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Neurophysiological mechanisms of chronic primary spine pain relief by chiropractic spinal manipulation

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Mécanismes neurophysiologiques du soulagement de la douleur vertébrale chronique primaire par les manipulations vertébrales chiropratiques

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Résumé

La chiropratique est une profession de la santé qui s'intéresse au diagnostic, au traitement, et à la prévention des troubles musculosquelettiques. L'intervention la plus communément utilisée en chiropratique est la manipulation vertébrale (dite « ajustement chiropratique »). D'ailleurs, les consultations en chiropratique sont principalement pour des douleurs vertébrales, particulièrement dans la région lombaire. La lombalgie est la principale cause d'incapacité à travers le monde. Elle engendre des coûts considérables pour la société et les individus atteints. Chez environ un tiers des individus, la lombalgie persiste et devient chronique, entraînant une incapacité et une diminution de la qualité de vie. Chez ces individus, aucun processus pathologique affectant les tissus vertébraux ne peut être mis en évidence. En effet, cette douleur, dite nociplastique, serait plutôt causée par des mécanismes pathologiques du système nociceptif. La lombalgie chronique, dite primaire chez ces individus, est ainsi considérée comme le diagnostic en soi, et non un symptôme secondaire à une pathologie sous-jacente. Chez certains individus, les manipulations vertébrales peuvent soulager la lombalgie chronique primaire. Cependant, leur efficacité comme intervention de première ligne et leurs mécanismes hypoalgésiques restent à démontrer.

L'objectif général de cette thèse est d'examiner les mécanismes hypoalgésiques des manipulations vertébrales. Le premier objectif spécifique est d'examiner les mécanismes hypoalgésiques d'une manipulation vertébrale à l'aide d'un modèle expérimental de douleur persistante chez des individus en santé. Le deuxième objectif spécifique est d'examiner les mécanismes du soulagement de la douleur lombaire chronique primaire par une intervention chiropratique de quatre semaines, qui comprend douze séances de manipulations vertébrales. La thèse comprend deux études empiriques, soit une étude expérimentale et une étude clinique, qui sont précédées d'une revue de littérature ciblée. Le premier article est une revue narrative explorant les mécanismes neurophysiologiques de la manipulation vertébrale pour soulager la douleur vertébrale. Le deuxième article décrit les résultats d'une étude expérimentale chez des individus en santé. Dans cette étude, nous avons examiné les mécanismes d'inhibition de la douleur en réponse à une manipulation vertébrale ciblant un segment vertébral dont la peau a été sensibilisée par une application topique de capsaïcine. Le troisième article est une revue narrative examinant l'efficacité des manipulations vertébrales pour le traitement des douleurs vertébrales. Le quatrième article

décrit les résultats d'un essai contrôlé randomisé avec groupe placebo chez des individus atteints de lombalgie chronique primaire. Dans cette étude, nous avons examiné si le soulagement de la lombalgie chronique primaire par une intervention chiropratique s'accompagne d'une atténuation de processus pathologiques contribuant à la douleur nociplastique.

Les résultats indiquent qu'une manipulation vertébrale peut atténuer l'hyperalgésie mécanique secondaire observée avec le modèle expérimental de douleur persistante. Ceci suggère qu'une manipulation vertébrale pourrait agir sur des processus pathologiques qui mènent à la douleur chronique. Ces résultats sont cohérents avec la réduction de la douleur observée chez les patients atteints de lombalgie chronique primaire recevant des manipulations vertébrales. De plus, la réduction de la lombalgie chronique était accompagnée d'une réduction de l'hyperalgésie mécanique lombaire et de la dramatisation de la douleur. Dans l'ensemble, ces résultats suggèrent qu'une intervention chiropratique comprenant des manipulations vertébrales est efficace pour réduire la lombalgie chronique primaire, et que cet effet pourrait découler en partie d'une réduction de processus contribuant à la douleur nociplastique. Ceci renforce les recommandations cliniques sur l'utilisation de la chiropratique pour le soulagement de la lombalgie chronique primaire. D'autres études seront nécessaires pour clarifier les mécanismes neurophysiologiques et anti-inflammatoires des manipulations vertébrales.

Mots-clés : Chiropratique ; manipulation vertébrale ; douleur lombaire chronique primaire ; douleur nociplastique; mécanismes neurophysiologiques ; sensibilisation centrale ; placebo ; dramatisation de la douleur ; hyperalgésie ; neuroinflammation.

Abstract

Chiropractic is a health profession focused on the diagnosis, treatment, and prevention of musculoskeletal disorders, mainly through spinal manipulation (also known as "chiropractic adjustment"). The majority of patients consult a chiropractor seeking spine pain relief, primarily in the lower back. Low back pain is the leading cause of global disability, generating considerable costs for society and affected individuals. At least one third of people with low back pain experience persistent pain, leading to chronic disability and a decrease in quality of life. In affected individuals, no pathological process affecting the spinal tissues can be identified. Instead, this pain, called nociplastic, is presumed to be caused by pathological mechanisms within the nociceptive system. Thus, in these individuals, low back pain is considered as chronic primary pain, and not the symptom of an underlying disease. In some individuals, spinal manipulations can relieve chronic primary low back pain. However, their effectiveness as a first-line intervention and their hypoalgesic mechanisms remain to be demonstrated.

The overarching aim of this thesis is to examine the hypoalgesic mechanisms of chiropractic spinal manipulations. The first specific objective is to investigate the hypoalgesic mechanisms of a spinal manipulation using an experimental model of persistent back pain in healthy individuals. The second specific objective is to investigate the mechanisms of relief of chronic primary low back pain by a four-week chiropractic intervention, including twelve sessions of spinal manipulations. The thesis includes two empirical studies: an experimental study and a clinical study, both preceded by a targeted literature review. The first study is a narrative review exploring the neurophysiological mechanisms of spinal manipulation to relieve spine pain. The second article describes the results of an experimental trial on healthy individuals, where we examined the mechanisms of pain inhibition following a spinal manipulation targeting a spinal segment sensitized by the topical application of capsaicin The third article is a narrative review examining the effectiveness of spinal manipulation for the treatment of spine pain. The fourth article describes the results of a randomized placebo-controlled trial with individuals suffering from chronic primary low back pain. In this study, we examined whether the relief of chronic primary low back pain by a chiropractic intervention is accompanied by an attenuation of pathological processes contributing to nociplastic pain.

The results indicate that a single spinal manipulation can mitigate segmental mechanical hyperalgesia observed with the experimental model of persistent pain. This suggests that spinal manipulations could act on pathological processes that lead to chronic pain. These results are consistent with the pain reduction observed in patients with chronic primary low back pain receiving spinal manipulations. Furthermore, low back pain relief was accompanied by a reduction in mechanical hyperalgesia and in pain catastrophizing. Overall, these results indicate that a chiropractic intervention including spinal manipulations is efficacious in reducing chronic primary low back pain, and that this effect could in part stem from a reduction in processes contributing to nociplastic pain. This reinforces clinical recommendations on the use of chiropractic for the relief of chronic primary low back pain. Further studies will be needed to clarify the neurophysiological and anti-inflammatory mechanisms of spinal manipulations.

Keywords: Chiropractic; spinal manipulation; chronic primary low back pain; nociplastic pain; neurophysiological mechanisms; central sensitization; placebo; pain catastrophizing; hyperalgesia; neuroinflammation.

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Acronyms and abbreviations

ALBP: Acute low back pain

CAD: Canadian dollar

CBT: Cognitive behavioral therapy

CLBP: Chronic low back pain

COVID-19: Coronavirus disease 2019

CPLBP: Chronic primary low back pain

CPM: Conditioned pain modulation

CS: Central sensitization

CSI: Central sensitization inventory

CT: Computerized tomography

fMRI: Functional magnetic resonance imaging

IL-: Interleukin-

LBP: Low back pain

MRI: Magnetic resonance imaging

NP: Neck pain

NSAIDs: Nonsteroidal anti-inflammatory drugs

PCS: Pain catastrophizing scale

PET: Positron emission tomography

PPTs: Pressure pain thresholds

QST: Quantitative sensory testing

SM: Spinal manipulation

SMT: Spinal manipulative therapy

TNF-α: Tumor necrosis factor alpha

US: United States (of America)

USD: United States dollar

WHO: World Health Organization

À mon père, où que tu sois, pour l'amour du travail bien fait,

Ta passion m'a inspiré, et elle guide encore mes pas.

A mi madre, por tu amor y tu apoyo incondicional.

Gracias por enseñarme a ser un hombre bueno.

به ضحا،

نور من، ستون من، همدم زندگيي ام، بدون مهرباني، ملايمت و عشق بيكرانت، نمي توانستم جايي كه هستم بايستم.

بچلونمت.

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Chapter 1 – Introduction and theoretical framework for the use of chiropractic spinal manipulation

This chapter establishes the theoretical foundations and offers a historical context for the use of chiropractic spinal manipulation. The history and development of the chiropractic profession beginning with its inception in 1895, in the hands of Daniel David Palmer are initially introduced. The second section highlights the spinal column as the central focus of chiropractic's professional identity and practice. Subsequently, the chapter delves on the predominant models of contemporary clinical practice, to discuss thereafter what are the primary interventional approaches used by chiropractors. Further, the utilization of chiropractic services and spinal manipulation, the core of its practice, are presented, followed by an examination of the scope of chiropractic practice and the most common patient presentations. Lastly, the known and potential benefits of chiropractic care and spinal manipulation are synthesized, with a particular emphasis on spine pain relief.

Historical background

Inception

The etymology of *chiropractic* stems from the Greek words *cheir* (hand) and *praktikos* (practice or to do). This healthcare profession is believed to have emerged in 1895 in Davenport, Iowa, when Canadian-born Daniel David Palmer performed the first chiropractic *adjustment* (Johnson, 2020). After manually examining his janitor's spine, Palmer applied deliberate manual force to a thoracic spine segment, reportedly restoring his patient's hearing (Palmer D.D., 1904). This event is considered the first chiropractic adjustment or spinal manipulation (SM), marking the birth of a new healthcare discipline. There is a certain degree of controversy regarding the exact date and targeted spinal segment of this foundational encounter, and even doubts concerning whether it truly occurred (Kaptchuk and Eisenberg, 1998; Troyanovich and Troyanovich, 2013). Nonetheless, September 18th, 1895, permeated as a historical milestone for the chiropractic profession, claiming this specific date and specific person for its birth.

Chiropractic's origins can be traced back to at least three distinct healthcare traditions that influenced Palmer: bone setting, magnetic healing, and orthodox science (Kaptchuk and Eisenberg,

1998). Prior to 1895, Palmer was already using his hands to treat ailments with a primarily self-taught combination of techniques (Johnson, 2020). In the latter half of the 19th century, bone setting and other healing crafts such as tooth-pulling and barber-surgery were popular treatment alternatives for problems generally overlooked by physicians due to their benign nature (Kaptchuk and Eisenberg, 1998). In this period of history, most medical education was informal, often limited to lectures, on-the-job training and hands-on experience acquired through apprenticeships with practicing professionals (Bonner, 2000; Kirkwood, 2005; Moffat, 2012). This era of healthcare discovery saw a steady evolution of both training and practice. Advances such as Röntgen's revelation of X-rays, Cajal's Neuron Theory, Fleming's discovery of penicillin, and the expansion of healthcare institutions revolutionized the way healthcare was delivered and conceived.

Training and professional development

Chiropractic rapidly evolved into an independent profession, spurred by the opening of the Palmer School of Chiropractic, where formal training was initiated in 1897 (Gibbons, 1982; Johnson et al., 2022). By 1931, the discipline had expanded to 39 states within the United States (US) and two Canadian provinces regulating its practice (Wardwell, 1992). Today, chiropractic is an established profession in at least 90 countries, although the number of practicing professionals remains relatively small, with a median of 10 chiropractors per country (Stochkendahl et al., 2019). In 90% of these countries, chiropractic is considered a primary healthcare profession and serves as a portal of entry to the healthcare system, with services partially or fully covered by public or private insurance in half of the jurisdictions. Consequently, the World Health Organization (WHO) defines chiropractors as primary healthcare providers (W.H.O., 2005).

Notwithstanding, only 48 higher education institutions across 19 countries offer training programs in chiropractic. These programs range from 4 to 8 years in duration, most often leading to a Master or Doctor in Chiropractic degree (Johnson, et al., 2022). In 1998, Coulter and colleagues quantitatively compared chiropractic and medical education curricula (Coulter et al., 1998), finding considerable resemblance in terms of basic and clinical sciences, although medical training required a higher number of clinical training hours. These parallels are evident in an educational program offered by the Faculty of Medicine at the University of Zürich, Switzerland. In this course, chiropractors are trained alongside Medical Doctors for the length of the bachelor’s degree (4 years), followed by a 2-year master's program required for practice (Humphreys and Peterson,

2016). Notably, the canton of Zürich was the first European jurisdiction to regulate chiropractic (Meeker and Haldeman, 2002). In Canada, two five-year programs, in Ontario and Québec, offer a Doctor of Chiropractic degree (Johnson, et al., 2022), which is a first cycle doctorate. However, significant disparities exist, even between neighboring countries. For example, while both Spain and France have two higher education institutions that train chiropractors (Johnson, et al., 2022), chiropractic is fully regulated in France but not in Spain (Milenkovic, 2020). These disparities contribute to a general lack of understanding of what the discipline is and what its practitioners do. Thus, the next section describes in more detail the primary focus of chiropractic as a healthcare discipline.

Chiropractors as spine experts

Historically, the cornerstone of chiropractic practice has centered on the spine. Palmer believed that a comprehensive understanding of the spine held the key to managing a majority of health conditions (Kaptchuk and Eisenberg, 1998; Palmer D.D., 1910). Palmer's fascination with the spine and osteology was well known. Over the years, his clinic and eventually the college, accumulated an extensive collection of human skeletons and spines (Brown, 2016). His son, Bartlett Joshua, expanded this collection to over 20,000 specimens displaying all known bony anomalies and pathologic conditions. By 1927, the Palmers' was considered one of the best collections of human spines in the US (Brown, 2016).

Contemporary professional identity

The focus on the spine as a means to achieve well-being has evolved into chiropractors' area of expertise. The general public associates chiropractic with conservative treatment for the spine (Weeks et al., 2015), and chiropractors advance knowledge production and transfer in the field by participating in scientific spine societies such as the American Back Society, the North American Spine Society or the International Society for the Study of the Lumbar Spine, to name a few (Meeker and Haldeman, 2002). World Spine Care, the first multinational charity dedicated to the promotion of universal care for spine conditions, was founded by chiropractor Dr. Scott Haldeman (Outerbridge et al., 2017). Numerous chiropractors have also contributed to high-quality clinical practice guidelines for the management of neck and low back pain (LBP), chronic spine-related conditions and spinal imaging best practice, reflecting their expertise in the field (Johnson, 2020; Zaina et al., 2023).

In 2005, the World Federation of Chiropractic convened a global panel of experts to participate in an identity task force. The task force issued a series of recommendations revolving around a consensus definition of chiropractors as "spinal health care experts" (Brown, 2016). This identity gained broad acceptance within the profession and, most importantly, aligned with public perceptions of chiropractic. In collaboration with healthcare providers from various fields, chiropractors likely have a significant impact on improving the quality of spinal care worldwide. However, the implementation in clinical practice remains less well-defined. The following section explores the most common systems of practice within the discipline of chiropractic.

Contemporary models of practice

Identity struggles have accompanied the profession since its early years. At least two distinct schools of thought can be identified, depending on whether the scope of practice is restricted to the correction of *vertebral subluxations* or if practice is aligned with mainstream healthcare for musculoskeletal conditions (Kaptchuk and Eisenberg, 1998; Meeker and Haldeman, 2002). The chiropractic vertebral subluxation model, which claims that spinal misalignments can compromise health, is often considered outdated and not scientifically sound (Funk et al., 2018), particularly as the current definition fails to meet Hill's criteria for causation (Mirtz et al., 2009). Despite this, some argue that dismissing the tenet that biomechanical lesions of the spine can negatively impact a person's well-being would be hasty (Haavik and Murphy, 2012; Henderson, 2012). To reconcile these discrepancies, an alternative model positioning chiropractors as primary spine care providers has emerged in the past 20 years from various political, scientific and clinical actors.

Simultaneously with the identity effort led by the World Federation of Chiropractic, researchers and clinicians began advocating for chiropractic to present itself as conservative spine care and chiropractors as portal-of-entry providers integrated within the healthcare system (Nelson et al., 2005). This model seemed to fit adequately within the context of a healthcare crisis partly driven by escalating costs related to the management of spinal disorders in the United States (Murphy et al., 2011). Murphy and colleagues designated the novel figure of a primary contact practitioner, with skills in differential diagnosis and conservative evidence-based management of spine-related disorders. Primary spine care bears resemblance to the general dentist's provision of care for problems related to a particular body region with a high prevalence, cost and societal

impact (Murphy, et al., 2011). It was suggested that chiropractors were already assuming this role in certain jurisdictions, with potential for growth in others, including Canada (Erwin et al., 2013). Even though chiropractors are already perceived by the public and legislators as possessing varying levels of proficiency in the domain of spine care (Schneider et al., 2016), for chiropractors to be considered spine experts, advanced or supplementary training may be required, for instance in the biopsychosocial approach or stratified care (Erwin, et al., 2013; Russell, 2013). While not all chiropractors need to be primary spine care providers, this presents an opportunity for the profession to demonstrate that it provides valuable services in patient care and reducing expenditures by decreasing hospitalizations, specialist consultations, and unnecessarily invasive treatments (Bezdjian et al., 2022; Whedon et al., 2020a).

The majority of chiropractors sees themselves as primary care practitioners with a focus on the spine (Glucina et al., 2020). This does not prevent them from ascribing to the hypothesis that chiropractic SM corrects aberrant joint biomechanics (referred to, or not, as vertebral subluxations) that negatively impact an individual's health. While some argue that this thinking displays cognitive dissonance (Swain M.S. et al., 2021), others contend that these two tenets are not mutually exclusive (Glucina, et al., 2020). What these discrepancies clearly highlight is a significant evidence gap concerning the mechanisms underpinning chiropractic treatment effectiveness. This is comparable to current research voids on physical exercise and depression. Strong evidence suggests that exercise is effective against depression (Heissel et al., 2023), yet, exercise does not target a specific lesion that is the root cause of depression. Instead, it may act through other mechanisms that we are just beginning to grasp (Schuch and Stubbs, 2019). Similarly, understanding the mechanisms behind chiropractic interventions may be more critical than identifying a specific lesion as the treatment target. The next section outlines the most common treatments offered in chiropractic settings.

Interventions and approaches used by chiropractors

The word *chiropractic* reveals that manual therapy, specifically chiropractic spinal manipulation (SM) or adjustment, is the central component of its clinical practice (Kaptchuk and Eisenberg, 1998; W.H.O., 2005). While both terms are used interchangeably in professional settings, SM is preferred in the research field. Some chiropractors maintain that *manipulation* is a broader concept, used to designate acts performed by other manual therapists, lacking the

specificity and therapeutic intent of the chiropractic adjustment (Clijsters et al., 2014; Dagenais and Haldeman, 2002; Meeker and Haldeman, 2002). While this distinction requires further research, it is evident that a chiropractic adjustment is a form of SM.

Chiropractic spinal manipulation

To identify the appropriate site for SM application, chiropractors rely on diverse diagnostic methods, primarily through the patient's clinical examination (Puhl et al., 2015; Triano et al., 2013). Manual palpation, orthopaedic maneuvers for pain provocation, and range of motion assessment are considered the most reliable tools for determining if and where to deliver a SM (Triano, et al., 2013). Once the target site is located, most SM techniques involve applying a high-velocity, low-amplitude force by hand to the articular tissues (Beliveau et al., 2017; Herzog, 2010). This force delivery consists of three phases: a slower tissue preload, followed by a rapid thrust, and a final resolution phase. The intention is to generate intervertebral movement by taking the joint to the limit of the end-range of motion or paraphysiological space (Herzog, 2010). This action often results in joint cavitation, accompanied by a characteristic audible crack or pop sound, caused by the formation and collapsing of carbon dioxide bubbles in the synovial fluid as a consequence of decreased joint pressure (Evans, 2022; Unsworth et al., 1971). The drop in intra-articular pressure is caused by the separation or gapping of the joint surfaces (Cramer et al., 2012), without necessarily taking the joint to the end-range (Evans, 2022). It is unclear whether joint cavitation is essential for a successful SM, but it often serves as feedback, potentially contributing to contextual placebo effects (Innes et al., 2020). Mechanisms dependent on successful joint cavitation may exist, but their influence on clinical outcomes remains uncertain (Moorman and Newell, 2022). Moreover, a single SM often results in multiple cavitations or cavitation sounds, indicating that joint gapping may not be limited to one vertebral segment (Cramer et al., 2011; Mourad et al., 2019). It was estimated that only about half of the cavitations originate from the targeted segment, with an average error of at least one segment (Ross et al., 2004). Overall, evidence does not support the idea that chiropractic SM is specific to a single vertebral segment. Whether this has an impact on the mechanisms and the effectiveness of SM is discussed in greater detail further in this thesis.

Chiropractic as conservative care

Chiropractors rarely administer SM as a standalone therapy. Instead, it is generally combined with other forms of manual therapy and a wide range of treatment tools (Dagenais and

Haldeman, 2002; Kaptchuk and Eisenberg, 1998; Walker et al., 2011). Beyond SM, chiropractors most commonly offer patients advice and reassurance, prescribe physical exercises, and apply soft tissue techniques, in descending order of prevalence (Adams J. et al., 2017; Ailliet et al., 2010; Beliveau, et al., 2017; Gevers-Montoro et al., 2021; Puhl, et al., 2015). Recent evidence suggests that chiropractors are also adept at remotely delivering exercise and self-management interventions (Gevers-Montoro et al., 2022a; Green et al., 2020; Haldeman et al., 2021). These treatment modalities share a conservative approach to care. Consequently, chiropractic tends to be perceived by the public and healthcare authorities as a drug- and surgery-free conservative option for spine care (Brown, 2016; 2018; Meeker and Haldeman, 2002; Nelson, et al., 2005; W.H.O., 2005).

A typical day in a chiropractic clinic witnesses the use of a wide array of conservative interventions; however, most encounters rely on the application of SM. One notable distinction between chiropractic and physiotherapy is the higher utilization of SM by the former (Carlesso et al., 2014). Arguably, SM falls more within the expertise of chiropractors than any other profession. The next section delves into the epidemiology of both chiropractic and SM utilization.

Epidemiology of the use of chiropractic services

Rates of utilization

In the 1980's, the rate of utilization of chiropractic services in the US and Canada saw significant growth. Between 1985 and 1991, visit rates in the US and Ontario doubled from previous 15-year estimates, reaching 101.2 and 140.9 per 100 person-years (Hurwitz et al., 1998). This expansion may be attributed to politico-legal historical events. From the 1960s until 1987, the medical establishment displayed remarkable and overt opposition to chiropractic's growth (Simpson, 2012). In the early 1980s, Dr. Chester Wilk and four co-plaintiffs filed an antitrust lawsuit against the American Medical Association. The lawsuit culminated with the issuance of a permanent injunction order against the medical corporation in 1987 for attempting to eliminate the chiropractic profession by using illegal boycott and antitrust strategies (Simpson, 2012). Medical Doctors could then associate with and refer patients back to chiropractors (Dagenais and Haldeman, 2002), contributing to the observed growth in subsequent years.

Chiropractic service utilization tripled in the following decade, with 11% of the US population visiting a chiropractor each year, resulting in an estimated total of 190 million annual

visits (Dagenais and Haldeman, 2002). In 2002, chiropractors were the most consulted complementary and alternative care providers in North America, with Canadians consulting them at three times the rate (McFarland et al., 2002). Utilization rates have remained stable since. Approximately 9% of the population uses chiropractic services in a given year, over 22% in a lifetime (Beliveau, et al., 2017; Cooper et al., 2013; Lawrence and Meeker, 2007). The majority of data were collected in the US, Canada, and Australia, where chiropractic is more popular among middle-aged women and those with back pain (Beliveau, et al., 2017). Nearly one third of people with back pain resort to chiropractic care. However, the fastest-growing population segment making use of these services is people with chronic pain (Pritchard et al., 2022). Chiropractic utilization rates rose from 6.9% in 1990 (Eisenberg et al., 1998) to 25.6% in 2019, making it the leading nonpharmacological option for cancer-free adults living with chronic pain in the US (Pritchard, et al., 2022). As mentioned earlier, a vast majority of these patients likely receive treatment based on SM, a treatment modality whose utilization is not limited to chiropractors. Thus, the use of SM within different disciplines is explored in the following section.

Prevalence of chiropractic spinal manipulation utilization

Spinal manipulative therapy (SMT) is the provision of treatment for a condition based on the administration of SM for one or multiple sessions or visits (W.H.O., 2005). Chiropractors, physiotherapists and osteopaths are the practitioners most frequently utilizing SMT (Hurwitz, 2012), with its use being more prevalent among chiropractors (Carlesso, et al., 2014; Rhon D. et al., 2018). In contrast, physiotherapists apply manipulation more often to the appendicular skeleton (e.g., the shoulder), and frequently use mobilization techniques (Rhon D., et al., 2018). Compared to SM, mobilization involves oscillation or stretching of the joint or its articular surfaces at the end range of motion, without rapid thrust (Paris, 1979). Thus, applying high-velocity low-amplitude forces to the spine may constitute a core competency among chiropractors. An experimental study demonstrating that experienced chiropractors can consistently control thrust forces under standardized conditions (Triano et al., 2015), supports this notion.

Data comparing SMT utilization among different practitioners are scarce and mostly limited to the US, where over 97% of SMT is performed by chiropractors (Hurwitz, 2012; Whedon et al., 2021). Notably, despite Australia having three times as many physiotherapists as chiropractors, the latter provided 2.5 times more services on average in 2012 (Engel R.M. et al., 2014). Considering

the high prevalence of chiropractic use for back pain, this may reflect chiropractors providing more care for this condition, likely based on SMT. The appropriateness of chiropractors' provision of SMT for back and neck pain (NP) has been examined. Chiropractic patients receiving SMT for LBP in the US had presentations for which it was indicated, with appropriateness rates similar to other medical procedures (Shekelle et al., 1998). More recently, fewer than 3% of chiropractic patients with chronic LBP and NP were estimated to receive inappropriate SMT (Coulter et al., 2021). Chiropractors may also avoid SMT when contraindicated for complicated NP (Chu et al., 2022). Moreover, available evidence ranks chiropractors highly in compliance with clinical practice guidelines for LBP management (Amorin-Woods et al., 2014; Smith et al., 2022b).

In summary, the evidence suggests that chiropractors are competent in providing conservative spine care, with SMT provision being their primary area of expertise. However, identifying which conditions and patient presentations can be adequately managed with SMT, and which cannot, is essential. With this in mind, the following section examines the scopes of practice and typical patient presentations in chiropractic practice.

Scope of practice and common patient presentations

The WHO defines chiropractic's scope of practice as the diagnosis, treatment and prevention of neuromusculoskeletal disorders and their impact on general health (W.H.O., 2005). The ability to improve the neuromusculoskeletal system's function is the first distinguishing feature qualifying the consensus statement defining chiropractors as experts in spine care (Brown, 2016). The inclusion of the nervous system in the scope of practice harkens back to DD Palmer's original theories, which proposed that chiropractic restores health by normalizing nervous system function through correcting subluxations of the spine (Palmer D.D., 1910; Rosner, 2016). It was suggested that one of chiropractic's main contribution to healthcare lies precisely in understanding the complex interplay between the spine and the nervous system, and how spinal dysfunction may lead to neurological disturbances (Rosner, 2016). Accordingly, chiropractors in North America predominantly identify their scope of practice as providing care for neuromusculoskeletal conditions (Gliedt et al., 2021; McGregor et al., 2014). The scope of practice may be influenced, to varying degrees, by the individual, educational, and professional backgrounds (Puhl, et al., 2015; Wiggins et al., 2022). However, jurisdictional frameworks, which are shaped by vital

considerations of patient safety and healthcare system structure, play a crucial role in its legal definition.

Legal scope of practice

Chiropractic is legal in at least 68 countries, with a scope of practice defined by law or regulation in over 25 (Stochkendahl, et al., 2019). Consequently, significant differences exist between jurisdictions. Even within the US, chiropractors' legal scope of practice varies widely between states (Chang, 2014). The common criterion for determining whether a procedure falls within the scope is its relation to the spine. In Canada, the chiropractic acts of Ontario and Québec share significant similarities ("*Chiropractic Act, 1991*," 1991; "*Loi sur la chiropratique*," 2020). Both concur in a focus on the diagnosis and (primarily) manual treatment of spinal disorders. One of the key elements defined by the scope of practice is the spectrum of conditions chiropractors treat (Bussieres et al., 2016). Expertise in conservative, non-surgical management of spine-related disorders and disability establishes a role for chiropractors within the healthcare system, positioning them as valuable contributors in addressing this global crisis (Brown, 2018).

Reasons to seek care

Most patients visit chiropractors for spine pain (Beliveau, et al., 2017). Specifically, half of adult patients present with LBP, and about 22% with NP. Extremity complaints account for 10% of the consultations, and less than 3.1% consult for non-musculoskeletal conditions (Beliveau, et al., 2017). Reasons for seeking chiropractic care have remained fairly stable in the past 30 years (Dagenais and Haldeman, 2002; Meeker and Haldeman, 2002; Rosner, 2016) and across jurisdictions (Coulter et al., 2002; Coulter and Shekelle, 2005; Mior et al., 2019). A recent study reported that the typical chiropractic patient in Ontario is referred by other patients, seeks care for musculoskeletal conditions (98%), notably back pain, and receives SM and soft tissue therapy (Mior, et al., 2019). Most patients report high satisfaction with care for spine conditions, particularly when compared to medical treatment for LBP (Dagenais and Haldeman, 2002; Hertzman-Miller et al., 2002; Kaptchuk and Eisenberg, 1998; Meeker and Haldeman, 2002). This satisfaction extends to various populations, including Medicare beneficiaries (Weigel et al., 2014), patients with chronic spine pain (Hays et al., 2020), and those seeking care after COVID-19 lockdowns (Gevers-Montoro, et al., 2021). A large percentage of satisfied patients also feel very confident in recommending chiropractic services (Herman et al., 2018).

Chiropractic care is vastly pursued to receive treatment for spine conditions, particularly LBP and NP. Access to care is associated with high levels of satisfaction for the management of these conditions. Given that greater satisfaction can predict clinical LBP outcomes (Hurwitz et al., 2005), the following section provides an overview of the benefits of chiropractic management for these conditions.

Benefits associated with access to chiropractic care

Care provided by chiropractors can be directly accessed by the patients seeking care without the need to receive a medical referral (Stochkendahl, et al., 2019). Chiropractic services are generally delivered in private clinic settings, which means that patients often pay out of their own pocket or with private health insurances (Mior, et al., 2019). Although frequently associated with complementary and alternative medicine, chiropractic is increasingly perceived as part of mainstream healthcare (Meeker and Haldeman, 2002). In the US and Canada, there is evidence of chiropractic services being integrated in community health centers, veteran's administration, and hospitals (Boudreau et al., 2006; Garner et al., 2007; Green et al., 2009; Prater et al., 2020), suggesting they are gradually becoming an integral part of the healthcare system, particularly within multidisciplinary settings (Johnson et al., 2008). As one of the most frequently accessed providers for neuromusculokeletal conditions, chiropractors could contribute to primary care delivery, with a focus on disease prevention and health promotion. Indeed, chiropractors have the potential to address a substantial portion of spine-related disorders (Erwin, et al., 2013). However, their role resembles more that of primary contact practitioners, rather than primary care providers (Jones-Harris, 2010). Generally, the evidence supports that chiropractors are skilled to diagnose, treat, manage and refer patients with acute or chronic musculoskeletal pain, more specifically when affecting the spine (Globe et al., 2016; Hawk et al., 2020). Accordingly, recent trends indicate that a larger proportion of patients with back pain choose chiropractic as their first option (Hartvigsen et al., 2011) and that it is becoming part of essential care for those living with chronic pain (Pritchard, et al., 2022).

Pragmatic studies

There is a scarcity of pragmatic studies investigating the clinical outcomes of chiropractic care in real-world settings. Studies are not numerous and of low quality, preventing strong conclusions (Blanchette et al., 2016). Existing data suggest that chiropractic management of LBP

is similarly effective and not more expensive than care provided by other practitioners. In healthcare systems with limited resources, cost considerations are crucial. A significant portion of direct healthcare costs may be attributable to inefficient and inappropriate care (Buchbinder et al., 2020; Hartvigsen et al., 2018). This includes the excessive use of costly and invasive diagnostic and treatment procedures, frequently associated with worst outcomes. In contrast, access to chiropractic SMT may lower costs by reducing the unnecessary imaging (Davis M.A. et al., 2019), treatment escalation (Anderson B.R. et al., 2021; Whedon et al., 2022), opioid and benzodiazepine prescriptions (Corcoran et al., 2020; Emary et al., 2022; Trager et al., 2022a; Whedon et al., 2020b) and low back surgeries (Davis M.A. et al., 2021; Trager et al., 2022b). Chiropractic care is associated with improvements in pain, disability and quality of life for spine-related disorders (Garner, et al., 2007; Goertz et al., 2018; Hays et al., 2022; Prater, et al., 2020; Walker, et al., 2011), including during the COVID-19 pandemic (Gevers-Montoro, et al., 2021). Further, long-term chiropractic treatment may also be effective for tertiary prevention, reducing the total number of days with bothersome chronic LBP (Eklund et al., 2018).

Efficacy and effectiveness studies

Despite the scarcity of pragmatic studies, literature on the effectiveness and efficacy of SMT for spine pain is abundant. Chapter 6 of this thesis offers a comprehensive narrative review of recent literature on this topic, including randomized controlled trials, systematic reviews, meta-analyses and clinical practice guidelines. Studies suggest potential benefits of SMT for other spine-related disorders such as pregnancy-related lumbopelvic pain (Weis et al., 2020), radiculopathy (Leininger et al., 2011; Zhu L. et al., 2016), lumbar stenosis (Ammendolia et al., 2022), and cervicogenic headaches (Fernandez et al., 2020). Notwithstanding, evidence for conditions other than NP and LBP remains weak and insufficient.

As a healthcare profession, chiropractic entered the 21st century maintaining a strong identity with manual care for the spine at its core. Mounting evidence suggests that chiropractors are competent in managing prevalent spine conditions using conservative approaches that align with current clinical guidelines. Patients experiencing spine pain may benefit from chiropractic services, reporting high satisfaction levels and potentially leading to significant cost-saving opportunities for society at large. In Canada, the profession has built capacities to disseminate

evidence-based practices, design a relevant research agenda, transfer knowledge and provide high-quality spine care that aligns with both evidence and professional identity (Bussieres, et al., 2016; Bussieres et al., 2014; Bussieres and Stuber, 2013; Bussieres et al., 2015; French et al., 2017). The global LBP crisis presents an unparalleled chance for chiropractors to become part of the solution (French et al., 2018). The coming chapter addresses the global challenge of LBP, before discussing in Chapter 3 how chiropractic can contribute to its resolution.

Chapter 2 – Chronic primary low back pain: a global challenge

Pain in the lower back is a common symptom that usually has a benign nature, but can also be caused by inflammatory disorders, infections, fractures, or malignancies. However, LBP can also be a condition in itself, when the nociceptive system becomes overly sensitive to peripheral stimulation, and central processes. Most cases of LBP are suggested to fall under this second category. In both cases, LBP can cause significant disability and considerable societal impact. Therefore, understanding what LBP is, and addressing its causes and burden should be a global priority. This chapter presents compelling evidence of the significant impact that LBP has at the societal and individual levels, as well as recent data on the nature, risk factors and mechanisms that contribute to chronic primary LBP.

A global leading cause of disability

The primary reason preventing humans globally from working and engaging in daily activities is pain affecting their spine (G.B.D.Collaborators, 2020). To be specific, LBP was identified as the leading cause of years lived with disability worldwide (Wu et al., 2020). Disability-adjusted life years quantify the impact of non-fatal health outcomes in years (Vos et al., 2012) by combining years of life lost from premature mortality with years lost to poor health (YLDs). In 2017, LBP was responsible for 64.9 million years lived with disability, over a 50% increase since 1990 (Wu, et al., 2020). Despite not causing mortality, LBP still ranked 9th among the global leading causes of disability-adjusted life years s in 2019 (G.B.D.Collaborators, 2020).

The prevalence of low back pain

Recent estimates indicate that 619 million people experience LBP at any given time, an increase of over 200 million since 1990 (Ferreira M.L. et al., 2023). Although prevalence increases with age, the disability burden peaks at 45 to 49 years of age, and is higher for women. LBP accounts for 69.0 million years lived with disability (8.1% of global disability), and 38.8% of these may be attributed to three modifiable factors: occupation, smoking habits, and body-mass index. Trends in LBP prevalence and disability are expected to remain stable over the coming 30 years.

Ageing populations from emerging economies are projected to drive a 36.4% increase in these numbers by 2050, reaching 843 million (Ferreira M.L., et al., 2023).

During the 1990–2019 period, Canada experienced one of the highest increases in age-standardized prevalence globally (Chen et al., 2022). This translates to 4.2 million Canadians with LBP at any time point and almost half a million years lived with disability (Ferreira M.L., et al., 2023). With this perspective in consideration, it is important to contemplate the limitations inherent to these studies (Maher and Ferreira, 2022). Global Burden of Disease studies often rely on modeling approaches due to limited observed data. Moreover, LBP severity and disability are extrapolated from care-seeking subpopulations, which present more severe and disabling LBP, and may not represent accurately temporal trends across populations (Maher and Ferreira, 2022). The subsequent section expands on these limitations.

Limitations of epidemiological studies

Discrepancies in prevalence data often stem from varying definitions of LBP episodes. A widely accepted definition describes LBP as pain in the lower back lasting more than 24 hours, preceded and followed by at least one LBP-free month (de Vet et al., 2002). However, this definition is scarcely used, introducing biases in prognostic research (Masse-Alarie et al., 2022) and resulting in inconsistent epidemiological data (Ardakani et al., 2018; Hoy et al., 2012). These limitations are at the heart of significant discrepancies found across epidemiological studies. When assessing metrics like annual prevalence, systematic reviews report ranges from 1% to 65% (Hoy, et al., 2012; Walker, 2000). Similarly, lifetime prevalence estimates vary widely from 0.8% to 84% (Hoy, et al., 2012; Walker, 2000). Given the large intervals, caution is advised when interpreting mean estimates. The most reliable data suggest that an 18.1% annual prevalence is reasonably accurate, and that about 38% of people experience LBP at least once in their lifetime (Hoy, et al., 2012).

The dimensions of the LBP crisis can be difficult to comprehend, as pain and suffering are often invisible. However, the associated costs are tangible, and the growing impact of LBP on societies and economies was anticipated over 30 years ago (Frymoyer and Cats-Baril, 1991). The next section discusses the current understanding of the socioeconomic impact of LBP.

The socioeconomic impact of low back pain

Estimating the costs of LBP is challenging due to its high prevalence and inherent methodological difficulties in defining episodes, duration, recurrence, and persistence. Even with stable prevalence, the rate of disability can grow, driving up costs, not just for care, but primarily for the consequences of disabling LBP (Frymoyer and Cats-Baril, 1991). Most data indicate that the largest costs derived from LBP are related to productivity loss and work absenteeism, considered indirect costs (Alonso-Garcia and Sarria-Santamera, 2020; Dagenais et al., 2008; Olafsson et al., 2018; Zemedikun et al., 2021). Both direct and indirect costs are outlined below.

Direct costs

Direct costs of a condition are those related to treatment. Research estimating the differential proportion of direct costs has produced conflicting results; however, outpatient expenditures are often the main contributor (Zemedikun, et al., 2021). Primary care and physiotherapy account for the largest share of direct costs (Dagenais, et al., 2008), although recent studies from Spain and Sweden reported alarmingly high costs associated with specialist visits (Alonso-Garcia and Sarria-Santamera, 2020) and inpatient care, including surgery (Olafsson, et al., 2018). The proportion of healthcare resources occupied by patients with LBP is often under-reported (Zemedikun, et al., 2021); notwithstanding, over 50% of total analgesic consumption and nearly 40% of visits to physiotherapist and specialists may be attributed to LBP episodes (Alonso-Garcia and Sarria-Santamera, 2020; Dagenais, et al., 2008). Most studies exclude visits to private medical or complementary and alternative practitioners (which may include chiropractors), meaning direct costs are likely underestimated (Hartvigsen, et al., 2018).

Indirect costs

Quantifying indirect costs is more arduous. These include absenteeism, presenteeism and early retirement. Presenteeism, the productivity loss of employees not fully functioning at work due to LBP, poses a methodological challenge as it is difficult to measure (Dagenais, et al., 2008; Zemedikun, et al., 2021). Therefore, it tends to be underestimated, and sometimes not estimated at all. Absenteeism is considered the most important driver for expenditures (Zemedikun, et al., 2021), accounting for up to 87% of indirect costs in Spain (Alonso-Garcia and Sarria-Santamera, 2020). The proportion of total expenditures that are indirect exceeds 60% (Alonso-Garcia and

Sarria-Santamera, 2020; Dagenais, et al., 2008; Olafsson, et al., 2018; Zemedikun, et al., 2021). Adding both direct and indirect costs yields astronomical figures. In 1991, it was predicted that the total expenditures for LBP in the US would approach $100 billion USD in the most extreme scenario (Frymoyer and Cats-Baril, 1991). Seven years later, only direct costs reached $90.7 billion USD, 1% of the total gross domestic product (Luo et al., 2004). At the turn of the century, the total expenditure attributable to LBP approached $25 and $10 billion USD in the United Kingdom and Australia, respectively (Maniadakis and Gray, 2000; Walker et al., 2003). Higher figures were found in Japan and Germany, with estimates of total costs approaching $40 billion and exceeding $70 billion USD respectively (Zemedikun, et al., 2021). In Canada, spine conditions accounted for $8.1 billion CAD in 1998, marginally above $6 billion USD (Coyte et al., 1998). In Ontario alone, recent estimates show direct healthcare expenditures of $750 million CAD, approximately $560 million USD (Wong et al., 2021a). Available data suggest that total expenses represent nearly 1% of countries' gross domestic product. However, these figures may be even greater. Dagenais et al. (Dagenais, et al., 2008) estimated that the total costs imputable to LBP in the US could rise to $624.8 billion USD per year. In fact, with $134.5 billion USD, LBP and NP combined are already the largest contributors to healthcare expenditure in the US, beyond the spending attributable to cardiovascular diseases or cancers (Dieleman et al., 2020).

Pain affecting the spine is not only the leading cause of global disability but also likely represents the greatest healthcare expenditure in North America. More than 1% of the economy of countries like the US is dedicated to helping millions of sufferers return to work or to replace their workforce. These efforts may seem futile, as expenses derived from LBP continue to rise. The substantial social and economic impact of LBP underscores the devastating effects it can have on individuals, as discussed in the next section.

The individual impact of low back pain

The relationship between pain and disability is neither direct nor simple. The complexity and intricacy of multiple factors have been the focus of ongoing research for the past 40 years. A small fraction of LBP patients experiences high levels of disability, which cannot simply be accounted for by higher pain severity. Instead, this relationship is most likely mediated by biopsychosocial factors that interact bidirectionally with LBP (La Touche et al., 2019; Liew et al., 2023).

Impact of low back pain on occupation

A common observation from epidemiological data is that a small proportion of patients is responsible for 65 to 75% of the total expenditures derived from LBP (Dagenais, et al., 2008; Frymoyer and Cats-Baril, 1991; Luo, et al., 2004). These are typically individuals developing long-standing and severe disability (Herman et al., 2019; Kongsted et al., 2017; Walker et al., 2004), accounting for 77% of the total years lived with disability linked to LBP (Hartvigsen, et al., 2018). Most LBP disability affects working-age individuals (Ferreira M.L., et al., 2023; Hartvigsen, et al., 2018), thereby impacting work productivity and leading to the perception of LBP as an occupational condition. Up to 37% of global LBP cases are attributed to occupational factors (Punnett et al., 2005), while work-related LBP constitutes approximately one third of all occupational disability worldwide (Driscoll et al., 2014). As an example, LBP was the most common cause of workers' compensation claims in Ohio, US (Dunning et al., 2010). The distribution of these claims also responded to occupational and ergonomic factors, implying that workplace interventions could potentially help prevent LBP (Hartvigsen, et al., 2018). However, it is important to note that the consequences of LBP are not confined to the workplace, as it can also negatively impact leisure time, rest, and mood.

Impact of low back pain on general health

LBP frequently coexists with mood and sleep disorders (Gore et al., 2012). Although pain can influence various sleep dimensions, this interaction may also be bidirectional (Kelly et al., 2011). Loss of sleep quantity and quality due to LBP may lead to mood disturbances, which in turn exacerbate LBP severity (Sribastav et al., 2017). Alternatively, recent findings indicate that sleep quality mediates the relationship between depression and pain (Karimi et al., 2023). This association is likely bidirectional (Yang H. et al., 2023). There is evidence for chronic pain increasing the odds of developing mood disorders (Fine, 2011; Turk et al., 2016), and also for depression and anxiety as adverse prognostic factors for LBP (Chou and Shekelle, 2010; Pinheiro et al., 2016). Twin studies suggest that LBP, sleep, and mood disorders may share common physiological mechanisms influenced by genetic or (early) environmental factors (Fernandez et al., 2017b; Pinheiro et al., 2015; Pinheiro et al., 2017; Pinheiro et al., 2018). Similar mechanisms may also underlie the association between LBP and other less-explored comorbid conditions.

Patients with LBP often present concomitant rheumatic, cardiovascular, respiratory or painful conditions (Ferreira P.H. et al., 2013; Ha et al., 2014; Hestbaek et al., 2003; Rafn et al., 2023). The best available explanation to date, is that LBP appertains to a cluster of chronic conditions with shared predisposition or subjacent mechanisms. This would also clarify the frequent co-occurrence of chronic LBP with pain in other body regions, more often upper back and NP, headaches, knee pain, or osteoarthritis (Gore, et al., 2012; Hartvigsen et al., 2013; Overas et al., 2021; Rafn, et al., 2023). In fact, most LBP presents with pain coexisting in multiple body sites (Overas, et al., 2021) and multisite musculoskeletal pain may be more common than chronic pain limited to one body region, including the low back (Carnes et al., 2007). Coexisting pain worsens a plethora of LBP-related outcomes, including pain severity, disability and sleep disturbance (Hartvigsen, et al., 2013). The higher the number of pain sites, the more interference with function, mood, and recovery (Bruusgaard et al., 2012), a correlation that is unexplained by depression and anxiety (Nordstoga et al., 2017; Wong et al., 2021b).

Taken together, these findings suggest that LBP may be an expression of an individual's poor general health status that manifests in a cluster of comorbid conditions (Ferreira P.H., et al., 2013; Hartvigsen, et al., 2013; Hestbaek, et al., 2003). As no condition appears to be central, the term multimorbidity may be more fitting (Lefevre et al., 2014). LBP likely shares similar aetiology and mechanisms with pain in other spine regions within this cluster (Leboeuf-Yde et al., 2012) and with chronic musculoskeletal pain as a whole. Indeed, a significant portion of coexisting chronic pain is primary or of unknown aetiology (Page M.G. et al., 2018). Musculoskeletal pain in multimorbidity is strongly associated with general physical health (van der Zee-Neuen et al., 2016). Further, individuals with spine pain and osteoarthritis face a higher risk for developing chronic conditions, mainly cancer and cardiovascular disease (Williams et al., 2018), a link that may be established at an early age (Hebert et al., 2019). Musculoskeletal pain also heightens all-cause, cardiovascular, and cancer mortality risk (Fernandez et al., 2017a; Holmberg et al., 2020), more so for women and those with severe and chronic pain (Roseen et al., 2019; Roseen et al., 2021; Zhu K. et al., 2007). Though causation is unclear, disability may mediate this association, influencing behaviors that increase mortality risk, such as drug consumption and self-harm (Martin et al., 2020; Roseen, et al., 2019). Body-mass index (Holmberg, et al., 2020) or physical activity and sex interactions (Beynon et al., 2022), may act as potential confounders explaining how LBP may indirectly raise the risk of mortality in vulnerable individuals.

Conditions comorbid with LBP also share numerous risk factors. For example, exposure to inflammatory conditions and psychological factors in childhood may predict LBP development in early adulthood (Beynon et al., 2020; Beynon et al., 2021), and are also known to play roles in the aetiology of chronic disease (Edwards et al., 2016; Furman et al., 2019; Miller G.E. et al., 2011). Despite unknown mechanisms and lacking causative inferences, analyzing processes and risk factors in LBP may help clarify relationships within this multimorbidity cluster. The following section defines LBP, its common aetiologies and risk factors potentially contributing to its development and persistence.

Understanding chronic primary low back pain

Rather than a disease, LBP is typically defined as a symptom of tension, stiffness or pain, confined to a specific body site in the lumbosacral spine (Dionne et al., 2008; Hartvigsen, et al., 2018; Koes et al., 2006; Vlaeyen et al., 2018). The boundaries of this region are delimited by the inferior margin of the last (12^{th}) ribs and by the lower gluteal folds. For epidemiological purposes, a consensus definition described LBP as symptoms limiting daily activities for at least one day (Dionne, et al., 2008). Most LBP is considered nonspecific, of unknown aetiology that can't be adjudicated to a single specific cause (Chiarotto and Koes, 2022). In cases where symptoms persist or recur, it was proposed that these cases of idiopathic LBP should not be regarded as a symptom, but rather that chronic pain is the actual pathophysiological condition (Nicholas et al., 2019; Treede et al., 2019). This section discusses definitions of acute and chronic LBP (CLBP), risk factors, potential aetiologies, and suspected mechanisms.

Definition of low back pain

The classification of LBP as a symptom, a disease, or part of a broader health spectrum remains controversial (Ardakani, et al., 2018), with various case presentations potentially fitting into these categories. LBP can arise from multiple structures within the neuromusculoskeletal system, such as muscles, ligaments, joint capsules, intervertebral discs, neural connective tissue, but also from surrounding viscera or vascular structures (Hartvigsen, et al., 2018). Therefore, LBP can be a symptom secondary to a multiplicity of pathological processes affecting lumbar spine or surrounding tissues. These conditions, usually considered serious (as in not benign) are labeled as specific causes of LBP. Deyo et al. (Deyo et al., 1992) first reported that less than 10% of primary care patients presenting with LBP had a specific condition, such as a fracture, malignancy,

infection, visceral pathology, spondylolisthesis, or axial spondyloarthropathies. The prevalence of these pathologies was even lower than 1% in an Australian cohort presenting with acute LBP (ALBP) to primary care (Henschke et al., 2009). Thus, only a minority of LBP can be traced back to a specific pathology (Hartvigsen, et al., 2018; Maher et al., 2017). Less "serious" pathological processes of spinal tissues may become specific sources of LBP (i.e., facet syndrome, disc herniation) however, neither clinical tests nor diagnostic imaging can reliably discriminate between potential sources (Chiarotto and Koes, 2022; Hancock et al., 2007; Maher, et al., 2017). Due to high incidental finding rates and potential treatment escalation, routine imaging tests are currently discouraged (Hall et al., 2021). This renders diagnosis complex and, unless the source of pain can be clearly identified, LBP is classified as nonspecific, meaning no underlying pathoanatomic cause or nociceptive contributor is accurately identified (**Figure 1)**.

Diagnosis of low back pain

Nonspecific LBP is a benign condition, albeit highly complex due to the interaction of multifactorial contributors to its aetiology (Chiarotto and Koes, 2022; Hartvigsen, et al., 2018). Most patients can be accurately identified through diagnostic triage based on a focused case history and clinical examination (Bardin et al., 2017; Hall, et al., 2021), as early or routine imaging does not improve diagnosis or outcomes (Hartvigsen, et al., 2018; Waddell G. and Burton, 2001). Positive findings from magnetic resonance imaging (MRI) or computerized tomography (CT) scans of the lumbar spine such as degenerated, bulged, or protruded discs are almost universal as we age and often unrelated to symptoms (Brinjikji et al., 2015b). Such findings may be present with or without LBP, and must be carefully interpreted, as they could be incidental (Kasch et al., 2022). Incidental findings are known to trigger unnecessary and potentially harmful escalation of medical treatment (Ganguli et al., 2019). When interpreted as its primary cause imaging findings concurrent with LBP may lead to downstream costs from unnecessary care, but most importantly, unintended patient harms (Jacobs et al., 2020). Beyond radiation exposure, iatrogenic effects may arise from labeling patients (O'Keeffe et al., 2022), increasing rates of invasive interventions, including surgery and opioids (Chou et al., 2012), and higher disability (Lemmers et al., 2019; Webster B.S. and Cifuentes, 2010). Hence, routine diagnostic imaging is only required if the clinical assessment is unable to rule out a serious underlying condition (**Figure 1**; (Bardin, et al., 2017; Chiarotto and Koes, 2022; Hall, et al., 2021).

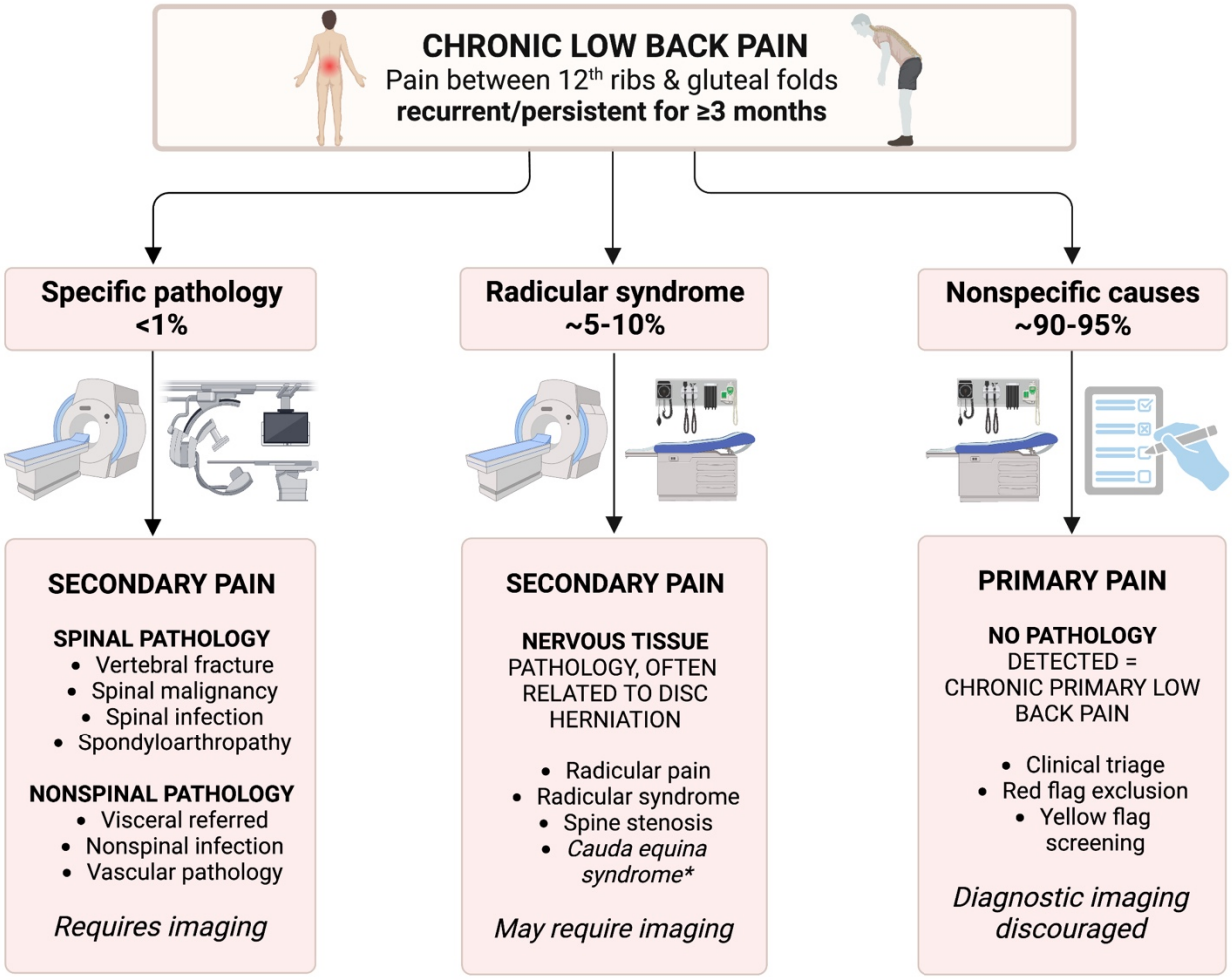

Figure 1 Diagnosis of chronic low back pain

Flowchart demonstrating the process of differential diagnosis for chronic low back pain.
** Cauda equina syndrome, although anatomically impacting nerve roots, is usually considered a specific cause of chronic low back pain*

The most important step in diagnostic triage is determining if LBP is specific or nonspecific (see **Figure 1**). Radicular syndrome (also known as sciatica) was proposed as a third descriptor (Bardin, et al., 2017), which is consistent with studies suggesting that neuropathic LBP is a distinct entity (Baron et al., 2016). Hence, nonspecific LBP is diagnosed by exclusion of specific and radicular aetiologies (Bardin, et al., 2017; Chiarotto and Koes, 2022; Maher, et al., 2017). Determining symptom duration discriminates between acute, subacute, and chronic LBP. Acute and subacute symptoms are commonly categorized jointly as acute or early-onset LBP, when symptom duration does not exceed 12 weeks (Vlaeyen, et al., 2018). It was suggested that the natural course of LBP is such that a vast majority of patients with a recent onset of symptoms

recover spontaneously, and only a few develop persistent, disabling pain (Hartvigsen, et al., 2018). However, although most ALBP patients present low levels of disability one year after inception, recurrent episodes are not uncommon. Roughly two thirds suffer at least one recurrent episode (da Silva et al., 2019; Itz et al., 2013) and one third experience activity limitations (da Silva et al., 2017; Medeiros et al., 2022). Thus, to understand the prognosis of LBP, standardization of recovery definitions is deemed essential (Costa et al., 2012; Itz, et al., 2013).

Following an initial LBP episode, most patients experience a rapid initial improvement, but three months after onset, flare-ups are common and the rate of improvement sharply declines (Costa, et al., 2012; Itz, et al., 2013). Those who experienced an episode are likely to have more in the future (Gatchel et al., 2018; Kongsted et al., 2016). Recurrence and recovery from LBP are complex constructs difficult to define, making the exact rates uncertain. The episodic nature of most cases challenges the traditional classification of LBP as acute, subacute, and chronic, with particular importance for defining CLBP, as presented in the next section.

Chronic primary low back pain

The current classification of LBP as acute or chronic based on a time threshold (Chiarotto and Koes, 2022) does not capture the complexity of the condition's temporal patterns (Gatchel, et al., 2018). LBP does not simply transition from acute to chronic; instead, its evolution is better understood through trajectory analysis (Axen and Leboeuf-Yde, 2013). Most patients neither experience acute, unrelated episodes nor endure chronic, constant pain (Kongsted, et al., 2016). For the majority, LBP follows a long-standing, recurrent or persistent pattern, resembling a chain of episodes that are not independent from each other, much like asthma or other chronic conditions (Axen and Leboeuf-Yde, 2013; Hartvigsen, et al., 2018). Accordingly, the understanding of LBP is shifting towards a life-course perspective of patients' trajectories (Dunn et al., 2013). This allows to distinguish subgroups of patients among the ones who do not recover (Kongsted, et al., 2017), thereby stratifying CLBP as episodic/recurrent or fluctuating/constant (persistent).

The temporal classification of acute and chronic pain is not exclusive to LBP. Chronic pain persists or recurs longer than 3 months (Treede, et al., 2019). The three-month threshold is meant to distinguish pain that is present beyond normal healing time (Nicholas, 2022), no longer serving a protective function. However, this tautological differentiation can be criticized as overly simplistic (Finnerup et al., 2022) and irreflective of the dramatic differences in risk factors,

predictors and mechanisms between acute and chronic pain (Loeser, 2022). These differences should also be imprinted in their diagnosis and management. The International Association for the Study of Pain recently developed a new taxonomic classification for chronic pain syndromes (Treede, et al., 2019). Chronic pain definitions are hereby reframed to better reflect the clinical reality and accumulating research indicating that chronic pain is not simply a longer-lasting symptom. Whereas chronic secondary pain can be regarded as a long-lasting symptom of a specific underlying primary condition (i.e., cancer, neuropathy, post-surgical), chronic primary pain is a disease in and of itself (Treede, et al., 2019). Chronic primary pain is a diagnosis of exclusion, when pain is not accounted for by any other condition (Nicholas, et al., 2019). Thus, the concept of primary pain replaces that of nonspecific LBP. Chronic primary LBP (CPLBP; see **Figure 1**) is not the result of identifiable pathology in other tissues (Fitzcharles et al., 2022), in lieu, pain processing itself is pathological (and therefore no longer protective).

Acute episodes and CLBP are distinct entities, with different aetiologies, mechanisms and risk factors (Finnerup, et al., 2022). ALBP serves an adaptive role to protect specific tissues from potential harm, and usually remits spontaneously. When LBP recurs or persists, it often cannot be easily traced to specific tissues and becomes maladaptive. Understanding the complex aetiology of CPLBP requires examining the interplay not only of biological factors, but of important psychological and social factors (Nicholas, et al., 2019). The subsequent section provides a perspective of the risk factors for the development and maintenance of CPLBP.

Who is at risk for developing chronic primary low back pain?

Occurrence and recurrence of LBP don't share the same aetiology (Axen and Leboeuf-Yde, 2013; da Silva, et al., 2017). After an initial episode of LBP, a patient can experience remission, recurrence, or persistence. Interestingly, the most significant predictor for a recurrent episode is a history of prior LBP (da Silva, et al., 2017). These trajectories are likely influenced by a range of biological, psychological, and social risk factors (Axen and Leboeuf-Yde, 2013). Recognizing this complexity prompted a shift from the traditional biomedical model towards a more comprehensive approach: the biopsychosocial model (Engel G.L., 1980). This model provides a holistic conceptual framework that takes into consideration the person as a whole. The recognition of the influence of psychological and social factors in health and disease is instrumental for the current understanding of LBP (Gatchel et al., 2007; Waddell G., 1992). The biopsychosocial approach discriminates

between the disease, as an objective biological event, and the subjective experience and consequent behavior, which necessarily have a psychosocial dimension to it. This resembles the distinction between nociception, the neurophysiological transmission of information coded as potentially noxious, and pain, the subjective perception, filtered by prior exposures, psychological status, and sociocultural influences (Gatchel, et al., 2007). This theoretical model helps explain poor correlations between tissue damage, pain, and disability, and has proven to be particularly useful for understanding the factors influencing the prognosis of individuals with LBP.

Biological risk factors

Biological risk factors may be split between genetic predisposition and environmental exposure. Longitudinal and cross-sectional twin studies, particularly those comparing identical to non-identical twin pairs, may help discern their relative contribution. A systematic review of such studies concluded that the heritability of LBP ranges from 21 to 67%, with a stronger influence on severe and chronic manifestations (Ferreira P.H., et al., 2013). Smoking and obesity were identified as environmental risk factors, consistent with their predictive role in LBP occurrence and recurrence (Shiri et al., 2019; Stevans et al., 2021). A recent study found a shared genetic signature for CLBP and other chronic pain conditions (Farrell et al., 2023), revealing common biopsychosocial traits that increase the risk of chronic pain, as well as genetic causal effects of chronic pain on increased risk of cardiovascular disease and depression.

