Musculoskeletal Science and Practice 80 (2025) 103409

Contents lists available at ScienceDirect

Musculoskeletal Science and Practice

journal homepage: www.elsevier.com/locate/msksp

Relative contribution of real/sham spinal manipulation performance, changes in cortisol levels, and patient expectations and fear behaviors in modulating short-term pain relief in people with neck pain: A secondary analysis of a randomized clinical trial

Juan Antonio Valera-Calero [a,b], Jorge Buffet-García [c,*], Magdalena Kocot-Kępska [d], Dariusz Kosson [e], Marcin Kołacz [f], Gustavo Plaza-Manzano [a,b]

[a] Department of Radiology, Rehabilitation and Physiotherapy, Faculty of Nursery, Physiotherapy and Podiatry, Complutense University of Madrid, 28040, Madrid, Spain
[b] Grupo InPhysio, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), 28040, Madrid, Spain
[c] Faculty of Health Sciences, Universidad Francisco de Vitoria, 28223, Madrid, Spain
[d] Faculty of Medicine, Department for Pain Research and Treatment, Jagiellonian University, 31-008, Krakow, Poland
[e] Department of Anaesthesiology and Intensive Care Medical University of Warsaw, Division of Teaching, 02-005, Warsaw, Poland
[f] 1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, 02-005, Warsaw, Poland

ARTICLE INFO

Keywords:
Expectations conditioning
Manual therapy
Neuroendocrine system
Spinal manipulation

ABSTRACT

Background: Spinal manipulation (SM) is a widely practiced, hands-on, non-invasive manual therapy aimed at alleviating musculoskeletal pain and improving functional capacity. Although the clinical effects of this intervention are well known, most reviews conclude that the underlying mechanisms needs further investigation. Therefore, the aim of this study was to analyze the individual contribution of SM execution, expectations, fear behaviors and neuroendocrine changes on short-term pain intensity variance following the interventions.
Design: Experimental study.
Methods: A secondary analysis from a previous randomized clinical trial was conducted. Sixty-two patients were randomized for two factors: the intervention assigned (cervical manipulation and sham manipulation) and the induced expectations (positive, neutral and negative) during treatment. A linear regression analysis was conducted to calculate the individual contribution of the SM execution (sham/real), expectations conditioning (positive/negative/neutral), fear behaviors (fear/no fear) and neuroendocrine changes (salivary cortisol) on the variance of immediate pain intensity changes (pre-post intervention difference) following the single intervention.
Results: Changes in salivary cortisol ($\beta = -0.027$, $p = 0.838$) and fear ($\beta = -0.192$, $p = 0.135$) were not significant explanatory variables of pain intensity response ($p > 0.05$). However, verbally-induced expectations ($\beta = 0.722$, $p < 0.001$) and the manipulation execution ($\beta = 0.207$, $p = 0.019$) showed a significant positive association with pain intensity response, suggesting that positive expectations had a meaningful impact on reducing pain intensity and a real intervention may involve specific hypoalgesic responses.
Conclusion: Clinicians should consider that patients' expectations may influence clinical outcomes. Verbally expressing positive or neutral expectations may improve pain-related outcomes, whereas conveying negative expectations could diminish the treatment's effectiveness.

1. Introduction

Spinal manipulation (SM) is a manual, non-invasive technique commonly employed to address musculoskeletal disorders, reduce pain, and enhance physical function. Widely endorsed for its therapeutic value, SM is integrated into clinical practice by various healthcare disciplines across the world (Trager et al., 2024). Its inclusion in numerous evidence-based treatment protocols and clinical guidelines further

---

* Corresponding author. M-515, km 1.800, 28223, Pozuelo de Alarcón, Spain.
E-mail addresses: juavaler@ucm.es (J.A. Valera-Calero), j.buffet.prof@ufv.es (J. Buffet-García), mkocotkepska@cm.uj.krakow.pl (M. Kocot-Kępska), dariusz.kosson@wum.edu.pl (D. Kosson), marcin.kolacz@wum.edu.pl (M. Kołacz).

https://doi.org/10.1016/j.msksp.2025.103409
Received 24 December 2024; Received in revised form 3 September 2025; Accepted 6 September 2025

supports its perceived efficacy (Blanpied et al., 2017; Chaibi et al., 2021; Liu et al., 2023).

Initial explanations of SM's effectiveness were largely grounded in biomechanical models. These included concepts such as vertebral realignment (Demoulin et al., 2018) and structural corrections presumed to have lasting effects which have been critically re-evaluated among healthcare professionals (Valera-Calero et al., 2021) as new studies have emerged. The assumed therapeutic benefits (such as pain reduction, enhanced mobility, and broader health improvements) were attributed to these anatomical and mechanical alterations (Herzog, 2010). However, most of these assertions lacked solid scientific backing. For instance, the transient increase in facet joint spacing following SM, which is the most consistently observed biomechanical change, is highly dependent on maintaining a specific posture during imaging (Young et al., 2024).

As the biomechanical explanations proved insufficient to justify the range of clinical outcomes seen with SM, attention turned toward neurophysiological models as other factors rather than the manipulation itself could modulate the clinical responses observed in clinical trials (Gevers-Montoro et al., 2021a; Gyer et al., 2019; Lima et al., 2020; Maigne and Vautravers, 2003; Young et al., 2024). Emerging evidence suggests that SM primarily acts through mechanisms involving neural pathways at peripheral, spinal, and supraspinal levels (Gevers-Montoro et al., 2021b; Gyer et al., 2019). The application of mechanical force during SM is thought to stimulate paraspinal mechanoreceptors, setting off reflex circuits that alter motor control by modulating alpha and gamma motor neuron excitability and reducing excessive muscle tone (Gyer et al., 2019). SM may also engage the autonomic nervous system, producing either sympathetic or parasympathetic responses based on the specific spinal region treated (Amoroso Borges et al., 2018). Additionally, neuroendocrine responses have been observed, including elevated levels of cortisol and catecholamines, potentially contributing to anti-inflammatory effects (Kovanur Sampath et al., 2024). The analgesic effects of SM are thought to result from a combination of local segmental modulation—consistent with gate control theory—and activation of descending inhibitory systems within the central nervous system (Gyer et al., 2019). Short-term neuroplastic adaptations, such as enhanced cortical excitability and modified sensorimotor integration, have also been reported (Gyer et al., 2019).

