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Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain.

C. Gevers-Montoro[1-3], B. Provencher[1,2], M. Descarreaux[1,4], A. Ortega de Mues[3] and M. Piché[1,2*]

[1]Department of Anatomy, Université du Québec à Trois-Rivières, 3351 Boul. Des Forges, C.P. 500, Trois- Rivières, QC, Canada, G9A 5H7.

[2]CogNAC Research Group, Université du Québec à Trois-Rivières, 3351 Boul. Des Forges, C.P. 500, Trois-Rivières, QC, Canada, G9A 5H7.

[3]Madrid College of Chiropractic – RCU María Cristina, Paseo de los Alamillos 2, 28200 San Lorenzo de El Escorial, Madrid, Spain.

[4]GRAN Research Group, Université du Québec à Trois-Rivières, 3351 Boul. Des Forges, C.P. 500, Trois-Rivières, QC, Canada, G9A 5H7.

***Corresponding author:**

Mathieu Piché, DC, PhD

Department of Anatomy

Université du Québec à Trois-Rivières

3351 boul. des Forges, C.P. 500

Trois-Rivières, Québec, Canada G9A 5H7

Ph.: 819-376-5011 Ext. 3998

Fax: 819-376-5204

E-mail: mathieu.piche@uqtr.ca

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Significance: Spinal manipulation inhibits back and neck pain partly through spinal segmental mechanisms and potentially through peripheral mechanisms regulating inflammatory responses. Other mechanisms remain to be clarified. Controls and placebo interventions need to be improved in order to clarify the contribution of specific and non-specific effects to pain relief by spinal manipulative therapy.

Abstract

Together, neck pain and back pain are the first cause of disability worldwide, accounting for more than 10% of the total years lived with disability. In this context, chiropractic care provides a safe and effective option for the management of a large proportion of these patients. Chiropractic is a healthcare profession mainly focused on the spine and the treatment of spinal disorders, including spine pain. Basic studies have examined the influence of chiropractic spinal manipulation on a variety of peripheral, spinal, and supraspinal mechanisms involved in spine pain. While spinal cord mechanisms of pain inhibition contribute at least partly to the pain-relieving effects of chiropractic treatments, the evidence is weaker regarding peripheral and supraspinal mechanisms, which are important components of acute and chronic pain. This narrative review highlights the most relevant mechanisms of pain relief by spinal manipulation and provides a perspective for future research on spinal manipulation and spine pain, including the validation of placebo interventions that control for placebo effects and other non-specific effects that may be induced by spinal manipulation.

Keywords: Low back pain; neck pain; pain inhibition; placebo; spinal manipulative therapy; manual therapy.

Introduction

Spine pain of musculoskeletal origin can affect the cervical, thoracic, or lumbar regions. Its duration may range from an acute episode of a few days or weeks to chronicity over several years (Borghouts et al., 1998; Urits et al., 2019). Low back pain (LBP) is the leading contributor to disability, followed closely by neck pain (NP) (James et al., 2018; Urits et al., 2019). Together, back pain and neck pain are responsible for more than 10% of the total years lived with disability worldwide (James et al., 2018). Spine pain can originate from myofascial tissues, facet joints, intervertebral discs, spinal ligaments, and other less common causes (Urits et al., 2019; Vlaeyen et al., 2018). However, it remains challenging to identify the source of pain in individual cases (Hartvigsen et al., 2018; Vlaeyen et al., 2018). Accordingly, chronic low back and neck pain are considered non-specific in a large majority of cases, meaning the pain cannot be attributed to a specific origin or to a pathology detectable with imaging methods (Borghouts et al., 1998; Vlaeyen et al., 2018). Recently, both chronic non-specific low back and neck pain have been classified as chronic primary pain syndromes under the new International Association for the Study of Pain (IASP) classification of chronic pain for the latest revision of the International Classification of Diseases (ICD-11) (Nicholas et al., 2019; Treede et al., 2019; Vlaeyen et al., 2018). Due to the dramatic impact of acute spine pain and chronic primary spine pain on individuals and society (Hartvigsen et al., 2018; James et al., 2018; Urits et al., 2019; Vlaeyen et al., 2018), safer and more effective interventions are needed. Among conservative approaches, chiropractic spinal manipulative therapy (SMT) is one of the potentially effective interventions for these conditions.

Chiropractic is a healthcare profession in the field of musculoskeletal health. Its main focus is on spine function and disorders, including spine pain (Brown, 2016; Murphy et al., 2011). Chiropractors use a variety of conservative approaches, including SMT as the most common intervention (Beliveau et al., 2017). SMT involves the application of spinal manipulation (SM; also referred to as chiropractic adjustment in the field of chiropractic) over several sessions (W.H.O., 2005). During a chiropractic SM, clinicians apply a controlled force of a specific magnitude and orientation to a targeted spinal segment (Herzog, 2010). The concept of SM specificity has been challenged by research showing that forces cannot be effectively directed to a single target segment and in a precise direction (Bereznick et al., 2002; Herzog et al., 2001; Ross et al., 2004). Nonetheless, the contact site may influence the neurophysiological responses to SM (Nim et al., 2020; Reed et al., 2015; Reed and Pickar, 2015). Whether biomechanical characteristics or neurophysiological mechanisms of SM

differ when applied by different providers remains unknown. Here, the neurophysiological mechanisms of SM are reviewed from a chiropractic perspective (Henderson, 2012), although informed by studies where SM was performed by chiropractors and other practitioners.

SM generally consists in the application of a mechanical force on spinal joints in the form of a high velocity and low amplitude (HVLA) thrust preceded by a slower preload phase (Pickar and Bolton, 2012; Reed et al., 2014). Both the preload and thrust phases impact paraspinal muscle responses (Nougarou et al., 2013; Reed et al., 2014) and load articular tissues, including the intervertebral discs, joint capsules, and ligaments (Funabashi et al., 2017). Previous studies suggest that the mechanical force applied during SM alters spinal biomechanics and activates paraspinal sensory terminals (Bialosky et al., 2009a; Gyer et al., 2019; Pickar and Bolton, 2012). It has been proposed that this afferent fiber stimulation initiates a cascade of peripheral and central neurophysiological effects (Bialosky et al., 2009a; Pickar and Bolton, 2012). In turn, these effects may underlie some of the clinical outcomes observed with SMT (Bialosky et al., 2009a; Pickar and Bolton, 2012). A comprehensive model including biomechanical and neurophysiological mechanisms for pain relief induced by manual therapy has been proposed (Bialosky et al., 2018; Bialosky et al., 2009a). Nonetheless, the exact neurophysiological mechanisms by which SM relieves pain remain unclear (Gyer et al., 2019). This is particularly important for pain affecting the spine, as most of the current Clinical Practice Guidelines (CPG) recommend the use of SMT for the management of LBP and NP (Bussieres et al., 2018; Cote et al., 2016; Foster et al., 2018; Kjaer et al., 2017; Qaseem et al., 2017).