Although multiple biological risk factors have been associated with the development of LBP, their role in the CPLBP is unclear. Physically demanding works can trigger or contribute to the onset of LBP (Chou and Shekelle, 2010; Waddell G. and Burton, 2001), which led to the assumption that most LBP was caused by physical injury, over-exertion and mechanical loads (Marras et al., 1995). However, the available evidence does not support strong associations between LBP and occupational sitting, specific spine postures, movements, or loads (Swain C.T.V. et al., 2020). On the other hand, unemployment may significantly contribute to chronic pain and disability (Campbell et al., 2013; Waddell G. and Burton, 2001).

Accordingly, physical examination and imaging findings are not effective at predicting outcomes or detecting patients at higher risk (Tonosu et al., 2017; Waddell G. and Burton, 2001). Only past history of LBP episodes and higher baseline pain intensity confer substantial increases in risk of chronicity (Campbell, et al., 2013; Chou and Shekelle, 2010; Costa et al., 2009). This

suggests that, although a biomedical model for LBP is attractive, in multifaceted conditions like CPLBP, the role of any individual factor is likely small (see **Figure 2**, (Cholewicki et al., 2019a). Research should focus less on any individual biological risk factor and more on whether it has sufficient influence for a significant proportion of patients. Instead, emphasis on psychosocial factors has provided deeper insights to understand LBP prognosis.

Psychological risk factors

In the context of CPLBP, factors such as attitudes, cognitions, beliefs, expectations, coping strategies, and fears about pain, play a crucial role (Hill and Fritz, 2011) and can be more disabling than the physical condition itself (Crombez et al., 1999; Waddell G., 1992; Waddell G. et al., 1984). Within this framework the fear-avoidance model posits that negative beliefs and emotions about pain, such as pain catastrophizing, precede the development of pain-related fear, which motivates escape and avoidance of activities expected to evoke pain, leading to functional disability (Vlaeyen and Linton, 2000). Activity avoidance and hypervigilance are initially protective against further injury, however, they become dysfunctional when persistent (Crombez et al., 2012). Individual differences in these cognitive, emotional, and behavioral factors contribute to different degrees of risk for CLBP (Meulders, 2019).

Low levels of fear-avoidance predict recovery, while high levels correctly identify those at risk for chronicity (Chou and Shekelle, 2010). Pain-related fear, anxiety, and avoidance behavior are significantly associated with pain intensity and disability in individuals with chronic musculoskeletal pain, including CLBP (Martinez-Calderon et al., 2019a). Pain catastrophizing is a key risk factor for disability (Martinez-Calderon et al., 2019b; Wertli et al., 2014b), while self-efficacy and fear mediate the interaction between pain and disability (Lee H. et al., 2015). Self-efficacy sits on the opposite end of the spectrum as catastrophizing and fear, negatively correlating with affective distress, disability, and pain intensity (Martinez-Calderon et al., 2018). Therefore, a patient's perspective towards their LBP may influence its prognosis. Accordingly, positive expectations of recovery from LBP are associated with return to work (Hayden et al., 2019), while greater perceived risk of persistence increases the odds of poor prognosis (Campbell, et al., 2013; Costa, et al., 2009; Henschke et al., 2008). As negative affect and emotions interact with expectations (Gatchel, et al., 2007), coexisting depression, anxiety, and psychiatric conditions also have the potential to influence LBP recurrence (Costa, et al., 2009; Pinheiro, et al., 2015; Stevans,

et al., 2021) and persistence (Axen and Leboeuf-Yde, 2013; Chou and Shekelle, 2010; Hill and Fritz, 2011).

Research on psychological risk factors suggests that the ability to function and beliefs that reflect or impact on it, are among the strongest predictors of poor prognosis and likelihood of developing CLBP. The influence of these factors can be better observed during social and occupational interactions (Waddell G. and Burton, 2001), presented below.

Social risk factors

Psychosocial risk factors, or *yellow flags*, are undisputedly associated with the onset of pain or the transition from acute to chronic pain. Yellow flags confer a higher risk of disability, often reflected in the workplace environment (Waddell G. and Burton, 2001). Low job satisfaction and psychosocial aspects of work seem to exert larger influences on LBP than biomedical factors (Dionne et al., 2007). Compensation and previous sick leave due to LBP are strong predictors for adverse prognosis (Costa, et al., 2009; Henschke, et al., 2008). Indeed, the more time off work, the less chances the worker will return in the same capacity (Waddell G. and Burton, 2001). Work-related fear, stress, beliefs, and lower social support may decrease the chances of returning to work due to LBP (Soucy et al., 2006), a relationship influenced by organizational practices (Villotti et al., 2020). Furthermore, occupational factors are likely to influence the relationship between social determinants of health and LBP outcomes (Yap et al., 2022), explored hereafter.

Occupational factors play a critical role in influencing and shaping other social determinants of health. For instance, they may be at the root of perceived injustice, particularly when the loss, compensation, and retribution due to disability are not seen as equitable (Carriere et al., 2020). Perceived injustice can, in turn, modulate musculoskeletal pain intensity and disability, including CPLBP (Carriere, et al., 2020; Penn et al., 2020). Further, work absenteeism and stigma may aggravate social dysfunction and isolation (Correa L.A. et al., 2022; Oliveira V.C. et al., 2015; Steenstra et al., 2005). In the broader social context, determinants like job strain, lower levels of formal education, and socioeconomic status play critical roles in determining LBP prognosis (Dionne et al., 2001; Hoy, et al., 2012; Karran et al., 2020; Yap, et al., 2022). These factors shape an individual's social stress early in life, potentially affecting biological processes (Palmer R.C. et al., 2019). Psychological distress from adverse life events and childhood experiences predisposes individuals to the development of chronic musculoskeletal and LBP (Burke et al., 2017; Dario et

al., 2022; Generaal et al., 2016; O'Hagan et al., 2023). However, exactly how these mechanisms contribute to chronic pain syndromes is still poorly understood.

Prognostic research on LBP has evolved towards a psychosocial approach. LBP disability appears to be tightly linked to beliefs and perceptions related to the condition itself and to social circumstances. Social determinants of health may modulate the predisposition for the development of CLBP early in life. For instance, the association between low socioeconomic status, particularly during childhood, and the emergence of chronic systemic inflammation (Milaniak and Jaffee, 2019) could provide an explanation for the complex interplay between CPLBP and its cluster of chronic multimorbidities. Research dedicated to unveiling the mechanisms underpinning the development of CPLBP explored in the next section, may shed some light on their aetiology.

Mechanisms of chronic primary low back pain

A myriad of multidimensional factors contributes, to varying extents, to a person's LBP presentation (**Figure 2**). A similar number of outcomes and biomarkers are expected to reflect an individual's LBP experience (Dutmer et al., 2019; Tagliaferri et al., 2020; Tagliaferri et al., 2022). Markers may serve as surrogates for potential mechanisms involved in the pathogenesis of LBP, including spinal tissue, neurophysiological, and psychosocial processes (Tagliaferri, et al., 2020). Indeed, examining mechanisms has been suggested as the optimal approach to distinguish between acute and CLBP (Finnerup, et al., 2022; Loeser, 2022). A recent meta-analysis revealed spinal column, neurophysiological, and psychosocial mechanisms involved in CPLBP to varying extents (Tagliaferri, et al., 2022). Specifically, intervertebral disc imaging, pain thresholds, and brain connectivity showed significant capacity to discriminate CPLBP patients. However, psychosocial factors (i.e., catastrophizing, fear or depression) displayed the largest effect sizes (Tagliaferri, et al., 2022). Accordingly, a multidisciplinary expert panel concluded that psychological components were the most central (Cholewicki et al., 2019b) of over 100 contributors to LBP (see **Figure 2**). The following sections delve into these mechanisms and their degree of involvement in CPLBP.

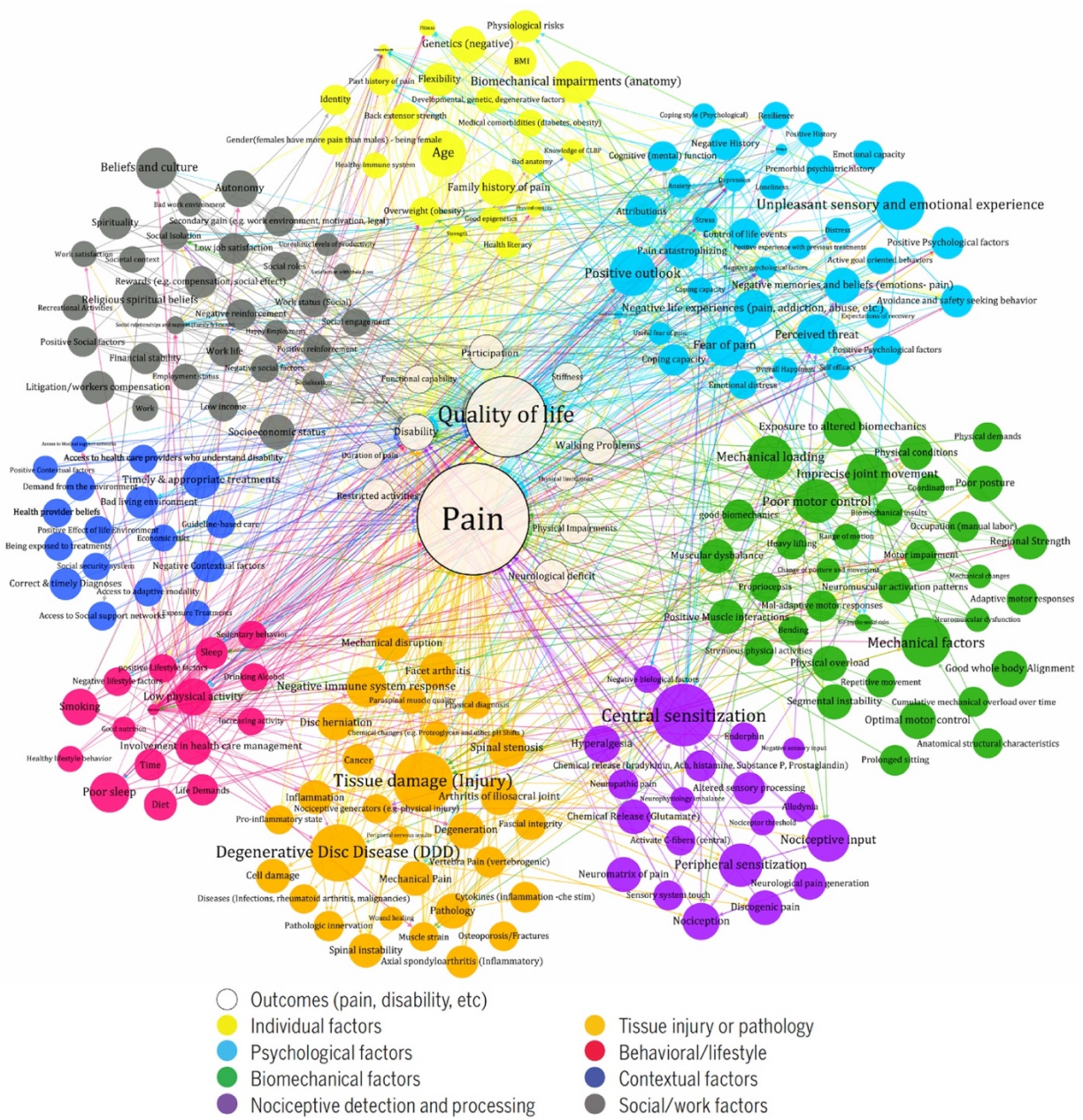

Figure 2 Factors contributing to low back pain outcomes.

Metamodel showing factors (colored circles), outcomes (white circles) and interactions (colored lines) contributing to low back pain. Diameters are proportional to the number of experts identifying these factors and the number and strength of connections.
Image reproduced with permission from (Cholewicki, et al., 2019a)

Spinal column mechanisms

Spinal tissues and structures have been extensively investigated as pain generators in the low back. Peripheral nociceptors in the intervertebral disc, the facet, and sacroiliac joint capsules, when activated, can generate pain (Allegri et al., 2016). Patient history and physical examination

provide clues to identify the most likely pain generator, but their accuracy in pinpointing specific structures is insufficient (Hancock, et al., 2007; Rubinstein and van Tulder, 2008). An exception seems to be LBP caused by nerve involvement, which deserves its own diagnostic classification (Bardin, et al., 2017). Nerve root compression or chemical irritation by the intervertebral disc are frequently the cause (Bardin, et al., 2017; Baron, et al., 2016). Other than for malignancy, the accuracy of clinical features indicating the presence of serious pathology, or red flags, is also uncertain (Downie et al., 2013; Hooten and Cohen, 2015; Verhagen et al., 2016) and may require the prescription of additional diagnostic tests (Bardin, et al., 2017; Finucane et al., 2020).

Imaging biomarkers

Radiographic examination provides insight into specific spinal and extraspinal tissues causing LBP (Bardin, et al., 2017; Hall, et al., 2021). However, for most patients, this task remains speculative, and imaging does not allow the inference of mechanisms. The presence of degenerative changes may be spurious (Brinjikji, et al., 2015b; Hopayian et al., 2023; Kalichman et al., 2008; Kasch, et al., 2022), and the association with LBP only meaningful for more severe (e.g., disc extrusions), diffuse findings, and in younger individuals (Brinjikji et al., 2015a; Rahyussalim et al., 2020; Smith et al., 2022a). Most disc extrusions undergo spontaneous resorption, reducing the chances that they may be primary drivers of CPLBP (Zhong et al., 2017). Anatomical variants or spondylolistheses also showed little to no association with clinical symptoms (Ishimoto et al., 2017; Kalichman et al., 2009; Sugiura et al., 2021). Overall, these data suggest that specific spinal tissues play only a limited role as nociceptive mechanisms for CPLBP. A longstanding hypothesis posits that CPLBP could stem from abnormal movement patterns and motor control (O'Sullivan, 2005). Notably, the term *mechanical* LBP was frequently employed as equivalent to nonspecific LBP (Deyo and Weinstein, 2001). This model, described hereafter, focuses on the role of paraspinal and trunk muscle volume, strength, performance, coordination, and activation patterns in patients with CPLBP.

Movement biomarkers

A prevailing conviction is that people with LBP move differently, and that LBP's clinical presentation is influenced by the way an individual moves (van Dieen et al., 2019; Wernli et al., 2020). Patients and clinicians often identify movement and postural factors that trigger, aggravate, or relieve LBP episodes. Researchers have identified specific biomechanical impairments that

distinguish CPLBP patients from healthy individuals (Cholewicki, et al., 2019a; Moissenet et al., 2021; O'Sullivan, 2005). In brief, people with CPLBP exhibit a lower sense of control, confidence and coordination in their movements (Wand and O'Connell, 2008). Although these impairments may be present in most patients, they may only be relevant in a few. A recent systematic review revealed that the most common biomechanical impairments are abnormal lumbar kinematics, poor lumbopelvic coordination, maladaptation to perturbations, and changes in paraspinal muscle structure and function (Moissenet, et al., 2021). Ample evidence supports the premise that patients with CPLBP have smaller multifidus muscles and a higher proportion of fat infiltration than healthy controls (Seyedhoseinpoor et al., 2022), and that this association may be causal (Ranger et al., 2017). Changes in muscle fiber types could lead to fatigue, activation of muscle nociceptors, and pain (Li et al., 2021). However, there is less agreement regarding which motor control dysfunctions drive or result from these muscle changes. Two phenotypes were postulated: either excessively tight (i.e., stiff) or loose (i.e., unstable) control of the lower back (van Dieen, et al., 2019), may both lead to higher spinal loads and to experiencing pain.

In sum, evidence suggests that biomechanical processes are associated to CPLBP, at least in potential patient subgroups (van Dieen, et al., 2019; Wernli, et al., 2020). The first pressing question is whether these processes are clinically relevant. Changes in spinal movement and in LBP outcomes only correlate in 31% of study participants (Wernli, et al., 2020). The second critical question is whether these processes are a cause or a consequence of CPLBP. Currently, there are insufficient data to interpret biomechanical changes as causative, and more evidence suggests that they may be the response to anticipation or fear of pain (Moissenet, et al., 2021; O'Sullivan, 2005; van Dieen, et al., 2019; Wand and O'Connell, 2008). Nonetheless, this does not exclude that these mechanisms may play a role for certain patients. Biomechanical abnormalities create spinal loads of higher magnitude, which may lead to pain in a subset of patients presenting with nociceptive sensitization (van Dieen, et al., 2019). Though this has yet to be explored, neurophysiological mechanisms leading to sensitization processes are likely to be involved in CPLBP.

Neurophysiological mechanisms

Multiple peripheral receptors in the lumbar spine and surrounding tissues are specialized in the detection of potentially noxious stimuli. The intervertebral disc is one of the most significant contributors to lower back nociception (DePalma et al., 2011; Manchikanti et al., 2018).

Nociceptive nerve endings in the outermost part of the disc (Groh et al., 2021) or adjacent nerve root (Deyo and Mirza, 2016) can be sensitized by inflammatory mediators (McCarron et al., 1987; Raj, 2008) or directly activated by tissue injury (Adams M.A. and Roughley, 2006). Hereon, transmission within nociceptive pathways may or may not result in a painful experience.

Pain circuitry

Primary afferent nociceptive fibers from spinal tissues comprise large-diameter, fast-conducting myelinated fibers from the A-group, labeled Aδ, and small-diameter, slow-conducting mostly unmyelinated C fibers (Julius and Basbaum, 2001). These fibers travel through spinal nerves, their rami and collateral branches, like the sinuvertebral nerve (Adams M.A. and Roughley, 2006; Groh, et al., 2021; Shayota et al., 2019). The cell bodies are located in the dorsal root ganglia and the central terminals synapse in the dorsal horn of the spinal cord (Todd A.J., 2010). Upon receipt in the dorsal horn, most nociceptive afferents terminate in the superficial layers, labeled laminae I and II (Rexed, 1952). Myelinated A fibers predominantly synapse within the borders of lamina I, while the central terminals of smaller C afferents are found in laminae I and II (Sandkuhler, 2013; Todd A.J., 2010). The outermost lamina I concentrates most neurons projecting to the brain. These projection neurons are influenced by interneurons and primary nociceptive afferents, a vast majority through peptidergic interactions engaging Substance P and NK_1 receptors (Todd A.J., 2010). These neurons decussate to the contralateral white matter and ascend towards higher brain centers. Supraspinal targets include the thalamus and important brainstem centers such as the periaqueductal gray and the lateral parabrachial area (Todd A.J., 2010).

Instead of relaying to a single specific supraspinal center, nociceptive inputs are distributed to numerous brain areas. The thalamus, the primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortices, form a brain network involved in acute pain processing (Apkarian et al., 2005; Wager et al., 2013). This pain signature distinguishes somatic-related areas (thalamus, primary and secondary somatosensory areas) which handle sensory-discriminative aspects of pain (i.e., location, duration and intensity), from regions processing emotional (anterior cingulate and insular cortices) and cognitive (prefrontal) pain dimensions (Wager, et al., 2013). Anterior cingulate cortex activation reflects affective pain dimensions such as unpleasantness, but not intensity (Rainville et al., 1997). In contrast, pain-evoked activation of the prefrontal cortex relates to cognitive processing of pain perception, potentially influencing behavior through interactions

with the amygdala, such as risk and reward assessment in the face of pain (Neugebauer and Li, 2002; Ossipov et al., 2010).

Nociception undergoes significant processing at multiple levels, leading to the pain experience. From peripheral receptors to each relay step in these pathways, all are subject to regulation and contribute to the final pain experience. Modulatory systems enhance the experience when the source of pain poses substantial risks and dampen the signal when other environmental stimuli are prioritized for survival. The regulatory capacity of the nociceptive system motivates appropriate adaptive behavior (e.g., escaping a threat or an aggressor), but this capacity can also be challenged (Bushnell et al., 2013). Over-facilitation or disinhibition of nociception can result in sensitization and persistent pain. The involvement of mechanisms operating at peripheral, spinal, and supraspinal levels in CPLBP are explored in subsequent sections and represented in **Figure 3**.

Peripheral neurophysiological mechanisms

Tissue damage, such as the one characterizing a disc herniation, can result in the activation of high threshold mechanoreceptors and/or polymodal nociceptors (Julius and Basbaum, 2001; Raja et al., 1988). This mechanical input may lead to acute pain perception, but does not appear to be the mechanism driving CPLBP (Vardeh et al., 2016). Most C fiber nociceptors are also responsive to chemical stimuli like capsaicin, the molecule responsible for the pungency of chili peppers (Hoegh, 2022; Julius and Basbaum, 2001). Repeated activation of capsaicin-sensitive transient receptor potential vanilloid 1 sensitizes the transduction by inducing conformational changes in the receptor protein (Woolf and Salter, 2000). Plasticity of such receptors may play a role in CPLBP (Wang D. et al., 2022). Rapid, short-lived increases in nociceptive responses to thermal or chemical, though not mechanical stimuli, are referred to as peripheral sensitization (Treede, 2016; Woolf and Salter, 2000).

Peripheral inflammation

The inflammatory response initiated by tissue damage is associated with a distinct form of hyperexcitability (Woolf and Salter, 2000). The release of intracellular contents from injured cells, and of inflammatory mediators by local mast cells, sensitize and directly activate nociceptors (Sommer and Kress, 2004; Vardeh, et al., 2016). The phosphorylation and upregulation of capsaicin-sensitive receptor channels underlie receptor sensitization in response to this *inflammatory soup* (Hoegh, 2022; Vardeh, et al., 2016). Protons, serotonin, prostaglandins, nerve

growth factor (NGF) and substance P all contribute to inflammation (Julius and Basbaum, 2001). Accordingly, substance P expression is a recurrent finding in intervertebral disc nerves of LBP patients, while NGF may distinctly contribute to sensitization by supplying new nociceptive fibers to previously aneural structures within the inner disc (Groh, et al., 2021). Reactive oxygen species (Westlund et al., 2010; Zhao et al., 2022) and cytokines secreted by migrating immune cells (Marchand et al., 2005; Sommer and Kress, 2004) amplify the inflammatory response (see **Figure 3)**. Most compelling data points to crucial roles for interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in mediating peripheral sensitization. These substances are found in human tissues of intervertebral disc degeneration, herniation and radicular pain (Risbud and Shapiro, 2014), with their expression correlating with CPLBP outcomes (Aripaka et al., 2021; Teodorczyk-Injeyan et al., 2019). Blood and urine samples from CPLBP patients reveal elevated levels of these cytokines, accompanied by a reduction in the anti-inflammatory interleukin-10 (IL-10; (Canli et al., 2022; Gevers-Montoro et al., 2022b; Morris et al., 2020). Therefore, inflammatory biomarkers may aid in the diagnosis and treatment of CPLBP (Khan et al., 2017).

Proinflammatory cytokines sensitize peripheral nociceptive terminals and facilitate the nociceptive afferent transmission (Goncalves Dos Santos et al., 2019). Facilitated C nociceptors release neuropeptides centrally and peripherally from their sensory endings (Hoegh, 2022; Julius and Basbaum, 2001). The antidromic (peripheral) release of peptides like substance P induces *neurogenic inflammation* in the tissues initially responsible for C fiber activation. These local changes lead to an increased gain in nociceptive input that manifests in reduced thresholds and a greater response confined to the site of injury (Starkweather et al., 2016; Vardeh, et al., 2016). Increased sensitivity to noxious stimuli is hyperalgesia. In this state, enhanced pain responses may be elicited by subthreshold or normally painful stimuli (Koltzenburg et al., 1992; Sandkuhler, 2009). Peripheral or primary hyperalgesia affects predominantly thermal sensitivity (Koltzenburg, 2000; Meyer et al., 2005; Raja, et al., 1988). Therefore, persistent pain accompanied by heat hyperalgesia suggests peripheral mechanisms (Starkweather, et al., 2016; Treede, 2016).

Peripheral sensitization

Quantitative sensory testing (QST) is a battery of psychophysical examination techniques used to assess various modalities of somatosensory perception, including nociceptive afferent function (Starkweather, et al., 2016). Multiple studies using QST reported that a subgroup of

patients with CPLBP exhibit increased heat sensitivity in the low back (Gerhardt et al., 2016; O'Neill et al., 2019; Puta et al., 2013). However, mechanical hyperalgesia was found to better differentiate CPLBP from healthy controls (Neziri et al., 2012). Pressure pain thresholds (PPTs) often appear diminished over painful lumbar segments (Correa J.B. et al., 2015; Gerhardt, et al., 2016; Imamura et al., 2013; O'Neill, et al., 2019; O'Neill et al., 2007; Puta, et al., 2013), and surrounding muscles (Blumenstiel et al., 2011; Farasyn and Meeusen, 2005; Imamura et al., 2016). These regional changes, although not strictly primary hyperalgesia, are compatible with peripheral sensitization mechanisms. Interestingly, some CPLBP patients also display higher thermal and mechanical pain sensitivity in remote non-painful body areas (den Bandt et al., 2019). Compared to healthy controls, these patients have higher number of remote tender points (Clauw et al., 1999) and lower widespread thermal and mechanical pain thresholds (den Bandt et al., 2022; Gerhardt, et al., 2016; Giesbrecht and Battie, 2005; Giesecke et al., 2004; Hubscher et al., 2014; O'Neill, et al., 2007; Puta, et al., 2013; Vaegter et al., 2017).

These observations are consistent with systemic mechanisms favoring a proinflammatory state sustained by increased circulating cytokine levels. While cytokine release may originate from spine tissues, systemic inflammation in CPLBP may also result from stress-induced cortisol depletion (Hannibal and Bishop, 2014). Alternatively, widespread changes in pain sensitivity may be attributed to neurophysiological mechanisms involving spinal and supraspinal structures. The following section details spinal cord mechanisms speculated to be involved in CPLBP.

Spinal neurophysiological mechanisms

Hardy first postulated that pain prolongation following tissue injury could be explained by central facilitation of spinal nociceptive neurons (Hardy et al., 1950). Mendell and Wall later showed that high-intensity electrical nerve stimulation at ~ 0.33Hz in cats increased the duration and intensity of nociceptive dorsal horn responses after each subsequent stimulation (Mendell and Wall, 1965). This nociceptive *windup* was interpreted as a physiological response of unmyelinated C afferents. Subsequently, similar results were observed in humans exposed to pulses of thermal noxious stimulation (Price et al., 1977). The perceived intensity of the first painful sensation decreased with each repeated stimulation, indicating suppression of faster Aδ afferents. In contrast, second (slower) pain sensations incremented with each successive heat pulse at frequencies equal or superior to 0.33Hz. This phenomenon, named temporal summation of pain, is the perceptual

correlate of windup (Price, et al., 1977). Both depend on central mechanisms of prolonged facilitation of C fiber activity, likely aiming to maintain appropriate protective responses after noxious stimulation has ceased. Although windup is a transient intrinsic property of C fibers and their central synapses (Herrero et al., 2000), changes in temporal summation may reflect synaptic plasticity in the dorsal horn potentially underlying persistent pain states (**Figure 3**; (Herrero, et al., 2000; Sandkuhler, 2009; 2013; Woolf, 1996).

Enhancement of temporal summation

Temporal summation is characterized by a progressive increase in perceived pain intensity after repeated noxious stimuli. It is frequently assessed by dividing the mean pain intensity rating of 10 identical stimuli repeated once per second by that of a single stimulus (den Bandt, et al., 2019; Rolke et al., 2006), which may be mechanical, electrical or thermal (McPhee et al., 2020). As a reliable correlate of the central pathways receiving input from C fibers, temporal summation may be measured to determine the involvement of central hyperexcitability (Arendt-Nielsen et al., 2018; Herrero, et al., 2000; Treede, 2016; Vardeh, et al., 2016). Compared to healthy controls, temporal summation is augmented in lumbar segments of CPLBP patients (den Bandt, et al., 2019; McPhee, et al., 2020; Neziri, et al., 2012), and may predict its prognosis (Marcuzzi et al., 2018; Overstreet et al., 2021; Petersen et al., 2020). The enhancement of temporal summation fades away when clinical pain intensity diminishes (McPhee and Graven-Nielsen, 2019). Therefore, the peripheral barrage of C fiber afferent activity could partially drive these changes.

Temporal summation can be used reliably to identify a pronociceptive phenotype (McPhee, et al., 2020). Beyond the temporal propagation of pain hyperexcitability, a spatial dispersion of pain during and after repetitive noxious stimulation was also described (Woolf, 1983). While temporal summation reflects dynamic, homosynaptic (localized) changes, spreading hyperalgesia might be indicative of more static, possibly heterosynaptic mechanisms (Hoegh, 2023).

Secondary hyperalgesia and allodynia

After provoking localized injuries to the skin of decerebrate rats, Woolf observed that previously subthreshold mechanical stimulation elicited nociceptive flexion reflexes (Woolf, 1983). The effect was not confined to the site of injury; instead, the receptive fields expanded, encompassing the contralateral limb. Spinal cord nociceptive hyperexcitability was found to underlie this process (Hardy, et al., 1950; Woolf, 1983). Increased sensitivity in tissues adjacent to

the site of injury characterizes secondary hyperalgesia. Subsequent experiments confirmed that this hyperexcitability represents a long-lasting enhancement in synaptic efficacy of dorsal horn neurons, sustained by plastic changes in synaptic structure (Latremoliere and Woolf, 2009). Long-term potentiation, a use-dependent plasticity that relies on the activation of presynaptic neurons (i.e, nociceptive afferents), was proposed as the underpinning mechanism (Ji et al., 2003; Sandkuhler, 2013). Postsynaptic responses enhanced beyond the duration and location of the nociceptive insult are thought to reflect heterosynaptic long-term potentiation involving C fibers and neighboring nonactivated synapses (Latremoliere and Woolf, 2009). Heterosynaptic long-term potentiation may also account for allodynia, which is elicited by mechanical stimuli, similarly to secondary hyperalgesia. The fundamental distinction is that allodynia represents pain evoked by previously innocuous cutaneous stimuli (i.e., dynamic light brushing; (Koltzenburg, et al., 1992; Sandkuhler, 2009). This effect is believed to be mediated by large myelinated (Aβ) fibers through activation of low-threshold mechanoreceptors. Under normal circumstances, Aβ fibers inhibit projection neurons via dorsal horn interneurons; thus, plastic changes leading to disinhibition of spinal nociception, including long-term potentiation, may underlie allodynia (Coull et al., 2003; Sandkuhler, 2009; Todd A.J., 2010). Accordingly, human surrogate models of long-term potentiation based on high-frequency stimulation evoked long-lasting increases in pain, secondary hyperalgesia and allodynia (Klein et al., 2004).

Central sensitization (CS) is the ensemble of neurophysiological plasticity-mediated processes explaining spatial, temporal, and threshold changes observed in the laboratory and clinical settings (Latremoliere and Woolf, 2009). Such mechanisms, presumed to occur in the spinal cord, cannot be directly measured in humans. Thus, we rely on perceptual correlates to serve as proxy measures (see **Figure 3)**. Characterizing secondary hyperalgesia in the clinical setting is particularly challenging for CPLBP (Nijs et al., 2010). The site of injury is unknown and the extension of the area of secondary hyperalgesia is, at best, speculative. The best attempt to identify this phenomenon relies on the assessment of spreading hyperalgesia outside of the primary symptomatic area, though experts lack consensus (Shraim et al., 2022). Abiding by its classic definition and presupposed mechanisms, secondary hyperalgesia spreads segmentally or heterosegmentally to adjacent tissues, not remote widespread locations (Hansson, 2014). Thus, reduced PPTs in adjacent tissues innervated by the same or up to two neighboring segments may indicate secondary hyperalgesia (Correa J.B., et al., 2015; Hansson, 2014), while spreading to

remote, non-adjacent tissues from the low back may reflect widespread hyperalgesia (Nijs, et al., 2010). Despite being considered another hallmark manifestation of CS (Treede, 2016; Vardeh, et al., 2016), allodynia was also not readily assessed in patients with CLBP, except for neuropathic cases (Baron, et al., 2016). Although allodynia elicited by dynamic brushing was present in most patients with neuropathic CLBP, it was largely absent (≤ 10%) in patients with axial CPLBP (Defrin et al., 2014). Hence, the validity of allodynia and secondary hyperalgesia as markers of CS in CPLBP is uncertain.

There is a paucity of research dedicated to investigating both secondary hyperalgesia and allodynia in CPLBP, partly due to challenges identifying the area of primary nociception. Using experimental injury models as CS surrogates can help circumvent this limitation. Topical or intradermal/intramuscular capsaicin, thermal heat injury and electrical stimuli, are reliable surrogate models used to induce secondary mechanical hyperalgesia, less consistently allodynia (Quesada et al., 2021). Although widely tested in healthy and patient cohorts, these models were seldom applied in CPLBP. Neuroimmune interactions offer an alternative promising avenue for examining plastic changes thought to underlie allodynia and hyperalgesia, as described below.

Spinal cord neuroinflammation

Animal studies revealed that inflammatory cytokines are involved in pathological pain transmission, not only peripherally, but also within the spinal cord. Cytokines can be released centrally as a response to signals from peripheral tissues and also originate from activated glial cells (Ji, et al., 2003). Experimentally-evoked allodynia and hyperalgesia may be dependent on the intrathecal expression or administration of inflammatory cytokines and activated microglia (Goncalves Dos Santos, et al., 2019; Laughlin et al., 2000; Tsuda et al., 2003). This led to the postulation of a potential role for glial cells in chronic pain states (Ji et al., 2013; Watkins et al., 2001). Reciprocal crosstalk between nociceptors and immune cells is essential for these processes. Firing of (predominantly) C fiber nociceptors after peripheral injury leads to activation of microglia and astrocyte in the spinal cord (Guo et al., 2007; Ji, et al., 2013). Activated glial cells then release TNF-α and IL-6, which contribute to long-term potentiation in the dorsal horn and CS (Guo, et al., 2007; Ji et al., 2018; Kawasaki et al., 2008).

Exploring these mechanisms in humans has limitations. Correlations between serum and cerebrospinal fluid levels of the proinflammatory cytokine interleukin-8 were found in patients

with lumbar disc herniation and degeneration (Palada et al., 2019). Concentrations were higher than for control participants, showing positive associations with pain intensity and PPTs. Another method to corroborate the presence of neuroinflammation consists in the detection of an inflammatory marker, the translocator protein, using positron emission tomography (PET) integrated with MRI (Albrecht et al., 2018). Elevated translocator protein levels were measured in the lumbar spinal cord and nerve roots of patients with radicular CLBP, which was interpreted as evidence for glial activation. Despite concerns questioning the specificity of the translocator protein (Grace, 2019), neuroinflammation deserves further investigation as a potential mechanism of CPLBP (see **Figure 3)**.

Prolonged, repeated, or intense nociceptor discharge can induce neuroinflammation and CS, which manifests as amplification of temporal summation, pain sensitivity and potentially allodynia in the site of injury or adjacent areas. These changes arise almost immediately and are generally short-lived in ALBP (Curatolo, 2023; Treede, 2016). In CPLBP, however, these effects persist and may spread remotely (Graven-Nielsen, 2022; McPhee, et al., 2020). It is plausible that remote hyperalgesia emerges not from changes in the spinal cord, but also in the control of its cytoarchitectural components by descending regulatory projections. Profound plasticity changes in these connections outlined in the next section may explain widespread alterations in pain sensitivity seen in CPLBP.

Supraspinal neurophysiological mechanisms

Spinal nociception is under constant inhibitory and facilitatory influence from brainstem centers. Through connections with the rostral ventromedial medulla, the periaqueductal gray exerts a top-down modulation of primary afferents and projection neurons, both directly and through dorsal horn interneurons (Millan, 2002). These pathways are utilized by higher brain centers to fine-tune nociceptive input and reflex nocifensive responses. Under most physiological conditions, spinal nociception is downregulated. Descending inhibition may be engaged to prioritize performance or escape during dangerous or stressful situations, but nociception can also be enhanced to avoid exposure to harmful environmental stimuli (Millan, 2002). However, CPLBP is not necessarily accompanied by a balanced and adaptive regulation of descending inhibition and facilitation.

Plasticity in the descending modulatory system

The dynamic equilibrium between descending inhibition and facilitation reflects the balance in activation between two subpopulations of cells in the rostral ventromedial medulla (Heinricher and Fields, 2013). Two distinct groups of rostral ventromedial medulla cells exhibit increased (ON-cells) or decreased discharges (OFF-cells) time-locked with nocifensive behavior in rats (Fields et al., 1983). ON-cells enhance nociceptive responsiveness through facilitation of spinal nociceptive reflexes and induction of hyperalgesia (Pertovaara et al., 1996; Sandkuhler, 2009). Increased activity in OFF-cells precedes inhibition of the same reflexes (Fields, et al., 1983; Heinricher et al., 1994). Evaluating these pathways in humans is not feasible directly. However, diffuse, widespread pain and hyperalgesia may reflect alterations in the balance between descending inhibition and facilitation (Arendt-Nielsen, et al., 2018; Treede, 2016). Alternatively, paradigms such as conditioned pain modulation (CPM) may inform about the integrity of these pathways (see **Figure 3** (McPhee, et al., 2020).

Diffuse noxious stimuli from various body parts result in inhibition of dorsal horn neurons that respond to both noxious and innocuous stimuli, named wide-dynamic range neurons (Le Bars et al., 1979a). The suppression of neural responses from convergent dorsal horn units to competing stimuli led to the formulation of diffuse noxious inhibitory controls, a mechanism that involves the medullary subnucleus reticularis dorsalis (Le Bars et al., 1979b; Villanueva et al., 1996). This hub receives spinal nociceptive input and descends back to the cord to inhibit dorsal horn cells, creating a surround inhibition to enhance the contrast between the noxious stimulus zone and adjacent areas (Heinricher and Fields, 2013). This mechanism is likely to be an important contributor to CPM (Piche, 2023), the term proposed to encompass psychophysical paradigms where a conditioning stimulus impacts a test stimulus (Yarnitsky et al., 2010). Patients with CPLBP demonstrate less efficient CPM in the low back (Christensen et al., 2020; Correa J.B., et al., 2015; den Bandt, et al., 2019; McPhee, et al., 2020; Mlekusch et al., 2016; Neelapala et al., 2020; O'Neill et al., 2014), associated with widespread hyperalgesia (den Bandt, et al., 2022; Gerhardt et al., 2017). Owing to its capacity to predict outcomes, dysfunctional CPM in the site of pain was proposed as an indicator of altered descending pain inhibition (Georgopoulos et al., 2019; Schuttert et al., 2021). Nevertheless, CPM responses are short-lived and may be insufficient to account for long-term effects observed in the clinic (Treede, 2016). This, along with methodological inconsistencies, could account for mixed results on the efficiency of CPM in CPLBP (Neelapala, et al., 2020), yet

a small link between CPM impairment and factors like pain chronicity, duration, and severity still prevails (McPhee, et al., 2020).

Impaired CPM responses and widespread hyperalgesia in chronic pain may reflect a global imbalance between descending inhibition and facilitation conveyed by multiple pathways (Arendt-Nielsen, et al., 2018). The mechanisms of CPM (or its animal correlate) partially rely on the same tracts (Bannister and Hughes, 2023) and the same neurotransmitters (norepinephrine and serotonin) involved in the descending modulatory system (Nemoto et al., 2022; Sirucek et al., 2023). Unfortunately, inconsistent use of reliable experimental protocols restricts the interpretation of these results (Kennedy et al., 2016; Piche, 2023). Further and more rigorous investigations are required before inferences can be made about CPM as a biomarker for CPLBP. As CPM receives afferent control from multiple cortical and subcortical areas (Bannister and Hughes, 2023), data concerning the supraspinal control of descending tracts are presented in the ensuing segment.

Structural and functional brain changes

Descending regulatory systems are actively engaged during clinical pain, as well as during exogenous and endogenous analgesia (Heinricher and Fields, 2013). The periaqueductal gray and rostral ventromedial medulla axis receives afferent impulses from multiple brain sources, such as the amygdala, the hypothalamus and the anterior cingulate cortex (Ossipov, et al., 2010), to exert inhibitory or facilitatory influences over spinal nociception during different physiological and psychological processes. Cognition and emotion influence pain perception through these mechanisms, driving appropriate behavior in the face of potential or actual danger. For instance, when attention is directed towards a painful stimulus, the perceived intensity increases, while diverting attention has opposite effects, engaging connections between forebrain areas and the periaqueductal gray–rostral ventromedial medulla axis (Bushnell, et al., 2013). Changes in these circuits may provide valuable insights for understanding widespread hyperalgesia and comorbid symptoms in CPLBP.

Experimental functional MRI (fMRI) paradigms revealed that CPLBP and fibromyalgia patients displayed increased activation of pain-discriminative brain regions during painful stimuli processing compared to controls (Giesecke, et al., 2004). CPLBP patients display gray matter volume atrophy, particularly in the prefrontal areas (Apkarian et al., 2004; Ng et al., 2018; Yuan et al., 2017), which was predicted by negative affect dimensions. A shift in brain processing from

sensory-discriminative areas involved in acute pain processing (i.e., somatosensory areas) towards sustained activity in the medial prefrontal cortex was observed during spontaneous LBP in patients (Baliki et al., 2006). Overall, in CPLBP, somatosensory areas are disengaged from coding pain intensity, while emotional areas become more active (Apkarian, et al., 2005; Hashmi et al., 2013). Functional connectivity changes from pain- to emotion-related networks involving the medial prefrontal cortex, nucleus accumbens (Baliki et al., 2012) and amygdala (Hashmi, et al., 2013) may predict the chronification of LBP, suggesting that CPLBP may be maintained by affective, motivational and cognitive brain circuits (Ng, et al., 2018; Yuan, et al., 2017). Although the directionality of such activation and connectivity changes remains elusive, they may be reversible plasticity processes induced by chronic nociceptive input (Henn et al., 2023; May A., 2008).

Similar shifts in neuronal oscillatory activity were observed in healthy subjects undergoing tonic experimental pain and patients with CLBP (May E.S. et al., 2019; Nickel et al., 2017). Stimulus intensity correlated with decreased neuronal oscillations in sensorimotor areas, while clinical and experimental pain were mainly encoded by prefrontal gamma oscillations (May E.S., et al., 2019; Nickel, et al., 2017). Higher prefrontal cortex synchrony and reorganization at gamma frequencies were used to distinguish chronic pain patients through a machine learning approach (Ta Dinh et al., 2019). An animal study revealed a link between increased cortical gamma power and downstream activation of the anterior cingulate cortex, the medial prefrontal cortex and the periaqueductal gray-rostral ventromedial medulla, thus, of descending modulation (Tan et al., 2019). Yet, the role of any specific spectral range of activity as a biomarker for chronic pain is still speculative (Zebhauser et al., 2022). There is a lack of compelling data to determine whether oscillatory patterns are mechanisms or consequences of pain (Kim J.A. and Davis, 2021). More than chronic pain states, gamma band oscillations may reflect the interaction between transient pain measures and the salience system in experimental paradigms. Improving our understanding of the interactions between brain regions and interneuron networks underpinning brain oscillations may help explain their significance in the aetiology of plastic changes seen during chronic pain (Kim J.A. and Davis, 2021), including a potential role for glial cells (Lee H.S. et al., 2014).

Brain neuroinflammation

Preclinical evidence from animal studies suggests that glial activation in the brain regulates neuroinflammation and pain after a peripheral injury (Goncalves Dos Santos, et al., 2019; Ji, et al.,

2018). Glial release of cytokines may account for the association between CPLBP and comorbid mood disorders. In CLBP patients, translocator protein expression was observed in the thalamus, as well as the low back and leg areas of the primary somatosensory area (Loggia et al., 2015). The degree of glial activation correlated with circulating levels of proinflammatory cytokines (IL-1β and IL-6), confirming a link between immunological responses in the blood and the brain (Kanegawa et al., 2016). Thalamic neuroinflammation emerged as a reliable marker discriminating patients with CLBP (Torrado-Carvajal et al., 2021). The relationship between primary somatosensory area neuroinflammation and increased connectivity with the thalamus appears to be influenced by the degree of CLBP "widespreadness" or the dispersion of symptoms (Alshelh et al., 2022). Interestingly, comorbid depressive symptoms in patients with CLBP are associated with translocator protein signal in limbic regions, such as the anterior cingulate cortex (Albrecht et al., 2021). For a summary of supraspinal mechanisms and correlates, see **Figure 3**

Brain neuroinflammation opens a promising avenue for future research not only in CPLBP, but also for the investigation of its multimorbidities and the factors predisposing or contributing to the development of poor health patterns. Some biomarkers may reflect the spread of pain and hyperalgesia in a subset of patients with CPLBP, which constitutes a hallmark of other poorly understood conditions such as fibromyalgia. For this condition, the extent to which pain spreads (i.e., widespreadness), particularly to the spine and shoulders, correlated with pain catastrophizing and cortical attention networks engagement (Ellingsen et al., 2021). These findings may help connect biological changes to behaviors linked to CPLBP discussed in the following section.

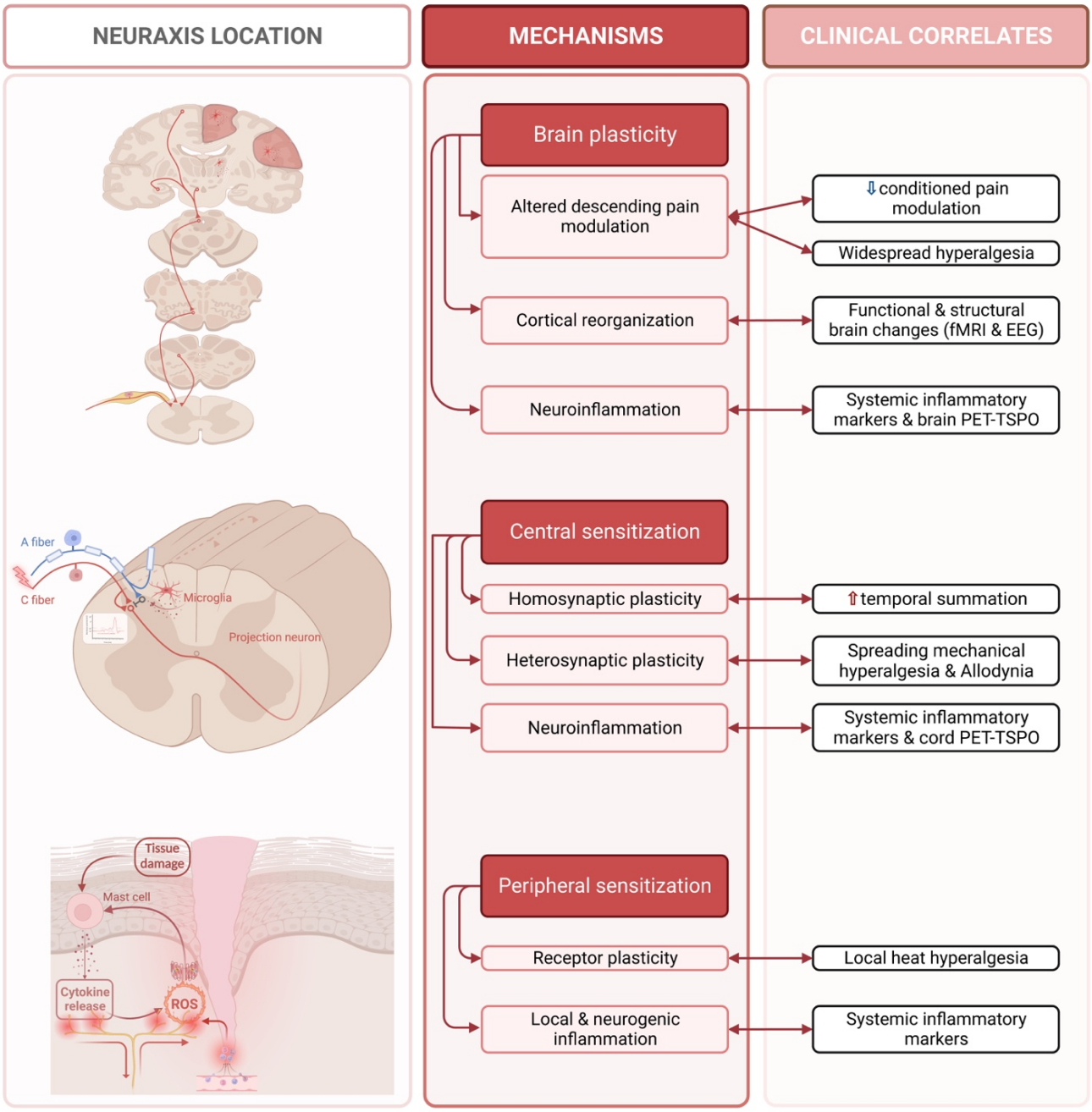

Figure 3 Neurophysiological mechanisms of chronic primary low back pain

Summary of the main neurophysiological mechanisms of chronic primary low back pain herein reviewed. The first column from the left provides a graphic illustration of the mechanisms, the middle column lists the presupposed mechanisms and processes involved, and the right column presents the correlates available to assess mechanisms in a clinical setting. *ROS: Reactive oxygen species*

Psychobehavioral mechanisms

Pain-driven behaviors and fear of pain contribute to the perpetuation of CPLBP (Tagliaferri, et al., 2022; Vlaeyen and Linton, 2000). Fear-avoidance behavior is considered a key mechanism, while catastrophizing, fear of pain and of movement (kinesiophobia) drive such behavior (Edwards, et al., 2016). Pain catastrophizing is traditionally defined as an exaggerated set of negative cognitions related to pain, encompassing rumination, magnification, and helplessness (Sullivan et al., 2001). Catastrophizers tend to amplify the threat value of pain, which leads to pain-related worry, generates hypervigilance and alters behavior (Petrini and Arendt-Nielsen, 2020). These cognitions are strongly associated with pain intensity, disability and altered nociceptive processing in CPLBP (Quartana et al., 2009).

From a behavioral perspective, pain is a motivational state prompting defensive and recuperative behavior to protect and facilitate recovery from injury (Vlaeyen, et al., 2018). Upon repeated exposure to pain, an opportunity for learning presents. Habituation and sensitization are two possible outcomes; however, due to the threatening nature of pain, habituation is rare and sensitization a more frequent output (Baliki and Apkarian, 2015). Pavlovian mechanisms help us learn predict pain (unconditioned stimulus) using non-nociceptive cues (conditioned stimuli; (Vlaeyen and Linton, 2012). Conditioned stimuli are neutral, non-pain cues, such as movements, memories, verbal (e.g., LBP messages) or visual cues (e.g., others' pain), associated with painful events. Exposure to neutral cues elicits predictions that are balanced against outcomes, either reinforcing or updating beliefs and behaviors (Vlaeyen and Crombez, 2020). The nonspecific nature of CPLBP complicates this process, as prediction and outcome do not intuitively match (e.g., poor correspondence between imaging findings and symptoms). Negative affect and pain cognitions such as catastrophizing further reinforce erroneous predictions (Baliki and Apkarian, 2015; Vlaeyen and Crombez, 2020). As a result, neutral stimuli are gradually perceived as salient and threatening, motivating pain behavior and contributing to disproportionate pain responses such as hyperalgesia, allodynia or aberrant cortical pain processing (Madden et al., 2016; Meints et al., 2019; Pressman et al., 2017; Taub et al., 2017; Vlaeyen, et al., 2018). In short, while adapting to environmental challenges through conditioned learning is essential, repeated exposure to pain, pain-conditioned stimuli, and catastrophic cognitions may reinforce rigid, maladaptive behavior that contribute to CPLBP (Quartana, et al., 2009).

While avoidance is a necessary behavioral output for survival, an excess may interfere with a person's work and social life (Crombez, et al., 2012). Baliki and Apkarian (2015) postulated that nociception engages motivational circuits to either drive coping behavior or enhance the pain gain. In response to or in anticipation of pain, we constantly make trade-offs, selecting specific behaviors and weighing in the influence of competing goals. The likelihood of choosing one over another depends on limbic influences (Baliki, et al., 2012; Vachon-Presseau et al., 2016) and the relative valence given to pain and alternative behaviors (Vlaeyen and Crombez, 2020). Reward learning was shown to be disrupted in CPLBP (Kim M. et al., 2020; Loffler et al., 2022), prioritizing pain-related behavior at the expense of other activities (Crombez, et al., 2012). Over time, excessive avoidance inevitably leads to disability (Meulders, 2019), deconditioning, guarding and stress, with potential consequences for multiple body systems (Sudhaus et al., 2009; Verbunt et al., 2003).

Some argue that pain can take place without peripheral nociception, but there is no doubt that pain is not possible without the cerebral, cognitive, and psychological dimensions. Recently, there has been a growing interest in phenotyping CPLBP and chronic pain based on contributing pain mechanisms, an ambitious task reflecting the multidimensional quality of CPLBP and its complex aetiology.

Mechanistic descriptors for chronic primary low back pain

It was proposed that classifying pain according to the predominance of peripheral *vs*. central mechanisms may be more accurate than the classic temporal classification (Loeser, 2022). This is not a novel concept; Woolf and colleagues refuted the validity of acute *vs*. chronic, and anatomical-based classifications in favor of a mechanistic system (Woolf et al., 1998). Pain was categorized as transient (or nociceptive) tissue injury pain, or nervous system injury pain. A decade later, a classification system was developed to translate this concept to clinical practice (Smart et al., 2008). By combining clinical signs and symptoms, the implication of pain mechanisms was characterized with high levels of reliability, (Smart et al., 2011). Patients with LBP were stratified to one of three clusters: nociceptive, neuropathic and CS pain (Smart et al., 2012). Grounded on this work, Nijs and colleagues (Nijs et al., 2015) offered guidance to discriminate LBP patients based on the involved mechanisms. Their guidelines differentiated between specific (nociceptive and neuropathic) and nonspecific LBP, the latter fitting more with CS mechanisms (Nijs, et al., 2015). This was problematic, as neuropathic pain displays signs compatible with CS (Latremoliere

and Woolf, 2009), and not all CPLBP relies on these mechanisms. Various methods have attributed approximately 25% of CPLBP cases to predominant CS mechanisms (Nim et al., 2021b; Roussel et al., 2013; Smart, et al., 2012). Thus, it is plausible that different mechanisms contribute to CPLBP to varying degrees for individual patients (Freynhagen and Baron, 2009). The distinction between these mechanisms and pain descriptors (Table 2.1) is clarified in the coming section.

Mechanistic descriptors: nociceptive, neuropathic and nociplastic pain

Nociceptive, inflammatory and neuropathic are the most common pathological descriptors used to define pain (Vardeh, et al., 2016). Nociceptive pain is that arising from the activation of peripheral nociceptors by damaged tissue, inflammatory pain is also nociceptive, with evidence of inflammation, and neuropathic pain emanates from damage to the somatosensory system (Kosek et al., 2016; Vardeh, et al., 2016). Pain occurring in the absence of a detectable lesion required a third mechanistic descriptor (Table 2.1). The term *nociplastic pain* was proposed to define chronic pain with clinical and psychophysical manifestations indicative of altered nociceptive processing (Kosek, et al., 2016; Nicholas, et al., 2019; Vardeh, et al., 2016). This descriptor required the exclusion of the other two, consistent with diagnostic criteria for chronic primary pain. The implicit reference to nociceptive plasticity makes it tempting to equate nociplastic pain with CS. However, whereas nociplastic is a clinical descriptor, CS is a neurophysiological mechanism (Kosek, et al., 2016).

Clinical features of the mechanistic descriptors

A Delphi panel agreed on a set of unique features to discriminate the relative contribution of each descriptor to musculoskeletal pain (Table 2.1; (Shraim, et al., 2022)). A majority of experts retained the following features for nociceptive pain: responsiveness to nonsteroidal anti-inflammatory drugs (NSAIDs), signs of inflammation, and recovery consistent with the expected healing time for acute tissue injuries. For neuropathic pain, the distinguishing features included radicular or peripheral nerve distribution of pain and sensory deficits, with evidence of nervous system injury. For nociplastic pain, less consensus was achieved for diffuse or poorly localized pain, widespread hypersensitivity, and other somatic symptoms (Shraim, et al., 2022). Nociplastic pain was also described as lasting more than three months, unexplained by nociceptive or neuropathic mechanisms, and regional rather than discretely localized (Kosek et al., 2021). The region of pain exhibits hyperalgesia, allodynia, or after-sensations, and may be accompanied by

hypersensitivity to non-somatosensory senses, fatigue, or sleep and cognitive disturbances (Table 2.1). Although these criteria are somewhat reminiscent of the ones proposed to detect CS (Nijs, et al., 2015), CS is not the sole nor the predominant mechanism for all patients with nociplastic pain (Nijs et al., 2021b). Similarly, although CPLBP has the best odds of being classified as nociplastic with regional, ill-defined localization, and hyperalgesia (Fitzcharles, et al., 2022), it is better understood by considering the contribution of multiple mechanistic descriptors (Fitzcharles et al., 2021).

Table 2.1 Characteristics of the different mechanistic descriptors for chronic low back pain

	Mechanistic descriptors		
Phenotype characteristics	**Nociceptive pain**	**Neuropathic pain**	**Nociplastic pain**
Pathological tissue	Peripheral spine tissue	Nervous system	Altered nociception
Low back pain diagnosis	Specific low back pain	Radicular syndrome	Chronic primary low back pain
Diagnostic methods	Imaging	Imaging, metabolomic profile	Quantitative sensory testing, pain & psychological questionnaires
Clinical features	Discrete localization Responds to NSAIDs Signs of inflammation Recovery ≤ 3 months	Dermatome/peripheral nerve localization Sensory deficits in the same distribution History of nervous system injury	Diffuse localization Hyperalgesia, allodynia, after-sensations Widespread hypersensitivity, including to other senses Fatigue, sleep, cognition

NSAIDs = Nonsteroidal anti-inflammatory drugs

Clinical identification of the predominant mechanistic descriptor

To transfer these findings to the clinical level, the most common methods used to discriminate between the three different descriptors were critically examined (Shraim et al., 2021). Five groups of clinical methods to triage between descriptors were discerned: clinical examination, QST, imaging, laboratory testing, and pain questionnaires. Complementing the clinical examination with psychological questionnaires (i.e., pain catastrophizing scale), local and remote PPTs, CPM, and temporal summation were encouraged (Table 2.1). Imaging may assist in ruling in or out specific sources of nociceptive and neuropathic pain, whereas urine metabolomic profile may identify neuropathic cases. Lastly, pain questionnaires (i.e., CS Inventory) have potential to discriminate nociplastic pain (Shraim, et al., 2021). Most methods lack robust reliability data and should therefore be interpreted with caution.

Nociplastic pain and CS, while distinct, are closely interrelated concepts with potential implications for CPLBP. Nociplastic pain is characterized by pain amplification or disinhibition (Fitzcharles, et al., 2021). Accordingly, features of CS contribute significantly to CPLBP, at least for a subset of patients (Nijs et al., 2021a), including enhanced pain sensitivity, psychological profiles, plastic brain changes, and neuroinflammation. However, as mechanisms at multiple levels are involved, relying solely on CS as an explanatory factor may be insufficient. A pattern of expanding pain and hyperalgesia in nociplastic pain could initially align with secondary hyperalgesia and CS, but a generalized gain in nociceptive function points to the involvement of descending modulatory systems (Fitzcharles, et al., 2021). Glial activation may precede these effects and account for overlapping somatic symptoms and comorbidities. Consequently, in the clinical setting, an integrated approach addressing peripheral (i.e., intervertebral discs), neurophysiological (PPTs) and psychosocial components (catastrophizing, fear, depression) may increase the odds of effectively targeting key processes contributing to CPLBP (Tagliaferri, et al., 2022).

Although still controversial, phenotyping patients according to their pain mechanisms seems to provide a breath of fresh air to CPLBP research, allowing progress in understanding, not only the aetiology, but most importantly, the most suitable treatment modalities for each patient. The next chapter delves into the current state of the literature concerning available treatment options for CPLBP, narrowing down to the use of chiropractic SMT.

Chapter 3 – Evidence-based management of chronic primary low back pain

Treatment options for chronic primary low back pain

The multifaceted nature, risk factors, and mechanisms of CPLBP have engendered a similar diversity of treatment options ranging from traditional methods like manual therapies, acupuncture, and herbal remedies, to cutting-edge surgical techniques. This does not mean that all interventions are suitable for every patient or circumstance, necessitating a tailored approach. Although current data do not allow for this, it is hoped that the identification of mechanisms contributing to each case will enable the design of customized interventions (Nijs, et al., 2021a). Meanwhile, clinical practice guidelines make different recommendations based on temporal criteria for ALBP and CLBP. While acute cases are generally treated as a symptom with a focus on addressing the source of nociception, CLBP should be addressed as a multidimensional disease with a biopsychosocial approach, preferably from a multidisciplinary team. This chapter presents the range of treatments available CPLBP, followed by the current recommendations suggested by clinical guidelines, and lastly, introduces the potential role of SMT.

Historical perspective

The way CPLBP is managed has not undergone significant changes over the past decades. There are, however, fundamental perspective changes that slowly permeate into most healthcare strata. The most notable evolution is the shift in emphasis from passive to active care, which was foreshadowed almost 40 years ago (Deyo and Weinstein, 2001; Waddell G., 1987). Historically, LBP management relied on passive treatment strategies that excluded patient involvement and participation and encouraged passive recovery (Deyo and Weinstein, 2001; Waddell G., 1987). Stemming from a biomedical perspective of LBP as a biomechanical injury of a vulnerable spine (Kori et al., 1990), this paradigm may lead to ineffective and potentially harmful practices, inducing maladaptive thoughts and fear-avoidance (Crombez, et al., 1999). Physical exercise and movement-based therapies were generally discouraged in favor of passive modalities such as bed rest, electrical currents, drugs, injections and, frequently, surgery (Abenhaim et al., 2000; Waddell G., 1987). This approach can be nefarious for CPLBP, worsening the natural history, delaying recovery, and resulting in iatrogenic complications and enormous costs. Passive and harmful

approaches have since transitioned to advocating for a prompt return to activity in all cases. This change is illustrative of the evolving nature of clinical recommendations for back pain management and holds the potential for further advancements (Foster et al., 2018). The following section presents the available evidence on the most prevalent interventions for CPLBP management.

Current approaches

There is a large diversity of treatments for CPLBP, ranging from invasive surgical procedures to non-invasive pharmacological and nonpharmacological options. To better appreciate the multiple dimensions, interventions are presented hereafter from most to less invasive.

Surgical interventions

Multiple surgical procedures are available for the treatment of specific causes of LBP (Hooten and Cohen, 2015). However, the surgical approach to nonspecific and CPLBP seems less justified and remains controversial (Mannion et al., 2016). Recent data specifically discourage the use of surgical interventions for CPLBP (Todd N.V., 2017; Wang X. et al., 2015; Xu et al., 2021) and segment fusion for axial LBP of any cause (Harris et al., 2018). Less invasive procedures, such as neurostimulation, radiofrequency denervation, and intrathecal analgesic pumps have not been rigorously investigated (Maher, et al., 2017; Provenzano et al., 2021). Invasive procedures may have a role in LBP, though only for confirmed specific causes such as herniated discs (Foster, et al., 2018; Vlaeyen, et al., 2018) or lumbar spine stenosis (Zaina et al., 2016), particularly for patients with progressive neurological disturbances (Deyo and Mirza, 2016). Cauda equina syndrome constitutes the only exception for which the consensus warrants immediate surgical referral (Maher, et al., 2017; Vlaeyen, et al., 2018). Despite this, invasive interventions are overutilized (Foster, et al., 2018) and for most cases, less invasive pharmacological interventions are preferred.

Pharmacological interventions

Pharmacotherapy is widely used to alleviate LBP, including non-prescription analgesia, which is likely underestimated (Chou et al., 2017b). While oral administration is more common, injections into facet, disc, sacroiliac joints, intramuscular, or epidural space are also possible (Hooten and Cohen, 2015). Epidural and facet joint corticosteroid injections may relieve radicular pain but are not indicated for CPLBP (Chou et al., 2015; Foster, et al., 2018; Maher, et al., 2017).