Supporting evidence from preclinical research adds further depth to this understanding. Findings from animal studies (Lima et al., 2020) indicate that SM can elicit a rapid and significant increase in muscle spindle activity in the paraspinal region. These responses appear sensitive to various thrust characteristics—such as amplitude, speed, and direction—and are not confined to the directly manipulated segment, implying a wider segmental impact. Further outcomes include changes in neuronal activity within both spinal and thalamic pathways, such as heightened activation thresholds in pain-sensitive neurons and decreased spontaneous activity in medial thalamic neurons, reinforcing SM's potential in modulating pain. Moreover, electromyography has shown increased activity in muscles like the multifidus following SM, while immunological assays reveal reductions in pro-inflammatory mediators (e.g., IL-1β, PKCγ) alongside increases in anti-inflammatory cytokines like IL-10. These neuroimmune responses have also been investigated in humans, showing that several sessions of manual therapy significantly reduced circulating levels of the pro-inflammatory cytokine IL-1β in patients with chronic neck pain, alongside improvements in pain and function (Konstantinos et al., 2019). However, a single session of spinal mobilisation/manipulation does not produce detectable changes in systemic neuroimmune markers such as IL-1β and TNF-α, despite clear reductions in pain intensity, highlighting a possible dissociation between systemic inflammation and immediate analgesic effects (Lutke Schipholt et al., 2023).

In addition, psychological factors (such as patients' expectations) have been increasingly recognized as modulators of the pain-relief response following SM. High expectations of improvement have been associated with greater reductions in pain and better clinical outcomes in patients receiving manual therapy, both in experimental settings and clinical populations with spinal pain (Bialosky et al., 2008; Eklund et al., 2019). Conversely, negative expectations or fear to be manipulated can dampen or even reverse the analgesic effects, leading to hyperalgesia in some cases (Bialosky et al., 2008). Similar findings have been observed in patients with chronic neck pain, where positive verbal suggestions enhanced clinical outcomes, while negative expectations diminished treatment efficacy (Malfliet et al., 2019). In addition to expectations, other psychological constructs such as fear of spinal manipulation and pain catastrophizing have been associated with increased pain sensitivity and poorer response to treatment. Together, these findings suggest that psychological factors may not only influence patients' experience of pain but also modulate the neurophysiological mechanisms underpinning the response to SM.

Since most reviews conclude that further research is needed to reach solid conclusions regarding how multiple factors modulate the clinical response after SM (Gevers-Montoro et al., 2021b; Pickar, 2002; Young et al., 2024). Therefore, quantifying the individual contribution of each factor to the variance in the analgesic response is still needed. Following this methodology, previous research focused on biomechanical aspects of SM to investigate how SM force magnitude (Duarte et al., 2022) or the facet joint movement of vertebrae during high-velocity, low-amplitude manipulations (Buzzatti et al., 2015) modulate the clinical response. However, manual therapy outcomes are likely shaped by a combination of neurophysiological, psychological, and procedural factors. Assessing these factors simultaneously may provide a more comprehensive understanding of how different components interact to influence treatment effects by identifying in a multivariate regression model which mechanisms most strongly contribute to pain modulation. Therefore, this research aimed to assess the individual contribution of intervention fear, expectations conditioning, intervention type and neuroendocrine responses on short-term pain intensity changes after SM.

2. Methods

2.1. Study Design

This research is a secondary analysis from previous randomized clinical trials (Malfliet et al., 2019; Valera-Calero et al., 2019) conducted between December 2016 and January 2017. In those studies, participants received one of three interventions (real SM, mobilization, or sham SM), with one trial analyzing differences in clinical outcomes and cortisol levels (Valera-Calero et al., 2019), and the other additionally manipulating participants' treatment expectations (positive, neutral, or negative) (Malfliet et al., 2019).

Since the original analyses were limited to compare group means on isolated variables using ANOVA, these analyses only evaluated changes over time after interventions and did not explore how different variables might interact to explain individual differences in pain-relief responses. As such, they are not suited to answer questions regarding the relative influence of multiple factors involved in hypoalgesia. The current secondary analysis addresses this gap by applying a multivariate regression model to simultaneously examine the individual contribution of intervention fear, expectations conditioning, intervention type and neuroendocrine responses to the variance in short-term pain intensity changes. This approach allows to identify which factors contributes on the pain response following SM and is the adequate statistical analysis to understand the interplay between neurophysiological and contextual factors. The protocol received approval from the Human Research Ethics Committee and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent before joining the study. The complete study protocol was registered prospectively on ClinicalTrials.gov (NCT02628470). This analysis was not pre-specified in the original trial registration or protocol and has been developed post hoc.

2.2. Participants

Participants were recruited through referrals from office workers. Eligible individuals were between 18 and 65 years old and had experienced mechanical non-specific neck pain for at least three months. This age range was selected due to the known influence of age on pain nociception (aging has been associated with altered pain sensitivity due to changes in peripheral and central pain pathways, which can increase variability in pain responses (Gibson and Farrell, 2004)) and the increased risk of contraindications for cervical manipulation in individuals over 65 years (Valera-Calero et al., 2019). Exclusion criteria included the use of hormonal therapy, adrenal gland pathology, medical conditions causing cortisol imbalance such as autoimmune adrenalitis or drug-induced adrenal insufficiency, severe psychological disorders related to anxiety, mood, or stress, pregnancy, and contraindications for manipulation or mobilization techniques (Grieve, 1989).

2.3. Allocation

Participants were randomized for two factors: the intervention assigned (cervical manipulation and sham manipulation) and the expectations communicated (positive, neutral and negative) during treatment. The randomization process was conducted using concealed allocation and computer-generated random numbers created prior to data collection by an independent researcher not involved in the study. A blocked randomization model was employed, with individual, sequentially numbered index cards folded and placed in opaque, sealed envelopes.

The treating physical therapist first opened the envelope specifying the assigned intervention, followed by the envelope indicating the expectations to be communicated to the participant during the intervention. As a result, participants within each intervention group were randomly assigned different expectation conditions.

