THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 12

EDITORIAL

Spinal Manipulation Within a Pain Neuroscience Education Framework: Towards a Synergistic Model of Care

Gospodin Ionut Ciprian, Physiotherapist PhD [1]; Giles Gyer, BSc (Hons) Osteopathy [2]; Jimmy Michael, BSc (Hons) Osteopathy [3]; Brogan Williams, EP, PhD [4]

[1] Step by Step Education, Romania; Step by Step Medical, Romania; Institutul de Educatie Fizica si Sport al Universtatii de Stat din Moldova, Republica Moldova, office@stepbystepeducation.ro
[2] London College of Osteopathic Medicine, 8-10 Boston Place, London, NW1, gilesgyer@yahoo.co.uk
[3] London College of Osteopathic Medicine, 8-10 Boston Place, London, NW1, jimmymichael81@gmail.com
[4] London College of Osteopathic Medicine, 8-10 Boston Place, London, NW1, brogan.s.williams@gmail.com

OPEN ACCESS

PUBLISHED
31 December 2025

CITATION
Gospodin, IC., Giles, G., et al., 2025. Spinal Manipulation Within a Pain Neuroscience Education Framework: Towards a Synergistic Model of Care. Medical Research Archives, [online] 13(12).

DOI

ISSN
2375-1924

ABSTRACT

N/A

Introduction

Musculoskeletal pain remains one of the leading causes of disability worldwide, with low back and neck pain ranking among the most prevalent and costly conditions. [1,7,18,54] Across healthcare systems, spinal manipulation (SM) is a frequently delivered intervention, used by physiotherapists, chiropractors, osteopaths, and manual therapists. [12,49] Despite its long history, the rationale behind spinal manipulation has evolved considerably, shifting from purely biomechanical explanations toward more nuanced neurophysiological interpretations· [2,3,5,21,23,29] However, the legacy of structural narratives "alignment," "realignment," "fixing," or "putting vertebrae back into place", continues to permeate clinical communication and patient beliefs. [13,19]

At the same time, pain neuroscience education (PNE) has emerged as a modern cognitive intervention designed to reduce the threat value of pain by explaining nociception, central sensitization, hypervigilance, and the influence of emotions, sleep, stress, and beliefs. [31,34,36,39] Pain neuroscience education has shown meaningful benefits when combined with movement-based and behavioral interventions, helping patients reinterpret pain as a protective output of the nervous system rather than a direct indicator of tissue damage. [20,28,34,37]

Although spinal manipulation and pain neuroscience education are both widely practiced, their integration is rarely deliberate. In many clinical settings, manipulation is performed first and explanations are added later, or a brief explanation is offered but framed using outdated or biomechanical metaphors that contradict the principles of pain neuroscience education. The result is conceptual inconsistency, patients receive mixed messages about fragility versus adaptability, mechanical correction versus neurophysiological modulation, and passive dependence versus active self-efficacy. [9,10,13,43,46]

This editorial argues that spinal manipulation should not simply coexist with pain neuroscience education, but should be embedded within it. When spinal manipulation is presented as a modulator of sensory processing, descending inhibition, and cortical representation, not a structural fix, its meaning to the patient becomes aligned with contemporary pain science. [2,3,5,21,23,24,25,29] This integration may enhance outcomes by shaping expectations, reducing fear, and creating a window of opportunity for movement and learning. [1,4,6,14,33,43,46]

A coherent framework linking pain neuroscience education and spinal manipulation has never been systematically articulated. Here we propose one, outline the theoretical rationale, and present a research agenda to test the central hypothesis: educated patients experience superior responses to spinal manipulation.

Why the Current Paradigm Requires Revision

Historically, spinal manipulation has long been conceptualised within a biomechanical framework: practitioners identify dysfunctional or misaligned segments through palpation and physical examination and then deliver a high-velocity, low-amplitude (HVLA) thrust to alter segmental biomechanics and thereby alleviate pain. Some of the most cited biomechanical theories include releasing entrapped synovial folds or meniscoids, restoring buckled motion segments, reducing articular or periarticular adhesions and normalising "hypertonic" muscle [15,16]. For years, these biomechanical fault correction theories have been a mainstay narrative across various manual therapy disciplines, such as physical therapy, chiropractic and osteopathy. However, there is still very limited evidence that the proposed biomechanical mechanisms have any clinical relevance with regards to the observed therapeutic outcomes [24,25].

