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The Role of Spinal Manipulation in Modifying Central Sensitization

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Central sensitization (CS) is characterized by adaptations to the central nervous system resulting in decreased sensory thresholds and widespread hypersensitivity. CS is often difficult to manage, with current treatment strategies primarily consisting of medication, pain science education, cognitive behavioral therapy, and graded exercise intervention. Spinal manipulation represents a potential alternative treatment for CS because of its centrally acting neurophysiological mechanisms. However, experimental trials utilizing spinal manipulation in persons with CS often lack the controls or methodology required to determine the technique's effect on meaningful clinical outcomes. This paper summarizes the mechanistic and experimental evidence on spinal manipulation for centrally mediated pain and hypersensitivity, and offers recommendations for future study considerations in this topic area.

Scientific discoveries over the past three decades have significantly advanced the understanding of how human beings perceive pain. The mechanisms driving the perception of pain are now known to be very complex, involving bidirectional interactions between the peripheral nociceptors, spinal cord, and supraspinal centers (Bialosky, Bishop, Price, Robinson, & George, 2009; Bingham, Ajit, Blake, & Samad, 2009; Nijs & Van Houdenhove, 2009). Where pain was once thought of primarily as a "bottom-up" experience, driven by peripheral nociceptors, more recognition is now being given to the "top-down" perpetuation of pain. This theoretical shift has supported the conceptual development of central sensitization (CS), whereby plastic changes in the spinal cord and supraspinal centers can become the main drivers of pain perpetuation (Woolf, 2011). CS is believed to be at work in fibromyalgia, complex regional pain syndrome (CRPS), and various chronic musculoskeletal disorders, which may help explain the challenging task of medical management for these conditions (Woolf, 2011).

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The development of CS has been associated with several physiological adaptations in the central nervous system. The dorsal horn neurons of the spinal cord have received considerable attention for their potential role in causing CS (Herrero, Laird, & Lopez-Garcia, 2000). Through a process known as temporal summation, a repetitive, consistent-level noxious stimulus to peripheral C-fibers has been shown to create a progressive increase in the perceived intensity level of the stimulus (Herrero et al., 2000). Although temporal summation occurs normally and is self-limiting when the noxious stimulus is short lived, the process is altered when a persistent noxious stimulus is introduced. In persons with chronic pain and hypersensitivity to painful stimuli, or hyperalgesia, temporal summation of C-fiber transmission may explain the decreased sensory threshold required for pain perception (George, Bishop, Bialosky, Zeppieri, & Robinson, 2006). Furthermore, temporal summation of A-beta fiber transmission, which has only been demonstrated in persons with hyperalgesia, may help explain the hypersensitivity to normally innocuous stimuli, or allodynia, common in persons with CS (Herrero et al., 2000).

Afferent pain signals project from the spinal cord to the supraspinal centers, where they have the potential to be magnified or inhibited based on the activation of key areas in the brain. The capacity for the supraspinal centers to magnify pain perception is believed to be a critical component in the development of CS and certain chronic conditions (Bialosky et al., 2009). The thalamus serves as the primary relay for sending afferent pain signals to the insular, somatosensory, and prefrontal cortices for processing (Bingham et al., 2009). When continuous, abnormal afferent input is presented to the somatosensory cortex, the result is altered sensorimotor integration and impaired movement, which can lead to pain and altered motor control (Haavik & Murphy, 2012). In the event that stress, depression, kinesiophobia, catastrophizing, or somatization is present, the insular and prefrontal cortices can also magnify pain perception by affecting the function of the midbrain periaqueductal gray (PAG) (Nijs & Van Houdenhove, 2009).

The midbrain PAG receives inputs from the frontal and insular cortices, amygdala, and hypothalamus to determine the contribution of physical and psychological stimuli to descending pain inhibition (Bingham et al., 2009). Normally, stimulation of the PAG is associated with facilitation of motor activity, excitation of the sympathetic nervous system (SNS), and hypoalgesia (Sterling, Jull, & Wright, 2001). However, physiological adaptations in the PAG associated with CS can lead to malfunctioning of the descending pain inhibitory pathways and inhibited function of the SNS (Nijs & Van Houdenhove, 2009). The disruption of descending pain inhibition is particularly evident when persons with CS perform isometric or aerobic exercise, or display inappropriate cognitive-emotional processing (Nijs & Van Houdenhove, 2009). In these cases, the presence of physical or psychological stimuli can create a negative feedback loop on the descending pain inhibitory pathways, thus serving to further perpetuate the person's pain and hypersensitivity.