2.4. Fear to spinal manipulation

Participants, prior to be allocated in any of the assignation groups (intervention and expectations), were interviewed as part of the data collection process to assess their perception of SM. They were asked whether they experienced fear related to the procedure. Their responses were recorded and categorized into two distinct groups: "yes," indicating the presence of fear, and "no," indicating its absence.

2.5. Spinal manipulation groups

All treatment groups were managed by the same physical therapist, who held a master's degree in physical therapy and had +10 years of experience in outpatient care. The International IFOMPT Cervical Framework was used as a reference to screen for potential vascular risks prior to cervical intervention (Rushton et al., 2014). Each participant received a single session of one of real or sham cervical manipulation.

The cervical manipulation technique followed the method described by Gibbons and Tehan (2006). It involved a high-velocity, mid-range rotational force applied to the C5–C6 segment, with right side-bending and left rotation, with the patient positioned in the supine position. Care was taken to avoid reaching the end range of rotational movement during the technique.

On the other hand, the sham manipulation was performed based on the protocol outlined by Vernon et al. (2012). Unlike cervical manipulation, this technique excluded the joint preload and thrust components. The therapist maintained the same degree of head rotation and manual support to the head and neck as in cervical manipulation but without applying a thrusting force. Instead, motion was simulated through the drop action of the headpiece cam mechanism, which produced an associated sharp sound to mimic the auditory experience of manipulation.

2.6. Expectations conditioning

The communication styles employed in this study to address treatment expectations were adapted from the work of Glaser et al. (2018). Participants in the positive expectation group were informed, "This is a very effective intervention used to treat neck pain, and we expect it to reduce your pain experience". Those in the negative expectation group were told, "This is an ineffective intervention used to treat neck pain, and we expect it to temporarily worsen your pain experience". Participants in the neutral expectation group were advised, "This is an intervention used to treat neck pain that has unknown effects on the perception of your pain".

2.7. Pain intensity

Pain intensity was assessed using the Visual Analog Scale (VAS) since this instrument is a reliable and valid tool for evaluating pain (Hjermstad et al., 2011). The VAS consists of a 10-cm horizontal line anchored at one end with "0 = no pain" and at the other with "10 = worst pain imaginable." Participants were instructed to place a vertical mark on the line at the point that best reflected their current pain intensity. To enhance accuracy, the VAS score was calculated as the mean of three measurements: the pain intensity at the current moment during the interview, the highest pain intensity experienced in the previous seven days, and the lowest pain intensity experienced in the previous seven days. This evaluation was conducted both before and seven days after the intervention to assess changes in pain levels.

2.8. Salivary cortisol

Salivary cortisol levels were measured using a Cortisol kit RE52611 ELISA® (IBL International GmbH, Hamburg, Germany) in March 2017, which is a recognized, reliable and accurate method to estimate cortisol levels (Hellhammer et al., 2009). Saliva samples were stored at −20 °C until analysis. The analysis process involved four steps: (1) adding 50 μL of saliva and 100 μL of enzyme conjugate to a tube; (2) incubating the closed tubes at room temperature (18 °C–25 °C) for 2 h while centrifuging at 400–600 rpm; (3) adding 100 μL of tetramethylbenzidine solution and centrifuging again under the same conditions; and (4) adding 100 μL of tetramethylbenzidine inhibitory solution and measuring results with a photometer at 450 nm within 15 min of adding the final reagent. This measurement was taken both before and 10 min after the intervention to evaluate changes in salivary cortisol concentration.

2.9. Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics Version 29 for Mac OS (IBM Corporation, Armonk, NY), applying a significance threshold of $p < 0.05$. First, pain intensity and salivary cortisol changes following SM scores were calculated. Later, Shapiro–Wilk tests were used to assess the normality of data distribution. After using descriptive statistics to determine the central tendency and dispersion of the data, an analysis of covariance (ANCOVA) was used to calculate the effects of intervention type, fear behaviors and expectations on salivary cortisol and pain intensity changes. Baseline measurements served as covariates, while intervention type (real vs. sham), expectation condition (positive/neutral/negative) and baseline fear of spinal manipulation (yes/no) were treated as between-subject factors.

Finally, a linear regression model was developed to determine the individual contribution of the intervention type, expectations, fear behaviors and hormonal responses to explain the variability in pain intensity changes following SM. Each explanatory variable was analyzed individually without combining explanatory variables into a single, comprehensive model. This approach allows for a focused assessment of each variable's independent effect on the outcome. The statistical estimates included each explanatory variable's individual contribution to the variance in pain intensity changes (adjusted R^2), the strength and direction of its effect (standardized beta coefficients, β), and the statistical significance of the explanatory variable (p-value and 95 % confidence intervals).

3. Results

As recognized in the primary analyses of the dataset (Valera-Calero and Varol, 2022), from 551 patients listed in the Campus Repsol Physical Therapy Department's database a total of 62 office workers were initially identified as potential candidates based on their reports of chronic pain and met the eligibility criteria to be enrolled in the study (Malfliet et al., 2019; Valera-Calero et al., 2019). As a result, 62 participants completed the baseline assessment (n = 4 patients were discarded due to ELISA processing errors), the interventions and the post-intervention measurements.

The participants' allocation and their descriptive information is available in Table 1. Pain intensity at baseline was comparable for both groups (p = 0.116), but after the interventions the real manipulation group reported a significant lower pain intensity score compared to the sham manipulation group (p < 0.001). Salivary cortisol and pain intensity changes based on the factors of intervention type, expectations, and fear of SM (along with their interactions) were also analyzed. The results revealed that the intervention significantly influenced pain score differences (F = 10.082, p = 0.003, ηp2 = 0.174). However, the group factor did not significantly affect cortisol responses (p = 0.216). Expectations did not significantly impact cortisol differences (p = 0.312) but impacted on pain responses (F = 26.591, p < 0.001, ηp2 = 0.526). Fear of SM significantly influenced cortisol responses (F = 6.509, p = 0.014, ηp2 = 0.119). However, fear did not have a significant effect on pain change responses (p = 0.551).

