *pre* and immediate *post-treatment* trunk kinematic assessment. As part of the kinematic evaluation, we quantified trunk angular displacement and trunk angular velocity. In addition, subjects underwent a third session of trunk kinematic assessment at the follow-up visit (visit 7). Kinematic testing for this study used a protocol previously reported as reliable and valid for healthy and low back pain subjects.[22] Subjects were asked to perform three trunk movement tasks comprising the entire spine at a non-imposed speed.[22] These three trunk motions tasks consisted of flexion and axial rotation (left and right) movements. These movements were chosen based on literature supporting the ability of these motions to discriminate healthy subjects from low back patients.[22] Subjects performed each of the movement tasks 15 times per session (recorded 10 trials). At the first visit, two kinematic sessions (*pre* and *post intervention*) were recorded us an opto-electronic motion measurement system (Vicon T-series, Denver, Colorado) consisting of eight cameras sampling at a frequency of 100 Hz. Nine reflective markers were placed on standardized bony landmarks by a blinded assessor (and experienced clinician) including five markers on the spinous processes of S2, L3, T12, T7, and C7; two markers on the right and left anterosuperior iliac spines; and two markers on the right and left acromioclavicular (AC) joints. Based on the position of the markers, we used a lab-made program in MATLAB (MathWorks, Natwick, MA) to calculate mean values for ROM (angular displacement) and SPEED (angular velocity) at six spinal regions for each subject. Data analyses

of kinematic parameters used the mathematical models and equations described in previous report.[165]

In order to limit the effects of hip motion, pelvic asymmetry, hamstring overactivity, and emphasize lumbar movement, all of the trunk movements were performed while seated on a stool.[22] Also, to preserve a normal physiological curvature from the starting position for each subject, the height of the stool was adjusted to establish a 120° angle between the thigh and trunk.[22] As suggested by Hidalgo et al,[22] subjects followed four rules during the trunk movements. These instructions included beginning and ending movements with a normal physiological curve, moving at a non-imposed speed as far as possible, keeping continuous contact between the ischial tuberosities and stool, and only moving within the stipulated plane of motion.[22] Also, investigators provided each subject with specific instructions for the movement task as stipulated by Hidalgo et al.[22]

As outlined in a previous report,[22] a kinematic spine model was constructed including the pelvic and shoulder regions. We considered each segment as rigid and homogenous and delimited by proximal and distal markers. The spine and shoulder were divided into 6 segments including the upper thoracic spine (UTS: C7-T7), lower thoracic spine (LTS: T7-T12), upper lumbar spine (ULS: T12-L3), lower lumbar spine (LLS: L3-S2), total lumbar spine (TLS: T12-S2), and shoulder segment (SS: AcRight-AcLeft). As per the recommendations from Millan et al,[67] all subjects were tested in the same location and room temperature along with the same warm-up protocol.

4.3.9 Data Analyses

Our primary aim consisted of investigating the relationship between SMT-induced changes in biological outcome measures in the intervention group. Following SMT, we hypothesized a

significant correlation between the change in clinical scores and change in PPT. For this hypothesis, the dependent variables (criterion variables) were clinical outcomes (NPRS and ODI), while the independent variable (predictor variable) was PPT. For each subject, we calculated the change (pre-first intervention to 3-week) in clinical scores (NPRS and ODI) and PPT values (3 anatomical testing locations) in the experimental group. In addition, we hypothesized a significant correlation between the change in kinematics and change in PPT. For this hypothesis, the dependent variables (criterion variables) were kinematic parameters (trunk angular displacement and velocity), while the independent variable (predictor variable) was PPT. For each subject, we calculated the change (pre-first intervention to post-first intervention and 3-week) in kinematic parameters (angular displacement and velocity) and PPT values (3 anatomical testing locations) in the experimental group.

We used individual *t*-tests and chi-square tests to assess for post-randomization group differences in demographic, clinical, kinematic, and pain sensitivity measures. We set our significance at .05 and performed all analyses using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL). Based on meeting the assumption of normality, we used the Pearson correlation coefficient to measure the relationship between the change in criterion and predictor variables for the experimental group.

4.3.10 Sample Size Estimation

Our primary aim was to examine the changes after SMT in PPT examined at a three different body sites. Bialosky et al[78] reported an effect size (Cohen's d) of 1.20 on thermal pain threshold measured on upper limb after spinal manipulation in comparison to a control group. We assumed that the PPT measured at the upper limb may show similar changes after our SMT

intervention compared to the control group. Assuming 80% statistical power and 0.05 alpha level, a sample size of 12 was required for each group in our study. Presuming a drop-out rate of 20%, we needed to recruit a total of 30 subjects.

4.4 Results

4.4.1 Baseline Demographics and Characteristics

We screened 51 individuals for the study and 29 (n = 29) signed the informed consent form. Within our sample, 38% of participants were female with a mean age of 23.86 (SD = 5.74) years. Individual groups did not differ by baseline demographic, clinical, kinematic, or PPT measures (Table 12).