The preceding paragraphs provide a simplistic description of the primary mechanisms believed to be at work in CS. A key concept in pain processing is the interconnectivity of the peripheral, spinal cord, and supraspinal centers. Pain processing in CS should not be viewed solely as a "top-down" event, but should also account for the role of peripheral ("bottom-up") nociception in the perpetuation of centrally mediated pain. The ability to address both central and peripheral nociception appears to be vital for the successful management of CS. Medical management of CS typically involves some combination of medication, pain science education, cognitive behavioral therapy, and graded exercise intervention (Nijs & Van Houdenhove, 2009). These treatments have generally been reported to achieve favorable outcomes in systematic reviews of the literature (Nijs & Van Houdenhove, 2009; Schneider, Vernon, Ko, Lawson, & Perera, 2009). The use of spinal manipulation for altering clinical outcomes in persons with signs of CS has received a limited amount of study to date. Rather, most studies related to this topic focus on describing the neurophysiological effects of spinal manipulation, with the view that finding a central nervous system mechanism supports the potential use of manipulation in conditions characterized by CS (Bialosky et al., 2009). The purpose of this paper is to review the latest evidence for the proposed neurophysiological mechanisms of spinal manipulation and to present evidence for the use of spinal manipulation in the management of conditions characterized by CS.

Methods

A literature search was performed in PubMed and CINAHL between the months of July and September 2013. Search terms were selected based on their use as PubMed "MeSH" or CINAHL "Headings." Table 1 lists the MeSH or Heading terms used to identify articles that included different forms of thrust or non-thrust spinal joint manipulation. For the purposes of this paper, spinal manipulation was defined as the manual (non-instrumented) application of passive accessory (e.g., glide) or physiological (e.g., rotation) motions to one or more levels of the spine for the purpose of altering spinal motion or position, or inducing a neurophysiological or psychological effect. Manipulation techniques considered for this paper had to be applied to the cervical, thoracic, or lumbosacral spine, but could vary in terms of their amplitude (depth), frequency rate (number of oscillations per second), and whether or not a thrust was incorporated. Thrust manipulation was defined as the utilization of a high-velocity, low-amplitude force at the end of the available joint range of motion, typically accompanied by an audible pop, or cavitation. Non-thrust

Table 1

MeSH and Heading Terms Used in PubMed and CINAHL Searches

Manipulation MeSH and Heading terms	CS-related MeSH and Heading terms
"Manipulation, Chiropractic"[ab]	"Pain"[ab]
"Manipulation, Spinal"[a]	"Chronic Pain"[ab]
"Manipulation, Orthopedic"[a]	"Pain Perception"[a]
"Musculoskeletal Manipulations"[a]	"Complex Regional Pain Syndromes"[a]
"Chiropractic"[a]	"Reflex Sympathetic Dystrophy"[a]
"Manipulation, Osteopathic"[a]	"Fibromyalgia"[a]
	"Thoracic Vertebrae"[a]
	"Sympathetic Nervous System"[a]

[a]Denotes MeSH Term.
[b]Denotes Heading Term.
CS = central sensitization.

manipulation was defined as the utilization of variable amplitudes and frequency rates to deliver force at the end of the available joint range without the application of a thrust.

Table 1 also lists the MeSH or Heading terms used to identify articles that investigated CS-related outcome variables or conditions characterized by CS. Pain, pain perception, and sympathetic nervous system were used as search terms because of their connection to CS-related outcome variables such as pressure pain threshold, allodynia, nociceptive reflex threshold, motor function, and SNS function. The terms chronic pain, fibromyalgia, complex regional pain syndrome, and reflex sympathetic dystrophy were chosen because these conditions have a strong link to CS. Finally, the term thoracic vertebra was chosen because manipulation to this region has the potential for wide-ranging central nervous system effects due to the close proximity of the thoracic costovertebral joints to the thoracic sympathetic chain ganglia, and the location of the critical vascular zone of the spinal cord between T4 and T9. Manipulation and CS-related terms were combined using Boolean operators to achieve search results. Both mechanistic and experimental studies were included for this review. Over 100 abstracts were assessed for their relevancy to this topic area. Forty-two articles and one text were chosen for inclusion in this review based on their ability to specifically address the dual purposes of this paper.

Results

Neurophysiological Effects of Spinal Manipulation

A review of mechanistic studies reveals that spinal manipulation may impact many of the same areas of the central nervous system that are altered by CS. The shared presence of neurophysiological changes at the dorsal horn, PAG, and cerebral cortex provides a potential mechanism by which manipulation could be considered as a treatment for centrally mediated pain. Support for a central neurophysiological effect is seen in studies that find *regional* mechanical hypoalgesia, changes in SNS function, changes in spinal cord hyperexcitability, and changes in sensorimotor integration and motor control following manipulation (Bialosky et al., 2009; Bishop, Beneciuk, & George, 2011; Coronado et al., 2012; Haavik & Murphy, 2012; Schmid, Brunner, Wright, & Bachmann, 2008). Additionally, support for a peripheral mechanism to manipulation is derived from studies that demonstrate *local* mechanical hypoalgesia and reflex changes to muscles innervated by the treated joint (Bialosky et al., 2009). Support for the neurophysiological effects of manipulation should not be equated with actual improvements in pain and muscle function in a symptomatic population, as many mechanistic studies are not designed to make this link. The following paragraphs will specifically review the central mechanisms of spinal manipulation most relevant for addressing the pathophysiology of CS in the midbrain, spinal cord, and cerebral cortex.