The interaction between intervention group and expectations was not significant for either cortisol (p = 0.100) or pain (p = 0.492). Similarly, the interaction between intervention group and fear of spinal manipulation was not significant for cortisol (p = 0.084) or pain (p = 0.106). The interaction between expectations and fear for cortisol (p = 0.129) and pain (p = 0.153) was not significant either. Finally, the three-way interaction between group, expectations, and fear for cortisol (p = 0.165) and pain (p = 0.437) showed no significant effects.

The regression model in Table 2 explores the individual contribution of each factor on explaining pain intensity changes following SM. Salivary cortisol changes did not significantly contribute to pain intensity changes (p = 0.838). This indicates that changes in salivary cortisol are not a meaningful explanatory variable of immediate pain intensity changes in this context. Fear of SM similarly showed a non-significant influence (p = 0.135). Intervention type significantly contributed to pain intensity changes (p = 0.019). The positive coefficient indicates that the real manipulation was associated with greater pain relief compared to the sham manipulation. Expectations were the strongest explanatory variable of immediate pain intensity changes (p < 0.001), with a very large effect size suggesting that positive expectations were highly predictive of greater reductions in pain intensity.

Table 1
Participants' (n = 62) descriptive information by intervention group.

	Real Manipulation (n = 32)	Sham Manipulation (n = 30)	P value
Sex (n)			
Males	8	6	0.638
Females	24	24	
Expectations induced (n)			
Positive	11	11	0.934
Neutral	11	9	
Negative	10	10	
Fear to spinal manipulation (n)			
Yes	12	10	0.732
No	20	20	
Pain intensity (0–10)			
Baseline	4.6 ± 1.1	5.1 ± 1.5	0.116
Post-intervention	3.7 ± 1.0	4.9 ± 1.5	<0.001
Difference	−0.91 ± 1.26	−0.20 ± 2.11	
Percentage of improvement	19.8	3.9	
Salivary cortisol (g/dL)			
Baseline	0.63 ± 0.28	0.90 ± 0.64	0.035
Post-intervention	0.54 ± 0.24	0.68 ± 0.41	0.113
Difference	−0.08 ± 0.10	−0.22 ± 0.52	

4. Discussion

This study highlights the differential impact of various factors on immediate pain intensity changes following SM. While sex distribution, expectations, and fear of SM were evenly distributed between groups and showed no baseline differences, real SM yielded significantly greater immediate pain relief than sham manipulation. Salivary cortisol changes were not significantly associated with pain reduction, and fear of SM showed only a marginal influence. The intervention type played a modest but significant role, with real manipulation yielding greater pain relief compared to sham manipulation. Expectations emerged as the strongest explanatory variable of pain intensity changes, with positive expectations leading to substantial reductions in pain. These findings underscore the critical role of patient expectations (which is considered a cognitive factor) in determining the outcomes of SM and suggest that expectations may have a stronger explanatory value than salivary cortisol changes in immediate pain relief. Since most effects of SM have been attributed to the manipulation itself (potentially attributed to other responses triggered by a successful SM), neuro-immune, neuroendocrine ways (in this study assessed as cortisol variations) and psychological aspects (assessed by analyzing the fear and expectations influence on clinical responses), each factor is structurally discussed in the following sections.

4.1. *Spinal manipulation execution*

Since the exact pathways by which SM alleviates pain, supports tissue repair, and restores function remain unclear as hypoalgesic responses following sham SM have been also observed (albeit of smaller magnitude than those observed after real SM) (Liu et al., 2023), the clinical effects of SM are believed to be modulated by both biomechanical and neurophysiological factors. Over the years, numerous theories have been proposed to explain these findings, yet supporting evidence is still limited.

Four primary theories have been proposed to explain the greater clinical effect of real versus sham SM: (1) the release of trapped synovial folds or meniscoids, (2) the correction of buckled motion segments, (3) the reduction of articular or periarticular adhesions, and (4) the normalization of hypertonic muscles through reflexogenic effects (Gyer et al., 2019). However, the clinical significance of these theories remains uncertain. While studies have measured motion resulting from SM, the observed biomechanical effects are generally transient, with no solid evidence supporting long-term positional changes (Cramer et al., 2013). Among these theories, the reflexogenic effect on hypertonic muscles has some supporting evidence, but the claim that SM alters muscle tone through changes in stretch reflex gain has not been definitively proven (Colloca et al., 2000; Lehman, 2012; Nogueira et al., 2020).

The success of SM is often attributed to biomechanical adjustments, specifically correcting movement and positional faults detected through palpation. However, this explanation remains controversial as palpation has shown low inter-rater reliability in identifying spinal abnormalities or intervertebral accessory range of movement (Haneline and Young, 2009; Jonsson and Rasmussen-Barr, 2018). Furthermore, the specificity of SM to be applied on the desired segment is questionable (Ross et al., 2004). In any case, the limitation in the specificity of manipulation techniques does not appear to be a significant issue, as targeting a

Table 2

Regression model to explain the individual contribution of potential underlying mechanisms of spinal manipulation on immediate pain intensity changes.

	Predictor Outcome	*Adj R^2*	*B*	SE B	95 % CI	β	t	p Value
Pain intensity changes following spinal manipulation	Salivary cortisol changes	−0.016	−0.130	0.632	−1.395; 1.135	−0.027	−0.206	0.838
	Fear	0.021	−0.695	0.460	−1.615; 0.224	−0.192	−1.513	0.135
	Intervention type	0.027	0.360	0.149	0.061; 0.659	0.207	2.410	0.019
	Expectations conditioning	0.513	1.523	0.189	1.146; 1.900	0.722	8.074	<0.001

specific segment has not been shown to produce superior clinical outcomes compared to global manipulations that address the painful segments in a nonspecific manner (Nim et al., 2021).

One reasonable hypothesis is that biomechanical changes from manipulation may trigger neurophysiological responses by altering sensory input to the central nervous system (Gevers-Montoro et al., 2021b). The mechanical force applied during manipulation could stimulate or inhibit mechanosensitive and nociceptive afferents in paraspinal tissues such as skin, muscles, discs, joints, tendons, and ligaments (Provencher et al., 2021). This input is believed to influence pain-processing mechanisms at spinal level (e.g. activation of gate closing mechanism) and other central nervous system related physiological systems (e.g. activation of descending antinociceptive pathways) (Gyer et al., 2019).