4.4.2 Relationship between Clinical Outcomes and PPT

We calculated Pearson product-moment correlation coefficients between the pre-first intervention to post-first intervention and 3-week change in PPT and change in clinical outcome variables (NPRS and ODI) for the SMT group. Based upon our analyses, the only significant correlation within the SMT group was a moderate, positive correlation ($r = .592$, $p = .033$) between change in PPT at the remote location (lateral epicondyle) by 3-weeks and change in ODI (Table 13).

4.4.3 Relationship between Trunk Kinematics and PPT

We calculated Pearson product-moment correlation coefficients between the pre-first intervention to post-first intervention and 3-week change in PPT and the pre-first intervention to post-first intervention and 3-week change in trunk kinematics (angular displacement and velocity) for the SMT group. Based upon our analyses, the only significant correlation within the SMT group was a moderate, negative correlation (r = -.556, p = .049) between change in PPT at the lateral epicondyle (LE) by 3-weeks and 3-week change in right rotation (RR) ROM (Table 14). In addition, immediate change in right rotation (RR) ROM and changes in PPT at the regional location (tibialis anterior muscle) along with the remote location (lateral epicondyle) demonstrated a trend towards significance. Also, immediate change in lower lumbar spine (LLS) ROM and 3-week change in PPT at the remote location (lateral epicondyle) demonstrated a trend towards significance. However, there were no other significant relationships (within the 84 comparisons) between the change in PPT and change in trunk ROM. Furthermore, we did not observe significant correlations between PPT values and trunk angular velocity quantities (Table 15).

4.5 Discussion

The primary aim of the current study was to examine the relationship between SMT-induced changes in biological outcome measures in chronic non-specific low back pain (CNSLBP) patients. Specifically, we investigated the relationship between clinical scores (NPRS and ODI) and PPT, along with the relationship between kinematic parameters (angular displacement and velocity) and PPT. Our results suggest a moderate, positive correlation between change in PPT at the remote location (lateral epicondyle) by 3-weeks and change in ODI. In other words, an improvement in PPT (hypoalgesia) at the remote location may be associated with recovery in low back pain-related disability by 3-weeks post-SMT. Thus, our findings indicate a plausible short-

term relationship between a neurophysiological (objective) quantity and a patient-reported (subjective) measure of disability following SMT in CNSLBP patients. However, this was the only significant correlation between patient-reported outcomes and PPT, limiting the implications of this result. Based upon our results, presuming that PPT is a valid marker of sensitization, modulation of peripheral and/or central sensitization may not be a fundamental neurophysiological mechanism associated with SMT in CNSLBP patients because we did not find a predictable, consistent relationship between pain threshold and patient-reported pain/disability.[207]

A plausible explanation for our limited relationship between PPT and clinical outcomes might be related to previous scientific literature. Recent scientific literature has contested the validity of pain sensitivity testing as a marker of peripheral and/or central sensitization.[210] A systematic review and meta-analysis reported a weak relationship between pain threshold and pain or pain-related disability.[207] Hübscher et al[207] concluded that either pain threshold is poor marker of sensitization or that sensitization does not assume a significant role in patient-reported pain and disability. Thus, our findings might be explained by the concept that a change in sensitization following SMT does not represent the therapeutic mechanism for pain modulation in CNSLBP patients. Also, it seems feasible that either our CNSLBP subjects might be represented by a heterogeneous sample with some subjects demonstrating sensitization, while others do not exhibit sensitization or sensitization is not a fundamental constituent of the pathology associated with CNSLBP patients.

Our outcomes are similar to previous studies[78,145,200] that reported significant associations between clinical outcomes and pain sensitivity following manual therapy applied to the spine. Following the application of SMT to CLBP patients, de Oliveira at al[145] reported a small correlation between pain (NPRS) and PPT at local (lumbar paraspinal musculature) and remote

(tibialis anterior muscle) testing sites. Bialosky et al[78] described a moderate association between local thermal pain sensitivity and patient-reported variables (pain catastrophizing and anxiety) subsequent SMT in low back pain patients. After SMT in patients with shoulder pain, Kardouni et al[200] quantified a moderate relationship between PPT at a remote testing site and clinical disability.

In addition, our results indicate a moderate, negative association between change in PPT at the remote location (lateral epicondyle) by 3-weeks and 3-week change in right rotation (RR) ROM. In other words, a reduction in PPT at the remote location may be associated with improved axial trunk rotation by 3-weeks post-SMT. Thus, our findings indicate a possible short-term relationship between a neurophysiological quantity and a biomechanical parameter following SMT in CNSLBP patients. Again, this was the only significant correlation of kinematic-related outcomes with PPT mechanistic measures, limiting the implications of this result. To the best of our knowledge, this is the first study explore the relationship between PPT and kinematic parameters. Based upon our results, there appears to be a limited relationship between mechanical pain sensitivity and spinal kinematics suggesting that pain sensitivity testing may have limited significance as a prognostic indicator for low back pain-related function.

4.5.1 Limitations

This proposal was a pilot study involving a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with CNSLBP. Because of the limited sample size associated with this pilot project, we did not perform a Bonferroni correction for multiple comparisons. Thus, we acknowledge the possibility of a type I error when interpreting our results.