Spinal manipulation appears to positively impact the midbrain at the level of descending pain pathway inhibition and SNS function, each of which are disrupted in persons with CS. Type I and II peripheral mechanoreceptors activated during thrust or non-thrust manipulation act on the PAG to trigger non-opioid descending pain inhibitory pathways (Olson, 2009). This process may help explain the regional (extrasegmental) mechanical hypoalgesia seen after manipulation, although evidence also exists to support the role of the spinal cord in producing regional (segmental) pressure pain threshold reduction (Coronado et al., 2012; Schmid et al., 2008; Srbely, Vernon, Lee, & Polgar, 2013). Additionally, manipulation is believed to elicit a sympathoexcitatory response from the PAG, which may provide an additional measure of extrasegmental pain inhibition and alteration of physiological function. Evidence for sympathoexcitation has been repeatedly shown through an elevation in skin conductance, heart rate, blood pressure, and respiratory rate immediately after joint manipulation (Moulson & Watson, 2006; Perry & Green, 2008; Perry, Green, Singh, & Watson, 2011; Schmid et al., 2008; Sterling et al., 2001). However, studies assessing changes in pupil diameter and plasma levels of circulating catecholamines have not consistently supported an SNS response to joint manipulation (Puhl & Injeyan, 2012; Sillevis, Cleland, Hellman, & Beekhuizen, 2010).

Recent studies have also provided strong evidence of decreased spinal cord hyperexcitability following spinal manipulation (Bishop et al., 2011; Sterling et al., 2010). The mechanism for this change, which has been demonstrated in normal subjects and those with pain, has been linked to an attenuation of dorsal horn excitability in the spinal cord and a reduction of abnormal afferent signaling to the somatosensory cortex (Herrero et al., 2000). Reduced spinal cord excitability may be measured as an increase in the nociceptive flexion reflex threshold or a reduction in temporal summation of thermal pain sensitivity (Herrero et al., 2000). Changes in temporal summation have been shown to occur in dermatomes caudal to the manipulated spinal region, but not in dermatomes cranial to the region (Bishop et al., 2011). The presence or absence of a cavitation during a thrust manipulation was not associated with any significant difference in the ability to decrease temporal summation following the technique (Bialosky, Bishop, Robinson, & George, 2010).

Evidence of a cortical change after spinal manipulation has only recently been presented in the medical literature. Haavik and Murphy (2012) hypothesize that areas of spinal dysfunction, characterized by local pathology or altered joint movement, can send faulty afferent input to the somatosensory cortex. This faulty input, known as disordered sensorimotor integration, can then contribute to altered motor control, pain, and functional disability. Thus far, researchers have largely focused on the ability of manipulation to address disordered sensorimotor integration and altered motor control by improving local joint movement. Alterations in somatosensory-evoked potentials and joint position sense (proprioception) have been observed immediately after manipulation (Haavik & Murphy, 2012). These measurements suggest improvements in somatosensory processing and integration of proprioceptive inputs, each of which may indirectly decrease pain through enhanced postural control. While it is possible that these changes could be produced by spinal cord or subcortical regions, the cortex is believed to contribute at least partially to the sensory and motor effects demonstrated (Haavik & Murphy, 2012). Additionally, evidence for the direct inhibition of experimentally induced pain is seen from functional magnetic resonance imaging, which shows a significant relationship between reduced oxygenation of the insular cortex and reduced subjective pain ratings (on an 11-point numeric pain rating scale) immediately after thrust manipulation in normal subjects (Sparks, Cleland, Elliott, Zagardo, & Liu, 2013).

The cortex is also believed to contribute to the degree of pain perceived after spinal manipulation. Evidence suggests that the participant's expectation of the likely response to manipulation can significantly impact the actual response to the technique (Bialosky, Bishop, Robinson, Barabas, & George, 2008). Participants who were told to expect a negative response to manipulation reported region-specific hyperalgesia post treatment, while those with neutral or positive expectations reported no significant change in technique response (Bialosky et al., 2008). These findings may support the potential for negative emotions stemming from the cortex to block descending anti-nociceptive pathways from the PAG.