The aim of this review is to discuss the pain-relieving mechanisms of SM for spine pain. In addition, a perspective on challenges and future directions for research on chiropractic SM and spine pain will be presented.

Mechanisms of pain relief by spinal manipulation

Previous studies on pain relief by SM have reported effects on the peripheral nervous system, spinal cord mechanisms, and supraspinal processes (Bialosky et al., 2009a; Gyer et al., 2019). In this section, the mechanisms of pain inhibition by SM will be reviewed critically, based on the location of the effect within the nociceptive system. A schematic summary of these potential mechanisms is presented in Figure 1. A summary of the most relevant mechanisms with supporting evidence is also presented in Table 1.

1. Peripheral mechanisms

Spine pain may be caused by an injury to musculoskeletal tissues of the spine (Vlaeyen et al., 2018) through direct activation of nociceptive afferents. In acute and chronic inflammatory states, spine pain may be modulated by sensitization and desensitization of nociceptors by pro- and anti-inflammatory mediators. Here we will discuss how SM may produce pain relief by modulating inflammatory processes and sensitization in peripheral tissues.

1.1. Cortisol release

Pain may be inhibited by hormones with a known anti-inflammatory function on the periphery, such as cortisol (Hannibal and Bishop, 2014; Hench et al., 1950; Saldanha et al., 1986). Cortisol levels rise in anticipation and as a response to acute stressful situations (Hannibal and Bishop, 2014; Mason et al., 1973). It has been proposed that stress induced by SM or its anticipation, particularly when applied to the cervical spine, may partially underlie its pain inhibitory effects (Kovanur-Sampath et al., 2017a; Plaza-Manzano et al., 2014; Valera-Calero et al., 2019; Whelan et al., 2002). However, the studies reported inconsistent changes in plasma or salivary cortisol levels after SM. Up to five minutes after SM, cortisol levels either increased (Plaza-Manzano et al., 2014; Valera-Calero et al., 2019), decreased (Kovanur-Sampath et al., 2017a) or remained unchanged (Lohman et al., 2019; Whelan et al., 2002) in healthy participants and patients with NP. Moreover, the short-term effects of SM were not significantly different from those observed with mobilization techniques (Valera-Calero et al., 2019). These conflicting results may be due to methodological discrepancies, including the participants' characteristics (only males vs. only females; healthy volunteers vs. patients with acute pain vs. patients with chronic pain), the site of SM (cervical vs. thoracic), cortisol sampling methodology (serum vs. saliva) and its collection (immediately following the intervention vs. 5 minutes or longer after SM). These inconsistencies prevent drawing any conclusion on the effect of SM on cortisol. This does not rule out the effect, but more high-quality studies with standardized methodology are needed to reach a conclusion. Thus far, the conflicting findings do not support the release of cortisol as a specific pain-relieving mechanism of SM.

1.2. Peripheral inflammation and sensitization

Following cervical SM, an increase in plasmatic substance P was reported, while pressure-pain sensitivity decreased (Kovanur-Sampath et al., 2017b; Molina-Ortega et al.,

2014). The authors proposed that augmented substance P may underlie the hypoalgesic effects of SM, based on previous reports showing that substance P can inhibit nociceptive transmission in the spinal cord via feedforward mechanisms (Nakatsuka et al., 2005; Wu et al., 2005). However, this contrasts with the large body of evidence that describes substance P as a pro-nociceptive neuromodulator (Dickenson, 1995; Hackel et al., 2010; Van Der Kleij and Bienenstock, 2007). Peripheral inflammation and tissue injury are associated with a release of substance P (Dickenson, 1995; Hackel et al., 2010; Van Der Kleij and Bienenstock, 2007). In turn, substance P is involved in neurogenic inflammation, hyperalgesia, and allodynia (Hackel et al., 2010). Both its peripheral and central release by primary afferents seems to be essential to experience moderate to intense pain (Cao et al., 1998). Also, elevated cerebrospinal fluid levels of substance P were observed in patients with chronic pain, likely reflecting levels in the spinal cord (Almay et al., 1988; Russell et al., 1994). Rather than a hypoalgesic mechanism, the increase in plasmatic substance P levels following SM may thus reflect a pro-inflammatory response due to spine tissue deformation, which has been shown to activate integrins, and in turn up-regulate substance P expression (Zhang et al., 2017). On the basis of the well-established pro-nociceptive and pro-inflammatory role of substance P, the hypothesis that it may contribute to pain relief by SM is unlikely.

Nociceptive fibers may be sensitized by reactive oxygen species (ROS) in tissues under oxidative stress resulting from acute injury (Westlund et al., 2010). In animal models, ROS such as hydrogen peroxide or nitric oxide have been shown to activate TRP (transient receptor potential nociceptor) channels, mediating pain and inflammatory changes (Westlund et al., 2010). In a rat model of immobilization-induced tactile allodynia, SM applied with a hand-held mechanical device prevented an increase in plasmatic ROS while improving indices of nerve function and allodynia (Duarte et al., 2019). In line with these findings, an increase in serum levels of antioxidant enzymes was reported after a 5-week treatment that included SM in patients with chronic spine pain (Kolberg et al., 2015). Future research is needed to examine whether these mechanisms contribute specifically to the pain-relieving effects of SM in patients with acute and chronic spine pain.

Cytokines and chemokines are immune regulatory substances that can induce inflammation and contribute to nociception (Abbadie et al., 2003; Marchand et al., 2005; Sommer and Kress, 2004). In patients with LBP, pro-inflammatory mediators are involved in the sensitization of nociceptors and their inflammatory profiles vary depending on pain duration (Teodorczyk-Injeyan et al., 2018; Teodorczyk-Injeyan et al., 2019). Preliminary

results suggest that SM may reduce pro-inflammatory responses (Roy et al., 2010; Teodorczyk-Injeyan et al., 2006; Teodorczyk-Injeyan et al., 2018), which in turn may produce pain relief through changes in peripheral inflammation and nociceptor sensitization.

The current literature suggests that SM may reduce pro-nociceptive or pro-inflammatory mediators that are increased during spine pain (Duarte et al., 2019; Roy et al., 2010; Teodorczyk-Injeyan et al., 2006). This may limit peripheral sensitization and produce pain relief (Kolberg et al., 2015; Teodorczyk-Injeyan et al., 2018). Although the quality of the evidence on the influence of SM on biological markers was considered to be moderate (Kovanur-Sampath et al., 2017b), the current available results are not consistent and their interpretation does not always provide plausible pain-relieving mechanisms that are specific to SM. Future high-quality and well-controlled studies including mechanistic trials are needed to provide support to this line of research.

2. Spinal cord mechanisms

Behavioral studies indicate that SM can decrease pain sensitivity in tissues linked anatomically to the spinal cord segment influenced by SM (Alonso-Perez et al., 2017; Bialosky et al., 2008; Bialosky et al., 2009b; de Camargo et al., 2011; Dorron et al., 2016; Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007; Fryer et al., 2004; George et al., 2006; Laframboise et al., 2016). This suggests that the pain inhibitory effect of SM may rely, at least in part, on segmental mechanisms. This hypothesis was examined in several studies that will be discussed in the following sections.