Furthermore, we did not attempt to blind the clinicians to the interventions received by the subjects. Thus, we cannot be assured that clinician bias did not influence our findings. In addition, we only conducted a 2-week trial followed by 1-week follow-up, so we only have information related to the short-term effects of SMT. Though it seems feasible that SMT may have an *immediate* therapeutic effect on CNSLBP subjects, perhaps long-term follow-up of outcome measures may allow for more favorable adaptive neuroplastic changes.

Pressure may be considered a non-specific stimulation that elicits a response from mechanoreceptors and nociceptors in surrounding tissues.[200] Pressure pain threshold (PPT) may be used as an *indirect* measure of peripheral and central sensitization for musculoskeletal disorders.[46] In addition, a slow, gradual application of pressure until a pain threshold is reached might reflect a different neural pathway than rapidly applied stimuli.[200] This investigation only examined the effect of SMT in response to mechanical stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT.

4.5.2 Future Directions

The biological mechanisms associated with SMT appear multifaceted and complex. Thus, we propose additional extensions of this body of work to address these complexities. Though the effectiveness of SMT on clinical outcomes has been previously investigated, there remains controversy as to the suitable dosage of SMT for low back disorders. Future investigations may study the effect of dosage on biological outcome measures to determine appropriate or optimal prescriptions.

The application of manual therapy or SMT has many differing techniques and nuances including patient position, clinician hand contact, force application (rate, duration, amplitude, direction), and patient contact (spinous process, transverse process). For example, future studies may examine the biological effects of SMT applied to patient side-posture positioning to patient supine positioning. Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, future studies should include longer-term follow-up of biological outcomes, thereby improving the clinical applicability of the effects of SMT on spinal disorders.

This investigation only examined the effect of SMT in response to *mechanical* stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT. According to Coronado et al,[144] limited investigations have combined more than one stimulus modality or multi-regional application of the stimulus. By implementing this, future research could determine whether SMT alters global pain sensitivity or modality-specific sensitivity.[144]

4.1.1 Conclusions

Following a 3-week course of SMT in CNSLBP patients, changes in PPT did not significantly correlate to trunk angular velocity, and only correlated with a single trunk angular displacement (ROM) parameter. In addition, changes in PPT at the remote testing site (lateral epicondyle) by 3-weeks correlated to a patient-reported measure of disability (ODI) in CNSLBP patients. Collectively, our results suggest that mechanical pain sensitivity testing may have limited significance as a prognostic indicator for low back pain-related pain and function.