Motor control alteration following manipulation represents another research area for consideration. Motor responses after manipulation are primarily reported in persons with pain, which begs the question whether motor changes should be linked to the manipulation itself, or the pain inhibition that may accompany the manipulation (Ferreira, Ferreira, & Hodges, 2007; Schmid et al., 2008). Both facilitation and inhibition of local and segmental muscle activation has been reported immediately post manipulation (Clark et al., 2011; de Camargo et al., 2011; Harvey & Descarreaux, 2013). Two types of inhibitory effects have been described in persons with low back pain. Direct inhibitory effects occur via an actual reduction in muscle activity post manipulation (DeVocht, Pickar, & Wilder, 2005), while indirect inhibitory effects occur through delayed (up to 30 minutes) increases in self-reported pain intensity and muscle activation when performing pain-inducing activity post manipulation (Harvey & Descarreaux, 2013). Alterations in muscle activation have long been associated with changes in excitation of spinal muscle motoneurons by peripheral mechanoreceptors in the joints, ligaments, and muscles (Olson, 2009). Attenuation of the local stretch reflex, possibly due to reduced sensitivity of muscle spindles or sites along the Ia reflex pathway, provides additional evidence for spinal cord-induced muscle inhibition after thrust manipulation accompanied by cavitation (Clark et al., 2011; Orakifar, Kamali, Pirouzi, & Jamshidi, 2012).

Evidence also suggests a supraspinal mechanism for motor control alterations, with both the PAG and cortex linked to these changes. Facilitation of the deep neck flexor muscles following non-thrust manipulation to the cervical spine has been hypothesized to stem from activation of the dorsal PAG, although no direct evidence has been provided in support of this claim (Schmid et al., 2008). Claims of a cortical connection to motor control changes appear more substantial, as evidenced by improvement in feed-forward muscle activation time after thrust manipulation (Haavik & Murphy, 2012). Furthermore, transcranial magnetic stimulation has been used to detect changes in short-interval-intracortical motor inhibition and facilitation responses following thrust manipulation (Haavik & Murphy, 2012). However, the duration of cortical motor responses may be brief, as motor-evoked potentials showed no evidence of alteration 10 minutes after manipulation (Clark et al., 2011).

In summary, the evidence to date on spinal manipulation suggests that both peripheral and central mechanisms are responsible for the physiological changes observed following the technique (Bialosky et al., 2009; Coronado et al., 2012). The majority of trials investigating the central mechanisms of spinal manipulation support the presence of short-term spinal cord and supraspinal physiological responses after treatment. Since many mechanistic studies are performed on normal participants using nonclinical outcome measures, the ability to extrapolate these physiological findings to pain or disability measures, in a population with CS, is limited. Furthermore, posttreatment testing is often immediate in mechanistic studies, which limits the ability to draw longer term conclusions regarding the effects of manipulation. Evidence for the actual clinical benefits of manipulation can be found in a multitude of experimental studies, with pain and functional improvements reported in those with low back pain, carpal tunnel syndrome, and lower extremity osteoarthritis (Bialosky et al., 2009). The following section will provide additional evidence for the clinical application of manipulation in conditions characterized by CS.

Spinal Manipulation for Modifying CS

The first step in determining optimal treatment for CS is proper recognition of the condition. Several signs have been proposed for making the clinical diagnosis of CS. The most typically reported findings include reduction in regional mechanical (but not thermal) pain threshold, presence of tactile allodynia, and reduced nociceptive reflex threshold (Nijs, Van Houdenhove, & Oostendorp, 2010; Woolf, 2011). Additional signs may include hypoesthesia or hypersensitivity to bright light, noise, pesticides, medications, and extreme temperatures (Nijs et al., 2010). Studies that include participants with these diagnostic signs typically use changes in pressure pain threshold, pain intensity, sensation, hyperalgesia, or SNS function as evidence of the clinical effects of spinal manipulation. The following section will describe the clinical effects of manipulation for central sensitivity syndromes. Central sensitivity syndromes are most often linked to fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, interstitial cystitis, headache, and myofascial pain syndrome (Kindler, Bennett, & Jones, 2011; Yunus, 2008). Specifically, this paper will focus on those central sensitivity syndromes where spinal manipulation has been tested most often, such as fibromyalgia, CRPS, chronic whiplash-associated disorders (WADs), temporomandibular disorders (TMDs), and lateral epicondylitis (Nijs et al., 2010; Woolf, 2011).