A growing body of evidence published over the years has forced researchers to make a paradigm shift toward neurophysiological mechanisms of spinal manipulation. Collectively, these studies suggest that SM modulates nociception and pain processing via peripheral, spinal and supraspinal pathways, with additional contributions from neuroimmune and autonomic mechanisms [21,23,29]. In this framework, the HVLA thrust triggers a series of complex neurophysiological mechanisms rather than a literal vertebral repositioning. Recent literature reviews of spinal manipulation mechanisms further highlight the theoretical limitations of a purely biomechanical framework. A 2025 living review of systematic, narrative, and scoping reviews concluded that there exists moderate quality evidence in support of neurovascular and neurological effects of SM, whereas biomechanical changes, such as altered tissue stiffness or segmental alignment, are supported only by critically low-quality evidence [29]. Experimental and clinical investigations of spinal manipulation similarly demonstrate modest, predominantly short-term improvements in pain and function, which are comparable to other guideline-recommended conservative interventions [21, 30]. Parallel work on contextual factors and placebo–nocebo mechanisms in physiotherapy showed that clinician communication, explanatory models and therapeutic rituals meaningfully influence pain, disability, and even adverse events [26,43] Despite the emerging body of evidence, clinical narratives around spinal manipulation are still surrounded by many myths: that spines are inherently fragile, that joints routinely subluxate, or that prophylactic manipulation or maintenance care is required to prevent degeneration [8, 27].These messages are no longer regarded as harmless simplifications. Instead, they are now recognized as potential drivers of fear-avoidance, catastrophizing, and nocebo responses in people with musculoskeletal pain [7–9]. Recent work in chiropractic, osteopathy, and physiotherapy explicitly warns that body-centric, structurally fearmongering narratives can amplify perceived danger, increase distress, and worsen outcomes rather than reassure patients [19,45].

Patient beliefs also play a significant role in spinal manipulation - induced therapeutic outcomes. In fact, a recent large meta-analysis across clinical pain conditions found that pain catastrophizing, fear of pain, and pain vigilance had medium-to-large associations with pain-related nocebo effects, undue anxiety and stress, pain intensity, and disability. Physical treatment had little influence on these associations 42. Emerging clinical evidence further suggests that when contemporary pain

neuroscience education is integrated with manual therapy, patients show greater improvements in pain, disability and pain-related cognitions than with physical treatments alone [8,28]. Taken together, in light of the above discussion, it can be said that continuing solely with biomechanical concepts of spinal manipulation risks reinforcing pseudoscientific beliefs and underutilizing the neurophysiological mechanisms that align with modern pain science. A revised framework that incorporates SM within a PNE-informed, biopsychosocial model is therefore not just theoretically appropriate but empirically warranted.

Mechanisms of Interaction: How Pain Neuroscience Education enhances Spinal Manipulation

To understand why spinal manipulation may work better when embedded within pain neuroscience education, we must examine the mechanisms through which education influences pain processing. Expectation and Meaning Response. Expectations are among the strongest modulators of manual therapy outcomes.[1,4,14,33,51] Positive expectations enhance descending inhibitory control, reduce activation of threat circuits, and amplify analgesic responses. [1,4,6,33] Pain neuroscience education provides a cognitive foundation that decreases fear and uncertainty, enabling patients to interpret manual input as safe and helpful. [31,34,36,39.] Conversely, mixed messages, such as biomechanical warnings, may limit the therapeutic potential of spinal manipulation. [9,10,13,19,43,46]

Threat Modulation and Fear Reduction. A central element of pain neuroscience education is reducing the perceived threat associated with pain. When patients understand that pain does not necessarily reflect tissue damage, the nervous system becomes less protective. This creates a context in which the high-velocity, low-amplitude thrust of manipulation is perceived not as dangerous but as a safe sensory event. Reduced threat perception may enhance spinal manipulations immediate hypoalgesic effect and facilitate motor improvement. [10,11,21,23,30,41,48] Descending Pain InhibitionPain neuroscience education activates prefrontal and anterior cingulate networks associated with cognitive control and descending modulation. When these . pathways are primed, the rapid afferent input from manipulation may be more effectively integrated, leading to stronger inhibitory responses. This aligns with the concept that spinal manipulation influences neurophysiological systems rather than mechanical alignment. [2,3,5,21,23,24,25,29]