Insufficient data exist regarding the safety and effectiveness of sacroiliac joint or intramuscular injections (Hooten and Cohen, 2015; Koes et al., 2018). These findings challenge the idea that the pain generator can be identified and targeted (Maher, et al., 2017). Consequently, systemic drugs may have better chances of benefiting patients.

Due to their known potent analgesic effects, popular belief has it that opioids must be effective for LBP resistant to other approaches. Contrarily, evidence does not support their effectiveness in providing more than limited relief for CLBP (Chou, et al., 2017b). Trials showing a benefit had conflicts of interest and suboptimal reporting of complications (Deyo et al., 2015; Tucker et al., 2020). Short- and long-term side effects, including severe complications with associated mortality risk (Deyo, et al., 2015; Foster, et al., 2018), limit their tolerance. Balancing the small benefits against the risks, opioids should not be a routine option for CPLBP. Nonopioid pharmacological options include over-the-counter medicines. Paracetamol, once a first choice, is now considered ineffective (Saragiotto et al., 2016). NSAIDs showed small to moderate benefits for CLBP (Chou, et al., 2017b), but caution is advised for patients with gastrointestinal, renal, or cardiac comorbidities, for whom toxicity represents a potential hazard (Foster, et al., 2018). Antidepressants may be beneficial for CPLBP (Chou, et al., 2017b; Ferreira G.E. et al., 2021), although not superior to placebo (Cashin et al., 2023). There is no evidence that muscle relaxants or anticonvulsants offer any benefit for CPLBP (Cashin et al., 2021; Chou, et al., 2017b; Enke et al., 2018), while emerging therapies like cytokine inhibitors and cannabinoids are still in early stages of investigation (Giossi et al., 2022; Hooten and Cohen, 2015; Koes, et al., 2018).

There is a cornucopia of drug choices available for patients and practitioners, though clearly not all have the same level of efficacy and safety. Recommendations in recent years for LBP have shifted towards safer nonpharmacological alternatives, with physical modalities such as exercise and manual therapies having the longest tradition.

Physical interventions

Physical modalities for LBP can include the application of heat or cold, electrical currents, light, needles, manual forces to manipulate tissues, and exercise (van Middelkoop et al., 2011). Active care (i.e., exercise) aims to improve function and prevent long-standing disability, being the only effective option for both treating and preventing CPLBP (Chiarotto and Koes, 2022; Foster, et al., 2018; Steffens et al., 2016). Numerous possible exercises for CPLBP exist, ranging from less

specific aerobic training to motor control exercise systems. Recent meta-analyses found Pilates to be superior to other forms of exercise for CPLBP (Hayden et al., 2021b; Owen et al., 2020). Specific exercises may be more effective for patient subgroups for which certain mechanisms are more prevalent (Luomajoki et al., 2018). However, interpreting the results of these findings is challenging due to small effect sizes and low study quality (Chou et al., 2017a; Hayden et al., 2021a). Exercise therapy not outperforming placebo (Miller C.T. et al., 2022) is a significant limitation shared by all physical modalities, including manual therapy.

Manual interventions are divided into those directed at articular tissues (i.e., SMT and mobilization) and those targeting soft tissues, (e.g., massage). These therapies have been used for millennia to treat multiple ailments, including LBP. Due to a low quantity and quality of studies, the effectiveness of massage is uncertain (Furlan et al., 2015). Mobilization and SMT carry similar effectiveness for CPLBP, comparable to that of exercise (Coulter et al., 2018; de Zoete et al., 2021; Rubinstein et al., 2019), as examined in Chapter 6. Low-quality evidence on acupuncture suggests only short-term pain relief and no superiority compared to sham (Chou et al., 2017a; Mu et al., 2020). Overall, passive modalities, such as traction, lumbar supports, TENS, diathermy, ultrasound, and taping, lack strong evidence for effectiveness and are generally discouraged by guidelines (Chou, et al., 2017a; Luz Junior et al., 2019; van Middelkoop, et al., 2011; Zaina, et al., 2023).

The extensive corpus of research on physical interventions unfortunately lacks quality to match its quantity. Movement-based interventions seem more effective, whether patients actively move or are passively moved. This suggests that movement is an important component in CPLBP factors, or alternatively, that movement results in neurophysiological, behavioral, or psychological effects that contribute to its relief. The latter is more plausible and may also explain the efficacy of psychological interventions, alone or combined with exercise, presented below.

Cognitive and behavioral interventions

Psychological interventions for LBP primarily address the fear and anxiety components of fear avoidance behavior, assisting patients in gradually resuming daily activities (Pincus et al., 2002; Vlaeyen, et al., 2018). Addressing maladaptive beliefs, negative affect, expectations, and psychological comorbidities may benefit numerous CPLBP patients (Gatchel and Rollings, 2008; Yang J. et al., 2022). Cognitive behavioral therapy (CBT), one of the earliest systematic approaches

(Pincus, et al., 2002), targets cognitions to modify behavior, helping patients cope with CPLBP and reduce disability. Despite the evidence, only a small percentage of patients are prescribed or have access to psychological services and CBT (Foster, et al., 2018). Integrating CBT with exercise therapy enhances accessibility and outcomes for function and fear avoidance compared to medical, physical, or psychological treatments alone (Ho et al., 2022).

The effectiveness of patient education is also bolstered when combined with exercise. The overwhelming consensus is that patient education should be a cornerstone of CPLBP treatment (Chiarotto and Koes, 2022; Foster, et al., 2018; Maher, et al., 2017). Of all psychological approaches, education yields the greatest improvements in fear avoidance and CPLBP disability (Ho, et al., 2022). However, its effects depend on the format (e.g., interactive *vs*. passive materials (Furlong et al., 2022)), duration (Engers et al., 2008) and content. Evidence-based education focuses on the multidimensional nature of the causes and benign prognosis of most LBP cases (Chiarotto and Koes, 2022), thereby reassuring patients (Traeger et al., 2015). A structured pain education approach reconceptualizing pain through a neurophysiological lens may provide benefits for pain, disability, kinesiophobia, and catastrophizing when added to exercise (Siddall et al., 2022; Wood and Hendrick, 2019). Ultimately, all education methods aim to facilitate the return to regular activities. Accordingly, educating on the importance of staying active is the most crucial piece of advice for patients with LBP, and the foundation for self-management (Chiarotto and Koes, 2022), yet, this is done in less than 25% of consultations (Foster, et al., 2018).

Lifestyle and self-management interventions

Effective patient education should extend beyond the clinical encounter, translating into behavioral changes and lifestyle modifications. Encouraging patients to stay active rather than in bed is paramount, as physical activity levels influence LBP prognosis (Alzahrani et al., 2019). Strong evidence supports that CPLBP patients benefit from tailored advice on physical activity or exercise types to foster active self-care (Liddle et al., 2007). A growing understanding of the psychosocial contributors to CPLBP has increasingly emphasized the importance of advocating for self-management strategies (Foster, et al., 2018; Vlaeyen, et al., 2018) focused on physical activity and stress reduction. The latter is mainly attained through meditation and mindfulness techniques (Anheyer et al., 2017; Chou, et al., 2017a; Ho, et al., 2022), which may have a role in ameliorating CPLBP outcomes and quality of life (Lin T.H. et al., 2022). However, self-management appears to

fall short of the high expectations, yielding only modest benefits compared to minimal intervention (Oliveira V.C. et al., 2012). In the long run, patient participation in their own care is expected to reinforce autonomy and self-efficacy (Kongsted et al., 2021), potentially contributing to change deeply rooted, erroneous beliefs that exacerbate the burden of CPLBP.

An abundance of data supports a conservative nonpharmacological approach for CPLBP (Foster, et al., 2018; Traeger et al., 2019b), independent of whether physical, cognitive-behavioral, or a combination of interventions is employed (O'Keeffe et al., 2016). However, to truly tackle the burden of CPLBP, treating patients and providing self-management tools may not suffice. Attitudes and beliefs about LBP are firmly established not only among patients, but also clinicians, educators, and decision-makers (Vlaeyen, et al., 2018). Societal-level interventions (Foster, et al., 2018) address pervasive misconceptions held by the general public, with the ultimate goal of raising awareness and modifying behavior. Mass media campaigns have this potential (Gross et al., 2010; Suman et al., 2021). However, sustainable changes require policy adjustments, promoting education on LBP, reducing inequalities in access to care, and targeting those with lower socioeconomic status (Foster, et al., 2018; Traeger et al., 2019a). These changes demand far longer time frames than those needed for implementation of clinical practice guidelines.

Current recommendations for chronic primary low back pain

Regrettably, Professor Waddell (1947-2017) did not have the opportunity to witness the significant changes in LBP management that he had envisioned and dedicated himself to (Waddell Gordon, 2004). Nevertheless, substantial advancements have been made through clinical practice guidelines, particularly over the last decade. Many criticized interventions and common procedures are no longer routinely implemented. Nonetheless, some practices leading to avoidable suffering persist. In this section, the concept of low-value care, and how current best practices align with Dr. Waddell's legacy, are discussed.

The prevalence and costs of low-value care

Prevalent biomedical perspectives may increase the likelihood of iatrogenesis and overmedicalization in LBP (Buchbinder et al., 2018). Numerous aspects of LBP management not only lack substantial evidence to justify their implementation but also contribute to escalating expenses and poorer outcomes. Exposure to guideline nonconcordant care at the onset of LBP was

found to increase the risk of transitioning to CLBP, proportionally to the number of such exposures (Stevans, et al., 2021). Adopting an alternative approach to managing LBP could yield considerable benefits at both individual and population levels (Buchbinder, et al., 2018). Nevertheless, a significant gap remains between this knowledge and its application in clinical practice, resulting in the persistence of low-value care (Hartvigsen et al., 2022).

The opioid crisis

Evidence indicates that opioids are not superior to other medications for CPLBP, and only slightly better than placebo comparators with added harms (Tucker, et al., 2020). The pervasiveness of low-value care for LBP is likely a significant contributor to the opioid crisis. In 2021, the number of annual deaths from drug overdose surpassed the threshold of 100,000 in the US, over 75% attributable to opioids (N.I.D.A., 2023). With over 7,000 opioid fatal overdoses in the same year, the data are lower for Canada, albeit not less alarming (Canada, 2022). This crisis is palpable in Europe (Helmerhorst et al., 2017), but its scale is not comparable to that of North America in terms of sheer numbers (Alho et al., 2020). Over 50% of long-term opioid users report LBP (Deyo, et al., 2015). Opioid doses prescribed for noncancer pain, especially if exceeding recommended thresholds, strongly correlate with the risk of fatal overdose and opioid-related mortality (Bohnert et al., 2011; Gomes et al., 2011). Consequently, prescribing long-acting opioids for chronic pain, including CPLBP, may significantly raise all-cause mortality risk (Ray et al., 2016). In the context of mitigating the opioid epidemic, enhancing the application of current evidence-based guidelines to CPLBP management assumes critical importance.

The evidence-practice gap

Clinical guidelines for managing LBP are not consistently implemented, resulting in frequent overuse of low-value care, and underuse of high-value care (Hartvigsen, et al., 2022). Despite recommendations for nonpharmacological first line care (Buchbinder, et al., 2020; Traeger, et al., 2019b), medication remains the most common treatment in primary care and emergency departments, while better alternatives like exercise and advice are underutilized (Foster, et al., 2018). Patients with LBP also prioritize visiting emergency departments over seeking primary care, which results in unnecessary imaging, opioid prescriptions, and surgeries. While wasting resources, this approach raises the risk of adverse outcomes. Factors such as availability, payment models, and patient uncertainty constrain access to best practices (Foster, et al., 2018). However, all

healthcare professions participate in low-value care provision (Hartvigsen, et al., 2022). Insufficient time and professional training likely contribute to the perpetuation of this ineffective approach. Meanwhile, the goal of achieving consensus on guideline recommendations appears increasingly attainable (Traeger, et al., 2019a).

Best practices for the management of chronic musculoskeletal pain

Overlap in risk factors, mechanisms, and prevalence is observed across musculoskeletal pain conditions, suggesting that common foundations are likely shared among them. Chronic primary musculoskeletal pain conditions (e.g., CPLBP) have complex aetiologies driven by biopsychosocial mechanisms rather than peripheral processes in specific tissues. Thus, it was proposed that optimal management of musculoskeletal pain, irrespective of body region, could embrace common principles (Caneiro et al., 2020), such as screening for biopsychosocial factors and comorbidities, using patient-centered communication and promoting self-management. Accordingly, high-quality guidelines for musculoskeletal pain from diverse origins consistently recommend similar approaches across conditions, prioritizing patient-centered, biopsychosocial, active care to facilitate return to activities (Lin I. et al., 2020). The most recent high-quality guidelines for CPLBP and their corresponding recommendations are presented hereafter.

Recommendations for chronic primary low back pain

The management of LBP may be kept simple and largely confined to primary care settings (Almeida et al., 2018). Patients should be triaged by clinical assessment to exclude specific causes, rather than relying on diagnostic imaging, unless red flags are strongly suspected. Thereafter, conservative, largely nonpharmacological interventions are advised for CPLBP (**Figure 4**). The sequencing and prioritization of these interventions remain subjects of contention. Guidelines explicitly endorse advice, education, and reassurance for CPLBP, generally alongside active care (Bussieres et al., 2018; George et al., 2021; Wong et al., 2017). Physical exercise is the first line of approach (Korownyk et al., 2022; Meroni et al., 2021). Manual therapy can also be considered a primary option (Bussieres, et al., 2018; Chou et al., 2018; George, et al., 2021; Qaseem et al., 2017; Wong, et al., 2017), or as part of a care package, complementing exercise (Bernstein et al., 2017; Korownyk, et al., 2022; Oliveira C.B. et al., 2018). Additionally, acupuncture, mindfulness, and oral medication are sparingly endorsed (Bernstein, et al., 2017; Korownyk, et al., 2022; Oliveira C.B., et al., 2018; Qaseem, et al., 2017).

Recent literature often stresses the need for a combination of multiple treatment modalities for CPLBP (Zaina, et al., 2023). Integrating physical and psychological modalities offers the advantage of aligning more closely with the biopsychosocial approach, potentially increasing the chances of success for CPLBP. Multimodal care is generally supported for complex cases, typically featuring exercise supplemented by SMT and CBT (Bernstein, et al., 2017; Korownyk, et al., 2022; Meroni, et al., 2021). A multidisciplinary biopsychosocial rehabilitation may be more effective than physical treatments alone (Kamper et al., 2014). However, the effectiveness of combined interventions is poorly understood, with small effects that must be weighed against costs, and is therefore suggested as a third step of the care pathway for a specific patient subset (**Figure 4**; (Almeida, et al., 2018; Corp et al., 2021; Traeger, et al., 2019a). Further research is needed to clarify the potential benefits of this amalgamation of therapies compared to individual modalities.

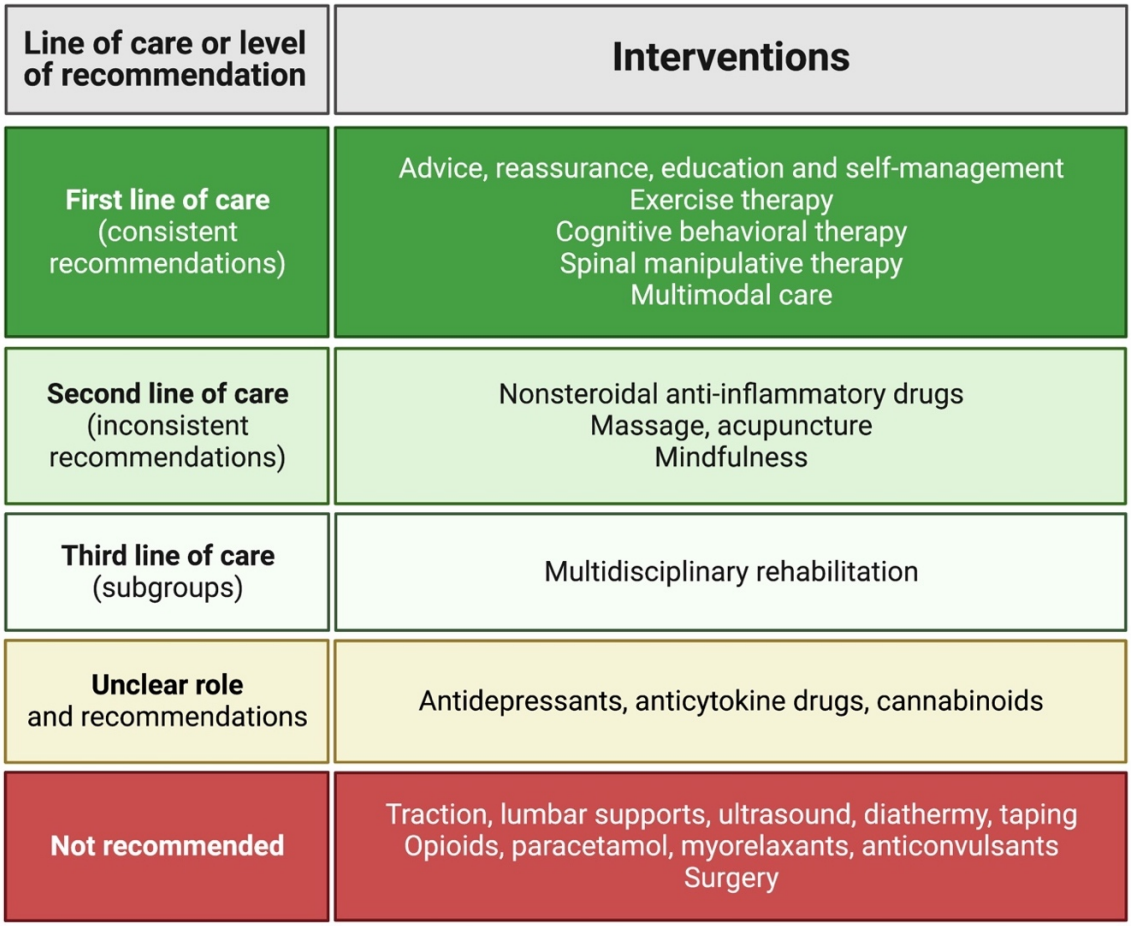

Figure 4 Treatment of chronic primary low back pain

Summary of the lines of care or levels of recommendation according to reviews and clinical practice guidelines for the management of chronic primary low back pain.

Adopting clinical practice guidelines offers a clear roadmap for achieving meaningful gains in patient outcomes and significant benefits for healthcare systems. However, effective implementation requires improved coordination among all agents to ensure guideline adherence. A primary spine practitioner, such as a physiatrist, physiotherapist, or chiropractor, could play a central role in this effort (Goertz et al., 2017). Although there is room for improvement (Bussieres, et al., 2016), care delivered by chiropractors for CPLBP is aligned with evidence-based recommendations (Coulter, et al., 2021; De la Ruelle et al., 2022), including for imaging prescription (Smith, et al., 2022b). Guideline-concordant chiropractic practice makes frequent use of SMT for CPLBP, for which the next section discusses specific indications.

Spinal manipulative therapy for chronic primary low back pain

The best evidence supports the use of physical interventions as the primary approach to treat CPLBP. Active care through physical exercise is the pillar for most patients. However, a subset of patients may respond similarly to passive physical care. Manual therapy may be a valid choice, either alone or in combination with other therapies. The main manual modality recommended is SMT, for which chiropractors are among the most proficient. In order to discriminate which patients may benefit the most from chiropractic SMT, it is important to understand the mechanisms that may be involved in its clinical effects.

Overview of the mechanisms

Original theories by DD Palmer posited that SMT acts by removing nerve pressure caused by vertebral misalignment (Palmer D.D., 1910). These tenets evolved to understand SMT as a means to restore movement to hypomobile spinal segments (Henderson, 2012). Thereafter, it was proposed that SMT may act via two distinct but likely interdependent mechanisms as a consequence of movement generated: biomechanical changes in spinal tissues and neurophysiological changes in afferent input. Two similar themes were identified by a review of the literature examining the potential mechanisms for enduring changes in lumbar stiffness following SMT (Jun et al., 2020). Direct biomechanical effects on spinal tissues or indirect neurophysiological effects mediated by stimulation of muscle afferents are the main hypotheses contemplated and outlined in the coming sections.

Biomechanical hypotheses

SMT may restore range of motion through different means. Human and animal studies demonstrated small translational and rotational movement of lumbar vertebrae after simulated SM thrusts (Funabashi et al., 2018; Nougarou et al., 2014; Pickar and Bolton, 2012). This movement results in greater loads on the intervertebral disc (Funabashi et al., 2021; Funabashi, et al., 2018), which may help reduce disc distortions and mechanical stresses (Gyer et al., 2019; Pickar and Bolton, 2012). In addition, significant increases in facet joint gapping (increased space) immediately after SM may facilitate the release of trapped meniscoids and adhesions, improving joint motion (Cramer et al., 2002). Changes in movement patterns and load distributions may alter high- and low-threshold mechanoreceptor input, potentially leading to pain relief, though this remains unknown. There are insufficient data to determine whether SMT parameters, such as force direction, duration, amplitude and magnitude, and the resulting loads and displacements, have any meaningful clinical impact (Pasquier et al., 2019). However, dose-response relationships between these parameters and neuromuscular responses outlined in the ensuing section may help grasp certain mechanisms.

Neuromuscular hypotheses

It was proposed that SM is a mechanical event that imposes sufficient loads on spinal tissues to activate mechanosensitive terminals (Pickar and Bolton, 2012). While higher peak forces during the SM thrust are associated with larger intervertebral displacement (Nougarou et al., 2016; Pasquier, et al., 2019), paraspinal electromyographic responses are increased by higher rates of force application (Nougarou, et al., 2014; Page I. et al., 2014; Reed et al., 2014). Therefore, neuromuscular responses may depend on parameters related to speed (Nougarou, et al., 2016). This was suggested as evidence for muscle spindle involvement, which is consistent with findings from animal studies. In these, short SM thrust durations compatible with velocities measured in the clinical setting, maximize muscle spindle responses (Herzog, 2010; Sung P.S. et al., 2005). These receptor terminals serve proprioceptive functions to signal dynamic changes in position, akin to the mechanical stimulus of SM (Pickar and Bolton, 2012). Input from muscle spindle afferents is likely responsible for electromyographic responses in paraspinal muscles triggered by SM (Herzog, 2010; Nougarou, et al., 2014). Their clinical significance is unclear; however, it is plausible that the sensory barrage from larger-diameter afferents induced by SM competes with afferent nociceptive input in the dorsal horn (Gyer, et al., 2019), as discussed below.

Neurophysiological hypotheses

In addition to hypotheses, it was proposed that the activation of mechanosensitive afferents from SMT result in neurophysiological responses that may reverse adverse neuroplasticity associated with CPLBP (Boal and Gillette, 2004; Henderson, 2012). Multiple studies suggest that SMT entails neurophysiological effects in peripheral tissues, spinal cord, and various supraspinal structures, including the somatosensory and prefrontal cortices (Gyer, et al., 2019). Whether the effects observed are specific to SMT or not, remains a subject of contention. If they are specific, effects are expected to be observed at the segmental level of SMT application. However, current evidence does not support the concept of SMT specificity (Nim et al., 2021a). Therefore, these effects could also stem from contextual factors and placebo mechanisms. This is the central focus of the present thesis, and as such, is reviewed at length in Chapter 4.

Overview of the effectiveness

There is growing interest in the study of pain mechanisms involved in chronic pain states and their surrogate measures (Cohen et al., 2021). The main assumption is that, by improving our understanding of these mechanisms and enhancing our knowledge about how specific treatments may impact them, we will be able to better match individuals to the most appropriate treatment (Fitzcharles, et al., 2021). Applying these precision medicine principles to SMT is still not feasible (Damian et al., 2022). Meanwhile, the best evidence shows that SMT is effective for managing CPLBP (Rubinstein, et al., 2019), albeit without sufficient data to determine which patients are more likely to benefit from SMT (de Zoete et al., 2021a). The clinical effectiveness and efficacy of SMT for LBP is reviewed in depth in Chapter 6.

Safety and adverse events

As stressed by recent changes in clinical practice guidelines, patient safety is critical for the endorsement of any intervention. Serious adverse events related to SMT targeting the lumbar region are very rare (Hebert et al., 2015), and the anecdotal nature of the reports makes it difficult to establish causation. Most events encountered in the literature are narrated in case reports or case series. Data from randomized controlled trials indicate that most adverse events following SMT to the low back are benign, mild, and transient (Swait and Finch, 2017). Due to the infrequency of severe adverse events, population-based studies are preferred for their investigation. Large population-based data from Ontario revealed positive associations between acute lumbar disc

herniations and previous visits to the chiropractor (Hincapie et al., 2018). However, the same association was also found for visits to primary medical care, suggesting that this presentation is common in both clinical settings. Similarly, a retrospective database analysis of nearly one million SMT visits identified only two severe adverse events, namely fractures in women with osteoporosis (Chu et al., 2023). Overall, the data suggest that SMT in the lower back is a safe procedure, with common benign, transient adverse events, and rare, poorly understood, severe reactions.

Motivations for the current work

Significant gaps remain in our comprehension of the specific mechanisms that contribute to the effectiveness of chiropractic SMT, whether as a standalone treatment modality or in combination with other approaches. Elucidating the mechanisms by which SMT reduces pain could help explain why it is effective for some individuals and not others. Identifying distinct mechanisms underlying SMT-induced relief may enable a more targeted approach for its use, allowing for the development of much-needed customized care pathways focused on addressing the most significant contributing factors to a patient's condition.

Discerning specific mechanisms behind chiropractic SMT is also an avenue to understand and validate the use of an intervention for its specific effects. All interventions involve a substantial proportion of nonspecific mechanisms. However, high-value treatments are expected to operate through specific mechanisms, distinguishable or not entirely attributable to contextual factors. Gaining this understanding is essential for future research, particularly in refining the design of appropriate placebo controls that exclude the "active" components of SMT. Additionally, this knowledge may enhance the standardization of protocols and dosage parameters for delivering SMT in both basic and clinical science settings.

Grasping the elements of SMT that significantly impact CPLBP may also enhance our understanding of this complex clinical condition. Surrogate measures with significant influence on clinical and patient-reported outcomes could potentially serve as biomarkers. This knowledge may contribute to the development of more targeted and personalized approaches for diagnosing and treating CPLBP using SMT and other interventions sharing similar mechanisms. Additionally, CPLBP shares mechanisms and risk factors with numerous chronic multimorbidities. It is conceivable that if SMT significantly affects one such mechanism in CPLBP, its application may also offer added value in managing other conditions within the same cluster.

Methodological considerations

Multiple methodological designs are available for investigating intervention mechanisms. Animal studies often elucidate molecular and cellular processes that may contribute to clinical changes. However, equivalent procedures cannot always be performed safely in humans. As an example, the neurophysiological phenomenon of CS can only be directly measured in animals through invasive electrophysiological techniques. Changes observed in animal models may not always transfer across species (Hackam and Redelmeier, 2006) or clinical settings. Experimental or surrogate models, such as capsaicin application, offer a safe and reversible approach to studying pain mechanisms. By generating a tonic noxious stimulus that primarily activates C fibers, this model simulates a persistent pain condition with a high likelihood of inducing CS (Quesada, et al., 2021). In contrast with the heterogeneity of CPLBP, surrogate models elicit relatively consistent responses across participants. The area of tissue injury and nociceptive activity is precisely delineated, thus allowing for the assessment of secondary hyperalgesia. Experimental pain models like capsaicin are also useful for identifying changes in neurophysiological activity, from a pain-free to a phasic or tonic pain state. These alterations provide insight into peripheral, spinal, and supraspinal processes involved in pain perception, likely with less heterogeneity than in clinical populations.

Notwithstanding, the clinical significance of laboratory findings is limited. Experimental pain models only provide partial information on clinical mechanisms. Measuring variables reflective of the same mechanisms in a CPLBP population is crucial for understanding the specific effects contributing to real-life improvement. Clinical studies should abide by consensus definitions for participant recruitment, and carefully exclude based on comorbid conditions that may obscure specific mechanisms. However, CPLBP is heterogeneous and the exclusion criteria required to reduce variability may jeopardize generalizability (Salmasi et al., 2022). Narrowing the focus to specific subpopulations based on mechanistic descriptors (e.g., nociplastic pain) offers a favorable compromise for achieving a more consistent and reproducible participant selection process. Observational studies offer a means to generate hypotheses concerning potential biomarkers or surrogate measures for mechanisms, which can then be compared to a pain-free, healthy control population. However, it is only through randomized experimental designs with placebo controls that the mechanisms underpinning clinical changes attributable to an intervention can be inferred.

Projects' aims and hypotheses

The overarching goal of the present thesis was to investigate the specific hypoalgesic mechanisms of chiropractic SM. The first specific objective was to investigate the hypoalgesic mechanisms of a SM using an experimental model of persistent pain in healthy individuals without back pain. The second specific objective was to explore the mechanisms of relief for CPLBP after a period of SMT. These objectives were achieved by conducting two experimental projects, each preceded by a narrative reviews conducted to justify the objective and support the study's hypothesis, which are included as four chapters, followed by two appendices.

In the first narrative review (Chapter 4) we appraised the literature examining potential mechanisms of SMT for the relief of spine pain. This review presented and classified the mechanisms explored in the literature, mostly through preclinical studies, according to the presupposed level of action within the neuroaxis: peripheral, spinal and supraspinal. Furthermore, the manuscript presents the literature exploring the potential contribution of nonspecific placebo effects, and how the design of control interventions influences mechanistic interpretations.

After identifying a predominant theme involving spinal segmental mechanisms, possibly related to CS processes, the second project aimed to investigate mechanisms of pain relief from a single SM in a capsaicin-induced experimental pain model (Chapter 5). In this preclinical experimental study, the application of topical capsaicin on the back of healthy individuals served as a surrogate model for tonic pain and CS. Specifically, the objective was to assess the impact of three types of SM (segmental, heterosegmental, or placebo), compared to no intervention, on pain intensity, pain unpleasantness, secondary hyperalgesia, and oscillatory brain activity evoked by capsaicin. Outcomes were assessed before and after the interventions during 40 minutes of exposure to capsaicin. We hypothesized that segmental SM would prevent or attenuate the development of capsaicin-mediated secondary hyperalgesia when compared to placebo and to no intervention.

The third project (Chapter 6) consisted in a comprehensive literature review examining the clinical efficacy and effectiveness of SMT as a means of reducing spine pain. We sought to analyze findings from randomized clinical trials to provide a comprehensive overview of the evidence surrounding the use of SMT as a therapeutic intervention for LBP and NP. The evidence was complemented with data from systematic reviews and recommendations from clinical practice

guidelines. In addition, this project investigated the inherent challenges associated with conducting clinical investigations on SMT and other manual therapies, primarily the absence of double-blinding and the difficulty in designing effective sham or placebo interventions.

The fourth project aimed to elucidate the contribution of mechanisms reflective of nociplastic pain to CPLBP, and the potential modulation of these mechanisms by SMT (Chapter 7 and Appendix II). This project was a mechanistic, randomized, placebo-controlled trial with three arms. To identify mechanisms that are specific to SMT, patients with CPLBP were randomly allocated to receive either real SMT or a validated placebo SMT. A third control arm enrolled healthy participants to confirm that the variables used as surrogates for nociplastic pain mechanisms accurately discriminate CPLBP patients from pain-free counterparts. This project led to the publication of a protocol manuscript (Appendix II) and the submission of the results of the clinical trial in a second manuscript (Chapter 7). We hypothesized that, compared to placebo, SMT would result in reductions in pain and disability in patients with CPLBP, and that variables suggestive of nociplastic pain would predict and contribute to this clinical benefit.

Prior to this, a fifth project sought to examine the potential use of urinary concentrations of the proinflammatory cytokine TNF-α as a biomarker for CPLBP (Appendix I). This was a case-control study recruiting patients with CPLBP and matched pain-free controls, to evaluate whether urinary levels of this cytokine could identify a subgroup of patients with CPLBP, and whether its fluctuations could predict clinical outcomes. Results from this study may support its usefulness as a surrogate for assessing neuroinflammation in patients with CPLBP, and thus, potentially nociplastic pain.

Chapter 4: Article 1 – Neurophysiological mechanisms of chiropractic spinal manipulation for spine pain

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Contribution des auteurs

Carlos Gevers-Montoro : Conception de l'étude, recension des écrits, rédaction de l'article, révision de l'article.

Benjamin Provencher : Recension des écrits.

Martin Descarreaux : Révision de l'article.

Arantxa Ortega de Mues : Révision de l'article, supervision de l'étude.

Mathieu Piché : Conception de l'étude, révision de l'article, supervision de l'étude.

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 (SM) 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 SM and provides a perspective for future research on SM and spine pain, including the validation of placebo interventions that control for placebo effects and other non-specific effects that may be induced by SM.

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.

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 NP 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 NP 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 NP have been classified as chronic primary pain syndromes under the new International Association for the Study of Pain classification of chronic pain for the latest revision of the International Classification of Diseases (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. Amongst 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 (WHO, 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 & 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), though informed by studies where SM was performed by chiropractors and other practitioners.

Spinal manipulation generally consists in the application of a mechanical force on spinal joints in the form of a high velocity and low amplitude thrust preceded by a slower preload phase (Pickar & 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., 2009; Gyer et al., 2019; Pickar & Bolton, 2012). It has been proposed that this afferent fibre stimulation initiates a cascade of peripheral and central neurophysiological effects (Bialosky, et al., 2009a; Pickar & Bolton, 2012). In turn, these effects may underlie some of the clinical outcomes observed with SMT (Bialosky, et al., 2009a; Pickar & Bolton, 2012). A comprehensive model including biomechanical and neurophysiological mechanisms for pain relief induced by manual therapy has been proposed (Bialosky et al., 2009a, 2018). 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 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 5**. A summary of the most relevant mechanisms with supporting evidence is also presented in Table 4.1.

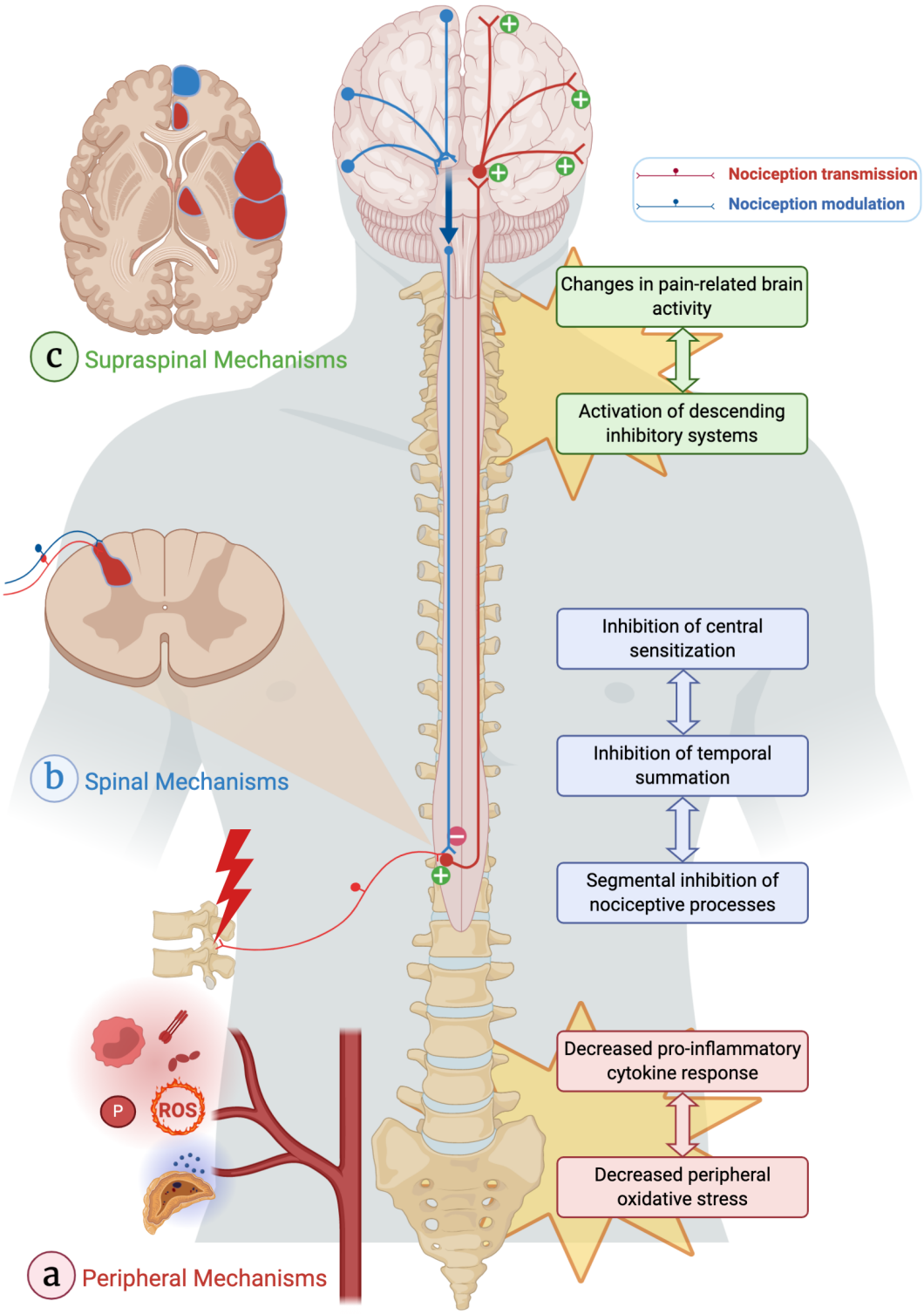

Figure 5 Pain mechanisms likely influenced by spinal manipulation (SM)

(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 the temporal summation of pain (George et al., 2006; Bialosky et al., 2008; Bialosky, et al., 2009b; Bialosky et al., 2014; Bishop, et al., 2011b; 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), though widespread pain inhibition suggests cerebrospinal mechanisms involving the descending inhibitory system (Aspinall, et al., 2019a; Dorron et al., 2016; Martinez-Segura et al., 2012; Salom-Moreno et al., 2014). Changes in pain-related brain activity may reflect the 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)

Peripheral mechanisms

Spine pain may be caused by an injury to musculoskeletal tissues of the spine (Vlaeyen et al., 2018) through the direct activation of nociceptive afferents. In acute and chronic inflammatory states, spine pain may be modulated by the 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.

Cortisol release

Pain may be inhibited by hormones with a known anti-inflammatory function on the periphery, such as cortisol (Hannibal & Bishop, 2014; Hench et al., 1950; Saldanha et al., 1986). Cortisol levels rise in anticipation and as a response to acute stressful situations (Hannibal & 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, Botnmark, et al., 2017; 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, Botnmark, et al., 2017) 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 min 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.

Table 4.1 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, 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.

Abbreviation: IL-1β, interleukin one beta; TNF-α, Tumor necrosis factor alpha.

Peripheral inflammation and sensitization

Following cervical SM, an increase in plasmatic substance P was reported, while pressure-pain sensitivity decreased (Kovanur-Sampath et al., 2017; 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 & Bienenstock, 2007). Peripheral inflammation and tissue injury are associated with a release of substance P (Dickenson, 1995; Hackel et al., 2010; Van Der Kleij & 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 fibres 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 & 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, 2019). Preliminary results suggest that SM may reduce pro-inflammatory responses (Roy et al., 2010; Teodorczyk-Injeyan et al., 2006, 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). Though the quality of the evidence on the influence of SM on biological markers was considered to be moderate (Kovanur-Sampath, Mani, et al., 2017), the currently 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.

Spinal cord mechanisms

Behavioural 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., 2009a; 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.

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; Millan et al., 2012). The duration and size of these effects are still unclear, though 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 favourable 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; 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 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., 2019; 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., 2019) 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 the 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 into specific mechanisms that influence nociceptive processes and pain behaviours. They also provide high-quality data on the dose-response relationship of a specific intervention (Hackam & 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 the 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%–78% of 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, 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 fibres (e.g. C fibres) or on central amplification processes such as wind-up.

Effects of spinal manipulation on the temporal summation of pain

Sustained or repeated activation of afferent nociceptive fibres induces the temporal summation of pain, the perceptual correlate of windup in the spinal cord (Price et al., 1977). More specifically, stimulation at constant C-fibre 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 & Wall, 1965; Price, 1972; Price et al., 1977). Temporal summation of pain is increased

in patients with chronic pain, suggesting that C-fibre activity is abnormally maintained in these cases (Staud et al., 2001, 2004). 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 behavioural studies suggests that SM may exert its hypoalgesic effects through attenuation of spinal processes related to temporal summation (Aspinall, et al., 2019b; Bialosky et al., 2008, 2009b, 2914; Bishop et al., 2011a, 2011b; 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-fibre 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, though 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 fibres (Magerl et al., 2001). Taken together, these findings suggest that SM inhibits temporal summation by modulating C-fibre activity selectively; however, this remains to be confirmed with neurophysiological methods.

Effects of spinal manipulation on central sensitization

Sustained or repeated noxious stimulation that activates C-fibres 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-fibre 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 the 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.

Potential propriospinal 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 the 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), though evidence supporting this hypothesis I 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).

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 (Millan, 2002). However, some of the same brain areas, endogenous substances and top-down mechanisms have also been associated with placebo analgesia (Colloca & Barsky, 2020; Eippert et al., 2009). Placebo effects are mainly the consequence of patients' expectations concerning their health or condition (Colloca & 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 (Colloca & 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; 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). Though 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, Bishop, 2009a; Gyer et al., 2019; Kovanur-Sampath et al., 2015; 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 min 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 the 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 manoeuvers (Meyer et al., 2019). With the currently available data, it is not possible to draw any conclusion regarding the potential supraspinal mechanisms of SM.

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%–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 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.

Placebo effects 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; Colloca & 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, 2014; Bishop, et al., 2011a, 2011b, 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, 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 with appropriate placebo interventions.

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 require 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., 1999, 2002; 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., 1999, 2002). In these studies, the placebo intervention consisted of doing the same preparation (instructions, palpation of the spine and instrument application with an associated sound), but no force was applied (Hawk et al., 1999, 2002). 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., 1999, 2002). Mechanically assisted and manual SM do not have identical force-time profiles (Colloca et al., 2005; Herzog, 2010; Pickar & 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 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 manoeuver 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 of 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 al. showed that the loads applied during the placebo intervention were lower compared with SM (10%–50%), but this does not ascertain the lack of a therapeutic effect, particularly considering that pain intensity reductions were no differences between both groups (Vernon et al., 2012).

Table 4.2 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	—

(Continues)

Table 4.2 (continued)

Authors	Year	Sample	Active SM intervention	Placebo SM intervention	Non-placebo control interventions
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 × 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

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 anaesthesia in the experimental group, while the control group did not receive any intervention other than the anaesthesia. In both groups, standardized visual and auditory cues were delivered before the participants recovered from anaesthesia. Participants did not recall any memory from the anaesthesia period, including the visual and auditory cues, indicating effective blinding (Kawchuk et al., 2009). Though the method is conceptually appealing, its applicability is limited and may be ethically questionable. In addition, the inertness of the anaesthetics utilized must still be confirmed (Kawchuk et al., 2009). This may explain why this placebo intervention has not been used in subsequent studies.

Table 4.2 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 conclusions

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 to guide 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 the 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 fibres. Modulation of C-fibres 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 mechanism 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, 2018). Additionally, human data suggest that SM hypoalgesia relies, at least partially, on specific mechanisms independent of expectations (Bialosky et al., 2008, 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 (Colloca & Barsky, 2020), or by avoiding messages that could influence patients beliefs negatively, resulting in increased vigilance, worry, or frustration (Colloca & Barsky, 2020; Darlow et al., 2013).

The gaps identified in research on pain mechanisms of SM should guide future investigations. Though 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-10, interleukin ten; IL-1β, interleukin one beta; LBP, low back pain; NICE, National Institute for Health and Care Excellence; NP, neck pain; PPTs, pressure pain thresholds; ROS, reactive oxygen species; SM, spinal manipulation; SMT, spinal manipulative therapy

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Conflict of interest

The authors report no financial or other relationship that may lead to any conflict of interest.

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 the 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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Chapter 5: Article 2 – Chiropractic spinal manipulation prevents secondary hyperalgesia induced by capsaicin in healthy individuals

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Abstract

Background and Aims: Spinal manipulation (SM) is currently recommended for the management of back pain. Experimental studies indicate that the hypoalgesic mechanisms of SM may rely on inhibition of segmental processes related to temporal summation of pain and, possibly, on central sensitization, although this remains unclear. The aim of this study was to determine whether experimental back pain, secondary hyperalgesia, and pain-related brain activity induced by capsaicin are decreased by segmental SM.

Methods: Seventy-three healthy volunteers were randomly allocated to one of four experimental groups: SM at T5 vertebral level (segmental), SM at T9 vertebral level (heterosegmental), placebo intervention at T5 vertebral level, or no intervention. Topical capsaicin was applied to the area of T5 vertebra for 40min. After 20min, the interventions were administered. Pressure pain thresholds (PPTs) were assessed outside the area of capsaicin application at 0 and 40min to examine secondary hyperalgesia. Capsaicin pain intensity and unpleasantness were reported every 4min. Frontal high-gamma oscillations were also measured with electroencephalography.

Results: Pain ratings and brain activity were not significantly different between groups over time ($p > 0.5$). However, PPTs were significantly decreased in the placebo and control groups ($p < 0.01$), indicative of secondary hyperalgesia, while no hyperalgesia was observed for groups receiving SM ($p = 1.0$). This effect was independent of expectations and greater than placebo for segmental ($p < 0.01$) but not heterosegmental SM ($p = 1.0$).

Conclusions: These results indicate that segmental SM can prevent secondary hyperalgesia, independently of expectations. This has implications for the management of back pain, particularly when central sensitization is involved.

Background

Back pain is the leading cause of disability worldwide, entailing individual, social, and economic costs (Collaborators, 2018; Hartvigsen et al., 2018). Every year, approximately 37% of the population is affected by low back pain (Hoy et al., 2012). In high-income countries where the prevalence is higher (Hoy, et al., 2012), the economic burden has been estimated to total in the billions of dollars (Alonso-Garcia and Sarria-Santamera, 2020; Hartvigsen, et al., 2018; Walker et al., 2003). In addition to the economic impact, inadequate clinical interventions can increase costs and worsen clinical outcomes (Buchbinder et al., 2020; Hartvigsen, et al., 2018).

Current clinical practice guidelines for the treatment of back pain recommend the use of conservative interventions (Bussieres et al., 2018; Foster et al., 2018; Qaseem et al., 2017). These include spinal manipulation (SM), among several other manual therapies. SM is the main intervention used by chiropractors for the management of back pain (Beliveau et al., 2017; Hurwitz, 2012). Recent meta-analyses including individual participant data indicate that SM may be as effective as other recommended therapies for the management of chronic low back pain (de Zoete et al., 2021b; Rubinstein et al., 2019). However, current data does not allow the identification of patients that will benefit more or less from SM therapy (de Zoete et al., 2021a), in part because the mechanisms of both low back pain and its relief by SM remain unclear.

For most cases of back pain, the source of pain cannot be determined, which makes the choice of clinical intervention challenging (Hartvigsen, et al., 2018; Vlaeyen et al., 2018). When pain recurs or persists over time, it has been proposed that it is a condition in and of itself and that altered pain-related mechanisms may contribute to the disorder (Nicholas et al., 2019; Treede et al., 2019). Altered pain sensitivity has been reported in patients with chronic primary low back pain (den Bandt et al., 2019). Central sensitization is one of the pathological processes that may contribute to altered pain sensitivity in these patients. It refers to increased spinal nociceptive transmission following sustained nociceptive inputs, which is involved in patients with chronic pain, including chronic back pain (Nijs et al., 2021; Woolf, 2011).

Although central sensitization cannot be measured directly in humans (Latremoliere and Woolf, 2009), its perceptual correlates have been examined in healthy individuals using experimental pain and in patients with clinical pain (den Bandt, et al., 2019; Sanzarello et al., 2016; Starkweather et al., 2016). A topical application of capsaicin can evoke secondary hyperalgesia,

one of the features of central sensitization that is characterized by hypersensitivity to mechanical pain stimuli beyond the area of capsaicin application (Ali et al., 1996; Andrews et al., 1999; Mohammadian et al., 2004; Morris et al., 1997; Quesada et al., 2021). Further, capsaicin-induced pain and ongoing clinical back pain induce changes in prefrontal cortex activity (Apkarian et al., 2004; Baliki et al., 2011; Baron et al., 1999). Recent findings also suggest that high-gamma oscillations can be used to examine ongoing pain-related brain processes (Li et al., 2016; May et al., 2019; Nickel et al., 2017; Schulz et al., 2015). Thus, the assessment of secondary hyperalgesia and cerebral high-gamma oscillations could be used to evaluate the pain-relieving mechanisms of SM for back pain.

The mechanisms underlying hypoalgesia induced by SM are still largely unknown (Gevers-Montoro et al., 2021). SM consists of the manual application of a mechanical force on the spine, in the form of a high velocity and low amplitude thrust (Herzog, 2010; Pickar and Bolton, 2012). This mechanical force alters spinal biomechanics, which impacts paraspinal tissues (Funabashi et al., 2017; Nougarou et al., 2013; Reed et al., 2014) and sensory afferents (Bialosky et al., 2018; Bialosky et al., 2009a; Pickar and Bolton, 2012). In turn, this initiates a cascade of neurophysiological effects that could be responsible for hypoalgesia and other clinical outcomes (Bialosky, et al., 2018; Gyer et al., 2019; Pickar and Bolton, 2012). It has been suggested that SM may inhibit pain through spinal segmental mechanisms, including the reduction of temporal summation during prolonged pain states (Bialosky et al., 2009b; Bishop et al., 2011; Gevers-Montoro, et al., 2021; Randoll et al., 2017). Temporal summation can lead to synaptic plasticity in the spinal cord and to central sensitization (Latremoliere and Woolf, 2009; Woolf, 1983). It remains to be determined whether SM reduces central sensitization and whether this reduction underlies clinical pain relief.

The aim of the present study was to determine whether SM could reduce the development of capsaicin-induced secondary hyperalgesia and frontal high-gamma oscillations. In addition, we examined whether these effects were greater when SM was applied to the spine segments where capsaicin was applied (T5 – painful area) compared with when SM was applied to spine segments without capsaicin (T9 – non painful area). We hypothesized that SM would reduce capsaicin pain and secondary hyperalgesia when applied to the painful area, through segmental mechanisms. We

also anticipated that SM would reduce frontal high-gamma oscillations associated with capsaicin pain.

Methods

Ethics approval

All experimental procedures in this study conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Université du Québec à Trois-Rivières (Canada), as well as the Clinical Research Ethics Board of the Hospital Clínico San Carlos, Madrid (Spain). All participants gave written informed consent acknowledging their right to withdraw from the experiment without prejudice, and received a compensation of €10 for their travel expenses, time, and commitment.

Participants

Participants were included if they were between 18 and 65 years old. They were excluded if they had been diagnosed with a physical or psychological condition, consumed alcohol regularly (> 3 days per week) or on the day of the experiment, had taken any drugs during the previous two weeks, had a spinal surgery or physical trauma to the spine in the previous three months, or if they reported having an allergy/intolerance to chili peppers. One hundred and two healthy volunteers were recruited via word of mouth on the campus of the Madrid College of Chiropractic to participate in the study. Nineteen participants were included in Experiment 1 (8 women and 11 men; range 20–37 years old; mean ± SD: 22.8 ± 3.8 years old) and 83 were recruited for Experiment 2. From these 83 participants, two did not complete the experiment, resulting in the inclusion of 81 participants for Experiment 2 (40 women and 41 men; range 18–64 years old; mean ± SD: 36.5 ± 11.7 years old).

Experimental design: Experiment 1

Experiment 1 was a pilot study and relied on a within-subject design to characterize tonic pain produced by capsaicin applied to the back, to confirm its suitability for the main study (Experiment 2). Since capsaicin has not been used to evoke primary and secondary hyperalgesia in the back previously, the experiment aimed at identifying the time course of this experimental pain model. Participants (n = 19) lay prone for the entire duration of the experiment and were instructed

to rate pain evoked by capsaicin for sixty minutes. These data were used to determine the duration capsaicin application for Experiment 2.

Experimental design: Experiment 2

Experiment 2 relied on a mixed design to compare changes in pain perception and pain-related brain activity between four groups. A random-number generator was used to create a randomisation sequence and assign participants to one of the four experimental groups: no intervention (control; n = 21), placebo (light mechanical stimulus applied segmentally to capsaicin pain; n = 20), SM applied segmentally to capsaicin pain (SM–T5; n = 20) and SM applied heterosegmentally to capsaicin pain (SM–T9; n = 20). Capsaicin was applied to the skin in the T5 vertebral segment area for 40 minutes while participants rated the capsaicin-evoked pain and brain activity was recorded. Pressure pain thresholds were measured in tissues surrounding the area of capsaicin application at the beginning and end of the experiment. After 20 minutes, the placebo, SM–T5, and SM–T9 groups received the designated intervention (see **Figure 6**).

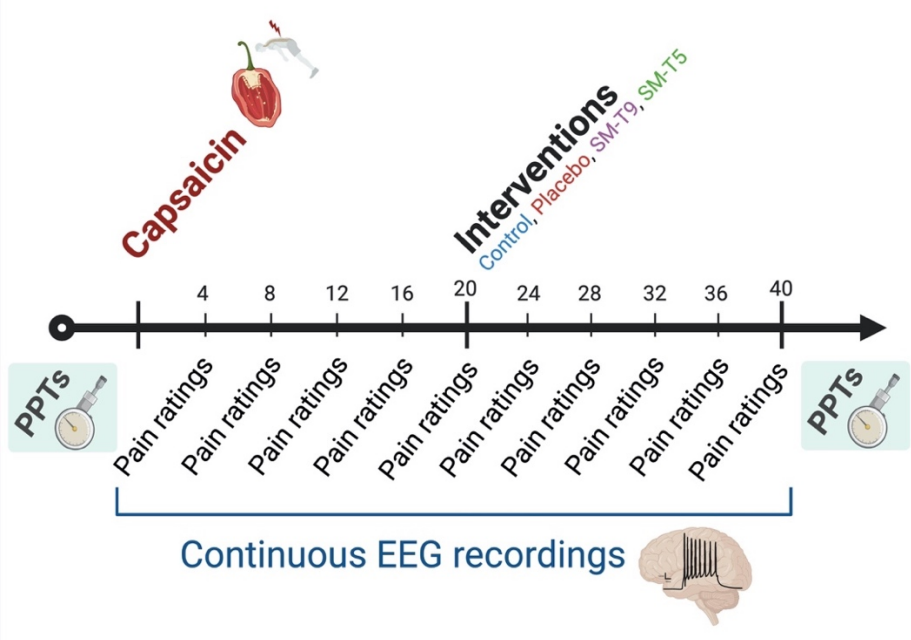

Figure 6 Experimental design of experiment 2

Schematic representation of the experimental design for Experiment 2. Pressure pain thresholds (PPTs) were measured before capsaicin application and at the end of the experiment. Capsaicin was applied to the back of participants for 40min. Pain intensity and unpleasantness were rated verbally (0–100) every 4min and continuous brain activity was recorded with EEG. Twenty minutes after capsaicin application, the intervention was performed (placebo; spinal manipulation at T9: SM–T9; spinal manipulation at T5: SM–T5), except for the control group.

Capsaicin pain

For both experiments, 0.6 mL of a capsaicin 1% cream (CapsiGroup, Palmira, Colombia) were applied over a 3x3 cm area of skin surrounding the spinous process of the T5 vertebra. This capsaicin concentration has been used to produce tonic pain in previous studies (Domnick et al., 2009; Ferland et al., 2018; Hullemann et al., 2015; Martel et al., 2017; Mohammadian, et al., 2004; Schaffler et al., 2017). Capsaicin was uniformly distributed and pressed against the skin by applying a piece of plastic wrap over the covered region. It remained in place for 60 minutes in Experiment 1 and for 40 minutes in Experiment 2.

Interventions

Two chiropractors performed SM. To avoid any bias that may be due to individual differences, participants were randomly assigned to one of the two chiropractors, while counterbalancing between groups. Accordingly, each chiropractor performed SM for half of the participants in both SM group. SM consisted of a short-duration, high-velocity, low-amplitude force applied to the spine to generate an audible release (cavitation). The spine was manipulated using a bilateral thenar or hypothenar contact over the transverse processes of the T5 or T9 vertebrae, depending on group allocation, after which a posterior to anterior thrust was applied to the spinal segment (Randoll, et al., 2017). These segments were chosen for SM to allow participants to lie prone in a stable position for the entire duration of the experiment, including the intervention period. This is necessary to allow artifact-free recording of EEG activity. A previous study showed a segmental reduction in temporal summation when SM was applied in the upper thoracic area (Randoll, et al., 2017). Therefore, T5 was chosen for segmental SM and T9 for heterosegmental SM. This type of manipulation typically lasts less than 200 ms and involves a force of approximately 500 Newtons (Triano et al., 2015). The placebo intervention consisted of a calibrated force of 25 N applied for 2 s on the T5 vertebral segment with a contact over the spinous process (Randoll, et al., 2017), using a hand-held dynamometer (model 01165, Lafayette Instrument Company, Lafayette, IN, USA). Choosing a placebo intervention for SM is challenging, as no placebo intervention can account for all aspects of SM (Puhl et al., 2017). A commonly used placebo intervention consists of skin contact with no thrust, or with only soft pressing (Puhl, et al., 2017). The intervention aims at reproducing the SM set-up and contact with the participant. For the placebo intervention in the present study, skin contact was achieved with a hand-held

dynamometer to standardize the applied force. This procedure is identical to that used in a previous study (Randoll, et al., 2017). In addition to the placebo group, we included a control group (no intervention) to determine if the placebo produced any effect and to measure non-specific temporal effects.

Pain ratings

In Experiment 1, an electronic VAS (e-VAS) consisting of a sliding transducer (Biopac Systems TSD115, Santa Barbara, CA, USA) was used to provide continuous pain intensity ratings evoked by capsaicin. Cursor position on a scale anchored at "no pain" and "worst pain imaginable" was converted to a numeric value from 0 to 100. In addition, participants were requested to rate unpleasantness verbally every 60 seconds using a numeric rating scale, where 0 indicated no unpleasantness and 100 indicated the worst unpleasantness imaginable. In Experiment 2, both dimensions were evaluated using verbal numeric rating scales from 0 to 100 with the same anchors. Ratings were provided every four minutes in order to limit artifacts in the EEG recordings.

In Experiment 2, before initiating the protocol for the three groups that received an intervention, participants were instructed to rate the expected change in capsaicin pain induced by the intervention. Expectations of pain relief have been shown to modulate or predict pain relief for both experimental and clinical pain (Cormier et al., 2016; Cormier et al., 2013). Participants were unaware of the segmental level of SM application and that different interventions were compared between groups. The ratings were provided using a visual analog scale anchored at -100 with the descriptor "maximum pain reduction," 0 with "no change," and +100 with "maximum pain increase."

Pressure pain thresholds (PPTs)

In Experiment 2, in order to examine secondary hyperalgesia induced by capsaicin, pressure pain thresholds (PPTs) were evaluated at points 15 mm superior and lateral to both upper corners of the area to which capsaicin was applied, using a pressure algometer (Wagner Force Dial FDK/FDN 10, Greenwich, CT, USA) fitted with a 1 cm diameter foam pad at the end (Hughes et al., 2019). Pressure was applied at a rate of approximately 1 kg/s, measurements were repeated twice, and threshold values were averaged (Balaguier et al., 2016). Participants were instructed to give a quick verbal response when pressure became painful (≥ 1/100). When thresholds exceeded

10 kg, the value assigned to the measurement was marked as equal to 10 kg. Thresholds were obtained before capsaicin application and at the end of the experiment, before removing the capsaicin.

Electroencephalographic Recordings

Continuous electroencephalographic (EEG) activity was recorded at electrodes FPz, Fz, F3, F4, Cz, and Pz according to the International 10-20 system, using a linked ear lobe reference (Electro-Cap International Inc., Eaton, OH, USA). Eye movements and blinks were recorded using electro-oculographic (EOG) activity with electrodes placed at the suborbital ridge and lateral to the external canthus of the right eye. EEG and EOG were grounded with an electrode applied on the nasium and electrode impedance was kept below 10 kΩ. EEG and EOG signals were filtered using a hardware 0.1 to 500 Hz band-pass filter and sampled at 1000 Hz for offline analyses.

Electroencephalographic Analyses

Continuous EEG and EOG data were exported to MATLAB (Mathworks, Natick, MA, USA) and analyzed with EEGLAB version 14.1.0 (Delorme and Makeig, 2004). Data was down-sampled to 500 Hz and band-pass filtered (1-100 Hz) (Li, et al., 2016). A 50 Hz notch filter was set to reduce noise from external electrical sources (Ebrahimian et al., 2018). The filtered data was then re-referenced to the common average and visually inspected for infrequent and non-stereotyped artifacts (Li, et al., 2016). Finally, eye movements and muscle artifacts were removed using an independent component analysis (ICA) algorithm (Jung et al., 2000). The pre-processed data was then imported into Spike2 (Cambridge Electronic Design, Cambridge, UK) to analyze the signal from Fz as reported previously (May, et al., 2019; Schulz, et al., 2015). The continuous signal at Fz was normalized to the whole recording period (Ellmore et al., 2017; Alday, 2019) using a Z transformation (Li et al., 2016). The normalized EEG signal was bandpass filtered to obtain high-gamma oscillations (60-90 Hz) using a fourth-order Butterworth filter (May et al., 2019). The continuous recording was then transformed into the frequency domain with a Fast Fourier Transform of 512 points (Li et al., 2016) with a Hanning window (May et al., 2019). High-gamma oscillation power was calculated as the area under the curve of the power spectrum from 60 to 90 Hz. This was done for each four-minute period, which included 236.1 s of data on average, after removal of artifacts. EEG data from three participants were excluded due to excessive noise (> 6.5% of the time recorded, representing more than three standard deviations from the mean data

rejection across participants). Rejected EEG data from the remaining participants were 1.97 % SD ±1.51 of the total recording on average, with no significant difference between groups (p = 0.16). The final sample for statistical analyses consisted of 70 EEG recordings (37 women and 33 men; range 18–64 years old; mean ± SD: 36.2 ± 11.8 years old; see Table 5.4 for the group allocation).

Statistical Analyses

Statistical analyses were performed with Statistica v13.0 (Dell Inc., Tulsa, OK, USA). All data are expressed as mean ± SD. SD values were corrected to remove between-subject variability (Cousineau, 2005) for the repeated measures. Values of $p \leq 0.05$ were considered statistically significant. Distribution normality was assessed with the Kolmogorov-Smirnov test and homogeneity of variance was assessed with the Levene test. Baseline measures were collected at 20 minutes for pain ratings (last pain rating reported before the application of the interventions) and between 16 and 20 minutes for gamma oscillations (last 4 min block measured before the application of the interventions). The change in pain ratings and gamma power relative to baseline was then calculated for subsequent time points and used to compare groups over time (5 time points) using Greenhouse-Geisser corrected mixed ANOVAs. Right and left PPT values were averaged and compared between groups over time (baseline *vs*. end of the experiment) using a Greenhouse-Geisser corrected mixed ANOVA. Significant effects were decomposed using Bonferroni-corrected planned contrasts to test a priori hypotheses (eight contrasts for changes in PPTs, and three contrasts for the effects of expectations). Effect sizes are reported based on partial eta squared (η^2_p).