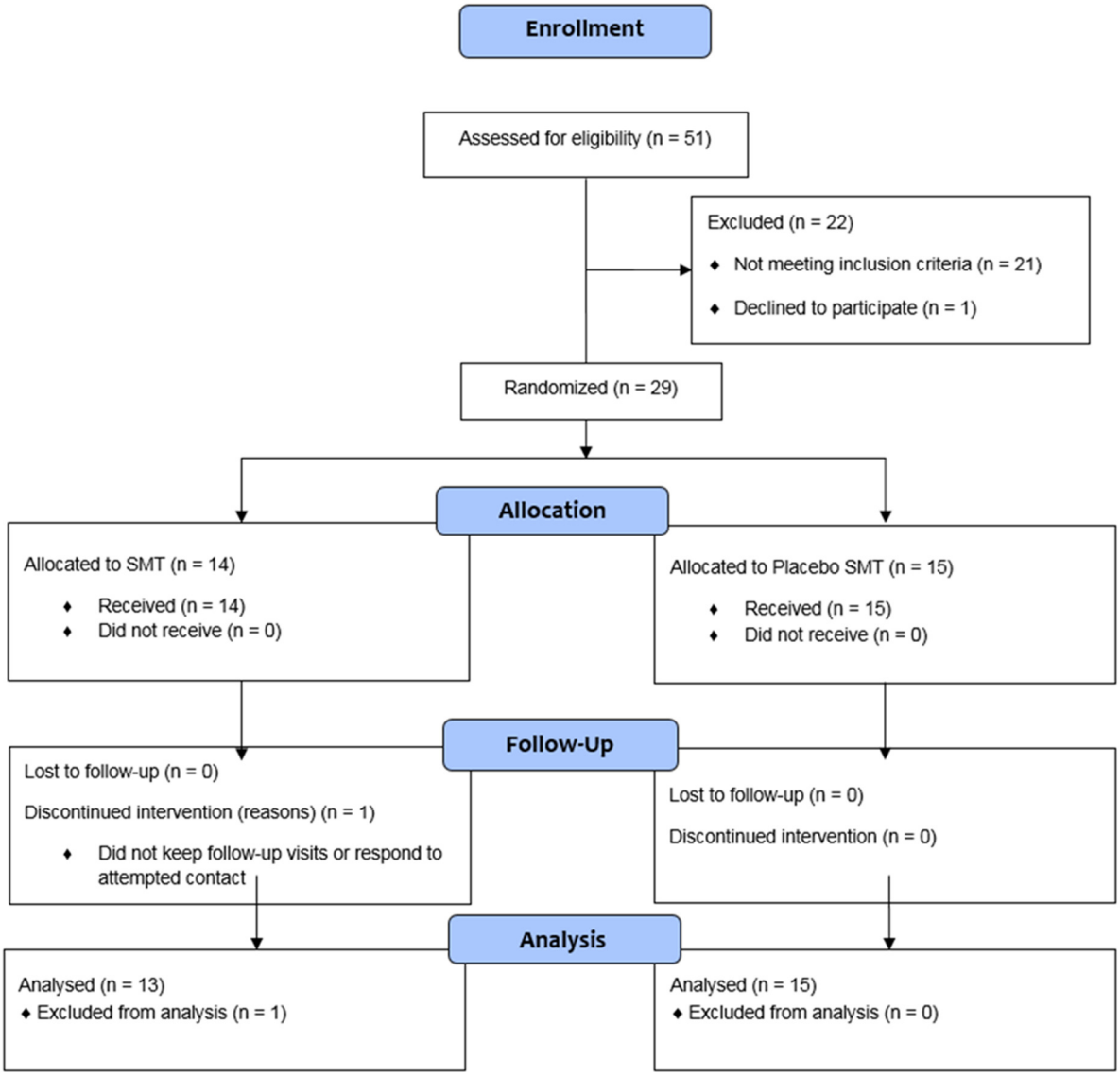

Figure 20: Overview of recruitment, enrollment, randomization, follow-up, and analysis for study. SMT = spinal manipulative therapy.

Figure 21: Spinal manipulative therapy and placebo spinal manipulative therapy.[79]

Table 12: Baseline Comparison of Intervention Groups.

	SMT	*Sham*	*Total Sample*	*p-value for difference*
Gender (% female)	6/14 (43)	5/15 (33)	11/29 (38)	.60
Age (years)	24.29 (7.33)	23.47 (3.94)	23.86 (5.74)	.71
Education (years)	17.00 (1.92)	17.20 (1.47)	17.10 (1.68)	.76
Duration of LBP (months)	45.07 (29.77)	43.00 (27.40)	44.00 (28.07)	.85
ODI	15.93 (6.23)	15.07 (6.79)	15.48 (6.91)	.74
NPRS	41.64 (12.70)	36.87 (17.25)	39.17 (15.15)	.41
PPT Local	3.39 (2.02)	3.36 (1.36)	3.37 (1.68)	.96
PPT Regional	4.36 (1.78)	4.88 (1.71)	4.63 (1.74)	.44
PPT Remote	2.95 (1.33)	3.19 (1.55)	3.08 (1.35)	.64
LTS (°)	101.34 (16.78)	100.36 (22.52)	100.81 (19.71)	.90
UTS (°)	104.83 (16.08)	106.86 (21.16)	105.92 (18.66)	.78
LR (°)	64.41 (10.07)	65.85 (8.89)	65.18 (9.31)	.69
RR (°)	63.84 (12.57)	70.28 (9.84)	67.29 (11.45)	.14
LLS (°/s)	40.97 (11.50)	33.15 (14.88)	36.78 (13.76)	.14
ULS (°/s)	63.46 (13.39)	57.85 (20.49)	60.45 (17.48)	.41
TLS (°/s)	53.86 (12.66)	49.37 (17.73)	51.45 (15.47)	.45
LTS (°/s)	66.65 (15.42)	63.42 (17.71)	64.92 (16.46)	.61
UTS (°/s)	50.26 (12.02)	45.28 (17.72)	47.58 (15.28)	.40

All data reported as mean (standard deviation) values. SMT = spinal manipulative therapy. LBP = low back pain. ODI = Oswestry Disability Index (0 – 100% with smaller numbers indicating less disability). NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. ° = degrees. °/s = degrees per second.

Table 13: Associations between Change in PPT and Change in Clinical Outcomes in CNSLBP Patients Receiving SMT.

Outcome Variable	*Immediate PPT Local*	*3-Week PPT Local*	*Immediate PPT Regional*	*3-Week PPT Regional*	*Immediate PPT Remote*	*3-Week PPT Remote*
NPRS						
Pearson r	-.115	-.005	.183	.425	-.309	.465
p value (2-tailed)	.709	.987	.550	.147	.305	.109
ODI						
Pearson r	-.211	-.198	.245	.121	-.206	.592*
p value (2-tailed)	.488	.517	.420	.694	.500	.033

SMT = spinal manipulative therapy. CNSLBP = chronic non-specific low back pain. ODI = Oswestry Disability Index (0 – 100% with smaller numbers indicating less disability). NPRS = numeric pain rating scale (0 = no pain to 100 = worst pain imaginable). PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. LLS = lower lumbar spine. *significant association at $p < .05$.

Table 14: Associations between Change in PPT and Change in Trunk Angular Displacement (ROM) in CNSLBP Patients Receiving SMT.