Sensorimotor Integration. spinal manipulation produces brief alterations in sensory processing, muscle spindle activity, joint position sense, and cortical representation of the manipulated region. If a patient is educated to understand these changes as functional and adaptive, they are likely to engage more confidently in movement afterward. This reciprocity between cognition and sensorimotor input reinforces positive neuroplastic changes. [21,23-25,41,48.] Placebo and Nocebo Dynamics. All therapeutic interventions carry contextual effects. Pain neuroscience education reduces nocebo responses by clarifying misconceptions, improving self-efficacy, and reducing apprehension. A patient who expects manipulation to "correct a problem" may feel disappointed when symptoms fluctuate, whereas a patient who understands manipulation as transient modulation will interpret these fluctuations as normal and non-threatening. .[8,20,28,31,34,37,43,46]

Window of Opportunity for Movement. Manipulation often produces short-term changes in range of motion, pain tolerance, or movement confidence. Pain neuroscience education helps patients understand that these improvements create a temporary window for meaningful movement. Instead of viewing SM as the primary treatment, the patient perceives it as a supportive component within a larger active rehabilitation strategy. [8,17,20,28,34,35,37,38]

The central hypothesis of this editorial is that patients who receive structured pain neuroscience education prior to spinal manipulation will experience better clinical outcomes than those who receive manipulation alone or manipulation accompanied by traditional biomechanical explanations. This hypothesis reflects a synergy model in which PNE prepares the nervous system, cognitively, emotionally, and physiologically, to respond more favorably to the afferent input generated by SM.

Justification of the Synergy Hypothesis. Modern pain science emphasizes that pain is influenced by expectations, threat perception, meaning, memory, and the broader psychosocial context. Spinal manipulation, although often perceived as a primarily mechanical intervention, produces rapid neurophysiological effects: changes in segmental inhibition, altered cortical representation, reduced temporal summation, and brief improvements in range of motion and pain pressure thresholds. These effects are not isolated; they are modulated by the cognitive-emotional state of the patient at the moment the stimulus is delivered. PNE shifts the patient's understanding of pain away from structural fragility toward adaptability and resilience. [9,31,34,36] When patients learn that pain reflects a protective decision by the nervous system and that manipulation serves as a non-threatening sensory reset and their expectations become more positive, their fear decreases, and their nervous system becomes less defensive. This is the ideal context in which spinal manipulation can exert its modulatory effects. [.2-5,11,21,23-25,29,41]. Conversely, biomechanical explanations such as "your vertebra is out," "the joint is stuck," or "your spine needs realignment" can increase vigilance, heighten protective muscle activity, and amplify the perceived threat of the procedure. This can limit the hypoalgesic response, reduce movement confidence, and reinforce dependency on passive treatment. Therefore, PNE does not simply add information, it primes the nervous system, allowing the neurophysiological effects of manipulation to be expressed more fully. [1-5,9,14,20,21,23-25,29,31,37,39,41,43,46,48]

Why Educated Patients Respond Better? Educated patients respond better to spinal manipulation for three main reasons: Reduced Threat = Enhanced Modulation. When pain is reconceptualized as non-dangerous, manipulation is interpreted as safe sensory input rather than a correction of a dangerous structural fault. This

reduces spinal and supraspinal protective responses. [11,21,23-25,29,41]

Improved Expectations = Stronger Descending Inhibition. PNE enhances treatment expectancy, a known amplifier of analgesic responses. Expectation-related circuitry in the prefrontal cortex and anterior cingulate cortex is activated, promoting endogenous pain inhibition during and after manipulation. [39,43,46,48]

Increased Self-Efficacy = Better Integration With Movement. If patients understand manipulation as a temporary window of opportunity rather than a fix, they are more likely to engage in active movement, reinforcing functional gains and preventing relapse. [34,35,37,38]

Clinical and Ethical Implications. The integration of spinal manipulation within a pain neuroscience education framework involves not just delivering manual interventions but also mastering the art of communication to maximise clinical outcomes. The benefits of integrating SM with PNE are also reported in contemporary work on contextual factors. In fact, a recent survey of healthcare providers found that the therapeutic relationship and clinician communication were the most influential contextual factors and that contextual effects contribute around half of treatment benefit, with most practitioners deliberately using them to optimise care [14], Rossettini et al.[44] further noted that contextual factors, such as verbal suggestion, patient's expectations, clinician's behaviour, therapeutic touch, a personalised treatment approach, and environmental cues, all function as active mechanisms triggering placebo and nocebo responses in musculoskeletal pain. This underscores an ethical responsibility: therapists must communicate current pain science transparently to patients rather than reinforcing their pseudoscientific beliefs using outdated biomechanical explanations such as vertebral misalignment or segmental dysfunction.