Results

Experiment 1

Capsaicin pain

In Experiment 1, participants reported a progressive increase in pain intensity and unpleasantness over time ($F_{60,1080} = 16.8$; $p < 0.001$; $\eta^2_p = 0.48$ and $F_{58,1044} = 22.6$; $p < 0.001$; $\eta^2_p = 0.56$, respectively; see **Figure 7**A-B). Between 8 and 60 min, capsaicin produced low pain intensity (mean ± SD: 20.3 ± 15.3) with a maximum of 40.1 ± 23.3. Between 2 and 60 min, capsaicin also produced low to moderate unpleasantness (mean ± SD: 31.5 ± 13.1) with a maximum of 57.6 ±

19.7. The sensation reached a plateau between 30 and 45 minutes after capsaicin application, from 31.1 min on average. These results were used to determine the duration of the protocol for Experiment 2 (40 min).

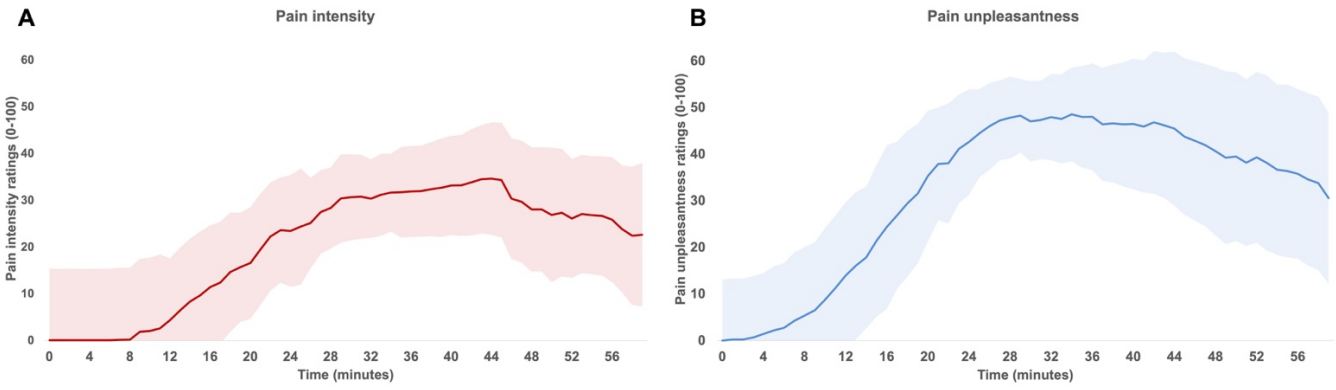

Figure 7 Time course of pain ratings during Experiment 1

Mean pain intensity **(A)** and unpleasantness **(B)** after capsaicin application. Both pain intensity and unpleasantness significantly increased over time (both $p < 0.001$). The shaded area represents standard deviations corrected to remove between-subject variability (see Methods).

Experiment 2

Capsaicin pain

Only the participants reporting minimum ratings of 5/100 in at least one of the two pain dimensions (intensity or unpleasantness) were included for analyses. The final sample comprised 73 participants (38 women and 35 men; range 18–64 years old; mean ± SD: 36.0 ± 11.8 years old; see Table 5.1 for participants' characteristics). Capsaicin pain ratings are reported for each time point during 40 minutes in Table 5.2 and the change in pain ratings from baseline are presented in **Figure 8**. After baseline, capsaicin pain intensity and unpleasantness did not change significantly over time for all groups combined (main effect of time: $F_{4,276} = 1.4$; $p = 0.2$; $\eta^2_p = 0.02$ and $F_{4,276} = 2.4$; $p = 0.10$; $\eta^2_p = 0.03$, respectively). Moreover, pain intensity and unpleasantness were not significantly different between groups over time (interaction: $F_{12,276} = 0.3$; $p = 0.9$; $\eta^2_p = 0.01$ and $F_{12,276} = 0.5$; $p = 0.8$; $\eta^2_p = 0.02$, respectively).

Table 5.1 Experiment 2: Characteristics of participants

	Control	Placebo	SM-T9	SM-T5	Total Sample
Number of participants per group	19	19	19	16	73
Sex ratio: Females/Males	10/9	9/10	10/9	9/7	38/35
Age: mean ± SD	35.5 ± 12.2	36.9 ± 9.4	37.4 ± 14.4	34.0 ± 11.2	36.0 ± 11.8
Expected change in pain: mean ± SD	-	-17.9 ± 41.5	-21.1 ± 57.4	-38.2 ± 45.5	-25.0 ± 48.7

Table 5.2 Experiment 2: Pain intensity and unpleasantness ratings (mean ± SD)

		4 min	8 min	12 min	16 min	20 min	24 min	28 min	32 min	36 min	40 min
Control $n = 19$	Intensity	1.3 ± 13.1	3.7 ± 12.1	7.1 ± 8.3	10.2 ± 7.2	13.7 ± 9.7	16.5 ± 6.6	18.5 ± 8.1	19.3 ± 9.5	18.8 ± 9.4	17.5 ± 9.6
	Unpleasantness	1.3 ± 11.7	4 ± 11.8	8.2 ± 7.9	12.1 ± 8.6	17.9 ± 9.1	21.3 ± 7.0	23.6 ± 8.1	23.4 ± 8.9	23.6 ± 9.5	21.7 ± 10.2
Placebo $n = 19$	Intensity	0.3 ± 9.6	0.8 ± 9.7	2.9 ± 8.3	7.6 ± 5.4	11.4 ± 7.4	13.1 ± 10.0	14.3 ± 8.4	14.6 ± 6.4	13.3 ± 7.1	12.4 ± 12.8
	Unpleasantness	0.4 ± 11.5	4.1 ± 12.3	6.8 ± 8.7	11.9 ± 6.4	15.6 ± 6.5	16.5 ± 7.0	20 ± 8.5	21.2 ± 9.1	18.7 ± 9.0	17.3 ± 14.1
SM-T9 $n = 20$	Intensity	0.3 ± 9.3	1.1 ± 8.7	1.4 ± 8.7	6.3 ± 7.7	8.9 ± 7.7	9.5 ± 6.1	12.3 ± 11.1	10.8 ± 8.3	9.1 ± 6.4	8.9 ± 7.4
	Unpleasantness	0.9 ± 10.4	4.7 ± 12.1	7.5 ± 10.6	12.3 ± 9.4	16.5 ± 10.6	15.5 ± 10.1	18.4 ± 13.1	16.8 ± 11.1	14.6 ± 11.8	14.9 ± 12.9
SM-T5 $n = 16$	Intensity	0.3 ± 9.2	1.6 ± 8.1	3.2 ± 8.3	7.1 ± 7.1	12.2 ± 10.1	11.8 ± 5.0	13.6 ± 5.5	14.3 ± 5.9	14.7 ± 8.1	13.4 ± 10.3
	Unpleasantness	1.1 ± 14.2	3.1 ± 12.4	5.8 ± 12.3	12.4 ± 11.7	18.3 ± 9.0	19.3 ± 5.4	23.1 ± 9.4	24.7 ± 10.9	24.4 ± 13.6	23.9 ± 13.6

In order to limit a potential floor effect, the analysis was repeated with participants that reported pain ratings of 20 or more. This resulted in a sample of 46 participants (35.1 ± 11.8 years old, 46 women), with the following group allocation: control: n = 13, placebo: n = 11, SM–T5: n = 11, SM-T9: n = 11. With this sample, pain intensity and unpleasantness did not change significantly over time (main effect: $F_{4,168} = 1.7$; $p = 0.20$; $\eta^2_p = 0.04$ and $F_{4,168} = 2.4$; $p = 0.10$; $\eta^2_p = 0.05$, respectively) and the pain intensity and unpleasantness were not significantly different between groups over time (interaction: $F_{12,168} = 0.3$; $p = 0.9$; $\eta^2_p = 0.02$ and $F_{12,168} = 0.6$; $p = 0.7$; $\eta^2_p = 0.04$, respectively). Thus, whether participants with light pain are included or not, results are similar.

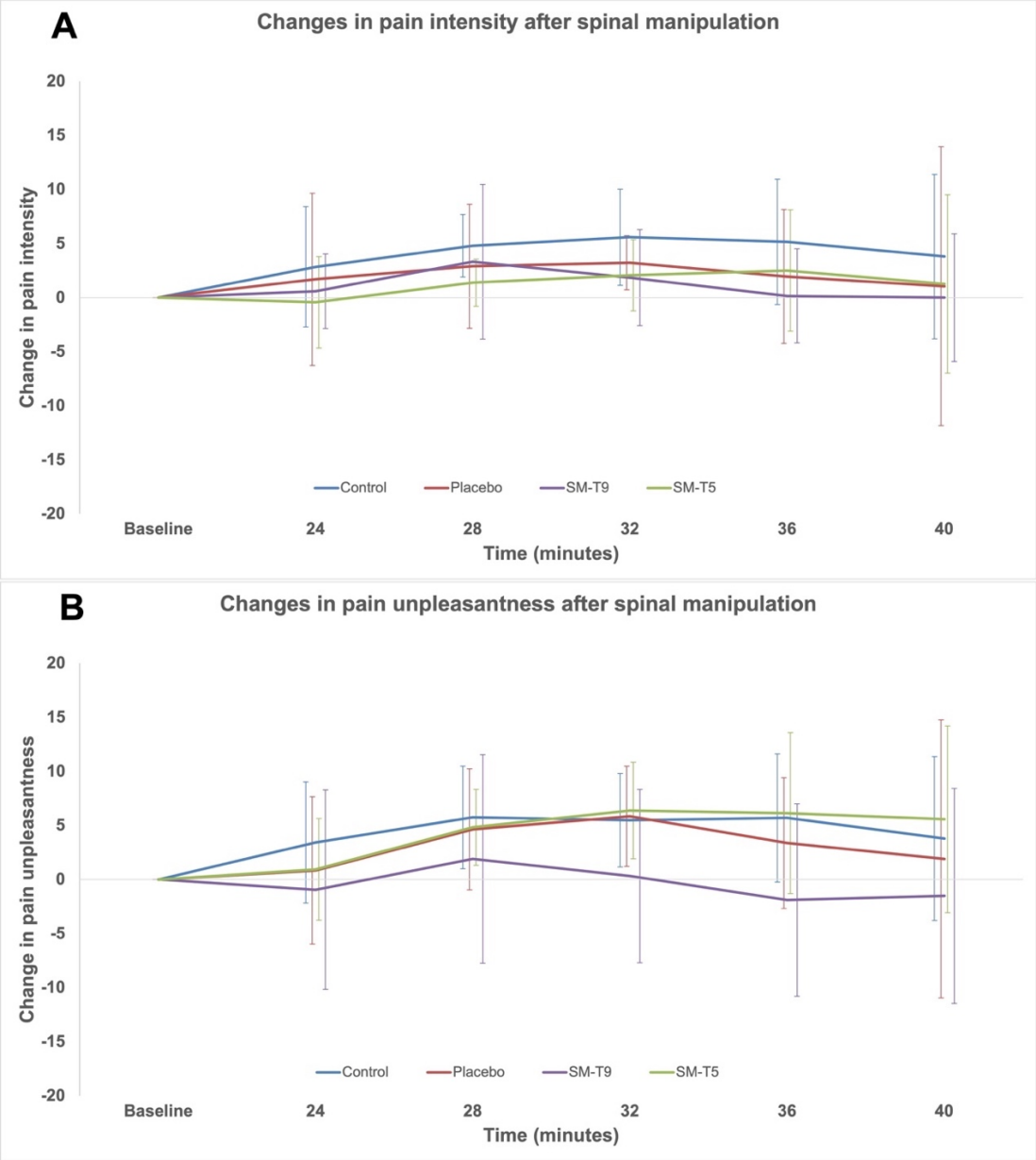

Figure 8 Changes in pain ratings relative to baseline in Experiment 2

Comparison of the change in capsaicin pain intensity **(A)** and unpleasantness **(B)** between groups over time, relative to baseline. Error bars represent standard deviations corrected to remove between-subject variability (see Methods). Pain intensity and unpleasantness were not significantly different between groups over time (p = 0.9 and p = 0.8, respectively). SM–T5 = spinal manipulation at T5. SM–T9 = spinal manipulation at T9.

Secondary Hyperalgesia

PPTs were significantly decreased over time (main effect: $F_{1,69} = 9.8$, $p = 0.003$; $\eta^2_p = 0.12$), and this effect was significantly different between groups (interaction: $F_{3,69} = 5.6$; $p = 0.002$; $\eta^2_p =$

0.19; see **Figure 9** and Table 5.3). Bonferroni-corrected planned contrasts revealed that PPTs were significantly decreased in the placebo group and the group that received no intervention ($p = 0.005$ and $p = 0.006$, respectively), indicative of secondary hyperalgesia. In contrast, no change was observed in groups that received SM at T5 ($p = 1.0$) or T9 ($p = 1.0$). Moreover, changes in PPTs were significantly different between the group that received SM at T5 and the placebo group ($p = 0.006$), indicating that SM at T5 prevented secondary hyperalgesia. However, changes in PPTs were not significantly different between the group receiving SM at T5 and the group receiving SM at T9 ($p = 0.7$). This suggests that SM at T9 produced some effects although they were not significantly different from placebo ($p = 0.6$). Lastly, the placebo group did not show significant effects compared with the group that received no intervention ($p = 1.0$).

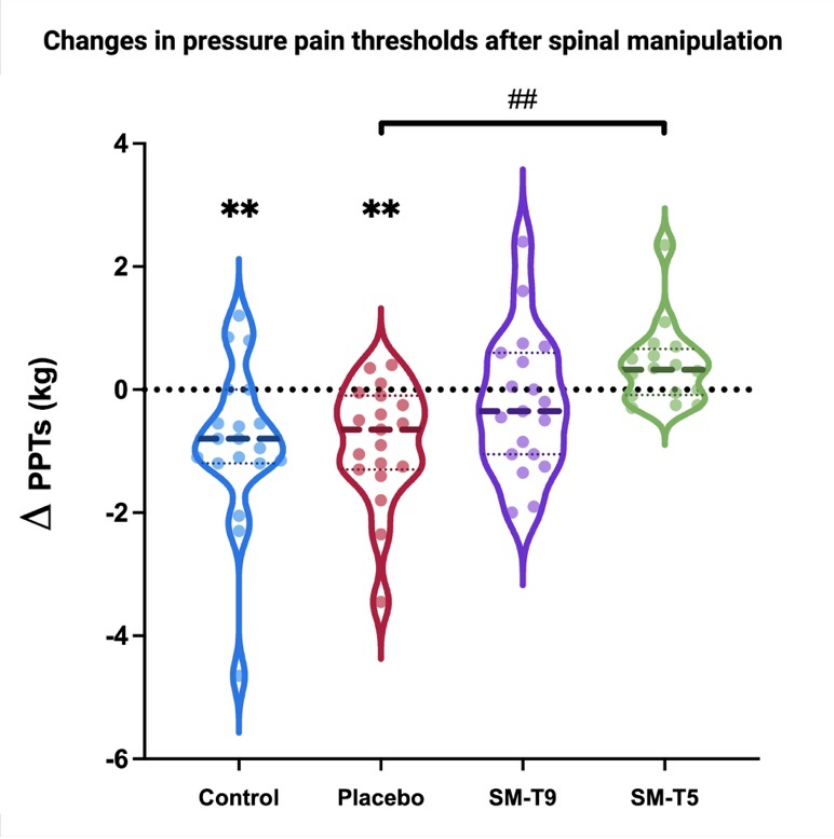

Figure 9 Pressure pain thresholds in Experiment 2

Comparison of changes in pressure pain thresholds (1PPT) between groups. Secondary hyperalgesia was observed in the control and placebo groups (both $p < 0.01$). SM at T5 prevented secondary hyperalgesia and the effect was significantly different compared with the placebo ($p < 0.01$). Thick dashed lines represent the median and thin dotted lines represent the 25th and 75th percentiles. SM–T5, spinal manipulation at T5. SM–T9, spinal manipulation at T9. **$p < 0.01$, within-group; ##$p < 0.01$, between-group.

Table 5.3 Experiment 2: mean pressure pain thresholds (mean ± SD in kg)

	Pre	Post	$\Delta_{(Post-Pre)}$	*p* value
Control n = 19	5.2 ± 2.4	4.4 ± 2.1	-0.9 ± 1.3	*0.006*
Placebo n = 19	4.2 ± 1.7	3.4 ± 1.2	-0.9 ± 1.0	*0.005*
SM-T9 n = 19	4.0 ± 1.4	3.8 ± 1.7	-0.2 ± 1.1	1.0
SM-T5 n = 16	4.0 ± 2.1	4.4 ± 2.4	0.4 ± 0.7	1.0

Expectations

Expectations of pain relief were compared between groups (placebo, SM-T5, and SM-T9) with a one-way ANOVA. Expectations were not significantly different between groups ($F_{2,51} = 0.8$, $p = 0.44$, $\eta^2_p = 0.03$; see Table 5.1), although the SM- T5 group expected approximately twice as much pain relief compared with the other two groups. To confirm the lack of contribution of expectations to the effect of SM on secondary hyperalgesia, a covariance analysis was conducted with PPTs from the placebo, SM-T5, and SM-T9 groups, with expectations as a covariate. This ANCOVA revealed that the decrease in PPTs over time was still significantly different between groups (interaction: $F_{2,51} = 7.5$; $p = 0.001$; $\eta^2_p = 0.23$), indicating that the group differences in secondary hyperalgesia over time were not explained by different (although not significant) expectations of pain relief between groups.

Brain Activity

High-gamma oscillation power is reported for each time point during 40 minutes in Table 5.4 and the change in high-gamma oscillation power from baseline is presented in **Figure 10**. High-gamma power significantly increased over time (main effect: $F_{4,264} = 9.4$; $p < 0.001$; $\eta^2_p = 0.10$), but this effect was not significantly different between groups (interaction: $F_{12,264} = 0.9$; $p = 0.5$; $\eta^2_p = 0.04$).

Table 5.4 Experiment 2: Normalized power spectral density of gamma oscillations ($\mu V^2/Hz$)

	4 min	8 min	12 min	16 min	20 min	24 min	28 min	32 min	36 min	40 min
Control *n* = 19	0.65 ± 0.22	0.81 ± 0.35	0.99 ± 0.40	1.06 ± 0.45	0.97 ± 0.36	0.81 ± 0.24	0.86 ± 0.30	0.91 ± 0.34	0.93 ± 0.37	0.92 ± 0.45
Placebo *n* = 19	0.64 ± 0.27	0.80 ± 0.30	0.89 ± 0.32	0.96 ± 0.30	0.96 ± 0.36	0.78 ± 0.27	0.84 ± 0.23	1.00 ± 0.31	1.01 ± 0.42	0.96 ± 0.42
SM-T9 *n* = 18	0.83 ± 0.32	1.02 ± 0.38	0.93 ± 0.27	0.90 ± 0.25	0.85 ± 0.32	0.72 ± 0.24	0.80 ± 0.26	0.97 ± 0.31	0.95 ± 0.42	0.94 ± 0.35
SM-T5 *n* = 14	0.66 ± 0.32	0.82 ± 0.35	0.89 ± 0.34	0.94 ± 0.30	0.88 ± 0.24	0.68 ± 0.27	0.84 ± 0.35	1.00 ± 0.30	1.13 ± 0.24	1.09 ± 0.29

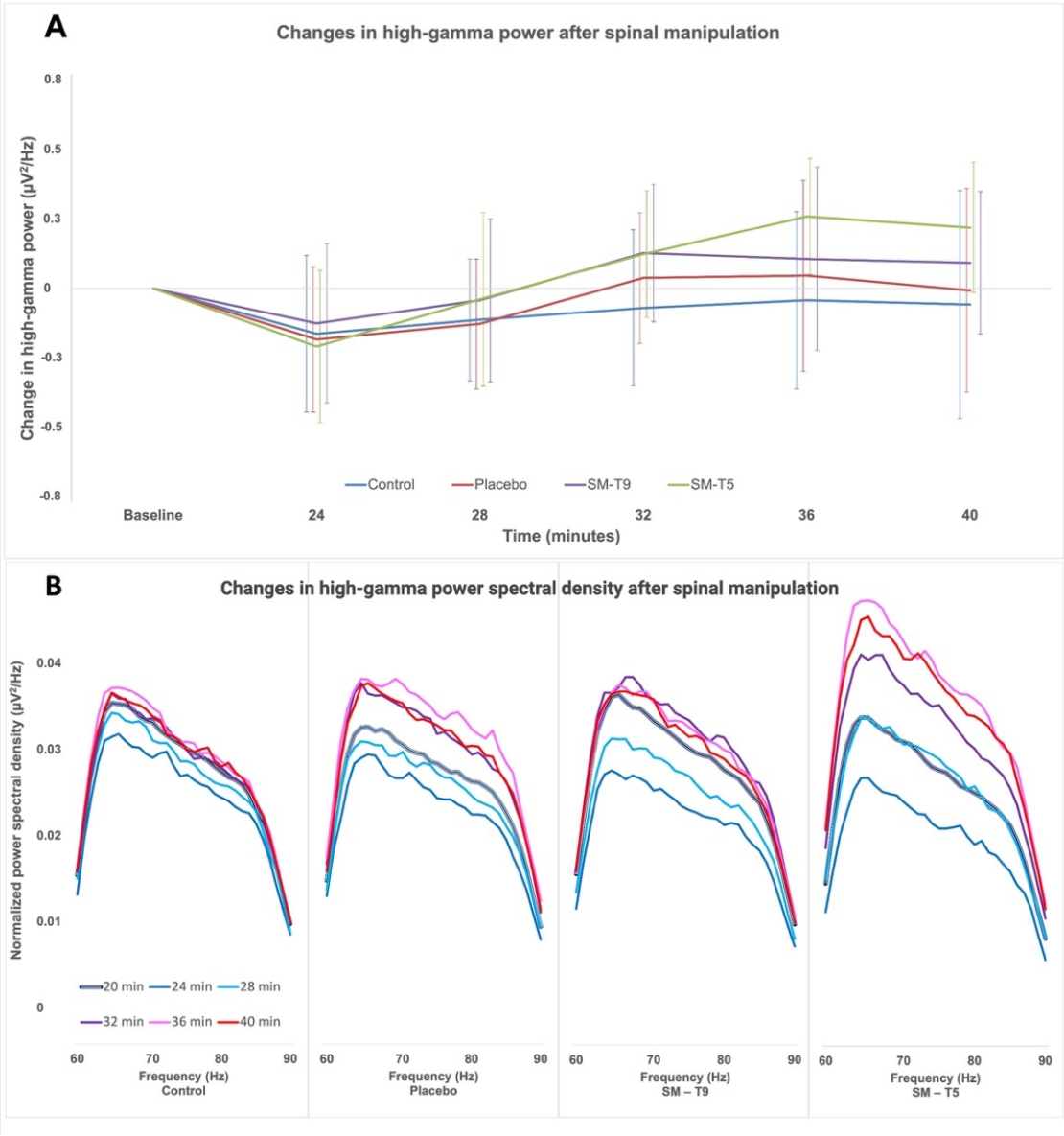

Figure 10 Changes in high-gamma power in Experiment 2

(A) Comparison of the change in high-gamma oscillation power relative to baseline between groups over time. Error bars represent standard deviations corrected to remove between-subject variability (see Methods). High-gamma power was not significantly different between groups over time ($p = 0.5$). **(B)** Changes in the power spectrum density in the high-gamma frequency range (60–90Hz, at a definition of 0.977Hz) relative to baseline, for the four different intervention groups. The thick black and white line represents the baseline (20min.). Subsequent time points are represented by lines of different colors: 4min. post-baseline (24min. - navy-blue), 8min. post-baseline (28min. - light blue), 12min. post-baseline (32min. - purple), 16min. post-baseline (36min. -

pink) and 20min. post-baseline (40min. - red). SM–T5, spinal manipulation at T5; SM–T9, spinal manipulation at T9.

Discussion

In the present study, topical capsaicin was applied to the back to evoke tonic pain. Spinal manipulation at the location of capsaicin-induced pain prevented the development of secondary hyperalgesia. However, capsaicin pain and frontal high-gamma oscillations were not significantly different between groups over time. The present findings suggest that SM produces anti-hyperalgesic effects that attenuate central sensitization.

Segmental Reduction of Secondary Hyperalgesia

Pressure algometry has excellent reliability in the assessment of PPTs with an intra-class coefficient ranging between 0.8 and 0.99 (Balaguier, et al., 2016; Mailloux et al., 2021). Deep PPTs as measured in the present study are commonly used to examine changes in central sensitization (Middlebrook et al., 2021). The results of the present study show that topical capsaicin applied to the back produces secondary hyperalgesia, as indicated by lower PPTs 15 mm outside the area of capsaicin application, in participants that received the placebo intervention or no intervention. This is consistent with previous studies that showed decreased mechanical pain thresholds 45 minutes to 2 hours after topical capsaicin application to the volar surface of the forearm, in an area 8-10 mm beyond the area of application (Andrews, et al., 1999; Zheng et al., 2000).

In the SM–T5 group, SM prevented secondary hyperalgesia and this effect was significantly greater than placebo. In the SM–T9 group, SM also attenuated the development of secondary hyperalgesia, although this effect was not significantly different compared with the placebo. These results are consistent with and extend findings from a previous study that showed a reduction in the area of secondary hyperalgesia following SM, compared with a control intervention consisting of SM positioning and light manual contact (Mohammadian, et al., 2004). In this study, SM was applied at one or multiple spinal segments irrespective of the region of capsaicin application (on the forearm). These findings provide support to the hypothesis that pain relief by SM is mediated centrally, however, no specific mechanism could be inferred. By controlling for segmental and heterosegmental effects, the present study provides novel findings that indicate that secondary hyperalgesia is attenuated by SM through segmental mechanisms. Similarly, an animal study showed that ankle joint mobilization could reverse secondary hyperalgesia induced by intradermal

capsaicin injection in the lateral ankle (Sluka and Wright, 2001). Together, these findings indicate that the activation of joint and/or muscle mechanoreceptors during SM or mobilization (Pickar and Bolton, 2012) regulates central sensitization processes, likely via segmental mechanisms.

The segmental effects of SM in the present study are consistent with a large body of evidence showing that PPTs are increased segmentally after the application of SM (Coronado et al., 2012; Honore et al., 2018; Millan et al., 2012). While previous research has focused predominantly on investigating segmental effects in non-painful segments in healthy participants, the present results indicate that SM may influence PPTs of sensitized segments. This is in line with an increase of PPTs when SM is applied to the segment with the highest pain sensitivity compared with the segment with the higher stiffness in patients with low back pain (Nim et al., 2020). However, it should be noted that in the SM–T9 group, SM also attenuated the development of secondary hyperalgesia, although the effect was not significantly different compared with placebo. This suggests that SM may also produce anti-hyperalgesic effects when applied heterosegmentally, although they may be weaker than when SM is applied to the painful segment.

In addition to the segmental mechanism underlying increased PPTs, SM-induced pain inhibition in the back or in related dermatomes was shown to depend on the inhibition of processes related to temporal summation (Bialosky, et al., 2009b; George et al., 2006; Randoll, et al., 2017). Repeated or sustained activation of nociceptive C-fibers is thought to be necessary for the induction of both temporal summation and secondary hyperalgesia (Latremoliere and Woolf, 2009; Price et al., 1977; Torebjork et al., 1992; Ziegler et al., 1999). Altogether, these results suggest that SM may regulate pain and prevent the transition from acute to chronic pain, which is associated with C-fiber activation through anti-hyperalgesic mechanisms involving the stimulation of joint and muscle receptors. This remains to be confirmed and should also be examined in patients with back pain using a series of SM interventions.

Contribution of Expectations

In the current study, expectations of pain relief were measured at the beginning of the experiment in the three intervention groups to control for a potential contribution of expectations to the effects of SM. Participants were not told that different interventions were compared so we expected no difference in expectations between groups. Accordingly, no significant difference was observed. Nevertheless, we conducted a covariance analysis and confirmed the lack of contribution

of expectations to the group difference in secondary hyperalgesia. This is consistent with previous findings that showed a C-fiber mediated hypoalgesic effect of SM independent of expectations (Bialosky et al., 2008; Bialosky et al., 2014). It should also be noted that the placebo intervention in the present study did not produce any effect compared with no intervention, despite some expectations of pain relief, indicating that expectations did not reduce secondary hyperalgesia and that the placebo was inert.

Capsaicin Pain

In the present study, capsaicin pain was not significantly decreased by SM. This contrasts with the significant decrease of capsaicin pain by SM reported previously (Mohammadian, et al., 2004). In this experiment, however, capsaicin was applied to the forearm and SM was delivered at multiple segments after the capsaicin was removed. These methodological differences may explain the different findings. More recently, no significant change in pain intensity or unpleasantness induced by a tonic cold stimulus was observed following SM (Navid et al., 2019). However, tonic pain was applied to the upper limb in that study, so it is not clear how these results are comparable.

It has been proposed that SM may have selective effects on pain thresholds, affecting mechanical pain sensitivity preferentially (Aspinall et al., 2019b). The present results are consistent with this hypothesis SM did not modulate chemically-mediated capsaicin pain but may attenuate the development of mechanical pain hypersensitivity. This suggests that the anti-hyperalgesic effects may be stronger than hypoalgesic effects or that primary hyperalgesia is not affected by SM, which may explain some discrepancies between studies (Aspinall et al., 2019a; Gevers-Montoro, et al., 2021). This remains to be confirmed in future studies and the anti-hyperalgesic effects of SM should also be examined in regard to primary hyperalgesia, with the application of a mechanical stimulus to skin sensitized by capsaicin.

Brain Activity

Consistent with the results for capsaicin pain, high-gamma power significantly increased over time, but this effect was not significantly different between groups. Navid and colleagues also reported no change in pain perception and in cerebral oscillations evoked by tonic pain after SM (Navid, et al., 2019).

Frontal high-gamma oscillations were shown to be related to tonic experimental pain (Li, et al., 2016; Nickel, et al., 2017; Schulz, et al., 2015) and spontaneous clinical pain (Lim et al., 2016; May, et al., 2019). An association between pain ratings and high-gamma oscillation power at sensorimotor electrodes has also been reported for phasic pain stimuli (Gross et al., 2007; Rossiter et al., 2013; Zhang et al., 2012). A limited number of studies have assessed whether gamma oscillations could be used as a biomarker of treatment-specific pain changes. For example, a significant reduction of pain-evoked gamma oscillations was reported after the use of Transcutaneous Electrical Nerve Stimulation (TENS) (Ebrahimian, et al., 2018). However, the specific location of this brain activity was not examined, and no control condition was included to confirm the specificity of TENS effects. Nonetheless, future studies in which SM inhibits tonic pain compared with placebo may show a reduction of gamma oscillation power.

Although the lack of gamma power reduction is consistent with the lack of effects on capsaicin pain, one factor to consider in future studies is the position of participants during EEG recording. In the present study, EEG recordings were performed while subjects were in a prone position and some participants reported discomfort, which may have influenced EEG activity. Indeed, a recent study reported that prolonged cervico-facial contractions (grimaces) increase gamma oscillations at fronto-temporal electrodes (Chouchou et al., 2021). Thus, future studies should limit or control for muscle activity and ensure that pain-evoked activity and muscle activity can be separated. Another alternative would be to examine the suppression of alpha oscillations, which are suggested to be less sensitive to muscle artifacts (Chouchou, et al., 2021). EEG recording with a larger number of electrodes would be essential in order to overcome these limitations and to allow the comparison of scalp topographies with previous studies.

Limitations of This Study

Topical application of capsaicin to the back has not been used to evoke experimental pain in previous studies. Pain intensity and unpleasantness induced by capsaicin did not exceed 5/100 in eight participants (~ 10%). Large variability in the response to capsaicin application has been reported (Liu et al., 1998) and this should be considered in the design of future experiments. In the present study, it is possible that the low pain ratings in some participants may have limited the sensitivity to detect an inhibition of capsaicin pain and pain-related brain activity by SM.

Another point to consider in future studies is to confirm to what extent participants were blind to different interventions by asking whether they think they received a real or a sham intervention. In the present study, participants were informed that a force would be applied to their spine in the middle of the experiment, but they were unaware that different interventions were performed in different groups. Thus, participants were not asked if they thought that the intervention was real or sham.

Conclusion

Overall, the present results indicate that segmental SM can prevent capsaicin-induced secondary hyperalgesia independently of expectations of pain relief. In contrast, spontaneous pain and frontal high-gamma oscillations induced by capsaicin were not modulated by SM. This suggests that SM may produce anti-hyperalgesic effects, which are relevant to patients with back pain in which central sensitization is involved. The anti-hyperalgesic effects of SM may also contribute to the treatment and prevention of chronic back pain, but this remains to be investigated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Research Ethics Board of the Hospital Clínico San Carlos, Madrid, Spain and Research Ethics Board of the Université du Québec à Trois-Rivières, Trois-Rivières, Canada. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CG-M contributed to study design, data collection, analyses and interpretation, and wrote the preliminary version of the manuscript. BP and SN contributed to data analyses, JS-L contributed to data collection. AO contributed to manuscript editing and guidance in the study design. MP contributed to study design, data analyses and interpretation, wrote the final version of the manuscript, and obtained funding for the study. All authors contributed significantly to this work and has read and approved the final version of the manuscript.

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Chapter 6: Article 3 – Clinical effectiveness and efficacy of chiropractic spinal manipulation for spine pain

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Abstract

Spine pain is a highly prevalent condition affecting over 11% of the world's population. It is the single leading cause of activity limitation and ranks fourth in years lost to disability globally, representing a significant personal, social, and economic burden. For the vast majority of patients with back and neck pain, a specific pathology cannot be identified as the cause for their pain, which is then labeled as non-specific. In a growing proportion of these cases, pain persists beyond 3 months and is referred to as chronic primary back or neck pain. To decrease the global burden of spine pain, current data suggest that a conservative approach may be preferable. One of the conservative management options available is spinal manipulative therapy (SMT), the main intervention used by chiropractors and other manual therapists. The aim of this narrative review is to highlight the most relevant and up-to-date evidence on the effectiveness (as it compares to other interventions in more pragmatic settings) and efficacy (as it compares to inactive controls under highly controlled conditions) of SMT for the management of neck pain and low back pain. Additionally, a perspective on the current recommendations on SMT for spine pain and the needs for future research will be provided. In summary, SMT may be as effective as other recommended therapies for the management of non-specific and chronic primary spine pain, including standard medical care or physical therapy. Currently, SMT is recommended in combination with exercise for neck pain as part of a multimodal approach. It may also be recommended as a frontline intervention for low back pain. Despite some remaining discrepancies, current clinical practice guidelines almost universally recommend the use of SMT for spine pain. Due to the low quality of evidence, the efficacy of SMT compared with a placebo or no treatment remains uncertain. Therefore, future research is needed to clarify the specific effects of SMT to further validate this intervention. In addition, factors that predict these effects remain to be determined to target patients who are more likely to obtain positive outcomes from SMT.

Background

Pain affecting the spine not only has a significant impact on the individual's health and functional ability but also carries considerable costs to the economy and society at large, mostly derived from treatment expenses and work absenteeism (Hurwitz et al., 2018; Manchikanti et al., 2009). Back and neck pain combined are the number one cause of years lived with disability and the fourth leading cause of years lost to disability globally (Collaborators, 2018; Hurwitz, et al., 2018). At any time, over 11% of the world population suffers from pain in the spine (Safiri et al., 2020; Wu et al., 2020). The prevalence has been increasing over the past decade (Hurwitz, et al., 2018), particularly among working-age females in high-income countries (Hoy et al., 2012; Safiri, et al., 2020; Wu, et al., 2020). Chronic cases where pain lasts for more than three months significantly contribute to the increasing burden of spine pain (Hurwitz, et al., 2018; Manchikanti, et al., 2009). Likewise, pain affecting the spine affects more than 50% of patients with chronic pain (Breivik et al., 2006; Manchikanti, et al., 2009), a condition whose estimated direct and indirect costs are hundreds of billions of dollars (Cohen et al., 2021). The frequent use of inappropriate and invasive clinical interventions has been suggested as one of the main reasons for this increasing burden (Buchbinder et al., 2020; Cohen, et al., 2021; Manchikanti, et al., 2009).

Throughout the past decade, recommendations for the evaluation and treatment of back pain have shifted toward less invasive, nonpharmacologic approaches. This is partly the consequence of the opioid use epidemic in North America, largely driven by high rates and doses of opioid prescriptions for noncancer pain (Bohnert et al., 2011; Gomes et al., 2011; Ray et al., 2016). The Lancet series on low back pain (LBP) highlighted an overreliance on secondary care, imaging, opioids, spinal injections, and surgery (Buchbinder, et al., 2020; Foster et al., 2018). Instead, currently available data provide stronger support for the use of conservative interventions and self-management strategies (Buchbinder, et al., 2020; Corp et al., 2021; Foster, et al., 2018; Kirkwood et al., 2021). This is reflected in the recent publication of systematic reviews and clinical practice guidelines exclusively devoted to summarizing the evidence and recommendations for noninvasive treatments for neck pain (NP) and LBP (Chou et al., 2018; Hurwitz et al., 2008; Qaseem et al., 2017). Among these interventions, manual therapy is frequently recommended as one of many front-line options for spine pain (Bailly et al., 2021; Chou, et al., 2018; Corp, et al., 2021; Foster, et al., 2018; Hurwitz, et al., 2008; Kirkwood, et al., 2021; Qaseem, et al., 2017).

Chiropractic is a health care profession concerned with the management of neuromusculoskeletal conditions and, more specifically, disorders affecting the spine (W.H.O., 2005). Arguably, chiropractors' area of expertise lies within the field of spine care and in the application of manual therapy (Nelson et al., 2005; Schneider et al., 2016). Most chiropractic patients seek care for spine-related conditions (Adams et al., 2017; Beliveau et al., 2017; Herman et al., 2018). Likewise, people with back pain frequently visit chiropractors in high-income countries (Adams, et al., 2017; Deyo, 2017; Walker et al., 2011). Chiropractors strongly rely on the use of manual therapy, particularly spinal manipulation (SM), which is the main form of care they provide (Beliveau, et al., 2017; Walker, et al., 2011). In the United States, where data are available, chiropractors perform a large proportion of all SM treatments (Hurwitz, 2012; Whedon et al., 2021). Chiropractic SM is sometimes referred to as a chiropractic or spinal adjustment in the literature (Haavik et al., 2021). Typically, a spinal adjustment consists of the application of a high-velocity, low-amplitude controlled thrust force to a spinal segment. For the purpose of this review, all interventions relying on the application of such thrust forces to the spine will be considered under the common terms SM and SMT (spinal manipulative therapy). The clinical indication of chiropractic SM has been the subject of controversy (Henderson, 2012). However, SM provided by chiropractors for spine pain was recently demonstrated to be cost-effective and rarely inappropriate (Coulter et al., 2021; Khodakarami, 2020). Furthermore, accumulating evidence on the effectiveness of SMT for the treatment of acute and chronic back and neck pain has rendered it an acceptable management option (Cohen, et al., 2021; Deyo, 2017).

Recent research on SMT suggests that chiropractic care may be evolving from the field of complementary and alternative medicine toward becoming a mainstream option for spine pain (Meeker and Haldeman, 2002; Schneider, et al., 2016). However, there is a need to summarize the most up-to-date research in the field for a better understanding of this evolution. Here, we aimed to review the most recent randomized clinical trials on the effectiveness and efficacy of SM and SMT for the management of NP and LBP, mostly published in the past decade. In addition, recommendations from state-of-the-art clinical practice guidelines will be presented, as well as a perspective on challenges and future directions for research on chiropractic SMT and spine pain. While the narrative review will be informed not exclusively by studies where chiropractors apply SM, this is done to inform chiropractic clinical practice with the best current available evidence.

Methods

For the purpose of this review, the literature search was limited to SMT and manual therapy, when it comprised SM. Studies were included if they concerned the effectiveness and efficacy of SM, with no selection criteria for the professionals performing the intervention. Among these studies, only those published in English language between January 1st, 2009 and October 1st, 2019 were considered during the original selection. Relevant studies published after 2019 were added to the original selection during the publication process.

The following Databases were searched: Pubmed or Medline, Cochrane, CINAHL and the Index to Chiropractic Literature (ICL). The key search terms used for efficacy and effectiveness studies were: "spinal manipulation", "spinal manipulative therapy", "manual therapy", "chiropractic" AND "efficacy" or "effectiveness". The results were filtered, and articles were selected with the key terms "lumbar" or "low back". Since most studies concerned the lumbar spine, the terms "cervical", "neck" and "thoracic" were added to search literature on neck pain.

To narrow the search in line with the research question, clinical studies on the shoulder, upper extremity, chest pain, headache, dizziness, fibromyalgia, dysmenorrhea, or visceral conditions were excluded. Studies on pediatric populations were also excluded. The selection only included randomized controlled trials, systematic reviews, and clinical practice guidelines. Relevant articles were screened using the title and abstract. Two reviewers performed the search independently using these same criteria. After duplicates were eliminated, disagreements about inclusion were resolved through discussion and consensus.

A distinction needs to be made between effectiveness and efficacy, as these concepts refer to different levels of clinical evidence for an intervention (Fritz and Cleland, 2003). Effectiveness studies assess the outcomes of a treatment usually under circumstances that more closely resemble clinical practice. To do so, the intervention is commonly compared to another active treatment, such as standard care provided for the condition investigated (Fritz and Cleland, 2003). In contrast, efficacy studies are usually conceived as randomized clinical trials that are run under ideal and highly controlled experimental conditions. The treatment to be explored is preferably compared to an inactive comparator with known inertness, such as a sham or placebo (Fritz and Cleland, 2003). The most up-to-date evidence regarding the effectiveness of SMT for spine pain will be reviewed first, followed by a presentation of studies discussing its efficacy below.

Effectiveness of Spinal Manipulative Therapy for Neck Pain

Nonspecific NP is defined as pain between the skull and the first thoracic vertebra in the absence of a specific pathology or neurological sign (Borghouts et al., 1998; Coulter et al., 2019). Most cases of NP have been described as being of mechanical origin (Binder, 2008), which categorizes them as nonspecific (Borghouts, et al., 1998). In at least 10% of patients, nonspecific symptoms persist beyond three months and can become chronic (Binder, 2008). In these cases, the condition is now defined as chronic primary (neck) pain (Nicholas et al., 2019; Treede et al., 2019). The effectiveness of SMT has been examined in several studies on chronic primary NP as well as on acute and subacute nonspecific NP. Most studies aimed to compare the effectiveness of a treatment based on SM to another active treatment, while fewer data are available concerning the efficacy of SMT compared to placebo (Coulter, et al., 2019; Masaracchio et al., 2019; Suvarnnato et al., 2013). The most frequent active comparators used against SMT were other interventions commonly used for the management of NP, such as exercise or physical therapy modalities (Bronfort et al., 2012; Cleland et al., 2010; Evans et al., 2012; Galindez-Ibarbengoetxea et al., 2018; Gonzalez-Iglesias et al., 2009; Gorrell et al., 2016; Lau et al., 2011; Saavedra-Hernandez et al., 2012). Additional studies compared the application of SM to that of mobilization techniques or examined the effect of different SM application sites (cervical *vs*. thoracic) (Alonso-Perez et al., 2017; Dunning et al., 2012; Gemmell and Miller, 2010; Griswold et al., 2018; Izquierdo Perez et al., 2014; Joshi et al., 2020; Masaracchio et al., 2013; Salom-Moreno et al., 2014; Suvarnnato, et al., 2013). However, these trials often measured short-term effects after short periods of care, which may not be as informative to clinical practice. All studies assessed pain intensity, the main outcome of interest for the present review, as measured with a numerical rating scale (NRS) or a visual analog scale (VAS). The second outcome measure of interest is the level of disability caused by NP, more commonly measured by the neck disability index (NDI) or the Northwick Park Neck Pain Questionnaire (NPQ). Outcomes may be assessed at variable follow-up times according to the study design. For both NP and LBP, a follow-up period of one month or less is generally considered short-term, intermediate-term is approximately six months and long-term follow-up after one year (Gross et al., 2015; Rubinstein et al., 2019). **Figure 11** provides an illustration of the main results from the studies that are discussed below.

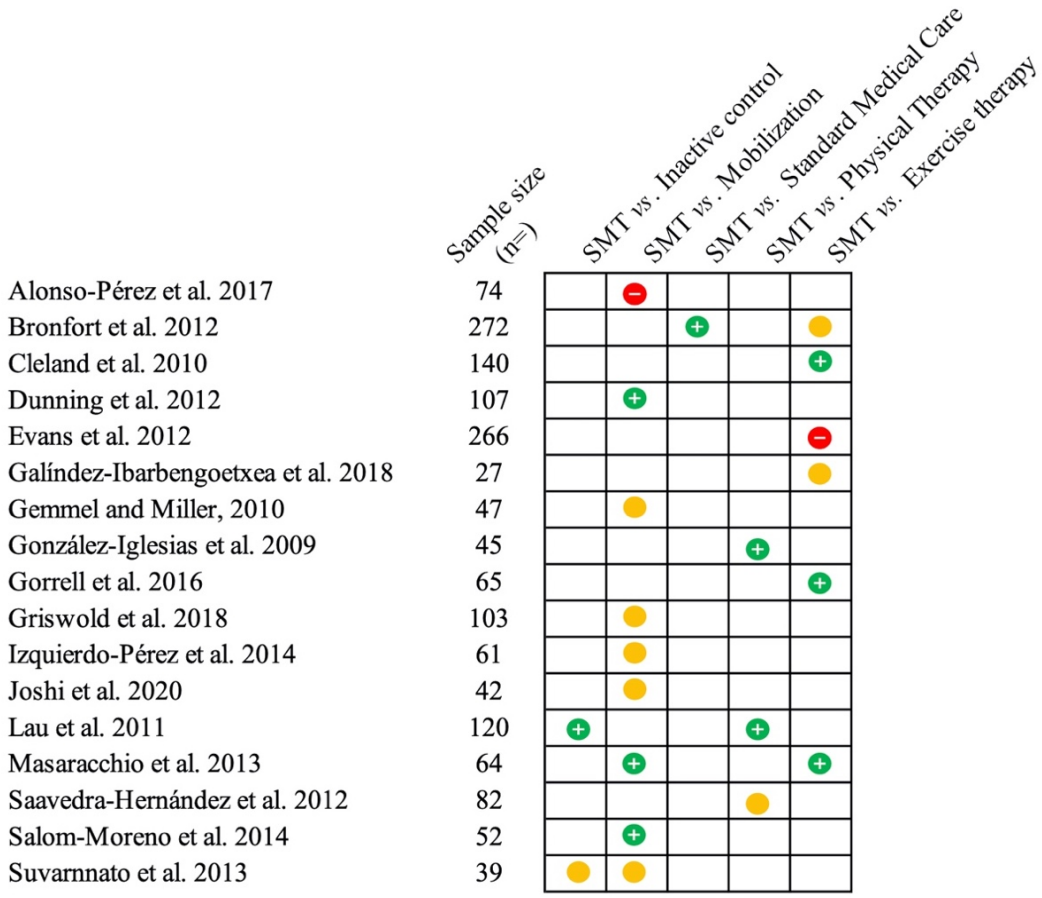

Figure 11 Summary of the studies reviewed on neck pain

This figure summarizes the main findings from the studies presented on the efficacy (compared to inactive controls) and effectiveness of spinal manipulative therapy (SMT) against different comparators for acute and chronic neck pain. The green circles with the positive sign indicate studies reporting pain-related outcomes in favor of SMT against or when added to the comparator. Yellow circles indicate similar effectiveness. Red circles with a negative sign indicate that SMT is inferior or does not add any value to the comparator.

Effectiveness of Spinal Manipulation Compared to Mobilization for Neck Pain

SM and mobilization are usually differentiated based on distinct biomechanical parameters of the forces applied, more specifically the force amplitude and rate of application (Bolton and Budgell, 2006). Whereas SM has been characterized as a high-velocity low amplitude thrust, mobilization techniques generally involve the application of a force to a region or specific joint with larger (but variable) amplitude and lower velocity, without the thrust force (Bolton and Budgell, 2006; Gross, et al., 2015). Hence, mobilization is sometimes referred to as nonthrust SM

(Gross, et al., 2015; Salom-Moreno, et al., 2014). When directly comparing the application of SM to mobilization, several studies reported no significant differences in pain intensity, disability, range of motion or quality of life, although all outcomes improved significantly regardless of the intervention (Alonso-Perez, et al., 2017; Gemmell and Miller, 2010; Griswold, et al., 2018; Izquierdo Perez, et al., 2014; Joshi, et al., 2020; Suvarnnato, et al., 2013). However, when comparing both interventions to a control (inactive treatment) group, neither was successful at reducing pain (Suvarnnato, et al., 2013). Thus, it is not clear if the reported effects were specific to the interventions, as will be discussed in Section 3.

Not all studies have reported consistent results. For example, a combination of cervical and thoracic SM produced greater reductions in NP and disability compared to mobilization of the same regions (Dunning, et al., 2012). In another study, patients with chronic primary NP experienced larger reductions in pain intensity with thoracic SM compared to mobilization (Salom-Moreno, et al., 2014). Furthermore, adding two sessions of thoracic SM to cervical mobilization and a home exercise program yielded greater improvement in pain ratings and disability than mobilization and exercise alone (Masaracchio, et al., 2013). What these studies have in common is thoracic SM being included as part of the active treatment. In contrast, studies reporting no differences between SM and mobilization often assessed cervical SM specifically (Alonso-Perez, et al., 2017; Gemmell and Miller, 2010; Izquierdo Perez, et al., 2014). This is consistent with the conclusions from a recent systematic review and meta-analysis that SM, when applied to the thoracic spine, has a significant effect on pain and disability compared to mobilization (Masaracchio, et al., 2019). It could be argued that only thoracic SMT has demonstrated superiority to mobilization in the short term for NP and disability (Gross, et al., 2015). Overall, the current body of literature provides stronger support for thoracic rather than cervical SMT for the treatment of NP (Cross et al., 2011; Gross, et al., 2015; Saavedra-Hernandez et al., 2013; Vincent et al., 2013; Young et al., 2014), suggesting that the site of application could influence the effectiveness of SMT for NP.

Effectiveness of Spinal Manipulative Therapy Compared to Usual Care for Neck Pain

To evaluate the effectiveness of SMT for NP, outcomes are frequently compared to those of usual care. Usual care for NP has not been readily defined in the literature and could refer to one of two different approaches: standard medical care based on medication, home exercise and advice,

or the application of standard physical therapy modalities including supervised exercise (Bronfort, et al., 2012; Masaracchio, et al., 2019). Two clinical trials compared the addition of SMT to a standard physical therapy treatment (electric or thermal stimulations, with or without educational material) for the management of acute (Gonzalez-Iglesias, et al., 2009) and chronic NP (Lau, et al., 2011). In both cases, adding thoracic SMT provided greater reductions in pain intensity and disability lasting up to six months (Gonzalez-Iglesias, et al., 2009; Lau, et al., 2011). Interestingly, one session of cervical SMT did not prove to be more effective than Kinesio taping for NP, an approach frequently used in physical therapy practice (Saavedra-Hernandez, et al., 2012). This may be interpreted as further evidence indicative of cervical SM being inferior to thoracic SM, although the evidence for this comparison is still scarce to draw inferences (Masaracchio, et al., 2019).

In patients with acute and subacute NP, one trial compared SMT against medication (acetaminophen, nonsteroidal anti-inflammatory drugs or both) or a home exercise program with advice (Bronfort, et al., 2012). The results from this study suggest that SMT is more effective than medication but not home exercise (Bronfort, et al., 2012). Along the same lines, no between-group differences in pain and disability were reported one week after a home exercise program or a single session of SMT for patients with chronic NP (Galindez-Ibarbengoetxea, et al., 2018). These data suggest that SMT is not superior to home exercise, although they do not allow us to determine whether SMT provides any additional benefit to exercise therapy. The addition of a single session of manual SM (as opposed to instrumental SM) to a stretching exercise program (used as a control intervention) was more effective in reducing NP intensity than the control exercise program alone (Gorrell, et al., 2016). Similar results were found when two sessions of thoracic SM were added to an exercise program, partially assisted by a physical therapist and partially performed at home (Cleland, et al., 2010). These findings may indicate that one or two sessions of SMT may add value to exercise therapy for NP in the short term. However, in the long term, supervised exercise with and without SMT was found to be superior to a home exercise program for decreasing chronic NP intensity (Evans, et al., 2012). Noteworthy, both studies assessing the effectiveness of multiple SMT sessions (> 12) showed no superior benefit of SMT compared to exercise for NP of any duration (Bronfort, et al., 2012; Evans, et al., 2012). These findings suggest that SMT does not provide additional benefits to certain forms of exercise in the longer term. In addition, they raise questions regarding the number of SMT sessions needed to influence NP outcomes. The available data do not indicate that a higher number of visits influences NP intensity, although this has only

been studied as a secondary outcome in studies where cervicogenic headaches was the primary outcome (Haas et al., 2018; Pasquier et al., 2019). It also remains to be clarified whether greater benefits are achieved with supervised or unsupervised exercise (as in a home exercise program) compared to SMT. Thus far, it has not been possible to identify one form of exercise that is superior to another for NP (Southerst et al., 2016). Therefore, the results from systematic reviews of the past decade aiming to reconcile these discrepancies are discussed below.

Two earlier reviews examined the effectiveness of adding manual therapy (including SMT) to exercise as a single modal intervention or combined with other physical therapy modalities (D'Sylva et al., 2010; Miller et al., 2010). The addition of manual therapy to exercise provided greater short-term pain relief (Miller, et al., 2010) and improved patient satisfaction (D'Sylva, et al., 2010) when compared to exercise alone in acute NP. However, subsequent reviews updated with newer data reached opposite conclusions on this question (Fredin and Loras, 2017; Hidalgo et al., 2017). The meta-analysis by Fredin and Loras suggested that adding manual therapy (including SMT in 4/7 studies included) to exercise therapy does not result in additional clinical benefits (Fredin and Loras, 2017). In contrast, Hidalgo et al. found moderate to strong evidence in favor of combining SMT and exercise for NP when compared to either of them alone (Hidalgo, et al., 2017). The most recent systematic reviews and meta-analyses examined the effectiveness of SMT by directly comparing it with usual management options (Coulter, et al., 2019; Masaracchio, et al., 2019). Both reviews concluded that SMT is an equally effective approach to reduce pain and disability in the short term when compared to other interventions, including exercise (Coulter, et al., 2019; Masaracchio, et al., 2019). Nevertheless, the strongest evidence was found in support of multimodal approaches, such as the combination of SMT and exercise (Coulter, et al., 2019).

Overall, the data reviewed indicate that SMT may be considered an effective intervention for the management of NP (Wong J.J. et al., 2016). Mobilization techniques seem to be comparable to SM, although some evidence suggests that thoracic SM may outrank mobilization. SMT is at least as effective as medication and physical therapy modalities for various stages of NP. The combination of SMT and exercise may provide one of the best approaches for the management of NP. These conclusions are summarized in Table 6.1.

Table 6.1 Effectiveness and efficacy (compared to inactive controls) of spinal manipulative therapy (SMT) for the management of neck pain (NP)

Comparisons studied	Conclusions from previous studies
SMT *vs*. Inactive control	Inconsistent evidence that thoracic SMT may be superior to inactive treatment but not placebo [a-d].
SMT *vs.* Mobilization	Evidence supporting thoracic SM (but not cervical) when compared to mobilization [c,e-i]
SMT *vs.* Standard Medical Care	Insufficient evidence for a combination of cervical and thoracic SM when compared to analgesic medication and a home exercise program[j].
SMT *vs*. Physical Therapy	Evidence supporting SMT when compared to physical therapy[a,d,k].
SMT *vs*. Exercise	Evidence supporting that SMT is not superior to exercise but may add value to unsupervised exercise [j,l-n], unclear about supervised exercise[o,p].
Guidelines' recommendations	SMT is recommended after advice/patient education alone[q], or in combination with exercise[r,s]. In acute NP, this combination may be offered before medication[s].

[a]Lau et al., 2011. [b]Suvarnatto et al., 2013. [c]Gross et al., 2015 [d]Coulter et al., 2019. [e]Dunning et al., 2012. [f]Saavedra-Hernández et al., 2012. [g]Masaracchio et al., 2013. [h]Salom-Moreno et al., 2014. [i]Young et al., 2014. [j]Bronfort et el., 2012. [k]González-Iglesias et al., 2009. [l]Cleland et al., 2010. [m]Gorrell et al., 2016. [n]Galíndez-Ibarbengoetxea et el., 2018. [o]Evans et al., 2012. [p]Masaracchio et al., 2019. [q]Chou et al., 2018. [r]Cote et el., 2016. [s]Kjaer et al., 2017.

Effectiveness of Spinal Manipulative Therapy for Low Back Pain

LBP can originate from multiple musculoskeletal and neurovascular tissues, but for a large majority of cases, the specific structures involved remain elusive (Vlaeyen et al., 2018). Therefore, LBP presenting to primary care is predominantly considered nonspecific, meaning that no specific source of nociception or pathology can be detected (Vlaeyen, et al., 2018). When this condition persists or recurs beyond three months, cases are classified as chronic primary LBP (Nicholas, et al., 2019; Vlaeyen, et al., 2018). Independent of duration, LBP is one of the most common complaints for patients presenting to primary care (Finley et al., 2018; Hartvigsen et al., 2018). Hence, the effectiveness of SMT is frequently evaluated by comparing its application to standard medical care or physical therapy (Bronfort et al., 2014; Bronfort et al., 2011; Cecchi et al., 2010; Ghasabmahaleh et al., 2021; Goertz et al., 2013; Juni et al., 2009; Nambi et al., 2018; Petersen et al., 2011; Schneider et al., 2015). Standard medical care based on medication is more frequently used during the early stages of LBP (Goertz, et al., 2013; Juni, et al., 2009; Schneider, et al., 2015),

while interventions based on exercise therapy are commonly prescribed for chronic primary LBP (Bronfort, et al., 2011; Ghasabmahaleh, et al., 2021; Nambi, et al., 2018; Petersen, et al., 2011). Fewer studies have examined the differences with sham/placebo interventions (Bialosky et al., 2014; Haas et al., 2014; Senna and Machaly, 2011; Thomas et al., 2020; Vieira-Pellenz et al., 2014; von Heymann et al., 2013), and a handful have contrasted SMT to mobilization techniques for LBP (Cook et al., 2013; Hondras et al., 2009; Xia et al., 2016). The outcome measures generally assessed include subjective reports of pain intensity and disability (the latter via the use of the Roland-Morris and Oswestry questionnaires), which are also the outcomes of interest for the present review. The main findings from the trials reviewed below are illustrated in **Figure 12**.

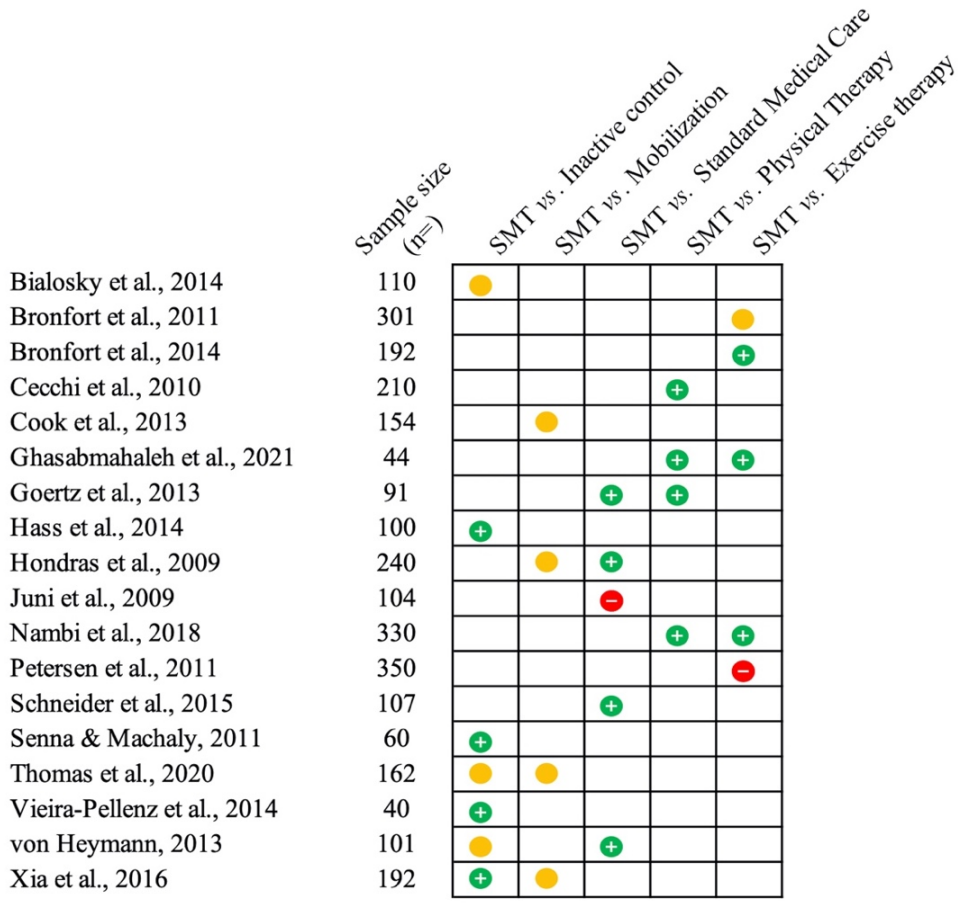

Figure 12 Summary of the studies reviewed on low back pain

This figure summarizes the main findings from the studies presented on the efficacy (compared to inactive controls) and effectiveness of spinal manipulative therapy (SMT) against different comparators for acute and chronic low back pain. The green circles with the positive sign indicate studies reporting pain-related outcomes in favor of SMT against or when added to the comparator. Yellow circles indicate similar effectiveness. Red circles with a negative sign indicate that SMT is inferior or does not add any value to the comparator.

Effectiveness of Spinal Manipulation Compared to Mobilization for Low Back Pain

A few studies have investigated the differences between SMT and mobilization for the management of LBP at different stages (Cook, et al., 2013; Hondras, et al., 2009; Xia, et al., 2016). Different mobilization techniques were employed, always consisting of the application of low-velocity forces of variable amplitude, without high-velocity thrust. Cook and colleagues recruited a sample of 149 patients with predominantly chronic LBP (symptom duration averaging > 7 months) to examine the differences between thrust SMT and nonthrust mobilization in a pragmatic setting (Cook, et al., 2013). No differences were found between groups, and more importantly, personal equipoises influenced pain and disability outcomes. In other words, different outcomes may be driven by practitioner preference for the technique (Cook, et al., 2013). A specific mobilization technique where a flexion-distraction table is used to apply low-velocity forces was compared to SMT for subacute and chronic LBP (Hondras, et al., 2009; Xia, et al., 2016). No differences were reported between SMT and mobilization for any outcome, while both techniques were shown to be more effective than a waiting list for reducing pain and disability (Xia, et al., 2016) and more effective than medication for disability (Hondras, et al., 2009). A recent systematic review reached the same conclusions regarding the equivalence of SMT and mobilization (Rubinstein, et al., 2019). For this reason, both techniques are often analyzed and recommended in guidelines as a single intervention (Chou, et al., 2018; Coulter et al., 2018).