Outcome Variable	*Immediate PPT Local*	*3-Week PPT Local*	*Immediate PPT Regional*	*3-Week PPT Regional*	*Immediate PPT Remote*	*3-Week PPT Remote*
Immediate LLS						
Pearson r	.311	-.155	-.307	-.098	-.303	.553
p value (2-tailed)	.301	.301	.308	.751	.314	.050
3-Week LLS						
Pearson r	-.309	-.121	.007	.117	-.120	.073
p value (2-tailed)	.304	.694	.983	.703	.696	.812
Immediate ULS						
Pearson r	.413	.042	-.352	.070	-.162	.210
p value (2-tailed)	.161	.893	.238	.820	.597	.492
3-Week ULS						
Pearson r	-.282	.220	.035	.251	.012	-.115
p value (2-tailed)	.350	.470	.910	.407	.968	.709
Immediate TLS						
Pearson r	.412	-.093	-.378	-.045	-.285	.466
p value (2-tailed)	.162	.763	.202	.885	.345	.109
3-Week TLS						
Pearson r	-.211	.038	.055	.120	-.104	.002
p value (2-tailed)	.489	.901	.859	.697	.736	.994
Immediate LTS						
Pearson r	.243	.122	-.309	.114	-.047	-.071
p value (2-tailed)	.423	.691	.305	.712	.880	.817
3-Week LTS						
Pearson r	.447	.358	.044	-.293	.298	-.478
p value (2-tailed)	.126	.230	.887	.332	.323	.099
Immediate UTS						
Pearson r	-.128	.121	-.186	.238	-.039	-.317
p value (2-tailed)	.678	.693	.544	.434	.900	.291
3-Week UTS						
Pearson r	.461	.276	.219	-.448	.298	-.520
p value (2-tailed)	.113	.362	.471	.124	.323	.069
Immediate LR						
Pearson r	-.354	-.449	-.024	-.302	.191	-.292
p value (2-tailed)	.236	.124	.939	.316	.533	.333
3-Week LR						
Pearson r	-.118	.135	-.037	.455	-.016	-.220
p value (2-tailed)	.701	.660	.904	.118	.958	.466
Immediate RR						
Pearson r	-.205	-.207	-.452	-.483	.480	-.489
p value (2-tailed)	.502	.498	.121	.095	.097	.090
3-Week RR						
Pearson r	.102	.189	-.061	-.024	.405	-.556*
p value (2-tailed)	.741	.537	.843	.937	.170	.049

SMT = spinal manipulative therapy. CNSLBP = chronic non-specific low back pain. PPT = pressure pain threshold. PS = paraspinal musculature. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine. LR = left rotation. RR = right rotation. *significant association at $p < .05$.

Table 15: Associations between Change in PPT and Change in Trunk Angular Velocity in CNSLBP Patients Receiving SMT.

Outcome Variable	*Immediate PPT Local*	*3-Week PPT Local*	*Immediate PPT Regional*	*3-Week PPT Regional*	*Immediate PPT Remote*	*3-Week PPT Remote*
Immediate LLS						
Pearson r	-.155	-.202	-.197	.228	-.261	.450
p value (2-tailed)	.614	.509	.518	.453	.389	.123
3-Week LLS						
Pearson r	-.360	.061	-.025	.167	-.083	.111
p value (2-tailed)	.228	.844	.935	.586	.787	.718
Immediate ULS						
Pearson r	-.427	-.340	-.062	.351	-.200	.304
p value (2-tailed)	.146	.256	.839	.239	.513	.313
3-Week ULS						
Pearson r	-.343	.230	-.001	.283	-.057	.118
p value (2-tailed)	.251	.450	.998	.349	.853	.701
Immediate TLS						
Pearson r	-.305	-.300	-.131	.291	-.250	.404
p value (2-tailed)	.310	.319	.670	.334	.410	.171
3-Week TLS						
Pearson r	-.299	.156	-.001	.201	-.091	.121
p value (2-tailed)	.321	.611	.997	.510	.768	.694
Immediate LTS						
Pearson r	-.473	-.317	.003	.365	-.120	.187
p value (2-tailed)	.103	.292	.994	.220	.697	.542
3-Week LTS						
Pearson r	-.063	.350	.088	.141	.029	.038
p value (2-tailed)	.837	.241	.774	.647	.926	.901
Immediate UTS						
Pearson r	-.495	-.258	.082	.362	-.076	.054
p value (2-tailed)	.085	.396	.791	.225	.805	.861
3-Week UTS						
Pearson r	-.128	.285	.243	.078	.057	-.007
p value (2-tailed)	.677	.345	.423	799	.852	.981

SMT = spinal manipulative therapy. CNSLBP = chronic non-specific low back pain. PPT = pressure pain threshold expressed in kg/cm^2. Local = paraspinal musculature. Regional = tibialis anterior muscle. Remote = lateral epicondyle. LLS = lower lumbar spine. ULS = upper lumbar spine. TLS = total lumbar spine. LTS = lower thoracic spine. UTS = upper thoracic spine.