Numerous studies have provided strong evidence of an association between fibromyalgia and CS (Nijs et al., 2010; Schneider et al., 2009; Woolf, 2011). Fibromyalgia is one of only a few conditions where CS is characteristic of the entire disorder, as opposed to being present in a subgroup of persons with the disorder (Nijs et al., 2010). The role of spinal manipulation in the management of fibromyalgia has received limited study to date, making it difficult to draw definitive conclusions on the efficacy of the intervention. The use of manipulation for fibromyalgia can at best be supported by weak evidence, based on a preponderance of case studies or case series that report reductions in pain intensity when multimodal treatment including manipulation is provided (Schneider et al., 2009). A systematic review considering four randomized-controlled trials found inconclusive evidence for the use of manipulation in fibromyalgia due to the studies lacking a true control group or a sufficient sample size (Ernst, 2009).

CRPS is another condition presenting with a preponderance of CS clinical signs (Woolf, 2011). The evidence on conservative treatment for CRPS is even more limited than it is for fibromyalgia. Two case studies specifically highlight the use of manipulation in the management of CRPS, with each reporting significant benefits to the patient (Beck, 2009; Menck, Requejo, & Kulig, 2000). The case study by Beck (2009) utilized spinal and extremity manipulation as part of a 12-week multimodal treatment approach including exercise, nutritional supplementation, and education to achieve lasting benefits in pain and function in a pediatric patient with CRPS-I of the lower extremities. The case study with the most dramatic short-term effects reported significant, immediate, and maintained changes in skin temperature and hyperhidrosis, joint range of motion, and pain rating immediately following one isolated application of spinal thrust manipulation in an adult patient with CRPS-I in the hand (Menck et al., 2000). In each case study, the early application of manipulation reduced hypersensitivity in the patient to the point where other treatments, such as exercise and movement, were better tolerated and more beneficial than before the manipulation.

Among other miscellaneous conditions associated with CS, chronic WAD and TMD are almost always linked with CS, while lateral epicondylitis is sometimes linked with the condition (Nijs et al., 2010). Evidence that spinal manipulation is an effective treatment for WAD and TMD is mostly limited to case studies and series, while the evidence for lateral epicondylitis includes more randomized-controlled trials. A pilot randomized-controlled trial found that non-thrust manipulation resulted in a reduced nociceptive flexion reflex threshold, but no change in pressure pain threshold, in patients with chronic WADs (Sterling et al., 2010). Complete resolution of allodynia was reported in a single case report of a patient with chronic WAD who received a short period (6 weeks) of thoracic spine thrust and cervical spine non-thrust manipulation (Lowry, O'Hearn, & Courtney, 2011). The results of these studies highlight the questionable link between clinically meaningful responses to treatment, such as elimination of allodynia, and physiological changes in nociceptive reflex or pressure pain thresholds following treatment.

Links between sympathoexcitation and pain reduction may provide more meaningful indications of a person's clinical response to manipulation. Cervical non-thrust manipulation was utilized in a study finding reduced pain intensity, reduced pressure pain thresholds, and sympathoexcitation in a group of people with TMDs and hypersensitivity (La Touche et al., 2013). Contrary to previous reports on faster oscillations being necessary for sympathoexcitation, the authors of this study utilized a slow (0.5 Hz) frequency to perform manipulation, and still achieved significant outcomes. In addition to supporting the use of spinal manipulation in TMD, this study also called into question the need to perform fast oscillations (at least 2 Hz) in order to achieve SNS responses.

Lateral epicondylitis is linked to CS primarily by way of the mechanical, but nonthermal, hyperalgesia demonstrated in persons with the condition (Fernandez-Carnero, Cleland, & Arbizu, 2011). Furthermore, a significant number of persons with lateral epicondylitis also have neck and/or thoracic spine pain and stiffness, making the association to spinal facilitation even more likely. Multiple high-quality studies have found a significant benefit to lateral elbow pain and pressure pain threshold with thrust and non-thrust manipulation directed at the cervical spine (Fernandez-Carnero, Fernandez-de-las-Penas, & Cleland, 2008; Olson, 2009). However, a recent study reported no improvement in pressure pain threshold at the lateral elbow with the application of a thoracic thrust manipulation (Fernandez-Carnero et al., 2011). This finding calls in to question the need to specify a region when applying spinal manipulation, as treatment effects may be contained within a segmental level of innervation.

Discussion

Several observations could explain the variation seen in physiological responses and clinical outcomes for persons receiving spinal manipulation to impact CS. One observation potentially affecting SNS response is whether or not pain reduction accompanied the manipulation. In subjects with chronic neck pain, a significant reduction in self-reported pain on a 100 mm visual analog scale (VAS) accompanied findings of increased skin conductance, while no difference in pain perception on a VAS was accompanied by no changes in pupil diameter post manipulation (Sillevis et al., 2010; Sterling et al., 2001). Another observation potentially affecting SNS response is the dosage and variety of the manipulative technique applied. Faster non-thrust manipulation rates of 2 Hz (2 oscillations per second) have been shown to preferentially activate the SNS compared to slower rates of 0.5 Hz (1 oscillation per 2 seconds) or 0 Hz (static hold) (La Touche et al., 2013; Perry & Green, 2008). The use of thrust manipulation has also been shown to achieve sympathoexcitatory results. However, the presence or absence of an audible pop during a thrust technique has not been associated with different levels of sympathoexcitation (Sillevis & Cleland, 2011). Since the applied rates of non-thrust manipulation are typically not standardized (or even reported) in many studies, the possibility exists that the interventions used may have been below the critical threshold to achieve sympathoexcitation.