Effectiveness of Spinal Manipulative Therapy Compared to Usual Care for Low Back Pain

Most clinical trials have examined the effectiveness of SMT for LBP by comparing SMT to another intervention recommended for LBP (Rubinstein, et al., 2019). Standard medical treatment offered in primary care for LBP of recent onset has been used as an active comparator against SMT alone or as an addition to medical care (Goertz, et al., 2013; Juni, et al., 2009; Schneider, et al., 2015). Standard medical care consisted of anti-inflammatory and analgesic medication, plus advice to maintain normal daily activity levels. In one of the studies, it was complemented with physical therapy modalities (Goertz, et al., 2013). When SMT was directly compared to usual medical care, patients receiving SMT reported significantly greater reductions in pain and disability at the four-week follow-up (Schneider, et al., 2015). However, where SMT

was provided in addition to standard care, the results were not consistent. Juni et al. reported no significant differences between groups in terms of pain reduction or use of analgesic medication after two weeks and six months (Juni, et al., 2009). In contrast, Goertz et al. found that adding SMT significantly improved pain and disability at two and four weeks (Goertz, et al., 2013). These conflicting results could be explained by differences in the experimental designs. In particular, the number of SMT sessions delivered was not standardized among studies. Both trials applying a higher dose frequency (eight sessions in four weeks) observed a significant effect of SMT (Goertz, et al., 2013; Schneider, et al., 2015). When a lower dose frequency of care was used (median of three SMT sessions in two weeks), no additional benefit of SMT was reported (Juni, et al., 2009). Although SMT frequency might not have a significant impact on outcomes, increasing the frequency of visits in a few weeks showed a trend for decreasing both pain and disability (Pasquier, et al., 2019). Frequency responses to SMT have not been assessed for early stages of LBP; therefore, a potential effect cannot be ruled out. It may be argued that three sessions (but not eight) of SMT may be insufficient to observe a significant effect. Conclusions from a recent meta-analysis provide support for the idea that SMT results in modest improvement in pain and function for acute LBP (Paige et al., 2017). The size of the benefit for pain was found to be approximately the same as that with nonsteroidal anti-inflammatory drugs (reduction in 9.9 points for SMT versus 8.4 points for anti-inflammatories, out of 100) (Paige, et al., 2017). In light of these findings, it remains unclear whether SMT adds value to standard medical care for the management of acute and subacute LBP, although the limited evidence available suggests that both may be comparable.

For chronic stages of LBP, the response to SMT has more often been compared to physical therapy modalities, including exercise (Bronfort, et al., 2014; Bronfort, et al., 2011; Cecchi, et al., 2010; Ghasabmahaleh, et al., 2021; Nambi, et al., 2018; Petersen, et al., 2011). For chronic LBP-related leg pain (referred and radicular), two clinical trials observed that SMT added significant value to home exercise (Bronfort, et al., 2014) and multimodal physical therapy, including exercise (Ghasabmahaleh, et al., 2021). After 12 weeks, both LBP, leg pain, and associated disability were significantly reduced when SMT was added to the active control treatments (Bronfort, et al., 2014; Ghasabmahaleh, et al., 2021). Adding SMT to exercise and laser therapy was also more effective than the provision of exercise alone or when combined with laser therapy for chronic LBP patients (Nambi, et al., 2018). The differences were maintained at the 12-month follow-up. In line with these results, a systematic review found moderate evidence to support the combination of SMT,

exercise, and standard medical care for chronic LBP (Hidalgo et al., 2014). Nevertheless, this does not allow us to determine how SMT directly compares to exercise.

A clinical trial examined the differences between SMT, back school (a combination of patient education and exercise), or physical therapy for patients with chronic LBP (Cecchi, et al., 2010). The authors reported that SMT conveyed the largest reduction in disability at six months, and in both pain and disability after one year. Conversely, the direct comparison of SMT to a home exercise program or supervised exercise did not show any differences between interventions in pain or disability outcomes, neither in the short nor long term (Bronfort, et al., 2011). Furthermore, a study allocated predominantly chronic LBP patients to receive either SMT or exercises derived from the McKenzie method, in addition to information and advice from the "Back book" (Petersen, et al., 2011). Both approaches resulted in clinically meaningful improvements, but the McKenzie method led to significantly larger improvements in disability after two and 12 months (Petersen, et al., 2011). It may be argued that different forms of exercise could have different effectiveness for chronic LBP and therefore compare differently with SMT. This hypothesis was rejected by a systematic review, which found that no form of exercise is superior to another for chronic LBP (van Middelkoop et al., 2010). More recently, these results were contradicted by a network meta-analysis reporting that Pilates, stabilization/motor control, resistance, and aerobic exercise are the most effective exercise approaches for LBP (Owen et al., 2020). Interestingly, McKenzie exercises were not found to be better than a true control. However, this must be interpreted with caution due to the low quality of the evidence available to date (Owen, et al., 2020).

Multiple systematic reviews have examined the effectiveness of SMT (with or without mobilization) compared to exercise. Equivalent clinical benefits have been reported for both interventions in patients with both acute and chronic LBP (Hidalgo, et al., 2014; Standaert et al., 2011). A recent meta-analysis by Coulter et al. found moderate-quality evidence to suggest that SMT significantly reduces pain and disability in patients with chronic LBP compared to both exercise and physical therapy (Coulter, et al., 2018). A set of three meta-analyses investigated the effects of SMT in patients with chronic LBP by comparing SMT or mobilization to currently recommended therapies (mainly exercise), nonrecommended or ineffective therapies (inactive controls), and a combination of interventions (de Zoete et al., 2021a; de Zoete et al., 2021b; Rubinstein, et al., 2019). The data pooled from 47 randomized controlled trials indicated that SMT

provides improvements in pain and disability that are similar to those of recommended therapies for the management of chronic LBP, including exercise (Rubinstein, et al., 2019). The analysis of individual participant data from 21 of these trials confirmed these findings while not being able to identify any individual characteristic that could act as a moderator of the benefits provided by SMT (de Zoete, et al., 2021a; de Zoete, et al., 2021b). Therefore, chronic LBP patients may benefit from SMT and exercise to a similar extent, although it is still not possible to determine which treatment approach will be more beneficial for which patients.

The presented data indicate that SMT conveys a therapeutic benefit at least as important as other standard and recommended approaches of care for LBP. Indeed, patient-centered outcomes of pain intensity and disability were found to respond similarly to SMT when compared to standard medical care or physical therapy (Goertz et al., 2012). Interestingly, a review of pragmatic trials found that chiropractic care (always including SMT) was as effective as standard physical therapy (Blanchette et al., 2016). This design does not allow the drawing of inferences regarding the contribution of a specific intervention offered by chiropractors (i.e., SMT). Nonetheless, the results are consistent with fastidious studies comparing SMT to the same modalities, indicating that chiropractic SMT should be considered as effective as any other recommended intervention, particularly for chronic LBP. These conclusions are summarized in Table 6.2.

Table 6.2 Effectiveness and efficacy (compared to inactive controls) of spinal manipulative therapy (SMT) for the management of low back pain (LBP)

Comparisons studied	Conclusions from previous studies
SMT *vs*. Inactive control	Insufficient evidence for SMT when compared to sham treatment[a-j].
SMT *vs.* Mobilization	Evidence supporting that SMT and mobilization are equally effective[k-n].
SMT *vs.* Standard Medical Care	Inconsistent evidence, only for acute LBP, could depend on dose[o-r].
SMT *vs*. Physical Therapy	Evidence supporting that SMT adds value to and is at least as effective as physical therapy for chronic LBP and leg pain[s-w].
SMT *vs*. Exercise	Evidence supporting SMT being as effective as exercise; stronger evidence for chronic LBP[n,r,x-z].
Guidelines' recommendations	For acute and chronic LBP with or without leg pain, SMT is recommended alone[aa-ac] or more often as part of multimodal care along with advice, education, reassurance and exercice[ad-ai].

[a]Senna & Machaly., 2011. [b]von Heymann et al., 2013. [c]Bialosky et al., 2014 [d]Haas et al., 2014. [e]Vieira-Pellenz et al., 2014. [f]Thomas et al., 2020. [h]Scholten-Peeters et al., 2013. [h]Ruddock et al., 2016. [i]Gianola et al., 2021. [j]Lavazza et el., 2021. [k]Hondras et al., 2009. [l]Cook et al., 2013. [m]Xia et al., 2016. [n]Rubinstein et al., 2019. [o]Juni et al., 2009. [p]Goertz et al., 2013. [q]Schneider et al., 2015. [r]Paige et al., 2017. [s]Cecchi et al., 2010. [t]Bronfort et al., 2014. [u]Nambi et al., 2018. [v]Ghasabmahaleh et al., 2021. [w]Goertz et al., 2012. [x]Bronfort et al., 2011. [y]Hidalgo et al., 2014. [z]Coulter et al., 2018. [aa]Chou et el., 2017. [ab]Qaseem et al., 2017. [ac]Kirkwood et al., 2021. [ad]Dagenais et al., 2010. [ae]Bernstein et al., 2017. [af]Wong et al., 2017. [ag]Bussieres et al., 2018. [ah]Stochkendahl et al., 2018. [ai]Bailly et al., 2021.

Efficacy of Spinal Manipulative Therapy for Low Back and Neck Pain

Few studies have used inactive treatment to assess the efficacy of SMT for patients with NP, and those who had, mostly examined the immediate effects of a single SM, which may or may not provide relevant clinical information (Coulter, et al., 2019; Gross, et al., 2015). Adding SMT to standard care for one group and comparing the outcomes to those of the group only receiving standard care (Gonzalez-Iglesias, et al., 2009; Lau, et al., 2011; Masaracchio, et al., 2013) could be interpreted as a comparison of SMT against no treatment (Gross, et al., 2015). However, an ideal comparator should be inactive and effectively blind patients. This design is less common in research on spine pain overall, as sham procedures are rarely inert or otherwise unsuccessful in blinding patients (Machado et al., 2008). For SMT or manual therapy in general, this is further limited by the complexity of designing a sham that mimics SM but that produces little or no effect (Hancock et al., 2006; Puhl et al., 2017). A graphic summary of the results from these studies is available in **Figure 11**.

A single thoracic SMT or mobilization was compared to a control consisting of manual contact held for two minutes (Suvarnnato, et al., 2013). No differences between groups were found in NP intensity postintervention, albeit significant increases in range of motion were observed after SMT. It is possible that participants were not successfully blinded, as this was not assessed (Suvarnnato, et al., 2013). Moreover, patients likely had different expectations for SMT compared to the control intervention, which may have influenced outcomes. Indeed, expectations are known to be a reliable predictor of clinical pain treatment outcomes (Cormier et al., 2016). Based on the fact that it only induces short-lasting superficial heating effects, infrared radiation might serve as a more suitable inactive control (Lau, et al., 2011). Significant improvement in NP and disability was reported after thoracic SMT compared to this control. However, expectations of pain relief were likely very different for both interventions. These studies seem to confirm that the control

procedures are heterogeneous and not always indistinguishable, which may result in inadequate blinding (Vernon et al., 2011). The latest Cochrane review concluded that thoracic SMT, when compared to inactive treatment, led to significant reductions in pain intensity at short and intermediate term for early stages of NP and in disability at any stage (Gross, et al., 2015). Notwithstanding, evidence favoring thoracic SMT specifically against placebo is scant (Masaracchio, et al., 2019). Therefore, the specific effects of SMT for NP when examined against placebo remain not well understood.

Sham SMT has been more frequently explored as a placebo comparator in efficacy trials of SMT for LBP (Ruddock et al., 2016). It is common to use a similar hand placement and patient position for sham SM while applying biomechanically different forces (e.g., lower force or velocity, nontherapeutic direction or point of application) or no force at all (Bialosky, et al., 2014; Senna and Machaly, 2011; Vieira-Pellenz, et al., 2014; von Heymann, et al., 2013). **Figure 12** illustrates the direction of the findings for each of the studies discussed below.

The immediate efficacy of a single SM for LBP of unspecified duration was compared against a sham manipulation, positioning the patient but not applying any force (Vieira-Pellenz, et al., 2014). Patients reported immediate pain relief after SMT compared to sham; however, these results may or may not be transferable to the clinical setting. In the longer term, SMT was compared to diclofenac or placebo for acute LBP (von Heymann, et al., 2013). The large rate of drop-out in the placebo group (11/25 subjects) compared to both treatment arms only allowed for comparisons between SMT and diclofenac (5/38 and 4/37, respectively) but may indicate the clinical superiority of both treatments over placebo (von Heymann, et al., 2013). Interestingly, the placebo used was a "real" SM, although applied to a distant and "nondysfunctional" segment (opposite sacroiliac joint). This placebo may have been successful at blinding patients but is not necessarily inert. In a clinical trial recruiting patients with LBP of any duration, no differences were found in clinical pain intensity and disability after SMT, placebo, or no treatment (Bialosky, et al., 2014). This was despite patients experiencing a significant decrease in temporal summation of pain immediately after receiving the first SM. Changes in temporal summation have been found to highly correlate with clinical pain. The authors attributed the negative results to the fact that most recruited patients had chronic pain (duration > 12 weeks), which may be less likely to respond to SMT (Bialosky, et al., 2014). Recent data do not necessarily support this hypothesis. The negative results may rather

be explained by a period of treatment and follow-up that was likely too short (two weeks) for patients with long pain duration (Bialosky, et al., 2014). The efficacy of SMT for patients with chronic LBP was also examined over a longer period of time (10 months) (Senna and Machaly, 2011). During the first month of treatment, two groups received the same SMT, and a third group was exposed to sham manipulation. After the first month, SMT performed better than the sham for pain and disability outcomes (Senna and Machaly, 2011). Subsequently, one of the two SMT groups continued to receive maintained SMT (every two weeks) for nine more months. The two remaining groups received no additional treatment. Upon completion of the study, continued exposure to SMT after the first month was significantly associated with lower pain and disability, suggesting a superior efficacy of maintained SMT compared to no treatment (Senna and Machaly, 2011). Similarly, to assess the dose response of SMT for chronic LBP, patients were randomized to receive a variable number of SMT sessions out of a total of 18 visits over six weeks (Haas, et al., 2014). When SMT was not applied, a light massage was used instead as an inactive control. In the short term, 12 SMT sessions were found to be the most efficacious, while in the long term, 18 visits with SMT yielded the greatest differences from the control (Haas, et al., 2014). However, the results are limited by the fact that the control massage cannot be considered a true sham but rather a potentially active comparator. In contrast to these studies, a recent trial using sham cold laser treatment as a placebo did not find any differences with SMT or mobilization (Thomas, et al., 2020). This may seem like an appropriate sham, apparently devoid of any therapeutic effect. Interestingly, treatment expectancy was rated by all groups, and although there were no significant baseline differences, the sham cold laser group had the strongest relationship between expectations and pain relief (Thomas, et al., 2020). Research on placebo effects indicates that different types of placebos may hinder different outcomes, even via independent neurophysiological mechanisms (Benedetti and Dogue, 2015). It is plausible that SMT and laser therapy may induce different placebo effects associated with distinct therapeutic rituals and expectations. Therefore, such a comparison may not be the best suited to answer this question concerning the efficacy of SMT for LBP.

Earlier Cochrane reviews on the effects of SMT for acute LBP concluded that SMT is not superior to inert or sham interventions (Rubinstein et al., 2013), except when used in combination with other modalities, including exercise and patient education (Walker, et al., 2011). A review for the American College of Physicians' guidelines found no effect over inert treatment for the

management of acute LBP and only a small effect for chronic cases (Chou et al., 2017). Two different systematic reviews with meta-analyses specifically examined the differences in outcomes between SMT and sham manipulation (Ruddock, et al., 2016; Scholten-Peeters et al., 2013). Scholten-Peeters et al. reported a standardized mean difference (SMD) of -0.73 in favor of SMT for NP intensity on a visual analog or numerical rating scale immediately after treatment, and an SMD of -0.47 for LBP in the short term (Scholten-Peeters, et al., 2013). Ruddock et al. found similar results (SMD of -0.36) in support of the efficacy of SMT for LBP intensity in the short term (Ruddock, et al., 2016). Along the same lines, a recent network meta-analysis found that manual therapy (including SMT) significantly reduced pain and disability in the short and intermediate terms compared with inert treatment for acute and subacute LBP (Gianola et al., 2021). Specifically, manual therapy was reported to be the most effective nonpharmacologic approach. However, the effects of manual therapy (including SMT) against sham treatment are still considered to be small and, more importantly, not clinically meaningful (Lavazza et al., 2021). The low quality of placebo interventions used for SMT trials may be partly to blame for the low quality of this evidence, the large degree of uncertainty, and the difficulty in drawing consistent conclusions (Puhl, et al., 2017).

Imperfect placebos are not uncommon in spine pain research and impact the quality of studies on other types of interventions (Machado, et al., 2008). However, trials on SMT for spine pain most likely suffer from lower quality due to inherent difficulties in designing and applying a credible yet inert sham SMT treatment (Gevers-Montoro et al., 2021). It is therefore essential to improve the quality of SMT placebos for future studies to reduce the uncertainty regarding its efficacy for the management of spine pain.

Discussion and Future Perspectives

Research on SM and SMT for the management of spine pain has progressed significantly in the past few years. Accumulating data provide evidence favoring the use of SMT in the management of acute, subacute, and chronic NP and LBP. The available clinical research suggests that SMT could be as effective as other conservative approaches used to treat nonspecific and chronic primary spine pain. Nevertheless, this does not lead to consistent recommendations in the management of these conditions, and SMT often comes after advice/education and in combination

with exercise. This probably suggests that the quality of evidence on the efficacy and effectiveness of SMT remains insufficient.

Accordingly, for the management of NP, recent guidelines recommend the use of SMT based mostly on consensus (Kjaer et al., 2017). In cases of recent onset (acute and subacute) NP, SMT is recommended before oral analgesics (Kjaer, et al., 2017), although not muscle relaxants (Cote et al., 2016). Overall, clinical guidelines currently recommend SMT for the management of NP and cervical radiculopathy in combination with other approaches, particularly exercise and patient education (Chou, et al., 2018; Cote, et al., 2016; Kjaer, et al., 2017).

For the management of LBP, most guidelines recommend SMT, with some discrepancies regarding the circumstances in which it should be administered (Bailly, et al., 2021; Oliveira et al., 2018). For example, the United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines make it imperative that SMT be offered alongside exercise therapy for LBP irrespective of the stage (Bernstein et al., 2017). In contrast, the American College of Physicians' guidelines endorse SMT as a frontline noninvasive intervention, partly because patients with acute LBP improve over time regardless of treatment (Qaseem, et al., 2017). Specifically, for acute stages with or without radiculopathy, clinical practice guidelines recommend the addition of SMT to education, advice to remain active, and self-management (Dagenais et al., 2010; Stochkendahl et al., 2018; Wong J.J. et al., 2017). For chronic LBP, the guidelines tend to recommend the use of SMT either alone or preferably in combination with other approaches (frequently second to advice, education, and reassurance) for patients with or without leg pain (Bussieres et al., 2018; Wong J.J., et al., 2017). Recently, a decision aid developed for managing chronic back pain by Canadian colleges of family physicians endorsed exercise and SMT as the only interventions for which benefits likely exceed harms (Kirkwood, et al., 2021). For low- and middle-income countries, the Global Spine Care Initiative produced guidelines taking into consideration practical aspects such as cost (Chou, et al., 2018). Their recommendations are to consider the use of manual therapy (SMT and mobilizations) as one of the primary treatment options in patients with both acute and chronic spine pain and SMT specifically for radicular pain (Chou, et al., 2018).

The recommendations for the use of SMT in patients with LBP and NP are mostly based on comparisons with other interventions, specifically, "recommended" interventions. Nevertheless, high-quality evidence indicates that SMT is not clinically superior to nonrecommended

interventions for the relief of chronic LBP (Rubinstein, et al., 2019). In fact, the main gap identified in clinical research on SMT for spine pain lies in the low quantity and quality of studies addressing its efficacy against inactive controls. Hence, the effects of SMT against placebo or sham SM remain uncertain. This parallels the state of research on most interventions for spine pain, as no treatment has been demonstrated to be superior to any other or to placebo (Artus et al., 2010; Machado et al., 2009; van Lennep et al., 2021). It could be argued that effective treatments for LBP and NP have a large share of nonspecific effects. In order to understand what the specific effects of SMT are in future clinical trials on spine pain, the studies should include a placebo intervention that is indistinguishable from SM and that does not produce therapeutic effects (Gevers-Montoro, et al., 2021). This can be achieved by determining the mechanisms of pain relief by SM and confirming that the placebo intervention does not influence these mechanisms. In addition, placebo interventions need to be validated by confirming that blinding was successful (Chaibi et al., 2015; Vernon et al., 2012).

Another important challenge for the immediate future of SMT research is the need to identify patients who will respond better to a trial of SMT. Research on clinical predictors of the response to SMT yielded mixed results (Cleland, et al., 2010; Hancock et al., 2008). It has been proposed that joint pain affecting multiple body regions may act as a moderator of the response to SMT. For example, in individuals with LBP, presenting NP complaints was associated with a decrease likelihood of responding to SMT (Hadizadeh et al., 2020). Similarly, the probability of benefitting from SMT for NP is reduced for patients presenting LBP complaints (Schellingerhout et al., 2008). Comorbidity is common in patients with chronic NP and LBP (Guez et al., 2006), with up to 50% of patients presenting symptoms in both regions (Overas et al., 2021). Patients with overlapping pain may represent a subgroup (i.e., nonlocalized LBP (Coggon et al., 2017)). It is also possible that chronic LBP and NP are different manifestations of the same disorder (Leboeuf-Yde et al., 2012). This is compatible with the proposed definition of chronic primary pain. If this is the case, the effectiveness of SMT for spine pain in different regions should be similar, and the differences reported in the present study may reflect limitations of the current literature. Recently, more effort has been directed toward identifying biomechanical factors that may influence the response, including spinal stiffness and multifidus muscle involvement (Fritz et al., 2011; Koppenhaver et al., 2011; Page and Descarreaux, 2019; Wong A.Y. et al., 2015). The results have not always been consistent, although recent models that include demographic, clinical,

biomechanical, and neurophysiological predictors are a promising avenue of research (Hadizadeh, et al., 2020; Nim et al., 2021). A better understanding of the specific effects of SMT via mechanistic research on specific subgroups of patients with high-quality designs that include validated placebo interventions is essential for future clinical research. This should translate into more homogenous recommendations on the use of SMT for specific patients, conditions, and pain states.

Author contributions

CG-M contributed to literature review and study selection and wrote the preliminary version of the manuscript. BP contributed to the literature review. MD contributed to manuscript editing. AO contributed to manuscript editing and guidance in its design. MP contributed to manuscript design, wrote the final version of the manuscript, and obtained funding. All authors have contributed significantly to this work and have read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

LBP, Low back pain; NP, Neck pain; SM, Spinal manipulation; SMT, Spinal manipulative therapy.

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Chapter 7: Article 4 – Reduction of chronic primary low back pain by chiropractic spinal manipulative therapy is accompanied by decreases in segmental mechanical hyperalgesia and pain catastrophizing

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Abstract

Chronic primary low back pain (CPLBP) refers to low back pain that persists over three months, that cannot be explained by another chronic condition, and that is associated with emotional distress and disability. Previous studies have shown that spinal manipulative therapy (SMT) is effective to relieve CPLBP, but the underlying mechanisms remain elusive. The present randomized placebo-controlled trial (NCT05162924) aimed to examine mechanisms that may underlie the clinical improvement of CPLBP by SMT. Ninety-eight individuals with CPLBP and 49 controls were recruited. Individuals with CPLBP received SMT (n=49) or a validated placebo intervention (n=49), twelve times over four weeks. The primary outcomes were CPLBP intensity (0-100 on a numerical rating scale) and disability (Oswestry Disability Index). Secondary outcomes included mechanical sensitivity (pressure pain thresholds in four body regions), pain catastrophizing, central sensitization inventory scores, depressive symptoms, and anxiety. Individuals with CPLBP showed widespread mechanical hyperalgesia (p<.001) and higher scores for all questionnaires (p<.001). SMT reduced pain intensity compared with the placebo intervention (mean difference: -11.7 [95% CI, -11.0 to -12.5], p=.01), but did not improve disability (p=.5). Moreover, SMT reduced segmental mechanical hyperalgesia (at the manipulated segment only) and pain catastrophizing compared with placebo (p<.05). Although the reduction of segmental mechanical hyperalgesia likely underlies the clinical benefits of SMT, it remains to be clarified whether the reduction of pain catastrophizing is a cause or a consequence of pain relief by SMT. Nonetheless, these results suggest that SMT may have an effect on neurophysiological and psychological mechanisms underlying CPLBP.

Introduction

Spine pain is the leading cause of disability worldwide (G.B.D.Collaborators, 2020) and is a personal, economic, and social burden (Hartvigsen, et al., 2018; Hurwitz et al., 2018). A recent study reported that low back and neck pain were the conditions for which health care spending was the largest, exceeding spending for cardiovascular diseases and cancer (Dieleman, et al., 2020). It was also reported that for low back pain (LBP), ineffective low-value care is overused, and effective high-value care is underused (Buchbinder, et al., 2020). This may worsen LBP and increase health care spending (Buchbinder, et al., 2020; Stevans, et al., 2021). Thus, high-value interventions must be established. Also, identifying factors associated with a positive response to high-value care may improve the management of LBP through personalized interventions.

In addition to education, reassurance and a progressive return to activities, most clinical practice guidelines recommend spinal manipulative therapy (SMT) for the management of LBP (George, et al., 2021; Qaseem, et al., 2017) (reviewed in (Gevers-Montoro et al., 2021b)). Notwithstanding, the benefits of SMT compared with placebo and its pain-relieving mechanisms remain elusive (Gevers-Montoro et al., 2021c). Contextual factors may contribute to the effects of SMT in patients with chronic LBP (Bishop F. et al., 2021; Sherriff et al., 2022; van Lennep et al., 2021). However, basic studies suggest that SMT relieves back pain by reducing inflammation and inhibiting nociplastic pain mechanisms, including the enhancement of spinal nociceptive transmission (Gevers-Montoro, et al., 2021c; Gevers-Montoro et al., 2021d; Jordon et al., 2017; Nim et al., 2020; Provencher et al., 2021b; Teodorczyk-Injeyan et al., 2021). Nevertheless, it is unclear how these results apply to patients with chronic LBP in clinical settings (Nim et al., 2022; Nim, et al., 2021a).

Based on the proposed mechanisms of SMT and the heterogeneous pathophysiology of chronic LBP, patients presenting with nociplastic LBP may respond differently to SMT depending on individual factors (Boal and Gillette, 2004; Gevers-Montoro, et al., 2021c; Zafereo and Deschenes, 2015). Targeting patients with favorable prognostic factors may contribute to the improvement of clinical outcomes (Nijs, et al., 2021b; Tagliaferri et al., 2023). However, the reduction of nociplastic pain and associated factors by SMT, and whether these changes contribute to better clinical outcomes remain to be clarified.

To classify musculoskeletal pain on mechanistic bases, three descriptors were proposed: nociceptive, neuropathic and nociplastic (Kosek, et al., 2016; Shraim et al., 2020). One advantage of this system is the possibility to classify painful conditions with unclear etiology (Fitzcharles, et al., 2021; 2022; Kosek, et al., 2016; Nijs, et al., 2021b), including chronic LBP (Nicholas, et al., 2019; Nijs, et al., 2015). For cases defined as chronic primary LBP (CPLBP), pain is the primary condition rather than a symptom secondary to a musculoskeletal condition (Nicholas, et al., 2019; Treede, et al., 2019). In CPLBP, altered nociceptive processing is presumed to contribute to the so-called nociplastic pain more than a pathology in specific musculoskeletal tissues (Fitzcharles, et al., 2022). Accordingly, central sensitization likely enhances spinal nociceptive transmission in CPLBP (Latremoliere and Woolf, 2009; Nijs, et al., 2015; Nijs, et al., 2021a; Nijs, et al., 2021b; Treede et al., 2022).

The aim of the present study was to assess processes underlying nociplastic pain and associated factors in patients with CPLBP treated with SMT to determine how they contribute to CPLBP and its clinical improvement. We hypothesized that the reduction of pain intensity and disability would be greater for SMT compared with a validated placebo intervention, and that measures of nociplastic pain and associated factors at baseline would predict these changes. We also hypothesized that changes in processes underlying nociplastic pain and associated factors contribute to CPLBP improvement.

Methods

This manuscript follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized clinical trials (Schulz K.F. et al., 2010) and the Template for Intervention Description and Replication guide for reporting placebo and sham controls (TIDieR–placebo) (Howick et al., 2020). The latter is reported using the recent update including items from the Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy Trials of Physical, Psychological, and Self-Management Therapies (CoPPS) Statement (Hohenschurz-Schmidt D. et al., 2023). The study protocol has been reported elsewhere, before the completion of this study (Gevers-Montoro et al., 2023). The study is a mechanistic randomized placebo-controlled clinical trial, registered *a priori* with clinicaltrials.gov (NCT05162924). Ethics approval was obtained from the Fundación Jiménez Díaz Clinical Research Ethics Committee. The trial comprised three parallel arms, two that included patients

with CPLBP, and one that included pain-free healthy controls. The primary outcomes were self-reported pain intensity and disability. The secondary outcomes included other clinical measures as well as psychometric and quantitative sensory testing (QST) variables. These variables were proposed for a mechanism-based classification of patients with chronic musculoskeletal pain, including CPLBP (Shraim, et al., 2021). In the present study, they were used as predictors and moderators of changes in the primary outcomes before and after the intervention. The initial protocol included urine samples, but they could not be included in the present study due to technical issues with the samples.

Participants

Participants were recruited between December 2021 and December 2022 at the Madrid College of Chiropractic teaching Clinic (hereon referred to as "the Clinic"). The Clinic is a primary care facility specialized in spine care. Recruitment was conducted by advertisement in San Lorenzo de El Escorial, social media platforms, and by word of mouth. Men and women between 18 and 70 years of age with symptoms compatible with CPLBP for at least 3 months were considered for inclusion in the study. For the patient groups, screening was conducted using a selection questionnaire administered online or in person, depending on patient preference. When deemed eligible, patients were scheduled for a physical examination at the Clinic to confirm the diagnosis of CPLBP, and to rule out exclusion criteria: evidence of a specific pathology causing LBP, evidence of a predominant neuropathic origin of LBP, diagnosis of mental health disorders (with the exception of anxiety and depression), pain of comparable or greater intensity affecting another body region, use of corticosteroids, opioids or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, and chiropractic SMT received within the previous 12 months. Participants in the healthy control group were recruited using a selection questionnaire and were age- and sex-matched to the SMT group. They were excluded if they presented acute or chronic pain, or a diagnosis of a systemic, inflammatory, neurological, or psychiatric condition.

Randomization and group allocation

Patients were randomized to one of the two groups receiving real or placebo SMT (hereon referred to as "SMT" and "placebo", respectively). Using a random number generator, a simple randomization sequence was generated by one of the investigators not involved in data collection. The patients recruited in the study were allocated either to the SMT or placebo groups according

to this randomization sequence. Group allocation was concealed from patients and investigators, except for the investigator that delivered SMT and placebo. The efficacy of blinding was assessed after the first, sixth and twelfth (last) treatment sessions. Patients were asked whether they thought that they received a real chiropractic treatment for back pain (Yes or No). In addition, they were asked to rate their certainty of having received the real treatment on a scale from 0 to 100, where 0 indicates that they were certain of not receiving a real chiropractic treatment and 100 indicates that they were certain of receiving a real chiropractic treatment (Chaibi et al., 2015).

Interventions

The interventions were provided to the patient groups over four weeks. Healthy controls did not receive any intervention, but all experimental measures were taken over the same time period. This allowed controlling for nonspecific temporal fluctuations in outcome variables. The same chiropractor (20 years of clinical experience) delivered both SMT and the placebo. The placebo intervention was practiced extensively before the study was initiated. All sessions were provided individually for a duration of approximately 10 minutes, always in the same room, using the same treatment table, with the same ambient conditions. Both interventions were explained verbally to participants with identical instructions before the first session. Once the treatment protocol was initiated, verbal and non-verbal communication was kept to a minimum necessary for both groups.

Spinal manipulative therapy

Patients in the SMT group received SMT three times per week over 4 weeks based on the available data for CPLBP (Haas et al., 2014). In each SMT session, the patient received a high-velocity low-amplitude spinal manipulation targeting the most painful vertebral segment, bilaterally (Gevers-Montoro, et al., 2023). First, manual palpation of the spine was performed in a prone position to localize the vertebral segment to be manipulated, as determined during the initial examination (most painful segment). Then, right and left lumbar manipulations were performed in a side posture, with a force sufficient to generate joint cavitation (associated with an audible release). If the manipulation did not cause joint cavitation, the procedure was repeated once.

Placebo intervention

Patients in the placebo group received a validated placebo intervention (Chaibi, et al., 2015) three times per week over 4 weeks. Although no SMT was used, manual palpation of the spine was performed in a prone position to localize the most painful vertebral segment, as in the SMT group. With the patient in a side posture, a force was then applied to the gluteal region, bilaterally (Chaibi, et al., 2015; Gevers-Montoro, et al., 2023). This simulates SMT, but the force is applied with lower velocity compared with SMT and produces no cavitation. Previous studies on SMT have used this validated placebo intervention (Aspinall et al., 2019; Picchiottino et al., 2020; Provencher, et al., 2021b). Patients in the placebo group were offered the possibility to receive SMT at the end of the protocol, following the same treatment procedures as the SMT group. These sessions were documented until the last follow-up.

Outcomes

Outcome variables used in the present study (clinical, questionnaire scores and QST) are based on established methods for the classification of patients based on pain mechanisms (Shraim, et al., 2021; Shraim, et al., 2022). Some of these variables were used to assess the efficacy of SMT (primary outcome variables: pain intensity and disability), while others (secondary outcome variables) were used as predictors or moderators of changes in the primary outcome variables produced by SMT. All outcome assessment, including adverse events, were conducted by investigators blinded to group allocation that were not involved in providing care.

Primary outcomes

CPLBP intensity and disability were the primary outcomes of this study, with changes between baseline and four weeks as the primary endpoint. In order to measure the effects of the 12 sessions at the primary endpoint, the primary outcomes were measured during the initial examination and 48 hours after the 12^{th} session. For exploratory purposes, primary outcomes were also measured at two additional time points (eight and sixteen weeks after baseline). Pain intensity was rated using a numerical rating scale displayed on a computer screen, with left and right anchors as 0 (no pain) and 100 (worst pain imaginable) (Haefeli and Elfering, 2006). Patients rated the current, maximum, minimum, and average pain intensity in the preceding 7 days (for baseline) and since the last session (for the primary endpoint). Average pain intensity was used for all statistical analyses and other measures were used to provide additional details (descriptive statistics).

Disability was assessed using the Oswestry disability index (ODI). The ODI is calculated based on a questionnaire that comprises 10 questions, providing a score from 0 to 50, where "0" indicates no disability and "50" indicates the worst disability (Alcántara-Bumbiedro et al., 2006).

Secondary outcomes

Quantitative sensory testing

QST was used to assess changes in pain processing, some of which may be used as surrogates of central sensitization (Arendt-Nielsen, et al., 2018). Pressure pain thresholds (PPTs) are the minimum pressure necessary to elicit pain (Fischer, 1986). They are used to examine mechanical sensitivity in deep musculoskeletal tissues. PPTs were suggested to be one of the most reliable and sensitive methods to assess central sensitization in a CPLBP population (den Bandt, et al., 2019; Neziri, et al., 2012; Vuilleumier et al., 2015). Four sites were examined for the purpose of the study. Pressure was applied over the erector spinae muscles, 2.5 cm from the spinous process (Pfau et al., 2014) of the most painful lumbar segment, bilaterally. Hypersensitivity at this site in the patient groups compared with controls was used to confirm local mechanical hyperalgesia (hereon referred to as segmental PPTs). To assess heterosegmental spreading of mechanical hyperalgesia, PPTs were assessed four segments cranial to the most painful lumbar segment, and compared between the patient groups and controls (hereon referred to as heterosegmental PPTs). To assess the segmental spreading of hyperalgesia, PPTs on the lower limb in the dermatome of the most painful lumbar segment were compared between the patient groups and controls (hereon referred to as dermatomal PPTs). To assess widespread hyperalgesia, PPTs on an area unrelated to the innervation of the back (thenar eminence) were compared between the patient groups and controls (remote PPTs) (Arendt-Nielsen, et al., 2018; den Bandt, et al., 2019). For the control participants, PPTs were assessed at the same locations as for the matched participant in the SMT group. The four PPT measures were compared between groups at baseline and after four weeks, as secondary outcome variables.

Psychometric assessment

The Pain Catastrophizing Scale (Garcia Campayo et al., 2008) (PCS) and the Central Sensitization Inventory (Cuesta-Vargas et al., 2016) (CSI) evaluate psychological constructs that are associated with nociplastic pain (Holm et al., 2022; Huysmans et al., 2018; Roussel, et al., 2013; Scerbo et al., 2018). The CSI measures symptoms presumably related to central sensitization.

A cut-off value of 40 points was proposed to infer central sensitization-like mechanisms (Scerbo, et al., 2018). Greater CSI scores are associated with greater pain catastrophizing (Huysmans, et al., 2018). Accordingly, it was suggested that pain catastrophizing may contribute to central sensitization and nociplastic pain (Edwards, et al., 2016; Owens et al., 2016; Roussel, et al., 2013; Shraim, et al., 2021). Validated versions in Spanish language of these questionnaires were compared between patient groups and controls, at baseline and at four weeks (Cuesta-Vargas, et al., 2016; Garcia Campayo, et al., 2008). The internal consistency and reliability are acceptable for both the PCS (Cronbach's α = 0.79; intraclass correlation coefficient = 0.84) and the CSI (Cronbach's α = 0.87; intraclass correlation coefficient = 0.91).

In addition, symptoms of depression and anxiety were assessed using the Beck Depression Inventory II (BDI) and the Generalized Anxiety Disorder (GAD) scale (García-Campayo et al., 2010; Sanz et al., 2005). Depression and anxiety are CPLBP comorbidities (Gore, et al., 2012; Wong, et al., 2021b). Depression and anxiety are associated with, or may aggravate symptoms suggestive of central sensitization and nociplastic pain (Aoyagi et al., 2019; Clark J.R. et al., 2019; Fitzcharles, et al., 2021; Smart et al., 2012b; Treede, et al., 2022). The validated Spanish versions of these questionnaires were filled at baseline and at four weeks. Both questionnaires have high internal consistency (Cronbach's α = 0.89 for the BDI, and 0.94 for the GAD). The GAD also has excellent reliability (intraclass correlation coefficient = 0.93).

Clinical examination

Data on CPLBP location, duration and frequency were collected at baseline. Pain duration was quantified in months since the onset of the first episode, while pain frequency was classified as fluctuating or episodic (Kongsted, et al., 2017). In addition, CPLBP was classified as proportionate or disproportionate, with a discrete or diffuse anatomical distribution, following criteria defined previously (Nijs, et al., 2015; Smart, et al., 2012b). Diffuse pain may be reflective of spreading hyperalgesia, suggestive of nociplastic pain (Fitzcharles, et al., 2021; Kosek, et al., 2021; Nijs, et al., 2021b). The classification of symptoms as proportionate or disproportionate was based on the pattern of pain provocation and aggravation, to rule in or out nociceptive pain *vs*. nociplastic pain (suggestive of central mechanisms) (Nijs, et al., 2021b).

Expectations of pain relief

Expectations of pain relief by SMT were measured in the patient groups at baseline. They were rated using a numerical rating scale with numerical anchors on the left, center and right, for total pain relief (-100), no change (0) and maximum pain increase (+100), respectively. Expectations may contribute to the placebo effect (Langford et al., 2022) and may predict treatment response in patients with chronic pain (Cormier et al., 2016). This measure was used to assess the potential contribution of the placebo response to changes in the primary outcome variables (Langford, et al., 2022).

Adverse events

Adverse reactions following each SMT or placebo sessions were reported by patients using an online questionnaire that was completed at the beginning of the following session. The questionnaire requested participants to describe the type of adverse event, the time of onset, the duration, and the severity of the events. Adverse events were categorized into four main categories: muscle stiffness, increased pain, radiating discomfort, and others (Walker et al., 2013). Categorical scales were used to report the onset (immediate, up to 24 hours, or >24 hours), duration (minutes, <24 hours, 24-48 hours, or >48 hours), and intensity (very mild to very severe) of these events. Participants were instructed to inform the chiropractor providing SMT in case of severe adverse events, or repeated moderate events. All reported adverse events were monitored by an investigator not involved in clinical care, who also informed the investigator delivering SMT when the patient reported a 30-point increase in pain intensity or moderate/severe adverse events during at least two consecutive visits. In this case, the events and the possibility to withdraw from treatment were discussed with patients.

Sample size calculation

The present study is a relatively short intervention (one month) for a chronic condition. Thus, it was powered to detect small to medium effects ($f = 0.175$). For 2 groups and 2 repeated measures (baseline and 4 weeks) with an effect size of $f = 0.175$, an alpha of 0.05, and a power of 0.8, a sample of 34 patients per group (total of 68) was required to detect statistically significant changes in clinical pain intensity and disability. Based on this calculation and an attrition rate of 10 %, 40 participants are sufficient to detect significant effects on the primary outcome variables. However, one objective of the study was to examine if secondary outcome variables predict

primary outcome variables. To detect significant effects in a multiple regression model, it is recommended to plan ten sample elements per predictor variable (Ortega Calvo and Cayuela Dominguez, 2002). We were interested in five predictor variables, including segmental PPTs, PCS scores, CSI scores, expectations of pain relief, and urinary concentrations of TNF-α (not used because of technical issues, but planned before the study). Accordingly, a sample size of 50 participants per group was required. Thus, we planned to recruit a final sample of 50 participants per group. This meets the requirements for both the primary and secondary analyses.

Statistical analysis

All analyses were performed with JASP v0.16.4, Jamovi v2.3.21 and R Studio v2022.7.1.554. The Kolmogorov-Smirnov test was used to assess the normality of distributions. The Levene's test was used to assess the homogeneity of variance. When the assumptions of normality and/or homogeneity of variance were not met, robust statistical tests were conducted using the WRS2 package (Mair and Wilcox, 2020). Robust post-hoc tests were carried out with the *mcp2atm* function of the same package. To examine the efficacy of SMT, changes in pain intensity and disability (primary endpoint compared to baseline) were compared between groups (SMT vs. placebo) using mixed analyses of variance (ANOVA), with sex as a categorical variable, to report potential sex differences. Both intention-to-treat (ITT) and per-protocol analyses were performed. Changes in pain and disability were also assessed at 8 and 16 weeks after initiating the treatment for exploratory purposes, with separate mixed ANOVAs. All significant effects were decomposed using robust planned contrasts. To control for a different number of SMT sessions received after the primary endpoint, the number of sessions was included as a covariate.

To confirm that higher values were observed for variables related to nociplastic pain in patients with CPLBP compared with controls, these values were compared between groups (3) and sexes (2) using two-way ANOVAs for baseline PPTs at each location. The same approach was used for psychological factors, with PCS, CSI, BDI-II and GAD scores as dependent variables. In addition, two-way ANOVAs were used to examine changes (delta values) between the three groups and sexes. This served to rule out nonspecific temporal effects, since healthy controls received no intervention. To test *a priori* hypotheses, significant effects were decomposed using robust planned contrasts. Adjusted p-values were calculated with a Bonferroni correction for multiple comparisons.

To examine which variables predicted SMT efficacy, differences in pain intensity and disability between baseline and the primary endpoint (delta values) were used as the dependent variables in separate multiple regression models, for which the estimates were obtained using bootstrapping (Mooney et al., 1993). The Durbin-Watson test was conducted to assess the independence of observations, and multicollinearity was tested using the variance inflation factor. Baseline PPTs, PCS and CSI questionnaire scores, and expectations of pain relief were entered as predictors. These analyses were conducted for the entire patient cohort first, and then individually for the SMT and placebo groups. To determine the contribution of changes in variables used as surrogates of nociplastic pain to clinical efficacy, the General Linear Model (GLM) was used with changes in PPTs, PCS and CSI scores and expectations introduced separately in different models as moderators. To evaluate their influence on group differences in primary outcomes, the group was introduced as the fixed factor, and changes in each of the primary outcomes as dependent variables, in separate models for pain intensity and disability.

Finally, expectations of pain relief were compared between groups using independent *t* tests. The degree of certainty of having received SMT was compared between groups over time (three measurements) using mixed ANOVAs, with sex as a categorical variable. Greenhouse-Geisser adjustments were used as needed. To control for the potential influence of expectation and certainty, values were also included as covariates in the analyses of primary outcomes that yielded significant results (Langford, et al., 2022). Mann-Whitney *U* tests were used to compare the total number of adverse events per participant between treatment groups. The type, onset, duration, and severity of these adverse events were compared between the SMT and the placebo group using Chi-square tests.

Results

Baseline demographic characteristics

For the two patient groups, a total of 155 individuals were screened for eligibility (see CONSORT diagram in **Figure 13**). Fifty-three were excluded and 102 were randomized to receive the interventions. After the physical examination, four randomized participants were excluded (two presented no pain at all in the previous seven days, one was taking opioids, and one presented signs

and symptoms of neuropathic LBP). Thus, a total of 98 patients were included in the study, 49 patients per group, with similar baseline characteristics (see Table 7.1).

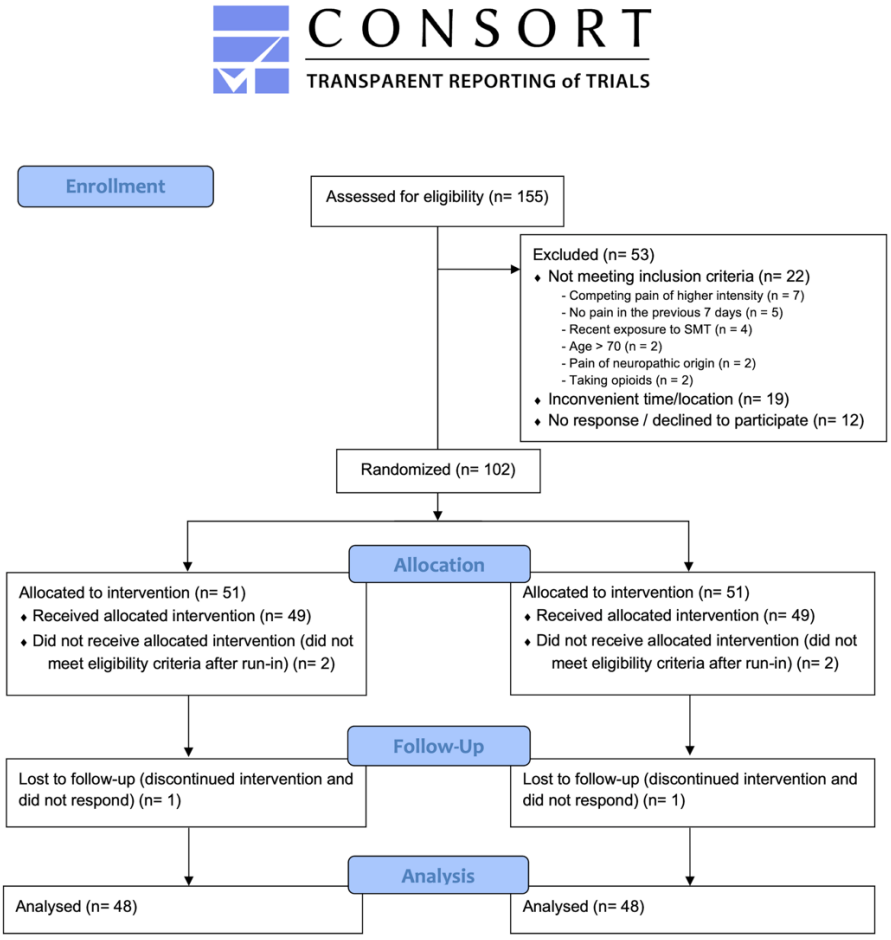

Figure 13 CONSORT diagram

A total of 87 healthy volunteers were screened for eligibility. After excluding 38 candidates (20 presented signs and symptoms that were compatible with the exclusion criteria and 18 did not respond or declined to participate), 49 healthy volunteers were included in the control group. Controls were age/sex-matched to patients in the SMT group. Baseline demographic characteristics of all participants are presented in Table 7.1.

Table 7.1 Baseline demographic characteristics of participants

Baseline characteristic	Placebo Group	SMT Group	Control Group
Participants, *n*	49	49	49
Sex, *n* (%)			
Women	32 (65.3)	31 (63.3)	31 (63.3)
Men	17 (34.7)	18 (36.7)	18 (36.7)
Age, years (SD)	48.3 (9.5)	48.3 (13.0)	48.3 (13.2)
Level of education, *n* (%)			
High School	23 (46.9)	24 (49.0)	13 (26.5)
University	26 (53.1)	25 (51.0)	36 (73.5)
Smoking (Yes), *n* (%)	13 (26.5)	16 (32.6)	10 (20.4)
Average daily sleep time, hours (SD)	6.9 (1.1)	6.7 (1.3)	7.1 (1.0)

Efficacy of spinal manipulative therapy

Out of 98 patients included in the clinical trial, 96 completed the protocol. Two patients discontinued treatment because they could not commit to complete the protocol. The 96 remaining participants adhered to the protocol as planned (see Table 7.2 for baseline clinical characteristics). This resulted in 2.04% of missing data. Little's MCAR test showed a χ^2 value of 9.8 (p = 1.0), indicating that the values were missing completely at random. Both the per-protocol and ITT analyses using the expectation-maximization algorithm for the missing primary endpoint measurements were conducted (Dong and Peng, 2013; Schafer, 1999). They yielded equivalent results and conclusions. Thus, only the per-protocol analyses are reported here for clarity.

Table 7.2 Clinical characteristics of patient groups at baseline

Clinical characteristic	Placebo Group	SMT Group
Pain duration, months (95% CI)	110 (71–148)	118 (84–151)
Average pain intensity, 0-100 (95% CI)	45.8 (40.1–51.5)	47.5 (42.5–52.5)
Current pain intensity, 0-100 (95% CI)	36.7 (32.2–47.2)	40.6 (34.3–46.7)
Maximum pain intensity, 0-100 (95% CI)	59.8 (53.5–66.1)	62.9 (57.3–68.5)
Minimum pain intensity, 0-100 (95% CI)	27.2 (21.1–33.3)	26.6 (20.4–32.7)

Oswestry disability index score, 0-50 (95% CI)	9.8 (8.0–11.5)	9.8 (7.9–11.7)
Pain extent, number of pixels x10^3 (95% CI)	32.9 (19.8–45.9)	33.7 (23.1–44.3)
Expectations of relief, -100/+100 (95% CI)	-68.7 (-76.5 to -60.9)	-68.8 (-75.6 to -62.0)
Pain characteristics, *n* (%)		
*Fluctuating**	36 (73.5)	40 (81.6)
*Episodic**	13 (26.5)	9 (18.4)
Diffuse location (Yes)	8 (16.3)	6 (12.2)
Disproportionate (Yes)	13 (26.5)	9 (18.4)
Lower extremity pain (Yes), *n* (%)	16 (32.6)	21 (42.9)
Taking pain medication (Yes), *n* (%)	18 (36.7)	22 (44.9)
Chronic comorbidities (Yes), *n* (%)	19 (36.7)	24 (49.0)

SMT efficacy was assessed by comparing average pain intensity and disability between baseline and the primary endpoint and between groups and sexes using mixed ANOVAs (see **Figure 14**). Average pain intensity at baseline was 47.5 (95% CI: 42.5 - 52.5) for the SMT group, and 45.8 (95% CI: 40.1 - 51.5) for the placebo group. At the primary endpoint, average pain intensity was reduced to 16.6 (95% CI: 12.5 - 20.7) for the SMT group, and to 27.9 (95% CI: 21.1 - 34.8) for the placebo group. Baseline disability scores were 9.8 (95 % C.I.: 7.9 - 11.7) for the SMT group, and 9.8 (95 % C.I.: 8.0 - 11.5) for the placebo group. At the primary endpoint, disability scores were 4.6 (95 % C.I.: 3.3 - 5.9) for the SMT group, and 5.6 (95 % C.I.: 4.0 - 7.1) for the placebo group. Average pain intensity was significantly different between groups over time ($F_{1,92} = 6.9$, $p = 0.01$, $\eta^2_p = 0.07$; mean difference: -11.7; 95% CI: -19.7 to -3.7), indicating that pain relief produced by SMT was greater compared with placebo (see **Figure 14**). This effect was not significantly different between sexes ($F_{1,92} = 2.4$, $p = 0.12$, $\eta^2_p = 0.03$). For disability, the between-group difference over time of -0.9 points (95% CI: -3.0 to 1.3) was not statistically significant ($F_{1,92} = 0.6$, $p = 0.5$, $\eta^2_p = 0.01$; see **Figure 15**), indicating that SMT did not reduce disability significantly compared with placebo. Also, changes in disability over four weeks were not significantly different between groups and sexes ($F_{1,92} = 0.1$, $p = 0.8$, $\eta^2_p = 0.001$).

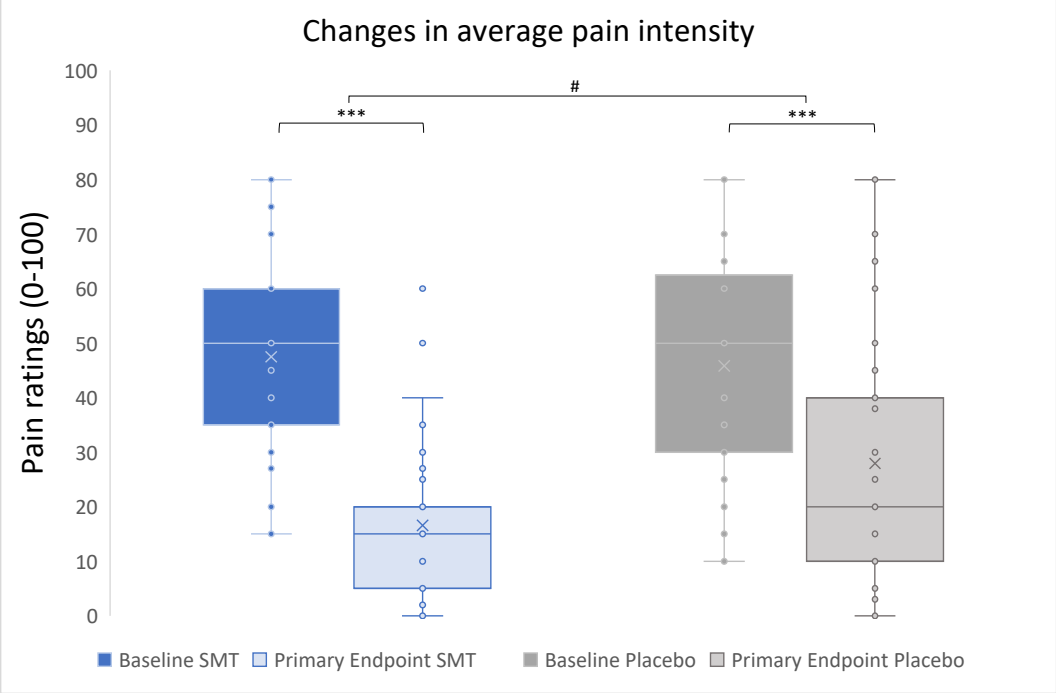

Figure 14 Average pain intensity

Average pain intensity. Boxplots showing mean, median, and interquartile ranges of average pain intensity ratings (0-100) at baseline and at the primary endpoint (4 weeks), for the SMT and placebo groups. Pain ratings were significantly lower at the primary endpoint compared with baseline for both groups, but the reduction was significantly greater for the SMT group compared with placebo group. **** $p < 0.001$ within group, ## $p < 0.01$ between groups.*

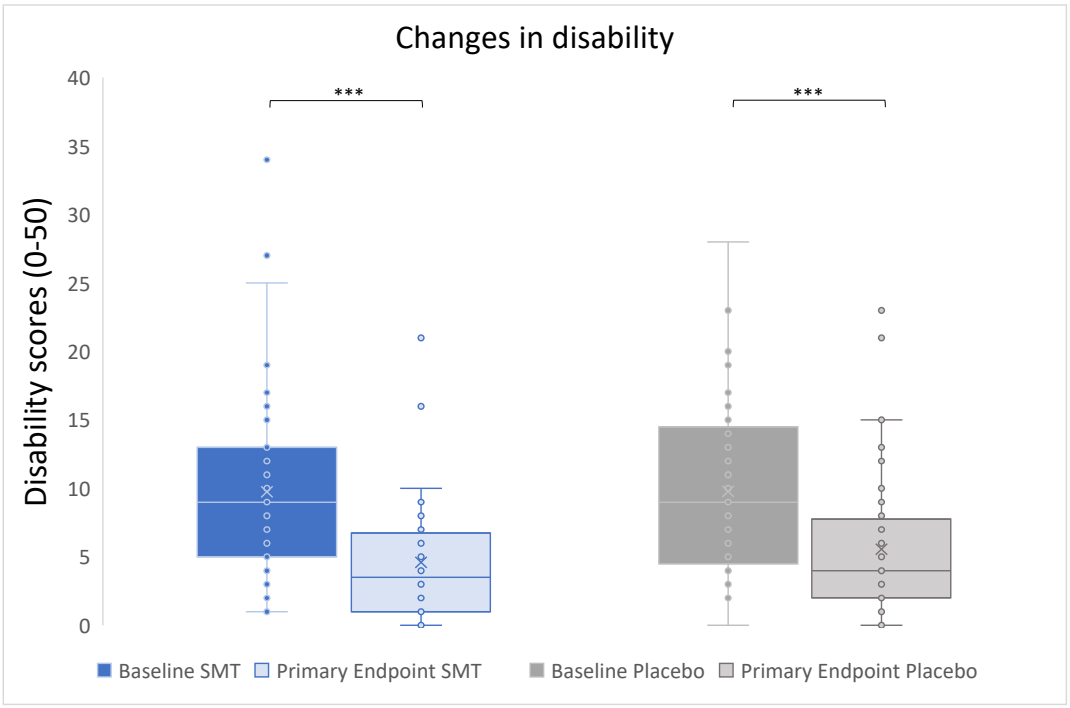

Figure 15 Disability

Boxplots showing the mean, median and interquartile ranges of disability scores (0-50) at baseline and at the primary endpoint (4 weeks), for the SMT and placebo groups. Disability was significantly lower at the primary endpoint compared with baseline for both groups, and the reduction was not significantly different between groups. *** $p < 0.001$ within group

Patients were contacted at 8 and 16 weeks (4 and 12 weeks after the end of the protocol) to examine if the clinical improvement persisted. At the 8-week follow-up, clinical pain intensity remained lower for SMT compared with placebo ($F_{1,87} = 8.7$, $p = 0.004$, $\eta^2_p = 0.09$; mean difference: -13.2; 95% CI: -22.3 to -4.1; n = 44 vs. 47), but this effect was not significantly different between sexes ($F_{1,87} = 0.04$, $p = 0.8$, $\eta^2_p < 0.01$). When controlling for the number of SMT sessions after the end of the protocol, the effect remained unchanged ($F_{1,86} = 9.9$, $p = 0.002$, $\eta^2_p = 0.10$). For disability, no significant difference was observed between groups ($F_{1,87} = 0.8$, $p = 0.4$, $\eta^2_p = 0.01$; mean difference: -0.7; 95% CI: -3.2 to -1.8; n = 44 vs. 47), or between groups and sexes ($F_{1,87} = 1.3$, $p = 0.2$, $\eta^2_p = 0.01$). Controlling for the number of SMT sessions after the end of the protocol did not change the results ($F_{1,86} = 1.1$, $p = 0.3$, $\eta^2_p = 0.01$).

At the 16-week follow-up, pain intensity remained significantly different between groups ($F_{1,83} = 6.1$, $p = 0.02$, $\eta^2_p = 0.07$; mean difference: -12.4; 95% CI: -22.2 to -2.6; n = 42 vs. 45, respectively), but not between groups and sexes ($F_{1,83} = 0.1$, $p = 0.7$, $\eta^2_p = 0.00$). When controlling for the number of SMT sessions after the end of the protocol, the effect remained unchanged ($F_{1,82} = 19.1$, $p < 0.001$, $\eta^2_p = 0.19$). For disability, no significant difference was observed between groups ($F_{1,83} = 1.6$, $p = 0.2$, $\eta^2_p = 0.02$; mean difference: -0.8; 95% CI: -3.4 to 1.8; n = 42 vs. 45, respectively), or between groups and sexes ($F_{1,83} = 2.8$, $p = 0.1$, $\eta^2_p = 0.03$). Controlling for the number of SMT sessions after the end of the protocol did not change the results ($F_{1,82} = 3.5$, $p = 0.06$, $\eta^2_p = 0.04$).

Mechanical pain sensitivity and psychological characteristics at baseline

Baseline PPTs were compared between the three groups and sexes using a two-way ANOVA for each of the four locations (see Table 7.3 and **Figure 16**). PPTs were significantly different between groups at the four regions (segmental: $F_{2,141} = 91.0$, $p < 0.001$, $\eta^2_p = 0.56$; heterosegmental: $F_{2,141} = 50.5$, $p < 0.001$, $\eta^2_p = 0.42$; dermatomal: $F_{2,141} = 44.9$, $p < 0.001$, $\eta^2_p = 0.39$; remote: $F_{2,141} = 25.4$, $p < 0.001$, $\eta^2_p = 0.26$), but these effects were not significantly different between sexes (all p's > 0.1). Bonferroni-corrected planned contrasts revealed that all

PPT's were significantly lower for the SMT group compared with controls and for the placebo group compared with controls (all corrected p's < 0.01). However, they were not significantly different between the SMT and placebo groups (all corrected p's > 0.4). This indicates that patients with CPLBP from both groups showed widespread hyperalgesia, consistent with nociplastic pain. Besides, PPTs were lower in females compared with males for the three groups combined, for the four locations (all corrected p's < 0.01). This suggests that mechanical pain sensitivity is greater in women, regardless of chronic pain.