Current understanding of spinal manipulation largely supports neurophysiological rather than biomechanical mechanisms. However, the neural responses demonstrated in mechanistic studies are mostly transient in nature, and thus their true clinical relevance with respect to the observed therapeutic outcomes remains unclear [23,29]. Pain neuroscience education offers a complementary framework for SM. A 2025 umbrella review with meta-analysis reported that combining pain neuroscience education with physical interventions yielded greater reductions in pain intensity and functional disability compared with PNE alone in chronic nonspecific low back pain [20].Similar findings were reported in another recent meta-analysis by Sánchez-Robalino et al.[47]. On the other hand, large retrospective analyses from military and Veterans Affairs cohorts showed that greater use of passive interventions predicted higher odds of opioid prescriptions, injections, and specialist visits, whereas manual therapy combined with active care was associated with fewer escalations of care events and approximately 30% lower odds of opioid use [17,38]. Attending a pain neuroscience education continuing education (CE) course by therapists also has a positive impact on clinical outcomes as well as on their practice patterns, including fewer visit frequencies, reduced total billing units, and the use of more active and manual interventions [35].This growing body of evidence suggests that combining SM as a short-term neuromodulatory adjunct within an educational, biopsychosocial model represents a scientifically defensible and ethically appropriate treatment approach that prioritizes patient understanding over passive dependency.

Informed consent is the final ethical cornerstone. A recent systematic review identified 334 serious adverse events following conservative physical procedures involving the neck: 58% were vascular (mainly arterial or vertebral artery dissection), with 75% of these events involving manipulation. Overall, 62% of patients recovered favourably, 16% were left with disability and 6% died [32]. While such events remain rare, therapists should clearly disclose to their patients that spinal manipulation benefits are typically modest and short-term, its mechanisms are primarily neurophysiological, and that serious complications, although extremely uncommon, may occur. Such disclosure, far from undermining therapeutic outcomes, respects patient autonomy and aligns practice with contemporary evidence, ethical principles, and professional standards.

Conclusion

Spinal manipulation can no longer be credibly framed as a mechanical "realignment" technique acting on a fragile spine. Instead, contemporary evidence supports spinal manipulation as a short-term neuromodulatory stimulus whose effects are shaped—sometimes decisively—by expectations, threat appraisals, contextual factors, and patient beliefs. When SM is embedded within pain neuroscience education, patients are invited to reinterpret pain as a protective, adaptable output rather than a structural defect, reducing fear, enhancing self-efficacy, and opening a window for meaningful, graded movement. This pain neuroscience education - informed integration is not merely a communication upgrade; it represents a shift toward an ethically coherent, biopsychosocial practice that avoids nocebo, challenges pseudoscientific narratives, and prioritizes long-term behavioural change over passive dependence. Future trials should explicitly compare PNE+SM versus spinal manipulation with biomechanical explanations, incorporate mediation analyses of expectations and fear, and investigate how this integrated framework influences clinical outcomes, healthcare utilization, and serious adverse event communication

References:

1. Benedetti F. Placebo and the new physiology of the doctor–patient relationship. *Physiol Rev*. 2013;93(3):1207-1246.
2. Bialosky JE, Beneciuk JM, Bishop MD, Coronado RA, Penza CW, George SZ. Unravelling the mechanisms of manual therapy: modeling an approach. *J Orthop Sports Phys Ther*. 2018;48(1):8-18.
3. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009;14(5):531-538.
4. Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation-induced hypoalgesia. *J Pain*. 2008;9(10):938-946.
5. Bialosky JE, George SZ, Bishop MD. How spinal manipulative therapy works: Modulation of pain and sensorimotor responses. *J Orthop Sports Phys Ther*. 2018;48(10):764-775.
6. Bingel U. Avoiding nocebo effects to optimize treatment outcomes. *Nat Rev Neurol*. 2020;16(4):197-208.
7. Buchbinder R, van Tulder M, Öberg B, et al. Low back pain: a call for action. *Lancet*. 2018;391(10137) 2384-2388.
8. Cancela JG, Conde Vázquez O, Navarro Ledesma S, Pruimboom L. The effectiveness of pain neuroscience education in people with chronic non-specific low back pain: An umbrella review with meta-analysis. Ann Phys Rehabil Med. 2025;68(8):102020.
9. Caneiro JP, O'Sullivan P, Lipp OV, et al. Evaluation of threat and protection responses in musculoskeletal pain. *Pain Rep*. 2017;2(3):e593.
10. Cleland JA, Flynn TW, Childs JD. Immediate effects of spinal manipulation on pain and mobility in patients with low back pain. *Arch Phys Med Rehabil*. 2008;89(5):927-934.
11. Coronado RA, Gay CW, Bialosky JE, et al. Changes in pain sensitivity and spinal excitability after manipulation. *J Orthop Sports Phys Ther*. 2012;42(9):752-759.
12. Coulter ID, Crawford C, Hurwitz EL, et al. Manipulative therapies: what works? *Spine J*. 2018;18(6):1026-1040.
13. Darlow B. Beliefs about back pain: the confluence of cultural, social and professional influences. *Physiotherapy*. 2016;102(1):5-12.
14. Druart L, Bailly-Basin E, Dolgopoloff M, Rossettini G, Blease C, Locher C, et al. Using contextual factors to elicit placebo and nocebo effects: An online survey of healthcare providers' practice. PLoS One. 2023;18(9):e0291079.
15. Evans DW, Breen AC. A biomechanical model for mechanically efficient cavitation production during spinal manipulation: prethrust position and the neutral zone. J Manipulative Physiol Ther. 2006;29(1):72-82.
16. Evans DW. Mechanisms and effects of spinal high-velocity, low-amplitude thrust manipulation: previous theories. J Manipulative Physiol Ther. 2002;25(4):251-62.
17. Farrokhi S, Bechard L, Gorczynski S, Patterson C, Kakyomya J, Hendershot BD, et al. The influence of active, passive, and manual therapy interventions for low back pain on opioid prescription and health care utilization. Phys Ther. 2024;104(3):pzad173.
18. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population. *Eur Spine J*. 2006;15(6):834-848.
19. Funk MF, Frisina-Deyo AJ, Mirtz TA, Perle SM. The prevalence of the term subluxation in chiropractic degree program curricula throughout the world. Chiropr Man Ther. 2018;26(1):24.
20. García Cancela J, Conde Vázquez O, Navarro Ledesma S, Pruimboom L. The effectiveness of pain neuroscience education in people with chronic non-specific low back pain: An umbrella review with meta-analysis. Ann Phys Rehabil Med. 2025;68(8):102020.
21. Gevers-Montoro C, Provencher B, Descarreaux M. Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain. Eur J Pain. 2021;25(7):1429-48.
22. Gyer G, Michael J, Inklebarger J, Ibne Alam I. Effects of biomechanical parameters of spinal manipulation: A critical literature review. J Integr Med. 2022;20(1):4-12.
23. Gyer G, Michael J, Inklebarger J, Tedla JS. Spinal manipulation therapy: Is it all about the brain? A current review of the neurophysiological effects of manipulation. J Integr Med. 2019;17(5):328-337.
24. Haavik H, Murphy B. The role of spinal manipulation in motor control: Evidence from studies of sensorimotor integration. *J Electromyogr Kinesiol*. 2012;22(5):768-776.
25. Haavik H, Niazi IK, Jochumsen M, et al. Manipulation of dysfunctional spinal joints affects cortical integration of somatosensory input. *Brain Sci*. 2017;7(2):2.
26. Hohenschurz-Schmidt D, Lange J-E, Napadow V, Harris RE. Avoiding nocebo and other undesirable effects in chiropractic, osteopathy and physiotherapy: A masterclass. Musculoskelet Sci Pract. 2022;58:102509.
27. Iben A, Lise H, Charlotte LY. Chiropractic maintenance care – what's new? A systematic review of the literature. Chiropr Man Ther. 2019;27:63.
28. Kasimis K, Apostolou T, Kallistratos I, Lytras D, Iakovidis P. Effects of manual therapy plus pain neuroscience education with integrated motivational interviewing in individuals with chronic non-specific low back pain: A randomized clinical trial. Medicina (Kaunas). 2024;60(4):556.
29. Keter DL, Bialosky JE, Brochetti K, et al. The mechanisms of manual therapy: A living review of systematic, narrative, and scoping reviews. PLoS One. 2025;20(3):e0319586.
30. Keter DL, Bialosky JE, Brochetti K, et al. The mechanisms of manual therapy: A living review of systematic, narrative, and scoping reviews. PLoS One. 2025;20(3):e0319586.
31. Lee H, McAuley JH, Hübscher M, et al. Does re-conceptualizing pain reduce pain and improve function? A systematic review and meta-analysis. *Pain*. 2016;157(10):2142-2151.
32. Leung B, Treleaven J, Dinsdale A, Marsh L, Thomas L. Serious adverse events associated with conservative physical procedures directed towards the cervical