Another possible reason for physiological response variability with manipulation is that manipulation may actually elicit sympathetic *relaxation* in certain parts of the brain (Ogura et al., 2011). An investigation using positron emission tomography to measure cerebral metabolism found potential evidence of sympathetic relaxation as measured by reduced activation in the cerebellar vermis, increased activation in certain structures of the limbic system, and reduced concentrations of salivary amylase post manipulation in subjects with neck pain (Ogura et al., 2011). These results were achieved using an activator manipulation instrument, which is a handheld, spring-loaded device that is designed to deliver a fast, low-force impulse to the spine. Similar sympathetic relaxation effects have been reported with the application of manual massage techniques targeting the soft tissues (La Touche et al., 2013).

Patient and provider beliefs may also play a large role in determining the clinical outcomes from manipulation. The capacity for improvement from spinal manipulation may be limited by a sense of fear or hesitancy on the part of the provider or person with CS. Elevated fear avoidance beliefs, or a history of negative associations with manipulation, can block the function of descending pathways that normally serve to inhibit pain when treatment is applied (Nijs & Van Houdenhove, 2009). The same can occur with manual therapies that are applied too vigorously in a person with high levels of irritability (Nijs & Van Houdenhove, 2009). On the other hand, low scores (<19/42 for the work subscale) on the Fear Avoidance Beliefs Questionnaire, and a positive expectation for the effects of manipulation, have been found to predict successful outcomes from applying thrust manipulation in persons with low back pain and neck pain, respectively (Flynn et al., 2002; Puentedura et al., 2012). Clinicians should consider the presence or absence of cognitive-emotional dysfunction and symptom irritability when determining how best to apply manipulation in the management of CS.

Manual therapists may enhance the clinical efficacy of manipulation by varying the type, location, duration, and intensity of treatment in response to the physical and psychological status of the patient. Clinicians are encouraged to supplement joint manipulation with soft tissue-based mobilization where indicated, as some conditions (e.g., fibromyalgia) may favor this approach (Nijs & Van Houdenhove, 2009). Additionally, clinicians should attempt to treat below the patient's pain threshold, and should encourage manipulation into the patient's directional preference to movement when possible. Non-thrust manipulation techniques applied remote to the primary painful area, and for a limited duration and intensity, may be better tolerated in persons with very high levels of pain, cognitive-emotional involvement, and hypersensitivity. Clinicians should test the patient's tolerance to non-thrust techniques before the application of thrust manipulation techniques, especially when performed at the primary site of pain. Clinicians may find that the early application of manual therapy, progressed in terms of intensity and proximity to the painful region, can result in gradually improved tolerance to movement and load-based exercise at the primary painful region.

Conclusion

Signs of CS may be found, on at least some level, in many chronic pain conditions. Since the presence of CS is associated with spinal cord and supraspinal physiological changes, management strategies for CS should have the potential for impact on these levels. Evidence strongly supports the presence of centrally mediated neurophysiological effects immediately after the application of spinal manipulation. However, current evidence for clinical outcomes is limited to the possibility that spinal manipulation may have a positive clinically significant effect on central sensitivity syndromes. Future studies should focus on the role of varying the type, location, duration, and intensity of manipulative techniques in persons with different manifestations of CS. It is possible that a more specific application of treatment techniques, tailored to a patient's symptom type and location, irritability level, directional preference to movement, and degree of cognitive-emotional impairment, could result in more widespread support for the clinical application of spinal manipulation in modifying CS.

References

Beck, R. W. (2009). Conservative therapy for complex regional pain syndrome type I in a paediatric patient: A case study. *The Journal of the Canadian Chiropractic Association*, *53*, 95–101.

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., & George, S. Z. (2009). The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Manual Therapy*, *14*, 531–538.

Bialosky, J. E., Bishop, M. D., Robinson, M. E., Barabas, J. A., & George, S. Z. (2008). The influence of expectation on spinal manipulation induced hypoalgesia: An experimental study in normal subjects. *BMC Musculoskeletal Disorders*, *9*, 19.