2.1. Segmental inhibition of nociceptive processes by spinal manipulation

The hypothesis that SM modulates pain thresholds and sensitivity in body regions related to the spinal segment influenced by SM is supported by systematic reviews and meta-analyses (Coronado et al., 2012; Honore et al., 2018; M. Millan et al., 2012). The duration and size of these effects are still unclear, although the available evidence suggests that they are transient, lasting less than ten minutes (Honore et al., 2019). A consistent finding is that SM has a more favorable and significant effect on segmental pain thresholds in comparison to inactive control or sham SM. Similar effects were observed with interventions such as non-thrust SM or mobilization (Alonso-Perez et al., 2017; Fryer et al., 2004; Honore et al., 2018; M. Millan et al., 2012; Salom-Moreno et al., 2014; Thomson et al., 2009). In healthy

volunteers, no significant differences were observed before and after applying cervical, thoracic or lumbar SM compared with mobilization on pressure pain thresholds (PPTs) (Alonso-Perez et al., 2017; Fryer et al., 2004; Thomson et al., 2009). Moreover, in patients with chronic NP, Salom-Moreno et al. reported similar small effects of thoracic SM and mobilization on PPTs (Salom-Moreno et al., 2014). The evidence comparing SM and mobilization is still scarce. Yet, it suggests that both interventions have comparable effects on segmental pressure pain sensitivity. It remains to be determined how they compare on other effects and mechanisms described below.

The effects of SM on PPTs around the SM application site or in a related dermatome have been assessed in several studies (Alonso-Perez et al., 2017; de Camargo et al., 2011; Dorron et al., 2016; Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007; Laframboise et al., 2016). Following a single cervical SM in healthy volunteers, PPTs were increased (i.e. pain sensitivity was decreased) in the dermatome corresponding to the level of application of SM (Alonso-Perez et al., 2017; Fernandez-de-las-Penas et al., 2007). Similar findings were observed in patients with musculoskeletal pain (Fernandez-Carnero et al., 2008). Regional effects have also been reported for PPTs of myofascial tissues innervated by a spinal segment (myotome) related to the spinal level on which SM was applied (de Camargo et al., 2011; Dorron et al., 2016; Laframboise et al., 2016).

In spite of this consensus on segmental effects of SM, it should be noted that two recent studies using a single-blinded placebo-controlled design obtained conflicting results (Aspinall et al., 2019a; Honore et al., 2020). The quality of studies on segmental hypoalgesia resulting from SM is variable. For musculoskeletal pain conditions, the quality was considered to be low (Aspinall et al., 2019b) and for healthy volunteers, the quality was rated as moderate to high (Coronado et al., 2012; Honore et al., 2018). Most studies showed a higher risk of bias due to the lack of appropriate blinding of participants, care providers and/or experimenters (Coronado et al., 2012). Future systematic reviews including high-quality studies may thus change the current conclusions.

A recent study indicates that the effects of SM depend on its application site (Nim et al., 2020). In this trial, patients with chronic LBP were randomly allocated to one of two groups, receiving SMT targeted either at the stiffest segment or at the segment with the highest mechanical pain sensitivity. Stiffness and LBP intensity were not significantly different between groups. However, PPTs were significantly increased immediately after SM

at the most sensitive segment (Nim et al., 2020). This supports the segmental effects of SM on pain-related processes, which may rely on the modulation of central sensitization (Jordon et al., 2017), as discussed below.

Animal models allow the use of invasive methods that provide insight on specific mechanisms that influence nociceptive processes and pain behaviors. They also provide high-quality data on the dose-response relationship of a specific intervention (Hackam and Redelmeier, 2006). These data are still scarce in SM research (Pasquier et al., 2019), but can be obtained with mechanical devices that deliver SM-like forces. Mechanically-assisted SM allows for regulation of the applied forces or force-time profiles (Descarreaux et al., 2013), which can be standardized for the animal's body (Reed et al., 2013). In a study by Reed and colleagues, a mechanical device was applied with different forces ranging from 25% to 85% of a cat's body weight, to imitate forces applied during a lumbosacral SM (ranging 31% to 78% of an average human body weight) (Reed et al., 2013).

Animal data have also shown that SM-like procedures could increase mechanical pain thresholds in limb dermatomes related to the spine segments on which SM was applied (Duarte et al., 2019; Grayson et al., 2012; Onifer et al., 2015; Onifer et al., 2018). Also, segmental changes in mechanical pain thresholds were observed after sensitization via inflammatory mediators (Grayson et al., 2012; Onifer et al., 2015) or peripheral neuropathic pain (Duarte et al., 2019; Onifer et al., 2018). However, thermal pain thresholds remained unchanged by SM (Grayson et al., 2012; Onifer et al., 2018), in accordance with reports in humans. Altogether, these findings from animal studies are consistent with the segmental effects of SM. It remains to be clarified whether SM can decrease temporal summation and whether this depends on its effects on nociceptive transmission by specific afferent fibers (e.g., C fibers) or on central amplification processes such as wind-up.

2.2. Effects of spinal manipulation on temporal summation of pain

Sustained or repeated activation of afferent nociceptive fibers induces temporal summation of pain, the perceptual correlate of windup in the spinal cord (Price et al., 1977). More specifically, stimulation at constant C-fiber strength at or above 0.3 Hz elicits a progressive increase in action potential firing over the course of the stimulus, reflected in enhanced pain (Mendell and Wall, 1965; Price, 1972; Price et al., 1977). Temporal summation of pain is increased in patients with chronic pain, suggesting that C-fiber activity is abnormally maintained in these cases (Staud et al., 2004; Staud et al., 2001). It has been

suggested that the enhancement of these spinal responses could be critical to the development of chronic LBP (Roussel et al., 2013; Woolf, 2011).

Evidence from behavioral studies suggests that SM may exert its hypoalgesic effects through an attenuation of spinal processes related to temporal summation (Aspinall et al., 2019b; Bialosky et al., 2008; Bialosky et al., 2009b; Bialosky et al., 2014; Bishop et al., 2011a; George et al., 2006; Randoll et al., 2017). Accordingly, it was reported that SM inhibits pain evoked by a pulse train or repeated thermal and electrical stimuli associated with C-fiber activation, but not pain evoked by a single stimulus (George et al., 2006; Randoll et al., 2017). In contrast, no difference in temporal summation induced by repetitive pinprick stimulation was observed after SM compared with a validated sham in patients with LBP (Aspinall et al., 2019a). This study successfully achieved blinding, although the authors acknowledge that the sham SM may not be inert. A potential explanation for the lack of effect reported by this study is that pinprick pain is primarily mediated by larger myelinated Aδ fibers (Magerl et al., 2001). Taken together, these findings suggest that SM inhibits temporal summation by modulating C-fiber activity selectively; however, this remains to be confirmed with neurophysiological methods.