CHAPTER 5

Conclusion

5.1 Summary of Findings

5.1.1 Chapter 2. Effect of spinal manipulative therapy on mechanical pain sensitivity in patients with chronic non-specific low back pain: a randomized, controlled trial

The purpose of this study was to examine the effect of SMT on clinical outcome measures and PPT at different anatomical sites in CNSLBP patients. These experiments were conducted to improve the understanding of the biological mechanisms associated with SMT. Our findings suggest that SMT and sham SMT reduced hypersensitivity (increased PPT) at local and regional anatomical sites at 3-weeks, as shown in a significant main effect for time. Furthermore, a significant main effect for time was observed for reduced pain and disability. However, no between-group differences were observed in measures of PPT, clinical pain, or disability over the three weeks of the study between the SMT and sham SMT groups. In summary, our findings indicate that SMT or sham SMT may influence peripheral and/or central pain pathways in CNSLBP patients, independent of *how* the spinal manipulation was applied.

5.1.2 Chapter 3. Effect of spinal manipulative therapy on trunk kinematics in patients with chronic non-specific low back pain: a randomized, controlled trial

While many studies have reported abnormal kinematics associated with low back disorders,[22,160-164] the effect of SMT on trunk angular displacement/ROM and velocity in CNSLBP remains unclear. [65,169-172] The purpose of this chapter was to examine the effect of SMT on sagittal and transverse plane trunk movements in patients with CNSLBP pain. Following a 3-week course of SMT or sham SMT in CNSLBP patients, we found no significant changes in trunk range of

motion (ROM) within the sagittal plane, while changes in trunk angular velocity, either improved or diminished, dependent upon the spinal region. Also, the sham SMT group exhibited an improvement in trunk rotational ROM, while the SMT group did not significantly increase transverse plane (rotation) trunk ROM. Finally, there was no difference between the two interventions in terms of trunk ROM or angular velocity, except upper lumbar spine (ULS) ROM in the SMT group compared to the sham SMT group. Collectively, our results suggest that the application of a mechanical load to the spine modulates kinematics disregarding *how* the force is applied. However, the standard SMT may produce superior improvement in spinal kinematic responses than the sham SMT at 3-weeks post-intervention in CNSLBP patients.

5.1.3 Chapter 4. Relationship between spinal manipulative therapy-induced changes in biological outcome measures in chronic non-specific low back pain patients

We further conducted an exploratory study to determine the relationship between SMT-induced changes in biological outcome measures in CNSLBP patients. We felt that these analyses of correlations were important because clinicians managing low back pain evaluate regional ROM to determine the severity of the condition or assign disability, along with use as outcome measure to determine treatment effectiveness.[208,209] Following successful SMT in CNSLBP patients, a significant correlation between reductions in PPT (hypolagesia) at local and/or remote anatomical regions and spinal kinematics (angular displacement and velocity) might suggest a relationship between diminished pain and improved trunk movements. Moreover, if modulation of peripheral and/or central sensitization following SMT are fundamental neurophysiological mechanisms associated with CLBP, and presuming that PPT is a valid marker of sensitization, then a predictable, consistent relationship might exist between pain threshold and patient-reported pain/disability.[207] Subsequent a 3-week course of SMT in CNSLBP patients, changes in PPT did

not significantly correlate to trunk angular velocity, and only correlated to a single trunk angular displacement (ROM) parameter. Furthermore, changes in PPT at the remote testing site (lateral epicondyle) by 3-weeks correlated to a patient-reported measure of disability (ODI) in CNSLBP patients. Collectively, our results suggest that mechanical pain sensitivity testing may have limited significance as a prognostic indicator for low back pain-related pain and function.

5.2 Clinical Implications

Past studies have suggested that SMT mitigates spinal pain and function through biomechanical and/or neurophysiological mechanisms, and pain modulation may include peripheral and central nervous system pathways.[45-52] Our research may contribute to the therapeutic principles related to managing low back disorders, thereby improving the clinical outcomes for low back pain patients, as specifically described in the following paragraphs.

The finding of the current study indicated that PPT can be improved at local and remote anatomical sites following 3-weeks (6 interventions) of SMT in patients with CNSLBP, and that the application of a mechanical load to the spine appears to elicit a neurophysiological response, independent of *how* the force is applied. Results of this study support the use of SMT or its variation in patients with chronic low back disorders. Furthermore, the specific technique of how the spinal manipulation is conducted may be less important, as long as a mechanical load is applied to the spine. This topic needs to be further explored in the future to determine the critical component of the spinal manipulation that lead to improvement in CNSLBP.

The finding of this study that SMT and sham SMT elicited a favorable kinematic response at 3-weeks post-intervention in CNSLBP patients suggests that neurophysiological and/or

mechanical responses lead to biomechanical adaptations that facilitate improvement in trunk angular velocity. Though not significant, the SMT group showed more favorable improvements in trunk angular displacement in the SMT group than the sham SMT group at 3-weeks post-intervention. It is therefore recommended to use the standard SMT in the clinical setting, even though some technique variations may influence trunk kinematics.

Our exploratory study examining the relationship between SMT-induced changes in biological outcome measures in CNSLBP subjects advocates that changes in PPT for the SMT group did not significantly correlate to trunk angular velocity, and only correlated with a single trunk angular displacement parameter. For clinical outcomes (NPRS and ODI), our results indicate that changes in PPT at the remote location (lateral epicondyle) by 3-weeks correlated to Oswestry Disability Index scores. Collectively, these results suggest that mechanical pain sensitivity testing may have limited significance as a prognostic indicator for low back pain-related pain and function. Because of the exploratory nature of this preliminary investigation, this topic needs to be further explored in the future to determine the precise relationship between pain and function in low back pain patients.