Our findings align with the hypothesis that SM exerts its clinical effects through a combination of biomechanical and neurophysiological pathways. The significant reduction in pain intensity observed in the real manipulation group compared to the sham manipulation group and the contribution on the pain intensity change variance supports the idea that SM can influence pain modulation. Mechanical forces applied during manipulation may alter sensory input to the central nervous system, thereby modulating pain-processing mechanisms.

4.2. Changes in salivary cortisol

The hypothalamus is central to coordinating stress responses by activating the hypothalamic-pituitary-adrenal (HPA) axis and a neural pathway involving the parasympathetic nervous system (Smith and Vale, 2006). The HPA axis, recognized as the primary stress response system, releases cortisol, a glucocorticoid with well-documented anti-inflammatory and immunosuppressive effects. Similarly, the sympathetic nervous system acts as a mediator between somatic and supportive processes, with both the sympathetic nervous system and HPA axis playing crucial roles in modulating acute and chronic inflammation. These systems are involved in neuroendocrine pathways that contribute to pain relief and tissue healing, often working in conjunction through overlapping neural pathways (Knezevic et al., 2023; Ortiz et al., 2020). Evidence suggests that SM can influence the activity of both the sympathetic nervous system and HPA axis, with studies reporting immediate increases in serum or salivary cortisol levels post-manipulation in both symptomatic and asymptomatic patients (Lohman et al., 2019; Plaza-Manzano et al., 2014; Valera-Calero et al., 2019).

Kovanur Sampath et al. (Kovanur Sampath et al., 2024; Kovanur-Sampath et al., 2017) hypothesized a link between changes in the sympathetic nervous system and HPA axis, suggesting that SM may trigger simultaneous responses in both systems. They proposed that high-velocity, low-amplitude thrusts at the thoracolumbar spine excite preganglionic sympathetic cells and stimulate mechanoreceptors, which transmit signals to brainstem regions. This process may influence the hypothalamus and periaqueductal gray matter, inducing endogenous analgesia. The hypothalamus would then release corticotropin-releasing factor, modulating the sympathetic nervous system and HPA axis to produce catecholamines and glucocorticoids, initiating anti-inflammatory and tissue-healing effects. However, only one study to date has investigated the combined sympathetic nervous system and HPA axis response to SM, reporting a reduction in salivary cortisol immediately after thoracic manipulation alongside sympathetic nervous system effects. The clinical significance of these neuroendocrine changes remains unclear, emphasizing the need for further research to understand their relevance to therapeutic outcomes.

Our findings indicated that salivary cortisol changes following SM were not significantly associated with immediate pain intensity changes, suggesting that cortisol release as a systemic stress-related hormonal responses play a limited role in the short-term analgesic effects of SM. This aligns with the notion that the therapeutic benefits are more likely mediated by localized neurophysiological factors, such as modulation of nociceptive processing or reflexogenic activity, rather than by systemic HPA axis activation. However, it should be noted that salivary cortisol changes may influence other clinical severity indicators such as pain pressure thresholds, and that different neuroendocrine biomarkers may contribute more substantially to explaining the variance in short-term pain relief.

4.3. Patients' expectations and fear behaviors

Several psychological modulators contribute to placebo, nocebo, and context-related effects, including expectation, learning processes such as classical conditioning and observational learning, reinforced expectations, mindset, and personality traits (Rossettini et al., 2020). Expectation refers to an individual's anticipation of a future event and serves as a powerful modulator of cognitive, emotional, and physical experiences (Lateef, 2011). However, these expectations are continuously shaped and adjusted by environmental inputs and can be easily conditioned by many contextual factors. Verbal suggestions are a particularly effective way to shape expectations, with substantial evidence demonstrating that positive or negative verbal cues can elicit placebo and nocebo effects, respectively. This has been tested in multiple trials and results are consistent: positive verbal suggestions significantly reduced pain intensity, regardless of whether real or sham neck manipulations are performed, while neutral information tends to produce a weaker effect, and negative suggestions a pain worsening (Hohenschurz-Schmidt et al., 2022; Reicherts et al., 2016).

Baseline fear of manipulation and verbal expectation conditioning serve as contextual factors that can up- or down-regulate endogenous analgesic circuits (e.g., descending inhibition), rather than direct mechanistic pathways. Recently Paleta et al. (2024), reported that cervical spine manipulation produces immediate hypoalgesic effects, evidenced by significant increases in pressure pain thresholds both at local and remote sites. However, contrary to the hypothesis, these changes in pain sensitivity did not correlate with patients' treatment expectations as measured by the Expectations for Treatment Scale. Although the majority of participants reported high treatment expectations, this factor was not predictive of the observed pain relief, indicating that the hypoalgesic effects of cervical manipulation might operate independently of patients' anticipatory beliefs. The lack of a relationship between expectations and pain sensitivity changes suggests that the placebo or context-related effects often associated with patient expectations were not a significant factor in this study.

As pointed out previously, there is an important difference between treatment expectations and expectations conditioning. While treatment expectations reflect a patient's conscious anticipation of therapeutic outcomes, expectation conditioning involves a learned association between a treatment and its effects, which can operate at a more subconscious level. Our results highlight that conditioning, rather than conscious treatment expectations, is the primary driver of pain relief following cervical spine manipulation. This suggests that the hypoalgesic effects observed in our study are likely mediated by neurophysiological processes reinforced through prior experiences or implicit learning, rather than by anticipatory cognitive beliefs.

4.4. Clinical implications, limitations and future research recommendations

Our results highlight that the verbal context in which SM are performed may be as therapeutically potent as the mechanical manoeuvre itself. In practical terms, a brief, positively framed introduction to the technique (emphasizing its safety and likely benefit) can markedly enhance immediate pain relief, whereas the physical component of real versus sham manipulation contributes a smaller share of the effect. Therefore, clinicians should deliberately integrate optimistic yet realistic expectation-shaping statements into their consent and treatment scripts, ensuring that patients enter the procedure with a mindset conducive to analgesia. Technical mastery of the thrust remains essential to secure its modest direct benefit, but optimal outcomes will likely arise from combining precise manual skill with skilled communication. Finally, when immediate hypoalgesia fails to materialize despite proper technique, practitioners might first reassess and reinforce the patient's expectations and contextual factors before intensifying force or frequency, potentially reducing unnecessary mechanical stress and attendant risks.