2.3. Effects of spinal manipulation on central sensitization

Sustained or repeated noxious stimulation that activate C-fibers may induce synaptic plasticity in the spinal cord termed "central sensitization" (Woolf, 1983). These changes persist beyond the duration of the noxious stimulation and are associated with the development of secondary hyperalgesia (pain hypersensitivity beyond the site of injury) and allodynia (pain evoked by stimuli that are usually not painful) (Woolf, 1983, 2011). Central sensitization has been linked to the development of chronic pain syndromes (Woolf, 2011) and is considered a useful concept to describe some of the mechanisms underlying chronic primary pain (Nicholas et al., 2019; Treede et al., 2019).

A preliminary study found that SM could reduce spontaneous pain, secondary hyperalgesia and allodynia induced by topical capsaicin (Mohammadian et al., 2004), which is known to evoke central sensitization through C-fiber activation (Woolf, 2011). Interestingly, ROS in the spinal cord were found to contribute to central sensitization induced by capsaicin (Lee et al., 2007; Schwartz et al., 2008) and peripheral nerve injury (Kim et al., 2010). This effect may be mediated by the expression of pro-inflammatory cytokines in the

spinal cord (Kim et al., 2010; Willemen et al., 2018) leading to central sensitization and chronic pain (Ji et al., 2018; Kawasaki et al., 2008).

Experimental studies have shown a modulation of peripheral ROS (Duarte et al., 2019) and cytokines (Teodorczyk-Injeyan et al., 2006) after SM. To our knowledge, only one study has assessed these changes in nervous tissue (Song et al., 2016). In this experiment, ten sessions of mechanically-assisted SM were applied to rats with neuropathic pain induced by compression of the dorsal root ganglia. Hyperalgesia and nociceptive primary afferent activity were decreased after SM (Song et al., 2016). In addition, a reduction of the pro-inflammatory cytokine IL-1β in the dorsal root ganglia and an increase of the anti-inflammatory IL-10 were observed (Song et al., 2016). This warrants further research in order to determine whether SM influences these and other markers of central sensitization in the spinal cord.

2.4 Potential propiospinal effects of spinal manipulation

Experimental studies have reported heterosegmental changes in pain sensitivity after the application of SM for chronic primary NP (Aspinall et al., 2019b; Bishop et al., 2011a; Casanova-Mendez et al., 2014; Martinez-Segura et al., 2012; Salom-Moreno et al., 2014). In these studies, pain sensitivity was reduced in somatic tissues not directly innervated by the spinal segment influenced by SM. It has been proposed that remote hypoalgesic effects may be produced by propriospinal pathways (Bishop et al., 2011a). Animal experiments have provided evidence for propriospinal inhibition of wide-dynamic range neurons by noxious conditioning stimuli (Cadden et al., 1983). Consistent with this, it has been proposed that SM could act as a conditioning stimulus to inhibit nociceptive activity (Bialosky et al., 2009a; George et al., 2006), although evidence supporting this hypothesis is lacking. Alternatively, widespread hypoalgesic effects may be produced by supraspinal mechanisms, including non-specific contextual effects and specific effects that can be attributed to SM (Aspinall et al., 2019b; Dorron et al., 2016; Martinez-Segura et al., 2012; Salom-Moreno et al., 2014).

3. Supraspinal mechanisms

Widespread reduction in mechanical pain sensitivity has been reported after SM or mobilization in patients with chronic primary NP (Martinez-Segura et al., 2012; Salom-Moreno et al., 2014). These results are limited by the lack of a control group, so inferring mechanisms or effects that are caused by SM is not possible (Martinez-Segura et al., 2012;

Salom-Moreno et al., 2014). Widespread hypoalgesia may be attributed to placebo or other non-specific effects (Aspinall et al., 2019b), but it may also reflect specific hypoalgesic mechanisms of SM involving cerebral structures and supraspinal mechanisms (M. J. Millan, 2002). However, some of the same brain areas, endogenous substances, and top-down mechanisms have also been associated with placebo analgesia (L. Colloca and Barsky, 2020; Eippert et al., 2009). Placebo effects are mainly the consequence of patients' expectations concerning their health or condition (L. Colloca and Barsky, 2020). They are not specific to one intervention and can contribute to the therapeutic effects of any treatment, including SMT (Bialosky et al., 2014; Martinez-Segura et al., 2012). As both non-specific and specific effects likely share some cerebral mechanisms, placebo-controlled neuroimaging studies may be useful to elucidate their specific contribution to hypoalgesia (L. Colloca and Barsky, 2020; Gyer et al., 2019).

The perception of pain undergoes substantial processing at supraspinal levels, where multiple brain areas contribute to its representation and modulation (Apkarian et al., 2005; M. J. Millan, 2002). The "neurologic signature of pain" describes the functional imaging correlate of pain, including the most relevant areas involved in pain perception and modulation (Wager et al., 2013). Although the mechanisms are still under debate, it has been proposed that brain plasticity in areas linked to that neurologic signature could underlie the transition from acute to chronic pain, which has been studied in patients with LBP (Apkarian et al., 2011; Vlaeyen et al., 2018; Wager et al., 2013). Nonetheless, the details of the mechanisms across the brain network involved in chronic pain remain to be clarified (Apkarian et al., 2011; Baliki et al., 2014).

As an explanation for widespread hypoalgesia detected after SM, it has been proposed that SM may influence supraspinal mechanisms by activating the periaqueductal gray matter (Bialosky et al., 2009a; Gyer et al., 2019; Kovanur-Sampath et al., 2015; M. Millan et al., 2012; Savva et al., 2014). In an attempt to identify specific changes in pain-related brain activity, two studies reported that thoracic SM but not a validated sham treatment modifies the activation of pain-related regions (Sparks et al., 2017; Weber II et al., 2019). A previous study used light touch sustained for 5 minutes as a control procedure. In this study, some changes in functional connectivity between pain processing regions were specific to SM, but others were observed for both SM and the control procedure (Gay et al., 2014). However, the effects observed in the brain may reflect changes in nociceptive transmission before nociceptive inputs reach the brain and may be unrelated to descending inhibition. With a similar approach, fMRI was used to measure the neural correlates of fear of movement and

anticipated pain from visualized exercises in chronic LBP patients, before and after SM (Ellingsen et al., 2018). Two SM sessions reduced clinical pain, fear of movement, and expected pain, and the two latter correlated with decreased brain responses evoked by observation of the back-straining exercises (Ellingsen et al., 2018). The authors posit that these findings could be driven by proprioceptive (non-conditioned) input arising from the painful area, but also by the reduction in clinical pain (Ellingsen et al., 2018). In both cases, it is difficult to conclude that any of the changes in brain activity are the direct consequence of SM and not an indirect effect of altering nociceptive transmission in the spinal cord. Accordingly, a recent systematic review suggests that most brain changes reported likely result from a change in ascending information rather than a specific supraspinal mechanism (Meyer et al., 2019). This review reported that studies on SM mechanisms potentially involving the brain were generally of low to moderate methodological quality, for which the main caveat was the credibility of the sham maneuvers (Meyer et al., 2019). With the current available data, it is not possible to draw any conclusion regarding the potential supraspinal mechanisms of SM.