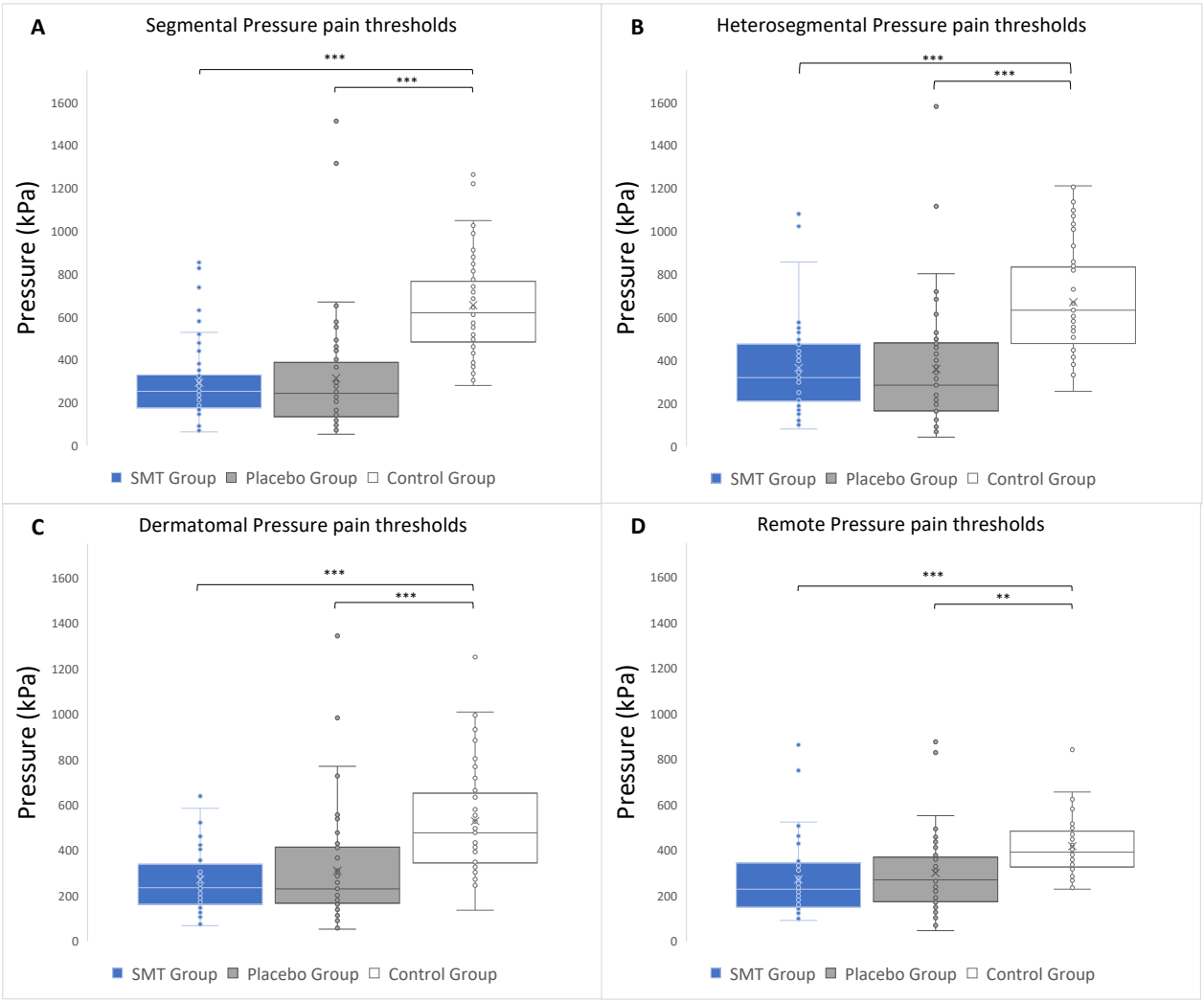

Figure 16 Baseline pressure pain thresholds

Boxplots showing the mean, median, and interquartile ranges of baseline pressure pain thresholds for **A)** segmental, **B)** heterosegmental, **C)** dermatomal and **D)** remote areas, for participants in the SMT, placebo, and control groups. PPTs were significantly lower for both patient groups compared with the control group. *** $p < 0.01$, **** $p < 0.001$ between groups*

Baseline scores for questionnaires (CSI, PCS, BDI, and GAD) were compared between the three groups and sexes using two-way ANOVAs (see Table 7.3). The scores from the four questionnaires were significantly different between groups (CSI: $F_{2,141} = 32.5$, $p < 0.001$, $\eta^2_p = 0.31$; PCS: $F_{2,141} = 87.1$, $p < 0.001$, $\eta^2_p = 0.55$; BDI: $F_{2,141} = 12.2$, $p = 0.005$, $\eta^2_p = 0.15$; GAD: $F_{2,141} = 18.6$, $p < 0.001$, $\eta^2_p = 0.21$). These effects were not significantly different between sexes (all p's > 0.05). Bonferroni-corrected planned contrasts revealed significantly higher scores for all questionnaires for the SMT group and the placebo groups compared with the control group (all corrected p's < 0.05). Moreover, no significant difference was observed between the two patient groups (all corrected p's > 0.8). Besides, no significant difference was observed between sexes for any questionnaire (all p's > 0.05). These results indicate that patients with CPLBP from both groups show a profile consistent with nociplastic pain.

Table 7.3 Mechanical pain sensitivity and psychological characteristics at baseline.

Pain phenotyping characteristic	Placebo Group	SMT Group	Control Group
Pressure pain thresholds, kPa (95% CI)			
Segmental	314 (233–396)***	294 (240–347)***	654 (588–720)
Heterosegmental	359 (278–440)***	364 (303–426)***	670 (598–742)
Dermatomal	310 (238–382)***	271 (228–313)***	529 (462–597)
Remote	300 (247–353)**	273 (227–318)***	418 (382–454)
Questionnaire scores (95% CI)			
Central sensitization inventory (0-100)	28.8 (24.8–32.9)***	30.3 (25.9–34.6)***	16.5 (14.0–19.0)
Pain catastrophizing scale (0-52)	23.3 (19.9–26.7)***	21.8 (18.9–24.7)***	5.8 (3.5–8.1)
Beck depression inventory-II (0-63)	7.0 (5.1–8.9)*	8.7 (6.4–11.0)**	3.2 (2.1–4.4)
Generalized anxiety disorder scale (0-21)	4.4 (3.2–5.7)**	4.5 (3.2–5.9)**	1.6 (1.0–2.2)

*95% CI = 95% Confidence Intervals * p < 0.05; ** p < 0.01; *** p < 0.001 compared with controls*

Changes in mechanical pain sensitivity and psychological factors

Changes (delta values) in mechanical pain sensitivity (PPTs) and scores of the four questionnaires (CSI, PCS, BDI, and GAD) were compared between the SMT and placebo groups and sexes using two-way ANOVAs. Table 7.4 presents the baseline and follow-up values for all primary and secondary outcome variables.

Changes in segmental PPTs were significantly different between groups (main effect: $F_{2,139} = 4.7$, $p = 0.01$, $\eta^2 p = 0.06$; see **Figure 17**) , but this effect was not significantly different between sexes (interaction: $F_{2,139} = 0.2$, $p = 0.8$, $\eta^2 p = 0.003$). Segmental PPTs were increased by 61.8 kPa (95% CI: 25.3 to 98.4) in the SMT group, were decreased by 9.7 kPa (95% CI: -47.4 to 28.1) in the placebo group, and were increased by 0.05 kPa (95% CI: -31.8 to 31.9) in the control group. Bonferroni-corrected planned contrasts revealed that segmental PPTs increased significantly in the SMT group compared with the placebo group (corrected $p = 0.016$), and marginally compared with the control group (corrected $p = 0.051$).

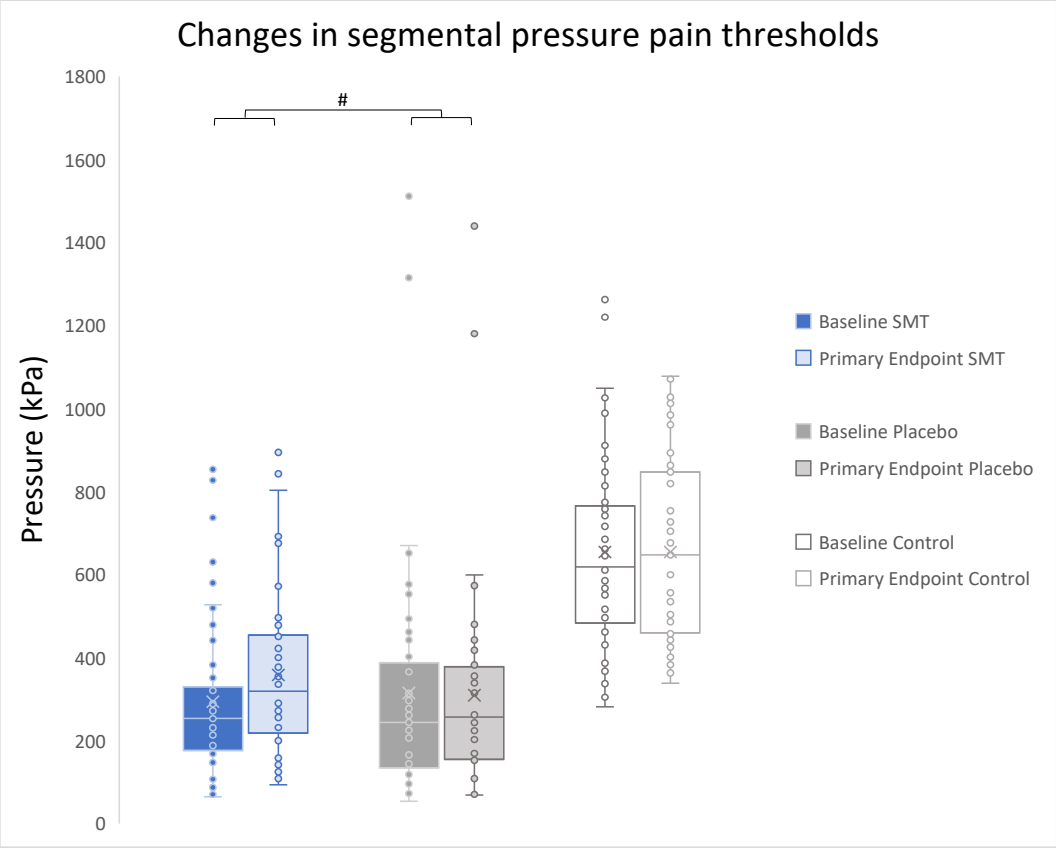

Figure 17 Changes in pressure pain thresholds

Boxplots showing the mean, median, and interquartile ranges of segmental pressure pain thresholds at baseline and at the primary endpoint (4 weeks), for participants in the SMT, placebo, and control groups. The increase of PPTs over time (indicating decreased pain sensitivity) was significantly greater in the SMT group compared with the placebo group. *# $p < 0.05$ between groups*

Changes in heterosegmental, dermatomal, and remote PPTs were not significantly different between groups (main effect: $F_{2,139} = 1.7$, $p = 0.4$, $\eta^2_p = 0.02$; $F_{2,139} = 1.8$, $p = 0.4$, $\eta^2_p = 0.02$;

$F_{2,139} = 0.6$, $p = 0.8$, $\eta^2_p = 0.01$, respectively). Moreover, changes were not significantly different between groups and sexes (interaction: heterosegmental: $F_{2,139} = 2.6$, $p = 0.3$, $\eta^2_p = 0.04$; dermatomal: $F_{2,139} = 3.1$, $p = 0.2$, $\eta^2_p = 0.04$; remote: $F_{2,139} = 0.8$, $p = 0.7$, $\eta^2_p = 0.01$).

In summary, these results indicate that segmental, but not heterosegmental, dermatomal, or remote mechanical pain sensitivity was decreased in the SMT group compared with the placebo group.

Regarding questionnaires, changes in CSI scores were not significantly different between groups (main effect: $F_{2,139} = 3.3$, $p = 0.2$, $\eta^2_p = 0.05$), or between groups and sexes (interaction: $F_{2,139} = 1.7$, $p = 0.4$, $\eta^2_p = 0.02$).

Changes in PCS scores were significantly different between groups (main effect: $F_{2,139} = 36.1$, $p < 0.001$, $\eta^2_p = 0.34$; see **Figure 18**), but not between groups and sexes (interaction: $F_{2,139} = 0.12$, $p = 0.9$, $\eta^2_p = 0.002$). Pain catastrophizing scores were reduced by 8.3 points (95% CI: -10.4 to -6.3) in the SMT group, by 4.9 points (95% CI: -6.9 to -2.9) in the placebo group, and increased by 0.3 points (95% CI: -1.3 to 1.9) in the control group. Bonferroni-corrected planned contrasts revealed that the reduction in pain catastrophizing scores was greater for the SMT group compared with the placebo group (corrected $p = 0.007$) and the control group (corrected $p < 0.001$). No significant difference was observed between the placebo and control groups (corrected $p = 0.17$).

Changes in depressive symptoms were significantly different between groups (main effect: $F_{2,139} = 7.0$, $p = 0.04$, $\eta^2_p = 0.09$), but this effect was not significantly different between sexes (interaction: $F_{2,139} = 1.6$, $p = 0.5$, $\eta^2_p = 0.02$). The BDI scores decreased by 2.4 points in the SMT group (95% CI: -3.5 to -1.2) by 2.4 points in the placebo group (95% CI: -3.7 to -1.1) and by 0.6 points in the control group (95% CI: -1.6 to 0.4). Bonferroni-corrected planned contrasts revealed that the reduction in depressive symptoms was not significantly different between the SMT group and the placebo group (corrected $p = 1.0$), between the SMT group and the control group (corrected $p = 0.09$), or between the placebo group and the control group (corrected $p = 0.08$).

Changes in anxiety were significantly different between groups (main effect: $F_{2,139} = 10.0$, $p = 0.01$, $\eta^2_p = 0.13$), but were not significantly different between groups and sexes (interaction: $F_{2,139} = 0.5$, $p = 0.89$, $\eta^2_p < 0.01$). Anxiety was reduced by 1.0 point (95% CI: -1.6 to -0.3) in the

SMT group, by 1.6 points (95% CI: -2.3 to -1.0) in the placebo group, and by 0.1 points (95% CI: -0.7 to 0.4) in the control group. Bonferroni-corrected planned contrasts revealed that the reduction in anxiety symptoms was not significantly different between the SMT group and the placebo group (corrected $p = 0.7$), between the SMT group and the control group (corrected $p = 0.7$), or between the placebo group and the control group (corrected $p = 0.1$).

In summary, these results indicate that pain catastrophizing was significantly decreased in the SMT group compared with the placebo group, but not central sensitization, depressive symptoms, or anxiety.

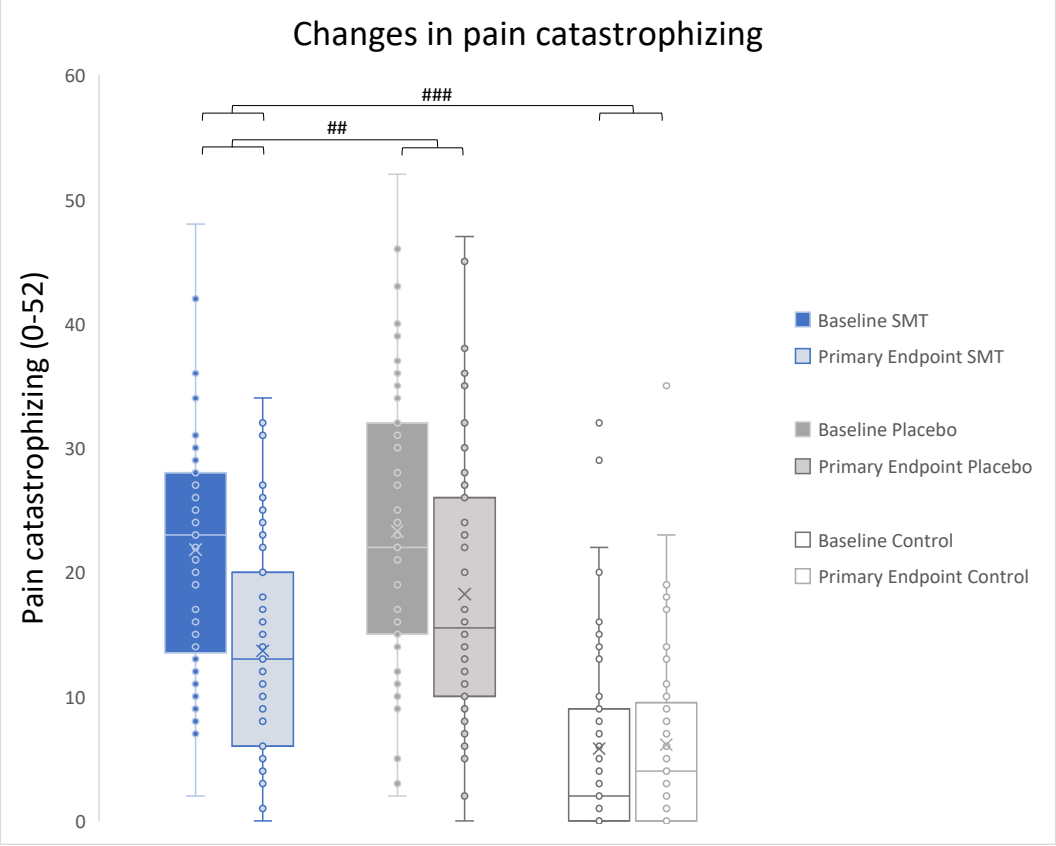

Figure 18 Changes in pain catastrophizing

Boxplots showing the mean, median, and interquartile ranges of pain catastrophizing (0-52) at baseline and at the primary endpoint (4 weeks) for participants in the SMT, placebo, and control groups. The decrease of pain catastrophizing over time was significantly greater in the SMT group compared with the placebo and control groups, and in the placebo group compared with the control group. *## $p < 0.01$, ### $p < 0.001$ between groups.*

Table 7.4 Changes in primary and secondary outcome variables (mean ± SD).

Outcome variables	Baseline	Primary Endpoint	8-week Follow-up	16-week Follow-up
Pain intensity ratings (0-100)				
SMT Group	47.5 (17.3)	16.6 (14.1)*** #	21.2 (17.6)*** ##	19.6 (17.7)*** #
Placebo Group	45.8 (19.9)	27.9 (23.7)*** #	35.1 (25.1)** ##	30.4 (25.1)*** #
Oswestry disability index scores (0-50)				
SMT Group	9.8 (6.6)	4.6 (4.3)***	4.1 (4.4)***	3.9 (4.7)***
Placebo Group	9.8 (6.1)	5.6 (5.3)***	5.4 (5.3)***	4.6 (4.8)***
Segmental pressure pain thresholds (kPa)				
SMT Group	293.5 (184.6)	357.9 (204.4)* #	-	-
Placebo Group	314.3 (283.2)	309.0 (253.3)#	-	-
Control Group	653.7 (230.0)	653.8 (210.1)	-	-
Heterosegmental pressure pain thresholds (kPa)				
SMT Group	364.5 (214.9)	403.1 (214.3)	-	-
Placebo Group	359.3 (281.7)	358.9 (302.6)	-	-
Control Group	670.0 (251.3)	678.0 (244.4)	-	-
Dermatomal pressure pain thresholds (kPa)				
SMT Group	270.9 (147.7)	302.3 (143.8)	-	-
Placebo Group	309.8 (250.3)	327.5 (272.5)	-	-
Control Group	529.2 (235.4)	533.3 (230.5)	-	-
Remote pressure pain thresholds (kPa)				
SMT Group	272.6 (158.9)	287.2 (140.1)	-	-
Placebo Group	300.2 (184.6)	308.9 (184.4)	-	-
Control Group	418.1 (126.5)	438.6 (144.0)	-	-
Central Sensitization Inventory score (0-100)				
SMT Group	30.3 (15.0)	24.1 (13.0)***	-	-
Placebo Group	28.8 (14.1)	24.7 (12.5)***	-	-
Control Group	16.5 (8.8)	14.5 (7.7)	-	-
Pain Catastrophizing Scale score (0-52)				
SMT Group	21.8 (10.0)	13.7 (8.9)*** ## §§§	-	-
Placebo Group	23.3 (11.7)	18.2 (11.0)*** ##	-	-
Control Group	5.8 (7.9)	6.1 (7.4)§§§	-	-
Beck Depression Inventory II score (0-63)				
SMT Group	8.7 (7.9)	5.8 (6.7)***	-	-
Placebo Group	7.0 (6.5)	4.7 (6.0)***	-	-
Control Group	3.2 (4.0)	2.6 (3.7)*	-	-
Generalized Anxiety Disorder score (0-21)				
SMT Group	4.5 (4.8)	3.2 (4.3)	-	-
Placebo Group	4.4 (4.3)	2.8 (3.7)***	-	-
Control Group	1.6 (2.2)	1.4 (2.4)	-	-

Note: **significant compared with baseline; # significant compared with baseline between the SMT and placebo groups; § significant compared with baseline between the SMT and control groups.*

Expectations of pain relief

Participants in the SMT and placebo groups expected a relatively large, but similar reduction of pain intensity at the primary endpoint (68.8% [95% CI: 62.0 to 75.6] in the SMT group and 68.7% [95% CI: 60.9 to 76.5] in the placebo group). Accordingly, expectations of pain reduction were not significantly different between groups ($t = 0.03$, $p = 0.97$). It has been shown that expectations of pain relief may contribute to pain reduction over time, with or without an intervention (Bishop et al., 2011; Cormier et al., 2016). To rule out this effect and to confirm that pain relief by SMT was not the result of expectations, expectations of pain relief were included as a covariate in the statistical model described above (see *Efficacy of spinal manipulative therapy*). This did not change the results and the difference in pain intensity between groups remained significant ($p = 0.01$). Therefore, expectations did not significantly contribute to the relief of CPLBP by SMT.

Blinding

The certainty of having received SMT was compared between groups over time (after the first, sixth and twelfth treatment sessions) using a mixed ANOVA. Certainty was not significantly different between groups (main effect: $F_{1,92} = 0.27$, $p = 0.6$, $\eta^2_p = 0.002$), sexes (main effect: $F_{1,92} = 0.03$, $p = 0.9$, $\eta^2_p = 0.00$), or over time (main effect: $F_{1.9,146} = 0.06$, $p = 0.9$, $\eta^2_p = 0.00$). Moreover, certainty was not significantly different between groups over time (interaction: $F_{1.6,146} = 0.77$, $p = 0.4$, $\eta^2_p = 0.002$), or between groups and sexes over time (interaction: $F_{1.6,146} = 0.34$, $p = 0.7$, $\eta^2_p = 0.00$). These findings indicate that patients could not distinguish placebo from SMT until the end of the protocol. For the SMT and placebo groups, certainty was respectively 62.2 (95% CI: 55.5 to 68.9) and 62.1 (95% CI: 55.2 to 69.0) after the first session, 61.0 (95% CI: 53.8 to 68.2, 95% CI) and 64.7 (95% CI: 57.3 to 72.2) after the sixth session, and 64.6 (95% CI: 56.6 to 72.5) and 61.9 (95% CI: 53.3 to 70.6) after the twelfth session. For patients who thought that they had received SMT (SMT group: n=38; placebo group: n=34), certainty increased from 66.0 (95% CI: 59.0 to 73.0) to 71.7 (95% CI: 63.3 to 80.1), and from 68.2 (95% CI: 60.1 to 76.3) to 76.7 (95% CI: 70.2 to 83.2), respectively. For patients who thought that they did not receive SMT (SMT group: n=10; placebo group: n=14), certainty decreased accordingly from

50.0 (95% CI: 30.5 to 69.5) to 37.5 (95% CI: 27.2 to 47.8), and from 48.2 (95% CI: 36.0 to 60.4) to 26.1 (95% CI: 15.1 to 37.1), respectively. To examine if certainty affected pain relief by SMT compared with placebo, ratings of certainty were included as covariates in the statistical model described above (see *Efficacy of spinal manipulative therapy*). Certainty had no significant effect on pain relief by SMT, where the between-group difference in pain intensity remained significant when controlling for any of the three certainty ratings (p = 0.01, 0.006 and 0.02, respectively). Altogether, these results confirm that blinding was successful and generally, that the SMT and placebo interventions could not be distinguished by participants in either group.

Predictors of the clinical response to SMT

The baseline values of the segmental PPTs, the PCS and CSI scores, and expectations of pain relief were assessed as predictors of changes in pain intensity at the primary endpoint using a multiple regression model. No evidence of multicollinearity or autocorrelation among the residuals was found for any of the predictors used in all regression analyses. For the SMT and placebo groups combined, lower segmental PPTs (higher mechanical sensitivity) significantly predicted greater reductions in CPLBP intensity (β = 0.22, p = 0.01). However, the reduction of CPLBP intensity was not predicted significantly by expectations of pain relief (β = 0.11, p=0.3), pain catastrophizing (β = -0.20, p=0.07), or CSI scores (β = 0.13, p=0.3). In addition, lower baseline segmental PPTs predicted greater reductions in CPLBP intensity in the SMT group (β = 0.34, p = 0.01), but not in the placebo group (β = 0.12, p = 0.3). However, the predictive value of segmental PPTs was not significantly different between the SMT and the placebo groups (β = 0.26, p = 0.067).

Despite the lack of group difference in disability over time, regression analyses were conducted to explore potential predictors that may have masked the group effect. For the SMT and placebo groups combined, segmental PPTs, the pain catastrophizing, CSI scores, and expectations of pain relief did not predict changes in disability at the primary endpoint (all p's > 0.1). However, higher baseline pain catastrophizing predicted the reduction of disability in the SMT group, (β = -0.43, p = 0.004), while no variable predicted reduced disability in the placebo group (all p' > 0.2). Nonetheless, the predictive value of pain catastrophizing was not significantly different between the SMT and the placebo groups (β = -0.26, p = 0.2).

Moderators of the clinical response to SMT

The moderation of changes in pain intensity by changes in components of nociplastic pain was examined with general linear models. Increases in segmental PPTs significantly moderated the reduction of CPLBP intensity (β = -0.24, p = 0.02, η^2_p = 0.06), but they did not alter the difference between the SMT and placebo groups, which remained significant (p = 0.02). Similarly, reductions in CSI scores significantly moderated the reduction of CPLBP intensity (β = 0.24, p = 0.01, η^2_p = 0.06), but they did not alter the difference between the SMT and placebo groups, which remained significant (p = 0.003). Besides, changes in PCS scores and expectations of pain relief did not moderate the reduction of CPLBP intensity (β = 0.16, p = 0.1, η^2_p = 0.03 and β = 0.16, p = 0.1, η^2_p = 0.03, respectively). This suggests that expectations of pain relief, the increases in segmental PPTs, and the decreases in CSI and PCS scores did not contribute to the difference in pain intensity between the SMT and placebo groups.

Although changes in disability were not significantly different between groups at the primary endpoint, reductions in pain catastrophizing and in CSI scores moderated the decrease in disability (β = 0.47, p < 0.001, η^2_p = 0.21 and β = 0.36, p < 0.001, η^2_p = 0.13, respectively), but they did not change the lack of group effect (p's = 0.8 and 0.5, respectively). Besides, changes in PPTs and expectations did not moderate changes in disability (β = -0.10, p = 0.4, η^2_p = 0.009 and β = 0.09, p = 0.4, η^2_p = 0.008, respectively).

Adverse events

A total of 377 adverse events were reported in the study, 198 in the placebo group and 179 in the SMT group, representing 34.1% and 30.7% of treatment sessions, respectively. The number of events was not significantly different between groups (Mann-Whitney U = 1261.0, p = 0.7). Also, no significant difference was observed for the types of events between groups ($\chi^2_{(4, 377)}$ = 4.6, p = 0.3). The most commonly reported events were an increase in back pain (36.3% in the SMT group, 41.9% in the placebo group), muscle soreness/stiffness (31.3% in the SMT group, 31.8% in the placebo group), pain irradiating to the lower extremity (22.4% in the SMT group, 14.2% in the placebo group), changes in the usual pain pattern or location (7.8% in the SMT group, 9.6% in the placebo group). Finally, some events could not be categorized as one of the above and were labeled "Other" (2.2% in the SMT group and 2.5 % in the placebo group).

Regarding the onset of adverse events, it was not significantly different between groups ($\chi^2_{(2, 375)} = 0.2$, $p = 0.9$). They were reported to begin within 24 hours after the session (52.5% in the SMT group, 53.0% in the placebo group), immediately after the session (28.3% in the SMT group, 29.3% in the placebo group), or more than 24 hours after the session (19.2% in the SMT group, 17.7% in the placebo group). Likewise, the duration of adverse events was not significantly different between groups ($\chi^2_{(3, 376)} = 1.8$, $p = 0.6$). They lasted less than 24 hours (45.5% in the SMT group, 43.9% in the placebo group), between 24 and 48 hours (28.1% in the SMT group, 24.6% in the placebo group), more than 48 hours (16.3% in the SMT group, 18.2% in the placebo group), or less than one hour (10.1% in the SMT group, 13.3% in the placebo group).

Regarding the severity of adverse events, it was significantly different between groups ($\chi^2_{(4, 375)} = 16.4$, $p = 0.003$). For SMT and placebo groups, events were 'Very mild' (23.0% and 26.9%, respectively), Mild (44.4% and 25.4%, respectively), 'Moderate' (28.1% and 41.6% respectively), or 'Severe' (4.5% and 5.6%, respectively). Only one 'Very severe' event was reported by a patient in the placebo group (0.5%). All events were transient and self-managed or improved after further care within the 12 sessions, including the very severe event. At the end of the treatment protocol, only five participants rated their pain intensity higher compared with baseline. Three rated their pain 10 points higher, one 15 points higher, and one 20 points higher. These five participants were all in the placebo group.

Discussion

In the present study, twelve sessions of SMT over 4 weeks significantly reduced average pain intensity compared with the placebo in patients with CPLBP. Moreover, the reductions in segmental mechanical pain sensitivity and pain catastrophizing were significantly greater for SMT compared with the placebo intervention. These results suggest that SMT may improve CPLBP through the regulation of neural processes underlying nociplastic pain.

Efficacy of spinal manipulative therapy

Previous studies on the efficacy of SMT have suggested that its clinical benefits may rely on nonspecific effects (Lavazza et al., 2021; Newell et al., 2017; Nim, et al., 2021a). In contrast, a study specifically designed to examine and control for nonspecific effects showed that pain reduction by SMT was independent of these effects (Bialosky et al., 2014). Accordingly, the

present study shows that SMT produces greater pain relief compared with a control intervention that could not be distinguished from SMT. This medium effect ($\eta^2_p = 0.07$) persisted up to 12 weeks after SMT. This suggests that SMT produces long-lasting pain relief, at least in part, through specific mechanisms.

Regarding the clinical significance of this effect, results can be interpreted from two perspectives. Firstly, pain reduction after four weeks of SMT was 30.9 points (65%) lower than baseline. The amplitude of this change is within the range of 2.5 to 4.5 points out of 10, or a 30% pain reduction from baseline, proposed for clinical significance (Ostelo et al., 2008; van der Roer et al., 2006). Secondly, the difference between SMT and placebo (-11.7 points) is superior to the 10 mm on a visual analogue scale proposed for clinical significance of a placebo-controlled intervention (Busse et al., 2015). These results indicate a statistically and clinically significant pain reduction by SMT. However, it should be noted that the metric to determine clinical significance is variable and may lead to different interpretations (Cook et al., 2023; Franceschini et al., 2023).

Consistent with efficacy of SMT, expectations of pain relief and treatment credibility did not influence the between-group difference in pain reduction. Moreover, comparable expectations of pain relief and treatment credibility between the SMT and placebo groups support the equality assumption between interventions, and therefore, that SMT produced effects beyond those attributable to placebo (Giandomenico et al., 2022). Furthermore, the blinding of outcome assessors (i.e., dual blinding) limits the potential bias in outcome assessment. Altogether, these factors support the efficacy of SMT for CPLBP.

It should be noted that expectations of pain relief were relatively high (SMT: 68.8 %; placebo: 68.7%). Although expectations did not contribute significantly to SMT efficacy, the present results may not generalize to other samples for which expectations of pain relief are lower. Besides, it should be mentioned that although the placebo intervention was not distinguishable from SMT, the interventions are not completely equivalent. Although patients were naïve to chiropractic and SMT, the cavitation and audible release associated with SMT may produce stronger placebo effects compared with the placebo intervention, which does not produce such effects. This is inherent to all placebo-controlled studies on SMT. Therefore, although the present results are statistically and clinically significant, the use of a biomarker specific to SMT, and not

measurable when placebo effects occur, remain to be established to rule out placebo effects completely in future studies.

In this regard, previous studies using the placebo intervention that was used in the present study reported that it was indistinguishable from SMT, but it produced effects similar to those of SMT (Aspinall, et al., 2019; Chaibi, et al., 2015). In the present study, the placebo group showed a mean pain relief of 17.9 points from baseline, exceeding the estimated short-term effect of 8 points for placebo interventions compared with no intervention (Strijkers et al., 2021). Thus, it could be argued that the placebo intervention also produced clinically meaningful effects (Gevers-Montoro, et al., 2021c). This should be considered in the design of future randomized placebo-controlled trials on SMT as the placebo intervention does not seem inert and may mask some clinical benefits of SMT.

Changes in mechanical pain sensitivity

The reduction in segmental mechanical hyperalgesia was significantly greater in the SMT group compared with the placebo group. Changes in other areas were not significantly different between groups. This suggests that SMT produces segmental effects on mechanical pain sensitivity in a clinical setting. Although the segmental specificity of SMT was questioned recently (Nim, et al., 2021a), the reduction of segmental hyperalgesia may contribute to clinically significant pain relief in patients with CPLBP. This is coherent with previous studies (Gevers-Montoro, et al., 2021c; Gevers-Montoro, et al., 2021d; Nim, et al., 2020). In one of these studies, it was reported that four sessions of SMT reduced mechanical hyperalgesia when SMT was applied to the most painful segment (Nim, et al., 2020), as in the present study. However, no effect was observed on clinical outcomes. As suggested by the authors, the reduction of hyperalgesia may require a longer intervention to translate into clinical benefits (Haas, et al., 2014; Nim, et al., 2020). This may explain why a statistically and clinically significant reduction of average pain intensity was observed with twelve sessions in the present study.

The present results also imply that SMT does not reduce secondary hyperalgesia. Accordingly, dermatomal (lower limb) mechanical hyperalgesia remained unchanged. In previous studies, it was suggested that spinal manipulation produces immediate effects on secondary mechanical hyperalgesia (Gevers-Montoro, et al., 2021d) and on temporal summation of pain in the back (Randoll et al., 2017), or in the lower limb dermatome corresponding to the manipulated

segment, both in healthy volunteers and in individuals with low back pain (Bialosky et al., 2009; Bialosky, et al., 2014; George et al., 2006b). Although these results contrast with the present findings, an important methodological difference should be noted. The reported effects in previous studies are immediate and possibly transient effects, while the effects were calculated between baseline and 4 weeks in the present study. Thus, the two measures likely capture different neurophysiological processes. In addition, segmental mechanical hyperalgesia was reduced by SMT in patients with CPLBP, but they still showed segmental mechanical hyperalgesia compared with healthy controls. It is possible that greater reduction of segmental hyperalgesia is necessary to observe significant changes in secondary hyperalgesia. Accordingly, greater changes in segmental hyperalgesia were associated with greater changes in secondary hyperalgesia in the present study (not shown). It may be possible to observe a reduction in secondary hyperalgesia in future studies with a greater reduction of segmental hyperalgesia.

Moderation of clinical improvement by nociplastic pain factors

The nociplastic pain factors assessed in the present study all showed a significant alteration in patients with CPLBP compared with controls. Both patient groups showed widespread hyperalgesia, along with increased pain catastrophizing, central sensitization scores, depressive symptoms, and anxiety. This is consistent with the definition of CPLBP (Nicholas, et al., 2019; Treede, et al., 2019) and with previous studies (den Bandt, et al., 2022; den Bandt, et al., 2019; Shraim, et al., 2021). In the present study, we examined if the reduction of these factors by SMT may contribute to clinical improvement patients with CPLBP. Only two factors were reduced by SMT, including segmental mechanical hyperalgesia and pain catastrophizing. Changes in segmental hyperalgesia moderated pain relief, while changes in pain catastrophizing moderated improvements in disability. In both cases, however, the moderation was nonspecific (Kraemer et al., 2002) and did not contribute to the group difference (or lack of). Larger samples may be necessary to detect significant effects.

Previous findings suggest that pain catastrophizing is a predictor of disability (Kovacs et al., 2011; Martinez-Calderon, et al., 2019b; Wertli, et al., 2014b) and a moderator of treatment efficacy, including manual therapy and SMT (Alonso-Perez et al., 2017; Bishop M.D. et al., 2015; Gevers-Montoro, et al., 2021a; Verhagen et al., 2010; Wertli et al., 2014a), in individuals with LBP and other musculoskeletal pain. Accordingly, pain catastrophizing contributes to fear-avoidance

behaviors and nociplastic pain (Quartana, et al., 2009; Shraim, et al., 2021), and its modulation may influence pain sensitivity in healthy individuals and patients with LBP (Meints, et al., 2019; Salomons et al., 2014; Taub, et al., 2017). Future research is needed to clarify how baseline and changes in pain catastrophizing moderate the clinical benefits of SMT, or whether SMT reduces pain catastrophizing as a clinical benefit (Kim H and Lee S, 2023).

Study limitations and future directions

Some limitations should be taken into account for the interpretation of the present findings. Firstly, although the sample size was large enough to detect a significant reduction of average pain intensity by SMT, the between-group difference in disability was not significant. Although average pain intensity was moderate at baseline, patients from both groups displayed relatively low disability compared with previous studies (Fairbank and Pynsent, 2000). In addition, the mean disability scores achieved at all endpoints for both groups fall below the cut-off value for disability (Tonosu et al., 2012). With these levels of disability, the lack of a between-group difference may be explained by a floor effect. Indeed, floor effects were reported for the Oswestry disability index (Brodke et al., 2017).

Secondly, only one clinician provided SMT for both groups. On one hand, this is a potential bias for the effects of SMT on clinical pain intensity. On the other hand, it limits variability in the application of SMT and the placebo intervention. In future studies, the different interventions could be provided by different clinicians, if this does not compromise feasibility. In addition, gender interactions during the intervention could be assessed and controlled for, if each intervention is provided equally by male and female clinicians. This would also improve the generalizability of the results.

Conclusion

In summary, the present study indicates that SMT reduces average clinical pain intensity, pain catastrophizing, and segmental mechanical hyperalgesia compared with a control intervention. This suggests that SMT may improve CPLBP through the regulation of neural processes related to nociplastic pain.

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Chapter 8 – General discussion

Review of the thesis objectives and main results

This thesis investigated the mechanisms of chiropractic SMT in the management of chronic primary spine pain, a leading cause of disability worldwide. Four studies were presented, with two more available as appendices, all investigating chiropractic SMT from different angles. The first study provided a narrative review of the most relevant mechanisms of pain relief by SMT, including mechanisms regulating inflammatory responses potentially in peripheral tissues, important spinal segmental mechanisms, and supraspinal processes, which have received less attention. The review highlighted the need for better controls and placebo interventions to clarify the contribution of specific and nonspecific effects to pain relief by SMT, particularly for spinal mechanisms linked to temporal summation, hyperalgesia and CS.

The second study examined the effects of segmental SM on secondary hyperalgesia evoked by topical capsaicin. Capsaicin-induced experimental pain served as a reliable surrogate model for studying CS mechanisms, which are relevant to a subgroup of patients with back pain, such as CPLBP. The findings may reflect that segmental SM prevents the development of experimental secondary hyperalgesia independent of expectations of pain relief and other placebo mechanisms. When SM targeted a remote segment, the effects measured were not different from placebo. There was no impact on direct measures of capsaicin pain, nor on pain-related brain activity, which is consistent with SM inducing anti-hyperalgesic effects, likely mediated at the spinal cord level. Altogether, the results suggest that SMT may act by modulating a state of central hyperexcitability through spinal segmental mechanisms.

The third study was a narrative review presenting evidence for the effectiveness and efficacy of SMT in the management of nonspecific and chronic primary spine pain, namely NP and LBP. The most recent randomized controlled trials reviewed reported comparable effectiveness for SMT and other recommended interventions for spine pain, particularly exercise therapy. The review also discussed current recommendations for SMT for these conditions and the need for future research to clarify the specific clinical effects of SMT. The study identified the need to improve the design of control groups and placebo maneuvers to be able to reach more robust

conclusions on the efficacy of SMT. This should help clarify the role of SMT in the management of CPLBP and whether it may be endorsed as a first-line treatment.

Finally, the fourth study investigated the potential role of mechanisms reflecting nociplastic pain and their modulation by chiropractic SMT in patients with CPLBP. This randomized clinical trial found that SMT, when applied to the most sensitive low back segment exhibiting hyperalgesia, is superior to a credible placebo SMT. Moreover, reductions in neurophysiological and psychological measures indicative of central nociceptive hyperexcitability and nociplastic pain accompanied clinical outcomes from segmental SMT. While baseline expectations did not directly impact CPLBP outcomes, the role of these and other contextual factors could not be excluded.

This clinical trial could not provide data on an inflammatory biomarker, whose potential role in CPLBP was previously investigated in a separate study (Appendix I). This case-control study offered evidence suggesting that urinary levels of TNF-α may help discriminate individuals with CPLBP from pain-free controls, potentially stratifying patients according to their capacity to recover from LBP episodes. In addition, baseline values and changes before and after treatment were predictive of clinical outcomes. Inflammatory biomarkers, such as urinary levels of TNF-α, may offer a useful tool for guiding the management of CPLBP and assessing the effectiveness of interventions such as SMT.

In conclusion, the studies included in this thesis provide evidence that chiropractic SMT is an effective and efficacious intervention for CPLBP, contributing to the clarification of the mechanisms underlying pain relief (see **Figure 19**). Altogether, the findings presented suggest that SMT may be more effective when targeting sensitized spinal segments or patients displaying signs or symptoms that are compatible with nociplastic pain. Future research is needed to determine the specific effects of SMT, particularly in the long term, and to identify factors that predict and contribute to positive outcomes from this treatment, including contextual factors.

Does chiropractic spinal manipulative therapy relieve chronic primary spine pain?

Spine pain is a major health concern that significantly affects the lives of hundreds of millions of people worldwide (Hurwitz et al., 2018). Both LBP and NP significantly contribute to disability, reduced quality of life, and increased healthcare costs. Most of the burden stems from a similar proportion of LBP and NP patients who develop chronic primary pain, of unknown origin, but comparable mechanisms and contributors (Hush et al., 2011; Nicholas, et al., 2019). Despite the similarities, CPLBP is more pervasive, impacting a larger proportion of the population and resulting in higher levels of disability (Hurwitz, et al., 2018). Its treatment remains a significant challenge for healthcare providers: with various therapeutic options available, no intervention has demonstrated unequivocal superiority, particularly when compared to placebo. This lack of clarity poses a challenge for clinicians and individuals seeking effective treatment and relief. Effectiveness studies comparing interventions to other established treatments or gold standards in real-world settings play a critical role in advancing our understanding of the most effective and efficient approaches to address CPLBP. These studies enable researchers and practitioners to evaluate the interventions' relative effectiveness and safety under conditions that better represent the complexities of real-life situations, including diverse populations and environmental factors that may impact intervention outcomes. Such data can inform clinical practice, policy-making, and future research initiatives. Ultimately, the results of effectiveness studies provide critical insights that can help improve the quality of healthcare and address the pressing health and social issues associated with chronic primary spine pain.

Clinical effectiveness

Noninvasive, nonpharmacological approaches are advised for managing chronic primary spine pain, regardless of the spinal region (Chou, et al., 2018; Corp, et al., 2021). Among these interventions, it appears that no single approach is superior; instead, a combination of physical and psychological treatments may be most effective for both CPLBP and chronic primary NP (Castellini et al., 2022; Coulter et al., 2019; George, et al., 2021). The evidence reviewed in Chapter 6 suggests that the effectiveness of SMT is comparable to other conservative and recommended treatments for both conditions. Since this thesis specifically focuses on CPLBP, the discussion of effectiveness and efficacy results will center on this condition.

No gold standard exists for CPLBP, but due to its safety and effectiveness profile, exercise therapy is universally and strongly recommended as first-line management (Meroni, et al., 2021). Exercise may improve pain and disability compared to all conservative treatments pooled together, but without a clear advantage over manual therapy in a direct comparison (Hayden et al., 2021). Systematic reviews conclude that exercise is not superior to SMT (Coulter, et al., 2018; Rubinstein, et al., 2019). Given similar effectiveness, costs could tip the scales towards one treatment or the other. However, both exercise and SMT appear to be similarly cost-effective for CPLBP (Andronis et al., 2017; Miyamoto et al., 2019). One of the strongest arguments in favor of prescribing exercise is that physical activity is not only associated with lower risk of LBP (Alzahrani, et al., 2019), but also positively influences most physiological body systems (Anderson E. and Durstine, 2019) and benefits the course of multiple chronic conditions (Pedersen and Saltin, 2015). By facilitating the return to daily activities and improving function, SMT may indirectly lead to similar benefits. This is speculative at this point, as data for an effect of SMT on physical activity levels is lacking.

Precisely, one of the main criticisms towards SMT is that it is a passive treatment by nature and has therefore been perceived as having low value (Rhon D.I. and Deyle, 2021; Short et al., 2023). While exercise therapy encourages patients to take an active role in their recovery, fostering a sense of empowerment and self-efficacy, this is not necessarily achieved through passive interventions. An approach for CPLBP uniquely based on SMT may promote overreliance on passive care, with the potential to perpetuate passive coping strategies, fear of movement and catastrophizing (Hohenschurz-Schmidt et al., 2022b; Short, et al., 2023). Thus, so-called passive treatments should carefully address the potential for nocebo effects through the utilization of language and communication that promote fear of pain and practitioner dependence (Rubinstein, et al., 2019). Contrary to this belief, data from the fourth study (Chapter 7) showed that SMT reduced pain catastrophizing and consequently, fear avoidance, challenging the notion of manual therapy as merely a passive treatment (Rhon D.I. and Deyle, 2021). We could postulate that, by enabling pain relief, sustained SMT can enhance the perception of self-efficacy, removing barriers to engage in beneficial physical activity and exercise (Thomas et al., 2023). This may be particularly important for CPLBP patients who experience less effective pain relief from exercise (Short, et al., 2023), or have individual preferences and positive prior experiences with manual therapy (Thomas, et al., 2023). Overall, it is plausible that SMT in isolation may be effective for CPLBP. Nevertheless, this approach is neither the most desirable nor reflective of actual

chiropractic clinical practice. Integrating SMT with active interventions and patient education to enhance activity levels is likely to yield more comprehensive and sustainable results for CPLBP.

Patient safety is an essential parameter when appraising an intervention. Regrettably, most randomized clinical trials fail to adequately examine adverse events of SMT or exercise for CPLBP (Hayden, et al., 2021; Rubinstein, et al., 2019). Despite these limitations, adverse effects seem to be of comparable mild-to-moderate and transient nature for both interventions. The fourth study supported that this is the case for adverse effects of SMT. These were not significantly different from the ones reported after placebo SMT, which is consistent with the hypothesis that a substantial proportion may be the consequence of natural history and nonspecific factors (Walker et al., 2013). In view of similar effectiveness and safety of SMT and exercise, treatment choice should rest on the patient and practitioner's preference. Care provided by chiropractors, mostly based on SMT, often receives high patient satisfaction ratings (Deyo, 2017), however, this does not translate into robust SMT endorsement from all clinical guidelines. The role of SMT is sometimes downgraded when compared to exercise, which is perceived as a safer option, and directly promotes active self-care. An additional factor is the low certainty of the evidence due to inconsistent data on the efficacy of SMT against placebo (Korownyk, et al., 2022). The forthcoming section synthesizes novel findings from this thesis regarding this issue.

Efficacy against placebo

Clinical trials and experiments that assess efficacy preferably employ highly controlled laboratory conditions and random assignment of placebo comparators (Fritz and Cleland, 2003). By reducing bias and maximizing control over variables, this methodology is best suited to elucidate the specific effects of interventions and the contribution of specific mechanisms to a clinical endpoint. The results presented in the fourth study offer novel evidence of the mechanisms and efficacy of SMT for clinical spine pain. The second study offers mechanistic data on an experimental pain condition that provides support for the clinical findings. In both investigations, SMT positively affected pain-related outcomes independent of expectations, and outperforming placebo. However, this does not imply that the utilized placebos were inert or that all nonspecific effects were controlled for. In fact, the placebo SMT used in the fourth study resulted in clinically meaningful changes. Contextual factors can explain changes in the placebo arm, but also contribute to clinical improvement from genuine treatments (Sherriff et al., 2022). These factors play a

significant role in CPLBP relief (Strijkers et al., 2021; van Lennep et al., 2021). Low certainty data modestly favor SMT over placebo for pain relief (Ruddock et al., 2016; Scholten-Peeters et al., 2013), an effect that is likely not clinically significant (Lavazza et al., 2021). However, this is disputed by results from the fourth study, for which between-group differences in pain intensity favoring SMT surpassed proposed thresholds for clinical significance (Busse et al., 2015). The next sections proceed to explore the potential underlying reasons.

Credibility of placebo spinal manipulative therapy

As reviewed in Chapters 4 and 6, designing placebo or sham SM interventions is a challenge. This impacts the quality of most placebo-controlled trials and limits the interpretation of the results (Puhl et al., 2017). Low similarity between placebo and experimental interventions compromises blinding, causing trials to overestimate treatment effects (Hohenschurz-Schmidt et al., 2022a). To overcome this obstacle, our efficacy trial used a validated placebo SMT, structurally equivalent to the real SMT and highly indistinguishable (Chaibi et al., 2015). Treatments were delivered by the same practitioner in an identical clinical context. These parameters were expected to improve the certainty in the results (Hohenschurz-Schmidt, et al., 2022a). Successful blinding was achieved throughout the study, implying comparable credibility levels for both interventions. Further, baseline expectations of improvement, a crucial component of placebo effects in clinical trials (Colloca, 2020; Hohenschurz-Schmidt, et al., 2022a), were also assessed and did not seem to impact differences between treatment arms. Under these conditions, greater certainty allows for attributing the differences in clinical outcomes between groups to specific effects of SMT (Colloca and Barsky, 2020; Hohenschurz-Schmidt, et al., 2022a). Notwithstanding, the potential role of expectations warrants further discussion.

Expectations

Patients' expectations (positive or negative) can shape the course of clinical conditions. Their contribution is largely described in terms of placebo and nocebo effects (Colloca and Barsky, 2020). Expectations for LBP are associated with prior episodes and predict the outcomes of chiropractic and medical treatment (Kongsted et al., 2014). Optimistic expectations of recovery lead to better outcomes and faster recovery (Cole et al., 2002; Hayden, et al., 2019; Iles et al., 2009). Patient expectations of improvement were associated with most chronic pain outcomes from multidisciplinary personalized care (Cormier, et al., 2016). This effect was mediated by the

patients' perceived improvement, which is consistent with the general consensus that expectations of treatment outcomes constitute a foundation for placebo effects (Kaptchuk et al., 2020). Results from this thesis (Chapters 5 and 7) insinuate a limited role for baseline expectations on treatment outcomes. Expectations did not differ between intervention groups, and adjusting for these scores did not significantly alter results. Although baseline expectations could not account for the superiority of SMT in the fourth study, they predicted and partially explained the benefits of both placebo and SMT at the 8- and 16-week follow-ups of the clinical trial (data not shown in the final version). Overall, expectations were a better predictor of CPLBP outcomes from placebo than from SMT at these endpoints. These findings must be interpreted with caution, as patients were unmasked at this point, and expectations almost certainly shifted. Expectations are indeed dynamic and thus, recalibration after per-protocol unmasking, or due to exposure to different degrees of relief or adverse events cannot be excluded (Langford et al., 2022). Indeed, other contextual factors could have potentially contributed to the effects of SMT, as introduced in the next segment.

Contextual factors

Unmeasured factors may have mediated placebo effects in our studies. Classical conditioning has been widely discussed as a model underpinning placebo mechanisms; however, its implication in chronic pain is unclear (Colloca, 2020). Exposure to a neutral (inert) stimulus paired with an active treatment (SMT), when followed by pain relief (conditioned response) may facilitate future responses simply by exposure to the neutral stimulus. Joint cavitation, occurring during most real but not placebo SMT, may act as the neutral stimulus, inducing placebo effects contributing to between-group differences (Innes, et al., 2020). After repeated exposures, patients could learn to associate cavitation with relief. This raises the possibility that patient-provider interactions and contexts were not identical between groups. Despite extensive training to deliver confidently placebo SMT (Puhl, et al., 2017), blinding the provider and completely eliminating this bias is not achievable (Giandomenico et al., 2022). Consciously or unconsciously exposing participants in both arms to different verbal or non-verbal cues could unbalance placebo effects and influence outcomes (Sherriff, et al., 2022). Moreover, other nonspecific effects, including regression to the mean and the natural progression of the condition (Colloca, 2020; Kaptchuk, et al., 2020), would have required the inclusion of a no-treatment group for proper evaluation. This limitations extends beyond SMT research, as portrayed in the challenges to discern specific from nonspecific effects of exercise for chronic pain (Miller C.T. et al., 2022). Recent estimations of

placebo effects in contemporary medicine suggest that they may account for an average of 65% of all treatment responses (Tsutsumi et al., 2023).

Previous research comparing SMT to placebo or sham SMT for LBP reached equivocal conclusions (Lavazza, et al., 2021; Rubinstein, et al., 2019). The work presented here sought to provide greater clarity on this subject. The results suggest that SMT applied to the most sensitive segment effectively relieves CPLBP when compared to a highly similar placebo SMT. Pain relief was clinically significant, as was the difference between interventions. Between-group differences in pain alleviation did not translate into different disability outcomes, possibly because distinct mechanisms contributed to each of these two outcomes. These findings may be better understood through a mechanistic lens that is explored hereafter.

How does chiropractic spinal manipulative therapy relieve chronic primary spine pain?

This thesis synthesizes prior findings and offers new data to expand our understanding of the mechanisms implicated in spine pain relief by chiropractic SMT. How these mechanisms relate to nociplastic pain is of particular interest, as it may influence the management of CPLBP. These novel results are congruent with a substantial body of literature supporting the hypothesis that SMT reduces mechanical pain hypersensitivity in tissues innervated by spinal cord segments targeted by SMT, as presented in Chapter 4. The literature review revealed that this is likely achieved through reduction of temporal summation and proinflammatory responses, both amplified in patients with CPLBP. It was suggested that SMT modulates C fiber afferent activity (**Figure 19**), however, this remains speculative. Recent studies produced data that are discrepant with the hypothesis of a specific segmental effect. Inconsistent findings could be attributed to variations in control interventions. The evidence presented in this thesis may help reconcile these divergent findings.

Spinal mechanisms of spinal manipulative therapy

Segmental modulation of experimental secondary hyperalgesia

The second study utilized topical capsaicin as an experimental injury model to generate pain and recreate CS processes (Quesada, et al., 2021). This model allows to characterize an area of primary (capsaicin) pain and hyperalgesia, and a region of secondary hyperalgesia. To identify

the latter, deep mechanical pain thresholds (PPTs) were measured at a distance of 1.5 cm from the borders of the area of capsaicin administration. A decrease in PPTs was observed 40 minutes after capsaicin application for those exposed to the placebo maneuver or no intervention, indicative of secondary hyperalgesia and CS. Participants receiving a single SM, irrespective of the targeted segment, did not develop significant changes in PPTs. However, only SMT targeting the capsaicin-sensitized segment prevented secondary hyperalgesia when compared to placebo, even after adjusting for expectations. This strongly suggests that the mechanisms of SMT impact a specific spinal cord segment. Furthermore, modulation of PPTs in areas adjacent to that of primary pain suggests that heterosynaptic processes of spinal cord plasticity may be specifically involved (**Figure 19**), although this requires further clarification.

Segmental modulation of clinical mechanical hyperalgesia

In the clinical trial (Chapter 7), deep mechanical hyperalgesia was detected at multiple segmental levels in patients with CPLBP when compared to healthy controls. This was indicative of primary, likely secondary and widespread hyperalgesia. Following SMT, hyperalgesia was attenuated exclusively in the segment of most intense clinical pain, which was also the targeted segment. To be specific, mechanical sensitivity was diminished in muscle tissue adjacent to the presumed segment of primary hyperalgesia. This effect was absent after placebo, which was interpreted as evidence for a specific segmental mechanism of SMT. By definition, primary hyperalgesia is characterized by increased sensitivity to noxious thermal stimuli in the area of injured tissue, while secondary hyperalgesia develops in adjacent tissues, responding to mechanical stimuli (Raja et al., 1984; Treede, 2016). However, CPLBP patients and clinicians cannot accurately localize the area of primary pain, which means assessing primary and secondary hyperalgesia in CPLBP may not be reliable. The assumed locations for these assessments might not have been suitable for their intended purpose. Moreover, SMT cannot be directed precisely to a single spinal level (Herzog et al., 2001; Ross, et al., 2004). As a result, it cannot be ruled out that the reduction in mechanical sensitivity reflects attenuation of secondary hyperalgesia. This would be consistent with the existing literature and the results from our experimental study (**Figure 19**). Assessing PPTs in each of the three segments adjacent to the presumed area of primary pain may have provided more insight into the anatomical boundaries of the areas of hyperalgesia and the potential effects of SMT.

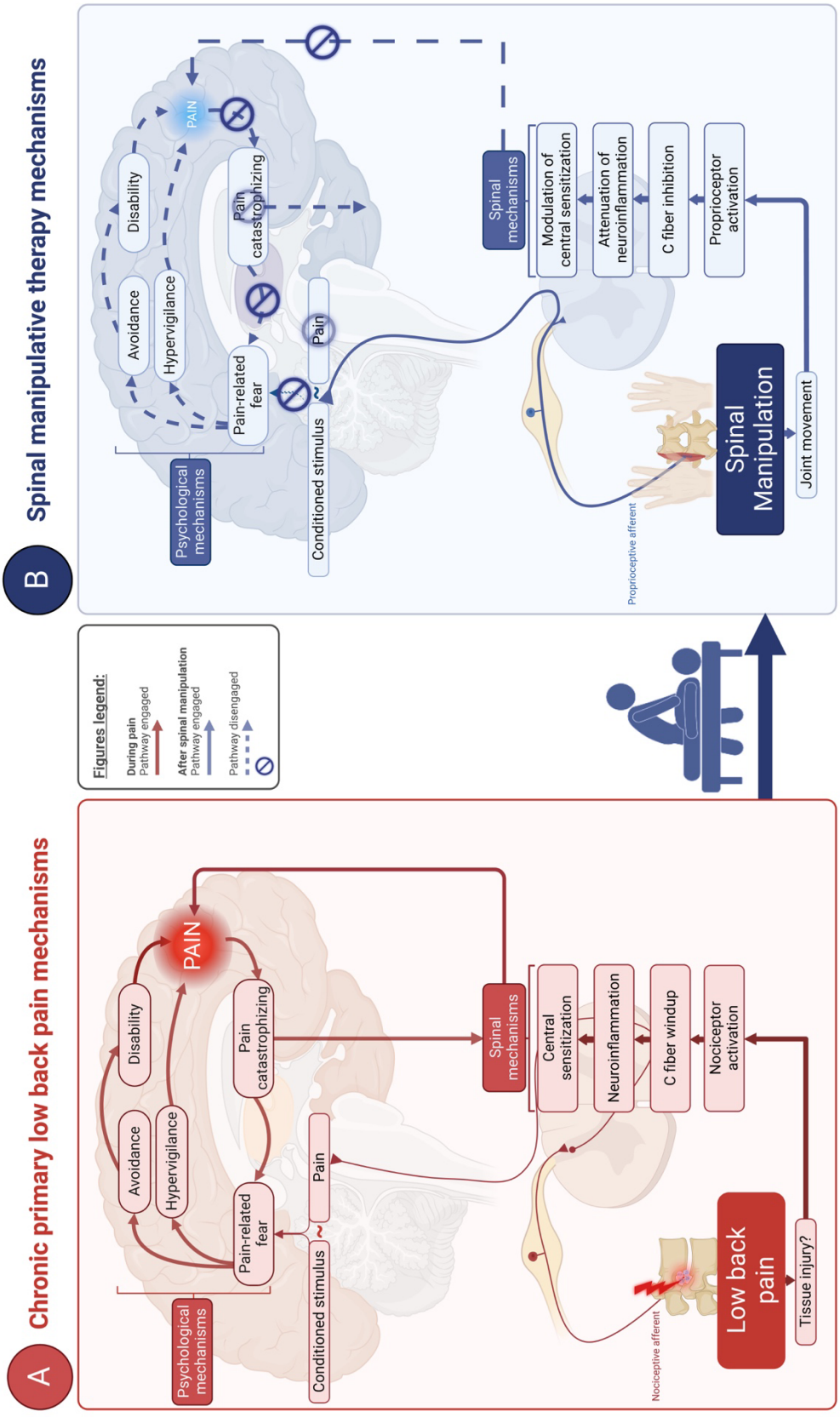

Figure 19 Mechanisms of spinal manipulative therapy for chronic primary low back pain

Proposed model for the **(A)** neurophysiological and psychological mechanisms of chronic primary low back pain investigated in spinal manipulative therapy research, including potential spinal, fear-avoidance mechanisms, and their interactions; and **(B)** potential effects of spinal manipulative therapy on these mechanisms. Anatomical representations are intended to serve illustrative purposes.

Segmental anti-hyperalgesic mechanisms

A recent review of the best evidence did not support that SMT leads to better clinical outcomes when targeting an indicated spinal segment, as opposed to one or multiple segments with no specific indication (Nim, et al., 2021a). This is in direct contradiction with our findings, which suggest that the level of application may influence PPTs and clinical pain. In the second and fourth studies, hyperalgesia was reduced, and clinical pain relief was achieved, by administering SMT to the same hyperalgesic segment. Similarly, Nim and colleagues applied SMT to the most sensitive segment in patients with CPLBP, which diminished hyperalgesia to a greater extent than targeting the stiffest segment (Nim et al., 2020). It was proposed that the impact of SMT on PPTs relies on the presence of enhanced nociceptive excitability (Jordon et al., 2017), which is congruent with segmental SMT preferentially inhibiting pain evoked by temporal summation rather than pain associated with a single noxious stimulus (Bialosky et al., 2009; George et al., 2006; Randoll et al., 2017). Along these lines, the reduction of laser-induced experimental pain by SMT, independent of Aδ fiber activity, led to speculations about an anti-hyperalgesic mechanism that relies on C fiber inhibition (**Figure 19**; (Provencher et al., 2021a)). This is particularly important for CPLBP, as C fiber activation is critical for the development of temporal summation, secondary hyperalgesia, and CS at large (Mendell, 2022).

Despite displaying anti-hyperalgesic effects, SM had no effect on primary pain from capsaicin (Chapter 5). Provencher and colleagues similarly reported no impact of a single SM on laser-evoked pain amplified by capsaicin in healthy individuals (Provencher et al., 2021b). Laser stimuli were applied within the area of primary hyperalgesia induced by capsaicin. The authors interpreted this as evidence for a centrally mediated effect independent of the modulation of primary hyperalgesia (Provencher, et al., 2021b). In addition, they postulated that one SMT session might not suffice to provide relief from primary or clinical pain. Although data on the optimal number and frequency of SMT are scant (Pasquier, et al., 2019), it is plausible that multiple encounters are required for these mechanisms to result in a clinical response. This may explain why increases in PPTs were unrelated to clinical improvement after four SMT sessions targeting

the most sensitive segment (Nim, et al., 2020), while in our trial, PPTs predicted clinical pain relief after twelve SMT sessions, but not after the first four (β = -0.02, p=0.8, using the same model; data not shown in the manuscript). This is largely consistent with available dose-response data used to design our protocol, suggesting that twelve SMT sessions may yield the best results for CPLBP compared to placebo (Haas et al., 2014).

Altogether, these results suggest that a single SM might modulate hyperalgesia through segmental mechanisms, potentially translating into specific clinical effects after administration of repeated SMT sessions (> 4 and ≤ 12). This could account for discrepancies between our findings and recent studies reporting no effect of SMT on PPTs beyond placebo, in healthy participants or LBP patients (Aspinall et al., 2019; Bond et al., 2020; Honore et al., 2020; Jordon, et al., 2017). Although these studies were methodologically sound, most applied a single SM, and none targeted segments displaying hyperalgesia. It could be argued that SMT does not directly suppress nociceptive afferent activity (i.e., no analgesic effect), but instead induces anti-hyperalgesic effects that may impact clinical pain after repeated exposure. This could hint at the involvement of spinal cord plasticity mechanisms, which are discussed hereafter.

Spinal cord neuroplasticity mechanisms

Spinal cord modulation of nociceptive activity was first discussed by Melzack and Wall in their Gate Control Theory of pain (Melzack and Wall, 1965). They postulated that pain is shaped by a balance of activity between large- and small-diameter afferents (A and C fibers, respectively), mediated by lamina II interneurons. These interneurons are responsible for silencing nociceptive activity in the absence of noxious stimuli, attenuating excessive responses, avoiding crosstalk between different modalities, and preventing the spread to neighboring somatotopic areas (Sandkuhler, 2009). Thus, these cells regulate homosynaptic and heterosynaptic nociceptive processes and failure to normally function likely contributes to amplified pain responses in CPLBP. Preclinical studies showed that SMT may activate large-diameter afferents from muscle and joint mechanoreceptors (Pickar and McLain, 1995; Pickar and Wheeler, 2001; Reed et al., 2013; Sung P.S., et al., 2005). Firing of these proprioceptive afferents could trigger neuromuscular reflex responses in paraspinal muscles (Gyer, et al., 2019; Pickar and Bolton, 2012), which may be altered in the presence of LBP (Currie et al., 2016). SM may yield large neuromuscular responses, that are coupled with decreases in pressure pain sensitivity in patients with chronic back pain (Lardon et

al., 2022). Consequently, large-diameter afferent input from SM might interact with small-diameter nociceptive fibers, potentially through dorsal horn interneurons and gating mechanisms (Gyer, et al., 2019). However, the gate control theory has since been expanded and refined (Woolf, 2022) and is currently not the best suited to explain anti-hyperalgesic effects observed with SMT, which rely on spinal cord neuroplasticity, as discussed hereafter.