Finally, some limitations need to be acknowledged. This study evaluated only a single treatment session and focused exclusively on immediate pain relief, which was sufficient for our variance-explaining objective but leaves unanswered how these predictors operate over multiple visits or in the medium to long term. The sample assessed was small and may not generalize to other patient populations, and our binary fear assessment lacks the granularity of validated psychometric measures. Moreover, the number of variables representing each domain was limited, which constrains the ability to fully characterize the relative contribution of each one. Finally, the negative-expectation script used may exceed typical clinical phrasing and could limit ecological validity; future work should test more subtle nocebo framings.

Future studies should prospectively power multi-arm trials that manipulate expectation scripts alongside real vs. sham manipulation across repeated sessions, incorporate validated cognitive and sensory measures, and assess clinical outcomes over longer follow-up periods to determine the durability and generalizability of these predictors.

5. Conclusion

SM demonstrated a significant impact on immediate pain intensity changes, with the real SM group experiencing greater pain relief than the sham group. Expectations emerged as the strongest explanatory variable of pain reduction, with positive expectations leading to substantial decreases in pain intensity, while fear of SM showed no significant effect on pain outcomes. Salivary cortisol changes were not significantly associated with pain intensity changes, suggesting that systemic stress-related hormonal responses play a limited role in short-term pain relief following SM. However, the influence of the HPA cannot be discarded in other pain-related responses such as pain mechanosensitivity. Additionally, the interaction between intervention type, expectations, and fear did not significantly influence pain or cortisol outcomes, indicating that these factors acted independently. These findings suggest that the pain-relieving effects of SM are predominantly driven by the nature of the intervention and the influence of positive expectations.

CRediT authorship contribution statement

Juan Antonio Valera-Calero: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jorge Buffet-García:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis. **Magdalena Kocot-Kępska:** Writing – review & editing, Visualization, Validation, Formal analysis. **Dariusz Kosson:** Writing – review & editing, Validation, Software, Methodology, Formal analysis. **Marcin Kołacz:** Writing – review & editing, Validation, Software, Methodology. **Gustavo Plaza-Manzano:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Universidad de Alcalá (IEC/HU/2015/10).

Data availability statement

All data derived from this study are presented in the text.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Amoroso Borges, B.L., Bortolazzo, G.L., Neto, H.P., 2018. Effects of spinal manipulation and myofascial techniques on heart rate variability: a systematic review. J. Bodyw. Mov. Ther. 22, 203–208. https://doi.org/10.1016/J.JBMT.2017.09.025.

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 Muscoskelet. Disord. 9, 1–9. https://doi.org/10.1186/1471-2474-9-19.

Blanpied, P.R., Gross, A.R., Elliott, J.M., Devaney, L.L., Clewley, D., Walton, D.M., Sparks, C., Robertson, E.K., 2017. Neck pain: revision 2017. J. Orthop. Sports Phys. Ther. 47, A1–A83. https://doi.org/10.2519/JOSPT.2017.0302.

Buzzatti, L., Provyn, S., Van Roy, P., Cattrysse, E., 2015. Atlanto-axial facet displacement during rotational high-velocity low-amplitude thrust: an in vitro 3D kinematic analysis. Man. Ther. 20, 783–789. https://doi.org/10.1016/J.MATH.2015.03.006.

Chaibi, A., Stavem, K., Russell, M.B., 2021. Spinal manipulative therapy for acute neck pain: a systematic review and meta-analysis of randomised controlled trials. J. Clin. Med. 10. https://doi.org/10.3390/JCM10215011.

Colloca, C.J., Keller, T.S., Gunzburg, R., Vandeputte, K., Fuhr, A.W., 2000. Neurophysiologic response to intraoperative lumbosacral spinal manipulation. J. Manip. Physiol. Ther. 23, 447–457. https://doi.org/10.1067/MMT.2000.108822.

Cramer, G.D., Cambron, J., Cantu, J.A., Dexheimer, J.M., Pocius, J.D., Gregerson, D., Fergus, M., McKinnis, R., Grieve, T.J., 2013. Magnetic resonance imaging zygapophyseal joint space changes (gapping) in low back pain patients following spinal manipulation and side-posture positioning: a randomized controlled mechanisms trial with blinding. J. Manip. Physiol. Ther. 36, 203–217. https://doi.org/10.1016/J.JMPT.2013.04.003.

Demoulin, C., Baeri, D., Toussaint, G., Cagnie, B., Beernaert, A., Kaux, J.F., Vanderthommen, M., 2018. Beliefs in the population about cracking sounds produced during spinal manipulation. Jt. Bone Spine 85, 239–242. https://doi.org/10.1016/J.JBSPIN.2017.04.006.

Duarte, F.C.K., Funabashi, M., Starmer, D., Partata, W.A., West, D.W.D., Kumbhare, D.A., Injeyan, S., 2022. Effects of distinct force magnitude of spinal manipulative therapy on blood biomarkers of inflammation: a proof of principle study in healthy young adults. J. Manip. Physiol. Ther. 45, 20–32. https://doi.org/10.1016/j.jmpt.2022.03.012.

Eklund, A., De Carvalho, D., Pagé, I., Wong, A., Johansson, M.S., Pohlman, K.A., Hartvigsen, J., Swain, M., 2019. Expectations influence treatment outcomes in patients with low back pain. A secondary analysis of data from a randomized clinical trial. Eur. J. Pain 23, 1378–1389. https://doi.org/10.1002/ejp.1407.

Gevers-Montoro, C., Provencher, B., Descarreaux, M., Ortega de Mues, A., Piché, M., 2021a. Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. Eur. J. Pain 25, 1429–1448. https://doi.org/10.1002/EJP.1773.