5.3 Limitations

The results of the present investigation should be examined with attention to several limitations.

5.3.1 Small Sample Size

The current study was a pilot study involving a prospective, randomized, single-blinded clinical trial of 3-week spinal manipulative therapy in individuals with CNSLBP. Although we met our sample size estimation (n = 29), our study may be underpowered to detect biological changes in CNSLBP patients after SMT. Based upon our *post-hoc* analyses, we obtained an observed power value < 80% for our dependent variables between-subjects effects, thus we acknowledge the possibility of a type II error. In addition, because of the limited sample size associated with this pilot project, we did not perform a Bonferroni correction for multiple comparisons for our exploratory study examining the relationship between SMT-induced changes in biological outcome measures. Thus, we acknowledge the possibility of a type I error when interpreting these results.

5.3.2 Study Design

There may be potential bias in the recruited sample, especially for a small sample. Scientific literature has suggested that within low back patients there may be sub-groups that respond differently to specific interventions.[19,193] For example, a clinical decision rule outlining acute low back patients likely to respond to spinal manipulation reported several predictor criteria, including symptom location (proximal to knee).[193] As an attempt to adhere to predictors of response to spinal manipulation, our study criteria limited the sample population to CNSLBP patients with *no* distal symptoms.

Another limitation of the current study was that the design of the study did not help us determine whether or not the differences we observed in the dependent variables were present in

the subjects before the onset of pain or after low back pain developed. There may have been adaptations in spinal tissues such as muscle and/or joint stiffness, and specific nervous system characteristics, such as individual variance in perception of pain that might have affected our results. However, we attempted to lessen the influence of these factors through random allocation of subjects to either intervention or control groups.

5.3.3 Long-Term Follow-up

This study may have been more clinically meaningful if we had monitored our subjects at some further time interval (6 months or 1 year). Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, long-term follow-up might provide us with a more consequential measure of the effect of SMT on CNSLBP, thereby contributing to the development of more comprehensive evidence-based practice guidelines for managing low back disorders.

5.3.4 Mechanical Stimulus

Pressure may be considered a non-specific stimulation that elicits a response from mechanoreceptors and nociceptors in surrounding tissues.[200] Pressure pain threshold (PPT) may be used as an *indirect* measure of peripheral and central sensitization for musculoskeletal disorders.[46] In addition, a slow, gradual application of pressure until a pain threshold is reached might reflect a different neural pathway than rapidly applied stimuli.[200] This investigation only examined the effect of SMT in response to mechanical stimuli, but other painful stimuli including

thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT.

5.3.5 Sham SMT

The placebo SMT used for our experimental design aimed to apply a thrust on the spine towards the table with the spine positioned in neutral (without trunk lateral bending). However, our sham SMT produced improvements in clinical, neurophysiological, and biomechanical outcome measures. Bialosky et al[79] conceded that this sham SMT applied a *mechanical load* to the spine. Thus, a *mechanical stimulus* following sham SMT may elicit a cascade of potential biological effects, thereby accounting for the therapeutic effects associated with our sham intervention.[45,46,72] Therefore, our results suggest that the application of a mechanical load to the spine elicited a neurophysiological response, but *how* the load is applied appears less important.

5.4 Future Directions

Based upon our literature review in the introduction chapter, the biological mechanisms associated with SMT appear multifaceted and complex. Thus, we propose additional extensions of this body of work to address these complexities.

5.4.1 Dosage Effect

Though the effectiveness of SMT on clinical outcomes has been previously investigated, there remains controversy as to the suitable dosage of SMT for low back disorders. Future investigations

may study the effect of dosage on biological outcome measures to determine appropriate or optimal prescriptions.

5.4.2 Technique Comparison

The application of manual therapy or SMT has many differing techniques and nuances including patient position, clinician hand contact, force application (rate, duration, amplitude, direction), and patient contact (spinous process, transverse process). For example, future studies may examine the biological effects of SMT applied to patient side-posture positioning to patient supine positioning.

5.4.3 Long-Term Follow-up

Our study only examined the immediate effects of SMT on CNSLBP patients, so it is feasible that neurophysiological and biomechanical adaptations manifest over a longer duration. Thus, future studies should include longer-term follow-up of biological outcomes, thereby improving the clinical applicability of the effects of SMT on spinal disorders.

5.4.4 Pain Stimulus

This investigation only examined the effect of SMT in response to *mechanical* stimuli, but other painful stimuli including thermal and chemical may elicit distinct neural responses or produce unique results after the application of SMT. According to Coronado et al,[144] limited investigations have combined more than one stimulus modality or multi-regional application of

the stimulus. By implementing this, future research could determine whether SMT alters global pain sensitivity or modality-specific sensitivity.[144]

5.5 Conclusions

The body of work represented in this dissertation expands the current literature related to the biological effects of SMT in CNSLBP subjects. The limited knowledge about the therapeutic mechanisms associated with SMT in patients with CNSLBP led us to develop this study. This is the first study that demonstrates the effect of SMT on PPT at local, regional, and remote testing sites in low back patients. Furthermore, the results demonstrate that SMT and sham SMT can lead to significant improvements in pain and patient-reported disability along with trunk kinematics in CNSLBP patients. Though not significant, the SMT group showed more favorable improvements in trunk angular displacement in the SMT group than the sham SMT group at 3-weeks post-intervention. It is therefore recommended to use the standard SMT in the clinical setting, even though some technique variations may influence trunk kinematics. However, the relationship between SMT-induced changes in biological outcome measures appears limited.