It was speculated that SM input could alter spinal cord neuroplasticity (Jun, et al., 2020; Niazi et al., 2015; Pickar and Bolton, 2012). A potential hypothesis is that SMT reverses C fiber-dependent long-term potentiation underlying homosynaptic and heterosynaptic sensitization in CPLBP (**Figure 19;** (Boal and Gillette, 2004)). Thus far, the evidence is limited to animal models, but warrants further investigation. The implication of these mechanisms in humans can only be explored using surrogate measures. Assuming that SM alters spinal cord neuroplasticity, the focus may shift towards mediators of this plasticity. Emerging data suggest that neuroinflammation plays a significant role in these processes (Andrade et al., 2011; Ji, et al., 2018; Vergne-Salle and Bertin, 2021), which is explained in the subsequent section.

Neuroinflammatory mechanisms

Beyond primary afferents and interneurons, non-neuronal cells (i.e., glia) contribute to spinal cord nociception and sensitization processes (Woolf, 2022). Proinflammatory cytokines mediate dorsal horn plasticity and CS, mainly through reduced inhibitory control from interneurons and facilitated excitatory transmission of primary afferents (Gustafson-Vickers et al., 2008; Kawasaki, et al., 2008; Vikman et al., 2003). In animal models evoking CS, the pathological expression of TNF and IL-1β, and IL-10 was partially reversed after multiple sessions of SMT or joint mobilization (Omura et al., 2021; Song et al., 2016). This modulation of spinal neuroinflammation was associated with anti-hyperalgesia and reversed spinal cord plasticity (**Figure 19**). This preliminary evidence cannot be replicated in humans without invasive procedures. Therefore, cytokine levels in body fluids are being explored as potential correlates.

The proinflammatory cytokine TNF-α is consistently elevated in fluid samples of patients with CPLBP (Canli, et al., 2022; Morris, et al., 2020). The fifth study (Appendix I) offered novel data suggesting that this cytokine is also increased in urine samples of CPLBP patients compared to matched pain-free controls. Improved clinical outcomes after SMT were accompanied and predicted by reductions in urinary TNF-α values. In the absence of inflammatory or painful

pathology, these values are almost null and remained stable in pain-free individuals over the course of the same period of time. Therefore, changes in urinary TNF-α before and after treatment may reflect CPLBP evolution. As the study did not include a control intervention group, attenuation of the inflammatory response cannot be attributed to SMT. It was not possible to expand these results by comparing changes after SMT and placebo in the clinical trial (Chapter 7). Despite collecting urine samples from all CPLBP patients, a significant number was damaged before quantification. Thus, the data provided cannot clarify specific effects of SMT on TNF-α levels.

Previous studies have similarly compared individuals with LBP receiving SMT to asymptomatic controls who did not receive treatment. Both single and multiple SMT sessions were associated with decreased TNF-α, TNF receptor, IL-6, and interferon gamma responses in CPLBP patients (Roy et al., 2010; Teodorczyk-Injeyan et al., 2021). Two trials that randomized participants to SMT or placebo also reported effects of SMT on TNF-α and IL-1β responses in both CPLBP patients (Licciardone et al., 2012) and in healthy individuals (Teodorczyk-Injeyan et al., 2006). Interestingly, the biomechanical parameters of SMT appeared to have specific effects on plasma concentrations of inflammatory markers in healthy young adults (Duarte et al., 2022).

Among four main inflammatory cytokines potentially influenced by SMT (TNF-α, IL-1β, IL-6, and IL-10), TNF-α likely plays a critical role. In the fifth study (Appendix I), baseline urinary TNF-α concentrations accounted for over one third of the variance in follow-up CPLBP disability, while its fluctuations predicted about two thirds of total pain relief. Beyond predicting clinical outcomes, TNF-α helped identify a subgroup of persistent CPLBP patients more likely to present nociplastic pain. Therefore, TNF-α could serve as a biomarker for a CPLBP subgroup, whose pain mechanisms might be targeted by SMT, or potentially for a subgroup of responders (Licciardone, et al., 2012). Further investigation through better placebo controls, may confirm whether attenuation of inflammation underlies SMT (**Figure 19**), and whether this effect is more significant in a subgroup of patients with nociplastic pain.

Altogether, these results expand on previous evidence suggesting that SMT potentially modulates nociplastic pain mechanisms, including CS and neuroimmune responses. The factors initiating these responses remain unknown, but SMT parameters such as dosage and frequency may influence this effect, implying that somatosensory activation may play a role (**Figure 19**). It is also plausible that the mechanical stimulation of tissues suffices to activate resident

macrophages, prompting cytokine release (Adams S. et al., 2019; Duarte, et al., 2022). Neuroinflammatory responses to SMT may be confined to peripheral tissues, or alternatively, could occur within the spinal cord after glial cell activation or crossing of the blood-brain barrier by inflammatory cells or molecules. Similarly, the imbalance between facilitatory and inhibitory nociceptive activity is not restricted to the spinal cord (Woolf, 2022) and SMT may influence supraspinal activity. The next section discusses our findings on the potential modulation of supraspinal mechanisms of CPLBP by SMT.

Supraspinal mechanisms of spinal manipulative therapy

Several neuroimaging studies have attempted to identify correlates of brain mechanisms involved in pain relief by SMT (see Chapter 4). However, most had methodological limitations, particularly in the choice of control interventions. In addition, the studies' design did not allow confirmation of whether SMT influenced brain mechanisms, or if the inhibition of ascending nociception at the peripheral or spinal level resulted in decreased bottom-up activation of brain activity. Determining whether supraspinal mechanisms are the cause or consequence of chronic pain remains challenging. Nonetheless, this should not limit the enthusiasm to explore these processes, as they offer valuable information for identifying potential biomarkers (van der Miesen et al., 2019; Zebhauser, et al., 2022). The primary biomarker of supraspinal mechanisms investigated in this thesis, prefrontal gamma band oscillations, is discussed below.

Oscillatory brain activity

The second study of this thesis aimed to quantify changes in prefrontal gamma oscillations induced by topical capsaicin and to determine the effects of SMT on this oscillatory brain activity. Prefrontal gamma power was previously linked to tonic experimental pain and persistent clinical pain (May E.S., et al., 2019; Schulz et al., 2015), reflecting pain intensity in experimental paradigms with high accuracy (van der Miesen, et al., 2019). However, distinct types of nociceptive stimuli can differently affect gamma band activity (Linde et al., 2023). To the best of our knowledge, ours was the first attempt to measure gamma band oscillations in a capsaicin model of tonic pain. No effect of SM on oscillatory brain activity was found, consistent with the lack of effect on capsaicin pain intensity and unpleasantness. It is plausible that a single SM may be insufficient to influence supraspinal mechanisms. Thus far, experiments measuring changes in pain-related brain oscillations or evoked potentials after one SM have failed to obtain positive

results (Navid et al., 2019; Provencher, et al., 2021a; Provencher, et al., 2021b). This does not mean that a period of SMT might not yield positive results. Assessing brain biomarkers of chronic pain is attractive because they can be considered more objective endpoints for clinical pain that can provide mechanistic insight (Davis K.D. et al., 2020). However, no marker of brain activity currently offers a clear advantage for its use in longitudinal studies (Zebhauser, et al., 2022). Of interest, as gamma power is believed to act as a correlate of attentional bias towards pain (Kim J.A. and Davis, 2021), abnormal oscillatory activity may reflect cognitive processes with a well-established role in the pathogenesis of CPLBP (e.g., pain catastrophizing). The subsequent section dissects the effects of SMT on such psychological constructs presented in the current thesis.

Psychological mechanisms of spinal manipulative therapy

Pain catastrophizing is a critical psychological factor that predicts the intensity, disability, and chronicity of LBP (Martinez-Calderon, et al., 2019b; Wertli et al., 2014a). The fifth study in this thesis showed a beneficial effect of SMT on pain catastrophizing. These reductions were clinically significant for CPLBP (Suzuki et al., 2020), and superior to placebo and nonspecific temporal effects. Limited evidence supports that manual treatments may be effective for diminishing catastrophizing (Kamonseki et al., 2021; Kim H. and Lee, 2023) and fear-avoidance beliefs (Martinez-Calderon et al., 2020) in patients with chronic musculoskeletal pain. Our findings present new evidence that reinforces this potential effect.

Pain catastrophizing as a predictor of treatment efficacy

Pain catastrophizing mediates the efficacy of both cognitive and physical interventions for CPLBP (Smeets et al., 2006; Wertli, et al., 2014a). Consequently, modulation of maladaptive pain cognitions may be a shared mechanism across various interventions for chronic pain (Burns et al., 2012). Our clinical trial revealed that baseline pain catastrophizing scale (PCS) scores had minimal impact on pain intensity but were an important factor predicting CPLBP disability after SMT at every clinical endpoint. Higher PCS scores predicted larger improvements in disability, however, these are generally linked to worst CLBP-related disability outcomes (Wertli, et al., 2014b). Therefore, considering that participants reported relatively low levels of baseline disability (Tonosu et al., 2012), and that the questionnaire used has demonstrated significant floor effects (Brodke et al., 2017), this finding could represent a false positive. Nonetheless, it is plausible that SMT targets mechanisms associated with pain catastrophizing, ultimately leading to reductions in

disability. Accordingly, our study found that decreases in PCS scores significantly contributed to improved disability outcomes. However, this effect was independent of the intervention. The absence of between-group differences in disability warrants caution in interpreting these results. Multiple mechanisms may lead to reductions in pain catastrophizing, including potential mechanisms specific to SMT and other nonspecific contextual factors. The mechanisms are unclear, but recent data offer potential explanations to this effect.

Disruption of conditioned fear-avoidance responses

An in-depth examination of the behavioral mechanisms through which fear-avoidance exacerbates disability in the context of CPLBP is presented in Chapter 2. Within this theoretical framework, when pain is paired with a movement or a posture, a proprioceptive cue may suffice to generate fear of pain (Meulders and Vlaeyen, 2013; Vlaeyen and Linton, 2012). Patients with LBP may avoid movements that elicit similar proprioceptive cues as movements previously associated with pain, thereby further contributing to disability. These conditioned responses may be extinguished if the conditioned stimulus (i.e., the movement) is decoupled from pain. It has been proposed that the proprioceptive input generated by SMT could help "unlearn" these responses in patients, particularly if it is associated with relief rather than followed by pain (Ellingsen et al., 2018). In a cohort of patients with CPLBP, clinical pain, fear of movement, and pain expectations from movement were all reduced after receiving either SMT or mobilization. Decreased fear and expected pain correlated with lower activation of brain regions involved in salience detection and pain anticipation (Ellingsen, et al., 2018). However, correlations were stronger for those receiving SMT. Similarly, incorporating SMT into exercise was associated with greater improvements in fear-avoidance beliefs than adding mobilization (Sung Y.B. et al., 2014).

Compared to mobilization, SMT elicits greater neuromuscular responses associated with larger reductions in mechanical pain sensitivity (Lardon, et al., 2022). Thus, the proprioceptive stimulus from SMT could disrupt movement-related conditioned responses in patients with CPLBP (**Figure 19**). Patients may perceive the movement as safe, and no longer a threat. Arguably, this could happen with mobilization, SMT, and placebo SMT. However, joint cavitation from SMT could provide an additional novel cue that patients may learn to associate with relief and relaxation, instead than pain (Clark B.C. et al., 2011; Innes, et al., 2020). The brain areas influenced by this putative effect of SMT are implicated in descending pain modulation (Ellingsen, et al., 2018).

Therefore, by altering brain activity in these areas, changes in pain cognitions could possibly down-regulate mechanisms of pain amplification and in turn, CPLBP outcomes (**Figure 19**). This effect may be particularly relevant for patients with high levels of pain catastrophizing, which is suggestive of nociplastic pain. The underlying neurophysiological foundations for these mechanisms are explored in the following section.

Neurobiological mechanisms of pain catastrophizing

Pain catastrophizing is associated with structural and functional changes in brain areas governing multiple dimensions of pain processing and attention to pain, such as the prefrontal cortex (Galambos et al., 2019; Malfliet et al., 2017; Seminowicz and Davis, 2006). Animal data suggest that fear-related prefrontal mechanisms influence future pain based on past experiences (Stegemann et al., 2023). These processes are likely engaged in chronic pain, thereby disengaging descending pain inhibition. Accordingly, CPM responses are negatively associated with PCS scores in CPLBP and healthy individuals (Christensen, et al., 2020; Traxler et al., 2019), suggesting that catastrophizing may impair descending inhibition of nociception or enhance its facilitation. Such a mechanism could potentially explain the contribution of pain catastrophizing to temporal summation (George et al., 2005) and deep-tissue hyperalgesia (Meints, et al., 2019) in CPLBP. For healthy individuals, PCS scores were found to moderate the relationship between experimental pain and secondary hyperalgesia (Pressman, et al., 2017), which were reduced by CBT targeting pain catastrophizing (Salomons et al., 2014). Two pilot studies on patients with chronic pain (including CPLBP) noted that instigating catastrophic-like thoughts enhanced temporal summation and mechanical allodynia (Taub, et al., 2017), stimulating the release of IL-6 and possibly TNF-α in women (Darnall et al., 2010). Similarly, experimental induction of negative expectations towards SMT was shown to enhance (instead of inhibiting) temporal summation responses after treatment (Bialosky et al., 2008). Thus, failure to modulate negative pain expectations, such as catastrophizing, may diminish the effects of SMT, reinforcing CS mechanisms, while their inhibition may contribute to clinical success (**Figure 19**). Collectively, these data suggest that pain catastrophizing could play a role in modulating nociplastic pain mechanisms, with potential implications for SMT. The psychological mechanisms of nociplastic pain involved are presented in greater detail below.

Psychological mechanisms of nociplastic pain

Supraspinal contributions to CS, including from psychological factors, have been extensively investigated (Harte et al., 2018; Treede et al., 2022). Stronger connections in ascending nociceptive pathways and weaker descending modulation connectivity were proposed to account for individual differences in the tendency to experience pain amplification (Cheng et al., 2015). Neuroimaging data support the notion that brain processes and cognitive factors like pain catastrophizing maintain or facilitate CS (Harte, et al., 2018). Patients with CPLBP exhibited strong associations between PCS and central sensitization inventory (CSI) scores, a measure of self-reported signs and symptoms related to nociplastic pain (Huysmans et al., 2018). In the fourth study, the CPLBP cohort displayed moderate correlations between PCS and CSI scores at baseline, follow-up, and when examining changes before and after care ($\rho = 0.38$, 0.54 and 0.41 respectively, data not shown in the manuscript). Only depression and anxiety scores displayed stronger correlations with the CSI ($\rho = 0.72$ and 0.65, respectively, data not shown in the manuscript). It was proposed that CSI scores reflect hypervigilance to somatic or psychological symptoms with some degree of correlation with depression and anxiety (Adams G.R. et al., 2022; Hendriks et al., 2020; Holm et al., 2022). These constructs could serve as mediators of the relationship between psychological factors (depression, anxiety, and catastrophizing) and CPLBP intensity (Shigetoh et al., 2019).

In the clinical trial (Chapter 7), all three groups, including the healthy controls, experienced reductions in CSI scores after four weeks. Furthermore, alterations in CSI scores contributed to reductions in pain and disability, irrespective of treatment allocation. This implies that self-assessed improvements in signs and symptoms related to CS may have played a role in the observed clinical benefits for both placebo and SMT groups. This effect could be interpreted as an indicator of decreased levels of anxiety and hypervigilance towards symptoms of CS and pain (Adams G.R., et al., 2022; Clark J.R. et al., 2019), relying on contextual and other nonspecific factors. Although this measure may be useful for assessing nociplastic pain comorbidities (Nijs, et al., 2021b), the current data do not support conclusions beyond the possible influence of nonspecific time-related factors.

Disentangling the mechanisms of an intervention poses a complex challenge, particularly when the intervention involves human interaction and physical touch. The specific effects of SMT presented in this thesis build upon earlier findings, suggesting that a single SM targeting a hyperalgesic segment may influence central hyperexcitability processes. It is plausible that repeated SMT sessions could induce more profound, enduring changes in nociplastic mechanisms, ultimately leading to the alleviation of clinical pain in CPLBP; however, further research is needed to confirm this hypothesis. Likewise, it could be hypothesized that when SMT is associated with clinical improvement, its somatosensory input may assist in unlearning conditioned responses and negative expectations contributing to pain chronicity (**Figure 19**). As with all interventions, the effects of SMT may be influenced by both specific and nonspecific or contextual factors. The primary factor contributing to placebo effects is thought to derive from positive patient expectations of improvement for a therapeutic intervention (Langford, et al., 2022). While baseline expectations did not appear to influence clinical outcomes immediately after treatment, they may have a role at different time points during treatment.

Implications for evidence-based practice

The work herein presented holds important implications for evidence-based management of CPLBP, a highly prevalent and disabling global condition. The research presented elucidates some of the mechanisms underpinning the effects of SMT on CPLBP and reveals that some of these processes are responsive to SMT, more so than to placebo. Notably, these mechanisms are not only relevant for discriminating patients with CPLBP from a healthy pain-free population over different time measurements, but may also predict patient response. Hence, they may be used as potential biomarkers or surrogate measures for treatment effectiveness. The studies also offer novel evidence of efficacy of SMT compared to a validated and credible placebo SMT. The mechanistic approach enables us to hypothesize that SMT efficacy relies on targeting specific processes related to a state of hyperexcitability and nociplastic pain, which is congruent with the available literature. Moreover, it may be posited that treatment outcomes are bolstered by manipulating the most painful vertebral segment expressing hyperalgesia.

Although more research is needed, these findings provide support for the ongoing development of a mechanism-based classification system for patients with CPLBP. If these research findings are replicated and expanded, it may be possible to adequately screen patients for

the appropriateness of initiating SMT. Previous clinical prediction rules for using SMT in patients with LBP showed promising results initially (Childs et al., 2004), but ultimately demonstrated limited predictive capacity (Hancock et al., 2008; Haskins et al., 2015). Data from this thesis may challenge certain assumptions of these prediction rules, such as the belief that patients with high levels of fear-avoidance are not candidates for SMT. The fourth study presented here offers conflicting evidence in this regard. Further exploration of these mechanisms may help identify a phenotype of CPLBP patients (e.g., nociplastic pain) that respond optimally to SMT. Meanwhile, screening tools such as questionnaires or algometers could be employed in primary care settings to inform clinical decisions based on these data. Additional assessment of cytokine levels in urine presents a more feasible and cost-effective alternative to blood samples, showing promising potential for clinical applications.

Provided more studies replicate these results, reconsideration of the guidelines for SMT in CPLBP may be warranted. Efficacy findings, although restricted to the short term, appear to be clinically significant, with high levels of adherence and safety. As others have argued, there is compelling data to suggest that manual therapy is not low value care, and may play a crucial role in active care (Rhon D.I. and Deyle, 2021). SMT may offer sufficient pain relief and reduction in catastrophizing to facilitate the return to activities and the prescription of exercise therapy. Thus, whether combined with exercise or not, SMT may offer a valuable option for first line care of a specific CPLBP patient subgroup that need to prioritize pain relief. These could be patients with high fear of movement and reduced levels of physical activity (Short, et al., 2023). This is not to say that the preferred management of CPLBP is not multimodal, particularly in the longer term where the benefits of SMT are less clear (Rubinstein, et al., 2019). Once initial analgesia has been established, physical exercise and self-management may be offered as the foundation for sustainable results. Despite the promising findings, the data presented must be interpreted in light of several limitations, extending beyond those of the individual studies. These are discussed in the next section.

Limitations of the current work

Although our investigations have yielded valuable insights, it is important to acknowledge several limitations that may influence the interpretation and generalizability of the findings. Two of the studies presented were narrative reviews of the literature. This approach has advantages,

such as synthesizing evidence from different types of studies (animal *vs*. human studies, clinical trials *vs*. reviews, clinical practice guidelines) and providing a more comprehensive understanding of the subject in question. However, systematic reviews are considered the gold standard for drawing inferences, particularly regarding effectiveness. These reviews rely on standardized, structured, rigorous protocols that reduce subjectivity and enhance the reliability and reproducibility of the results. Due to the narrative format, important data may have been missed, and specific findings overrepresented in the reviews. However, the primary aim was not to provide a quantitative synthesis of the findings, or an overall estimate of SMT effects. Instead, we sought to offer a broad and comprehensive understanding of two highly complex topics, considering not only the findings, but also the multiple methodological approaches. The overarching aim of the reviews was to identify research gaps in the latest literature to guide the development of the experimental studies. Thus, despite limitations in the approach, the objectives were achieved.

The experimental studies presented aimed to address some of the research gaps identified by the narrative reviews. In these studies, SMT administered by one or two chiropractors was investigated. Limiting the number of practitioners reduces treatment variability, which assists in drawing mechanistic inferences, albeit at the cost of reducing generalizability. In the second study, two chiropractors performed real SM on an equal number of participants, and no differences were found between them. The participant remained in the prone position without interacting with the chiropractor, thereby reducing potential biases that could arise from the encounter. In the fourth study, a single chiropractor applied all real and placebo SMT. Despite efforts to limit the patient-clinician interaction, potential biases emanating from this interaction cannot be entirely eliminated. This concern holds particular relevance for manual therapies, wherein a substantial element of physical contact may generate unmeasured placebo effects. These effects may inherently differ from one encounter to another, and likely account for a considerable part of the variance between patients and groups. Moreover, as previously mentioned, masking the clinician is not feasible, inevitably raising the potential for performance biases. The knowledge of treatment allocation may, consciously or unconsciously, influence the clinician's behavior. Different enthusiasm or attention to patients in different treatment arms could have impacted the observed outcomes. However, these potential biases, if present, did not appear to influence patient expectations or treatment credibility, suggesting that they were at least partially controlled.

Selecting an appropriate placebo intervention for manual therapy is challenging and failing to do so can limit the validity of the results. In the second study, the placebo SMT consisted of a force equivalent to SMT delivered with a dynamometer. Based on previous work (Randoll, et al., 2017), this maneuver was preferred over a validated placebo SM consisting of a manual thrust force applied towards the scapulae, thus, away from the spine (Chaibi, et al., 2015). As a mechanistic study, it was deemed more important for the placebo forces to be applied directly to the capsaicin-sensitized segment, in order to mimic the delivery of segmental SM. This allowed to control for the effects of nonspecific activation of superficial low-threshold mechanoreceptors. Baseline expectations did not influence the results, but it is possible that treatment credibility was not the same as for real SM, since blinding was not assessed. On the other hand, the placebo chosen for the clinical trial (Chapter 7) effectively addressed blinding concerns by offering a treatment sufficiently similar and credible to mask participants throughout the study. However, it remains unclear whether this procedure is indeed a sham, or if it contains any active element of genuine SMT. Patient positioning and initial set-up (before delivering the force) were identical to real SMT (see Appendix II). This was sufficient to induce joint gapping in some patients, demonstrating that tissues may be under similar stresses and strains at this point. The force delivered, albeit unintentional and allegedly nontherapeutic, might result in significant vertebral movement, neurophysiological input, or proprioceptive cue. There are no data to confirm whether these factors influence clinical outcomes, however, they may account for treatment effects attributed to this seemingly innocuous intervention (Aspinall, et al., 2019).

Other important limitations are methodological in nature. Assessing pain is complex due to its subjective and multidimensional nature. Potential errors from pain rating scales must be considered; relying exclusively on them may not provide a comprehensive assessment of pain intensity (Karcioglu et al., 2018). Identifying biomarkers help partially overcome this limitation, but the potential for error and false results must be recognized (Davis K.D., et al., 2020). The choice of surrogate measures for CS, such as mechanical hyperalgesia, remains contentious. Assessing PPTs offers the best discriminative properties for CPLBP (Neziri, et al., 2012). Yet, challenges in determining boundaries between primary, secondary, and widespread hyperalgesia limit the interpretations. Alternatively, temporal summation or descending modulation measures may offer additional insights into CS mechanisms. Electrophysiological methods have intrinsic limitations that may influence the choice of SMT. To minimize patient movement in the second study, SMT

targeted a thoracic segment, as neurophysiological mechanisms of SMT are not expected to differ between spine regions. When investigating interventions like SMT, movement artefacts are inevitable and can be particularly bothersome for the study of tonic pain paradigms (Chouchou et al., 2021). Lastly, significant limitations in quantifying concentrations of urinary TNF-α for the clinical trial must be acknowledged. Most samples were lost, likely due to damage caused by a breach in the cold chain, preventing the study from offering an unprecedented integration of psychological, psychophysical, and inflammatory data in CPLBP patients undergoing SMT.

Short-follow-up periods and small sample sizes may also be subjects of discussion, as two of the most common limitations of manual therapy trials (Alvarez et al., 2021). This is critical when enrolling patients with CPLBP, an extremely heterogeneous condition. Therefore, it seems reasonable to object that the results of the clinical trials are not generalizable to all CPLBP populations. The sample sizes, endpoints and follow-up periods were chosen with the mechanistic aims in mind and were successful in achieving the intended goals. Yet, it may be argued that, for the clinical trial, unmasking could have been deferred until the conclusion of the 16-week follow-up period. However, offering a brief trial period (4 weeks) followed by immediate access to care for patients in the placebo arm may have facilitated patient enrollment and retention, as evidenced by the minimal attrition observed in both arms. Assessing treatment expectations at multiple time points, particularly before the actual SMT commencement for the placebo group, could have provided more comprehensive data, offering important insights for interpreting the results observed in the longer-term follow-ups of the clinical trial.

Future directions

The findings of this thesis open the door to multiple research avenues that will enhance our knowledge of the mechanisms and appropriate use of SMT for CPLBP, and potentially other spine-related and chronic pain conditions. There is a pressing need for in-depth investigation into SMT mechanisms, and to determine whether they are specific to SMT. Future research should attempt to better understand the influence of contextual factors and nonspecific effects in SMT (Sherriff et al., 2023). For instance, generating and implementing detailed scripts for SMT provision in efficacy trials may help standardize patient-provider interactions and minimize bias. Assessing the neurophysiological mechanisms of alternative placebo SMT including different candidates with distinct active elements of SMT may be equally important.

Notably, it is essential to enhance the understanding of spinal mechanisms in relation to CS and its potential attenuation through SMT. Clarifying whether these effects are contingent upon the segment of application is of particular significance, as it could directly influence clinical practice. To gain a better understanding of spinal mechanisms, the temporal and spatial dimensions of hyperalgesia need to be better characterized. Examining temporal summation of deep mechanical pain in CPLBP is challenging but feasible using computer-controlled algometers to generate a train of repeated PPT-like stimuli compatible with windup (Nie et al., 2009). As for the assessment of secondary hyperalgesia, measuring PPTs at multiple locations allows to generate a topographical map (O'Neill, et al., 2019) that may help characterize the spatial distribution of pain hypersensitivity. How these maps change after a course of SMT, along the same or across multiple segments, may reflect changes in the expansion of nociceptor receptive fields compatible with CS. However, for some patients, hyperalgesia may be widespread, rendering this task futile.

Beyond QST, neuroimaging techniques offer invaluable data to confirm or refute the involvement of neural mechanisms and structures. Investigating other neural correlates besides gamma oscillations may yield different results worth exploring. An alternative to continuous brain oscillatory activity may be measuring resting-state electroencephalography before and after completing the treatment protocol, potentially with more direct clinical application (Ta Dinh, et al., 2019). In addition, there is potential in the measurement of C fiber evoked potentials as a surrogate measure to detect changes in nociceptor activation, either by sensitization or by its attenuation. Regrettably, a suitable protocol is still lacking (Provencher, et al., 2021a). Despite its potential, spinal cord fMRI, has not been applied to manual therapy research. Synaptic scaling, i.e., the recruitment of more neurons in the same spinal segment or over multiple spinal segments, may reflect CS processes when enhanced (Margerison et al., 2022). Another promising fMRI biomarker is the *Tonic Pain Signature*, an fMRI biomarker based on whole-brain functional connectivity that is sensitive to individual variations in tonic pain and may predict differences in chronic back pain, with great potential for clinical translation (Lee J.J. et al., 2021).

Selecting appropriate biomarkers that are physiologically and clinically pertinent to chronic pain states is vital, yet remains elusive (van der Miesen, et al., 2019). Future preclinical and clinical designs might correlate QST and clinical outcomes with neuroimaging markers, before and after exposure to SMT. Furthermore, the role of inflammatory cytokines (including TNF-α) in SMT

hypoalgesia requires clarification. Investigating associations between cytokine concentrations in peripheral fluid samples and indicators of spinal tissue, nerve, and spinal cord inflammation (Albrecht, et al., 2018; Alshelh, et al., 2022; Palada, et al., 2019) may be insightful. Both positive and negative findings would help determine whether the anti-inflammatory effects of SMT are specific to central or peripheral tissues, or neither.

Although the focus of this work was on neurophysiological mechanism, this does not mean that other mechanisms are not at play. Spinal tissue contributors should not be disregarded, and the interplay between biomechanical effects and neurophysiological mechanisms can offer important insights into SMT mechanisms (Lardon, et al., 2022). Identifying the component of SM that triggers its neurophysiological and putative cognitive effects is crucial. Preclinical data suggest that the proprioceptive input from muscle spindles is responsible for SMT's neuromuscular and neurophysiological effects (Currie, et al., 2016; Haavik et al., 2021). Changes in proprioception, which appear to be altered for at least a subgroup of CPLBP patients (Tong et al., 2017), were scarcely assessed with regards to SMT (Learman et al., 2009). Further investigating how SMT affects somatosensory input may clarify several hypotheses, including a potential relationship with fear-avoidance beliefs and behavior. As the precise influence of SMT and other manual therapies on pain cognitions remains uncertain, it is crucial to explore whether these changes are treatment-specific, and whether they are indirectly affected by pain reductions, or alternatively, contribute to them. Further research is also needed to establish causality and understand the potential connection with pain cognitions. Of relevance, terms like pain catastrophizing may eventually need to be revised in favor of patient-centered terminology (Crombez et al., 2020; Webster F. et al., 2023).

One of the most important targets of future investigations should be to clarify the optimal dose and frequency parameters for SMT responses (Pasquier, et al., 2019; Short, et al., 2023). These likely depend on the targeted mechanisms and their relevance for a particular patient or patient subgroup's clinical presentation. Identifying optimal parameters for targeting specific mechanisms could help clarify the distinct role of SMT and mobilization in CPLBP management. Although their effects are similar (Rubinstein, et al., 2019), mechanisms may differ (Duarte, et al., 2022; Lardon, et al., 2022), suggesting that distinct patient subgroups may benefit from different manual therapies and dose parameters.

Recruiting larger patient cohorts may be necessary for identifying predictors, mediators, and moderators of SMT efficacy more accurately. A potential avenue to increase sample size while focusing on more homogenous CPLBP subgroups (e.g., mechanism-based), is to conduct multicentric trials. As mechanisms become better understood, effectiveness studies can target these more homogeneous patient populations in real-world settings and assess longer follow-up periods. To address generalizability concerns and facilitate results interpretation, it is important to use standardized CPLBP definitions and measures. The adoption of minimum datasets that are gaining popularity in research designs would be an important step (Angarita-Fonseca et al., 2023). For SMT research, whether results can be generalized or not also prompts the question of the importance of the provider's background and expertise. Analysis of aggregate data suggests comparable clinical outcomes for CPLBP when SMT is delivered by clinicians from different professional backgrounds and levels of expertise (Rubinstein, et al., 2019). However, there is scant evidence specifically examining direct comparisons and this needs cautious interpretation and clarification.

Finally, more and better reporting of adverse events is needed. Data from clinical trials may not suffice to provide estimates of the frequency of serious adverse reactions, which tend to be rare. Nonetheless, they may offer an insight into the mechanisms leading to adverse events and potential strategies to identify people at risk and therefore mitigate them. Similar analyses to the ones conducted to examine predictors and contributors of clinical outcomes could be easily applied to understand the risk factors contributing to the development of adverse reactions in future trials. These data could assist in designing strategies to mitigate undesired SMT effects.

Chapter 9 – General conclusion

The studies presented in this thesis reveal that chiropractic spinal manipulation, when applied to a hyperalgesic segment, may effectively impact tonic experimental spine pain, and spinal manipulative therapy, when applied during repeated sessions, may alleviate chronic primary low back pain. The attenuation of deep segmental mechanical hyperalgesia was identified as a potential mechanism underpinning pain relief from spinal manipulation. By reducing hyperalgesic activity in targeted spinal cord segments, a favorable impact on conditioning mechanisms related to pain catastrophizing may potentially contribute to the reduction of low back pain-related disability. These mechanisms collectively suggest that chiropractic spinal manipulative therapy may mitigate processes linked to nociplastic pain in patients with chronic primary low back pain. Although spinal manipulation showed superior effects compared to placebo, which could not be solely attributed to treatment expectations, the impact of these and other contextual factors, particularly on long-term outcomes, should not be overlooked. Further research is needed to determine if these or other factors can elucidate the response to SMT and predict which patients will benefit the most.

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Appendix I: Article 5 – Urinary TNF-α as a potential biomarker for chronic primary low back pain

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Keywords: TNF-alpha; urine biomarkers; chronic pain; instrument-assisted spinal manipulation; ; pain trajectories; back pain.

Contribution des auteurs

Carlos Gevers-Montoro : Conception de l'étude, recension des écrits, collecte des données, analyse des données, rédaction de l'article, révision de l'article.

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Abstract

Introduction: Over two thirds of individuals with low back pain (LBP) may experience recurrent or persistent symptoms in the long term. Yet, current data do not allow to predict who will develop chronic low back pain and who will recover from an acute episode. Elevated serum levels of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) have been associated with poor recovery and persistent pain following an acute episode of LBP. Inflammatory cytokines may also mediate mechanisms involved in nociplastic pain, and thus, have significant implications in chronic primary low back pain (CPLBP).

Methods: This study aimed to investigate the potential of urinary TNF-α levels for predicting outcomes and characterizing clinical features of CPLBP patients. Twenty-four patients with CPLBP and 24 sex- and age-matched asymptomatic controls were recruited. Urinary TNF-α concentrations were measured at baseline and after 4 weeks, during which CPLBP patients underwent spinal manipulative therapy (SMT).

Results: Concentrations of TNF-α were found to be elevated in baseline urine samples of CPLBP patients compared to asymptomatic controls. Moreover, these values differed among patients depending on their pain trajectory. Patients with persistent pain showed higher levels of TNF-α, when compared to those with episodic CPLBP. Furthermore, baseline TNF-α concentrations and their changes after 4 weeks predicted alterations in pain intensity and disability following SMT in patients with CPLBP.

Discussion: These findings warrant further research on the potential use of urinary TNF-α concentrations as a prognostic biomarker for CPLBP.

Introduction

A large proportion of the general population will be afflicted with low back pain (LBP) at some point in their lifetime (Hoy et al., 2012; Vlaeyen et al., 2018), particularly in working age groups (Hartvigsen et al., 2018). It is likely that more than half a billion individuals suffer from LBP at any time point (Wu et al., 2020), some on an ongoing basis (Hoy et al., 2012). The exact proportion of patients who develop chronic LBP is currently unknown, but recent estimates suggest that one to two thirds of people seeking care for acute LBP may eventually experience recurrence or persistence of symptoms (Itz et al., 2013; da Silva et al., 2017).

Aiming to identify those who recover from an acute episode of LBP and those who do not, efforts have been directed towards investigating the patients' trajectories (Axen and Leboeuf-Yde, 2013; Kongsted et al., 2016). Most patients exhibit symptom trajectories characterized by either fluctuating or episodic LBP (Kongsted et al., 2017). Identifying the factors that influence distinct trajectories can enhance our ability to predict and categorize the course of LBP in individual patients. The severity of pain trajectories generally shows positive associations with female gender, history of LBP, the presence of leg pain, and comorbidities such as depression (Kongsted et al., 2015; Kongsted et al., 2016). In addition, LBP episodes and trajectories are strongly influenced by inflammation (Klyne et al., 2017).

Several potential inflammatory biomarkers have been identified in the context of LBP (Khan et al., 2017; Morris et al., 2020). Of these, the proinflammatory cytokine Tumor Necrosis Factor-alpha (TNF-α) has been associated with poor long-term recovery from acute episodes of LBP and symptom persistence (Klyne et al., 2017; Queiroz et al., 2017; Klyne and Hodges, 2020; Morris et al., 2020; Klyne et al., 2022). Moreover, TNF-α plays a significant role in the development and maintenance of central sensitization (Andrade et al., 2011; Ji et al., 2018; Vergne-Salle and Bertin, 2021), one of the main neurophysiological mechanisms underpinning nociplastic pain conditions (Nijs et al., 2021; Treede et al., 2022). The presence of nociplastic mechanisms in LBP is highly suggestive of chronic primary low back pain (CPLBP), previously classified as nonspecific (Kosek et al., 2021; Treede et al., 2022). CPLBP is chronic LBP of an unexplained etiology that is not fully attributable to either nociceptive or neuropathic mechanisms. Identifying biomarkers for CPLBP remains an unresolved challenge, which could prove extremely useful to

understand the pathogenesis, prognosis and treatment response of individual patients or patient subgroups (Davis et al., 2020).

It has been proposed that nonpharmacological approaches, such as manual therapy, may modulate inflammatory responses and nociplastic pain mechanisms in patients with CPLBP, however, this remains unclear (Licciardone et al., 2012; Lima et al., 2020; Gevers-Montoro et al., 2021). Elevated in vitro production of TNF-α in whole blood cultures of patients with CPLBP was significantly reduced after a period of spinal manipulative therapy (SMT) (Teodorczyk-Injeyan et al., 2021). These findings were recently replicated in urine samples of individuals with CPLBP (Gevers-Montoro et al., 2022), suggesting that TNF-α levels may reflect clinical outcomes or mechanisms relevant to their prognosis. A better understanding of the role TNF-α plays in persons with CPLBP could have the potential to inform mechanisms involved in the course and recovery from CPLBP, in particular, for patients undergoing SMT.

Therefore, the aim of this study was to assess the predictive value of urinary concentrations of TNF-α for outcomes and clinical characteristics in patients with CPLBP. First, we aimed to confirm that baseline urinary concentrations of TNF-α were elevated in patients with CPLBP compared with age-sex matched pain-free controls. Secondly, we compared changes in urinary concentrations of TNF-α over 4 weeks, during which patients received standardized SMT and controls received no intervention. We hypothesized that TNF-α concentrations would decrease in patients with CPLBP, approaching values observed in controls. Thirdly, we examined the predictive value of urinary TNF-α concentrations for clinical characteristics and outcomes in patents with CPLBP that received SMT. We hypothesized that urinary TNF-α concentrations may be used as a biomarker to discriminate patients with CPLBP according to their pain trajectory and to predict clinical recovery.

Methods

Study design and ethical approval

This was a prospective case-control study with longitudinal follow-up, assessing the predictive value of urinary TNF-α concentrations for baseline characteristics and clinical evolution of CPLBP patients undergoing chiropractic instrument-assisted SMT. The study protocol was approved by the Madrid College of Chiropractic Research subcommittee (San Lorenzo de El

Escorial, Madrid, Spain) and the Fundación Jiménez Díaz Hospital Clinical Research Ethics Committee (Madrid, Spain). The study was conducted between January 2018 and December 2022 at the Madrid College of Chiropractic Outpatient Clinic. All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki.

Participant recruitment

Patients were recruited from the population visiting the outpatient clinic for an initial consultation with a chief complaint of CPLBP. Patients seeking care for symptoms of LBP were screened for inclusion and exclusion criteria by performing a complete case history and physical examination, following routine protocols from the outpatient clinic. The inclusion criteria were: being between 18 and 80 years of age and presenting a chief complaint of persistent or recurrent pain ≥3 months, in any anatomical location included between the lower margin of the 12th rib to the lower gluteal folds, with or without referring to the lower limbs (Vlaeyen et al., 2018). The exclusion criteria were the following: detection of a specific pathology as the cause for the LBP, including evidence for pain of neuropathic origin, such as radicular symptoms, as this is considered chronic secondary LBP (Nicholas et al., 2019; Kosek et al., 2021); presence of chronic pain of higher perceived severity than LBP in any other body region; previous diagnosis of an inflammatory or rheumatic condition (e.g., inflammatory spondyloarthropathies); any contraindication to SMT (vertebral instability, history of any spine or pelvis fracture or surgery, namely spinal fusion or discectomy); having received any form of manual therapy to the spine in the previous two years; current use of prescribed pain medication, with the exception of non-steroidal anti-inflammatory drugs and over-the-counter analgesics; and pregnancy. Exclusion criteria allowed to identify a population with a diagnosis of chronic primary LBP (Nicholas et al., 2019). Once the diagnosis was confirmed, patients deemed eligible were informed about the study and were offered to participate. Patients accepting to participate read and signed an informed consent form before initiating treatment and collecting samples. Patients declining participation continued their regular course of care at the clinic without prejudice.

A cohort of pain-free controls matched by sex and age to the patient cohort was enrolled to serve as a reference for the levels in inflammatory cytokines that were collected and assessed from the patient cohort. Individuals eligible for the pain-free cohort were to meet the following criteria: aged between 18 and 80 years old, without acute or chronic pain symptoms or diagnoses, and

without a current or prior diagnosis of any systemic, inflammatory, neurological, or psychiatric conditions. Pain-free individuals accepting to participate read and signed an informed consent form before urine sample collection. Informed consent was also obtained from all subjects for publication of identifying information/images in an online open-access publication.

As the first aim of the study was to assess urinary levels of TNF-α in patients with CPLBP before and after receiving SMT, the targeted sample size was based on a previous observational study reporting elevated levels of urinary TNF-α that decreased after exposure to chiropractic care mainly based on SMT (Gevers-Montoro et al., 2022). Considering a more homogenous CPLBP population and more standardized care for the current study, similar or larger effect sizes were expected. Thus, power calculations were based on an effect size of Cohen's d = 0.6, an alpha of 0.05 and a statistical power of 0.8 for a mixed model assessing both within- and between-subject interactions. The required sample size was of 24 participants per group (G*Power version 3.1.9.6 (Faul et al., 2007), 24 patients with CPLBP and an identical number of pain-free controls matched for sex and age.

Treatment procedures

Patients recruited for the study were scheduled for the first treatment session 24-48 hours following the initial examination. They underwent a standardized unimodal care plan, based exclusively on the delivery of instrument-assisted SMT by a chiropractor, twice a week for a total duration of four weeks. Frequency of care was standardized in order to reflect clinical practice (Schneider et al., 2015) and comply with clinical practice guidelines (Globe et al., 2016). Re-assessment took place within 24 hours of the eighth and last session. Treatment consisted in the delivery of high-velocity low amplitude manipulations with the assistance of the Activator IV mechanical device (FDA approval # K003185, Manufacturer: Activator Methods International Ltd., Phoenix, AZ). This instrument is a hand-held device (**Figure 20A**) containing a spring-loaded mechanism that delivers a mechanical impulse with four different settings. The use of an instrument-assisted protocol of SMT was preferred in order to standardize treatment protocols and reduce variability in force application (Kawchuk et al., 2006; Descarreaux et al., 2013). This would allow to determine whether the site, number and magnitude of force applications had any impact on the primary outcome. To date, it remains unclear whether the dosage or the site of force application have an impact on clinical or neurophysiological outcomes (Pasquier et al., 2019; Nim

et al., 2021). Settings 1-3 were used in the cervical and thoracic spines with peak forces ranging from 115 to 123 N, while setting 4 was used in the lumbopelvic spine (including T12) and delivers forces around 211 N, all force applications with a duration of ~ 5ms (Colloca et al., 2005). Manipulations were applied in the prone position (**Figure 20B**) to segmental levels determined by the Activator Methods protocol and manual palpation (Fuhr et al., 1996; Schneider et al., 2015). Upon completing the last treatment session, a physical re-evaluation of the patient was performed, including evaluation of the outcome measures, described below.

Figure 20 An Activator IV instrument **(A)**. A chiropractor applying a spinal manipulation to the lumbar spine using the Activator IV instrument **(B)**.

Primary Outcome: Urinary Levels of TNF-α

Patients and controls provided a baseline urine sample of the first morning micturition on the day they received their first SMT session (patients) or on the day after being recruited (controls). All participants were instructed to store their urine samples in the refrigerator (~ 4ºC) immediately after collection and until visiting the clinic. Once urine samples were collected, they were immediately aliquoted and stored in a container at -20ºC. The procedure was identical for the follow-up sample, which was collected 4 weeks after the baseline sample collection. For patients, this corresponded to the day after the eighth and final SMT session. All participants were requested

to refrain from taking any anti-inflammatory medication within 24 hours of the dates when both samples were collected.

Urinary TNF-α concentrations were measured in duplicate by using specific commercial sandwich enzyme-linked immunosorbent assay (ELISA) following manufacturer's recommendations (Cloud-Clone Corp., Tx, USA) (Sirera et al., 2003). Urinary concentrations of TNF-α (pg/ml) and creatinine (mg/dl) were assessed for each sample, following the same method that was reported previously (Gevers-Montoro et al., 2022). The ratio of urinary TNF-α to urinary creatinine in pg/mg was calculated to correct for changes in urine volume (Ortega et al., 2019). All statistical analyses and figures used and display the corrected values in pg/mg.

Secondary outcomes: clinical outcome measures

Clinical variables describing comorbidities, CPLBP duration and trajectories were collected in the initial clinical interview. The presence of comorbidities included chronic non-painful conditions and pain affecting other body sites. Duration since the onset of the first episode was recorded in years. CPLBP trajectories were classified as either 'ongoing', 'fluctuating' or 'episodic' (independent of severity), according to suggested criteria (Kongsted et al., 2017). Episodic CPLBP was defined as pain occurring with pain-free periods of at least 4 weeks. The trajectory was classified as fluctuating when patients recalled variations of 2 or more points in an 11-point numerical rating scale (NRS), without pain-free periods of 4 weeks or longer. Finally, ongoing pain implied a relatively stable pain intensity (± 1 point in the NRS) present at least four days a week (Kongsted et al., 2017). Available data suggest that patients may recall their recent LBP trajectory (for up to six months) with an acceptable degree of precision (Hestbaek et al., 2019). These variables were used to identify potential patient subgroups with different levels in urinary TNF-α.

To examine changes in pain intensity, patients reported their current pain intensity in a NRS ranging from 0 to 10, anchored by two verbal descriptors. The anchor 0 indicated "no pain", while 10 indicated "worst pain imaginable". Functional impairment caused by CPLBP was measured by means of the Oswestry LBP Disability Index (ODI) questionnaire, a scale that is widely used in LBP research (Fairbank and Pynsent, 2000). Its validated version in Spanish has good to excellent reliability (Alcántara-Bumbiedro et al., 2006). The ODI score ranges from 0 to 50, with higher numbers representing higher levels of self-reported disability. It consists of ten questions with six

possible answers that are graded from 0 to 5 points, based upon the severity of self-perceived disability for each of the activities of daily living. Both pain intensity and disability were measured at the baseline session (before initiating care) and within 24 hours of the last treatment session (**Figure 21**).

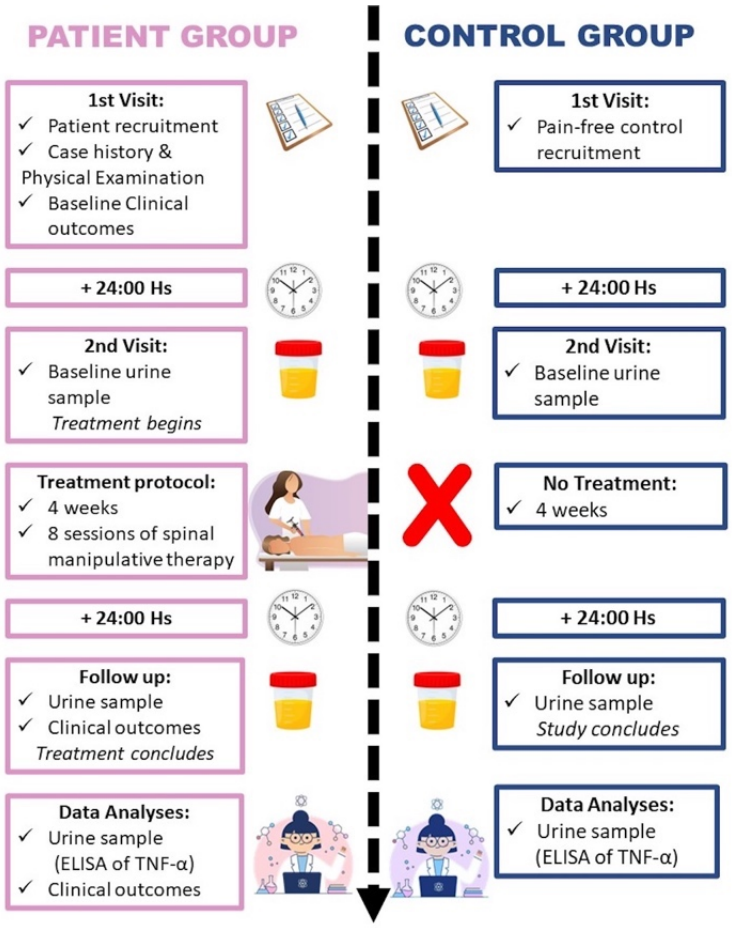

Figure 21 Flowchart representation of the study protocol.

Statistical analysis

All statistical analyses were conducted using JASP v0.16.4 (JASP team, 2022) and Jamovi v2.3.21 (the Jamovi project, 2022). Normality distribution was assessed for baseline quantitative data by means of Shapiro-Wilk tests and homoscedasticity with Levene's tests. A p value threshold of 0.05 was considered statistically significant for all analyses. Values presented in the results section represent mean ± standard deviation. TNF-α data were not normally distributed, therefore, to test a priori hypotheses, baseline urinary TNF-α concentrations were compared between both groups by means of a Welch's t-test due to heteroscedasticity and non-normal distribution. Further,

changes in TNF-α before and after the 4 weeks were analyzed using a linear mixed model (Schielzeth et al., 2020), with time (repeated measures; follow-up – baseline), group (patients vs. controls), and the time × group interaction as fixed effects, and participants as random effects (intercept modeled). Pain intensity ratings and disability scores at baseline and after eight sessions of SMT were compared using paired t-tests for exploratory purposes.

To identify potential differences in urinary concentrations of TNF-α at baseline, according to sex, pain trajectories and the presence of comorbidities, Mann-Whitney tests or Kruskal-Wallis analyses of variance (ANOVA) were conducted using these categorical variables as grouping variables. Significant ANOVA effects were decomposed using Dwass-Steel-Critchlow-Fligner pairwise comparisons. In addition, Spearman rank correlation coefficients were calculated to examine the associations between baseline values of TNF-α, the number of years with CPLBP, pain intensity and disability. To explore the predictive value of urinary TNF-α, baseline, follow-up, and percent-changes in TNF-α values were assessed as predictors in simple regression models with follow-up and percent change values in pain intensity and disability as dependent outcomes, for which estimates were obtained using 5000 bootstrap replications.

A supplementary exploratory analysis was conducted to identify associations with SM dosage and target site. Spearman correlations were assessed between changes and follow-up values of TNF-α, and the total number of SM applied to low back segments (sacroiliac joints, L5, L4, L2 and T12), to the lumbopelvic area and to the whole body.

Results

For the thirty-nine patients that were screened for eligibility, twenty-four met the selection criteria and were included in the study. Eighteen patients were women and six were men, with a mean age of 53.9 ± 10 years, and a mean of 11.5 ± 8.3 years with CPLBP (Table 10.1). The fifteen patients that were excluded from the study presented pain of neuropathic origin, were taking opioid medication, presented complaint of neck pain of similar severity, received chiropractic care or manipulation recently, or presented with a diagnosis of spondyloarthropathy. Twenty-four pain-free controls were recruited to match the CPLBP patients, with the same proportion of women and men as the patient group, and a mean age of 53.6 ± 9 years (Table 10.1).

Table 10.1 Baseline demographic and clinical data of participants in the study

Baseline characteristic	Patient Group	Control Group
Participants, *n*	24	24
Sex (women), *n* (%)	18 (75)	18 (75)
Mean age, years (SD)	53.9 (10.0)	53.9 (8.8)
Smokes (Yes), *n* (%)	0 (0)	4 (17)
Mean TNF-α values (pg/mg), (SD)	3.7 (4.6)	0.3 (1.4)
Chronic low back pain characteristics		
Mean pain intensity (0-10), (SD)	5.8 (1.7)	-
Mean disability score (0-50), (SD)	14.7 (7.0)	-
Mean years with pain, (SD)	11.5 (8.3)	-
Pain trajectory, *n* (%)		
Ongoing	9 (37)	-
Fluctuating	11 (46)	-
Episodic	4 (17)	-
Comorbidities (Yes), *n* (%)	14 (58)	-
Taking NSAIDs (Yes), *n* (%)	8 (33)	-

**SD = Standard Deviation; NSAIDs = Nonsteroidal anti-inflammatory drugs*

Urinary levels of TNF-α in patients and pain-free controls

The mean baseline urinary concentration of TNF-α corrected for urine volume was 3.7 ± 4.6 pg/mg in the patient group and 0.3 ± 1.4 pg/mg in the control group (see Table 10.1 and **Figure 22**). The mean difference of 3.37 pg/mg (1.37 to 5.38 pg/mg, 95% confidence interval (CI)) was statistically significant ($p = 0.002$, $d = 0.99$). Follow-up values were 0.4 ± 1.2 pg/mg for the CPLBP group and 0.3 ± 1.6 pg/mg for the control group. The estimated difference between group means over time was of -3.25 pg/mg (-5.35 to -1.16, 95% CI), which was statistically significant (interaction: $F_{1,92} = 9.5$, $p = 0.003$, $\eta^2 p = 0.11$, **Figure 22C**). As some patients (n = 14) were taking nonsteroidal anti-inflammatory drugs, this variable was introduced as a categorical covariate in the mixed model to examine the potential confound. The results remained unchanged (interaction: $p = 0.003$).

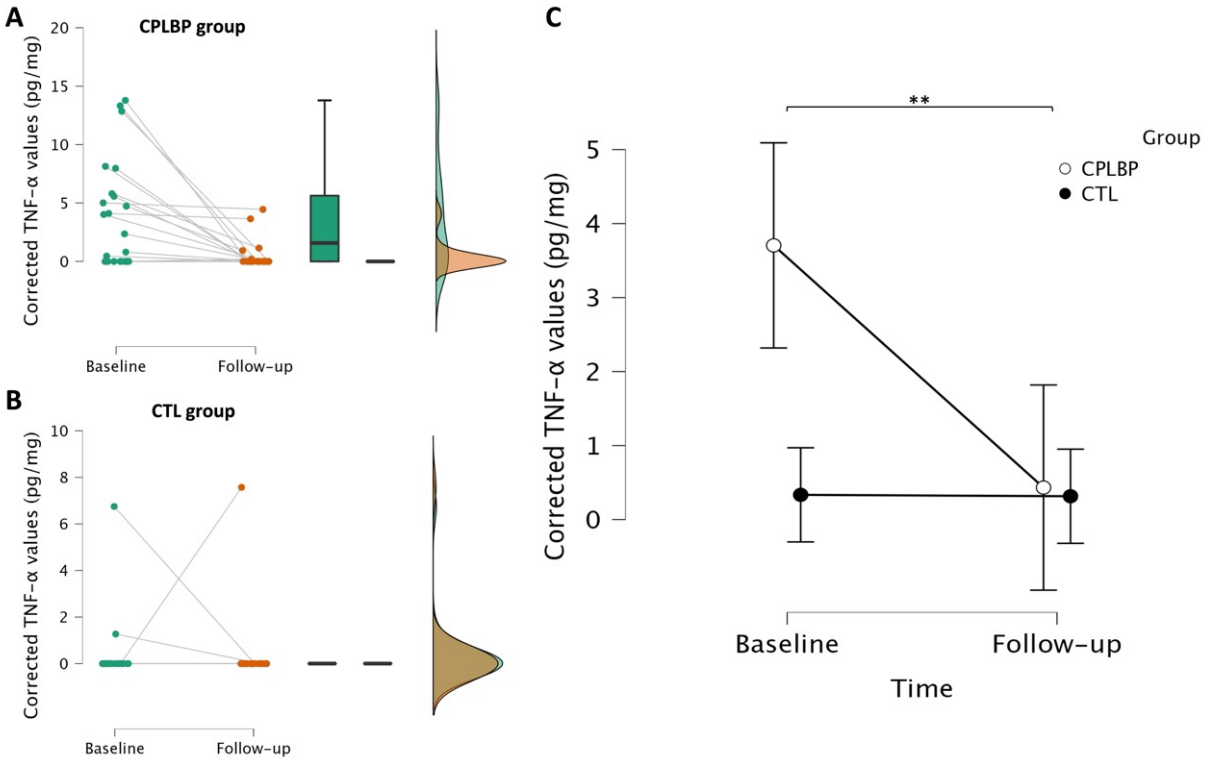

Figure 22 Raincloud plots of urinary concentrations of TNF-α

Raincloud plots (Allen et al., 2019) combining a cloud of points with a box plot and a one-sided violin plot of the distribution of urinary concentrations of TNF-α corrected for volume (using urine creatinine) at baseline and follow-up for the control (**A**) and patient (**B**) groups. Individual dots represent individual participant values and the lines within the box plot represent the median. Descriptive plot of the mean urinary concentrations of TNF-α corrected for volume at baseline and follow-up for the control and patient groups. Bars represent 95% confidence intervals (**C**). *** $p < 0.01$ (significance level for the time × group interaction). 'CTL' = control group; 'CPLBP' = chronic low back pain group*

Clinical outcomes in patients with CPLBP

Significant reductions were observed in clinical outcomes following the eight sessions of SMT in the patient group. Pain intensity was reduced in 4.6 ± 2.1 points in the 0-10 NRS scale, $p < 0.001$, $d = 2.2$ (Table 10.1 and **Figure 23A**). Furthermore, the degree of disability caused by CPLBP was also reduced by 6.9 ± 5.5 points in the ODI 0-50 scale, $p < 0.001$, $d = 1.24$ (Table 10.1 and **Figure 23B**).

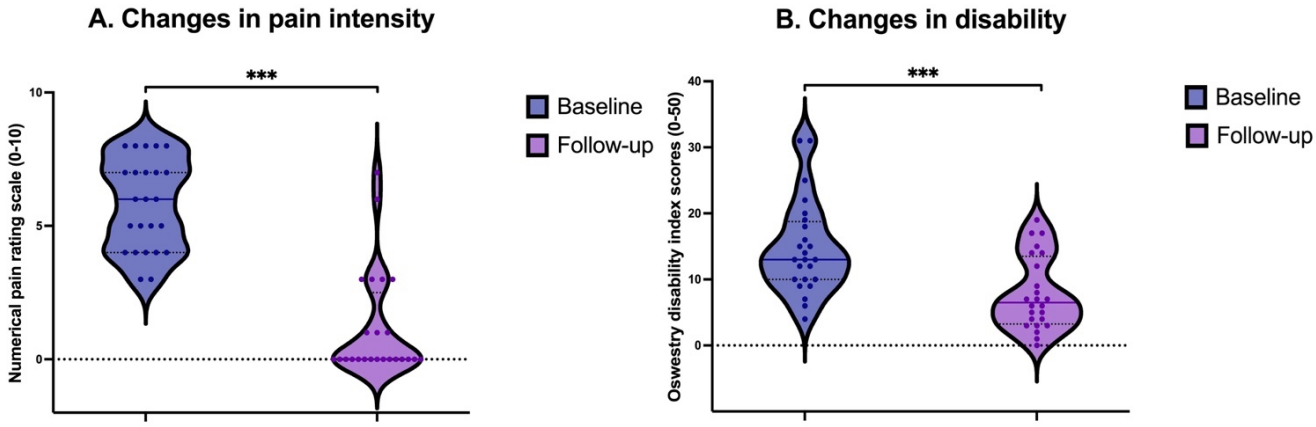

Figure 23 Violin plots of clinical outcomes

Violin plot of the distribution of **(A)** Pain intensity ratings in the numerical rating scale (NRS) from 0 to 10 and **(B)** disability scores measured with the Oswestry Disability Index, both at baseline and follow-up. Individual dots represent individual participant values. The continuous line represents the median and dotted lines represent 25th and 75th quartiles. *** $p < 0.001$

Differences in TNF-α values at baseline by grouping variables in patients with CPLBP

Analyses were conducted to examine differences in TNF-α values at baseline according to sex, pain trajectory, and the presence of comorbidities in the patients with CPLBP. Baseline concentrations of TNF-α were significantly different between subgroups of patients with different pain trajectories (χ^2 = 9.28, p = 0.01, df = 2, ε^2 = 0.4). Baseline values were then calculated separately for patients with ongoing (6.6 ± 4.6 pg/mg, n = 9), fluctuating (2.7 ± 4.2 pg/mg, n = 11) and episodic (0 pg/mg, n = 4) CPLBP. Pairwise comparisons revealed that ongoing pain trajectory levels were significantly different from episodic (p = 0.03), but not fluctuating (p = 0.1). TNF-α levels did not significantly differ between fluctuating and episodic CPLBP (p = 0.12). Moreover, baseline TNF-α did not differ by sex (Mann-Whitney U = 32.0, p = 0.1). Fourteen patients presented comorbid conditions with CPLBP (see Table 10.1). Comorbidities were cardiovascular disease (n=3), neck pain (n=3), depression (n=2), full spine pain (n=2), headaches (n=2), type II diabetes (n=1), anxiety (n=1), carpal tunnel syndrome (n=1) and plantar fasciitis (n=1). There were no differences in TNF-α levels based on the presence of comorbidities (Mann-Whitney U = 69.0, p = 1.0).

Associations with TNF-α values at baseline in patients with CPLBP

Spearman rank correlation coefficients revealed only one significant (negative) association between the number of years with CPLBP and baseline TNF-α (ρ = -0.42, p = 0.04, **Figure 24**). This association, however, was not significant when correcting for the number of comparisons.

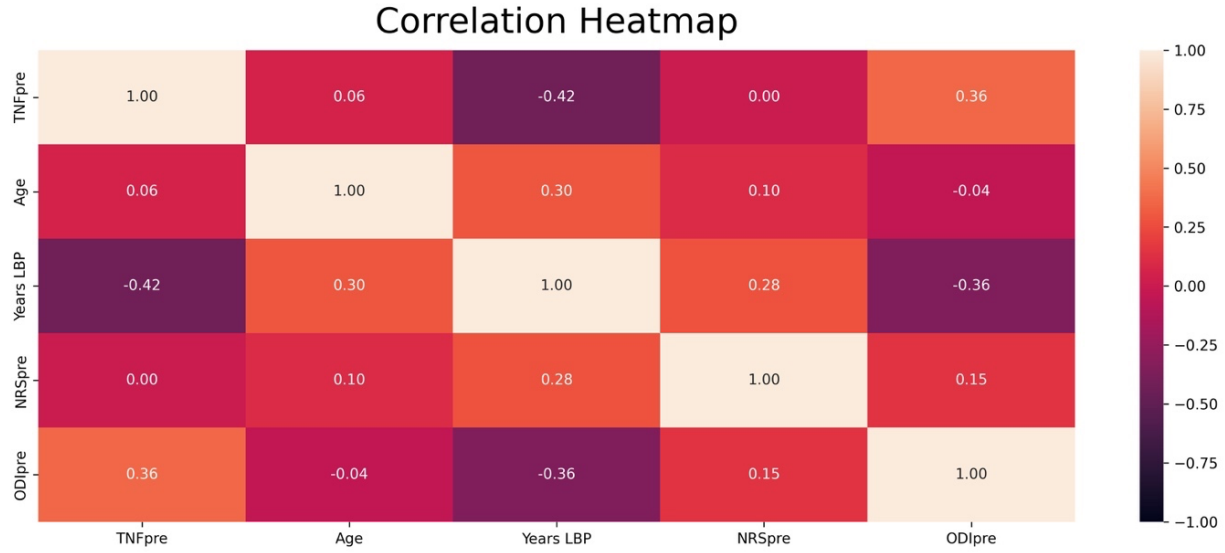

Figure 24 Heatmap of Spearman rank correlations between all variables of interest.