Bialosky, J. E., Bishop, M. D., Robinson, M. E., & George, S. Z. (2010). The relationship of the audible pop to hypoalgesia associated with high-velocity, low-amplitude thrust manipulation: A secondary analysis of an experimental study in pain-free participants. *Journal of Manipulative and Physiological Therapeutics*, *33*, 117–124.

Bingham, B., Ajit, S. K., Blake, D. R., & Samad, T. A. (2009). The molecular basis of pain and its clinical implications in rheumatology. *Nature Clinical Practice. Rheumatology*, *5*, 28–37.

Bishop, M. D., Beneciuk, J. M., & George, S. Z. (2011). Immediate reduction in temporal sensory summation after thoracic spinal manipulation. *The Spine Journal: Official Journal of the North American Spine Society*, *11*, 440–446.

Clark, B. C., Goss, D. A., Jr, Walkowski, S., Hoffman, R. L., Ross, A., & Thomas, J. S. (2011). Neurophysiologic effects of spinal manipulation in patients with chronic low back pain. *BMC Musculoskeletal Disorders*, *12*, 170.

Coronado, R. A., Gay, C. W., Bialosky, J. E., Carnaby, G. D., Bishop, M. D., & George, S. Z. (2012). Changes in pain sensitivity following spinal manipulation: A systematic review and meta-analysis. *Journal of Electromyography and Kinesiology: Official Journal of the International Society of Electrophysiological Kinesiology*, *22*, 752–767.

de Camargo, V. M., Alburquerque-Sendin, F., Berzin, F., Stefanelli, V. C., de Souza, D. P., & Fernandez-de-las-Penas, C. (2011). Immediate effects on electromyographic activity and pressure pain thresholds after a cervical manipulation in mechanical neck pain: A randomized controlled trial. *Journal of Manipulative and Physiological Therapeutics*, *34*, 211–220.

DeVocht, J. W., Pickar, J. G., & Wilder, D. G. (2005). Spinal manipulation alters electromyographic activity of paraspinal muscles: A descriptive study. *Journal of Manipulative and Physiological Therapeutics*, *28*, 465–471.

Ernst, E. (2009). Chiropractic treatment for fibromyalgia: A systematic review. *Clinical Rheumatology*, *28*, 1175–1178.

Fernandez-Carnero, J., Cleland, J. A., & Arbizu, R. L. (2011). Examination of motor and hypoalgesic effects of cervical vs thoracic spine manipulation in patients with lateral epicondylalgia: A clinical trial. *Journal of Manipulative and Physiological Therapeutics*, *34*, 432–440.

Fernandez-Carnero, J., Fernandez-de-las-Penas, C., & Cleland, J. A. (2008). Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia. *Journal of Manipulative and Physiological Therapeutics*, *31*, 675–681.

Ferreira, M. L., Ferreira, P. H., & Hodges, P. W. (2007). Changes in postural activity of the trunk muscles following spinal manipulative therapy. *Manual Therapy*, *12*, 240–248.

Flynn, T., Fritz, J., Whitman, J., Wainner, R., Magel, J., Rendeiro, D., et al. (2002). A clinical prediction rule for classifying patients with low back pain who demonstrate short-term improvement with spinal manipulation. *Spine*, *27*, 2835–2843.

George, S. Z., Bishop, M. D., Bialosky, J. E., Zeppieri, G., Jr, & Robinson, M. E. (2006). Immediate effects of spinal manipulation on thermal pain sensitivity: An experimental study. *BMC Musculoskeletal Disorders*, *7*, 68.

Haavik, H., & Murphy, B. (2012). The role of spinal manipulation in addressing disordered sensorimotor integration and altered motor control. *Journal of Electromyography and Kinesiology: Official Journal of the International Society of Electrophysiological Kinesiology*, *22*, 768–776.

Harvey, M. P., & Descarreaux, M. (2013). Short term modulation of trunk neuromuscular responses following spinal manipulation: A control group study. *BMC Musculoskeletal Disorders*, *14*, 92.

Herrero, J. F., Laird, J. M., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: Much ado about something? *Progress in Neurobiology*, *61*, 169–203.

Kindler, L. L., Bennett, R. M., & Jones, K. D. (2011). Central sensitivity syndromes: Mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Management Nursing: Official Journal of the American Society of Pain Management Nurses*, *12*, 15–24.

La Touche, R., Paris-Alemany, A., Mannheimer, J. S., Angulo-Diaz-Parreno, S., Bishop, M. D., Lopez-Valverde-Centeno, A., et al. (2013). Does mobilization of the upper cervical spine affect pain sensitivity and autonomic nervous system function in patients with cervico-craniofacial pain?: A randomized-controlled trial. *The Clinical Journal of Pain*, *29*, 205–215.