Results of this study support the use of SMT or its variation in patients with CNSLBP. Furthermore, the specific technique of *how* the spinal manipulation is conducted may be less important, as long as a mechanical load is applied to the spine. Overall, the presented work stipulates concomitant evidence that SMT is an effective intervention in patients with CNSLBP. Nevertheless, further study with a larger sample size and longer-term outcome is required to better appreciate the biological mechanisms associated with SMT. The findings of this work have implications for research/rehabilitation of individuals with CNSLBP, a common musculoskeletal disorder impairing the daily lives of the far-reaching global population.

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Appendix A

Oswestry Disability Index

Oswestry Disability Index

Section 1 – Pain Intensity

- ❑ I have no pain at the moment.
- ❑ The pain is very mild at the moment.
- ❑ The pain is moderate at the moment.
- ❑ The pain is fairly severe at the moment.
- ❑ The pain is very severe at the moment.
- ❑ The pain is the worst imaginable at the moment.

Section 2 – Personal Care (washing, dressing, etc.)

- ❑ I can look after myself normally but it is very painful.
- ❑ I can look after myself normally but it is very painful.
- ❑ It is painful to look after myself and I am slow and careful.
- ❑ I need some help but manage most of my personal care.
- ❑ I need help every day in most aspects of my personal care.
- ❑ I need help every day in most aspects of self-care.
- ❑ I do not get dressed, wash with difficulty, and stay in bed.

Section 3 - Lifting

- ❑ I can lift heavy weights without extra pain.
- ❑ I can lift heavy weights but it gives extra pain.
- ❑ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned (i.e. on a table).
- ❑ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned.
- ❑ I can lift only very light weights.
- ❑ I cannot lift or carry anything at all.

Section 4 – Walking

- ❑ Pain does not prevent me walking any distance.
- ❑ Pain prevents me walking more than 1mile.
- ❑ Pain prevents me walking more than ¼ of a mile.
- ❑ Pain prevents me walking more than 100 yards.
- ❑ I can only walk using a stick or crutches.
- ❑ I am in bed most of the time and have to crawl to the toilet.

Section 5 – Sitting

- ❑ I can sit in any chair as long as I like.
- ❑ I can sit in my favorite chair as long as I like.
- ❑ Pain prevents me from sitting for more than 1 hour.
- ❑ Pain prevents me from sitting for more than ½ hour.
- ❑ Pain prevents me from sitting for more than 10 minutes.
- ❑ Pain prevents me from sitting at all.

Section 6 – Standing

- ❑ I can stand as long as I want without extra pain.
- ❑ I can stand as long as I want but it gives me extra pain.
- ❑ Pain prevents me from standing more than 1 hour.
- ❑ Pain prevents me from standing for more than ½ an hour.
- ❑ Pain prevents me from standing for more than 10 minutes.
- ❑ Pain prevents me from standing at all.

Section 7 – Sleeping

- ❑ My sleep is never disturbed by pain.
- ❑ My sleep is occasionally disturbed by pain.
- ❑ Because of pain, I have less than 6 hours sleep.
- ❑ Because of pain, I have less than 4 hours sleep.
- ❑ Because of pain, I have less than 2 hours sleep.
- ❑ Pain prevents me from sleeping at all.

Section 8 – Sex life (if applicable)

- ❑ My sex life is normal and causes no extra pain.
- ❑ My sex life is normal but causes some extra pain.
- ❑ My sex life is nearly normal but is very painful.
- ❑ My sex life is severely restricted by pain.
- ❑ My sex life is nearly absent because of pain.
- ❑ Pain prevents any sex life at all.

Section 9 – Social Life

- ❑ My social life is normal and cause me no extra pain.
- ❑ My social life is normal but increases the degree of pain.
- ❑ Pain has no significant effect on my social life apart from limitingmy more energetic interests, i.e. sports.
- ❑ Pain has restricted my social life and I do not go out as often.
- ❑ Pain has restricted social life to my home.
- ❑ I have no social life because of pain.

Section 10 – Traveling

- ❑ I can travel anywhere without pain.
- ❑ I can travel anywhere but it gives extra pain.
- ❑ Pain is bad but I manage journeys of over two hours.
- ❑ Pain restricts me to short necessary journeys under 30 minutes.
- ❑ Pain prevents me from traveling except to receive treatment.

Section 11 - Previous Treatment

Over the past three months have you received treatment, tablets or medicines of any kind for your back or leg pain? Please check the appropriate box.

- ❑ No
- ❑ Yes (if yes, please state the type of treatment you have received)