4. Placebo effects in spinal manipulative therapy

In experimental and clinical studies, non-specific effects on pain perception include non-specific temporal changes (e.g., habituation), regression to the mean (when pain is measured at several time points), the natural course of the disease or spontaneous improvement (Kaptchuk et al., 2020). In a meta-analysis it was reported that pain reduction after SMT (96 and 67 % of the total variance in acute and chronic LBP, respectively) could not be solely attributed to the specific effects of treatment (Menke, 2014). According to this analysis, the evidence for SMT is superior to sham only for chronic LBP. Consistent with this, the level of evidence supporting SMT over sham for musculoskeletal pain is considered to be low at short-term follow-up (< 3 months) (Scholten-Peeters et al., 2013). However, this is not unique to SMT (Menke, 2014). Indeed, 50 to 75 % of responses to pharmacological treatments for chronic pain can be attributed to non-specific effects (Kaptchuk et al., 2020). These non-specific effects can be measured and controlled for by including no-treatment groups (Hancock et al., 2006; Kaptchuk et al., 2020). When comparing sham to active treatment, oral medication does not largely outperform the placebo in patients with LBP (Machado et al., 2009; Puhl et al., 2011). The placebo effect is a non-specific effect that is

more challenging to measure and control for in studies on SM (Hancock et al., 2006), which warrants further discussion.

4.1 Placebo effect in studies on pain reduction by spinal manipulation

Placebo analgesia is produced, in part, by expectations of pain reduction by a particular intervention (Benedetti et al., 1999; L. Colloca and Barsky, 2020; Kaptchuk et al., 2020). To measure and control for placebo analgesia, expectations can be measured with subjective rating scales (Cormier et al., 2013; Kaptchuk et al., 2020; Puhl et al., 2017).

The contribution of placebo effects induced by expectations to pain relief by SM was investigated in a few studies (Bialosky et al., 2008; Bialosky et al., 2014; Bishop et al., 2011b; Bishop et al., 2017). In healthy volunteers, it was reported that pain relief by SM is influenced by expectations, where negative expectations produce region-specific pain increases (Bialosky et al., 2008). In this study, however, SM-induced hypoalgesia was independent of positive expectations (Bialosky et al., 2008). In patients with LBP, it was also shown that SMT produces pain relief that cannot be attributed to expectations (Bialosky et al., 2014). In addition, it was shown that treating LBP with SM in patients that meet the clinical prediction rule of good prognosis is more important than patient's preference, and that the provider's preference is a better predictor of pain relief compared with patient's expectations (Bishop et al., 2011b; Bishop et al., 2017). Together, these results indicate that SM hypoalgesia and pain relief by SMT rely on specific mechanisms that are independent of expectations. This does not rule out the modulation of these effects by expectations or the influence of other non-specific effects that should also be measured and controlled for with appropriate placebo interventions.

4.2 Placebo interventions for studies on spinal manipulation

Every intervention induces non-specific effects related to the clinical or experimental context (Kaptchuk et al., 2020). Thus, a group receiving a placebo intervention is required to determine the specific therapeutic effects of an intervention. To achieve blinding, an appropriate placebo intervention must be structurally equivalent to (same context, positioning, duration and number of sessions) and indistinguishable from the studied intervention. In addition, the placebo intervention must not produce any therapeutic effect (inertness) (Hancock et al., 2006; Puhl et al., 2017). Currently, there is no consensus on what constitutes an appropriate placebo intervention for SM and SMT (Hancock et al., 2006). Developing an appropriate placebo remains challenging due to the lack of knowledge on

what are the active components of SM (Hancock et al., 2006; Hawk et al., 2002; Koes, 2004; Puhl et al., 2017). Systematic reviews have reported that the placebo interventions used for SMT frequently lack at least one important element to be indistinguishable from SM (Puhl et al., 2017; Vernon et al., 2011). The concern regarding inadequate placebo interventions in spine pain research is not limited to SMT (Machado et al., 2008). A systematic review reported that only 20% of the trials on LBP used placebo interventions that were indistinguishable and equivalent to the active treatment, while blinding success was assessed in only 13% of the trials (Machado et al., 2008).

Inadequate blinding has been highlighted as one of the main weaknesses of research on manual therapies (Koes, 2004; Puhl et al., 2017; Vernon et al., 2011). As opposed to pharmacological research in which the patients and experimenters cannot distinguish active or placebo (inert) medication, single blinding remains challenging in SM research and double blinding is essentially impossible (Koes, 2004). Indeed, participants may not be aware of the intervention that they are receiving (real or placebo SM), but the force and cavitation associated with most SM requires that participants are naïve to SM to increase the odds of successful blinding (Puhl et al., 2017). In addition, the experimenter is always aware of the intervention that is provided in the case of SM. To partially compensate for the lack of experimenter blinding, the placebo SM must be delivered in the most convincing way, which requires extensive practice (Hawk et al., 2002; Hawk et al., 1999; Koes, 2004; Vernon et al., 2011). Despite these limitations, high quality research on SM and SMT is not impossible and some approaches to reduce the impact of these limitations will now be discussed.

Instrument-assisted SM has been used in previous studies with the idea that the placebo intervention would be indistinguishable from SM (Hawk et al., 2002; Hawk et al., 1999). In these studies, the placebo intervention consisted in doing the same preparation (instructions, palpation of the spine, and instrument application with an associated sound), but no force was applied (Hawk et al., 2002; Hawk et al., 1999). This was effective in blinding participants (50% in each group correctly guessed their group assignment). Yet, a major limitation is that the placebo intervention was not equivalent and that it might not be inert (Hawk et al., 2002; Hawk et al., 1999). Mechanically-assisted and manual SM do not have identical force-time profiles (C. J. Colloca et al., 2005; Herzog, 2010; Pickar and Bolton, 2012). Yet, mechanical instruments are commonly used by chiropractors as a clinical intervention (Huggins et al., 2012). These techniques offer the advantage of standardizing forces applied during SM, with a lesser degree of variability compared with manually-applied SM (Kawchuk et al., 2006). In the laboratory setting, further standardization of SM

parameters can be reached by using linear motors, which mimic the force-time profiles measured during manually delivered SM. This allows determining the dose-physiological response characteristics of SM (Descarreaux et al., 2013). By adjusting the biomechanical parameters of SM, it may be possible to determine the therapeutic thresholds, as well as the sub-therapeutic doses that may constitute a placebo SM. Indeed, the biomechanical dosage parameters of SM to effectively induce analgesia are still unknown (Pasquier et al., 2019; Puhl et al., 2017). This remains to be explored and the validation of the appropriate placebo remains to be demonstrated.