Values in the boxes represent Spearman coefficient ρ. 'TNFpre': Baseline levels of TNF-α; 'Age': Age in years; 'Years LBP': years since onset of low back pain; 'NRSpre': Baseline pain intensity ratings; 'ODIpre': Baseline disability scores; 'ODIpost': Follow-up disability scores; '%ODI': Percent changes disability scores.

Urinary TNF-α as a predictor of clinical outcomes in patients with CPLBP

Simple regression analyses revealed that baseline TNF-α values explained 20.7% of the variance in changes in pain intensity (F = 5.8, p = 0.03), however baseline TNF-α only marginally predicted percent changes in pain intensity (β = -0.45; p = 0.05). Follow-up pain intensity ratings were not predicted by baseline urinary TNF-α (β =0.24; p =0.4). Percent changes in disability could not be predicted by baseline TNF-α (β = -0.25; p =0.1), but follow-up values in disability could (β = 0.64; p = 0.002). The latter model was significant as well (F = 15.2, p < 0.001), 38.1% of the variance in follow-up ODI scores were explained by baseline TNF-α.

Regression analyses with the percent change in TNF-α as a predictor showed that 65% and 33% of the variance in pain intensity and disability percent changes respectively, could be explained by fluctuations in TNF-α (β = 0.81; p < 0.001 and β = 0.58; p = 0.003, respectively). Both models were also significant: F =41.1, p < 0.001 for pain intensity and F = 11.0, p = 0.003

for disability. However, changes in TNF-α did not predict follow-up values in pain intensity (β = -0.02; p = 0.8) nor disability (β = - 0.27; p = 0.1).

Associations between the segments targeted by SM and TNF-α in patients with CPLBP

Associations between follow-up values and percent changes in TNF-α with the number of SM received were examined with exploratory purposes. However, no strong or significant associations were detected, with the exception of a marginal association between the total number of lumbopelvic manipulations and changes in TNF-α (ρ = -0.40, p = 0.049). See supplemental **Figure 25** for the correlation heatmap.

Discussion

The present study corroborates previous reports of elevated levels of TNF-α in both serum and urine samples of patients with CPLBP (Teodorczyk-Injeyan et al., 2019; Morris et al., 2020; Gevers-Montoro et al., 2022). Furthermore, in this cohort of patients, urinary concentrations of this pro-inflammatory cytokine were reduced after SMT, compared to values in matched pain-free controls. Baseline levels in urinary TNF-α discriminated patients according to their CPLBP trajectory, the highest levels being measured in patients with unremitting pain. In turn, baseline TNF-α concentrations and their fluctuations predicted changes in both pain intensity and disability scores.

The present findings are consistent with prior research suggesting that patients with CPLBP have elevated concentrations of TNF-α in urine (Gevers-Montoro et al., 2022). Moreover, this study shows that urinary TNF-α may accurately discriminate patients with CPLBP from age- and sex-matched asymptomatic individuals. In the absence of inflammation, both serum and urinary levels of TNF-α are presumed to approach zero, with minimal fluctuations (McLaughlin et al., 1991; Feghali and Wright, 1997; Biancotto et al., 2013; Wang et al., 2016; Moledina et al., 2019). Levels detected in an asymptomatic population in this study are consistent with suggested reference values of 0.4 ± 0.8 pg/mg (Gevers-Montoro et al., 2022). Moreover, the absence of significant fluctuations over a 4-week period in pain-free individuals was confirmed. Notably, baseline values differed significantly among patients with distinct pain trajectories, specifically between those with ‘ongoing’ compared to ‘episodic’ pain. Patients categorized as ‘ongoing’ generally exhibited

higher urinary levels of TNF-α (6.6 ± 4.6 pg/mg), followed by patients classified as 'fluctuating' (2.7 ± 4.2 pg/mg). In contrast, patients with 'episodic' CPLBP had undetectable levels of this cytokine, rendering them biochemically indistinguishable from healthy individuals in this regard. This suggests that different mechanisms may underlie different pain trajectories. A previous assessment of urinary TNF-α values in CPLBP patients showed mean values of 6.0 ±7.0 pg/mg, in a cohort where 75% of patients were classified as 'ongoing' (Gevers-Montoro et al., 2022), which is consistent with data from the current study.

The results presented in this study indicate that TNF-α may emerge as a potential patient stratification biomarker, which is crucial in health conditions with heterogeneous pathophysiology, such as CPLBP (Davis et al., 2020). Urinary TNF-α could help discriminate patients with CPLBP according to their pain trajectory. Specifically, patients experiencing persistent pain (whether ongoing or fluctuating, but not remitting), may be better identified by this biomarker. Evidence from systematic reviews highlights an association between TNF-α and the presence of CPLBP (Khan et al., 2017; van den Berg et al., 2018; Lim et al., 2020; Morris et al., 2020). Generally, higher serum levels of TNF-α are linked to more severe CPLBP (Teodorczyk-Injeyan et al., 2019), radicular pain (Uceyler et al., 2007; Zu et al., 2016) and disability (Wang et al., 2016). Additionally, owing to its predictive capacity, urinary TNF-α may serve to discriminate between responders and non-responders in future clinical studies.

Biomarkers can also serve as indicators of recovery or predictors of treatment response (Khan et al., 2017; Davis et al., 2020). Our findings are compatible with urinary TNF-α being a potential biomarker to assess clinical recovery in this cohort of CPLBP patients. This holds particular relevance, as changes in both clinical outcomes may be considered clinically meaningful (Ostelo et al., 2008). Baseline values of urinary TNF-α explained 20.7% of the changes in pain intensity and 38.1% of the variance in disability scores following treatment. Likewise, the percent change in TNF-α predicted 65% and 33% of the changes in pain intensity and disability scores respectively, suggesting its potential as a reliable, objective measure of treatment response. Similar data have not been reported thus far. However, in a cohort of elderly women with an acute episode of LBP, serum TNF-α levels decreased concurrently with reductions in LBP intensity over twelve months (Queiroz et al., 2017). Similarly, Klyne and colleagues observed that higher baseline TNF-α levels and depressive symptoms were associated with lower probability of recovery from acute

LBP (Klyne et al., 2017; Klyne and Hodges, 2020; Klyne et al., 2022). Thus, reduction in TNF-α levels may be indicative of recovery from episodes of LBP, which is consistent with our data. Alternatively, persistently elevated levels may be associated with a lack of recovery (Klyne et al., 2017; 2022) or with ongoing CPLBP symptoms with minor or major fluctuations, but without long pain-free periods. It could be argued that patients with persistent pain have higher levels of TNF-α consistent with no recovery, while patients with episodic CPLBP display the lowest levels, reflecting their capacity to recover from an episode.

It may be suggested that TNF-α could mediate neuroinflammatory changes associated with a subgroup of patients with a more severe CPLBP trajectory. Notably, TNF-α has been identified as an important cytokine for the development of changes in the central nervous system that lead to pain hypersensitivity and persistence (Andrade et al., 2011; Zhang et al., 2011; Cairns et al., 2015; Ji et al., 2018; Goncalves Dos Santos et al., 2019). Here, we hypothesized that TNF-α could serve as a biomarker for a subgroup of patients with CPLBP. Particularly, where neuroinflammation, and therefore, central sensitization exists. Previous attempts to classify patients with CPLBP according to pain mechanisms suggested three subgroups: nociceptive, neuropathic, and central sensitization pain (Smart et al., 2012; Nijs et al., 2015). However, there is no consensus on the clinical methods that can accurately discriminate between pain mechanisms. A recent systematic review highlights that urine metabolomics analysis is one of the most reliable measures identified to distinguish neuropathic pain mechanisms (Shraim et al., 2021), suggesting that urine could be a promising environment for pain biomarkers. Despite the limited range of available neuropathic pain biomarkers, serum levels of TNF-α have been demonstrated to be particularly effective in detecting neuropathic pain in patients with spinal cord injury (Xu et al., 2015). Given that the present study specifically excluded patients presenting evidence of neuropathic pain, it is plausible that elevated TNF-α may reflect processes related to central sensitization in individuals with both neuropathic and nociplastic pain (Carlton et al., 2009; Woolf, 2011; Nijs et al., 2021).

Biomarkers can also provide insights into the mechanisms of interventions (Davis et al., 2020). The results from the present study may contribute to our understanding of the potential mechanisms underpinning SMT for CPLBP. Higher baseline TNF-α was associated with better clinical recovery, suggesting that SMT may be more effective for a subgroup of patients with elevated TNF-α levels. This is congruent with literature suggesting that SMT may act by

modulating mechanisms related to central sensitization (Gevers-Montoro et al., 2021). Nevertheless, no causal relationship can be inferred from the data and caution is advised when interpretating them.

Limitations of the study

The discussed findings must be interpreted in light of a series of limitations, which include the lack of a control intervention group and the small sample size. As an observational study, changes cannot be attributed to the intervention or any other factors. Future experimental research with appropriate comparators may examine whether reductions in urinary TNF-α reflect a specific mechanism of SMT for CPLBP. A placebo-controlled design is also required to confirm previous findings suggesting that SMT dosage may influence plasma concentrations of inflammatory cytokines, including TNF-α (Licciardone et al., 2012; Duarte et al., 2022). Based on our data, an association between the total number of SM applied to the low back cannot be confirmed or excluded.

Additionally, this study's categorization of CPLBP, acknowledged as a heterogeneous condition, inherently poses a risk of overgeneralization. The extent and predominance of nociplastic mechanisms likely differ among CPLBP patients, potentially affecting TNF-α expression and complicating the extrapolation of the study results. Furthermore, the limited sample size demands caution when interpreting the subgroup analyses. Prudence is warranted in light of recent evidence suggesting that patients' recollection of their LBP pattern (episodic vs. fluctuating) using visual pain trajectories may not be as reliable as indicated by previous data (Nim et al., 2023). In future studies, longer follow-up periods may help determine whether changes in cytokines and clinical variables, and their association, persist over time. In addition, variables such as diet or exercise that were not accounted for, may have influenced systemic inflammation, and thus, TNF-α levels. Future research should take these and other potential confounders into consideration.

Urine samples were collected during different seasons for the CPLBP (January to April) and control (September to January) groups. Seasonal variations of serum TNF-α were reported in conditions with seasonal variability, though not for healthy individuals. The highest TNF-α values were observed during summer-fall, and the lowest from January to spring (Spath et al., 2017; Weckmann et al., 2021). This pattern is contrary to our findings, suggesting that seasonal variations may not have influenced the results. Despite the aforementioned limitations, a strength of this study

lies in the advantages of urine sampling compared to the traditional serum sampling. It is plausible that using urine samples provides similar results with much greater accessibility, fewer logistic challenges and at a lower cost.

Conclusion

This exploratory study presents evidence suggesting that urinary levels of TNF-α may serve as a potential biomarker for patients with CPLBP. Specifically, urinary TNF-α levels discriminated patients with CPLBP from pain-free controls in our sample. These results warrant further study to assess urinary TNF-α levels among patients with different pain trajectories. In addition, our findings indicated that baseline values and fluctuations in TNF-α could predict pain intensity and disability outcomes. Consequently, urinary TNF-α levels may potentially reflect the involvement of inflammatory mechanisms in CPLBP evolution, although this remains to be examined. Further research, preferably in the form of a randomized controlled trial, is needed to better ascertain the utility of this potential biomarker for CPLBP.

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Author contributions

CG-M: Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft preparation. **MP-T:** Investigation, Formal analysis. Manuscript revision. **AM:** Investigation, Formal analysis, Manuscript revision. **FMC-B:** Investigation, Resources, Manuscript revision. **MP:** Supervision, Funding acquisition, Writing- Review and editing. **AO-DM**: Conceptualization, Methodology, Funding Acquisition, Supervision, Writing- Review, editing and approval of final version.

Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Supplemental material

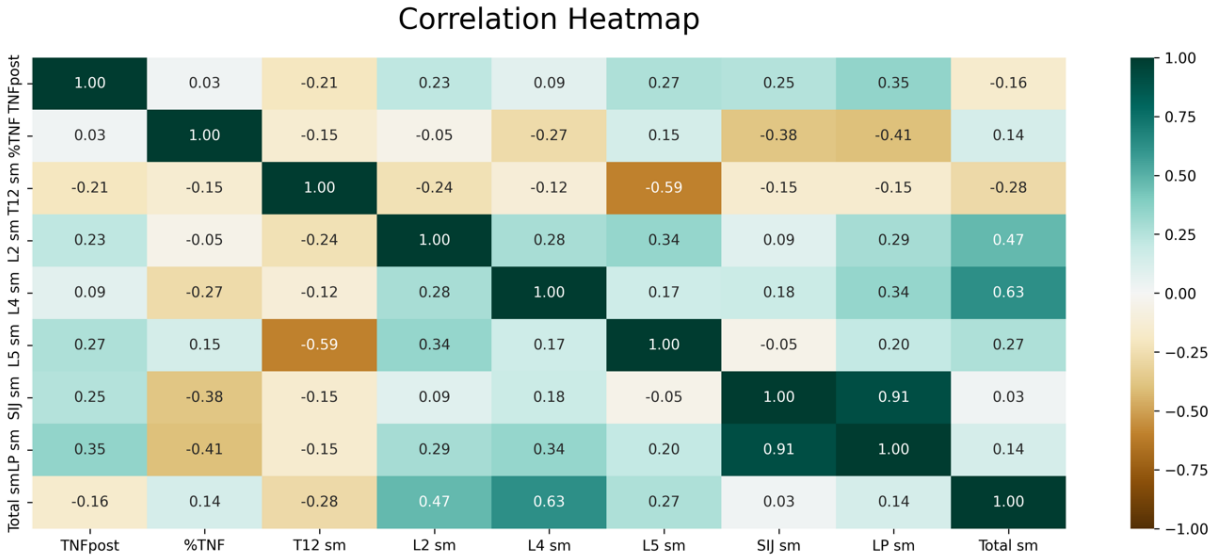

Figure 25 Supplemental heatmap

Heatmap of Spearman rank correlations between follow-up and percent changes in TNF-α and the number of manipulations targeting different segments. Values in the boxes represent Spearman coefficient ρ. *'TNFpost': Follow-up levels of TNF-α; '%TNF': Percent changes in TNF-α; 'T12 sm': number of spinal manipulations targeting T12; 'L2 sm': number of spinal manipulations targeting L2; 'L4 sm': number of spinal manipulations targeting L4; 'L5 sm': number of spinal manipulations targeting L5; 'SIJ sm': number of spinal manipulations targeting the sacroiliac joints; 'LP sm': number of spinal manipulations targeting the lumbopelvic spine; 'Total sm': total number of spinal manipulations applied.*

Appendix II: Article 6 – Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Keywords: Randomized controlled trial; Low back pain; Patient stratification; Central Sensitization; Chiropractic Manipulation

Contribution des auteurs

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Arantxa Ortega-De Mues : Révision de l'article, supervision de l'étude.

Mathieu Piché : Conception de l'étude, révision de l'article, supervision de l'étude.

Abstract

Introduction: Chronic low back pain (CLBP) is a highly prevalent and disabling condition. Identifying subgroups of patients afflicted with CLBP is a current research priority, for which a classification system based on pain mechanisms was proposed. Spinal manipulative therapy (SMT) is recommended for the management of CLBP. Yet, little data are available regarding its mechanisms of action, making it difficult to match this intervention to the patients who may benefit the most. It was suggested that SMT may influence mechanisms associated to central sensitisation. Therefore, classifying CLBP patients according to central sensitisation mechanisms may help predict their response to SMT.

Methods and analysis: This protocol describes a randomised placebo-controlled trial aiming to examine which variables linked to central sensitisation may help predict the clinical response to SMT in a cohort of CLBP patients. One hundred patients with chronic primary low back pain will be randomized to receive 12 sessions of SMT or placebo SMT over a 4-week period. Pain intensity and disability will be assessed as the primary outcomes after completing the 4-week treatment (primary endpoint), and at 4- and 12-week follow-ups. Baseline values of two pain questionnaires, lumbar pressure pain thresholds, concentrations of an inflammatory cytokine and expectations of pain relief will be entered as predictors of the response to SMT in a multiple regression model. Changes in these variables after treatment will also be used in a second multiple regression model. The reference values of these predictors will be measured from 50 age and sex-matched healthy controls to allow interpretation of values in patients. Mixed analyses of variance will also be conducted to compare the primary and secondary outcome measures between groups (SMT *vs*. placebo) over time (baseline *vs*. post-treatment).

Ethics and dissemination: Ethical approval was granted by the Fundación Jiménez Díaz Clinical Research Ethics Committee.

Trial registration number: NCT05162924

Strengths and limitations of this study:

- This study will expand our understanding of the relevance of clinical, psychological, psychophysical and inflammatory variables in predicting the response of patients with chronic low back pain to manual therapy.
- The design including a control group with healthy participants will allow confirming the usefulness of a classification system for patients with chronic primary low back pain according to the underlying pain mechanisms.
- The blinding of outcome assessors, statistician, laboratory technician, and of the investigator providing care to the patients' progress will contribute to reduce bias.
- A high degree of similarity between the sham and real manipulations increases the odds of successfully blinding participants. However, the sham intervention may produce clinical effects.
- Clinical trials on manual therapy, including the present study, are limited by the impossibility of blinding the investigator providing care to the intervention.

Introduction

Low back pain (LBP) is the single most important cause of disability globally (Hartvigsen et al., 2018), with a high proportion of patients whose pain persists or recurs (Axen and Leboeuf-Yde, 2013; Hartvigsen, et al., 2018; Itz et al., 2013; Kongsted et al., 2015). Aiming to identify patient profiles that respond more favourably to specific treatments and their prognosis, recent investigations highlight the importance of identifying subgroups among people with chronic LBP (CLBP). One of the proposed classification systems stratifies patients into specific subgroups according to pain mechanisms (nociceptive, neuropathic or central sensitisation) (Nijs et al., 2015; Nijs et al., 2021a; O'Sullivan et al., 2014; Shraim et al., 2021; Smart et al., 2012; Vardeh et al., 2016). It has been suggested that a large proportion of CLBP patients presents chronic primary pain, which has been linked to altered nociceptive processing (Kosek et al., 2021; Nicholas et al., 2019). Among the phenomena that may underlie this aberrant processing, central sensitization (CS) is likely the predominant mechanism (Kosek, et al., 2021; Shraim et al., 2020), and its involvement in CLBP deserves further research (den Bandt et al., 2019).

One of the currently recommended interventions for the management of CLBP is spinal manipulative therapy (SMT; de Zoete et al., 2021b; Rubinstein et al., 2019). However, not all patients have an identical response (Wirth et al., 2019). There is insufficient data to determine which CLBP subgroups respond better to this intervention (Axen and Leboeuf-Yde, 2017; de Zoete et al., 2021a). This may be so because the analgesic mechanisms are still largely unknown. It was proposed that the pain relieving effects of SMT partly rely on segmental pain inhibition processes (Gevers-Montoro et al., 2021b). These processes influence temporal summation of pain (Bialosky et al., 2009; Randoll et al., 2017), primary, and secondary hyperalgesia (Gevers-Montoro et al., 2021c; Nim et al., 2020), which may be measured to identify patients with a CS phenotype. Further, emerging data from animal and human studies support the hypothesis that SMT modulates the inflammatory response, influencing inflammatory cytokines (Roy et al., 2010; Song et al., 2016; Teodorczyk-Injeyan et al., 2006; Teodorczyk-Injeyan et al., 2021). Cytokines can induce neuroinflammation, which may mediate the development of CS (Ji et al., 2018; Kawasaki et al., 2008) in the transition towards chronic pain (Nijs, et al., 2021a; Woolf, 2011). SMT may thus relieve CLBP by impacting mechanisms linked to CS (Boal and Gillette, 2004; Nim, et al., 2020; Nim et al., 2021; Zafereo and Deschenes, 2015).

Altered pain sensitivity in a specific musculoskeletal region may indicate nociplastic pain (Graven-Nielsen, 2022; Kosek, et al., 2021; Nijs et al., 2021b), likely reflecting CS (Shraim, et al., 2020). Abundant studies have reported that a subgroup of CLBP patients demonstrate segmental mechanical hyperalgesia, assessed via lower pressure pain thresholds (PPTs) in low back or lower extremity areas, when compared to healthy controls (Blumenstiel et al., 2011; Correa et al., 2015; Farasyn and Meeusen, 2005; Imamura et al., 2016; Imamura et al., 2013; O'Neill et al., 2007). Changes in pain sensitivity are not confined to lumbar segments but rather may be present in remote anatomical locations (Clauw et al., 1999; den Bandt, et al., 2019; Giesbrecht and Battie, 2005; Giesecke et al., 2004; O'Neill, et al., 2007). Increased pain sensitivity is a clinical indicator possibly reflecting CS not just at the spinal level, but potentially implicating supraspinal structures (den Bandt, et al., 2019; Nijs, et al., 2021a; Woolf, 2011). Thus, it is plausible that mechanical pain sensitivity may play an important role in defining a CS phenotype in CLBP (Nijs, et al., 2021b).

Pain catastrophising has been described as a psychological trait and pain cognition linked to the development of CLBP with an altered pain sensitivity profile and a CS phenotype (Christensen et al., 2020; Owens et al., 2016; Roussel et al., 2013). CLBP patients with higher pain sensitivity often demonstrate higher levels of catastrophising and other negative psychological traits (Aoyagi et al., 2019; Gerhardt et al., 2017; Klyne et al., 2019; Nim, et al., 2021). Similarly, higher pain catastrophising was associated with higher central sensitization inventory (CSI) scores (Huysmans et al., 2018). The CSI and a clinical presentation suggestive of CS mechanisms has been proposed to identify a specific CLBP subgroup (Goubert et al., 2017; Nijs, et al., 2015; Roldan-Jimenez et al., 2020; Smart, et al., 2012).

Currently, the mechanisms leading to CS are still unknown, however, recent data suggest an important role for neuroinflammation (Ji, et al., 2018). Neuroinflammation may act at multiple levels, from the periphery (Klyne, et al., 2019) to the brain (Torrado-Carvajal et al., 2021), including the dorsal horn of the spinal cord (Goncalves Dos Santos et al., 2019). The release of inflammatory cytokines, including the pro-inflammatory tumour necrosis factor alpha (TNF-α), was identified as a potential mechanism supporting this phenomenon (Andrade et al., 2011; Ji, et al., 2018; Kawasaki, et al., 2008; Nicol et al., 1997). Studies have shown an association between proinflammatory cytokines and CLBP (Gevers-Montoro et al., 2022; Klyne et al., 2017; Li et al.,

2016; Lim et al., 2020), suggesting that these may serve as a reliable biomarker to identify patients with a CS phenotype.

The classification of mechanism-based pain phenotypes is a complex and controversial task (Hoegh et al., 2022; Nijs, et al., 2021b; Shraim et al., 2022), for which a variety of clinical, inflammatory, psychological, and psychophysical constructs must be considered (Holm et al., 2022; Shraim, et al., 2021). Although CS may influence changes in pain sensitivity induced by SMT (Nim, et al., 2021), pain phenotyping has been scarcely applied to manual therapy research (Damian et al., 2022). Therefore, the response of this subgroup of patients to SMT has yet to be assessed. The aim of this clinical trial is to investigate whether variables associated with a CS phenotype may help predict the response to SMT. The specific objectives are: 1) to identify the clinical, psychological, psychophysical and inflammatory variables linked to CS in a cohort of CLBP patients; and 2) to examine which of these variables predict the clinical response to SMT.

Methods

Experimental design and setting

The study consists of a mechanistic randomized placebo-controlled clinical trial with a mixed experimental design, whose objective is to assess which variables linked to CS in chronic pain patients can predict the response of CLBP patients to SMT (**Figure 26**). This protocol is reported according to the guidelines for clinical trial protocols Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT statement; Chan et al., 2013). Starting in November 2021, 150 participants will be recruited through the Madrid College of Chiropractic (MCC) teaching clinic in San Lorenzo de El Escorial (Spain). This includes 100 patients with CLBP and 50 healthy participants. The MCC clinic is a primary care setting specialized in spine care, including chiropractic and physical therapy services. Clinical, psychological, psychophysical and inflammatory variables will be measured in CLBP patients, which will be exposed to either SMT or a placebo SMT for 12 visits over a 4-week period. A group made up of 50 age and sex-matched healthy volunteers will be used to determine the reference values of the same psychological, psychophysical, and inflammatory variables in a healthy population and compare them with the clinical population, before and after exposure.

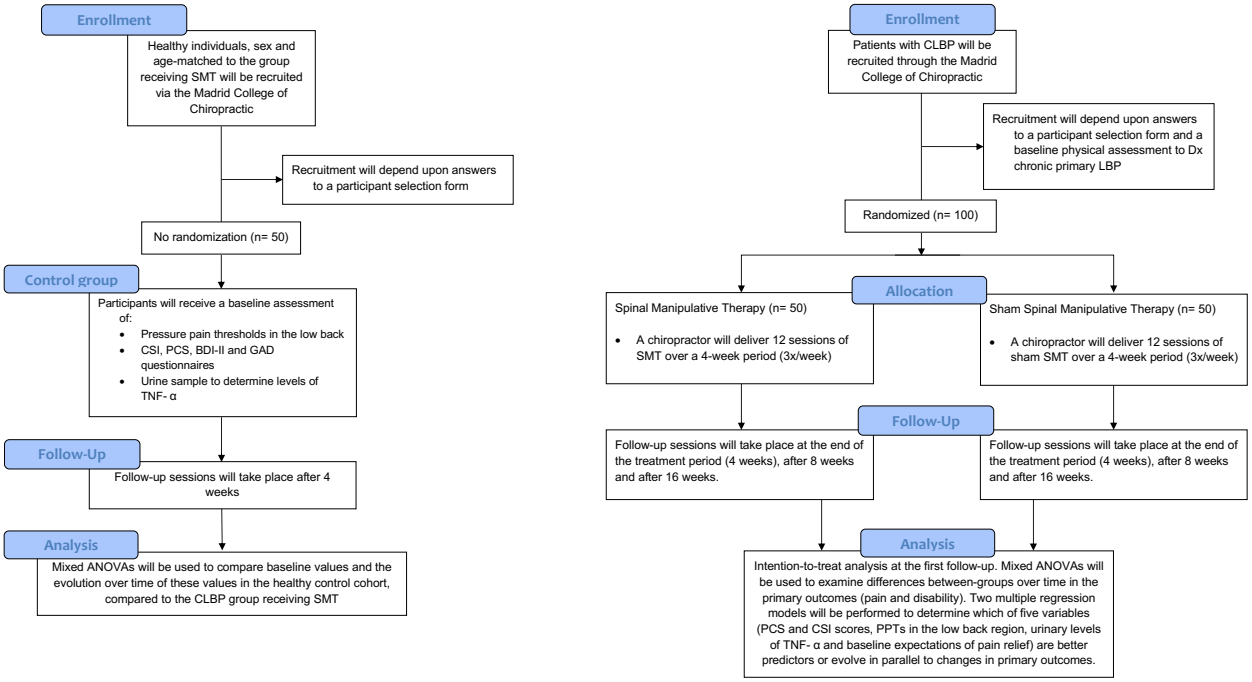

Figure 26 CONSORT diagrams of the randomised clinical trial proposed

ANOVAs, analyses of variance; BDI-II, Beck Depression Inventory II; CLBP, chronic low back pain; CONSORT, Consolidated Standards of Reporting Trials; CSI, central sensitisation inventory; GAD, Generalized Anxiety Disorder; PCS, Pain Catastrophizing Scale; PPTs, pressure pain thresholds; SMT, spinal manipulative therapy; TNF-α, tumour necrosis factor alpha.

Selection criteria

An investigator with over twenty years of clinical experience will be responsible for the selection of participants. To be eligible to participate in the study, patients must be 18 to 70 years old, receive a diagnosis of chronic primary LBP of at least 3-month duration, with or without leg pain (according to a clinical examination carried out at the MCC). If pain affecting the low back or lower limb is suspected to be predominantly of neuropathic origin, the patient will be excluded (Kosek, et al., 2021). Additionally, patients will be excluded from the study if they present any of the following criteria: evidence of specific pathology as the cause of their CLBP, diagnosis of mental illness (with the exception of anxiety and depression, as these conditions are frequently comorbid with CLBP (Gore et al., 2012; Wong et al., 2021) and may suggest a CS phenotype (Aoyagi, et al., 2019; Smart, et al., 2012), presence of pain of equal or higher intensity affecting any other body region, use of corticosteroids, opiates or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, having received chiropractic SMT in the 12 months prior to the beginning of the study (Gerhardt, et al., 2017; Klyne, et al., 2019; Smart, et al., 2012).

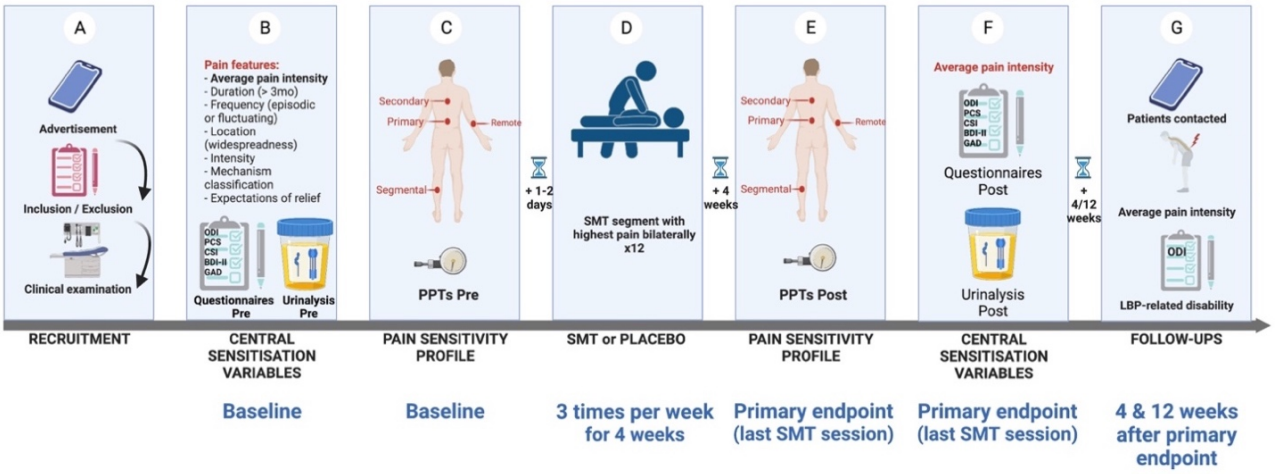

Figure 27 Study protocol for the clinical trial.

The recruitment process is illustrated in **(A)**, the collection of variable data during the initial examination is depicted in **(B,C)**. **(D)** Illustration of the treatment protocol and **(E,F)** the collection of variable data at the end of the 4-week treatment (ie, primary endpoint), and **(G)** the collection of pain intensity and disability data at the 4-week and 12-week follow-ups. BDI-II, Beck Depression Inventory II; CSI, Central Sensitisation Inventory; GAD, Generalized Anxiety Disorder; LBP, low back pain; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; PPTs, pressure pain thresholds; SMT, spinal manipulative therapy.

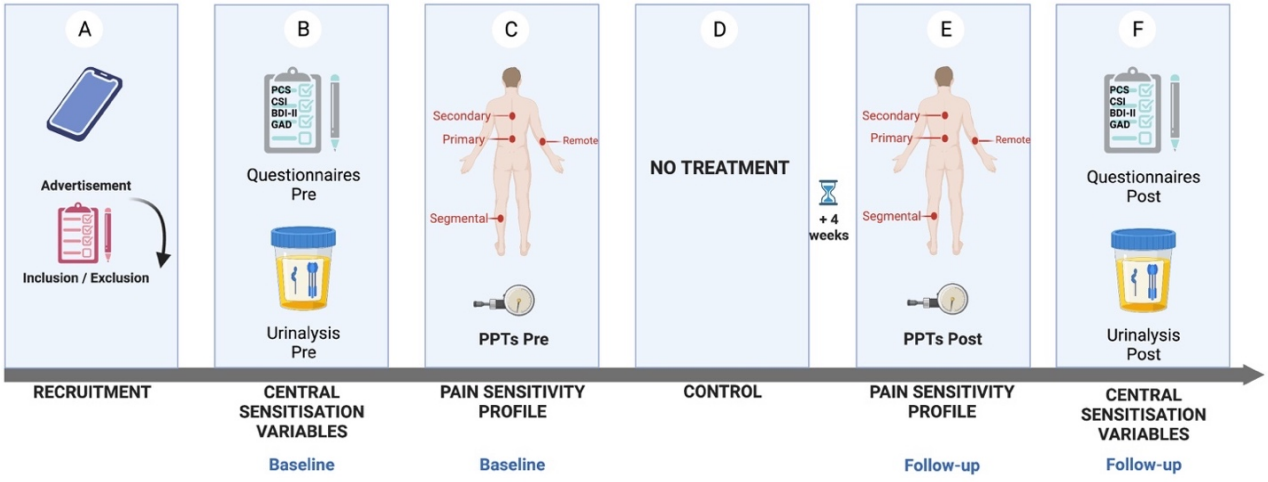

Figure 28 Study protocol for the healthy control arm.

The recruitment process is illustrated in **(A)**, the collection of variable data during the initial examination is depicted in **(B,C)**. Participants will receive no treatment **(D)** and variable data will collected after 4 weeks of follow-up **(E,F)**. BDI-II, Beck Depression Inventory II; CSI, central sensitisation inventory; GAD, Generalized Anxiety Disorder; PCS, Pain Catastrophizing Scale; PPTs, pressure pain thresholds.

A cohort of healthy volunteers will be recruited to be used as a reference for the psychological, psychophysical, and inflammatory variables collected in the sample of CLBP patients. They will be age- and sex-matched to the patients allocated to the group receiving SMT. Individuals meeting the following criteria are eligible to participate: being 18 to 70 years old; presenting no current or chronic pain condition, as well as not having received any diagnosis of a systemic, inflammatory, neurological or psychiatric condition.

Randomisation, concealed allocation, and blinding

A computer application (random-number generator) will be used to generate a balanced randomisation sequence. Participants will be allocated in a 1:1 ratio to the intervention (SMT) or placebo arms following the chronological order of recruitment. Patients, outcome assessors and statistician will be blinded to group allocation. To confirm the efficacy of the patients' blinding, participants will respond in three occasions to the questions: "Do you think that the treatment you have received is a real chiropractic treatment for back pain?"; and "On a numerical rating scale of 0–100, please rate the degree of certainty for having received a real chiropractic treatment" (with 0 being total uncertainty and 100 being absolute certainty; Chaibi et al., 2015).

Additionally, to avoid biases in the reporting of patient-reported outcome measures and to blind the investigator delivering the interventions, participants will provide these data via electronic questionnaires without the presence or interference of any investigator.

Interventions

Both real and placebo SMT will be delivered by a chiropractor with twenty years of experience that is part of the research team (CG-M). Two real SMT will be performed with the patient positioned in the lateral decubitus position (once on each side), by applying a high-velocity, low-amplitude force on the manipulated segment, with the aim of generating at least one joint cavitation (associated with an audible sound). For this, the chiropractor will use the hypothenar surface or the last phalanx of the 2nd and / or 3rd fingers of the hand to contact the spinous process of the vertebral segment with the most intense clinical pain (see supplemental **Figure 30A**), as detected in the initial patient examination. In case of not perceiving a cavitation or satisfactory joint movement, SMT may be repeated once on each side. Therefore, all participants will receive a

minimum of two and a maximum of four SMT thrusts. Participants in the placebo arm will receive a validated sham SMT that is very similar to SMT (Chaibi, et al., 2015). The patient is positioned in the same lateral decubitus position, with the lower leg in extension and the upper leg in flexion, and an unintended force is applied bilaterally to the gluteal region (**Figure 30B**). The number of real or placebo SMT attempts resulting in joint cavitation will be recorded. Participants in both groups will receive 3 treatment session per week for 4 weeks (see **Figure 27D**). Healthy volunteers will receive no intervention during the same timeframe of 4 weeks (see **Figure 28**).

Outcome variables

Primary outcomes

Patients will rate their current CLBP intensity, as well as the average, minimum and maximum pain throughout the preceding seven days or since the time of the previous session, once the study is underway (de Andres Ares et al., 2015; Tan et al., 2004), using a numerical rating scale between 0 (no pain) and 100 (maximum pain imaginable). Average pain intensity will be used as the primary outcome for all statistical analyses. The primary endpoint will be the change from baseline at the completion of the 12 sessions of SMT. For the follow-up, average pain intensity will be assessed 4 and 12 weeks after the completion of the trial.

Disability caused by CLBP will also be assessed as a primary outcome. After completing the case history, patients will fill out the Oswestry low back disability index questionnaire (Alcántara-Bumbiedro et al., 2006). The questionnaire will also be completed after the 12th treatment session with the primary endpoint, and at subsequent 4- and 12-week follow-ups.

Secondary outcomes

Five topics were identified to discriminate pain mechanisms between groups of patients, including CS mechanisms: clinical examination, questionnaires, quantitative sensory testing, laboratory tests, and imaging tests (Shraim, et al., 2021). For the present study, all categories will be considered except the last one, which will only be used to rule out pain of suspected neuropathic or nociceptive aetiology. Variables belonging to these categories will be assessed for exploratory purposes and five of them will be examined as predictors of the response to SMT (two questionnaires, one quantitative sensory testing variable, one laboratory test variable and the expectations of pain relief).

Clinical examination variables

Data on the characteristics of the patients' CLBP will be collected at baseline for exploratory purposes: CLBP trajectory (duration and frequency) and localization. The duration of CLBP will be calculated as the number of months since the onset of the first episode of LBP. As for pain frequency, participants' CLBP trajectory will be classified as either fluctuating or episodic, depending on whether they recall asymptomatic periods of at least 4 weeks (episodic) or not (fluctuating; Kongsted et al., 2017) For pain localization, patients will also draw the area affected by their pain on a tablet, using an application (Symptom Mapper) that will allow to calculate the degree of pain widespreadness (Ellingsen et al., 2021).

Additionally, CLBP will be classified as either proportionate or disproportionate to the degree or nature of the injury or pathology, with a discrete or diffuse distribution, according to criteria that were defined in the literature (Nijs, et al., 2015; Smart, et al., 2012). A diffuse rather than a discrete pain distribution was identified as a key criterion of a CS phenotype (Kosek, et al., 2021; Smart, et al., 2012). Also, classifying symptoms as proportionate (or not) was proposed to differentiate nociceptive pain from CS mechanisms (Nijs, et al., 2021b). The pattern of pain distribution and the provocation and response to aggravating and palliative factors will be assessed during case history and physical examination. This will be complemented with information provided by diagnostic imaging when available (Shraim, et al., 2021).

Finally, other variables will be reported such as the intake of pain medication compatible with the selection criteria, both at baseline and at after treatment. Similarly, whether the patient regularly smokes will be documented, since smoking has been associated with increased serum levels of pro-inflammatory cytokines (Petrescu et al., 2010). The average number of hours of sleep will also be recorded, as it may help predict pain patterns (Edwards et al., 2008). Additionally, the presence of any chronic condition (including pain) that are comorbid with the CLBP will be recorded for exploratory purposes.

Questionnaire variables

The Pain Catastrophizing Scale (PCS) and CSI will be completed before the beginning of the treatment (baseline) and at a single follow-up after the 12th treatment session (Cuesta-Vargas et al., 2016; Garcia Campayo et al., 2008). The PCS will be used to identify specific pain cognitions that are frequently present in patients with a CS phenotype, this measure will be used to evaluate

the association of CLBP with psychosocial factors described by Smart et al. (2012). When combined with a clinical presentation suggestive of CS (Nijs, et al., 2021b), the CSI is an useful tool to identify patients compatible with certain CS mechanisms, particularly when using the cut-off value of 40 points (Scerbo et al., 2018). Both these scores will be examined as predictors due to their intrinsic association with a CS phenotype.

In addition, the Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disorder scale (GAD) questionnaires will be used to screen and quantify symptoms of depression and anxiety (García-Campayo et al., 2010; Sanz et al., 2005). The scores in these questionnaires will be measured both at baseline and after the 12th treatment session for exploratory purposes. We will examine whether these variables are associated with the primary outcomes. Pre and post reference values of all questionnaires (PCS, CSI, BDI-II and GAD) will be taken from the healthy control participants in the same timeframe (**Figure 28**).

Quantitative sensory testing variables

Quantitative sensory testing based on the German protocol (Rolke et al., 2006; Starkweather et al., 2016) will be performed with the aim of evaluating pain thresholds and sensitivity (**Figure 27C**). Testing will consist of the exploration of the PPTs in deep tissues (**Figure 29**), using an algometer (Wagner Force Dial FPX, Greenwich, CT, USA). In addition, patients will rate the intensity of the first stimulus above threshold, using a numerical rating scale 0–100 (Pfau et al., 2014) PPTs will be assessed by two interns completing their Master's in Chiropractic degree, after three months of training and pilot data collection. One of the two outcome assessors will be randomly assigned to each patient to perform both baseline and follow-up measurements. Two measurements will be taken bilaterally at a rate of about 50 kPa/s, and the arithmetic mean of both the thresholds and sensitivities reported calculated. Two consecutive measurements provide excellent reliability when assessing both populations with and without LBP (Balaguier et al., 2016a); b) while performing two repetitions per side of the lower back was proposed to optimize inter-session reliability (Liew et al., 2021). PPTs will be performed over muscle tissue in 4 different locations. Primary pain will be assessed 2.5 cm lateral to the spinous process in the erector spinae (Pfau, et al., 2014) of the vertebral segment with the highest clinical pain intensity indicated by the patient and verified by palpation (**Figure 29**). Manual palpation will be performed to confirm that the selected segment either reproduces clinical pain or is the closest to the area (or to the centre) of

CLBP symptoms. This will allow to assess the area of primary pain or hyperalgesia (segmental sensitivity). In addition, PPTs will be measured on both lower limbs in the dermatome corresponding to the segment of highest clinical pain intensity (dermatomal sensitivity), in the erector spinae four to six segments cranial to the most painful lumbar segment (heterosegmental sensitivity in a non-symptomatic segment: secondary hyperalgesia), and in a remote location in both thenar eminences (widespread sensitivity). PPTs will be assessed during the initial examination for baseline and after the final treatment session (see **Figure 27C** and **Figure 27E**). Reference values will be taken in healthy volunteers in the same locations as the CLBP participants receiving SMT (lumbar segmental, dermatomal, heterosegmental, widespread) at baseline and after 4 weeks (**Figure 28**).

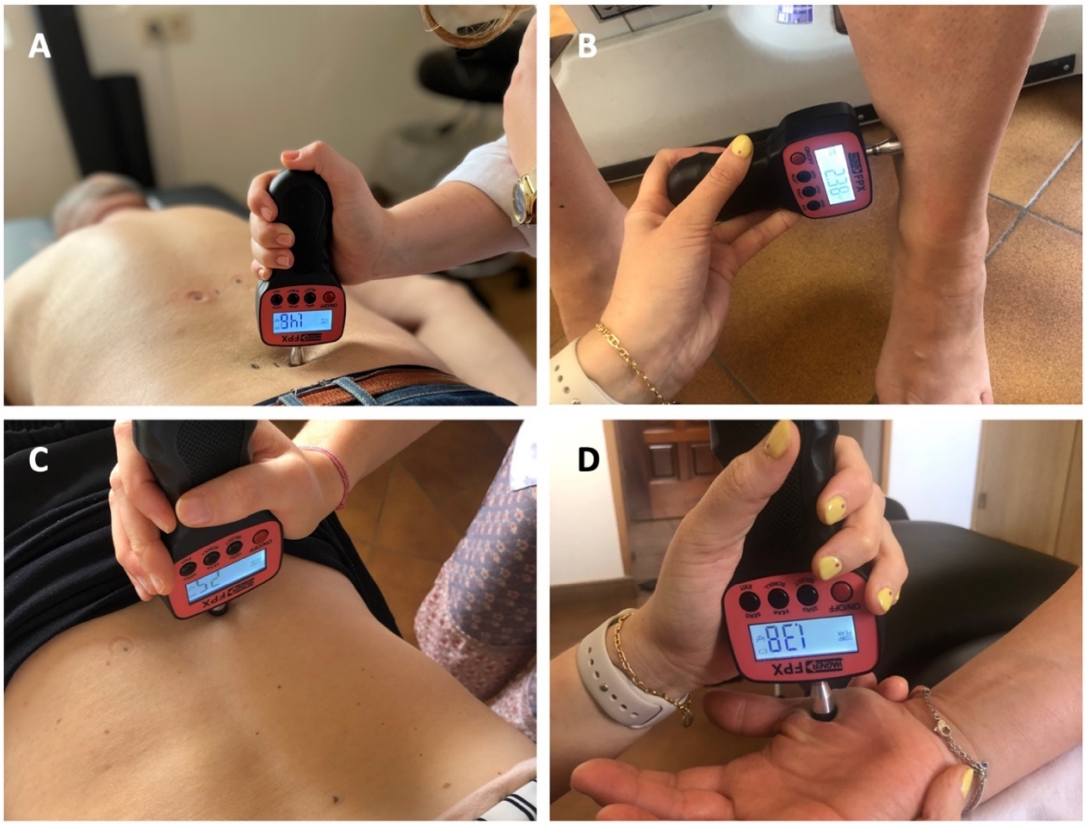

Figure 29 Quantitative sensory testing.

Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. **(A)** Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest clinical pain intensity identified by the patient or via posterior to anterior manual palpation. **(B)** Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). **(C)** Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of an asymptomatic vertebral segment

located four to six segments cranial to the segment identified in (A). **(D)** Remote PPTs measured over muscle tissue in the centre of the thenar eminence. All participants whose image was used for this figure provided written consent to the inclusion of this image in the manuscript.

Laboratory test variables: TNF-α as an inflammatory biomarker in urine

Before initiating the first treatment session and on the day of the last treatment session, urine samples will be collected (first morning micturition) and stored at -20º C (**Figure 27B** and **Figure 27F**). Additionally, the first morning micturition will be collected twice from healthy individuals in the same timeframe (two samples with a 4-week delay, see **Figure 28**; Gevers-Montoro, et al., 2022) Samples will be deidentified by using only the participant's ID code, and the laboratory technicians will be blinded to group allocation. Urine concentrations of tumour necrosis factor alpha (TNF-α) will be quantified for each sample using specific ELISA for TNF-α following manufacturer's instructions. The cytokine to creatinine ratio will be calculated to correct for differences in urine volumes (Ortega et al., 2019). TNF-α values, including urinary concentrations, were found to be elevated in CLBP patients and may respond to a treatment based on SMT (Gevers-Montoro, et al., 2022; Lim, et al., 2020; Morris et al., 2020; Teodorczyk-Injeyan, et al., 2006, 2021).

Expectations

Before initiating treatment, each participant will be asked to rate their expectations of pain relief upon completion of the study. To do this, a verbal evaluation will be provided using a visual analogue scale with the descriptors -100, equivalent to "total pain relief," 0, equivalent to "no change," up to +100, equivalent to "maximum pain increase". Such an assessment of patients' expectations allows to identify their contribution as part of the placebo response, which were found to predict the response to treatment for chronic pain (Cormier et al., 2016).

Adverse events reporting

At the beginning of every SMT or placebo treatment sessions, patients will inform whether they have suffered any adverse effects that they feel could be related to the treatment received via an electronic questionnaire. Adverse effects will be classified into four categories most frequently reported after lumbar SMT as identified in a clinical trial: muscle stiffness, increased pain, radiating discomfort, and others (Walker et al., 2013). In addition, patients will indicate whether they were triggered immediately, up to 24 hours, or more than 24 hours after the previous session, whether

their duration was of minutes, hours (< 24 hours), between 24 and 48 hours, or longer than 48 hours (Walker, et al., 2013), and according to their intensity (very mild, mild, moderate, severe, very severe). The reporting of adverse events will be monitored by an investigator not involved in clinical care or examination. A 30-point increase in pain intensity or the reporting of moderate to severe adverse events in three consecutive visits will raise the alarm and the patient will be interviewed to determine whether care should be interrupted.

Healthy volunteers will be contacted one week prior to the follow-up appointment to rule out any of the following criteria that would exclude them from the follow-up: presence of pain or other symptoms for > 7 days, trauma or injury, initiating a new treatment or receiving a diagnosis compatible with the exclusion criteria. In addition, if the participant reports any pain or taking any pain medication within 24 hours of the follow-up, this session will be postponed for up to one week.

Procedures

Candidates interested in participating in the study will initially complete a form with the selection criteria (Supplemental Appendix 1). If the criteria are met, patients will schedule an appointment at the MCC clinic where they will read and sign a participant information sheet, and the informed consent (Supplemental Appendices 2 and 3). Subsequently, patients will undergo a clinical examination (consisting of a case history and physical examination) to confirm the diagnosis of chronic primary LBP, during which all outcomes will be collected, except for the urine sample that will be provided before the first treatment session. Patients will then participate in 12 treatment sessions divided into three weekly sessions for 4 weeks. All outcome measures will be re-assessed at the 12th and last treatment session (i.e., the primary endpoint). After completing data collection at the primary endpoint, patients allocated to the placebo arm will be offered the possibility of receiving the "real" SMT, free of charge, at the MCC. In addition, all patients will be contacted for the follow-up of CLBP intensity and disability, 4 and 12 weeks after the primary endpoint (**Figure 27G**). Meanwhile, healthy volunteers will participate in two visits (baseline and follow-up after 4 weeks) when all relevant outcomes will be assessed (**Figure 28**). The study will have a total estimated duration of one year.

Sample size calculation

To determine the ideal number of participants, the second aim to identify the variables linked to a CS phenotype that could help predict the response to treatment based on SMT for CLBP was considered. A multiple regression analysis will be performed using five independent variables described in the statistical analysis section as predictors. These variables include baseline values of local PPTs, urinary concentrations of TNF, scores in PCS and CSI questionnaires and a priori expectations of pain relief. For each predictor variable, it is recommended to estimate about 10 sample elements, therefore we predict that a sample size of 50 patients per group will be necessary (Ortega Calvo and Cayuela Dominguez, 2002). A total of 110 patients will be recruited, accounting for an estimated dropout rate of 5-10%.

Regarding the primary outcome variables, a reduction in pain intensity and disability after one month in patients who receive 12 sessions of SMT compared to placebo will be expected. We aim to detect small to moderate effects since it is a one-month intervention in patients with chronic pain unresolved by other treatments over at least 3 months. Therefore, based on an effect size of f = 0.175, an alpha of 0.05, a power of 0.8 for 2 groups and 2 repeated measures (baseline and primary endpoint), and a correlation between the repeated measures of 0.5, the size of the necessary sample is 34 patients per group, thus a total of 68 patients to detect statistically significant changes in clinical pain and disability. Therefore, the analysis based on the regression model to predict the clinical course provides with a large enough size for identifying small between-group differences.

Statistical analysis

The normal distribution of the data will be verified using the Kolmogorov-Smirnov test. Data deviating from normality will be transformed to obtain a normal distribution before being entered into the data analysis. In order to interpret the values in outcomes measured in patient groups, these will be compared with reference values obtained from the healthy controls to the CLBP group receiving SMT. This will allow characterizing the patients' groups (aim 1) to determine whether they show increased psychological symptoms, pain sensitivity and hyperalgesia as well as increased TNF-α levels compared with a reference healthy population. A series of mixed analyses of variance (ANOVA) will be performed to examine differences in PPTs, urinary TNF-α levels, PCS, CSI, BDI-II and GAD scores before and after the 4-week treatment period between the three groups (control, SMT and placebo). To test a priori hypotheses, significant effects will be

decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparisons between group means.

Pearson's product-moment correlation analyses will be carried out to examine the association between the primary and secondary variables that demonstrate significant effects between groups over time. Subsequently, two multiple regression models will be used to examine the predictors of improvement in clinical pain and disability over time in patients who have received SMT (aim 2). The variables used as predictors for this analysis will be: baseline PCS and CSI score, baseline PPTs in the primary pain region, baseline TNF-α levels, and (baseline) expectations of pain relief. In addition, in another regression model, the changes (delta) in these variables (except expectations of pain relief, which are only measured a priori) after 4 weeks of treatment will be used as predictor variables. This is done to identify the variables most associated with clinical evolution to answer the mechanistic question.

The primary outcome variables (clinical pain intensity and disability) will be compared between groups (SMT *vs*. placebo) over time at the primary endpoint using a mixed ANOVA. Average pain intensity since the last treatment visit and in the seven days prior to the initial visit will be the variable used for statistical analyses. With an exploratory objective, the secondary variables (PCS, CSI, BDI-II, GAD scores, PPTs, degree of pain widespreadness, urinary cytokine levels, number and severity of reported adverse effects, presence of leg pain, pain medication use) will be compared between groups (SMT *vs* placebo) over time (baseline and post-treatment) using mixed ANOVAs. To test a priori hypotheses, significant effects will be decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparison between group means.

As recommended by White et al., efforts will be directed towards following up all participants for every time point (White et al., 2011). An intention-to-treat analysis including all randomized study participants with a baseline endpoint assessment will be performed. The use of mixed model ANOVA allows to include all study participants with a lower attrition bias (Bell et al., 2013), while handling missing data using maximum likelihood estimations. Further, a per-protocol analysis will be also performed excluding study participants who voluntarily drop out from the study, develop a severe adverse reaction (increase in >30 points average pain intensity associated to treatment) or fail to attend three consecutive visits, or more than two treatment weeks.

Finally, in order to test whether the data is not missing at random, a sensitivity analysis will be conducted to explore the effect of attrition (White, et al., 2011).

Data management and monitoring

All data will be collected at the MCC teaching clinic of the Real Centro Universitario María Cristina. The clinic utilizes a password-protected computer app that generates a patient file number linked to their clinical and personal data. This file number will be connected to a unique participant ID code made up of three numbers and a letter. This ID code will be used to deidentify all clinical trial data. Only the investigator involved in delivering care will have knowledge of which clinic file number corresponds to which study ID code. The participants' selection, information, consent forms and outcome measures collected in paper format will be securely stored in a file cabinet at the MCC clinic. Patient-reported outcome measures will be collected electronically using the study ID code to complete a google form (Google Inc.). Both paper and online data will be transferred to a password-protected spreadsheet, only accessible to the principal investigator. Data will be stored deidentified for 25 years after final publication. The dataset will be made available after publication of the trial, upon request to the corresponding author.

Patient and public involvement

The local chiropractic patient and professional associations (Asociación Española de Usuarios de Quiropráctica and Asociación Española de Quiropráctica) have been involved throughout the study in the recruitment process and in promoting the trial. Upon completion of the study, the results will be disseminated to the patient community in the general assembly of the patient association, as per a formal agreement with the investigators.

Ethics and dissemination

This clinical trial obtained ethical approval by the Fundación Jiménez Díaz Clinical Research Ethics Committee. All participants in the study will sign an informed consent. Any amendment to the protocol will be communicated to the ethics review board and the clinical trial registry. The results of the study will be submitted for publication in peer-reviewed journals and disseminated via scientific conferences and presentations directed to the professional and patient associations.

Discussion

The stratification of patients with CLBP is essential to better understand the needs of individual patients and provide targeted treatment. A mechanism-based classification is a promising avenue to match patients with the care that is best suited with their CLBP mechanism. However, there is an ongoing debate regarding the definition of these subgroups and the best available tools to diagnose them (Hoegh, et al., 2022; Kosek, et al., 2021; Nijs, et al., 2015; Nijs, et al., 2021b; Shraim, et al., 2022). The most recent guidelines for the management of CLBP in both a primary care and a physiotherapy setting recommend SMT as one of the first options for care (George et al., 2021; Kirkwood et al., 2021). Nonetheless, it is not yet possible to identify which patients may benefit the most. The current study describes a protocol for a mechanistic randomised placebo-controlled trial that may contribute to unveil the CS-related mechanisms involved in CLBP relief by SMT. The main objective of the proposed trial is to provide some insight on potential mechanisms of SMT that may be particularly relevant for a subgroup of patients with CLBP. Grasping these mechanisms may help better guide conservative care for patients with CLBP by assessing clinical, neurophysiological, cognitive and/or biochemical variables at baseline.

Strengths and limitations

The main strength of the current study is the robust design using a validated placebo and assessing the blinding of participants, while ensuring the blinding of outcome assessors, statistician, laboratory technician. Moreover, the investigator delivering care will be blinded to the patients' progress. This will reduce biases that are typically introduced in manual therapy trials. Additionally, the use of a control group will help determine reference values and their stability in a healthy population, which has not been readily reported, particularly concerning urinary levels of inflammatory cytokines (Gevers-Montoro, et al., 2022). Further to this, the multidimensional approach to defining central sensitization and the mechanisms leading to it may render relevant data in better defining pain mechanisms involved in CLBP.

Regarding potential limitations, having only one clinician may limit the generalizability of the SMT effects. However, it also has the advantage of standardizing the interventions and reducing variability in the procedures. It should also be noted that, although blinding the investigator providing care is desirable, it is impossible in manual therapy trials (Hohenschurz-Schmidt et al.,

2022a), including the present study. As the sham and real SMT have a high degree of similarity, effective blinding of participants is feasible (Chaibi, et al., 2015). The inability to distinguish the placebo from the real treatment is desirable to limit interpretation bias, particularly in a mechanistic trial as in the present study (Hohenschurz-Schmidt et al., 2022b). However, the sham SMT may rely on specific mechanisms that overlap with those of real SMT, leading to treatment effects (Gevers-Montoro et al., 2021a; Hohenschurz-Schmidt, et al., 2022b). Accordingly, the sham SMT should not be considered as an inert placebo and the lack of between-group differences should be interpreted with caution, with a potential risk for type II errors.

Author contributions:

All authors contributed to the design of this protocol. CG-M and MP conceptualised and designed the protocol, except for every aspect related to laboratory analyses, which was conceptualised by AO-DM. The protocol was drafted by CG-M, and revised by MP and AO-DM. The statistical analysis was designed by MP. CG-M was responsible for ethical committee approval. All listed authors meet authorship criteria and have read and approved the final manuscript.

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Competing interests:

The authors have no conflict of interest and no commercial interest to declare.

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Supplemental material:

Figure 30 Photographs depicting the real and sham spinal manipulative therapy procedures.

Supplemental appendix 1: Participant selection form

Supplemental appendix 2: Participant information sheet

Supplemental appendix 3: Informed consent form

Appendix III – Liste des publications durant mes études doctorales

1. **Gevers-Montoro C**, Romero-Santiago B, Medina-García I, Larranaga-Arzamendic B, Álvarez-Gálovich L Ortega-De Mues A, Piché M. (**soumis**) Reduction of chronic primary low back pain by chiropractic spinal manipulative therapy is accompanied by decreases in segmental mechanical hyperalgesia and pain catastrophizing. *PAIN*

2. **Gevers-Montoro C**, Puente-Tobares M, Monréal A, Conesa-Buendia FM, Ortega-De Mues A, Piché M. (2023) Urinary TNF-α as a potential biomarker for chronic primary low back pain. *Frontiers in Integrative Neurosciences* https://doi.org/10.3389/fnint.2023.1207666

3. **Gevers-Montoro C**, Liew BXW, Deldar Z, Conesa-Buendia FM, Ortega-De Mues A, Falla D, Khatibi A. (2023) A network analysis on biopsychosocial factors and pain-related outcomes assessed during a COVID–19 lockdown. *Scientific Reports.* https://doi.org/10.1038/s41598-023-31054-4

4. **Gevers-Montoro C**, Ortega-De Mues A, Piche M. (2023). Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial. *BMJ Open*. http://dx.doi.org/10.1136/bmjopen-2022-065999

5. **Gevers-Montoro C**, Deldar Z, Furlan A, Lazar EA, Ghalibaf E, Ortega de Mues A, Khatibi A. (2022). From hands-on to remote: Moderators of response to a novel self-management telehealth programme during the COVID-19 pandemic. *European Journal of Pain*. https://doi.org/10.1002/ejp.1968

6. **Gevers-Montoro C**, Romero-Santiago M, Losapio L, Conesa-Buendia FM, Newell D, Alvarez-Galovich L, Piche M, Ortega-De Mues A. (2022). Chiropractic Care Influences Inflammatory Cytokine Levels in Urine Samples of Chronic Low Back Pain Patients: a Preliminary Prospective Cohort Study. *Frontiers in Integrative Neurosciences*. https://doi.org/10.3389/fnint.2022.879083

7. **Gevers-Montoro C**, Murray K, Santamaria B, Dominguez G, Álvarez-Galovich L, Vindigni D, Azari M, Ortega de Mues A, Castro-Mendez A. Combined Chiropractic and Podiatric Treatment for Chronic Low Back Pain Concomitant with a Unilateral Pronated Foot: Protocol for a Multicentre Pilot Randomised Controlled Trial. (2021). *Journal of Chiropractic Medicine*. https://doi.org/10.1016/j.jcm.2021.12.012

8. **Gevers-Montoro C**, Deldar Z, Conesa-Buendía FM, Lazar EA, Mahillo-Fernandez I, Khatibi A, Ortega de Mues A. (2022). Pain catastrophizing mediates rapid benefits of

accessing in-person chiropractic care during the COVID–19 lockdown. *European Journal of Pain*. https://doi.org/10.1002/ejp.1872

9. **Gevers-Montoro C**, Provencher B, Descarreaux M, Ortega de Mues A, Piché M. (2021). Clinical effectiveness and efficacy of chiropractic spinal manipulation for spine pain. *Frontiers in Pain Research*. https://doi.org/10.3389/fpain.2021.765921

10. **Gevers-Montoro C**, Provencher B, Northon S, Stedile-Lovatel JP, Ortega de Mues A, Piché M. (2021) Chiropractic Spinal Manipulation Prevents Secondary Hyperalgesia Induced by Topical Capsaicin in Healthy Individuals. *Frontiers in Pain Research*. https://doi.org/10.3389/fpain.2021.702429

11. **Gevers-Montoro C**, Provencher B, Ortega de Mues A, Piché M. (2021) Neurophysiological Mechanisms of Chiropractic Spinal Manipulation for Spine Pain. *European Journal of Pain*. https://doi.org/10.1002/ejp.1773

12. **Deldar Z & Gevers-Montoro C***, Khatibi A, Ghazi-Saidi L. (2021) The interaction between language and working memory: a systematic review of fMRI studies in the past two decades. AIMS Neurosciences. 10.3934/Neuroscience.2021001 ***co-first authors**

13. Provencher B, Northon S, **Gevers-Montoro C**, O'Shaughnessy J, Piché M. (2021). Spinal manipulation reduces back pain independently of nociceptive processes related to Aδ fibers. *Journal of Physiological Sciences*. https://doi.org/10.1186/s12576-021-00804-2

14. Khatibi A, Sharpe L, Dehghani M, Ghalibaf E, Hosseinchi P, Mazidi M, Ranjbar S, Deldar Z, **Gevers-Montoro C**, Alizadeh P, Alidoust S, Babaei A, Telkabadi F, Ghadiri T. (2021) Suppression may improve adaptation to worry when facing uncertainty: studying COVID19 pandemic. *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2021.778375