spine: A systematic review. J Bodyw Mov Ther. 2025;41:56-77.
33. Linde K, Witt CM, Streng A, et al. The impact of patient expectations on outcomes in low back pain. *Pain*. 2007;128(3):264-271.
34. Louw A, Diener I, Fernández-de-las-Peñas C, Puentedura EJ. The effect of PNE on pain, disability, and psychosocial factors. *Musculoskelet Sci Pract*. 2018;38:47-56.
35. Louw A, Puentedura EJ, Denninger TR, Lutz AD, Cox T, Zimney K, et al. The clinical impact of pain neuroscience continuing education on physical therapy outcomes for patients with low back and neck pain. PLoS One. 2022;17(4):e0267157.
36. Louw A, Puentedura EJ. A neuroscience approach to treating chronic pain: How a short educational session changes pain biology knowledge. *Man Ther*. 2013;18(6):495-500.
37. Louw A, Zimney K, O'Hotto C, Hilton S. The clinical application of pain neuroscience education for chronic pain: A systematic review and meta-analysis. *Physiother Theory Pract*. 2016;32(5):332-355.
38. Mayer JM, Highsmith MJ, Maikos J, Patterson CG, Kakyomya J, Smith B, et al. The influence of active, passive, and manual therapy interventions on escalation of health care events after physical therapist care in veterans with low back pain. Phys Ther. 2024;104(10):pzae101.
39. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain*. 2015;16(9):807-813.
40. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain*. 2015;16(9):807-813.
41. Pickar JG, Bolton PS. Spinal manipulative therapy and somatosensory processing. *J Electromyogr Kinesiol*. 2012;22(5):785-793.
42. Rogers AH, Farris SG. A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related disability and pain intensity. Eur J Pain. 2022;26(8):1611-35.
43. Rossettini G, Camerone EM, Carlino E, Benedetti F, Testa M. Context matters: The psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. Arch Physiother. 2020;10:11.
44. Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. BMC musculoskeletal disorders. 2018 Jan 22;19(1):27.
45. Rossettini G, Colombi A, Carlino E, et al. Unraveling negative expectations and nocebo-related effects in musculoskeletal pain. Front Psychol. 2022;13:789377.
46. Rossettini G, Testa M. Manual therapy: exploiting the role of placebo, nocebo, and expectations. *J Clin Med*. 2018;7(10):434.
47. Sánchez-Robalino A, Sinchi-Sinchi H, Ramírez A. Effectiveness of Pain Neuroscience Education in Physical Therapy: A Systematic Review and Meta-Analysis. Brain Sciences. 2025 Jun 18;15(6):658.
48. Seminowicz DA, Wideman TH, Naso L, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci*. 2011;31(20):7540-7550.
49. Stochkendahl MJ, Kjaer P, Hartvigsen J, et al. National clinical guidelines for non-surgical management of low back pain. *Eur Spine J*. 2018;27(1):60-75.
50. Tabor A, Keogh E, Eccleston C. Embodied pain-negotiating the boundaries between pain and self. *Neurosci Biobehav Rev*. 2017;74:34-48.
51. Testa M, Rossettini G. Enhance placebo, avoid nocebo: How contextual factors influence physiotherapy outcomes. *Man Ther*. 2016;22:65-70.
52. Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic pain: the next generation. *Clin J Pain*. 2012;28(6):475-483.
53. Wood L, Hendrick P, Thomson OP. A review of the content and quality of PNE delivered by physiotherapists. *Man Ther*. 2016;25:35-42.
54. Wu A, March L, Zheng X, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017. *Ann Rheum Dis*. 2020;79(6):737-745.