Only a few studies examined the validity of placebo SM by assessing the degree of blinding (Chaibi et al., 2015; Vernon et al., 2012). To determine if blinding was successful, participants were asked whether they had received the real/active treatment or the placebo (Chaibi et al., 2015; Vernon et al., 2012). In one of these studies, participants reported their treatment group correctly in 50 % and 47 % for the active and placebo interventions, respectively, indicating that blinding was successful (Vernon et al., 2012). In the placebo intervention, the joint preload and thrust phases were not performed and the maneuver consisted in a rapid motion through the drop action of the table's head-piece mechanism. The drop mechanism and the associated sound may be important factors that made blinding effective (Vernon et al., 2012). In the other study, the placebo intervention consisted in non-specific contacts with lower force delivered on the gluteal and scapular regions instead of the spine, which did not produce cavitation (Chaibi et al., 2015). This placebo intervention was effective at blinding participants throughout 12 treatment sessions over three months. For each session, more than 80% reported that they had received the active treatment, irrespective of group allocation (Chaibi et al., 2015). Both studies seem to provide structurally equivalent and indistinguishable placebo interventions, even in patients with previous experience with SMT. Notwithstanding, it should be confirmed that the placebo interventions did not induce therapeutic effects (Chaibi et al., 2015; Vernon et al., 2012). Vernon et el. showed that the loads applied during the placebo intervention were lower compared with SM (10 to 50%), but this does not ascertain the lack of a therapeutic effect, particularly considering that pain intensity reductions were no different between both groups (Vernon et al., 2012).

A unique study showed that true blinding is possible for SM (Kawchuk et al., 2009). In this experiment, SM was administered under short propofol/remifentanil anesthesia in the experimental group while the control group did not receive any intervention other than the anesthesia. In both groups, standardized visual and auditory cues were delivered before the

participants recovered from anesthesia. Participants did not recall any memory from the anesthesia period, including the visual and auditory cues, indicating effective blinding (Kawchuk et al., 2009). Although the method is conceptually appealing, its applicability is limited and may be ethically questionable. In addition, the inertness of the anesthetics utilized must still be confirmed (Kawchuk et al., 2009). This may explain why this placebo intervention has not been used in subsequent studies.

Table 2 summarizes the placebo and control groups from studies presented in this review. In order to improve basic and clinical research on pain relief by SM, the quality of control and placebo interventions must be improved. This will further our understanding of the SM mechanisms and clinical effectiveness, by ruling out non-specific effects. In addition, more research on the dosage parameters of an effective SM is needed to determine what are the therapeutic or active components of SM, including the biomechanical loads and forces, the peripheral afferent and central processes as well as other variables.

Future perspectives and conclusion

Research on the mechanisms of SM has progressed significantly in recent years. Some of the mechanisms underlying treatment outcomes are becoming clearer and the advancement of pain research is contributing to this development. The new classification recently provided by the pain research community should allow a better understanding of chronic primary pain conditions, including those affecting the spine (Treede et al., 2019). The adoption of these changes by the spine pain research community should improve evidence on the use of SMT in the management of acute, subacute, and chronic NP and LBP.

Future basic research can contribute to improving the recommendations for the management of spine pain. Gaining a better understanding of the mechanisms by which SM can attenuate pain may help guiding clinical research by determining the specific mechanisms on which SM may act and in which conditions this may translate into clinical benefits. The use of appropriate, standardized placebo interventions and blinding strategies in both mechanistic and clinical trials is deemed essential to improving the quality of research.

The evidence presented in this review suggests that SM produces neurophysiological effects mainly via spinal cord mechanisms. These include segmental mechanisms of pain inhibition involving a reduction in temporal summation of pain. These mechanisms could

partially explain some of the effects of SM observed locally and regionally. However, the reason why certain modalities seem to be more affected than others remains to be clarified. This could be due to SM influencing a specific group of nociceptive fibers. Modulation of C-fibers may influence the development of secondary hyperalgesia, which is characterized by increased sensitivity to mechanical but not thermal painful stimuli (Ali et al., 1996; Simone et al., 1989; Torebjork et al., 1992). Future research should explore potential anti-hyperalgesic effects of SM that are particularly relevant to chronic pain.

Some of the hypoalgesic effects cannot be explained by segmental mechanisms. In order to better understand these effects, measuring variables related to peripheral pain mechanisms should be considered (e.g., ROS and cytokines). Regarding supraspinal mechanisms, showing that brain activity changes after SM is not sufficient to conclude on the underlying mechanisms, so it remains to be determined how and whether SM may induce changes in brain activity, which in turn produce pain inhibition.

Recent experiments have provided insight into changes induced by SM in peripheral tissues that are most likely mediated by local growth factors and not by the nervous system (Conesa-Buendia et al., 2020; Lopez-Herradon et al., 2017). These effects provide a new avenue for investigating peripheral mechanisms involved in tissue damage and inflammation, likely influencing musculoskeletal pain. It has also been suggested that SM might regulate the activity of the sympathetic nervous system, which in turn could modulate inflammation (Gyer et al., 2019; Kovanur-Sampath et al., 2015). However, most mechanistic experiments have failed to identify clinically relevant changes induced by SMT (Honore et al., 2019). In order to close the gap between basic and clinical research, translational research is needed. Randomized controlled trials on the effectiveness of SMT on spine pain in which neurophysiological variables are measured are one possibility that could link experimental and clinical research findings (Clark et al., 2018). Further exploration of mechanistic trial designs will improve our understanding of the biological mechanisms underlying the efficacy (or physiological and clinical effects) of SM while optimizing the clinical management of spine pain with SMT and other conservative approaches (Karanicolas et al., 2009).

Besides the limitations related to the difficulties in translating evidence from basic science studies to the clinical realm, another important limitation comes from the quality of the placebo interventions and controls. The use of validated placebo interventions is not universal in SM research, which dramatically impacts the quality of studies. Therefore, the data from the studies presented need to be interpreted with caution. Designing an appropriate placebo for SM is challenging but is essential for future research on the mechanisms and

clinical effectiveness of SMT. Meanwhile, the available findings from animal studies provide support to a specific effect of SM, particularly influencing segmental mechanisms of pain inhibition (Duarte et al., 2019; Grayson et al., 2012; Onifer et al., 2015; Onifer et al., 2018). Additionally, human data suggests that SM hypoalgesia relies, at least partially, on specific mechanisms independent of expectations (Bialosky et al., 2008; Bialosky et al., 2014; Bishop et al., 2011b; Bishop et al., 2017). Validation studies have demonstrated that it is possible to design credible placebo interventions that are structurally equivalent to and indistinguishable from SM, even for multiple sessions in patients previously exposed to SM (Chaibi et al., 2015; Vernon et al., 2012). Nevertheless, a question that remains unanswered is whether these placebo interventions lack any therapeutic effects (Chaibi et al., 2015; Vernon et al., 2012). Indeed, these placebo interventions allowed successful blinding, but reported no significant group difference (Aspinall et al., 2019a; Honore et al., 2020). This was interpreted as a lack of therapeutic effect of SMT, but it could be argued that the placebo intervention may not be inert and may have masked therapeutic effects.