Lowry, C. D., O'Hearn, M. A., & Courtney, C. A. (2011). Resolution of whiplash-associated allodynia following cervicothoracic thrust and non-thrust manipulation. *Physiotherapy Theory and Practice*, *27*, 451–459.

Menck, J. Y., Requejo, S. M., & Kulig, K. (2000). Thoracic spine dysfunction in upper extremity complex regional pain syndrome type I. *The Journal of Orthopaedic and Sports Physical Therapy*, *30*, 401–409.

Moulson, A., & Watson, T. (2006). A preliminary investigation into the relationship between cervical snags and sympathetic nervous system activity in the upper limbs of an asymptomatic population. *Manual Therapy*, *11*, 214–224.

Nijs, J., & Van Houdenhove, B. (2009). From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, *14*, 3–12.

Nijs, J., Van Houdenhove, B., & Oostendorp, R. A. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, *15*, 135–141.

Ogura, T., Tashiro, M., Masud, M., Watanuki, S., Shibuya, K., Yamaguchi, K., et al. (2011). Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain. *Alternative Therapies in Health and Medicine*, *17*, 12–17.

Olson, K. A. (2009). Manipulation: Theory, practice, and education. *Manual physical therapy of the spine* (pp. 76–78). St. Lois, MO: Saunders.

Orakifar, N., Kamali, F., Pirouzi, S., & Jamshidi, F. (2012). Sacroiliac joint manipulation attenuates alpha-motoneuron activity in healthy women: A quasi-experimental study. *Archives of Physical Medicine and Rehabilitation*, *93*, 56–61.

Perry, J., & Green, A. (2008). An investigation into the effects of a unilaterally applied lumbar mobilisation technique on peripheral sympathetic nervous system activity in the lower limbs. *Manual Therapy*, *13*, 492–499.

Perry, J., Green, A., Singh, S., & Watson, P. (2011). A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. *Manual Therapy*, *16*, 190–195.

Puentedura, E. J., Cleland, J. A., Landers, M. R., Mintken, P. E., Louw, A., & Fernandez-de-Las-Penas, C. (2012). Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *The Journal of Orthopaedic and Sports Physical Therapy*, *42*, 577–592.

Puhl, A. A., & Injeyan, H. S. (2012). Short-term effects of manipulation to the upper thoracic spine of asymptomatic subjects on plasma concentrations of epinephrine and norepinephrine-a randomized and controlled observational study. *Journal of Manipulative and Physiological Therapeutics*, *35*, 209–215.

Schmid, A., Brunner, F., Wright, A., & Bachmann, L. M. (2008). Paradigm shift in manual therapy? evidence for a central nervous system component in the response to passive cervical joint mobilisation. *Manual Therapy*, *13*, 387–396.

Schneider, M., Vernon, H., Ko, G., Lawson, G., & Perera, J. (2009). Chiropractic management of fibromyalgia syndrome: A systematic review of the literature. *Journal of Manipulative and Physiological Therapeutics*, *32*, 25–40.

Sillevis, R., & Cleland, J. (2011). Immediate effects of the audible pop from a thoracic spine thrust manipulation on the autonomic nervous system and pain: A secondary analysis of a randomized clinical trial. *Journal of Manipulative and Physiological Therapeutics*, *34*, 37–45.

Sillevis, R., Cleland, J., Hellman, M., & Beekhuizen, K. (2010). Immediate effects of a thoracic spine thrust manipulation on the autonomic nervous system: A randomized clinical trial. *The Journal of Manual & Manipulative Therapy*, *18*, 181–190.

Sparks, C., Cleland, J. A., Elliott, J. M., Zagardo, M., & Liu, W. C. (2013). Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *The Journal of Orthopaedic and Sports Physical Therapy*, *43*, 340–348.

Srbely, J. Z., Vernon, H., Lee, D., & Polgar, M. (2013). Immediate effects of spinal manipulative therapy on regional antinociceptive effects in myofascial tissues in healthy young adults. *Journal of Manipulative and Physiological Therapeutics*, *36*, 333–341.

Sterling, M., Jull, G., & Wright, A. (2001). Cervical mobilisation: Concurrent effects on pain, sympathetic nervous system activity and motor activity. *Manual Therapy*, *6*, 72–81.

Sterling, M., Pedler, A., Chan, C., Puglisi, M., Vuvan, V., & Vicenzino, B. (2010). Cervical lateral glide increases nociceptive flexion reflex threshold but not pressure or thermal pain thresholds in chronic whiplash associated disorders: A pilot randomised controlled trial. *Manual Therapy*, *15*, 149–153.

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152* (3 Suppl), S2–15.

Yunus, M. B. (2008). Central sensitivity syndromes: A new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Seminars in Arthritis and Rheumatism*, *37*, 339–352.