Gevers-Montoro, C., Provencher, B., Descarreaux, M., Ortega de Mues, A., Piché, M., 2021b. Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. Eur. J. Pain 25, 1429–1448. https://doi.org/10.1002/EJP.1773.

Gibbons, P., Tehan, P., 2006. HVLA thrust techniques: what are the risks? Int. J. Osteopath. Med. 9, 4–12. https://doi.org/10.1016/J.IJOSM.2006.02.005.

Gibson, S.J., Farrell, M., 2004. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin. J. Pain 20, 227–239. https://doi.org/10.1097/00002508-200407000-00004.

Glaser, T., Woud, M.L., Labib Iskander, M., Schmalenstroth, V., Vo, T.M., 2018. Positive, negative, or all relative? Evaluative conditioning of ambivalence. Acta Psychol. 185, 155–165. https://doi.org/10.1016/J.ACTPSY.2018.02.006.

Grieve, G.P., 1989. Contra-indications to spinal manipulation and allied treatments. Physiotherapy 75, 445–453. https://doi.org/10.1016/S0031-9406(10)62623-5.

Gyer, G., Michael, J., Inklebarger, J., Tedla, J.S., 2019. Spinal manipulation therapy: is it all about the brain? A current review of the neurophysiological effects of manipulation. J Integr Med 17, 328–337. https://doi.org/10.1016/J.JOIM.2019.05.004.

Haneline, M.T., Young, M., 2009. A review of intraexaminer and interexaminer reliability of static spinal palpation: a literature synthesis. J. Manip. Physiol. Ther. 32, 379–386. https://doi.org/10.1016/j.jmpt.2009.04.010.

Hellhammer, D.H., Wüst, S., Kudielka, B.M., 2009. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology 34, 163–171. https://doi.org/10.1016/J.PSYNEUEN.2008.10.026.

Herzog, W., 2010. The biomechanics of spinal manipulation. J. Bodyw. Mov. Ther. 14, 280–286. https://doi.org/10.1016/J.JBMT.2010.03.004.

Hjermstad, M.J., Fayers, P.M., Haugen, D.F., Caraceni, A., Hanks, G.W., Loge, J.H., Fainsinger, R., Aass, N., Kaasa, S., 2011. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J. Pain Symptom Manag. 41, 1073–1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016.

Hohenschurz-Schmidt, D., Thomson, O.P., Rossettini, G., Miciak, M., Newell, D., Roberts, L., Vase, L., Draper-Rodi, J., 2022. Avoiding nocebo and other undesirable effects in chiropractic, osteopathy and physiotherapy: an invitation to reflect. Musculoskelet Sci Pract 62, 102677. https://doi.org/10.1016/J.MSKSP.2022.102677.

Jonsson, A., Rasmussen-Barr, E., 2018. Intra- and inter-rater reliability of movement and palpation tests in patients with neck pain: a systematic review. Physiother. Theory Pract. 34, 165–180. https://doi.org/10.1080/09593985.2017.1390806.

Knezevic, E., Nenic, K., Milanovic, V., Knezevic, N.N., 2023. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. Cells 12. https://doi.org/10.3390/CELLS12232726.

Konstantinos, Z., Theodoros, B., Anastasios, P., Michalis, K., 2019. The impact of manual therapy techniques on pain, disability and IL-1B levels in patients with chronic cervical pain. Int. J. Physiother. 6, 268–276. https://doi.org/10.15621/IJPHY/2019/V6I6/190224.

Kovanur Sampath, K., Treffel, L., P.Thomson, O., Rodi, J.D., Fleischmann, M., Tumilty, S., 2024. Changes in biochemical markers following a spinal manipulation - a systematic review update. J. Man. Manip. Ther. 32, 28–50. https://doi.org/10.1080/10669817.2023.2252187.

Kovanur-Sampath, K., Mani, R., Cotter, J., Gisselman, A.S., Tumilty, S., 2017. Changes in biochemical markers following spinal manipulation-a systematic review and meta-analysis. Musculoskelet Sci Pract 29, 120–131. https://doi.org/10.1016/J.MSKSP.2017.04.004.

Lateef, F., 2011. Patient expectations and the paradigm shift of care in emergency medicine. J. Emergencies, Trauma, Shock 4, 163. https://doi.org/10.4103/0974-2700.82199.

Lehman, G., 2012. Kinesiological research: the use of surface electromyography for assessing the effects of spinal manipulation. J. Electromyogr. Kinesiol. 22, 692–696. https://doi.org/10.1016/J.JELEKIN.2012.02.010.

Lima, C.R., Martins, D.F., Reed, W.R., 2020. Physiological responses induced by manual therapy in animal models: a scoping review. Front. Neurosci. 14. https://doi.org/10.3389/FNINS.2020.00430.

Liu, Z., Shi, J., Huang, Y., Zhou, X., Huang, H., Wu, H., Lv, L., Lv, Z., 2023. A systematic review and meta-analysis of randomized controlled trials of manipulative therapy for patients with chronic neck pain. Compl. Ther. Clin. Pract. 52, 101751. https://doi.org/10.1016/J.CTCP.2023.101751.

Lohman, E.B., Pacheco, G.R., Gharibvand, L., Daher, N., Devore, K., Bains, G., AlAmeri, M., Berk, L.S., 2019. The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non-specific mechanical neck pain: a randomized clinical trial. J. Man. Manip. Ther. 27, 186–196. https://doi.org/10.1080/10669817.2018.1553696.

Lutke Schipholt, I.J., Coppieters, M.W., Reijm, M., Bontkes, H.J., Scholten-Peeters, G.G.M., 2023. Immediate systemic neuroimmune responses following spinal mobilisation and manipulation in people with non-specific neck pain: a randomised placebo-controlled trial. Sci. Rep. 13. https://doi.org/10.1038/S41598-023-39839-3.

Maigne, J.Y., Vautravers, P., 2003. Mechanism of action of spinal manipulative therapy. Jt. Bone Spine 70, 336–341. https://doi.org/10.1016/S1297-319X(03)00074-5.

Malfliet, A., Lluch Girbés, E., Pecos-Martin, D., Gallego-Izquierdo, T., Valera-Calero, A., 2019. The influence of treatment expectations on clinical outcomes and cortisol levels in patients with chronic neck pain: an experimental study. Pain Pract. 19, 370–381. https://doi.org/10.1111/papr.12749.