Research on placebo analgesia has shown that deceptive experiments (in which the participant receives the instruction that the placebo is in fact effective) achieve greater placebo effects compared with trials in which group allocation is uncertain (Kaptchuk et al., 2020; Vase et al., 2002). Open-label placebo experiments have shown that the placebo effect can be used to influence treatment outcomes effectively (Kaptchuk et al., 2020). In clinical practice, this could be attained by, for example, providing realistic but positive information about the prognosis (L. Colloca and Barsky, 2020), or by avoiding messages that could influence patients beliefs negatively, resulting in increased vigilance, worry, or frustration (L. Colloca and Barsky, 2020; Darlow et al., 2013).

The gaps identified in research on pain mechanisms of SM should guide future investigations. Although basic and clinical research on SMT provide some converging results, it remains a constant challenge to design basic studies that provide results that inform clinical research. Mechanistic trials in which basic research measures are implemented in clinical trials offer an interesting possibility to bridge this gap. Improving our understanding of how SM mediates pain relief through specific and non-specific mechanisms should translate into more homogenous recommendations on its use for specific patients, conditions, and pain states.

Abbreviations

ACP: American College of Physicians; CPGs: Clinical Practice Guidelines; IL-1β: Interleukin one beta; IL-10: Interleukin ten; LBP: Low back pain; NICE: National Institute for Health and Care Excellence; NP: Neck pain; PPTs: Pressure pain thresholds; SM: Spinal manipulation; SMT: Spinal manipulative therapy; ROS: Reactive oxygen species.

Author contributions

Each author contributed significantly to this work and has read and approved the final version of the manuscript. C.G-M. contributed to literature review, study selection and wrote the preliminary version of the manuscript. B.P. contributed to the literature review, M.D. contributed to manuscript editing, A.O contributed to manuscript editing and guidance in its design, M.P. contributed to the literature review, wrote the final version of the manuscript and obtained funding.

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Conflicts of interest

The authors report no financial or other relationships that may lead to any conflicts of interest.

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Figure Legend

Figure 1. Pain mechanisms likely influenced by spinal manipulation (SM).

(a). In the periphery, SM may decrease pro-inflammatory cytokine responses (Roy et al., 2010; Teodorczyk-Injeyan et al., 2006, 2018) and oxidative stress (Duarte et al., 2019; Kolberg et al., 2015). (b) At the spinal segmental level, SM may induce segmental inhibition (Alonso-Perez et al., 2017; de Camargo et al., 2011; Dorron et al., 2016; Fernandez-Carnero et al., 2008; Fernandez-de-las-Penas et al., 2007; Fryer et al., 2004; Laframboise et al., 2016; Coronado et al., 2012; Honore et al., 2018; Millan et al., 2012, decrease temporal summation of pain (George et al., 2006; Bialosky et al., 2008, 2009, 2014; Bishop et al., 2011; Aspinall et al., 2019; Randoll et al. 2017), and inhibit central sensitization (Mohammadian et al., 2004; Song et al., 2016). (c) At the supraspinal level, no specific mechanism has been reported (Meyer et al., 2019), although widespread pain inhibition suggests cerebrospinal mechanisms involving the descending inhibitory system (Dorron et al., 2016; Salom-Moreno et al., 2014; Aspinall et al., 2019; Martinez-Segura et al., 2012). Changes in pain-related brain activity may reflect modulation of nociceptive activity at the spinal or supraspinal levels (Gay et al., 2014; Sparks et al., 2017; Weber II et al., 2019; Ellingsen et al., 2018).

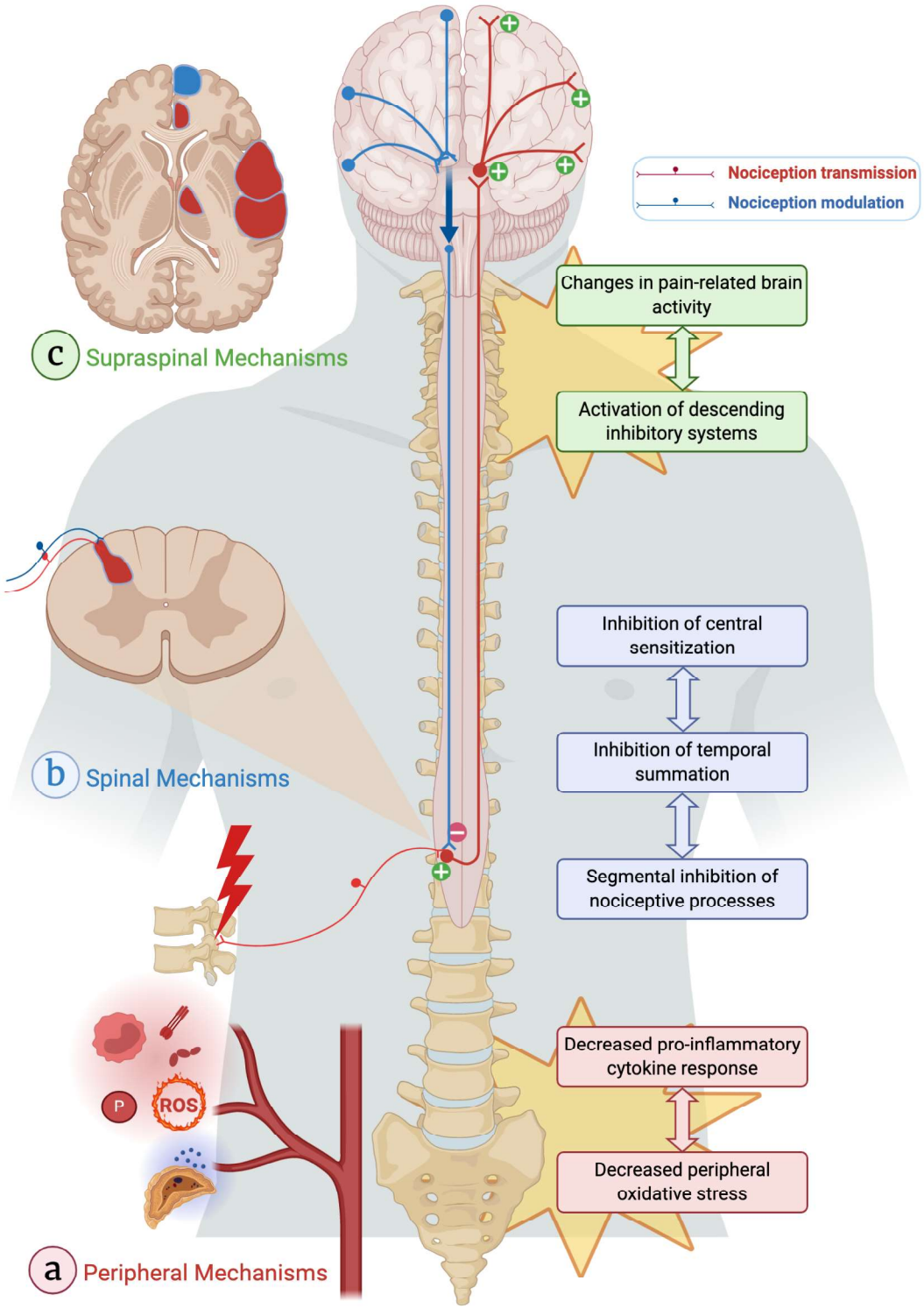
Table 1. Hypoalgesic mechanisms of spinal manipulation