Nim, C.G., Downie, A., O'Neill, S., Kawchuk, G.N., Perle, S.M., Leboeuf-Yde, C., 2021. The importance of selecting the correct site to apply spinal manipulation when treating spinal pain: myth or reality? A systematic review. Sci. Rep. 11 (1), 1–13. https://doi.org/10.1038/s41598-021-02882-z, 2021 11.

Nogueira, N., Oliveira-Campelo, N., Lopes, Â., Torres, R., Sousa, A.S.P., Ribeiro, F., 2020. The acute effects of manual and instrument-assisted cervical spine manipulation on pressure pain threshold, pressure pain perception, and muscle-related variables in asymptomatic subjects: a randomized controlled trial. J. Manip. Physiol. Ther. 43, 179–188. https://doi.org/10.1016/J.JMPT.2019.05.007.

Ortiz, R., Gemmill, J.A.L., Sinaii, N., Stegmann, B., Khachikyan, I., Chrousos, G., Segars, J., Stratton, P., 2020. Hypothalamic-Pituitary-Adrenal axis responses in women with endometriosis-related chronic pelvic pain. Reprod. Sci. 27, 1839–1847. https://doi.org/10.1007/S43032-020-00201-X.

Paleta, D., Karanasios, S., Diamantopoulos, N., Martzoukos, N., Zampetakis, N., Moutzouri, M., Gioftsos, G., 2024. Associations of treatment outcome expectations and pain sensitivity after cervical spine manipulation in patients with chronic non-specific neck pain: a cohort Study. Healthcare 12, 1702. https://doi.org/10.3390/HEALTHCARE12171702, 2024, Vol. 12, Page 1702.

Pickar, J.G., 2002. Neurophysiological effects of spinal manipulation. Spine J. 2, 357–371. https://doi.org/10.1016/S1529-9430(02)00400-X.

Plaza-Manzano, G., Molina, F., Lomas-Vega, R., Martínez- Amat, A., Achalandabaso, A., Hita-Contreras, F., 2014. Changes in biochemical markers of pain perception and stress response after spinal manipulation. J. Orthop. Sports Phys. Ther. 44, 231–239. https://doi.org/10.2519/JOSPT.2014.4996.

Provencher, B., Northon, S., Piché, M., 2021. Segmental chiropractic spinal manipulation does not reduce pain amplification and the associated pain-related brain activity in a capsaicin-heat pain model. Frontiers in Pain Research 2, 733727. https://doi.org/10.3389/FPAIN.2021.733727/FULL.

Reicherts, P., Gerdes, A.B.M., Pauli, P., Wieser, M.J., 2016. Psychological placebo and nocebo effects on pain rely on expectation and previous experience. J. Pain 17, 203–214. https://doi.org/10.1016/J.JPAIN.2015.10.010.

Ross, J.K., Bereznick, D.E., McGill, S.M., 2004. Determining cavitation location during lumbar and thoracic spinal manipulation: is spinal manipulation accurate and specific? Spine 29, 1452–1457. https://doi.org/10.1097/01.BRS.0000129024.95630.57.

Rossettini, G., Camerone, E.M., Carlino, E., Benedetti, F., Testa, M., 2020. Context matters: the psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. Arch Physiother 10. https://doi.org/10.1186/S40945-020-00082-Y.

Rushton, A., Rivett, D., Carlesso, L., Flynn, T., Hing, W., Kerry, R., 2014. International framework for examination of the cervical region for potential of Cervical Arterial Dysfunction prior to Orthopaedic Manual Therapy intervention. Man. Ther. 19, 222–228. https://doi.org/10.1016/j.math.2013.11.005.

Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin. Neurosci. 8, 383–395. https://doi.org/10.31887/DCNS.2006.8.4/SSMITH.

Trager, R.J., Bejarano, G., Perfecto, R.P.T., Blackwood, E.R., Goertz, C.M., 2024. Chiropractic and spinal manipulation: a review of research Trends, Evidence Gaps, and Guideline recommendations. J. Clin. Med. 13, 5668. https://doi.org/10.3390/JCM13195668/S1.

Valera-Calero, A., Lluch Girbés, E., Gallego-Izquierdo, T., Malfliet, A., Pecos-Martín, D., 2019. Endocrine response after cervical manipulation and mobilization in people with chronic mechanical neck pain: a randomized controlled trial. Eur. J. Phys. Rehabil. Med. 55, 792–805. https://doi.org/10.23736/S1973-9087.19.05475-3.

Valera-Calero, J.A., Guodemar-Pérez, J., Cleland, J.A., Ojedo-Martín, C., Gallego-Sendarrubias, G.M., 2021. Physical therapist attitude and opinion about cervical spine examination: a national Spanish survey. Int. J. Clin. Pract. 75, e13781. https://doi.org/10.1111/ijcp.13781.

Valera-Calero, J.A., Varol, U., 2022. Correlation among routinary physical activity, salivary cortisol, and chronic neck pain severity in office workers: a cross-sectional Study. Biomedicines 10. https://doi.org/10.3390/biomedicines10102637.

Vernon, H.T., Triano, J.J., Ross, J.K., Tran, S.K., Soave, D.M., Dinulos, M.D., 2012. Validation of a novel sham cervical manipulation procedure. Spine J. 12, 1021–1028. https://doi.org/10.1016/J.SPINEE.2012.10.009.

Young, K.J., Leboeuf-Yde, C., Gorrell, L., Bergström, C., Evans, D.W., Axén, I., Chance-Larsen, K., Gagey, O., Georgopoulos, V., Goncalves, G., Harris, C., Harsted, S., Kerry, R., Lee, E., McCarthy, C., Nim, C., Nyirö, L., Schweinhardt, P., Vogel, S., 2024. Mechanisms of manipulation: a systematic review of the literature on immediate anatomical structural or positional changes in response to manually delivered high-velocity, low-amplitude spinal manipulation. Chiropr. Man. Ther. 32, 1–23. https://doi.org/10.1186/S12998-024-00549-W/TABLES/9.