Mechanisms	Effects on measured outcomes	Supporting evidence
Decreased peripheral oxydative stress	Reduction in plasmatic levels of ROS.	Duarte 2019; Kolberg 2015.
Decreased pro-inflammatory cytokine response	Decline in production of CCL3 and CCL4 chemokines, TNF-α and IL-1β.	Teodorczyk-Injeyan 2006, 2018; Roy 2010.
Segmental inhibition of nociceptive processes	Segmental (dermatomal and myotomal) increase of pressure pain thresholds.	Coronado 2012; Honore 2018; Millan 2012; Alonso-Perez 2017; Fryer 2004; de Camargo 2011; Dorron 2016; Fernandez-Carnero 2008; Fernandez-de-las-Penas 2007; Laframboise 2016; Duarte 2019; Grayson 2012; Onifer 2015; Onifer 2018; Nim 2020.
Inhibition of temporal summation	Reduction in pain evoked by repeated thermal and electrical stimuli.	Aspinall 2019b; Bialosky 2008, 2009b, 2014; Bishop 2011a; George 2006; Randoll 2017.
Inhibition of central sensitization	Reduction of spontaneous pain, secondary hyperalgesia, and allodynia induced by topical capsaicin. Increased spinal levels of IL-10.	Mohammadian 2004; Song 2016.

Table 2. Active interventions and placebo used in the spinal manipulation (SM) studies

Authors	Year	Sample	Active SM intervention	Placebo SM intervention	Non-placebo control interventions
Kovanur-Sampath K, et al.	2017	N=24 Humans	HVLA SM T5	SM positioning, no thrust	-
Plaza-Manzano G, et al.	2014	N=30 Humans	HVLA SM C4-5 or T3-5	-	No intervention
Valera-Calero A, et al.	2019	N=83 Humans	HVLA SM cervical	SM positioning, no thrust	-
Whelan TL, et al.	2002	N=30 Humans	HVLA SM cervical	SM positioning, no thrust	No intervention (supine position)
Lohman EB, et al.	2019	N=28 women	HVLA SM cervical	SM positioning, no movement, no thrust	-
Molina-Ortega F, et al.	2014	N=30 Humans	HVLA SM C5-6 or T4	SM positioning, no thrust	-
Duarte FCK, et al.	2019	N=30 Rats	HVLA SM instrument L4-5	Lighter SM force, no preload	-
Kolberg C, et al.	2015	N=23 Humans	10 sessions HVLA SM full spine	-	-
Roy RA, et al.	2010	N=21 Humans	HVLA SM instrument lumbar	-	No intervention (leg length evaluation)
Teodorczyk-Injeyan JA, et al.	2018	N=63 Humans	6 sessions HVLA SM lumbosacral	-	-
Teodorczyk-Injeyan JA, et al.	2006	N=64 Humans	HVLA SM thoracic	SM with different position and force orientation	No intervention (venipuncture)
Alonso-Perez JL, et al.	2017	N=75 Humans	HVLA SM C7	-	HVLA to C5. Right lateral glide mobilizations
Bialosky JE, et al.	2008	N=60 Humans	HVLA SM lumbar	-	HVLA with positive, negative or neutral expectations
Bialosky JE, et al.	2009	N=36 Humans	4 HVLA SM pelvis	-	Stationary bike. Extension exercises
de Camargo VM, et al.	2011	N=37 Humans	HVLA SM C5-6	-	No intervention
Dorron SL, et al.	2016	N=34 Humans	HVLA SM L5-S1	-	Comparison of right and left sides
Fernandez-Carnero J, et al.	2008	N=10 Humans	HVLA SM cervical	Manual contact	-
Fernandez-de-las-Penas C, et al.	2007	N=15 Humans	HVLA SM C5-6	SM positioning with no tissue tension, no thrust	-
Fryer G, et al.	2008	N=96 Humans	HVLA SM thoracic	Sham laser acupuncture	Extension mobilization
George SZ, et al.	2006	N=60 Humans	HVLA SM lumbar	-	Stationary bike. Extension exercises
Laframboise MA, et al.	2016	N=26 Humans	HVLA SM C5-6 drop-table	SM positioning and preload, thrust into headpiece by supporting hand	-
Salom-Moreno J, et al.	2014	N=52 Humans	HVLA SM T3-6	-	Posteroanterior mobilization
Aspinall SL, et al.	2019	N=80 Humans	HVLA SM L5	Lighter SM with extraspinal thrust	-
Honore M, et al.	2020	N=50 Humans	HVLA SM T5 prone	Lighter SM with extraspinal thrust	-
Nim CG, et al.	2020	N=132 Humans	HVLA SM lumbar	-	HVLA to stiffest or more sensitive segment
Grayson JE, et al.	2012	N=12 Rats	3 x 1 min mobilizations L5	Manual contact	-
Onifer SM, et al.	2015	N=24 Rats	10 min LVVA SM L5	-	No intervention
Onifer SM, et al.	2018	N=27 Rats	10 min LVVA SM L5	-	No intervention (table positioning)
Bialosky JE, et al.	2014	N=110 Humans	HVLA SM lumbar	SM positioning, no thrust	No intervention
Bishop MD, et al.	2011	N=90 Humans	HVLA SM thoracic	-	Cervical flexion exercise. Rest for 5 min
Randoll C, et al.	2017	N=31 Humans	HVLA SM T4	Light mechanical stimulus	No intervention
Mohammadian P, et al.	2004	N=20 Humans	HVLA SM thoracic	SM positioning, no thrust	-
Song XJ, et al.	2016	N=96 Rats	HVLA SM instrument L5	-	Force settings 1 and 2. No intervention
Casanova-Méndez A, et al.	2014	N=60 Humans	HVLA SM T4	-	Two techniques were compared
Martínez-Segura R, et al.	2012	N=90 Humans	HVLA SM C3-4 or T1-4	-	Comparison of two levels and laterality
Gay CW, et al.	2014	N=24 Humans	HVLA SM lumbar	Manual contact	Mobilization
Sparks CL, et al.	2017	N=24 Humans	HVLA SM thoracic	SM positioning, no thrust	-
Weber II KA, et al.	2019	N=24 Humans	HVLA SM T4-5	SM positioning, no thrust	-
Ellingsen DM, et al.	2018	N=31 Humans	HVLA SM lumbar	-	Mobilization
Bishop MD, et al.	2011	N=112 Humans	HVLA SM lumbar	Lower velocity SM or no thrust	-
Bishop MD, et al.	2017	N=60 Humans	HVLA SM lumbar	Manual contact for 5 min	-

SM = Spinal Manipulation; HVLA = High Velocity Low Amplitude; LVVA = Low Velocity Variable Amplitude



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